The START (Starting Tuberculosis and Anti-Retroviral Therapy) Trial: A Randomized Controlled Trial to Assess the Effect of Integrated Tuberculosis and HIV Care on the Incidence of AIDS-Defining Conditions or Mortality in participants Co-Infected with Tuberculosis and HIV.

Sponsored by:
National Institute of Allergy and Infectious Diseases (NIAID)
Division of AIDS (DAIDS)

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10 November 2004
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This study is being conducted at CAPRISA (Centre for the AIDS Programme of Research in South Africa) in Durban, South Africa. All enrollments and follow-ups during TB treatment are scheduled to take place at a single site, the Prince Zulu Communicable Disease Centre (CDC) and all post-TB treatment follow-ups are scheduled to take place at a single site, the King Edward VIII Hospital (KEH).

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STUDY DEFINITIONS

**Diagnosis of Tuberculosis:** The presence of either two positive acid-fast bacilli (AFB) sputum smears or one positive sputum smear with a clinical picture consistent with tuberculosis (TB).

**Intensive Phase of TB Therapy:** In accordance with the South African TB Clinical and Diagnostic Treatment Guidelines (Appendix VIII), the intensive phase of TB therapy is the period during which 4 anti-TB drugs are administered. This phase usually lasts 2 months but may be extended.

**Continuation Phase of TB Therapy:** The continuation phase begins immediately after the intensive phase ends and comprises a period during which 2 anti-TB drugs are administered. This phase usually lasts 4 months but may be extended.

**Uninterrupted TB Treatment:** Defined as at least 130 TB directly observed therapy (DOT) doses within 9 calendar months (approximately 274 days since initiation of TB therapy). Participants must receive at least 43 intensive phase DOT doses within 3 calendar months with no interruptions of 14 or more consecutive days and at least 87 continuation phase DOT doses within 6 calendar months.

**TB Cure:** Completion of TB treatment with protocol-defined uninterrupted TB treatment; and at least two consecutive negative sputum cultures at or beyond 2 months of TB therapy with one of the cultures at or beyond 5 months of TB therapy.

**Successful TB Treatment Completion (“Clinical Cure”):** Completion of TB treatment based on protocol-defined uninterrupted TB treatment, with a clinical and radiologic response to TB treatment without two adequate sputum samples obtained at or beyond 2 months, including one at or beyond 5 months of treatment.

**TB Treatment Failure:** The presence of a positive smear or culture obtained at or beyond 5 months after initiating treatment.

**Clinical TB Treatment Failure:** Clinical or radiological evidence of failure to respond to therapy but without a positive culture or smear obtained at or beyond 5 months after initiation of treatment.

**Other, Non-Specified TB Outcomes:** All Participants who did not qualify as a “cure,” “successful TB treatment completion,” “treatment failure,” or “TB recurrence.”

**TB Recurrence:** The diagnosis of TB following TB cure or successful TB treatment completion. This includes culture proven TB relapse and TB re-infection (both based on the RFLP pattern, see below), culture and smear-positive recurrences without a conclusive RFLP pattern, and clinical recurrence diagnosed on the basis of clinical or radiologic evidence without a positive culture or smear.

**TB Relapse:** The diagnosis of TB following TB cure or successful TB treatment completion with isolation of an organism having a RFLP pattern similar to that isolated from the previous TB episode.
**TB Re-infection**: The diagnosis of TB following TB cure or successful TB treatment completion with isolation of an organism having a different RFLP pattern compared to that isolated from the previous TB episode.

**Progression of HIV Disease (AIDS Diagnosis)**: A WHO Clinical Stage IV AIDS-defining opportunistic infection or malignancy, excluding extrapulmonary TB (Appendix II).

**Virologic Failure**: HIV-1 RNA ≥ 1,000 copies/mL on two consecutive measurements obtained after completion of 16 weeks or longer of study treatment.
### ACRONYMS/ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>3TC</td>
<td>Lamivudine</td>
</tr>
<tr>
<td>ABC</td>
<td>Abacavir</td>
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<tr>
<td>AE</td>
<td>Adverse event</td>
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<tr>
<td>AIDS</td>
<td>Acquired immune deficiency syndrome</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
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<tr>
<td>ANC</td>
<td>Absolute neutrophil count</td>
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<td>ANOVA</td>
<td>Analysis of variance</td>
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<tr>
<td>APV</td>
<td>Amprenavir</td>
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<tr>
<td>ART</td>
<td>Antiretroviral therapy</td>
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<tr>
<td>ASP</td>
<td>Adherence Support Program</td>
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<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
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<td>AUC</td>
<td>Area under the curve</td>
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<td>BMI</td>
<td>Body mass index</td>
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<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
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<tr>
<td>Cmax</td>
<td>Maximum concentration</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
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<tr>
<td>CRF</td>
<td>Case report form</td>
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<tr>
<td>d4T</td>
<td>Stavudine</td>
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<td>DAIDS</td>
<td>Division of AIDS</td>
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<td>DSMB</td>
<td>Data Safety Monitoring Board</td>
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<tr>
<td>ddi</td>
<td>Didanosine</td>
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<tr>
<td>ddi-EC</td>
<td>Didanosine enteric coated</td>
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<tr>
<td>DLV</td>
<td>Delavirdine</td>
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<tr>
<td>DOT</td>
<td>Directly observed therapy</td>
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<tr>
<td>EAE</td>
<td>Expedited adverse event</td>
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<tr>
<td>EC</td>
<td>Enteric coated</td>
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<tr>
<td>EFV</td>
<td>Efavirenz</td>
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<tr>
<td>FAHI</td>
<td>Functional Assessment of HIV Infection</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>GBV-C</td>
<td>GB virus C</td>
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<tr>
<td>GEE</td>
<td>Generalized estimating equations</td>
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<tr>
<td>GI</td>
<td>Gastrointestinal</td>
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<tr>
<td>HAART</td>
<td>Highly active antiretroviral therapy</td>
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<td>HBc</td>
<td>Hepatitis B core antibody</td>
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<td>HCV</td>
<td>Hepatitis C virus</td>
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<td>HDL</td>
<td>High density lipoprotein</td>
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<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<td>HSR</td>
<td>Hypersensitivity reaction</td>
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<td>IDV</td>
<td>Indinavir</td>
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<td>IEC</td>
<td>Independent Ethics Committee</td>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>IIT</td>
<td>Intent to treat</td>
</tr>
<tr>
<td>IRIS</td>
<td>Immune reconstitution syndrome</td>
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<tr>
<td>IUD</td>
<td>Intrauterine device</td>
</tr>
<tr>
<td>KEH</td>
<td>King Edward VIII Hospital</td>
</tr>
<tr>
<td>LFT</td>
<td>Liver function test</td>
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<tr>
<td>LPV</td>
<td>Lopinavir</td>
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<tr>
<td>LPV/r</td>
<td>Lopinavir/ritonavir</td>
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<td>MANOVA</td>
<td>Multivariate analysis of variance</td>
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<tr>
<td>MAR</td>
<td>Missing at random</td>
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<tr>
<td>MCAR</td>
<td>Missing completely at random</td>
</tr>
<tr>
<td>MDR</td>
<td>Multi-drug resistant</td>
</tr>
<tr>
<td>MCC</td>
<td>Medicines Control Council</td>
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<td>mmHg</td>
<td>Millimeters of mercury</td>
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<tr>
<td>MOP</td>
<td>Manual of Procedures</td>
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<td>MTCT</td>
<td>Mother-to-child transmission</td>
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<td>NFV</td>
<td>Nelfinavir</td>
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<tr>
<td>NIAID</td>
<td>National Institute for Allergy and Infectious Diseases</td>
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<tr>
<td>NMAR</td>
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<tr>
<td>NNRTI</td>
<td>Nonnucleoside reverse transcriptase inhibitor</td>
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<td>Nevirapine</td>
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<td>OHRP</td>
<td>Office for Human Research Protections</td>
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<tr>
<td>PBMC</td>
<td>Peripheral blood mononuclear cell</td>
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<td>PCP</td>
<td>Pneumocystis carinii pneumonia</td>
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<td>PCR</td>
<td>Polymerase chain reaction</td>
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<tr>
<td>PEP</td>
<td>Post-exposure prophylaxis</td>
</tr>
<tr>
<td>PI</td>
<td>Principle Investigator</td>
</tr>
<tr>
<td>PI</td>
<td>Protease inhibitor</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Hepatitis B surface antigen</td>
</tr>
<tr>
<td>HBV</td>
<td>Hepatitis B virus</td>
</tr>
<tr>
<td>PR</td>
<td>Paradoxical reaction</td>
</tr>
<tr>
<td>PRC</td>
<td>Paradoxical Reaction Committee</td>
</tr>
<tr>
<td>PTT</td>
<td>Prothrombin time</td>
</tr>
<tr>
<td>QA</td>
<td>Quality assurance</td>
</tr>
<tr>
<td>QC</td>
<td>Quality control</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RCC</td>
<td>Regulatory Compliance Center</td>
</tr>
<tr>
<td>RFLP</td>
<td>Restriction Fragment Length Polymorphism</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>RTV</td>
<td>Ritonavir</td>
</tr>
<tr>
<td>SGOT</td>
<td>Serum glutamic oxaloacetic transaminase</td>
</tr>
<tr>
<td>SGPT</td>
<td>Serum glutamic pyruvic transaminase</td>
</tr>
</tbody>
</table>
START: Starting Tuberculosis and Anti-Retroviral Therapy

**Design:** This is a two-armed, randomized, open-label clinical trial evaluating whether the integration of HIV care into existing TB care services is feasible and practical in resource-poor settings. The primary objective is to assess the effectiveness of integrated TB and HIV care provision enhanced with an adherence support program (ASP) versus sequential treatment of TB and HIV, by comparing the progression to AIDS-defining illnesses/mortality in participants with pulmonary TB co-infected with HIV during the first 18 months after enrollment in the study. The study is conducted in two phases. The first phase represents the duration of TB therapy. The second phase represents the period after completion of TB therapy. Study participants will be randomized to one of the following arms stratified by CD4+ cell count, 50-200 cells/µL vs. > 200 cells/µL. Participants randomized into the integrated arm will receive anti-retroviral therapy (ART) consisting of didanosine (ddI)/ didanosine enteric coated (ddI-EC), lamivudine (3TC), and efavirenz (EFV) in conjunction with TB therapy upon randomization. Participants randomized to the sequential arm will complete TB treatment and then start ART consisting of ddI/ddI-EC, 3TC, and EFV. In instances where ddI/ddI-EC, 3TC, and EFV are contraindicated, an alternative regimen will be used.

**Duration:** Study duration is 24 months after randomization.

**Sample Size:** 592 participants will be enrolled.

**Population:** Men and women ≥ 18 years of age with documented HIV infection and smear-positive pulmonary TB.

**Regimen:** At entry, participants will be randomized (1:1) to one of the following treatment arms:

**Integrated arm:** (ddI/ddI-EC) + 3TC + EFV once daily concurrently with standard TB treatment upon randomization.

**Sequential arm:** (ddI/ddI-EC) + 3TC + EFV once daily initiated after completion of TB therapy.

ART substitution options will be available for participants who become pregnant, experience toxicities, or have treatment failure.
1.0 INTRODUCTION

1.1 Background

1.1.1 Access to Anti-retroviral (ART) Therapy

The introduction of Highly Active Antiretroviral Therapy (HAART) in 1996 has transformed the course of Human Immunodeficiency Virus (HIV) infection in industrialized countries into a chronic, manageable disease (Palella et al., 1998; Bozette et al., 1998; van Praag, 1996). In contrast, in the developing world where HAART is much less available, the number of symptomatic people in need of care is large and continues to escalate unabated. Until recently, silence on the provision of care has been deafening. This silence arose from the false dichotomy created between prevention and care and a perception that therapy was simply unaffordable. The XIIIth International AIDS Conference, hosted in Durban, South Africa in July 2000, marked the turning point in the response to the HIV/Acquired Immune Deficiency Syndrome (AIDS) epidemic in resource-constrained settings, particularly with respect to increasing access to treatment. The current discourse with respect to access to anti-retroviral therapy (ART) in resource-constrained settings has shifted from “should” we be making ART available to “how to” make ART available.

Social movements and activists continue to challenge decision-makers in government, pharmaceutical companies, non-governmental, and philanthropic organizations to accelerate access to AIDS treatment. However, drug costs and the lack of the basic health care infrastructure continue to be the most substantial obstacles to this goal. The cost of ART drugs has been partially removed as a barrier to treatment as a result of reduction in drug prices, negotiations on tiered pricing, generic production of drugs, and the ruling of the High Court in South Africa in favor of the State in the case of the State versus the Pharmaceutical Industry (The Pharmaceutical Manufacturers Association and Others v. The President of the Republic of South Africa and Others, case no: 4183/98, High Court of South Africa (Transvaal Provincial Division)). The need for simple, accessible, and sustainable strategies for delivery of HIV care to large numbers of participants in the context of the existing under-developed health care delivery systems remains a challenge for the safe and effective use of ART in many resource-constrained settings. Of significance in this regard is the Joint United Nations Programme on HIV/AIDS (UNAIDS) six-country pilot project to introduce ART in developing countries as part of their increasing drug access program, which has demonstrated that the use of ART drugs in resource-constrained settings is feasible (UNAIDS Increasing Drug Access Initiative).

In South Africa, major companies and industries in the private sector, including the mines, utility companies, and clothing manufacturers, are beginning to provide ART to their employees. However, in the public sector, where HIV/AIDS
has its greatest impact, ART drugs are largely unavailable. This is set to change following the August 8, 2003 announcement by the South African government that ART will be introduced in the public health service. The ART rollout began in 2004, but on a limited basis. ART drugs are currently being used in perinatal transmission prevention, pharmaceutical company sponsored clinical trials, and occupational post-exposure prophylaxis in South Africa. The use of ART drugs for treatment of HIV disease is guided by the use of a modified version of the International AIDS Society (USA) guidelines developed and distributed by the South African HIV Clinician’s Society (October, 2002). The increasing availability of simpler regimens, such as daily dosing drug combinations and newer formulations of triple drug combinations in a single tablet taken twice daily, further increase the options and possibilities to enhance the quality of life for the millions living with HIV in developing countries.

1.1.2 The HIV/AIDS and Tuberculosis (TB) Epidemics in South Africa

South Africa is experiencing one of the largest and fastest growing HIV epidemics in sub-Saharan Africa and the world (UNAIDS, 2001). About 4.7 million people are living with HIV/AIDS in South Africa (Department of Health, RSA, 2001). During the first six months of 2000, approximately 320,000 South Africans were infected, contributing to half of all new infections in sub-Saharan Africa (UNAIDS, 2001). Sixty percent of all infected adults acquire their infection before age 25, and young women between the ages of 20-24 years have the highest HIV prevalence and incidence rates (Abdool Karim et al., 1999). HIV prevalence among antenatal clinic attendees in one rural district of the KwaZulu-Natal province increased from 4.2% in 1992 to 34.0% in 1999 (Wilkinson et al., 1999). It is projected that by 2005, about 250,000 South Africans will have died from AIDS (Doyle, 1991).

Tuberculosis (TB) is the most common serious infectious complication associated with HIV infection in sub-Saharan Africa (Raviglione et al., 1992; de Kock et al., 1992; Churchyard et al., 2000). As the HIV epidemic has matured in sub-Saharan Africa, there has been a dramatic increase in the incidence of TB. TB is also the most common cause of mortality among patients with HIV disease in developing countries (Mukadi et al., 2001; de Kock et al., 1995; Whalen et al., 1996; Colvin et al., 2001). HIV has a substantial deleterious impact on TB outcomes. The development of TB has been shown to accelerate the course of HIV disease and adversely affect HIV outcomes (Whalen et al., 1995). In the presence of HIV, TB is associated with substantially higher case fatality rates regardless of initiation, or in the presence, of effective TB chemotherapy (Elliott et al., 1995; Schluger, 1999).
Ongoing monitoring of TB in the 19,000 mineworkers employed by AngloGold demonstrated a high but stable incidence rate of 500 cases per 100,000 population years prior to 1990. Since 1991, TB case rates have been increasing primarily as a result of co-infection with HIV. TB cases have increased from 1,174 per 100,000 in 1990 to 2,476 per 100,000 in 1996 despite the introduction in 1993 of a comprehensive TB directly observed therapy (DOT) program that ensures over 90% cure rates (Churchyard et al., 1999). HIV prevalence in this population of TB patients rose from 15% in 1993 to 45% in 1996.

At AngloGold, TB is increasingly becoming the major cause of mortality among mineworkers. A review of records from 2,236 men with sputum-positive pulmonary TB between 1993 and 1997 demonstrated an increase in case fatality rates from 1.6% in 1993-1994 to 5.3% in 1995-1996 (Churchyard et al., 2000). Significantly more HIV-infected men died within the first 6 months of TB treatment compared to HIV-negative men (10.5% vs. 1.0%). Patients with CD4+ counts < 200 cells/mm³ had a 31.2% case fatality rate compared to 2.8% case fatality rate in those with CD4+ counts between 200 and 500 cells/mm³ and 1.5% in those with CD4+ count > 500 cells/mm³.

Studies among high HIV prevalence populations in Malawi and Hlabisa, South Africa, have demonstrated that the case fatality rate from all forms of TB was 31% and 24.7%, respectively (Harries et al., 1998; Connolly et al., 1998). Data on temporal trends in TB from one rural district in South Africa demonstrate trends that parallel the increase in HIV prevalence in the general population (Wilkinson & Davies, 1997). The TB case fatality rate in smear-positive TB patients increased from 4.4% in 1991 to 10.3% in 1995 and from 13% in 1991 to 24.7% in 1995 among smear-negative TB participants. Further, the case fatality rate was 2.5 times higher among patients co-infected with HIV compared with HIV-negative TB patients. In contrast, data from mineworkers in South Africa have demonstrated a lower case fatality rate of 3.6% within the first 6 months of initiation of treatment in a high HIV incidence setting (Churchyard et al., 2000). However, the case fatality rate more than tripled, from an initial 1.6% to 5.3%, over the second half of the study corresponding to the advancing HIV epidemic and increasing immunosuppression in this population.

Prior to the introduction of HIV in South Africa, the country was already experiencing a major TB epidemic. The disease burden is unevenly distributed in South Africa. The highest TB incidence rates are recorded in the Western, Eastern, and Northern Cape Provinces, yet in terms of the absolute numbers of TB cases, the most severely affected provinces are KwaZulu-Natal, Eastern Cape, and Gauteng (Fourie, 2001) (Table 1).
Table 1: Annual TB Burden for South Africa with Proportion Co-Infected with HIV

<table>
<thead>
<tr>
<th>Province</th>
<th>Total TB Cases</th>
<th>Proportion HIV+</th>
</tr>
</thead>
<tbody>
<tr>
<td>KwaZulu-Natal</td>
<td>65,654</td>
<td>64.6%</td>
</tr>
<tr>
<td>Gauteng</td>
<td>45,598</td>
<td>44.8%</td>
</tr>
<tr>
<td>Western Cape</td>
<td>34,211</td>
<td>31.6%</td>
</tr>
<tr>
<td>Eastern Cape</td>
<td>56,495</td>
<td>40.0%</td>
</tr>
<tr>
<td>Northern Province</td>
<td>23,338</td>
<td>36.3%</td>
</tr>
<tr>
<td>Mpumulanga</td>
<td>15,657</td>
<td>59.1%</td>
</tr>
<tr>
<td>North West</td>
<td>15,549</td>
<td>45.5%</td>
</tr>
<tr>
<td>Free State</td>
<td>14,654</td>
<td>51.7%</td>
</tr>
<tr>
<td>Northern Cape</td>
<td>4,649</td>
<td>33.2%</td>
</tr>
<tr>
<td>South Africa</td>
<td>273,365</td>
<td>47.6%</td>
</tr>
</tbody>
</table>

*Source: National Tuberculosis Research Programme, Medical Research Council*

The increasing HIV infection rate is compounding the TB epidemic in South Africa. In KwaZulu-Natal, 64.6% of newly diagnosed cases of pulmonary TB are co-infected with HIV. In 1999, the TB case fatality rate was estimated to be 40% despite directly observed TB treatment completion and cure rates that range from 60-90%. A survey at the King Edward VIII Hospital (KEH) in Durban, KwaZulu-Natal in 1998 reported that 54% of adult in-patients have an AIDS-related illness (Colvin et al., 2001). Active pulmonary TB with HIV co-infection is the most common AIDS-related diagnosis (see Appendix II for a list of AIDS-defining illnesses) in the medical wards and accounts for 59% of AIDS-related deaths. A cross-sectional study at KEH demonstrated mortality rates of 22% among HIV-infected patients compared to 9% in HIV negative patients (Colvin et al., 2001).

1.1.3 Health Care Services in South Africa

The health system as it currently stands is still reeling from the history of inequity and apartheid that preceded it. The system was conceived to have no social security net for those without resources, and it was designed as a “residual” health care service. The responsibility for health care was and still is mostly in the hands of private care physicians. These doctors provide services for approximately 23% of the country’s population. These patients have insurance or can pay out-of-pocket. The other 77% of the population uses “public” health services, which are largely under-funded and understaffed. Thus, the majority of the country is served in a system that is overcrowded and with scarce resources.
The HIV/AIDS epidemic has only exacerbated this problem. Not only has health utilization increased, but other illnesses that deserve attention (such as diabetes, infections, hypertension, etc.) are being crowded out by the increasing patient morbidity that AIDS brings. As a consequence the South African health care system is currently being overwhelmed.

Health care services for TB are provided through a three-pronged system. Non-governmental organizations, such as SANTA (South Africa National TB Association), provide hospital care and outreach, provincial governments provide TB hospitalization, and primary outpatient care is provided through local governments (Benatar, 1997). DOT on an outpatient basis is the standard policy and has been very successful in some areas; others, however, continue to have difficulty achieving high rates of treatment completion and cure, especially in patients co-infected with HIV.

1.1.4 DOT

In many developing countries, an established, acceptable and familiar infrastructure is available to provide treatment for patients with TB. TB patients receive ongoing clinical care, have secure access to medications, and most receive this treatment through DOT programs. Staff at health facilities is trained to identify TB, to manage the patients and to provide the appropriate linkages and support to ensure completion of and adherence to treatment. National guidelines exist to guide and monitor TB treatment and its outcomes. The DOT strategy has been effective in TB treatment and prophylaxis (Weis et al., 1994; Chaulk et al., 1995) and is the strategy that has been adopted by the World Health Organization (WHO) as the standard of care for management of active TB globally (WHO, 2003).

The importance of adherence to TB medications is fundamental to treatment success. Poor adherence affects both the individual and public health, resulting in an increased morbidity and mortality and the emergence of multi-drug resistant (MDR) TB. The infrastructure for TB treatment incorporates DOT as a means of enhancing adherence.

1.1.5 King Edward VIII Hospital (KEH)

KEH is the second largest hospital in South Africa, with a budget of R380 million (2000/2001 fiscal year). With 13,000 deliveries per annum, KEH has a bed status of 1,300 with about 3,000 out-patients per day.

The hospital has a staff of 3,300 and provides tertiary services for the entire province of KwaZulu-Natal (with a population of approximately 9 million), part of Mpumulanga, and the Eastern Cape provinces. KEH is also the main teaching hospital for the University of KwaZulu-Natal’s Nelson R. Mandela School of Medicine.
At the King George V Hospital, the provincial TB referral center (800 beds), 60-70% of patients are estimated to be HIV infected (Padayatchi N, personal communication, 2002).

An active HIV/AIDS clinic is ongoing within the KEH and has served the community for years. The clinic is an established entity within the hospital and is ready and prepared to treat these additional participants.

1.1.6 Prince Cyril Zulu Communicable Disease Centre (Prince Cyril Zulu CDC)

The Prince Cyril Zulu Communicable Diseases Centre (Prince Cyril Zulu CDC) is the designated clinic for the diagnosis and treatment of TB cases from North and South Central Durban. The clinic serves mainly the local black community and is staffed by medical officers who provide examinations and treatment. Patients are either referred from primary health care centers and hospitals with a diagnosis of TB or are self-referred and considered “walk-in” patients. Upon arrival to the clinic, self-referred patients are screened by a clinic attendant and are directed to the professional nurse who questions patients by asking a series of screening questions to ascertain whether patients have signs and symptoms of TB. Patients who have had a cough for six weeks or more, show other constitutional symptoms of TB, and are from within the Durban metropolitan region are admitted into the system.

Over the last 3 years, TB cases in the central Durban region have increased by 38%. In the year 2000, 79,738 patients were examined and 6,802 new cases were diagnosed of whom 70% were pulmonary TB, 3% primary TB, and 17.8% other TB cases (Prince Cyril Zulu CDC records, KwaZulu Natal, South Africa). A retrospective analysis of all patient records from this clinic for one week in October 2000 showed that 138 new patients were diagnosed with TB during this period. The mean age of the patients was 34 years (range 5 to 72 years). Sixty-six percent were men and 34% were women. Unemployment is high with a rate of 56.2% of the patients unemployed. The majority of patients are black (88%), followed by Asians (8%), coloreds (2%), and whites (2%).

DOT remains the cornerstone of TB management, and all patients are encouraged to receive their medication under supervision. Newly diagnosed TB patients are counseled on the importance of completing treatment and given options for treatment support. They choose from a range of medication supervisors, including supervision by staff at the Prince Cyril Zulu CDC, workplace-based supervisors or community-based supervisors (neighbors, shopkeepers, and friends).

Ninety-one percent of patients who were supervised by the Prince Cyril Zulu CDC reported being compliant to their treatment regimen at 6 months. TB management at the Prince Cyril Zulu CDC is in accordance with the National Tuberculosis Programme guidelines as set out by the Department of Health and entails the daily administration of isoniazid, rifampicin, pyrazinamide, and
ethambutol for the first 2 months of TB treatment, and isoniazid and rifampicin for the duration of TB treatment.

The Prince Cyril Zulu CDC clinic currently provides the community with TB testing, TB treatment, hospital referrals, and HIV voluntary counseling and testing (VCT). It is a natural extension for this clinic to provide the next logical step in a continuum of care, specifically HIV treatment.

1.1.7 Antiretroviral Therapy during Anti-TB Treatment

The rates of infectious complications associated with HIV disease have decreased significantly with the use of potent ART as a direct result of the dramatic associated immune recovery. The impact of ART on TB manifestations is evidenced by the substantial declines in TB case reporting in the US and other countries where ART drugs are widely available for management of HIV disease (Jones et al., 1999; Ledergerber et al., 1999). An Italian study comparing TB cases prior to and since emergence of HAART (Girardi et al., 2000) demonstrated that TB cases occurring after the use of antiretrovirals were associated with higher CD4+ cell counts (median 105 cells/mm³ versus 43 cells/mm³) and more classic clinical findings associated with TB as those in non-immunosuppressed patients, e.g., 45% of patients on ART had typical chest x-ray findings versus 25% prior to ART.

Until recently, the complex HAART regimens with multiple daily drug dosages made it unrealistic to employ a strategy of DOT. The simplification of regimens and favorable pharmacological properties has made once-daily dosing of selected ART drugs possible. Once-daily drug dosing is now possible with commercially available ddI, EFV, and 3TC. These drugs are approved by the US Food and Drug Administration (FDA) for once-daily dosing. The intracellular half-lives of these agents, an important measure of dosing intervals for this class of drugs, are substantially more prolonged. For example, the intracellular half-life of 3TC is 15 hours. The nucleoside abacavir (ABC) also has a prolonged intracellular half-life of 12 hours; however, there are limited data available on its clinical efficacy in once-daily dosing (Gazzard B., et al., 2003). The half-life of the non-nucleoside reverse transcriptase inhibitors (NNRTI) EFV and nevirapine (NVP) are also prolonged (40 hours and 20-25 hours, respectively). Several drugs in current use or in development will likely add to the therapeutic armamentarium of once-daily regimens, but are currently not commercially available.

In a trial of 75 treatment-naïve patients receiving daily treatment with 300 mg ddI, 300 mg 3TC, and 600 mg EFV (Maggiolo et al., 2001) with baseline CD4+ cell counts of 251 cells/mm³ and HIV-1 RNA of 123,000 copies/mL, in an intent-to-treat (ITT) analysis, 78.3% of patients with HIV-1 RNA levels above 100,000 copies/mL and 76.3% with HIV-1 RNA levels < 100,000 copies/mL achieved suppression of < 50 copies/mL at 24 weeks. At 1 year, CD4+ cell counts rose by
216 cells/mm$^3$ and 78% of patients attained virologic suppression to less than 50 copies/mL. Of the 75 patients enrolled, 15 (20%) did not complete therapy; reasons included rash (2), gastrointestinal (GI) intolerance (2), central nervous system (CNS) intolerance (2), non-adherence (3), virologic failure (4), increased liver enzymes (1), and unrelated death (1). A related pilot study of 40 predominantly male, ART-naïve patients with baseline CD4+ counts of > 100 cells/mm$^3$ and HIV-1 RNA < 5,000 copies/mL on a once-daily combination of 200 mg 3TC, 400 mg (if ≥ 60 kg)/250 mg (if < 60 kg) ddI, and 600 mg EFV demonstrated that this combination was safe and well tolerated and its potent antiviral and immunologic effects lasted for 64 weeks (Molina et al., 2001). At week 64, 36 of 40 patients (90%) maintained HIV-1 RNA < 400 copies/mL with the median baseline CD4+ count of 373 cells/mm$^3$, increasing by a median of 159 and 219 cells/mm$^3$ at weeks 24 and 64, respectively. The most common treatment-related adverse events occurred during the first 24 weeks of treatment and consisted of mild to moderate CNS symptoms (73% of patients), diarrhea (37% of patients), rash (10% of patients), and biochemical abnormalities. Two patients experienced severe hypertriglyceridemia that was possibly related to treatment; no other treatment-related severe or serious adverse events were reported. A once-daily regimen of 3TC 300 mg, ddI 400 mg, and NVP 400 mg was also shown to be effective in intravenous drug users (Staszewski et al., 1998). Preliminary studies in Uganda (P. Mlegenyi, personal communication, 2002) and Senegal (Landman et al., 2003) in treatment-naïve patients with once-daily dose ART regimens have achieved similarly encouraging results.

Thus, preliminary data suggest that once-daily regimens can be offered with substantial potency and acceptable side effects and toxicities. For our purposes, the most appealing once-daily ART regimen is EFV, ddI/ddI-EC, and 3TC, as these drugs can be administered simultaneously with TB medications (MMWR, 2000) and provide the best combination of substantial potency and tolerability. In the event that participants become pregnant, experience intolerance, have treatment-limiting toxicities, have ART treatment failure, or require other concomitant medications that preclude treatment with this regimen, substitutions with NVP, saquinavir plus ritonavir (SQV + RTV), lopinavir/ritonavir (LPV/r), tenofovir (TDF), or ABC will be possible (see Section 5.0). In each case, the Medicines Control Council (MCC) registered doses of these alternative agents will be used, where available. Since TDF is not registered in South Africa, access via a Section 21 mechanism, within the confines of the trial, will be necessary. For that reason, more extensive data on the use of this agent are provided.

1.1.7.1 Efavirenz (Stocrin®, DMP-266, EFV)

EFV is a once daily NNRTI that has been shown to be effective in the treatment of HIV disease. Published 48-week data from an open-label, randomized study showed that the combination of 3TC/ZDV/EFV was superior to the combination of 3TC/ZDV/indinavir (IDV) in persons
naïve to 3TC, protease inhibitors (PIs), and NNRTIs. In an ITT analysis, 68% of patients taking 3TC/ZDV/EFV had HIV-1 RNA levels < 400 copies/mL versus 49% of those taking 3TC/ZDV/IDV at week 48, and 62% of the 3TC/ZDV/EFV group versus 43% of the 3TC/ZDV/IDV group had HIV-1 RNA levels < 50 copies/mL at week 48 (Staszewski et al., 1999). Preliminary follow-up data at 72 weeks were also recently presented. At 144 weeks of follow-up, in an ITT analysis, 55% and 52% of the 3TC/ZDV/EFV group and 34% and 30% of the 3TC/ZDV/IDV group had HIV-1 RNA < 400 and < 50 copies/mL, respectively (Tashima et al., 2001). In a double-blind, placebo-controlled study of nucleoside reverse transcriptase inhibitor (NRTI) experienced patients (ACTG 364), 33% on NFV plus NRTIs and 60% on EFV plus NRTIs had < 500 copies/mL of HIV-1 at week 48 (Albrecht et al., 2001).

There is evidence that EFV dosing should be adjusted in those patients over 50 kg when given with rifampicin. Body weight has been shown to be a major determinant of plasma EFV levels (Lopez-Cortes et al, 2002). In addition, a correlation between low plasma levels and virologic failure has been noted (Marzolini et al., 2001). Dose adjustment in larger participants will therefore be done, as indicated in Section 5.1.1.

EFV has been studied in over 2,000 persons. The most notable side effects associated with EFV are CNS symptoms and rash. Fifty-three percent of those receiving EFV reported CNS symptoms. These symptoms included, but were not limited to, dizziness, impaired concentration, somnolence, abnormal dreams, and insomnia. Symptoms usually begin during the first or second day of therapy and generally resolve after the first 2 to 4 weeks of therapy. Potential for additive symptoms may occur if used concomitantly with alcohol or psychoactive drugs. In controlled trials, nervous system symptoms were severe in 2.0% of patients receiving EFV 600 mg once per day and in 1.3% of patients receiving control regimens. In clinical trials, 2.1% of EFV-treated patients discontinued therapy because of nervous system symptoms.

There have been reports (approximately one or two per thousand EFV-treated patients) of delusions and aberrant behavior, predominantly in those with a history of mental illness or substance abuse. Severe acute depression (including suicidal ideation/attempts) has also been infrequently reported in both EFV-treated (0.9%) and control-treated (0.5%) patients. Persons who experience these symptoms should contact their doctor immediately to assess the possibility that the symptoms may be related to EFV.
In controlled clinical trials, 26% (266/1008) of patients treated with EFV 600 mg once per day experienced new onset skin rash compared with 17% (111/635) of patients treated in control groups (see the package insert). Rash associated with blistering, moist desquamation, or ulceration occurred in 0.9% (9/1008) of patients treated with EFV. Among approximately 2,200 treated patients in all studies and expanded access programs, the incidence of Grade 4 rash (e.g., erythema multiforme and Stevens-Johnson Syndrome) was 0.14%. The median time to onset of rash in adults was 11 days, and the median duration was 16 days. The discontinuation rate for rash in clinical trials was 1.7% (17/1008). EFV should be discontinued in persons developing severe rash associated with blistering, desquamation, mucosal involvement, or fever. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash.

Other side effects associated with EFV include upset stomach, diarrhea, anorexia, headache, tiredness, pancreatitis, elevated cholesterol (including high density lipoprotein (HDL)), elevated triglycerides, and elevated transaminases. Birth defects were seen in some monkeys treated with EFV, and whether similar birth defects will be seen in humans is unknown. EFV should not be given to pregnant or breastfeeding women.

For additional information regarding EFV, please refer to the most recent Stocrin® package insert.

1.1.2 Didanosine (Videx®, ddI, ddI-EC)

ddI is an acid-labile ART NRTI; the tablet formulation of ddI (Videx®) includes antacids to prevent acid hydrolysis of the drug in the stomach. In most studies, the 400 mg once-daily dose has demonstrated both pharmacokinetic and virologic equivalence and similar toxicity rates to the 200 mg twice-daily dose through week 24. In a multicenter, open-label study that randomized 84 participants to either once- or twice-daily ddI (both groups also receiving twice-daily stavudine (d4T)), ddI oral chewable/dispersible tablets given once daily were as effective in reducing HIV-1 RNA and increasing CD4+ cell counts as twice-daily ddI. Participants weighing ≥ 60 kg received ddI 400 mg/day plus d4T 80 mg/day; participants weighing less than 60 kg received ddI 250 mg/day plus d4T 60 mg/day. The duration of therapy was 12 weeks (Monno et al., 1999). Results from study AI454-148, however, indicated an inferior virologic response at 48 weeks in patients on a regimen of once daily ddI, ZDV, and nelfinavir (NFV) compared with patients on a regimen of ZDV, 3TC, and NFV. The
proportions of patients with HIV-1 RNA < 400 copies/mL were 50% and 59%, respectively, while the proportions of those with HIV-1 RNA < 50 copies/mL were 34% and 47%, respectively. CD4+ cell counts were comparable between the two arms. Other studies comparing in a randomized fashion the once-daily versus the twice-daily dosing have shown that once-daily dosing is equivalent and preferred compared to twice-daily dosing. The most common toxicities associated with ddI are GI upset, peripheral neuropathy, and pancreatitis.

In addition, an enteric-coated (EC) capsule of ddI is available. The capsule does not require the buffering used in the tablet formulation. Pharmacokinetic studies comparing the EC capsule to the buffered tablets indicate that the area under the curves (AUCs) are equivalent, the maximum concentration (C_{max}) of the EC formulation is 60% of the C_{max} of the tablets, and the median maximum time (T_{max}) values are 2.33 hours for the EC formulation and 0.67 hour for the tablets (Bristol-Myers Squibb). Gamma scintigraphy indicates the delay in T_{max} is related to the time needed to dissolve the capsule in the stomach and that absorption is rapid once the drug enters the small intestine. In healthy volunteers, following a high-fat meal, mean AUC was reduced 19%, C_{max} was reduced 46%, and T_{max} was increased from 2.00 hours (fasting) to 5.25 (fed). Therefore, the same restrictions on food intake apply to the EC capsules as to the tablets. Overall, participants on the EC formulation have experienced similar rates of GI toxicity (primarily diarrhea) as those on tablets. The EC formulation has recently been registered in South Africa and is expected to become available soon. The EC formulation would be preferred, if available.

Patients with renal impairment (creatinine clearance < 60 mL/min) may be at increased risk of developing pancreatitis or other adverse effects from ddI if treated without dosage adjustment. See Section 5.0 for dose adjustment recommendations that will be applied in this trial.

For more information on ddI and ddI-EC, please refer to the most recent Videx® package insert.

1.1.7.3 Lamivudine (Epivir®, 3TC)

3TC is a potent nucleoside that is widely used in the management of HIV-infected patients. Although 3TC is an effective NRTI, virus with a resistance mutation at codon 184 rapidly emerges within 2 weeks of monotherapy and is also seen with dual nucleoside regimens.

3TC is one of the best tolerated nucleoside analogues. Adverse events
occur in less than 5% of patients. Toxicities include headache, nausea and vomiting, malaise, fatigue and sleeplessness, anorexia, dizziness, rash, depression, anemia, neutropenia, and hyperamylasemia.

Persons who are co-infected with hepatitis B may experience increased values on liver function tests (LFTs) and exacerbation of hepatitis symptoms when 3TC is stopped. Usually these symptoms are self-limiting; however, death has been reported. The causal relationship to 3TC discontinuation is unknown. Patients should be followed closely for the first several months following 3TC discontinuation.

Although the currently registered dose for 3TC in South Africa is 150 mg twice daily, the manufacturer has registered a 300 mg once-daily formulation in the US and elsewhere. This is not a sustained-release formulation, and the same effects can be obtained with two 150-mg tablets given once daily. As noted previously, once-daily 3TC 300 mg, ddI 400 mg, and NVP 400 mg was shown to be effective in intravenous drug users (Staszewski et al., 1998). A once-daily dose of 3TC will therefore be used in this trial.

For dose adjustment recommendations in participants older than 18 years who have pre-existing renal impairment, see Section 5.0 for further instructions.

For more information on 3TC, please refer to the most recent Epivir® package insert.

1.1.7.4 Nevirapine (Viramune®, NVP)

NVP is an NNRTI with activity against HIV. The most frequently reported adverse events related to NVP therapy are rash, fever, nausea, headache, and abnormal LFTs. The safety of NVP has been assessed in more than 2,800 patients in clinical trials. The experience from clinical trials and clinical practice has shown that the most serious adverse reactions are clinical hepatitis/hepatic failure, Stevens-Johnson Syndrome, toxic epidermal necrolysis, and hypersensitivity reactions (HSRs) characterized by rash, constitutional findings, and organ dysfunction.

Hepatic Toxicity

In clinical trials, the risk of hepatitis is approximately 1%. Increased aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels before the start of ART treatment and/or history of hepatitis B or C infection are associated with a greater risk of hepatic adverse events. Severe, life-threatening, and in some cases fatal, hepatotoxicity
(including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure) has been reported in patients treated with NVP. In some cases, patients presented with non-specific prodromal signs or symptoms of hepatitis and progressed to hepatic failure with transaminase elevation, with or without hyperbilirubinemia, prolonged prothrombin time (PTT), or eosinophilia. Physicians and patients should be vigilant for the appearance of signs or symptoms of hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness, or hepatomegaly. The diagnosis of hepatotoxicity should be considered in this setting, even if LFTs are initially normal or alternative diagnoses are possible. Hepatic dysfunction may be isolated or associated with signs of hypersensitivity including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, and/or hepatitis, eosinophilia, granulocytopenia, or renal dysfunction.

Women with CD4+ cell counts > 250 cells/µL are at considerably higher risk (12-fold) of hepatotoxicity. While evidence is not conclusive, pregnancy may be an additional risk factor for hepatic toxicity. Males with CD4+ cell counts > 400 cells/µL are at a 3-fold higher risk of hepatotoxicity. Some of these events have been fatal. This subset of patients was identified by analyses of CD4+ cell count at the time of initiation of NVP treatment. The greatest risk of severe and potentially fatal hepatic events (often associated with rash) occurs in the first 6 weeks of NVP treatment. However, the risk continues after this time and patients should be monitored closely for the first 18 weeks of NVP treatment. In some cases, hepatic injury progresses despite discontinuation of treatment.

Intensive clinical and laboratory monitoring, including LFTs, is essential at baseline and during the first 18 weeks of NVP treatment to detect potentially life-threatening hepatic events and skin reactions. The greatest risk of severe rash or hepatic events associated with rash occurs in the first 6 weeks of therapy. However, the risk of any hepatic event (with or without rash) continues past this period, and monitoring should continue at frequent intervals. NVP should not be restarted following severe hepatic, skin, or HSRs. In addition, the 14-day lead-in period with NVP 200 mg once daily dosing must be strictly followed. LFTs monitoring is required after initiation of NVP weekly for the first 6 weeks, at week 8, and then monthly for the first 20 weeks on NVP treatment. All patients developing a rash at any time during NVP treatment should have LFTs performed at that time. After the initial 20-week period, frequent clinical and laboratory monitoring should continue throughout NVP treatment.
Rash

The most common clinical toxicity of NVP is rash, with NVP-attributable rash occurring in 16% of patients on combination regimens in Phase II/III controlled studies. Severe and life-threatening skin reactions, including fatal cases, have occurred in participants treated with NVP. These have included cases of Stevens-Johnson Syndrome, toxic epidermal necrolysis, and HSR characterized by rash, constitutional findings, and organ dysfunction.

Severe rashes occur most frequently within the first 28 days of treatment; 25% of the patients with severe rashes required hospitalization, and one patient required surgical intervention. Approximately 7% of patients discontinue NVP due to rash.

In a recent trial, concomitant use of prednisone to prevent NVP-associated rash increased the incidence and severity of rash during the first 6 weeks of NVP therapy. The use of prednisone to prevent NVP-associated rash is not recommended. Patients should be advised to promptly notify their health care provider if they develop any rash or signs and symptoms of HSR. Patients who experience rash during the first 2 weeks of treatment should not have their dose of NVP increased until the rash has resolved.

Patients developing signs or symptoms of clinical hepatitis, severe skin reactions, or HSRs must discontinue NVP immediately and not be re-challenged.

Drug Resistance Following Single-Dose NVP Prophylaxis

In HIVNET 012, pregnant women received a single dose of NVP at the onset of labor. NVP resistance mutations were detected in 21 of 111 (19%) women 6-8 weeks after delivery (Eshleman, 2001). Those mutations faded from detection in all evaluable women by 12-24 months. The most common NVP resistance mutation detected was K103N, which is associated with cross-resistance to all NNRTIs.

EFV Substitution with NVP

The strategy for substituting NVP for treatment-limiting toxicity related to EFV has not been well studied. Given the known toxicity profiles of the two drugs, it would seem reasonable to try substitution of NVP for treatment-limiting CNS toxicity (e.g., dizziness, somnolence, bad dreams, and confusion) ascribed to EFV. Although the molecular structures of NVP and EFV are not related, substitution for NNRTI class-specific toxicities (e.g., increased AST/ALT, rash) is
less supported, although some anecdotal information is available (Clarke et al., 2000; Podzamczer et al., 2000; Soriano et al., 2000).

Clarke et al reported eight participants who experienced NVP-related adverse events (six with Grade 3 rash, three with AST > 5 times the upper limit of normal (ULN) and seven with flu-like symptoms) and subsequently changed to an EFV-containing regimen. Of these eight, five continued their EFV regimen without recurrence of side effects, one had no side effects in the first 3 months after starting the EFV regimen but was then lost to follow-up, one had a facial rash diagnosed as eosinophilic folliculitis and discontinued the EFV regimen, and one developed an anxiety disorder ascribed to EFV, prompting a change in regimen. Podzamczer et al reported two participants who experienced severe HSRs with NVP, then changed to an EFV-containing regimen (with a corticosteroid taper) with good tolerance. Soriano et al reported findings from their participants participating in an EFV expanded access program: of eight access participants with a history of NVP-associated rash, only one developed a rash after beginning EFV. Although the temporal sequence was NVP to EFV in each report, these case series suggest cross-toxicity between the two drugs may be uncommon.

Additional information regarding NVP is available in the current Viramune® package insert.

1.1.7.5 Tenofovir Disoproxil Fumarate (Viread®, TDF)

TDF is licensed for the treatment of HIV infection in a number of countries, but not in South Africa as yet. TDF is an orally bioavailable prodrug of TDF, an acyclic nucleotide analogue with activity in vitro against retroviruses, including HIV-1 and HIV-2, and against hepadnaviruses. TDF is metabolized intracellularly to the active metabolite, tenofovir diphosphate (PMPApp), which is a competitive inhibitor of HIV-1 reverse transcriptase that terminates the growing DNA chain.

Clinical Experience

Study 907 was a 24-week, double-blind, placebo-controlled, multicenter study of TDF added to a stable background regimen of ART agents in 550 treatment-experienced patients (Pozniak et al., 2002). This trial showed that the addition of TDF resulted in a reduction of viral load of approximately $0.6 \log_{10}$ copies/mL compared with the addition of placebo. Only 3% of patients in each arm
discontinued treatment because of adverse events. This study suggests that TDF has potent ART activity in a treatment-experienced cohort.

Study 903 indicated that TDF is safe and efficacious in treatment-naïve patients as well (Staszewski et al., 2002). Study 903 was a randomized, double-blind, active-controlled clinical trial conducted at 81 sites in the United States, Europe, and South America. The trial was designed to compare the efficacy and safety of a treatment regimen of TDF, 3TC, and EFV to a regimen of d4T, 3TC, and EFV in 600 ART treatment-naïve patients with HIV infection. In an ITT missing=failure (M=F) interim analysis, an identical 87% of patients in the TDF arm (n=299) and the d4T arm (n=301) achieved suppression of HIV-1 RNA to < 400 copies/mL at 48 weeks of treatment (95% CI: -6%, +5%). In another ITT M=F analysis, 82% of patients in the TDF arm compared with 81% of patients in the d4T arm achieved HIV-1 RNA suppression to < 50 copies/mL (95% CI: -6%, +6%). Patients in both treatment groups had significant increases in CD4+ cell count. At 48 weeks, combination therapy with the TDF and d4T arms was associated with a mean increase from baseline of 169 cells/mm³ and 167 cells/mm³, respectively. In both treatment groups, therapy was generally well tolerated; the study discontinuation rate was 9%. The incidence of Grades 3 and 4 adverse events in the TDF-containing study arm was 19% compared with 17% in the d4T-containing arm. The incidence of Grades 3 and 4 laboratory abnormalities in the TDF arm was 28% compared with 31% in the d4T arm.

Safety Profile

More than 1,000 patients have been treated with TDF alone or in combination with other ART medications for periods of 28 days to 143 weeks in Phase I, II, and III clinical trials and a compassionate access study. Assessment of adverse events is based on two studies, 902 (Schooley et al., 2002) and 907 (Pozniak et al., 2002), in which 653 treatment-experienced patients received double-blind treatment with TDF 300 mg (n=443) or placebo (n=210) for 24 weeks followed by extended open-label treatment with TDF.

The most common adverse events in patients receiving TDF with other ART in clinical trials were mild to moderate GI events, such as nausea, diarrhea, vomiting, and flatulence. Less than 1% of patients discontinued participation in the clinical studies because of GI adverse events. A summary of treatment-related adverse events is provided below.
Table 2: Treatment-Related Adverse Events (Grades 1-4) reported in ≥ 3% of TDF-Treated Patients in the Pooled 902 - 907 Studies (0-24 weeks)

<table>
<thead>
<tr>
<th></th>
<th>TDF 300 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients Treated</td>
<td>443</td>
<td>210</td>
</tr>
<tr>
<td>Nausea</td>
<td>11%</td>
<td>10%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Headache</td>
<td>6%</td>
<td>7%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Flatulence</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Laboratory Abnormalities

Laboratory abnormalities observed in these studies occurred with similar frequency in the TDF and placebo-treated groups. A summary of Grades 3 and 4 laboratory abnormalities is provided below.

Table 3: Grades 3 and 4 Laboratory Abnormalities Reported in ≥ 1% of TDF-Treated Patients in the Pooled 902 - 907 Studies (0-24 weeks)

<table>
<thead>
<tr>
<th></th>
<th>TDF 300 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients Treated</td>
<td>443</td>
<td>210</td>
</tr>
<tr>
<td>Number of Patients with Grade 3 or 4 Laboratory Abnormalities</td>
<td>117 (26%)</td>
<td>78 (37%)</td>
</tr>
</tbody>
</table>

Laboratory Abnormalities

- Triglycerides (> 750 mg/dL) 37 (8%) 28 (13%)
- Creatine kinase (> 782 U/L) 53 (12%) 38 (18%)
- Serum amylase (> 175 U/L) 21 (5%) 14 (7%)
- AST (M: > 180 U/L) (F: > 170 U/L) 16 (4%) 6 (3%)
- Urine glucose (3+ or 4+) 12 (3%) 6 (3%)
- ALT elevation (Male: > 215 U/L) (Female: > 170 U/L) 10 (2%) 4 (2%)
- Serum glucose (> 250 mg/dL) 8 (2%) 8 (4%)
- Neutrophil (< 650/mm³) 6 (1%) 3 (1%)
In Study 903, rates were similar between the d4T/3TC/EFV and TDF/3TC/EFV arms, although cholesterol levels and triglyceride levels were generally higher in the d4T-containing arm.

In rare cases, hypophosphatemia, proteinuria, glycosuria, and reduced creatinine clearance have been seen, and five cases of renal tubular injury have been reported (Reynes et al., 2003; Coca and Perazella, 2002; Schaaf et al., 2003). TDF is effective in reducing hepatitis B virus (HBV) in co-infected patients (Nunez et al., 2002).

TDF administered in toxicology studies to rats, dogs, and monkeys at exposures (based on AUCs) between 6- and 12-fold of those observed in humans caused bone toxicity. In monkeys, the bone toxicity was diagnosed as osteomalacia, and appeared to be reversible upon dose reduction or discontinuation of TDF. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown. It is not known whether long-term administration of TDF (≥ 1 year) will cause bone abnormalities. Therefore, appropriate consultation should be sought if bone abnormalities are suspected.

Because there is a limited amount of information on the use of TDF by pregnant women, pregnant women who remain on study will not be permitted to take TDF.

Participants who are co-infected with hepatitis B may experience increased LFTs and exacerbation of hepatitis symptoms when TDF is stopped. Usually these symptoms are self-limiting; however, serious complications have been reported. The causal relationship to TDF discontinuation is unknown. Participants should be followed closely for the first several months following TDF discontinuation.

There is little data supporting the use of four-nucleoside/nucleotide regimens (e.g., ABC/ZDV/3TC + TDF). These regimens should be used cautiously with frequent monitoring for adverse events.

Further information on TDF can be found in the Viread® package insert.

1.1.7.6 Abacavir (Ziagen®, 1592U89, ABC)

ABC is a potent and generally well tolerated nucleoside analogue which offers the convenience of one tablet, twice-daily dosing. Although ABC is licensed for twice-daily dosing, data are available to support once-daily dosing through the Zodiac study (Gazzard B. et al.,
In combination with ZDV and 3TC, the triple nucleoside analogue regimen demonstrates virologic activity comparable to PI-based regimens and offers the advantage of sparing both the NNRTI and PI classes of ART agents.

ABC is generally well tolerated. Most clinical adverse events are mild to moderate in severity and generally self-limiting. The most frequently reported clinical adverse events across Phase III studies were nausea/vomiting, headache, malaise or fatigue, and diarrhea. Elevated triglycerides and anorexia have also been reported. Clinical adverse events and clinical laboratory abnormalities common to some nucleoside ART agents (i.e., pancreatitis, peripheral neuropathy, anemia, and neutropenia) have not been commonly seen with ABC therapy. No differences in the safety profile of ABC based on gender, race, or age are apparent; however, safety in selected populations (i.e., moderate to severe hepatic impairment) has not been evaluated. There is a potential for HSR, which can be life threatening.

**HSR**

The following is a brief description of the signs, symptoms, and laboratory abnormalities that have been associated with ABC HSR.

In clinical studies, approximately 3-5% of patients receiving ABC develop an HSR that in rare cases has proved fatal. HSR is characterized by the appearance of symptoms indicating multiorgan/body system involvement. Symptoms usually appear within the first 6 weeks of starting treatment with ABC (median time to onset is 11 days), but may occur at any time while on therapy, and most often include fever, rash, GI symptoms (nausea, vomiting, diarrhea, or abdominal pain), respiratory symptoms (dyspnea, sore throat, cough), and lethargy or malaise. Other signs and symptoms may include musculoskeletal symptoms (myalgia, rarely myolysis, arthralgia), headache, paresthesia, and edema. Respiratory tract symptoms (dyspnea, sore throat, cough) have been observed in approximately 20% of patients who experience HSR. Some patients with HSRs were initially thought to have respiratory tract disease (pneumonia, bronchitis, pharyngitis) or a flu-like illness. The multisystem nature of the HSR has led to misdiagnosis of the HSR as an intercurrent medical illness or as being related to another medication. HSR also has been unrecognized when it presents with less common symptoms or as a single symptom.

This misattribution of the symptoms of HSR to another medical condition or delay in diagnosis of hypersensitivity has resulted in ABC
being continued or reintroduced, leading to more severe or rapid (within hours) onset of HSR or death. Therefore, the diagnosis of HSR should be carefully considered for patients presenting with symptoms of these diseases, even if another medical diagnosis seems likely. Renal failure and anaphylaxis have also been reported in association with HSR. Reintroduction of ABC in patients after treatment interruption, with no preceding symptoms of HSR, has, rarely, resulted in HSR.

Physical findings may include lymphadenopathy and, occasionally, mucous membrane lesions (conjunctivitis and/or mouth ulceration) and hypotension. The rash is variable and may be absent, but often appears maculopapular or urticarial. Laboratory abnormalities that may accompany ABC hypersensitivity include elevated LFTs, creatine kinase, or creatinine or lymphopenia.

Symptoms related to HSR worsen with continued therapy and usually resolve upon discontinuation of ABC. Restarting ABC following an HSR results in a prompt return of symptoms within hours. This recurrence of the HSR may be more severe than on initial presentation and may include life-threatening hypotension and death. Patients who develop an HSR must discontinue ABC and must not be re-challenged with ABC.

Symptoms usually start to resolve soon (within 24 hours) after stopping therapy. Symptomatic support, such as intravenous fluids for those who develop hypotension, is advised. There are no clinical data demonstrating the benefit of antihistamines or corticosteroids in the management of hypersensitivity. Nevertheless, symptomatic and/or supportive treatment may be reasonable.

Patients who have had an HSR must be advised that they should never take ABC (or Ziagen®) again, as a life-threatening second HSR can occur.

In a crossover design study evaluating single doses of ABC, 3TC, and ZDV alone or in combination, data analysis demonstrated no clinically relevant changes in the pharmacokinetics of ABC with the addition of 3TC or ZDV or the combination of 3TC/ZDV (Wang et al., 1999). Although ABC is registered as a twice-daily drug, there is growing evidence that it can be used on a once-daily basis (Gazzard et al., 2003). Based on this evidence, this trial will use a once-daily ABC dosing schedule, when substituted as a second-line option.
Please see the most recent package insert for additional information regarding Ziagen® (ABC).

1.1.7.7 Saquinavir/ritonavir (SQV + RTV, Invirase®) and Lopinavir/ritonavir (Kaletra®, ABT-378-r, LPV/r)

SQV, LPV, and RTV are inhibitors of HIV protease. SQV hard gel capsule formulation (Invirase®) is not recommended except in combination with RTV. The dosages used in the study will be SQV-HGC 400 mg twice daily and RTV 400 mg twice daily. All doses should be taken with food or within 2 hours of a meal.

A study comparing SQV soft-gel capsules (Fortovase®) boosted with RTV and Invirase® boosted with RTV demonstrated that higher SQV levels are achieved with Invirase®/RTV, and Invirase®/RTV is better tolerated than Fortovase®/RTV (Kurowski et al., 2003). The use of rifampicin with SQV is contraindicated, unless using RTV-boosted SQV. A dose of SQV + RTV 400/400 mg twice daily is recommended in this study when rifampicin is coadministered (Blumberg et al., 2003; CDC Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents, 2004).

LPV is used as a fixed-dose combination product with low-dose RTV. The recommended dose for adults and children over 12 years of age is 400/100 mg (LPV/r, respectively) twice daily taken with food. A dose increase to 533/133 mg twice daily is recommended when LPV/r is taken concomitantly with EFV, NVP, amprenavir (APV), or NFV. LPV alone has poor oral bioavailability related to rapid metabolic clearance. When given with low-dose RTV, cytochrome P450-3A-dependent metabolism of LPV is strongly inhibited, resulting in high and sustained LPV plasma levels. The AUC of LPV has been increased by up to 300-fold with concurrent low-dose RTV. RTV is given solely for this purpose and not for antiviral effects. LPV is 99% protein-bound; peak LPV plasma levels have occurred in about 5 hours when combined with RTV. The majority of LPV is metabolized by the cytochrome P450 3A isoenzyme.

All PIs have been associated with hyperglycemia in patients with or without diabetes. The most commonly reported adverse effects in patients receiving SQV are abdominal discomfort, diarrhea, and nausea. Predominant adverse effects of LPV/low-dose RTV are headache, fatigue, diarrhea, and nausea. Increased blood lipids and infrequent cases of pancreatitis have been reported. As with other PIs, lipodystrophy syndrome (i.e., increased blood glucose, redistribution of body fat) is possible.
For more information on SQV, LPV, and RTV, see the Invirase® and Kaletra® package inserts.

1.1.8 Rationale for Focusing on TB Participants Co-Infected with HIV as a Target Population for ART

1.1.8.1 Efficient Strategy for Identifying Participants Eligible for ART

The majority of individuals infected with HIV in resource-constrained settings are unaware of their HIV status. Further, facilities for measurement of laboratory markers such as CD4+ cell count or HIV-1 RNA levels are costly and not widely available. TB is a familiar, commonly diagnosed, and treated clinical disease in sub-Saharan Africa. The high rates of HIV among those with active TB provide one efficient approach for identifying individuals with HIV who are likely to benefit from ART.

1.1.8.2 HIV-Related TB has a High Case Fatality Rate

Despite the availability of appropriate TB chemotherapy, HIV-related TB is associated with higher case fatality rates, and ART may have a substantial beneficial impact on HIV-related TB. Thus, a significant impact may be achieved due to the potential effectiveness of the ART in the large populations co-infected with HIV and TB.

1.1.8.3 Patients with TB Receive Treatment through an Established Infrastructure

In many developing countries, an established, acceptable, and familiar infrastructure is available to provide treatment for patients with TB. TB patients receive ongoing clinical care, have secure access to medications, and most receive treatment through DOT programs. Staff at health facilities is trained to identify TB, manage the patients, and provide the appropriate linkages and support to ensure completion of and adherence to treatment. National guidelines exist to guide and monitor TB treatment and its outcomes.
1.1.8.4 Adherence is a Fundamental Component of TB Treatment through DOT

The importance of adherence to TB medications is fundamental to treatment success. Poor adherence affects both the individual and public health resulting in increased morbidity and mortality and the emergence of MDR TB. The infrastructure for TB treatment incorporates DOT as a means of enhancing adherence. The DOT strategy has been effective in TB treatment and prophylaxis (Weis et al., 1994; Chaulk et al., 1995). Indeed, this strategy has been adopted by WHO as the standard of care for management of active TB globally (WHO, 1997). Available data demonstrate that TB treatment success in countries that have adopted DOT is 77-79% compared with 54-57% in non-DOT countries. Similarly, adherence to ART regimens is essential for therapeutic success and strategies to assure adherence to therapy are required.

1.1.8.5 Synergy between TB DOT and HIV ART Adherence

A wide array of interventions to improve adherence to ART agents are presently under study but few have produced convincing results. In a randomized, controlled trial of an adherence intervention in HIV therapeutics, ART-naïve participants in the experimental group received a counseling intervention. This included information about therapy, an adapted medication schedule, and adherence problem solving training. Both self-reported adherence and virologic measures were significantly improved in the intervention compared to the control group (Tuldra et al., 2000). Among 116 patients, at week 48, 94% of those receiving intervention and 69% of the control group achieved adherence levels of > 95% (p=0.008). In addition, 89% of the intervention group and 66% of the control group had HIV-1 RNA levels < 400 copies/mL at 48 weeks (p=0.008). Another study has successfully employed a pharmacist-based intervention and has demonstrated significant improvement in both adherence and biologic outcome as measured by HIV-1 RNA levels and CD4+ cell count (Knobel et al., 1998). A small study carried out among methadone recipients illustrates an important principle of adherence intervention and the necessity for maintenance of the intervention over time (Wall et al., 1998). In this study, patients were randomly assigned to an 8-week supervised therapy program versus conventional care. Adherence improved significantly during the intervention, but returned to pre-study levels soon after cessation. Other adherence interventions under investigation that have shown some promise include: electronic reminder devices (Mannheimer et al., 1998; Andrade, 2001), cue-dose training with and without monetary reinforcement (Rigsby, 2000),
trained medication adherence nurses (Mannheimer et al., 2001; Goujard et al., 2001), and peer counselors (S. Mannheimer, personal communication, 2002).

In the past, HAART regimens were too complex and drug half-lives too short to realistically employ this strategy for HIV disease. There has been substantial progress in this area in the past 2 years. A pilot project, among a physician-referred poorly adherent patient population, has reported favorable preliminary data (Urbina, 2001). Outreach workers were employed to reach patients and administer ART at home or at community sites. Preliminary results have shown declines in HIV-1 RNA levels and increases in CD4+ cell counts in a small number of patients. Studies in institutional settings have shown the most impressive results. In one prison-based study, treatment-naïve patients enrolled in four clinical trials who received DOT were compared to a community-based sample enrolled in the same trials. The proportion of patients with declines in HIV-1 RNA levels was significantly higher in the incarcerated DOT group, an indication of both the importance of adherence and the value of this intervention to improve adherence and therapeutic outcome (Fischl et al., 2001).

It is important to emphasize the limitations of most current intervention studies. Many are uncontrolled, of short-term duration, and the generalization of the results is not clear. The dose of intervention needed to produce the desired behavioral and, most importantly, biologic and clinical outcome is not clear. Nevertheless, they represent the beginning of what is likely to be a rich literature of intervention studies, which may point to ways of improving adherence and therapeutic outcome.

DOT for TB and HIV disease has important differences and similarities. Therapy for TB is simpler, less frequent, and time limited, whereas ART regimens can be more complicated and are likely to be lifelong. Current DOT strategies for TB are based on providing medication 3-5 times a week. The use of DOT infrastructure for ART will require it to be extended to accommodate a 7-day treatment regimen. Both address the central issue of adherence to therapy and require monitoring for side effects and toxicities as well as efficacy. The appeal of combining once daily ART regimens with the mechanism of DOT may represent a major step forward in assuring sufficiently high levels of adherence to ensure individual therapeutic success and population-based reduction in morbidity associated with HIV and TB.
Thus, there is a logical synergy in linking both treatments to a supportive medication adherence system. The benefits and disadvantages of such a strategy need to be compared in a formal and rigorous study. The simplification of ART regimens, coupled with existing TB DOT programs, and the growing need and demand to begin administration of ART drugs in the public sector in sub-Saharan Africa offer an opportunity to test the hypothesis that ART drugs can be successfully administered through the existing TB DOT programs as one strategy to increasing access and adherence to ART.

1.1.9 Challenges Associated with Use of ART During Anti-TB Therapy

1.1.9.1 Drug Interactions

Among the existing classes of ARTs, PI and NNRTIs have pharmacologic interactions with the rifamycins (rifampicin, rifabutin, and rifapentin) used to treat mycobacterial infections (Piscitelli et al., 2001). These interactions result from induction and inhibition of the GI and hepatic cytochrome CYP450 enzyme system.

Rifamycins induce CYP450 and may decrease blood levels of those ART drugs that are metabolized by this system, resulting in potential therapeutic failure and promoting the development of drug resistance. Rifampicin is the most potent CYP450 inducer; rifabutin has substantially less activity; and rifapentin (a newer rifamycin) has intermediate activity as an inducer. The currently approved PIs are all, to differing degrees, inhibitors of CYP450. The rank order of the ART agents in terms of potency in inhibiting CYP450 is RTV (the most potent), APV, IDV, and NFV (with similar intermediate potency), and SQV (the least potent). The three approved NNRTIs have diverse effects on CYP450: NVP is an inducer, delavirdine (DLV) is an inhibitor, and EFV is both an inducer and an inhibitor. The NRTIs (ZDV, ddl, d4T, 3TC, zalcitabine, and ABC) and nucleotide reverse transcriptase inhibitor TDF are not metabolized by CYP450.

The current Centers for Disease Control and Prevention (CDC) guidelines indicate that rifampicin can be used for the treatment of active TB in patients whose ART regimen includes the NNRTI, EFV, and two NRTIs and recommend dose adjustment to 800 mg once daily for EFV when used together with rifampicin due to 22% decrease in EFV AUC level (CDC, 2004). Additional information indicates that for individuals weighing > 50 kg, a dose increase to 800 mg/day is advisable (Lopez-Cortes et al., 2002).
1.1.9.2 Paradoxical Reaction (PR) or Immune Reconstitution Syndrome (IRIS)

The initiation of ART during TB treatment has been linked to the development of a paradoxical reaction (PR) most likely as a result of immune reconstitution syndrome (IRIS). A transient worsening of TB symptomatology and lesions following ART may occur, but its frequency appears to be low (Fishman et al., 2000; Chien and Johnson, 1998). Navas (2002) showed that PRs started at a median time from the start of ART of 22.5 days. All patients with PRs had initiated ART within the first 2 months of anti-TB treatment. These reactions were more likely to occur in patients with larger reduction in HIV-1 RNA levels and higher increases in CD4+ cell count. A 1998 report by Narita showed that PRs occur in 36% of patients dually treated. Price (2001) also estimated a paradoxical reaction rate of 30-40% in patients who start treatment with a low (i.e., < 100) CD4+ cell count.

1.1.9.3 Side Effects and Toxicities

The treatment of TB requires intake of 2-4 medications on a daily basis while the treatment of HIV requires intake of 3 medications on a daily basis. Each of these regimens may be associated with adverse events. These include GI intolerance, hepatitis, pancreatitis, HSRs, peripheral neuropathy, rash, and neuro-psychiatric difficulties. The combination of both regimens may result in additive toxicity and side effects. Some studies suggest that HIV-infected patients have a higher rate of adverse events while other studies do not support these findings (Girardi et al., 2001). Notwithstanding, the concern about additive side effects and toxicities warrants collection of detailed toxicity and tolerability data in future studies of combined therapy.

1.1.9.4 Stigma and Non-Disclosure of HIV Status

Disclosure of HIV status continues to be an obstacle to care and prevention. In a pilot study conducted in a rural district of KwaZulu-Natal, South Africa, approximately two-thirds of the patients interviewed reported that they had disclosed their HIV status to one other person. The main reason influencing people to disclose their status to friends and family centered on whether they would receive support from them. However, of those who did disclose their HIV status, only 2 out of 20 disclosed to their primary sexual partner.

The main reason offered by patients for non-disclosure of their HIV status was that they felt people around them would not respond positively or that they did not want to worry family members. This was particularly seen in patients that had families who had recently
experienced an AIDS-related death. Non-disclosure of HIV status seems to be tightly linked with issues of stigma. One patient did not disclose his HIV status because he said that “people point at you. I don’t want to be a bad example. Until there is a cure, people will continue to stigmatize.”

1.1.10 Optimal Time to Initiate ART in TB Patients

When patients with HIV develop TB, the questions of whether and when to initiate ART treatment have not been answered. The immune recovery associated with use of ART is likely to enhance recovery from TB. On the other hand, vigorous immune reconstitution can also be associated with transient increase in symptoms. The co-administration of ART during TB treatment may alter the pharmacokinetics of both anti-TB and ART medications and increase side effects and toxicities. In contrast, deferral of ART until after TB treatment is completed may result in progression of HIV disease, and in some patients, failure to survive until completion of anti-TB therapy. The advantages of the two possible strategies relating to the timing of initiation of ART, namely, initiation of ART during TB treatment versus deferral of ART until completion of TB treatment, are summarized in Table 4.

Table 4: Advantages of Integrated versus Sequential Initiation of HIV ART in the Context of TB Treatment

<table>
<thead>
<tr>
<th>Integrated HIV ART during TB Treatment</th>
<th>Sequential HIV ART after Completion of TB Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>• May impact positively on TB treatment outcomes (failure, relapse rates)</td>
<td>• Decreases the pill burden at any given point</td>
</tr>
<tr>
<td>• May impact positively on survival</td>
<td>• Avoids the increased risk of paradoxical reactions/immune reconstitution syndromes</td>
</tr>
<tr>
<td>• Utilizes the TB DOT program as an opportunity to monitor treatment and promote adherence</td>
<td>• Avoids side effects and toxicities resulting from multiple drug combinations</td>
</tr>
<tr>
<td>• Utilizes the existing TB DOT infrastructure</td>
<td>• Avoids pharmacologic interactions between TB and HIV ART drugs</td>
</tr>
<tr>
<td></td>
<td>• Avoids overburdening the TB DOT infrastructure</td>
</tr>
</tbody>
</table>
1.1.11 Pilot Data

To assess the feasibility of implementing the trial at the Prince Cyril Zulu CDC, a pilot study was initiated at this facility in 2001. One of the reasons for undertaking this pilot study arises from the fact that the use of ART drugs during treatment for TB has conventionally been sequential because of concern for drug interactions. These drug interactions may affect the blood levels of agents administered, and there is fear of increased side effects and toxicities. While the US CDC guidelines support co-administration of TB and ART medication, the pilot study was devised to assess these concerns, which remain the most important barrier to concomitant drug administration.

As part of this pilot study, a total of 20 patients with HIV disease and active pulmonary TB were enrolled and monitored for drug interactions and toxicities. These patients received their usually prescribed anti-TB medication (isoniazid, rifampicin, pyrazinamide, ethambutol) as once-daily DOT. In addition, they received once-daily doses of ART [3TC, ddI, and EFV] introduced and administered through direct observation 5 days/week concomitantly with TB medications at the Prince Cyril Zulu CDC. Their weekend doses of HIV medication were dispensed on Friday and self-administered. Upon completion of their TB therapy, patients were referred to KEH for continuing HIV care. Patients continued their ART through self-administration of the drugs and monthly follow-up at KEH. Monthly supplies of their antiretrovirals were provided during their monitoring visits to KEH.

This pilot study demonstrated that the TB DOT program can serve as sites for HIV identification as well as an introduction to and monitoring of ART in a resource-limited setting. Preliminary data indicate that HIV testing and ART administration during TB treatment in the DOT program is acceptable. These data indicate that the once-daily regimen of ddI + 3TC + EFV with the TB standard regimen was effective and safe, and excellent therapeutic success was achieved with > 80% non-detectable HIV-1 RNA levels at 6 months. Minimal side effects and toxicities and high levels of weekend adherence are possible (Jack et al., 2003).

1.1.12 Economic Analysis

The economic analysis comprises a number of components, each of which will provide insight and policy-relevant data for the planning of ART expansion. The components of the analysis involve an examination of cost of resources involved in identifying potential trial participants and providing treatment to them in each of the arms. The costs measured will include the costs of treatment provision, the second round costs incurred by the health system, and the costs to the participants themselves. The effectiveness of each arm as measured by time to primary endpoint will also be incorporated into the analysis for cost effectiveness.
These components will provide important information in a number of ways. Recruiting suitable participants for ART will be a key issue in regard to the expansion of treatment programs. Understanding the cost implications of the START approach to recruitment will assist in identifying the lowest cost strategies. Examining the costs of providing treatment to each arm will, if one of these methods is adopted more widely, provide critical input into the planning process in terms of budget estimates.

The remaining components, such as examining cost of hospitalization associated with treatment, costs to participants, and the effectiveness of the arms can be used to evaluate the relative efficiency of the provision and outcome of treatment for each arm. While efficiency is only one consideration in policy selection in resource-poor settings such as South Africa, it is an important concern. By doing so, this research will provide important input into the policy debate, assisting in the understanding of the relative efficiencies of integrated and sequential TB and HIV care.

1.2 Rationale

In South Africa, it is estimated that there are approximately 5 million HIV positive people. Despite the availability of voluntary counseling and testing centers in South Africa, it is estimated that less than 10% of these people are aware of their HIV positive status, and only 1% are aware of their CD4+ cell count status. This presents a challenge to the provision of ART. Since South Africa, like most developing countries, does not have the resources to test large numbers of people for HIV infection, and thereafter perform a CD4+ T-cell count on those who are HIV positive, an alternative approach needs to be found to affordably identify HIV-positive people eligible for ART.

In southern Africa, TB is the most common first AIDS-defining condition. In this setting, between 50% and 80% of TB patients are HIV positive, the majority with low CD4+ cell counts. HIV-1 testing and CD4+ cell count assays are cost-efficient in this group since most TB patients are HIV-1 positive and most HIV-1 positive TB patients will have CD4+ counts at or below the threshold for treatment initiation. Hence HIV-1 positive TB patients are the most readily identifiable and accessible group that fulfill the criteria for ART. Initiating ART in HIV-1 positive TB patients will lead to the inclusion of the majority of HIV/AIDS patients fulfilling the criteria for therapy.

The key question then becomes whether HIV care provision should be integrated with TB care. Protagonists argue that the TB DOT infrastructure could play an important role in enhancing ART drug adherence and that treating both conditions simultaneously will reduce the high mortality rates observed in TB and HIV co-infected patients. Antagonists argue that integrating care for HIV and TB will compromise the TB control program by overburdening the already stressed system, creating harmful drug interactions, increasing drug side effects and toxicities, and necessitating unacceptable pill burdens as a result of the required administration of 6-7 drugs.
The overall aim of this project is to assess whether the integration of HIV/AIDS care into existing TB care services is feasible as a practical approach to the implementation of ART in resource-poor settings. The introduction of ART in resource poor settings will need policies that provide a pragmatic, efficient, and effective approach to the introduction of ART, maximizing the available health care infrastructure in the context of underdeveloped health care services. Such policies will need to be based on feasibility while being cognizant of the following key questions:

- Does integrated TB and HIV care reduce mortality and the rate of progression to subsequent AIDS-related conditions?
- When participants are treated with the combination of drugs used to treat both conditions, is it safe, well tolerated, and without negative pharmacologic interaction?
- Does this approach lead to improved level of biological makers and improved HIV clinical outcomes?
- Does it maintain, at least, current levels of TB drug adherence and lead to higher levels of ART drug adherence?
- Does it reduce resistance rates to either anti-TB or ART drugs?
- Does it lead to increased incidence of immune reconstitution events and affect responses of biological markers potentially related to PR or IRIS?
- Does it alter the patient’s HIV risk-reducing behaviors and the patient’s quality of life?
- Does the integration of HIV care into the TB program enhance or undermine TB outcomes and the Tuberculosis Control Programme?
- Is this approach cost-effective?

This study attempts to answer these questions through the operational research approach of a health systems intervention trial comparing two strategies of HIV care provision.
2.0 STUDY OBJECTIVES

2.1 Primary Objective

2.1.1 To assess the effectiveness of integrated TB and HIV care provision, including ART administered through a TB DOT program enhanced with an adherence support program (ASP), versus sequential treatment of TB and HIV, by comparing progression to AIDS-defining illnesses (Appendix II)/mortality in participants with pulmonary TB and HIV co-infection during the first 18 months after enrollment in the study. This emphasizes the comparison of the time-to-event (i.e., progression to AIDS or death) distributions.

2.2 Secondary Objectives

2.2.1 To assess the safety and tolerability as well as the drug interactions associated with combining anti-TB drugs with ART.

2.2.2 To assess the impact of integrated TB and HIV care on adherence to anti-TB and ART.

2.2.3 To assess the impact of integrated TB and HIV care on CD4+ cell counts and viral load.

2.2.4 To determine and compare the incidence of IRIS/PR among TB/HIV co-infected participants who receive integrated versus sequential ART treatment and to examine the nature of the relationship between the incident PRs and potential immune markers of the immune reconstitution syndrome.

2.2.5 To assess the impact of integrated TB and HIV care on TB and ART drug resistance.

2.2.6 To assess the impact of integrated TB and HIV care on HIV risk-related behaviors and quality of life in co-infected participants.

2.2.7 To assess the impact of integrating TB and HIV care on the TB outcomes (cure, successful completion, other non-specified TB outcomes, failure, and recurrence).

2.2.8 To assess the cost-effectiveness of integrated and sequential TB and HIV care.

2.2.9 To assess the effectiveness of integrated TB and HIV care provision versus sequential treatment of TB and HIV by comparing progression to AIDS-defining illnesses/mortality during the entire study follow-up (approximately 2 years).
3.0 STUDY DESIGN

3.1 Study Arms

This study is a two-armed, randomized, open-label clinical trial. Five hundred and ninety-two participants who have pulmonary TB and HIV co-infection and who successfully complete all screening procedures, meet eligibility criteria, and sign the informed consent form will be enrolled into the study. Study participants will be randomized to one of the following arms stratified by CD4+ cell count, 50-200 cells/µL vs. > 200 cells/µL:

3.1.1 The Integrated Arm (n=296)

During the TB treatment period, participants on the integrated arm will receive their ART and TB medication concomitantly 5 days per week and ART by self-administration on weekends. For the duration of the TB treatment both regimens will be provided through a DOT strategy that will be enhanced by ASP, which is described in Section 3.2. Once TB treatment has been completed, these participants will continue with ART taken through self-administration.

3.1.2 The Sequential Arm (n=296)

Participants will receive their TB medication through DOT until TB treatment completion and then start self-administered ART thereafter.

3.2 Description of Trial Interventions

The first-line ART drug combination that will be used in this study is EFV (in the integrated arm, 600 mg once daily for participants weighing < 50 kg and increased to 800 mg once daily for participants weighing ≥ 50 kg ONLY while receiving rifampicin), ddi/ddI-EC (400 mg once daily for participants weighing ≥ 60 kg and 250 mg once daily for participants weighing < 60 kg), and 3TC (300 mg once daily). Study agents are further described in Section 5.0. Doses of ddi/ddI-EC and 3TC will also be adjusted based on creatinine clearance levels in those participants with impaired renal function. Alternative ART options are described in Table 6 of Section 5.1.1.

In this clinical trial, the ART drugs will be considered the study regimen, and the anti-TB regimen will be considered background therapy.

The anti-TB regimen is the regimen prescribed under the South African TB Clinical and Diagnostic Treatment Guidelines (Appendix VIII). The anti-TB regimen consists of rifampicin, isoniazid, pyrazinamide, and ethambutol for the first 2 months of therapy and rifampicin and isoniazid for the remaining duration of TB therapy (usually 4 months).

The ASP is part of the intervention that will be provided to participants assigned to the integrated arm and consists of four 15-20 minute one-on-one educational sessions. The intervention will be delivered during the course of the participants’ TB DOT program.
These sessions will be conducted by trained health educators using the following methods and tools: Information-Motivation-Behavioral Skills Model; select constructs from the Extended Parallel Process Model; and key techniques from Motivational Interviewing. Each educational session will introduce two key messages that will be important for participants to remember and begin incorporating into their daily activities. Participants will be told what they need to know about ART and what they will gain from treatment. Words will be carefully chosen and sensitive to cultural differences. Key messages will be repeated on a routine basis at the beginning of each session when participants are observed taking their medications. All sessions build on one another and have been designed to encourage self-management skills related to taking ART consistently and correctly.

The ASP is further described in Appendix IV.

3.3 **Expected Duration of Participation**

A total of 592 participants will be enrolled in the study over the course of an approximate 24-month accrual period. Each participant will remain on study for a total of 24 months (beginning on the day of randomization). This includes the duration of TB treatment and at least a 12-month post TB treatment follow-up period.

4.0 **SELECTION AND ENROLLMENT OF PARTICIPANTS**

4.1 **Description of Population**

A concerted effort has been made to choose a study population that is reflective of the larger population of South and sub-Saharan Africa. By recruiting participants who attend the Prince Cyril Zulu CDC for services, a study population comprising a cross-section of different races, ages, and genders in South Africa can be recruited. Participants from throughout the greater Durban area who may have TB are routinely evaluated at this health center. They may be referred from several sources, i.e., self-referral, from a physician, from a local treatment clinic, from a hospital setting, or from a local “traditional” healer. The Prince Cyril Zulu CDC does not treat complex cases of TB, including TB meningitis and miliary TB. Complex cases are referred to KEH for management and are not eligible for this study.
4.2 **Inclusion Criteria**

4.2.1 Males or females age ≥ 18 years.

4.2.2 At least one positive acid-fast sputum smear for TB by microscopy with clinical symptoms of TB or two positive smears by microscopy. This is the diagnostic criteria for TB as defined by the Prince Cyril Zulu CDC and the South African TB Clinical and Diagnostic Treatment Guidelines (Appendix VIII).

4.2.3 Receiving standard regimen anti-TB therapy (isoniazid, rifampicin, ethambutol, pyrazinamide) (Appendix VIII).

4.2.4 Participating in the Prince Cyril Zulu CDC DOT program and receiving supervised treatment daily at the Prince Cyril Zulu CDC.

4.2.5 HIV infection, as documented by two positive rapid HIV tests (e.g., OraQuick or Smart Check or other tests approved by the US FDA or the South African Department of Health) and confirmed by HIV-1 RNA polymerase chain reaction (PCR).

4.2.6 Ability and willingness of participant or legally authorized representative to provide written informed consent to take part in the study.

4.2.7 Karnofsky score ≥ 70 within 14 days prior to entry (Appendix III).

4.2.8 The following laboratory parameters from samples obtained within 14 days prior to study randomization:

4.2.8.1 AST ≤ 2.5 x the upper limit of normal (ULN).

4.2.8.2 ALT ≤ 2.5 x ULN.

4.2.8.3 Creatinine ≤ 1.5 x ULN.

4.2.8.4 Total bilirubin ≤ 2.5 x ULN.

4.2.8.5 Absolute neutrophil count (ANC) ≥ 1000.

4.2.8.6 Hemoglobin ≥ 7.0 g/dL.

4.2.9 Not intending to relocate out of the current geographical area for the duration of study participation.

4.2.10 Willingness of participant to adhere to study follow-up schedule.

4.2.11 Women must agree to undergo serum or urine β-HCG pregnancy testing at Day 0 and during regularly scheduled monthly visits during ART therapy.
4.2.12 Negative serum or urine $\beta$-HCG pregnancy test obtained within 14 days prior to study entry for women with reproductive potential (defined below). The urine test must have a sensitivity of $\leq 50$ mIU/mL.

“Female participants without reproductive potential” are defined as women who have reached menopause or undergone hysterectomy, bilateral oophorectomy, or tubal ligation or female participants whose male partner has undergone successful vasectomy with documented azoospermia or has documented azoospermia for any other reason.

“Female participants of reproductive potential” are defined as girls who have reached menarche or women who have not been post-menopausal for at least 24 consecutive months (i.e., who have had menses within the preceding 24 months) or have not undergone sterilization (e.g., hysterectomy, bilateral oophorectomy, or salpingotomy).

4.2.13 All participants must agree not to participate in a conception process (e.g., active attempt to become pregnant or to impregnate, donate sperm, in vitro fertilization).

- Female participants who are participating in sexual activity that could lead to pregnancy and who are receiving EFV, must agree to use two reliable methods of contraception: a barrier method of contraception (male or female condoms or diaphragm with spermicide or cervical cap with spermicide) together with either an intrauterine device (IUD) or hormonal-based contraception while receiving the protocol-specified drugs and for 6 weeks after stopping the drugs. Another ART drug will be substituted for EFV if participants are not able, or willing, to use two forms of contraception simultaneously.

  Note: Female participants who are taking rifampicin, but not taking EFV, must agree to use a barrier method of contraception or an IUD while receiving rifampicin.

- Female participants who are participating in sexual activity that could lead to pregnancy, but who are not receiving EFV, must use at least one barrier method of contraception or an IUD while receiving the protocol-specified drugs.

- Female participants who are not of reproductive potential, as defined above, or whose male partner(s) have undergone successful vasectomy or have documented azoospermia for any other reason, are eligible without requiring the use of contraception. Participant-reported history is acceptable documentation of menopause, hysterectomy, bilateral oophorectomy, or tubal ligation.
4.3 Exclusion Criteria

4.3.1 ≥ 28 days of cumulative ART prior to study entry.

NOTE: Past Mother to Child Transmission (MTCT) and Post Exposure Prophylaxis (PEP) prevention treatments are allowed.
4.3.2 < 10 days or > 28 days since the initiation of TB treatment.

4.3.3 Temperature > 38.5°C, ≥ Grade 3 rash, ≥ Grade 3 nausea, or ≥ Grade 3 vomiting at time of screening or enrollment.

4.3.4 Hospitalized or referred for hospitalization for care and treatment of opportunistic infections, TB, or other causes at time of screening or enrollment.

4.3.5 CD4+ cell count < 50 cells/µL within 28 days of study entry.

4.3.6 Active TB meningitis or miliary TB.

4.3.7 History of prior TB treatment or any prior active TB episode.

4.3.8 History of current or prior AIDS-defining condition(s) as described in the modified WHO Stage IV clinical staging system (Appendix II).

4.3.9 Previous or current acute or chronic pancreatitis.

4.3.10 ≥ Grade 2 peripheral neuropathy.

4.3.11 Currently taking allopurinol, zalcitabine, astemizole, terfenadine, ergotamine or ergot derivatives, midazolam, triazolam, cisapride, phenytoin, phenobarbitone, carbamazepine, voriconazole, ribavirin, Echinacea-containing complementary medicines or supplements, St. John’s Wort-containing complementary medicines or supplements.

4.3.12 Pregnant at the time of study entry. Breastfeeding mothers are not excluded.

4.3.13 Suspected MDR-TB, defined as “participant’s awareness of contact with someone diagnosed with MDR-TB at home or in the workplace.”

4.3.14 Any other condition that, based on the opinion of the participant’s study clinician, would preclude provision of informed consent or result in the participant being unable to fully participate in required study procedures.

4.3.15 Participation in any other trial or study with objectives and intervention(s) that may interfere with the START study.

4.4 Study Enrollment Procedures

4.4.1 Protocol Registration

Prior to implementation of this protocol, sites must have the protocol and consent form approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). Sites must be registered with and approved by DAIDS through the Regulatory Compliance Center Protocol Registration Office (Telephone:
Protocol registration must occur before any participants may be enrolled in this study. Once a candidate for study entry has been identified, the study will be carefully discussed with the participant. The participant will be asked to read and sign the consent form approved by both the Nelson R Mandela School of Medicine, Faculty of Health Sciences Ethics Committee, and the DAIDS/Regulatory Compliance Center Protocol Registration Office.

### 4.4.2 Prisoner Participation

The Division of AIDS has concluded that this protocol does NOT meet U.S. Federal requirements governing prisoner participation in clinical trials and should NOT be considered by local Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) for the recruitment of prisoners.

### 4.5 Randomization/Registration

At randomization, study staff will access the assigned treatment group, integrated or sequential, from the randomization envelopes (see Section 12.5). Randomization envelopes will be stored in a safe, locked location with restricted access at the Prince Cyril Zulu CDC and opened in sequential order at eligible participants’ enrollment visits by study staff members authorized to perform randomization procedures by the Principal Investigator. After opening the envelopes, staff members will record the date and time of opening the envelopes, as well as their names, on the envelopes. This information will then be noted on the randomization sheets. Opened envelopes and their contents will be stored with other participant study records for purposes of study monitoring and quality control/quality assurance review. Assigned envelope numbers will also be recorded on the study screening and enrollment log.

#### 4.5.1 Sequential Arm

Upon completion of TB therapy (or a maximum of 12 months of TB therapy), participants in the sequential arm will be evaluated for eligibility for entry into Phase II at the Phase II screening visit prior to initiating ART. Participants who present with a temperature of > 38.5°C, ≥ Grade 3 nausea or vomiting, or ≥ Grade 3 rash, and safety laboratory evaluations (AST, ALT, total bilirubin (T. BILI), ANC, hemoglobin, and creatinine) outside of the limits used for eligibility (see Section 4.2.8) will not be eligible to initiate ART. The participants will remain on Phase I visit schedule with visits at KEH. Laboratory results must be from samples obtained within the previous 14 days. Initiation of ART will be delayed and participants will be re-evaluated bi-weekly until eligibility criteria are met. Participants meeting eligibility criteria for Phase II will be registered into Phase II and then initiate ART.
4.5.2 Integrated Arm

Upon completion of TB therapy, participants in the integrated arm will be registered into Phase II, but will not undergo an eligibility assessment or screening process for Phase II.

4.6 Co-Enrollment Guidelines

Participants enrolled in this study may not take part in any other TB or HIV therapeutic clinical trial or study with objectives and intervention(s) that may interfere with the START study. Consideration must be given to participant burden associated with this and other studies to avoid potential adherence and retention problems. Co-enrollment in another study must be approved by the START Principal Investigator or his designee and the chair of the other study.

5.0 STUDY TREATMENT

ART study drugs used in the START study will be provided for the duration of the study (24 months for the integrated arm and 12-18 months for the sequential arm, depending on when TB treatment is completed). Since all study participants will be attending KEH for follow-up until they complete the study, it is anticipated that their ongoing ART will be provided through the South African National Treatment Plan. KEH is part of the leading group of health services that is currently participating in the national ART plan and is therefore well placed to provide the START trial participants with ongoing AIDS care, including ART provision. Upon completion of the START study, the investigators cannot guarantee access to ART agents that are not listed as part of the national treatment plan – currently the proposed START first-line study agents are included in the national treatment plan.

5.1 Regimens, Administration, and Duration

At entry, participants will be randomized (1:1) to one of the following treatment arms:

**Integrated arm:** ddI/ddI-EC + 3TC + EFV once daily concurrently with standard TB treatment upon randomization.

**Sequential arm:** ddI/ddI-EC + 3TC + EFV once daily initiated after completion of TB therapy.

ART substitution options will be available for participants who become pregnant, experience toxicities, or have treatment failure. Figure 1 illustrates the relationship between TB therapy and ART for both the integrated and sequential arms.
START Treatment Regimen

Figure 1
Note: Duration of TB therapy will vary depending on the time of enrollment and the time needed to successfully complete therapy.

Approximate Time on Study

Integrated Arm:

<table>
<thead>
<tr>
<th></th>
<th>Months 0-2</th>
<th>Months 3-6</th>
<th>Months 7-24</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB Therapy</td>
<td>H/R/Z/E</td>
<td>H/R</td>
<td>No TB Therapy</td>
</tr>
<tr>
<td>ART</td>
<td>No ART</td>
<td>ART</td>
<td></td>
</tr>
</tbody>
</table>

Sequential Arm:

<table>
<thead>
<tr>
<th></th>
<th>Months 0-2</th>
<th>Months 3-6</th>
<th>Months 7-24</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB Therapy</td>
<td>H/R/Z/E</td>
<td>H/R</td>
<td>No TB Therapy</td>
</tr>
<tr>
<td>ART</td>
<td>No ART</td>
<td></td>
<td>ART</td>
</tr>
</tbody>
</table>

H = Isoniazid; R = Rifampicin; Z = Pyrazinamide; E = Ethambutol
5.1.1 ART Regimen

The study drugs used in START include EFV, ddl/ddI-EC, 3TC, NVP, TDF, ABC, SQV + RTV, and LPV/r. The ART regimen EFV + ddl/ddI-EC + 3TC will be considered the first-line study agents. NVP, TDF, ABC, SQV + RTV, and LPV/r may be used as substitutions in cases of toxicity, intolerance, pregnancy, or concomitant conditions precluding treatment with the first-line study agents. In the event of ART failure, the first-line regimen will need to be discontinued. Study clinicians may select a second-line regimen from the available study drugs or options available according to drug availability.

Study drug dosages of EFV and ddl/ddI-EC will be adjusted according to weight. Participants weighing 50 kg or greater will receive EFV 800 mg once daily while on rifampicin, and participants weighing less than 50 kg will receive EFV 600 mg once daily both while on and off rifampicin. Participants weighing 60 kg or greater will receive ddl/ddI-EC 400 mg once daily and participants weighing less than 60 kg will receive ddl/ddI-EC 250 mg once daily. Additional dosing considerations for ddl/ddI-EC, 3TC, and TDF will be made for participants with impaired renal function based on creatinine clearance levels, as described in Table 7. See Table 5 for an illustration of the first-line study drug regimen.

Table 5: First-Line ART Regimen (with weight adjustments)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Frequency</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>EFV</td>
<td>600 mg</td>
<td>Once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR 800 mg</td>
<td>Without food.</td>
</tr>
<tr>
<td>Didanosine</td>
<td>ddl, ddl-EC</td>
<td>400 mg</td>
<td>Once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR 250 mg</td>
<td>Without food. If given with TDF, reduce 400</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>mg ddl/ddI-EC dose to 250 mg once daily.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Data are not available to recommend a dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>adjustment for ddl/ddI-EC in individuals</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>weighing &lt; 60 kg.</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>3TC</td>
<td>300 mg</td>
<td>Once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>With or without food.</td>
</tr>
</tbody>
</table>

<sup>1</sup>Dosage adjustment requirements—see Table 7

Participants who experience toxicity, intolerance, ART failure, pregnancy, or require other concomitant medications that preclude treatment with the first-line regimen will receive an alternative ART regimen.
<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Frequency</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine</td>
<td>200 mg once daily x 14 days then 200 mg twice daily</td>
<td>Once daily x 14 days, then twice daily</td>
<td>With or without food. The site health care provider should review the signs and symptoms of NVP-related hypersensitivity and hepatitis with the participant prior to dispensing NVP. Participants should contact their study clinician if they develop rash or signs and symptoms of hypersensitivity or hepatitis. If rash occurs during the lead-in period, do not escalate the dose until the rash has resolved. After reaching full dose, if NVP dosing is interrupted for &gt; 7 days, NVP should be started with the lead-in of 200 mg orally once daily for 14 days, then 200 mg orally twice daily. LFT monitoring is required after initiation of NVP weekly for the first 6 weeks, at week 8, and then monthly for the first 20 weeks of NVP treatment.</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>300 mg</td>
<td>Once daily¹</td>
<td>With or without food. Use TDF with caution in participants with renal insufficiency. Do not use if renal function is progressively deteriorating. If stable and creatinine clearance is &lt; 50 mL/min, may start TDF at discretion of START Project Director and/or START Principal Investigator (START PI), but must adjust dose (Table 7) and monitor renal function carefully. Serum phosphate must be monitored according to Schedule of Events.</td>
</tr>
<tr>
<td>Abacavir</td>
<td>600 mg</td>
<td>Once daily²</td>
<td>With or without food. Monitor closely for hypersensitivity reaction.</td>
</tr>
<tr>
<td>Saquinavir (hgc)/ritonavir</td>
<td>400 mg/400 mg</td>
<td>Twice daily</td>
<td>Within 2 hours after a meal.</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>400 mg/100 mg</td>
<td>Twice daily</td>
<td>With food. ddI/ddI-EC should be given 1 hour before or 2 hours after taking LPV/r.</td>
</tr>
</tbody>
</table>

¹Dosage adjustment requirements-see Table 7.
²Once-daily dosage will be used for ABC based on results from the Zodiac Study (Gazzard B et al., 2003).
Table 7: Dose Reduction Table

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DAILY DOSE</th>
<th>REDUCED DAILY DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV</td>
<td>800 mg once daily for participants ≥ 50 kg while taking rifampicin.</td>
<td>600 mg once daily after discontinuation of rifampicin</td>
</tr>
<tr>
<td></td>
<td>600 mg once daily for participants &lt; 50 kg both taking and not taking rifampicin</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>600 mg once daily for participants ≥ 50 kg not taking rifampicin</td>
<td>None</td>
</tr>
<tr>
<td>ddI</td>
<td>400 mg once daily for participants ≥ 60 kg</td>
<td>Creatinine clearance 30-59 mL/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200 mg once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Creatinine clearance 10-29 mL/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>150 mg once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Creatinine clearance &lt;10 mL/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 mg once daily</td>
</tr>
<tr>
<td>ddI</td>
<td>250 mg once daily for participants &lt; 60 kg</td>
<td>Creatinine clearance 30-59 mL/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>150 mg once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Creatinine clearance 10-29 mL/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 mg once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Creatinine clearance &lt; 10 mL/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75 mg once daily</td>
</tr>
<tr>
<td>ddI-EC</td>
<td>400 mg once daily for participants ≥ 60 kg</td>
<td>Creatinine clearance 30-59 mL/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200 mg once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Creatinine clearance 10-29 mL/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>125 mg once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Creatinine clearance &lt; 10 mL/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>125 mg once daily</td>
</tr>
<tr>
<td>DRUG</td>
<td>DAILY DOSE</td>
<td>REDUCED DAILY DOSE</td>
</tr>
<tr>
<td>---------</td>
<td>------------------------------------------------</td>
<td>--------------------------------------------------------</td>
</tr>
<tr>
<td>ddI-EC</td>
<td>250 mg once daily for participants &lt; 60 kg</td>
<td>Creatinine clearance 30-59 mL/min 125 mg once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Creatinine clearance 10-29 mL/min 125 mg once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Creatinine clearance &lt; 10 mL/min ddI (not ddI-EC) 75 mg tablet once daily</td>
</tr>
<tr>
<td>3TC</td>
<td>300 mg once daily</td>
<td>Creatinine clearance 30-49 mL/min 150 mg once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Creatinine clearance 15-29 mL/min 150 mg once daily first dose, then 100 mg once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Creatinine clearance 5-14 mL/min 150 mg first dose, then 50 mg once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Creatinine clearance &lt; 5 mL/min 50 mg first dose, then 25 mg once daily</td>
</tr>
<tr>
<td>NVP</td>
<td>200 mg once daily x 14 days then 200 mg twice daily</td>
<td>None</td>
</tr>
<tr>
<td>TDF</td>
<td>300 mg once daily</td>
<td>Creatinine clearance 30-49 mL/min 300 mg every 48 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Creatinine clearance 10-29 mL/min 300 mg twice a week</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Creatinine clearance &lt; 10 mL/min None</td>
</tr>
<tr>
<td>ABC</td>
<td>600 mg once daily</td>
<td>None</td>
</tr>
<tr>
<td>SQV + RTV</td>
<td>400/400 mg twice daily</td>
<td>None</td>
</tr>
<tr>
<td>LPV/r</td>
<td>400/100 mg twice daily</td>
<td>None</td>
</tr>
</tbody>
</table>
5.1.2 Anti-TB Regimen

The anti-TB regimen will be considered background therapy, and therefore not considered the study regimen in this study.

All participants, regardless of treatment regimen, will receive their TB therapy in accordance with the TB Clinical and Diagnostic Treatment Guidelines (Appendix VIII). For the first 2 months of TB therapy, the regimen consists of rifampicin/isoniazid/pyrazinamide/ethambutol fixed-dose combination tablets at the dosages specified by the TB Clinical and Diagnostic Treatment Guidelines. After approximately the first 2 months of TB therapy, participants will receive specified doses of rifampicin and isoniazid for the duration of TB therapy. Administration of TB therapy will occur under supervision via DOT at the Prince Cyril Zulu CDC.

Both TB regimens are 5-day regimens administered from Monday to Friday each week over the duration of TB therapy. The duration of anti-TB treatment is usually 6 months though it may be extended at the clinician’s discretion.

A participant will be allowed to remain in Phase I for a maximum of 48 weeks after study entry. Sequential arm participants who are still receiving TB drugs at Week 48 will enter Phase II and be offered ART.

Participants in the integrated treatment arm of this study will receive their anti-TB and ART medications concurrently for the duration of their TB therapy. Their ART drugs will be administered and supervised by the same clinic staff who administers their anti-TB drugs from Monday to Friday. Participants in the integrated treatment arm will self-administer their ART medication on Saturday and Sunday for the duration of their TB therapy.

Participants from both study arms who have completed TB therapy will be referred to the KEH Infectious Disease Unit. Following their first study visit at this clinic they will be provided with a supply of ART medication for self-administration. The ART drug supplies will be replenished during study visits. Study participants will continue on an ART drug combination for the duration of the study period.
5.2 Drug Formulation

Table 8: First-Line Study Drugs

<table>
<thead>
<tr>
<th>Medication</th>
<th>Formulation</th>
<th>Storage</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV</td>
<td>200 mg capsules</td>
<td>Store at 25°C (77°F). Excursions permitted to 15°C-30°C or (59°C-86°F)</td>
</tr>
<tr>
<td></td>
<td>600 mg tablets</td>
<td>Store at 25°C (77°F). Excursions permitted to 15°C-30°C or (59°C-86°F)</td>
</tr>
<tr>
<td>ddl</td>
<td>150 mg/100 mg/50 mg/25 mg tablets</td>
<td>Tablets: 15°C-30°C or (59°C-86°F)</td>
</tr>
<tr>
<td></td>
<td>2g/4g powder</td>
<td>ddl powder: Should be stored at 15°C-30°C or (59°C-86°F). The admixture may be stored up to 30 days in a refrigerator, 2°C-8°C or (36°C-46°F)</td>
</tr>
<tr>
<td>ddl-EC</td>
<td>400 mg/250 mg enteric-coated</td>
<td>Store at 25°C (77°F). Excursions permitted to 15°C-30°C or (59°C-86°F)</td>
</tr>
<tr>
<td></td>
<td>capsules</td>
<td></td>
</tr>
<tr>
<td></td>
<td>200 mg/125 mg enteric-coated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>capsules if available</td>
<td></td>
</tr>
<tr>
<td>3TC</td>
<td>150 mg tablets</td>
<td>Store at 25°C (77°F). Excursions permitted to 15°C-30°C or (59°C-86°F)</td>
</tr>
<tr>
<td></td>
<td>10 mg/mL oral solution</td>
<td>Store in tightly closed bottles at 25°C (77°F)</td>
</tr>
</tbody>
</table>
### Table 9: Alternative ART Options

<table>
<thead>
<tr>
<th>Medication</th>
<th>Formulation</th>
<th>Storage</th>
</tr>
</thead>
<tbody>
<tr>
<td>NVP</td>
<td>200 mg tablet</td>
<td>Store below 25°C (77°F). Excursions permitted to 15°-30°C or (59°-86°F)</td>
</tr>
<tr>
<td>TDF</td>
<td>300 mg tablet</td>
<td>Store at 25°C (77°F). Excursions permitted to 15°-30°C or (59°-86°F)</td>
</tr>
<tr>
<td>ABC</td>
<td>300 mg tablet</td>
<td>Store at controlled room temperature 20° to 25°C (68° to 77°F). DO NOT freeze. May be refrigerated.</td>
</tr>
<tr>
<td>SQV + RTV</td>
<td>200 mg hard-gelatin capsule (SQV)</td>
<td>SQV: Store at 15° to 30°C (59° to 86°F) in tightly closed bottles. RTV: Store at 2° - 8° C (36° - 46°F) until dispensed. Protect from light. Avoid exposure to excessive heat. Keep bottles tightly closed. Refrigeration by the participant is recommended but not required if used within 30 days and stored below 25°C (77°F).</td>
</tr>
<tr>
<td></td>
<td>100 mg soft-gelatin capsule (RTV)</td>
<td></td>
</tr>
<tr>
<td>LPV/r</td>
<td>133.3mg/33.3mg coformulated soft-gelatin capsules</td>
<td>Store at 2° - 8° C (36° - 46°F) until dispensed. Avoid exposure to excessive heat. Keep bottles tightly closed. Refrigeration by participant is recommended. If stored at room temperature up to 25°C (77°F), capsules should be used within 2 months.</td>
</tr>
</tbody>
</table>

### 5.3 Alternative ART Options

In cases of treatment-limiting toxicities or conditions, the first-line combination of ART drugs may be changed by the study clinicians. The entire regimen may be switched or individual drugs may be substituted depending on the nature of the treatment-limiting toxicity or condition. Treatment-limiting toxicities or conditions include:

- Severe or recurring toxicities
- Concomitant conditions or required medications for which first-line options are contraindicated
• Pregnancy
• ART failure

5.3.1 Drug Substitution for ART Failure

ART failure is defined in this study using disease progression (see Appendix II) and/or immunological measures via CD4+ cell counts.

The table below shows definitions of clinical and CD4+-related ART treatment failure as recommended by WHO.

Table 10: Modified Clinical and CD4+ Cell Count Definitions of Treatment Failure in HIV+ Adults and Adolescents (WHO, 2003)

<table>
<thead>
<tr>
<th>Clinical Signs of Treatment Failure</th>
<th>CD4+ Cell Criteria for Treatment Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Occurrence of new opportunistic infection or malignancy signifying clinical disease progression. This must be differentiated from IRIS which can occur in the first three months following the initiation of ART. ¹The latter does not signify treatment failure and the opportunistic infection should be treated as usual, without changes in the ART regimen.</td>
<td>• Return of CD4+ cell to pre-therapy baseline or below without other concomitant infection to explain transient CD4+ cell decrease. ²</td>
</tr>
<tr>
<td>• Onset or recurrence of WHO Stage III conditions (including but not restricted to HIV wasting, chronic diarrhea of unknown etiology, prolonged fever of unknown etiology, recurrent invasive bacterial infections, or recurrent/persistent mucosal candidiasis, but excluding pulmonary TB). ³</td>
<td>• &gt; 50% fall from on therapy CD4+ peak level without other concomitant infection to explain transient CD4+ cell decrease. ²</td>
</tr>
</tbody>
</table>

¹ IRIS is characterized by the appearance of signs and symptoms of an opportunistic disease a few weeks after the start of potent ART in the setting of advanced immunodeficiency, as an inflammatory response to previously sub-clinical opportunistic infection. It is also possible that this immunological reconstitution may lead to the development of atypical presentations of some opportunistic infections.
² If participant is asymptomatic and treatment failure is being defined by CD4+ cell criteria alone, consideration should be given to performing a confirmatory CD4+ cell count if resources permit.
³ The complete listing of WHO Stage III conditions is listed in Appendix X.

First options for post-treatment failure include the study-provided drugs. Subsequent options for post-treatment failure ART drugs will be at the research clinician/investigator’s discretion and alternative choices will be made based on drug availability, cost, the participant’s prior ART drug experience, and the research clinician/investigator’s clinical judgment.
5.3.2 Virologic Failure

Virologic failure is defined as HIV-1 RNA $\geq$ 1000 copies/mL on two consecutive measurements obtained after completion of 16 weeks or longer of study treatment. The presence of virologic failure alone does not require a change in the ART regimen. However, virologic failure should trigger further investigation of the cause of the virologic ART treatment failure.

The decision to change therapy will require a thorough review of the participant’s clinical history, treatment history, evaluation of adherence, virologic and CD4+ measures, and the availability of useful drugs.

5.3.3 Drug Substitutions for Toxicity Reasons

Switching to an alternative regimen will be necessary when toxicities occur as a result of the original ART regimen. Refer to Section 7.0, Toxicity Management.

Choices of alternative drugs beyond the principal alternate drugs previously shown in Table 5 will depend upon the reason for ART switching and the availability of ART drugs in South Africa, and will also be at the discretion of the research clinician/investigator.

In the case of treatment-limiting toxicity, the following drug substitutions will be permitted:

Table 11: Drug Substitutions for Treatment-Limiting Toxicities

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Suspect Drug</th>
<th>Recommended switch during TB Treatment</th>
<th>Recommended switch post TB Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness, inability to concentrate</td>
<td>EFV</td>
<td>NVP* or SQV + RTV</td>
<td>NVP* or LPV/r</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>ddl or ddl-EC</td>
<td>TDF (first choice) ABC (second choice)</td>
<td>TDF (first choice) ABC (second choice)</td>
</tr>
<tr>
<td>Dermatologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>EFV</td>
<td>NVP* for Grade 1-2 rash or SQV + RTV (first choice) ABC (second choice)</td>
<td>NVP* for Grade 1-2 rash or LPV/r (first choice) ABC (second choice)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SQV + RTV or ABC for Grade 3-4 rash</td>
<td>LPV/r or ABC for Grade 3-4 rash</td>
</tr>
</tbody>
</table>

* See Section 5.3.3.2 for restrictions on Nevirapine use.
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Suspect Drug</th>
<th>Recommended switch during TB Treatment</th>
<th>Recommended switch post TB Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia, Nausea/Vomiting</td>
<td>ddI or ddI-EC</td>
<td>TDF (first choice)</td>
<td>TDF (first choice)</td>
</tr>
<tr>
<td></td>
<td>EFV</td>
<td>ABC (second choice)</td>
<td>ABC (second choice)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>ddI or ddI-EC</td>
<td>TDF (first choice)</td>
<td>TDF (first choice)</td>
</tr>
<tr>
<td></td>
<td>EFV</td>
<td>ABC (second choice)</td>
<td>ABC (second choice)</td>
</tr>
<tr>
<td>Hepatitis (Grade 3/4)</td>
<td>EFV</td>
<td>SQV + RTV (first choice)</td>
<td>LPV/r (first choice)</td>
</tr>
<tr>
<td></td>
<td>ddI/ddI-EC</td>
<td>TDF</td>
<td>TDF</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>ddI or ddI-EC</td>
<td>TDF (first choice)</td>
<td>TDF (first choice)</td>
</tr>
<tr>
<td></td>
<td>ABC (second choice)</td>
<td>ABC (second choice)</td>
<td>ABC (second choice)</td>
</tr>
<tr>
<td>Metabolic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactic Acidosis</td>
<td>ddI or ddI-EC</td>
<td>TDF (first choice)</td>
<td>TDF (first choice)</td>
</tr>
<tr>
<td></td>
<td>ABC (second choice)</td>
<td>ABC (second choice)</td>
<td>ABC (second choice)</td>
</tr>
</tbody>
</table>

* See Section 5.3.3.2 for restrictions on Nevirapine use.

5.3.3.1 Do not use the following drug combinations:

- ABC + TDF + 3TC
- TDF + ddI/ddI-EC + 3TC
- ZDV + d4T (Stavudine/Zerit®)
- ddI + d4T should only be used when no other antiretroviral options are available and potential benefits outweigh the risks. ddI + d4T must never be used in pregnant women.

5.3.3.2 Nevirapine:

Nevirapine should not be used in females with CD4+ cell counts > 250 cells/µL, in males with CD4+ cell counts > 400 cells/µL, in participants co-infected with HIV and hepatitis B (HBV) and/or hepatitis C (HCV), in participants with underlying liver disease of any severity, and in participants with elevated hepatic transaminases at the time of NVP initiation.

If a participant falls within the criteria described above and there are no other options for ART, NVP may be allowed with permission from the START Project Director and/or START PI after a risk/benefit analysis on whether to use NVP given the participant’s entire clinical
presentation.

The use of protease inhibitors instead of NVP will be allowed in participants without the criteria for restriction of NVP use listed above at the study clinician’s discretion since there is a continuum of risk.

For all participants starting NVP, LFTs will be measured at the time NVP is initiated weekly for the first 6 weeks, at week 8, and then monthly until week 20 of NVP treatment, and every 3 months thereafter. In addition to these timeframes, LFTs will be measured when any symptoms of rash or hepatitis develop.

5.3.4 Drug Substitutions for Pregnant Participants

Women who become pregnant while receiving ART and TB therapy concomitantly may require a modification or temporary discontinuation of their ART regimen but must not remain on EFV. In these cases, management of the ART regimen is left to the clinical judgment of the research clinician/investigator.

For women who become pregnant while receiving ART treatment, EFV will be discontinued immediately and may be replaced with NVP 200 mg once daily for 14 days and then 200 mg twice daily for the full course of pregnancy or with protease inhibitors. For all participants starting NVP, LFTs will be measured at the time NVP is initiated weekly for the first 6 weeks, at week 8, and then monthly until week 20 of NVP treatment, and every 3 months thereafter. In addition to these timeframes, LFTs will be measured when any symptoms of rash or hepatitis develop.

Nevirapine should not be used in females with CD4+ cell counts > 250 cells/µL, in participants co-infected with HIV and HBV and/or HCV, in participants with underlying liver disease of any severity, and in participants with elevated hepatic transaminases at the time of NVP initiation.

The use of protease inhibitors instead of NVP will be allowed in participants without the criteria for restriction of NVP use listed above at the study clinician’s discretion since there is a continuum of risk.

If a participant falls within the criteria for restriction of NVP use described above and there are no other options for ART, NVP may be allowed with permission from the START Project Director and/or START PI after a risk/benefit analysis on whether to use NVP given the participant’s entire clinical presentation.

It will be at the discretion of the research clinician/investigator to determine whether a woman should remain on NVP following pregnancy or return to EFV. Pregnant women will receive folic acid supplement (5 mg once daily).
SQV + RTV (if taking rifampicin), LPV/r (if not taking rifampicin), or ABC (to preserve once daily dosing) can also be substituted for EFV in pregnant participants as second-line options when NVP cannot be used.

ddi/ddI-EC + d4T is prohibited due to the risk of severe lactic acidosis in pregnant women.

5.4 Concomitant Medications

In addition to the TB drugs listed above in Section 5.1.2, participants will be receiving pyridoxine as part of their anti-TB medications. The dosage of pyridoxine is 25 mg and is taken once daily. This is not a study drug, but is dispensed as standard of care for participants receiving TB treatment who are considered at high risk of peripheral neuropathy.

Participants will be provided with trimethoprim/sulfamethoxazole (2 x 80/400 mg tablets once daily) for Pneumocystis carinii pneumonia (PCP) prophylaxis as a part of clinical care, when indicated. The trimethoprim/sulfamethoxazole is not a study drug in this study. Other medications recommended for prophylaxis of AIDS-defining illnesses are listed in the Manual of Operations.

5.5 Prohibited Concomitant Medications

Table 12: Prohibited Medication List

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Prohibited Concomitant Medication</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz (EFV)</td>
<td>Astemizole, Cisapride, Midazolam, Triazolam, Ergot derivatives, Terfenadine, Voriconazole,</td>
<td>Midazolam (Dormicum®) can be used with caution as a single dose when given in a monitored situation for procedural sedation.</td>
</tr>
<tr>
<td></td>
<td>anticonvulsants, Echinacea-containing complementary medicines or supplements and St. John’s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wort-containing complementary medicines or supplements.</td>
<td></td>
</tr>
<tr>
<td>Didanosine (ddI/ddI-EC)</td>
<td>Hydroxyurea</td>
<td>Causes four-fold increase in pancreatitis.</td>
</tr>
<tr>
<td></td>
<td>Stavudine</td>
<td>Lactic acidosis and severe hepatitis with steatosis.</td>
</tr>
<tr>
<td></td>
<td>Allopurinol</td>
<td></td>
</tr>
<tr>
<td>Ribavirin</td>
<td></td>
<td>May increase intracellular triphosphate levels of didanosine. Coadministration is not recommended.</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>Zalcitabine</td>
<td>May inhibit the phosphorylation of each, and concurrent administration is not recommended.</td>
</tr>
<tr>
<td>Study Drug</td>
<td>Prohibited Concomitant Medication</td>
<td>Comments</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Nevirapine (NVP)</td>
<td>Astemizole, Terfenadine, Cisapride, St. John’s Wort (Hypericum perforatum) or St. John’s Wort containing products, Echinacea or products containing Echinacea, Ergotamine and ergot derivatives.</td>
<td>Systemic ketoconazole: NVP concentrations increase 15-30% and ketoconazole AUC decreases &gt; 60% due to induction of CYP450 3A4 and inhibition of NVP and ketoconazole, respectively.</td>
</tr>
<tr>
<td>Tenofovir (TDF)</td>
<td>No prohibited drugs identified</td>
<td></td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>Alcohol</td>
<td>Alcohol increases ABC levels by 41%.</td>
</tr>
<tr>
<td>Saquinavir plus Ritonavir (SQV + RTV)</td>
<td>Amiodarone, Flecainide, Propafenone, Bepridil, Quinidine, Astemizole, Terfenadine, Pethidine, Ergot derivatives (e.g., Ergotamine, Dihydroergotamine, ergonivine, methylergonovine), Pimozide, Cisapride, products containing St. John's wort, lovastatin, simvastatin, midazolam, triazolam, Echinacea or products containing Echinacea, voriconazole</td>
<td>Midazolam (Dormicum®) can be used with caution as a single dose when given in a monitored situation for procedural sedation.</td>
</tr>
<tr>
<td>Lopinavir/ritonavir (LPV/r)</td>
<td>Amiodarone, Flecainide, Propafenone, Bepridil, Quinidine, Midazolam, Triazolam, Pethidine, Ergot derivatives (e.g., Ergotamine, Dihydroergotamine, ergonivine, methylergonovine), Pimozide, Cisapride, Astemizole, Terfenadine, St. John’s Wort, Echinacea or products containing Echinacea, Voriconazole, lovastatin, simvastatin</td>
<td>Midazolam (Dormicum®) can be used with caution as a single dose when given in a monitored situation for procedural sedation. Concomitant use of lovastatin and simvastatin should be avoided. The risk of myopathy, including rhabdomyolysis, may be increased when protease inhibitors are used in combination with HMG-CoA Reductase inhibitors.</td>
</tr>
</tbody>
</table>

5.6 Precautionary Medications

Caution must be exercised whenever the following medicines are to be used in combination with the first- or second-line ART choices. Doses may have to be adjusted or administration times altered.
<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Concomitant Medication Precaution</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz (EFV)</td>
<td>Alcohol or Psychoactive drugs</td>
<td>May have an additive effect on CNS effects.</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td></td>
<td>Efavirenz may decrease the plasma concentration of clarithromycin; consideration of alternatives to clarithromycin, such as azithromycin, is recommended since coadministration of azithromycin with efavirenz did not result in any clinically significant pharmacokinetic interactions; other macrolide antibiotics, such as erythromycin, have not been studied in combination with efavirenz; Liverpool Group rates this interaction as a “potential interaction.”</td>
</tr>
<tr>
<td>Ritonavir</td>
<td></td>
<td>May result in dizziness, nausea, and paresthesia and laboratory abnormalities (elevated liver enzymes).</td>
</tr>
<tr>
<td>Saquinavir</td>
<td></td>
<td>Plasma concentrations may be decreased by efavirenz.</td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td>Close monitoring of INR should be ensured (plasma concentrations and clinical effects may be either increased or decreased).</td>
</tr>
<tr>
<td>Alfentanil, Fentanyl, Methadone, Tramadol, Amiodarone, Bepridil, Disopyramide, Flecaïnine, Lignocaine, Mexilitine, Propafenone, Quinidine, Rifabutin, Rifampicin, Streptomycin, Carbamazepine, Clonazepam, Ethosuximide, Bupropion, Nefazodone, Fenoxifène, Loratadine, Cyclophosphamide, Paclitaxel, Vincristine, Pimozide, Alprazolam (and other benzodiazepines, but not lorazepam, oxazepam, or temazepam), Nifedipine (and other calcium channel blockers), Apomorphine, Sildenafil, Lansoprazole, Dronabinol, Garlic supplements,</td>
<td>Listed as “potential interactions.” May require close monitoring, alteration of drug dosage, or timing of administration on NNRTI drug interactions.</td>
<td></td>
</tr>
<tr>
<td>Study Drug</td>
<td>Concomitant Medication Precaution</td>
<td>Comments</td>
</tr>
<tr>
<td>----------------------------</td>
<td>---------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Efavirenz (EFV) (cont’d)   | Milk thistle, Cyclosporin, Sirolimus, Tacrolimus, Atorvastatin, Cerivastatin, Fluvastatin, Simvastatin, Dexamethasone, Prednisolone, Progesterone, Stanazolol, Testosterone Itraconazole, Fluconazole, systemic ketoconazole | Interactions between these drugs may occur resulting in reduced levels. In addition to providing dual protection with an appropriate barrier method (e.g., condoms), the following dose adjustments, in line with standard TB care, should be made:  
  - Any combined oral contraceptive used should contain at least 50µg of ethinyloestradiol; the pill-free interval should be reduced from 7 to 4 days.  
  - If injectable progesterone contraceptives are used, the inter-dose interval should also be shortened from 12 weeks to 8 weeks for medroxyprogesterone acetate 150 mg IM and from 8 to 6 weeks for norethisterone oenanthate 200 mg IM. |
<p>|                           | Hormonal Contraception                                                                             |                                                                           |
| Didanosine (ddI/ddI-EC)    | Alcohol, Asparaginase, Azathioprine, Oestrogens, Furosemide, Methyldopa, Nitrofurantoin, IV Pentamidine, Sulfonamides, Sulindac, Tetracyclines, Thiazide diuretics, Valproic acid | These are drugs associated with pancreatitis.                              |
|                           | Chloramphenicol, Cisplatin, Dapsone, Ethambutol, Ethionamide, Hydralazine, Isoniazid, Lithium, Metronidazole, Nitrofurantoin, Nitrous oxide, Phenytoin, Stavudine, Vincristine, Zalcitabine | These are drugs associated with peripheral neuropathy.                    |</p>
<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Concomitant Medication Precaution</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Didanosine (ddI/ddI-EC) (cont’d)</td>
<td>Dapsone, Itraconazole, Ketoconazole, fluoroquinolones</td>
<td>These are drugs poorly absorbed with didanosine. They should be administered at least 2 hours before or 2 hours after didanosine is given (due to decreased absorption of these agents in the buffered environment caused by some didanosine formulations).</td>
</tr>
<tr>
<td>Tenofovir</td>
<td></td>
<td>Tenofovir increases didanosine levels requiring dosage decrease of ddI/ddI-EC to 250 mg/day for participants ≥ 60 kg. Data are not available for participants &lt; 60 kg.</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td></td>
<td>Concomitant ganciclovir may increase plasma didanosine levels by as much as 111%.</td>
</tr>
<tr>
<td>Nevirapine (NVP)</td>
<td>Itraconazole, Fluconazole, Voriconazole</td>
<td>Reduced itraconazole serum concentrations and increased NVP concentrations from co-administration with itraconazole. Coadministration of NVP and fluconazole resulted in an approximate 100% increase in NVP exposure. Because of the risk of increased exposure to NVP, caution should be used in concomitant administration and participants should be monitored closely for NVP-associated adverse events. Frequent monitoring for drug toxicity with voriconazole is recommended.</td>
</tr>
<tr>
<td>Anticonvulsants, phenytoin, phenobarbitone, carbamazepine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lovastatin, simvastatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>St. John’s Wort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir (TDF)</td>
<td>Didanosine, amphotericin B and other nephrotoxic drugs</td>
<td>In adults weighing &gt; 60 kg, the didanosine dose should be reduced to 250 mg when it is co-administered with TDF. Data are not available to recommend a dose adjustment of didanosine for individuals weighing &lt; 60 kg. Concurrent or recent use of nephrotoxic drugs should be avoided in participants taking TDF. Participants with a risk or history of renal dysfunction or who are on nephrotoxic drugs should be carefully monitored for changes in serum creatinine and phosphate.</td>
</tr>
<tr>
<td>Study Drug</td>
<td>Concomitant Medication Precaution</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>Methadone</td>
<td>Methadone clearance increases by 22% and dose modification may be required in some individuals.</td>
</tr>
<tr>
<td>Ritonavir-boosted Saquinavir (SQV + RTV) or Lopinavir</td>
<td>Ritonavir is an inhibitor of the P450 isoform CYP3A.</td>
<td>Coadministration with drugs primarily metabolized by CYP3A may result in increased plasma concentrations of the other drug that could increase or prolong its therapeutic and adverse effects.</td>
</tr>
<tr>
<td></td>
<td>Sildenafil, Vardenafil, Tadalafil</td>
<td>Dose reduction is required. The maximum dose of sildenafil is 25 mg/48 hours. The maximum dose of vardenafil is 2.5 mg/72 hours. The maximum dose of tadalafil is 10 mg/72 hours.</td>
</tr>
<tr>
<td></td>
<td>Garlic supplements</td>
<td>Garlic supplements significantly decreased SQV levels in healthy participants by approximately 50% after 19 days.</td>
</tr>
<tr>
<td></td>
<td>Trazodone</td>
<td>Plasma concentrations may be increased by ritonavir. Adverse effects including nausea, hypotension, and syncope were observed when ritonavir and trazodone were coadministered.</td>
</tr>
<tr>
<td></td>
<td>Grapefruit juice</td>
<td>Increases SQV levels.</td>
</tr>
<tr>
<td></td>
<td>Oral contraceptives</td>
<td>Participants receiving estrogen-based hormonal contraceptives should be instructed that additional or alternate contraceptive measures should be used during therapy with protease inhibitors.</td>
</tr>
<tr>
<td></td>
<td>Carbamazepine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phenobarbitone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atorvastatin, Fluvastatin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Theophylline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ketoconazole, Itraconazole</td>
<td>Increases azole levels.</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>Coadministration of phenytoin and SQV may result in reduced SQV serum concentrations.</td>
</tr>
<tr>
<td></td>
<td>Calcium Channel Blockers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dextropropoxyphene, Zolpidem</td>
<td>Potential interaction that may require close monitoring, alteration of drug dosage, or timing of administration.</td>
</tr>
</tbody>
</table>
All of the drugs mentioned above may not be marketed in South Africa, nor may they be available in the State sector; however, the full list should be considered whenever participant medication histories are elicited or clinical decisions made.

During the trial, regular updates to this list will be made, based on material published by the Liverpool HIV Pharmacology Group and the US Pharmacopeia Drug Information.

Please see the most recent package inserts for additional information regarding prohibited and precautionary medications for the study drugs.

5.7 Supply, Distribution, and Pharmacy of ART Drugs

The CAPRISA Program will acquire innovator (i.e., non-generic) antiretroviral drugs for use during this study. The following drugs will be supplied through the study: EFV, 3TC, ddI/ddI-EC, ABC, TDF, NVP, SQV + RTV, and LPV/r.

ART drugs will be received, checked, and stored at the KEH pharmacy and then dispensed by the study pharmacist. The study pharmacist obtains the study agent in accordance with the study-specific pharmacy standard operating procedures (SOPs). Eligible participants will be registered into Phase II through the data management system and will obtain new prescriptions.

ART drugs will be dispatched to the Prince Cyril Zulu CDC on request from the authorized study clinicians and following the study-specific pharmacy SOPs.

Upon completion of TB therapy, participants on the integrated arm will be registered to Phase II through the data management system and will receive their ongoing care and monitoring at the KEH Infectious Disease Unit, including the dispensing of their ART drugs. ART drugs will be provided during the monthly study visits for self-administration. Drugs for each study participant will be dispensed in compliance with the study-specific pharmacy SOPs.

Upon completion of TB therapy, eligible participants on the sequential arm of the study will be registered to Phase II through the data management system and will have their ART initiated at the KEH Infectious Disease Unit. Participants on the sequential arm who start ART prior to the completion of TB therapy will also be registered to Phase II through the data management system and have their ART initiated at the KEH Infectious Disease Unit. Participants will receive their ongoing care and monitoring at the KEH Infectious Disease Unit and will self-administer their ART drugs. Drug requests and dispensing procedures followed will be identical to that described for participants in the integrated arm being monitored at KEH Infectious Disease Unit.

Only study clinicians will be authorized to prescribe the study agents. The pharmacist will maintain an Authorized Prescribers Log in the pharmacy. Dispensing of study agents will be done according to the study-specific pharmacy SOPs.
5.8 **Storage**

Study drugs will be stored according to the manufacturers’ directions and in accordance with the study-specific pharmacy SOPs. Study drugs will be stored in a secure environment with access limited to essential pharmacy personnel and pharmacy-approved study staff. None of the first line medications require refrigeration, but the room temperature will be monitored through maintaining a daily temperature log. Adequate supply of study drug will be maintained at all times.

5.9 **Accountability**

The CAPRISA pharmacist is required to maintain accountability records of all study products received and subsequently dispensed. The procedures to be followed are provided in the study-specific pharmacy SOPs and the Manual of Procedures (MOP). At the end of the study, unused licensed study drug will be donated to KEH for ongoing treatment of START study participants. Unused TDF will be destroyed in accordance with study-specific pharmacy SOPs. If TDF becomes licensed, unused TDF will then be donated to KEH for ongoing treatment of START study participants.

5.10 **Adherence Assessment**

Adherence is defined as taking the correct ART and TB medications at the correct time and the exact number of pills prescribed with the required dietary restrictions for each dose. Adherence also encompasses the extent to which the participant’s behavior – taking medication, food-dosing requirements, or executing lifestyle changes – corresponds with recommendations from the study team. Adherence of > 95% is regarded as ideal.

Adherence to study ART and TB medications will be measured by reconciliation of clinic DOT records, structured pill counts to calculate the percentage of doses missed, and brief quantitative interviews conducted at monthly study visits that will include a self-report by participants (Appendix VI).

5.10.1 **DOT Records**

**Phase I**

For participants in the integrated arm, antiretroviral drugs will be administered by DOT at the study clinic along with TB therapy for 5 days of the week. On Fridays, sufficient ART for weekend self-administration will be provided. This will consist of 2 doses of each medication, sufficient for Saturday and Sunday. Additional doses for an extra day, if the patient is away for a long week-end or cannot attend the clinic mid-week, may be provided by special arrangement with study staff. Participants will be requested to return all unused medication to the clinic.
During each weekday DOT encounter, the DOT record will reflect the names and doses of both the ART and TB therapy administered to the participant in addition to the signature of the staff member that witnessed the administration of the drugs. DOT visits that are missed will also be reflected on these records. On Monday mornings, the number of ART doses returned by the participant will be documented on the DOT records.

Participants in the sequential arm will also be monitored daily for adherence to the TB treatment regimen. DOT records will include the name and dose of the TB drug and the corresponding signature of the staff witnessing the administration of the TB drug.

5.10.2 Structured Pill Counts

**Phase I**

Pill counts will be conducted at the monthly study visits in the integrated arm. This will be achieved by reconciliation of clinic DOT records and pills left over at the clinic. Monthly percentage adherence will be calculated, based on attendance at weekday DOT sessions (for TB and ART therapy) and the post-weekend pill counts when ART is self-administered.

\[
\% \text{ Adherence} = \frac{\text{Number of actual doses taken}}{\text{Number of doses intended}} \times 100
\]

*number of doses issued minus number of doses returned, or number of potential DOT visits minus number of DOT visits missed. A dose is not defined as the number of pills but dosing opportunity per drug. If only a portion of a dose is taken then the entire dose is regarded as missed.

In the sequential arm, assessment of the DOT records will be used to calculate percentage adherence to TB treatment.

**Phase II**

Once TB treatment is complete, study participants in both arms transition to Phase II and will be issued with ART drugs for a 30-day period. All participants will be requested to return all unused study medication to the clinic at monthly study visits. At each monthly study visit pill counts will be conducted and percentage adherence will be calculated.
5.10.3 Seven Day Adherence Recall

**Phase I and Phase II**

A 7-day recall adherence assessment interview with a self-report section (Appendix VI) will be used to determine reasons for missed ART and/or TB doses and barriers to adherence. This interview will be conducted at each study visit in both the integrated and sequential arm throughout the study. During Phase I this interview will be conducted weekly for the first 3 weeks in the integrated arm; thereafter, it will be conducted monthly in both arms until Phase II, where the assessment will be conducted weekly in the first 3 weeks of ART initiation in the sequential arm, and thereafter monthly in both arms for the entire duration of the study.
### 6.0 CLINICAL AND LABORATORY EVALUATIONS

#### 6.1 Schedule of Events

**Phase I**
Integrated and Sequential Arm Until Completion of TB Therapy (Prince Cyril Zulu CDC)

<table>
<thead>
<tr>
<th>Key:</th>
<th>Phase Screening</th>
<th>Phase Day of Baseline</th>
<th>Phase Weekly x 3</th>
<th>Phase Month 1</th>
<th>Phase Month 2</th>
<th>Phase Month 3</th>
<th>Phase Month 4</th>
<th>Phase Month 5</th>
<th>Phase Month 6</th>
<th>Phase Month 7</th>
<th>Phase Month 8</th>
<th>Phase Month 9</th>
<th>Phase Month 10</th>
<th>Phase Month 11</th>
<th>Phase Month 12</th>
<th>End of TB Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>I = Integrated Arm</td>
<td>S = Sequential Arm</td>
<td>X = Both Arms</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

| EVALUATION | Phase Screening | Phase Day of Baseline | Phase Weekly x 3 | Phase Month 1 | Phase Month 2 | Phase Month 3 | Phase Month 4 | Phase Month 5 | Phase Month 6 | Phase Month 7 | Phase Month 8 | Phase Month 9 | Phase Month 10 | Phase Month 11 | Phase Month 12 | End of TB Therapy |
|-------------|-----------------|-----------------------|------------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|-----------------|
| Sputum Smear and Resistance Testing | X | | | | | | | | | | | | | | | |
| Restriction Fragment Length Polymorphism Analysis (RFLP) | | | | | | | | | | | | | | | | |
| Chest X-Ray | X | | | | | | | | | | | | | | | |
| Screening Informed Consent | X | | | | | | | | | | | | | | | |
| Documentation of HIV Rapid Testing Results | X | | | | | | | | | | | | | | | |
| Study Informed Consent | X | | | | | | | | | | | | | | | |
| Specimen Storage Informed Consent | X | | | | | | | | | | | | | | | |
| Demographic/Locator Information | X X X X X X X X X X X X X X X X | | | | | | | | | | | | | | | |
| Medical History, Medication History, Concomitant Medications | X2 | X X X X X X X X X X X X X X X X | | | | | | | | | | | | | | |
| Targeted Physical Exam (+Karnofsky Score), Signs & Symptoms, Diagnoses | X X X X X X X X X X X X X X | | | | | | | | | | | | | | | |
| Vital Signs and Weight | X X X X X X X X X X X X X X X X | | | | | | | | | | | | | | | |
| Randomization | X | | | | | | | | | | | | | | | |
| Assessment for symptoms of IRIS5 | X X X X X | | | | | | | | | | | | | | | |
| Urine Pregnancy Test | X | | | | | | | | | | | | | | | |
| HBsAg, anti-HBc, HCV, GBV-C | X | | | | | | | | | | | | | | | |
| AST, ALT, T. BIL, hemoglobin, hematocrit, WBC, differential, ANC, platelets, creatinine, (phosphate)6.7 | X X8 | X X X X | X X X X | X X | X X X X | X | | | | | | | | | | |
| ART Initiation Eligibility Assessment | | | | | | | | | | | | | | | | |
| ART Initiation9 | | | | | | | | | | | | | | | | |
| Distribution of Study Drug (ART) | | | | | | | | | | | | | | | | |
| DOT Visits | | | | | | | | | | | | | | | | |

*Note: TB therapy Day 1 = start of treatment.*
### Phase I

#### Integrated and Sequential Arm Until Completion of TB Therapy (continued)

<table>
<thead>
<tr>
<th>EVALUATION</th>
<th>Phase I Screening</th>
<th>Phase I Day 0</th>
<th>Phase I Weekly x3</th>
<th>Phase I Month 1</th>
<th>Phase I Month 2</th>
<th>Phase I Month 3</th>
<th>Phase I Month 4</th>
<th>Phase I Month 5</th>
<th>Phase I Month 6</th>
<th>Phase I Month 7</th>
<th>Phase I Month 8</th>
<th>Phase I Month 9</th>
<th>Phase I Month 10</th>
<th>Phase I Month 11</th>
<th>Phase I Month 12</th>
<th>End of TB Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4+/CD8+ Count</td>
<td>X, 10</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Plasma Rifampicin PK level (peak)</td>
<td></td>
<td></td>
<td></td>
<td>X, 4</td>
<td></td>
<td>X, 4</td>
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<td>X</td>
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</tr>
<tr>
<td>Plasma Efavirenz PK level (trough)</td>
<td>I</td>
<td>I</td>
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<td>I</td>
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<tr>
<td>Plasma HIV-1 RNA PCR</td>
<td></td>
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<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td></td>
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<tr>
<td>HIV-1 Resistance Testing</td>
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<td></td>
<td></td>
<td>X</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Whenever clinically indicated</td>
</tr>
<tr>
<td>Stored Plasma/Serum</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td>Stored PBMCs</td>
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<td>X</td>
<td>X</td>
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1. Results from the initial pre-study TB diagnostic sputum smear and chest X-ray will be obtained from the CDC by study staff. Study staff will ensure that these evaluations are available from all potential study participants at screening.
2. Medical history will include verification of initial HIV results, TB clinical symptoms at time of diagnosis, and TB treatment records, in addition to all HIV, TB, and general medical history findings.
3. ART must be started within 72 hours of eligibility assessment/randomization date in the Integrated Arm.
4. Randomization must occur within 4 weeks after initiation of TB treatment.
5. Assessment of symptoms of IRIS includes: temperature, assessment for lymphadenopathy, respiratory rate, and lung auscultation. If any of these assessments represent new or worsening findings, a chest X-ray, blood cultures, urine culture, and additional diagnostic work-up is indicated.
6. Increase frequency of LFT monitoring (weekly for the first 6 weeks, at week 8, and monthly until week 20 after initiation of NVP, then every 3 months) if switched to NVP during study. In addition to these timeframes, LFTs will be measured when any symptoms of rash or hepatitis develop.
7. Serum phosphate levels are required only if taking TDF.
8. Safety Labs (AST, ALT, T. BILI, ANC, hemoglobin, and creatinine) will be drawn at screening and again at Day 0 of Phase I if screening results are more than 14 days old prior to initiation of ART.
9. Participants with a temperature of ≥ 38.5°C, ≥ Grade 3 nausea/vomiting, ≥ Grade 3 rash, or safety labs (AST, ALT, T. BILI, ANC, hemoglobin, and creatinine) outside of the limits used for eligibility are to be restricted from ART until these symptoms subside.
10. If the screening CD4+ count is obtained within 28 days prior to study entry, it does not have to be repeated at Day 0/Baseline and can be captured on the CRFs as the baseline CD4+ count.
11. HIV-1 RNA assay results from screening must be available prior to study entry for study eligibility and will also be used for Day 0/Baseline. On-study HIV-1 RNA assays are batched. Results will not be available in real-time.
12. Initial ASP session must occur within 72 hours prior to initiation of ART.
13. Refer to Section 6.2.4.4 for directions on End of TB Therapy visit and transition to Phase II.
## Phase II

### After Completion of TB Treatment – Must Meet Phase II Eligibility Requirements (KEH)

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<th>Phase II Weekly x 3</th>
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1. Keypoint

I = Integrated Arm
S = Sequential Arm
X = Both Arms

^9 Phase II Screening Sequential Arm Only

^10 Phase II Registration

^11 ART Initiation

^12 Distribution Of Study Drug (ART)
Phase II
After Completion of TB Treatment – Must Meet Phase II Eligibility Requirements (continued)

Phase II Schedule of Events--Footnotes

1 Assessment of symptoms of IRIS includes: temperature, assessment for lymphadenopathy, respiratory rate, and lung auscultation. If any of these assessments represent new or worsening findings, a chest x-ray, blood cultures, urine culture, and additional diagnostic work-up is indicated.

2 Increase frequency of LFT monitoring (weekly for the first 6 weeks, at week 8, and monthly until week 20 after initiation of NVP, and then every 3 months) if switched to NVP during study. In addition to these timeframes, LFTs will be measured when any symptoms of rash or hepatitis develop.

3 Serum phosphate levels are required only if taking TDF.

4 Safety Labs (AST, ALT, T. BILI, ANC, hemoglobin, and creatinine) will be drawn at Phase II screening and again as needed until eligibility criteria are met for the Sequential Arm. Safety labs will be repeated at Day 0 of Phase II if screening results are more than 14 days old prior to initiation of ART.

5 Participants with a temperature of > 38.5°C, ≥ Grade 3 nausea/vomiting, ≥ Grade 3 rash, or safety labs (AST, ALT, T. BILI, ANC, hemoglobin, and creatinine) outside of the limits used for eligibility are to be restricted from ART until these symptoms subside.

6 Sequential Arm must start ART within 72 hours after Phase II registration.

7 HIV-1 RNA assays are batched. Results will not be available in real time.

8 The End of Study visit occurs upon completion of 24 months on study with a visit window of ± 14 days. (i.e., 24 months after randomization ± 14 days). If participant has completed a total of 24 months on study, corresponding to at least 12 to 18 months in Phase II (depending on the length of Phase I), the last visit occurring between month 12 and 18 (± 14 Days) of Phase II will become the final study visit. All evaluations listed on the Final Study Visit will be conducted at this time. No additional study visit is required after the participant has completed a total of 24 months on study (± 14 days).

9 Refer to Section 6.2.4.4 for directions on End of TB Therapy visit and transition to Phase II.

10 Participants on both arms must be registered to Phase II through the data management system.
6.2 Timing of Evaluations

6.2.1 Pre-Screening Evaluations

All participants diagnosed with active TB at the Prince Cyril Zulu CDC are also routinely offered HIV counseling and testing by a local non-governmental organization known as Open Door. Those who test HIV-positive and who have started TB treatment through the Prince Cyril Zulu CDC DOT program will be referred for study screening within 14 days after initiating TB DOT. Written informed consent will be obtained before any screening procedures are initiated.

6.2.2 Screening

The study screening visits will take place at the Prince Cyril Zulu CDC. The visit will begin after the initiation of TB therapy. Multiple visits may be conducted to complete all required procedures if necessary. For participants who do not meet study eligibility criteria, the screening process will be discontinued when ineligibility is determined. Screening laboratory evaluations may be repeated for participants who do not qualify upon initial referral as long as the results are available within 28 days after TB therapy was initiated. Blood that is left over after all required screening testing is done will be discarded. Written informed consent will be obtained before any baseline procedures are initiated.

6.2.3 Baseline Evaluations (Phase I-Day 0)

This visit must take place no more than 28 days after the start of TB therapy and no more than 14 days after the screening visit/ART safety evaluations. Those results that are necessary to meet inclusion/exclusion criteria must be available at the time of this visit. If all the pre-requisite information for randomization is not available, then a repeat screening visit must be conducted before this baseline visit can proceed. Once all the necessary information for the inclusion/exclusion criteria has been reviewed, randomization can proceed.

Participants will be randomized into either the integrated (I) or the sequential (S) arm at the enrollment visit, which is study Day 0. Those randomized to the integrated arm will start ART within 72 hours after randomization.

ART will not be started if participants have a temperature > 38.5°C, ≥ Grade 3 nausea/vomiting, or ≥ Grade 3 rash on the day they are scheduled to initiate ART. If delayed, ART can be initiated after symptoms resolve (even if > 72 hours after entry) without any violation, but safety evaluations (see Section 4.5.1) need to be repeated if results are > 14 days old.
6.2.4 Follow Up Evaluations

During TB treatment, visits will take place at the Prince Cyril Zulu CDC. Visits occurring after TB therapy completion will take place at the KEH Infectious Disease Unit.

6.2.4.1 Weekly Follow-Up Visits

For the first month of the study, participants in both treatment arms will be seen on a weekly basis during Phase I. Participants on the sequential arm will be seen weekly for the first month during Phase II. Visits should be completed within a 3-day window around the scheduled date (i.e., ± 3 days from the target date).

6.2.4.2 Monthly Follow-Up Visits

Monthly follow-up visits will be scheduled based on the date of enrollment (Day 0). Follow-up visits will be scheduled monthly with the physician for the duration of the study. Visits should be completed within a 14-day window around the scheduled date (i.e., ± 14 days from the target date).

6.2.4.3 ASP for the Integrated Arm

Participants randomized to the integrated arm will receive ASP interventions as described in Appendix IV. These interventions are scheduled for the following times:

1. Within 72 hours prior to the start of ART-DOT
2. Two weeks after the start of ART-DOT
3. Two months after the start of ART-DOT
4. Within 1-3 weeks prior to the end of TB treatment

6.2.4.4 End of TB Therapy Visit and Transition to Phase II

For Participants in Both Arms

- When participants complete TB therapy (usually after 130 DOT doses) or are still receiving TB therapy after Phase I Month 12, they are evaluated at the Prince Cyril Zulu CDC for their End of TB Therapy visit and then have an initial KEH visit. If these evaluations cannot be conducted on the same day, they must occur within 14 days after completion of TB therapy.
NOTE: During the allowed 14-day interval before the initial KEH visit, integrated arm participants must complete any regularly scheduled monthly Phase I visits at the Prince Cyril Zulu CDC so they can continue to receive ART and be monitored for safety.

- When the End of TB Therapy visit is combined on the same day with the initial KEH visit, participants are evaluated by the study clinician at Prince Cyril Zulu CDC for successful TB therapy completion and then transported to KEH for their initial visit.

- After the initial KEH visit, all subsequent study visits and clinical follow-up will be conducted at KEH.

**For Participants in the Integrated Arm**

- The End of TB Therapy visit at the Prince Cyril Zulu CDC may occur on the same day as the initial KEH visit.

- Participants will not undergo an eligibility assessment or screening process for Phase II.

- Participants will be registered to Phase II through the data management system at the initial KEH visit. At this time, they will have their Phase II Day 0/Baseline evaluations and will be supplied with ART (non-DOT).

**For Participants in the Sequential Arm**

- The End of TB Therapy visit at the Prince Cyril Zulu CDC may be combined with the Phase II entry screening and ART eligibility screening evaluations at the initial KEH visit.

- If participants are eligible based on screening evaluations performed at the initial KEH visit (see Section 4.5.1), then they will be registered to Phase II through the data management system and initiate ART therapy at the Phase II Day 0/Baseline visit.

- If participants are not eligible based on screening evaluations performed at the initial KEH visit (see Section 4.5.1), then they will stay on the Phase I schedule and repeat Phase II ART eligibility screening evaluations at KEH until eligible to enter Phase II and initiate ART.
Participants entering Phase II will be given their initial supply of ART (non-DOT) at KEH on Phase II Day 0/Baseline. Participants must initiate ART within 72 hours after Phase II registration.

6.2.5 Evaluations for Sequential Arm Participants Who Do Not Start Study Treatment

If participants in the sequential arm cannot initiate ART after completing the TB treatment phase due to specified symptoms or safety laboratory evaluations that are out of acceptable range, they should remain on the Phase I study schedule with visits at KEH until able to begin ART. When values are within eligibility limits, they should then be registered into Phase II and initiate ART within 72 hours. Eligibility laboratory evaluations (see Section 4.5.1) > 14 days old must be repeated before initiating ART.

6.2.6 Evaluations for Participants Initiating ART Prior to the Completion of TB Therapy

This applies to (1) participants who are in the sequential arm who initiate ART before the end of TB therapy (see Section 9.1), and (2) participants on both arms who remain on TB therapy after Phase I Month 12.

These participants will continue TB treatment at the CDC, but will be registered to Phase II and follow the Phase II schedule at KEH.

6.2.7 Premature Treatment Discontinuation Evaluations

All participants will be followed according to study visit schedule and procedures irrespective of whether they are on or off study drugs unless the participant or investigator discontinues study participation as outlined in Section 8.2.

6.2.8 End of Study Visit

The End of Study visit occurs upon completion of 24 months on study with a visit window of ±14 days. (i.e., 24 months after randomization, ± 14 days). If the participant has completed a total of 24 months on study, corresponding to at least 12 to 18 months in Phase II (depending on the length of Phase I), the last visit occurring between month 12 and 18 (± 14 days) of Phase II will become the final study visit. All evaluations listed on the Final Study Visit will be conducted at this time. No additional study visit is required after the participant has completed a total of 24 months on study (± 14 days).
6.3 **Special Instructions and Definitions of Evaluations**

6.3.1 **Documentation of HIV Rapid Testing Results**

HIV status will be documented by obtaining the results of two positive rapid HIV tests (e.g., OraQuick or Smart Check or other tests approved by the US FDA or the South African Department of Health) performed before study screening.

6.3.2 **Demographic Locator Information**

The Demographic Locator Information form identifies contact information for participants.

6.3.3 **Medical History**

A medical history must be present in source documents. The medical history should include any previous HIV-related diagnoses and non-HIV-related diagnoses of major organ systems. Conduct review for eligibility determination, including current and past history of TB, DOT records, TB symptoms, smear, chest X-ray, history of pancreatitis, peripheral neuropathy, and an enquiry about current participation in other studies. For women, current contraceptive practices and willingness to undergo regular pregnancy tests will be assessed. During eligibility assessment, initial TB diagnostic records will be reviewed (smear, chest x-ray, DOT records).

Any allergies to any medications and their formulations must be documented.

6.3.4 **Medication History**

A medication history must be present in source documents, including:

- Complete HIV and TB treatment history, including start and stop dates of any ART medication (estimated if the exact dates cannot be obtained), immune-based therapy, or HIV-related vaccines, including blinded study medications.

- Complete treatment history of any prescription medications taken for the treatment or prophylaxis of opportunistic infections, including actual or estimated start and stop dates.

- All prescription medications (in addition to those noted above) taken within 30 days of entry/since the last clinic visit, including actual or estimated start and stop dates.

- Non-prescription medications taken within 30 days of entry or since the last clinic visit. Include actual or estimated start and stop dates.
- Complementary therapies and/or dietary supplements taken within 30 days of entry or since the last clinic visit. Include actual or estimated start and stop dates.

6.3.5 Concomitant Medications

All concomitant medications taken since the last report will be recorded in the source documentation.

Please refer to the most recent study medication package inserts and Sections 5.5 and 5.6 of the protocol to access additional current information on prohibited and precautionary medications.

6.3.6 Clinical Assessments

6.3.6.1 Targeted Physical Exam

A targeted physical examination (including recording of Karnofsky score) (Appendix III) will be performed during the study to be driven by any signs or symptoms previously identified that the participant has experienced since the last visit (to include examination for the presence of thrush, lymphadenopathy, presence of rash, and lung examination).

6.3.6.2 Signs and Symptoms

At baseline, record all signs and symptoms within 14 days prior to study entry. For post-baseline assessments, record all Grade 3-4 signs and symptoms on the case report forms (CRFs). Any signs or symptoms that led to a change in treatment, regardless of grade, must be recorded on the CRFs.

All signs and symptoms, including HIV-related and AIDS-defining events, deaths, and toxicities, must be documented in the participant’s record, and signs and symptoms Grade 3-4 must be recorded on the CRFs within 96 hours throughout the course of the study.

Refer to the Division of AIDS Table for Grading Severity of Adult and Pediatric Adverse Events, which can be found on the Regulatory Compliance Center (RCC) website: http://rcc.tech-res-intl.com/.

6.3.6.3 Diagnoses

All confirmed and probable diagnoses made since the last visit will be recorded in the source documentation and CRFs, including current status at the time of study visit.
Appendix II will be used to report AIDS-defining conditions. The ACTG Criteria for Clinical and Other Events will be used to report non-HIV diagnoses and other events. The ACTG Criteria for Clinical and Other Events will be located in the study Manual of Operations.

For each diagnosis, the source document must include:

1) Date of diagnosis, date of resolution.

2) Method of confirmation of diagnosis or evidence for probable diagnosis.

6.3.6.4 Weight (in kilograms)

6.3.6.5 Vital Signs

Temperature, pulse, and any other relevant signs will be collected as part of all clinical examinations.

6.3.6.6 Assessment for Symptoms of Immune Reconstitution Inflammatory Syndrome (IRIS)/Paradoxical Reactions (PR)

During Phase I, participants on both arms will be assessed for symptoms of IRIS at Day 0; Weeks 1, 2, and 3; and the Month 1, 2, and 3 visits. During Phase II, participants on the sequential arm will be assessed for symptoms of IRIS/PR at Day 0; Weeks 1, 2, and 3; and the Month 1, 2, and 3 visits. The IRIS/PR screening assessment will include temperature, assessment for lymphadenopathy, respiratory rate, and lung auscultation. See Section 9.3 for recommendations for participant management of IRIS/PR.

6.3.6.7 Chest X-ray

Results of the chest radiograph used to diagnose TB will be accessed from the medical record review and recorded on CRFs. During the study, chest radiographs will be obtained at 2 months after initiation of TB therapy (TB Therapy Day 1) and at any time when clinically indicated.

6.3.6.8 ART Initiation Eligibility Assessment

Safety evaluations will be conducted and must fall within the defined parameters (see Section 4.5.1) in order for participants to be eligible to initiate ART.

6.3.6.9 DOT Visits

During Phase I, the integrated arm will attend the Prince Cyril Zulu
CDC DOT program Mondays through Fridays for administration of their anti-TB and antiretroviral medications. The sequential arm will attend the Prince Zulu CDC DOT program Mondays through Fridays for administration of their anti-TB medications.

6.3.7 Laboratory Evaluations

At baseline, all laboratory values will be recorded on the CRFs. For post-baseline assessments, all laboratory values must be documented in the participant’s record, and all laboratory values Grade 3-4 must be recorded on the CRFs. All Grade 3-4 laboratory results must be recorded on the CRFs within 96 hours throughout the course of the study. Any laboratory toxicities that lead to a change in treatment, regardless of grade, must be recorded on the CRFs.

To determine the severity grade of laboratory values, refer to the Division of AIDS Table for Grading Severity of Adult and Pediatric Adverse Events, which can be found on the RCC website: http://rcc.tech-res-intl.com/.

See Appendix V for specimen collection and processing guidelines.

6.3.7.1 Hematology

Hemoglobin, hematocrit, white blood cell count (WBC) differential, absolute neutrophil count (ANC), and platelets will be tested.

6.3.7.2 Serum Chemistries

Creatinine will be tested. Participants on tenofovir will also have serum phosphate evaluated.

6.3.7.3 Liver Function Tests

Total bilirubin (T. BILI), AST (SGOT), and ALT (SGPT) will be tested.

6.3.7.4 Pregnancy Test

For women with reproductive potential, urine β-HCG (urine test must have a sensitivity of ≤ 50 mIU) will be tested monthly during ART therapy.

6.3.7.5 Hepatitis Serologies

Hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, and GB virus C RNA PCR will be tested at baseline.
6.3.8 Immunologic Studies

6.3.8.1 CD4+/CD8+ Cell Count

CD4+/CD8+ cells counts (both absolute and subset percentage counts) will be performed throughout the study at the CAPRISA Laboratory. This laboratory participates in an external proficiency testing program (UKNEQAS/IQA). Testing will be conducted in “real time.”

Each time a CD4+/CD8+ cell count is obtained, the local laboratory must perform a WBC and differential from a sample obtained at the same time.

6.3.8.2 Immune Parameters for IRIS/PR

Additional assays will be performed for participants with signs or symptoms of suspected IRIS/PR from stored or real time samples (see section 9.3.1) as defined in Section 6.3.6.6. If a participant has at least one of the symptoms of IRIS/PR, 30 mL of blood for peripheral blood mononuclear cells (PBMCs), will be collected for immune parameters. The immune parameters that may be studied include: CD4+ and CD8+ cell count, CD4+ and CD8+ memory and naïve cells, and cytokine production such as IFN-γ, IL-10, IL-2, and IL-12. If PBMCs are available within 14 days of the suspected PR, additional blood collection is not required.

6.3.9 Virologic Studies

6.3.9.1 HIV-1 RNA

HIV-1 RNA assay results from screening must be available prior to study entry for study eligibility and will also be used for Phase I Day 0/Baseline. Samples for HIV-1 RNA obtained after study entry will be batch tested with results available within approximately 4 weeks after collection. HIV-1 RNA will be performed at the CAPRISA Laboratory using the Roche Amplicor Monitor assay (Version 1.5).

6.3.9.2 HIV Resistance Testing

Specimens will be batched and stored for retrospective (not in real time) testing by the Africa Centre Laboratory. Specimens will be tested from stored specimens in the event of indications of virologic, clinical, or immunologic failure.

6.3.10 Pharmacokinetic Studies

Dose/plasma concentration data will be obtained over time from participants in each arm of the study. Pharmacokinetic testing will be conducted on frozen
samples by the Division of Pharmacology at the University of Cape Town.

**Integrated Arm:**

**Phase I:** To obtain sufficient data points, EFV trough levels (samples taken immediately prior to dosing) and rifampicin peak levels (approximately 2.5 hours post dose) will be measured at the end of months 1, 2 and 3. This is designed to show the extent of the interaction over time.

**Phase II:** Additional trough EFV levels will be measured at the end of the first, second, and third month after TB treatment is completed (Phase II) to show how this interaction resolves over time.

**Sequential Arm:**

**Phase I:** Peak rifampicin levels will be analysed at the end of months 1, 2 and 3.

**Phase II:** After completion of TB treatment, when ART is initiated in Phase II, EFV trough levels will be assessed at the end of months 1, 2 and 3.

The choice of sampling times is determined by the long half-life of EFV, estimated to be between 52-76 hours, making the measurement of trough levels feasible. Rifampicin peak levels were selected based on the relatively short half-life of 2-5 hours of this agent. Previous studies have also shown the median $T_{\text{max}}$ after dosing to be 2.5 hours (Zent & Smith, 1995; Taylor & Smith, 1998; McIlleron et al., 2002). Levels taken 8-12 hours post dosing are low to undetectable in the average participant.

The exact time of blood draw and time of last efavirenz and rifampicin dose will be recorded on CRFs.

6.3.11 Stored Plasma/Serum/PBMCs

Participants who consent to have additional samples stored for future testing will have serum stored from 5 mL blood (plain tube), plasma stored from 5 mL of blood (EDTA tube), and PBMCs stored from 30 mL of blood (ACD tube) according to the schedule of events. Possible uses of plasma include additional viral load assays. Possible uses of serum include additional safety serology and evaluation of suspected IRIS on participants where indicated. The PBMCs will be used to test for IRIS/PR when suspected. The immune parameters that may be studied include: CD4+ and CD8+ cell count, CD4+ and CD8+ memory and naïve cells, and cytokine production such as IFN-$\gamma$, IL-10, IL-2, and IL-12. Other potential tests that may be performed on the stored specimens include new generation assays of immunity.
6.3.12 Other Laboratory Studies

6.3.12.1 Sputum Smear, Culture, and Sensitivities

Results of pre-study sputum smears will be accessed from the clinical records at the Prince Cyril Zulu CDC to confirm diagnosis of TB after informed consent is obtained. Smear and culture will be obtained at month 2 and month 6 after the initiation of TB therapy (TB Therapy Day 1) and at the completion of TB therapy. Additionally, sputum will be collected upon suspicion of TB treatment failure or TB recurrence.

6.3.12.2 M. Tuberculosis Susceptibility Testing

M. tuberculosis susceptibility testing will be performed on each positive culture to assess for drug resistance.

6.3.12.3 Restriction Fragment Length Polymorphism Analysis (RFLP) Testing

RFLP testing will be performed from stored bacterial isolates on all positive cultures in which recurrence is suspected and compared to the initial positive culture used to diagnose the TB initially. This technique utilizes the differential distribution of genetic markers in different strains of M. tuberculosis to identify specific strains of M. tuberculosis. These results will allow differentiation between re-infection and relapse.

6.3.13 Additional Evaluations

6.3.13.1 Quality of Life Assessment

This assessment will require an additional 30 minutes of time by the participant.

6.3.13.2 Sexual Behaviour Survey

This assessment will require an additional 30 minutes of time by the participant (Appendix XII).

7.0 TOXICITY MANAGEMENT

Study participants will be closely monitored for signs and symptoms of drug toxicity related to the ART and anti-TB medications. The current Division of AIDS Table for Grading Severity of Adult and Pediatric Adverse Events (hereafter referred to as “DAIDS toxicity table”) will be used as a guideline for managing toxicities related to study treatment. Symptoms and laboratory findings will be graded using the DAIDS toxicity table.

Toxicity management will rely on laboratory markers, clinical symptoms, and clinician
judgment since alternatives to study-provided medications may be limited, and baseline levels of certain laboratory parameters (e.g., hemoglobin) may be different than those on which the DAIDS toxicity table was based. Interpretation of laboratory markers will include consideration of locally applicable ranges.

This section provides guidelines and recommended strategies for management of toxicities related to study drugs only. In general, when one study drug is withheld for resolution of toxicity, all study drugs in the regimen should be withheld concurrently to avoid mono- or dual therapy. All ART drugs will be withheld if it becomes necessary to stop one or more of them, since resistance to remaining ART agents is more likely to develop during sub-optimal viral suppression.

Every attempt should be made to continue to follow participants who discontinue study treatment because of an adverse event until resolution of the adverse event can be documented.

All clinical study staff responsible for monitoring study participants for toxicity will be trained to recognize and respond to potential drug-related toxicities. All participants with Grade 3 and 4 toxicities will be evaluated by a physician and, where indicated, referred to the Infectious Disease Unit for evaluation and hospital admission.

A guiding principle for all clinical study staff will be to retain study participants on treatment regimens to the extent possible while dealing with toxicities. For toxicities where ART drugs are temporarily or permanently discontinued, liver, pancreatic, and renal function, as well as hematological parameters, may be repeated as needed until there is final resolution or stabilization of the toxicity.

7.1 ART Dose Reductions

In the event of toxicity, dose reductions in the table below are permitted as specified in the toxicity management sections:
Table 14: Toxicity Dose Reductions

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DAILY DOSE</th>
<th>REDUCED DAILY DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV</td>
<td>800 mg once daily for participants ≥ 50 kg taking rifampicin</td>
<td>600 mg once daily for participants ≥ 50 kg while taking rifampicin</td>
</tr>
<tr>
<td></td>
<td>600 mg once daily for participants &lt; 50 kg both taking and not taking rifampicin</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>600 mg once daily for participants ≥ 50 kg not taking rifampicin</td>
<td>None</td>
</tr>
<tr>
<td>3TC</td>
<td>300 mg once daily</td>
<td>None</td>
</tr>
<tr>
<td>ddl/ddI-EC</td>
<td>400 mg once daily for participants ≥ 60 kg</td>
<td>250 mg once daily for participants ≥ 60 kg</td>
</tr>
<tr>
<td>ddl/ddI-EC</td>
<td>250 mg- once daily for participants &lt; 60 kg</td>
<td>125 mg once daily for participants &lt; 60 kg</td>
</tr>
<tr>
<td>NVP</td>
<td>200 mg once daily x 14 days, then 200 mg twice daily</td>
<td>None</td>
</tr>
<tr>
<td>ABC</td>
<td>600 mg once daily</td>
<td>None</td>
</tr>
<tr>
<td>TDF</td>
<td>300 mg once daily</td>
<td>None</td>
</tr>
<tr>
<td>SQV + RTV</td>
<td>400/400 mg twice daily</td>
<td>None</td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td>400/100 mg twice daily</td>
<td>None</td>
</tr>
</tbody>
</table>

7.2 Grade 1 or 2 Adverse Event

Participants who develop a Grade 1 or 2 adverse event or toxicity may continue study drugs without alteration of the dosage except as stated in the following sections. Participants experiencing Grade 1 or 2 toxicities will be managed at the discretion of the study clinicians.

7.3 Grade 3 Adverse Event

If there is compelling evidence that the adverse event has NOT been caused by the study drug(s), dosing may continue. Except as stated in the following sections, participants who develop a Grade 3 adverse event or toxicity thought secondary to study medications or of unknown etiology should have their ART study drugs withheld, at the study clinician’s discretion. Study clinicians are encouraged to discuss toxicity management with the START Project Director and START PI to resolve complex toxicity management issues. The participant should be reevaluated weekly until the adverse event returns to ≤ Grade 2, at which time the study drugs may be reintroduced at the discretion of the study clinician or according to standard practice.

7.4 Grade 4 Adverse Event

Participants who develop a symptomatic Grade 4 adverse event or toxicity not specifically addressed below will have all study drug(s) withheld until resolution of the
adverse event to ≤ Grade 2. Under certain circumstances the study drug thought most likely to be related to the adverse event may be resumed at the discretion of the study clinician in discussion with the START Project Director and START PI. Alternative study-provided medications should be considered.

Participants with Grade 4 asymptomatic laboratory abnormalities, not specifically addressed below, may continue study drug therapy if the study clinician has compelling evidence that the toxicity is NOT related to the study drug(s).

7.5 Specific Management of Laboratory Abnormalities and Clinical Syndromes

7.5.1 Rash management for participants not receiving NVP:

7.5.1.1 Grade 1 or 2

Study medications should continue without interruption. Participants with a Grade 1 or 2 rash may be treated symptomatically with permitted antipyretic, antihistamine, and/or nonsteroidal anti-inflammatory medications, but should be monitored closely by the study clinician. Participants should be advised that the rash may worsen and to seek medical care or contact the site clinicians as soon as possible if there is any worsening of the rash or if systemic signs or symptoms develop. If rash does not resolve within 14 days of onset, the START Project Director and/or START PI should be contacted.

7.5.1.2 Grade 3

All study medications should be held for any Grade 3 rash and EFV permanently discontinued, unless the rash is determined to be unrelated to study medications. May restart study medications (except for EFV) if clinically indicated after rash has resolved to Grade ≤ 1 and discussion with the START Project Director and/or START PI. If rash was associated with EFV, either SQV + RTV (if receiving rifampicin) or LPV/r, but NOT NVP, should be used as a substitute for EFV. ABC is the second choice agent (if its use is feasible/not contraindicated) but should not be started until rash and any other associated symptoms have fully resolved.

7.5.1.3 Grade 4 Rash

Discontinue all study medications permanently. A new antiretroviral regimen may be substituted after rash has resolved to ≤ Grade 1 and discussion with the START Project Director and/or START PI. If rash was associated with EFV, either SQV + RTV (if receiving rifampicin) or LPV/r, but NOT NVP, should be used as a substitute for EFV. ABC is the second choice agent (if its use is feasible/not contraindicated) but should not be started until rash and any other associated symptoms
have fully resolved.

7.5.2 Rash Management for Participants on NVP

Any rash that occurs in the setting of NVP use should prompt an investigation for NNRTI HSR and hepatitis to include clinical evaluation for systemic symptoms and laboratory evaluation of liver transaminases. Clinical symptoms and supporting laboratory values consistent with NNRTI hypersensitivity include fever, rash, elevated transaminases, angioedema, peripheral eosinophilia, arthralgia, or myalgia.

Anyone with severe rash or signs and symptoms of HSR must seek medical attention immediately. They must not take more NVP until they are evaluated. NVP must be permanently discontinued for participants who experience:

- Rash of any grade with either of the following:
  - Constitutional symptoms consistent with HSR (e.g., fever, angioedema, myalgias/arthralgias; or
  - Organ dysfunction not thought to be due to an intercurrent illness;

  OR

- Blistering rash;

  OR

- Rash with oral mucosal lesions.

Participants experiencing HSR to NVP must not be re-challenged with NVP. Isolated rash in the setting of NVP therapy does not constitute a HSR.

All participants developing a rash at any time during NVP treatment (and particularly during the first 20 weeks) should have liver function tests performed promptly. If LFTs are elevated above study entry level, NVP must be permanently discontinued regardless of the grade of the rash or grade change in the LFTs.

Participants must also be evaluated for signs and symptoms relating to clinical hepatitis at that time. If participants have signs or symptoms of clinical hepatitis (which may include nausea and/or vomiting, anorexia, jaundice, acholic stools, hepatomegaly, hepatic tenderness, upper abdominal pain/discomfort, fever, fatigue, arthralgia) and rash, NVP should be permanently discontinued.
7.5.2.1 Grade 1 or 2

For participants on NVP who develop a Grade 1 or 2 rash but with no constitutional/HSR symptoms, no increase above baseline of transaminases, and no evidence of clinical hepatitis, NVP may be continued with very close follow-up, at the discretion of the study clinician. Participants should be closely monitored for worsening of the rash, signs and symptoms of HSR, clinical hepatitis, or isolated changes in LFTs. If any of these conditions develop on NVP, then participants should immediately and permanently discontinue it. If rash does not resolve within 14 days of onset, the START Project Director and/or START PI should be contacted.

Participants who experience mild rash during the first 2 weeks of NVP may increase the dose of NVP only after the rash fully resolves.

If NVP is interrupted for Grade 1 or 2 rash without constitutional/HSR symptoms, increase above baseline of the LFTs, or evidence of clinical hepatitis, NVP can be re-instituted after full resolution and discussion with the START Project Director and/or START PI. If NVP was interrupted for > 7 days, it must be re-instituted with a lead-in dose of 200 mg once daily for 2 weeks, then 200 mg twice daily.

7.5.2.2 Grade 3 or 4

For participants on NVP who develop a Grade 3 or 4 rash, NVP should be permanently discontinued. A new antiretroviral regimen may be substituted after rash has resolved to ≤ Grade 1 and discussion with the START Project Director and/or START PI. Either SQV + RTV (if receiving rifampicin) or LPV/r (if not receiving rifampicin), but NOT EFV, should be used as a substitute for NVP. ABC is the second choice agent (if its use is feasible/not contraindicated) but should not be started until rash and any other associated symptoms have fully resolved.

For participants who have mild to moderate urticaria, without constitutional symptoms, without increases above baseline of the LFTs, or without evidence of clinical hepatitis, NVP may be continued with close follow-up at the discretion of the study clinician. If participants have an urticarial rash and NVP is discontinued for whatever reason, NVP must not be restarted.

7.5.3 Abacavir HSR

In clinical studies, approximately 5% of participants receiving an abacavir-containing product developed a HSR as described in section 1.1.7.6, which in rare cases has proved fatal.
7.5.3.1 Management of HSR

Participants developing signs or symptoms of hypersensitivity MUST contact the study clinician immediately for advice.

If HSR is diagnosed, the abacavir-containing study drug MUST be discontinued immediately. The participant should be asked to return all unused supplies of the abacavir-containing study drug for disposal to prevent an accidental re-challenge.

An abacavir-containing medication (Ziagen®, Trizivir®, or the abacavir/lamivudine fixed dose combination) MUST NEVER be administered following HSR, as more severe symptoms will recur within hours and may include life-threatening hypotension and death.

To avoid a delay in diagnosis and minimize the risk of a life-threatening HSR, the abacavir-containing study drug should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (respiratory diseases, flu-like illness, gastroenteritis, or reactions to other medications).

Symptomatic support for abacavir hypersensitivity may be indicated. This should include, for example, administration of intravenous fluids to participants who develop hypotension. Antihistamines or corticosteroids have been used in cases of abacavir hypersensitivity, however, there are no clinical data demonstrating the benefit of these in the management of the reaction.

Laboratory and other investigations which may be useful in the evaluation and treatment of abacavir hypersensitivity include, but may not be limited to, measurement of ALT, AST, creatine phosphokinase, serum creatinine and white blood cell differential count and chest x-ray, if respiratory symptoms are present.

7.5.3.2 Special Considerations following an Interruption of Abacavir Therapy

If therapy with abacavir has been discontinued and restarting therapy is under consideration, the reason for discontinuation should be evaluated to ensure that the participant did not have symptoms of a hypersensitivity reaction. If HSR cannot be ruled out, no study medication containing abacavir (Ziagen®, Trizivir®, or the abacavir/lamivudine fixed dose combination) should be restarted.

There have been infrequent reports of HSR following reintroduction of an abacavir-containing medication where the interruption was preceded by a single key symptom of hypersensitivity (rash, fever, malaise/fatigue, GI symptoms, or a respiratory symptom). If a decision
is made to restart any abacavir-containing study medication in these participants, this should be done only under direct medical supervision by the study clinician.

On very rare occasions HSR has been reported in participants who have re-started therapy, and who had no preceding symptoms of HSR. If a decision is made to re-start an abacavir-containing study medication, this must be done only if medical care can be accessed readily by the participant.

### 7.5.3.3 Essential Participant information

Study clinicians must ensure that participants are fully informed regarding the following information on the HSR. Each participant should be reminded to read the patient information leaflet included in the pack. This leaflet is provided by the pharmacist the first time abacavir is dispensed to the participant (Appendix XI).

Participants must be made aware of the possibility of an HSR to abacavir that may result in a life-threatening reaction or death.

Participants developing signs or symptoms possibly linked with an HSR MUST CONTACT their study clinician IMMEDIATELY.

Participants who are hypersensitive to abacavir should be reminded that they must never take any abacavir-containing medicine (Ziagen®, Trizivir®, or the abacavir/lamivudine fixed dose combination) again.

In order to avoid restarting the abacavir-containing study medication, participants who have experienced an HSR should be asked to return the remaining tablets or oral solution to the pharmacy.

Participants who have stopped an abacavir-containing medication for any reason, and particularly due to possible adverse reactions or illness, must be advised to contact the study clinician before restarting.

Each participant should be reminded to read the Package Leaflet included in the pack.

Participants should be reminded of the importance of removing the Alert Card included in the pack and keeping it with them at all times.

### 7.5.3.4 Reporting HSR

All cases of potential abacavir hypersensitivity should be reported as expedited adverse events (EAE) (see Section 10.2).
7.5.3.5 Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, or Erythema Multiforme

Serious skin reactions such as Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, or Erythema Multiforme have been reported very rarely in participants taking abacavir-containing medications. These participants generally do not have the cluster of additional symptoms (e.g., GI and respiratory) that characterize the abacavir HSR, but they do have features typical of these serious skin reactions.

If a serious skin reaction develops, the abacavir-containing study medication should be discontinued, and the participant should not be re-challenged with any abacavir-containing medication (Ziagen®, Trizivir®, or the abacavir/lamivudine fixed dose combination).

As many products other than abacavir also cause these serious skin reactions, all other medications that the participant is receiving should also be reviewed and discontinued as appropriate.

7.5.3.6 Management of Rash that is not Accompanied by Systemic Symptoms

Participants receiving abacavir who develop rash of any grade should be evaluated for the possibility of an HSR or a serious skin reaction such as Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, or Erythema Multiforme and managed appropriately as outlined above. Rash may be caused by therapies in any of the major ART classes or by other therapies commonly used as concurrent medications, such as cotrimoxazole. As it is not possible to provide an exhaustive list of products that may cause rash in this protocol, please consult the product information leaflets for other products for information relating to rash.

The rash and any associated symptoms should be reported as adverse events (see Section 10.0), and appropriate toxicity ratings should be used to grade the events.

If the etiology of the rash can be definitively diagnosed as being due to a specific medical event or a concomitant medicinal product, routine management should be performed and documentation of the diagnosis provided.
7.5.4 Lipase Elevations and Pancreatitis

Pancreatitis will be reported as a clinical finding (i.e., symptomatic pancreatitis). The enzyme abnormality that will be used for making diagnoses is the lipase level. Lipase will be obtained for participants if development of clinical symptoms suggests pancreatitis. A triglyceride level should be drawn with the lipase. If a baseline measurement is needed, it will be performed from stored entry samples.

Lipase will be obtained for participants who develop clinical symptoms suggestive of pancreatitis (including abdominal pain, tenderness, nausea, and vomiting). If the lipase is within the normal range, evaluate for other causes of symptoms. If none are found and symptoms persist, lipase should be repeated within 2 weeks.

For abnormal lipase values in the presence of symptoms suggestive of pancreatitis:

- Grade 1: Search for other causes of symptoms. If none are found and symptoms persist, repeat lipase within 2 weeks. The decision to hold study medication until repeat is performed will be at the discretion of the study clinician. IF REPEAT IS ELEVATED, THEN PARTICIPANT SHOULD SWITCH DDI/DDI-EC TO TDF. ABC is the second choice substitute if its use is feasible/not contraindicated.

- ≥ Grade 2: Follow participant and repeat lipase as soon as possible. If lipase is persistently elevated and accompanied by symptoms, then participant should be considered to have clinical pancreatitis. CT scan of the abdomen, if available, may also be helpful in determining whether clinical pancreatitis is present. Exclude other possible diagnoses (e.g., renal insufficiency causing false elevations in lipase). If none is found, diagnose as clinical pancreatitis.

For a diagnosis of pancreatitis (clinical), all study medications should be held.

After complete resolution of the episode, in a setting in which other concomitant drugs might have reasonably contributed to the development of pancreatitis, re-challenge with some of the study medications may be performed in consultation with the START Project Director and/or START PI. If the study regimen included ddl/ddI-EC, substitute with tenofovir as first choice. ABC is the second choice substitute if its use is feasible/not contraindicated.

Upon re-challenge, lipase determinations should be performed monthly. Any elevation of lipase of ≥ Grade 2 or any recurrence of symptoms during this period will lead to a re-evaluation and permanent discontinuation of the suspected study drugs(s).
7.5.5 AST and ALT Elevation

Nearly all the antiretrovirals as well as antituberculosis therapy can cause alterations in LFTs. Further, concomitant illness may also alter these laboratory parameters. Therefore, changes in AST or ALT should be evaluated within the clinical context of the abnormalities.

7.5.5.1 Asymptomatic Elevations of AST or ALT

**Grade 3 AST or ALT Elevation**

For asymptomatic elevation in AST or ALT (i.e., 5-10 x ULN – Grade 3), study medications other than NNRTIs may be continued at the discretion of the study clinician. Careful assessments should be done to rule out the use of alcohol, non-study medication-related drug toxicity, the lactic acidosis syndrome, and viral hepatitis as the cause of the transaminase elevation. If the AST/ALT elevation is considered most likely to be due to concomitant illness or medication, standard management, including discontinuation of the likely causative agent, should be undertaken.

For asymptomatic elevation (i.e., 5-10 x ULN – Grade 3) believed to be possibly secondary to any study medications, all study medications should be withheld. NVP or EFV should be discontinued unless NVP or EFV can be excluded as the cause. After transaminase levels are ≤ Grade 2, therapy may be reintroduced with the substitution of NVP or EFV. First choice for this substitution is SQV + RTV (if receiving rifampicin) or LPV/r (if not receiving rifampicin). ABC is the second choice substitute if its use is feasible/not contraindicated.

**Grade 4 AST or ALT Elevation**

For asymptomatic or symptomatic elevation of AST or ALT (i.e., >10 x ULN – Grade 4), all medications should be held until levels are ≤ Grade 2. Study medications may be restarted if the laboratory abnormalities were thought secondary to a concomitant illness. HOWEVER, if the participant was receiving an NNRTI (EFV or NVP), either of these medications should be considered the most likely cause of the elevations and discontinued. First choice for substitution of NVP or EFV is SQV + RTV (if receiving rifampicin) or LPV/r (if not receiving rifampicin). ABC is the second choice for substitution if its use is feasible/not contraindicated.
If elevations > 10 x ULN (Grade 4) recur in the absence of an NNRTI drug, all current ART should be held. Alternative ART and TB regimens may be considered and re-introduced after levels are ≤ Grade 2 at the discretion of the study clinician after discussion with the START Project Director and/or START PI.

7.5.6 Clinical (Symptomatic) Hepatitis with NVP or EFV

Participants taking EFV or NVP must be carefully monitored for the development of signs and symptoms of hepatitis, which include fatigue, malaise, anorexia, nausea, vomiting, acholic stools, bilirubinuria (dark colored urine), jaundice, liver tenderness, upper abdominal pain/discomfort, or hepatomegaly and fever with or without initially abnormal serum transaminase levels. Anyone with these signs and symptoms must seek medical attention immediately from the study clinician and have LFTs performed and instructed to not take more NVP or EFV until they are evaluated. NVP or EFV must be discontinued immediately if the study clinician determines that the participant has clinical hepatitis with or without LFT abnormality. Unless NVP or EFV can be excluded as the cause, they must be permanently discontinued.

For participants on rifampicin, SQV + RTV is the first choice substitute for EFV or NVP. LPV/r is the first choice substitute for EFV or NVP for participants not taking rifampicin. ABC is the second choice substitute if its use is feasible/not contraindicated and symptoms of hepatitis have fully resolved.

Hepatitis B and Hepatitis C:

Hepatitis B and hepatitis C seropositivity are not inclusion or exclusion criteria or criteria for enrollment into specific study arms.

At study entry, hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), and hepatitis C core antibody (HCV) testing will be obtained. Results will be made available to study clinicians.

The hepatitis B results will be used to facilitate management of hepatitis B co-infected participants in the event 3TC or TDF need to be discontinued, which could potentially worsen hepatitis B disease.

The hepatitis B and C results will be used when the study clinician is considering use of NVP.
7.5.7 CNS Symptoms with EFV

Participants should be informed that EFV may cause dizziness, impaired concentration, and/or drowsiness and instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery. Participants should be informed that these symptoms usually resolve with continued use of EFV.

Dosage reduction to 600 mg is allowed for those participants receiving EFV 800 mg on a weight-adjusted basis while receiving rifampicin.

If side effects are bothersome, regardless of EFV dose, consideration of EFV dosing before bedtime is at the discretion of the study clinician.

Those receiving EFV should be alerted to the potential for additive CNS effects when EFV is used concomitantly with alcohol or psychoactive drugs.

There have been reports of delusions and inappropriate behavior, predominantly in participants with a history of mental illness or substance abuse. Severe acute depression has also been infrequently reported in both EFV-treated and control-treated participants. In the event a participant experiences these or other treatment-limiting CNS adverse events attributable to EFV, EFV should be discontinued. NVP or a protease inhibitor may be substituted at the discretion of the study clinician based on the considerations in Section 5.3.3.2.

7.5.8 Peripheral Neuropathy

Participants should be monitored for the development of peripheral neuropathy, which is usually characterized by numbness, tingling, or pain in the feet or hands.

7.5.8.1 Grade 1

Study medications may be continued at the present dosage. Symptomatic treatment may be provided at the discretion of the study clinician.

7.5.8.2 Grade 2

Those experiencing Grade 2 symptoms will be managed per study clinician discretion, which may include temporary cessation, dose reduction of ddI/ddI-EC, and/or symptomatic management.

7.5.8.3 Grade 3 or 4

ddI/ddI-EC will be permanently discontinued for peripheral neuropathy ≥ Grade 3. TDF is the first line substitution. ABC is the second choice substitute if its use is feasible/not contraindicated.
Symptomatic treatment of peripheral neuropathy is at the discretion of the study clinician.

7.5.9 Nausea (With or Without Vomiting)

Although common, nausea following initiation of therapy with antiretroviral medications usually subsides or resolves during the first few weeks of treatment.

Steps in the management of nausea include taking the medication with food (with the exception of ddI) and administration of antiemetics. An enteric coated ddI formulation (ddI-EC) with improved GI tolerance may be available after study initiation and may be substituted for the buffered tablet formulation. In the event of intractable nausea despite medication, substitution of ddI/ddI-EC is permitted. The first choice for this substitution is TDF. ABC is the second choice if its use is feasible/not contraindicated. If EFV is thought to be the cause of intractable nausea or vomiting, NVP or a protease inhibitor may be substituted at the discretion of the study clinician based on the considerations in Section 5.3.3.2.

7.5.10 Diarrhea

Diarrhea is a common side effect of infection and medication toxicity. If no infectious cause of diarrhea is found, and it is apparently related to new medication, symptomatic management with antidiarrheal agents is appropriate.

If ddI is suspected as the cause of severe or intractable diarrhea, an enteric-coated ddI formulation (ddI-EC) with improved GI tolerance may be available after study initiation and may be substituted for the buffered tablet formulation. In the event of intractable diarrhea despite medication, substitution of ddI/ddI-EC is permitted. The first choice for this substitution is TDF. ABC is the second choice if its use is feasible/not contraindicated. If EFV is suspected as the cause of severe diarrhea, NVP or a protease inhibitor may be substituted at the discretion of the study clinician based on the considerations in Section 5.3.3.2. If SQV + RTV or LPV/r is suspected, alternatives will be at the discretion of the study clinician.

7.5.11 Lactic Acidosis

The relevance of asymptomatic lactic acid elevations is unclear, and lactates are not part of the routine safety evaluations for this study. Routine lactate monitoring is not currently recommended. No baseline lactic acid levels will be obtained.

A sometimes-fatal syndrome of lactic acidosis, often associated with evidence of hepatic steatosis, is a recognized but rare complication of NRTI therapy. This syndrome is felt to be secondary to mitochondrial toxicity induced by the inhibitory effect of NRTIs on DNA polymerase gamma, a key enzyme needed for mitochondrial DNA synthesis. Current knowledge regarding this syndrome is incomplete. Obesity, gender, and prolonged NRTI exposure may be risk factors.
Symptoms of lactic acidosis frequently involve nonspecific symptoms such as fatigue, weakness, and fever, but in the majority of cases also involve symptoms suggestive of hepatic dysfunction such as nausea, vomiting, abdominal or epigastric discomfort, abdominal distension, hepatomegaly, and new onset elevated liver enzymes. A high index of suspicion may be required to diagnose this condition. Alternatively, it is possible that unwarranted concern may be raised by over interpretation of lactic acid levels. NRTI toxicity is only one cause of lactic acidosis. Lactic acid elevations are also seen in the context of diabetes mellitus, uremia, liver disease, infections, malignancies, alkaloses, and drug and toxin ingestion of substances such as ethanol, methanol, ethylene glycol, and salicylates.

The following case definition of symptomatic lactic acidosis will be used in START:

**Symptomatic Hyperlactatemia**

New, otherwise unexplained, and persistent (≥ 2 weeks) occurrence of one or more of the following symptoms:

- Nausea and vomiting.
- Abdominal pain or gastric discomfort.
- Abdominal distention.
- Increased LFTs.
- Unexplained fatigue.
- Dyspnea.

**AND**

Lactate level (if available) > 2 x ULN confirmed by repeat lactate level analysis. In the absence of lactate levels, serum bicarbonate levels and anion gap should be assessed. The presence of depressed bicarbonate levels or an increased anion gap would suggest the possibility of lactic acidosis

**NOTE:** All lactates > 2 x ULN should be repeated as soon as possible, generally within 1 week.

If the second result confirms hyperlactatemia (> 2 x ULN), participants should immediately discontinue their current study regimen. Substitution of ddl/ddI-EC with TDF should be considered once symptoms resolve and lactate levels return to < 2 x ULN. ABC is the second choice substitute if its use is feasible/not contraindicated and symptoms have fully resolved.
7.5.12 Hypertriglyceridemia/Hyperlipidemia

If elevated triglyceride levels are from a non-fasting blood draw, repeat the draw after a 12-hour fast; only levels done in a fasting state should be graded for severity. Participants with asymptomatic ≥ Grade 3 triglyceride elevations may continue study medications at the discretion of the study clinician. Appropriate dietary modification and antihyperlipidemic therapy should be considered. The preferred first line treatment is gemfibrozil 600 mg q 12 hours, 30 minutes prior to the morning and evening meals. It is suggested that fasting triglycerides be rechecked at 2-week intervals. For persistent uncontrolled hypertriglyceridemia, the addition of niacin and/or an HMG-coA reductase inhibitor may be considered. These medications should be introduced with caution. Niacin has the propensity to worsen the control of blood sugar in participants with diabetes mellitus or a history of hyperglycemia. Many HMG-coA reductase inhibitors have substantial interactions with PIs and the use of pravastatin or other medication within this class unlikely to cause substantial interaction is advised.

7.5.13 Hyperglycemia

Participants with ≥ Grade 3 hyperglycemia may continue study medications at the discretion of the study clinician and be managed with oral hypoglycemic medications or insulin. If SQV + RTV or LPV/r are suspected as causes, alternatives will be at the discretion of the study clinician.

7.5.14 Hypophosphatemia (for participants on TDF)

7.5.14.1 Grade 1 and 2

For Grade 1 and 2 hypophosphatemia, phosphate should be repeated as soon as possible (within 2 weeks is optimal), and TDF may be continued without other signs of renal tubular acidosis/tubular dysfunction at the discretion of the study clinician. If there are signs of renal tubular acidosis/tubular dysfunction, phosphate should be repeated as soon as possible, and if it is confirmed or progressing, TDF may be held at the discretion of the study clinician.

7.5.14.2 Grade 3 and 4

For Grade 3 and 4 hypophosphatemia, the phosphate should be repeated preferably within 1 week and supplemental phosphate should be given. Other causes of low phosphate should be investigated. For Grade 4 hypophosphatemia, hold antiretrovirals. Re-test phosphate levels weekly until ≤ Grade 2, then restart the regimen. Phosphate supplementation may be continued at the discretion of the study clinician. If ≥ Grade 3 phosphate levels persist despite phosphate supplementation, permanently discontinue TDF. ABC may be substituted for TDF if its use is feasible/not contraindicated.
With other persistent or worsening signs of renal tubular acidosis/tubular dysfunction (including decreased serum bicarbonate, hyperchloremia, hypokalemia, glycosuria, or proteinuria) discontinuation of TDF should be considered after discussion with the START Project Director and/or START PI.

7.5.15 Renal Insufficiency

Dose modifications are recommended for TDF, ddI/ddI-EC, and 3TC in participants with reduced creatinine clearance (see Table 7).

Baseline serum creatinine will be calculated as the mean of screening and entry values. If at any time serum creatinine is increased > 1.5-fold above baseline, the serum creatinine should be repeated as soon as possible (preferably within one week). Participants with confirmed serum creatinine increases > 1.5-fold above baseline should undergo an evaluation for potential causes of decreased renal function. Participants with confirmed increased serum creatinine > 1.5-fold above baseline should have serum creatinine monitored more frequently (e.g., monthly) at the discretion of the study clinician, until serum creatinine either stabilizes or decreases to ≤ 1.5-fold above baseline.

*Calculate a creatinine clearance from the serum creatinine concentration in mg/dL using the method of Cockcroft and Gault:

- For men: \((140 – \text{age in years}) \times (\text{body weight in kg}) \div (\text{serum creatinine in umol/L} \times 0.82)\).
  - For women, multiply the result by 0.85

All calculated creatinine clearances should be recorded in the CRF.

Participants at risk for, or with a history of, renal dysfunction and participants receiving concomitant nephrotoxic agents should be carefully monitored for changes in serum creatinine and phosphate.

If the calculated creatinine clearance (by the Cockcroft-Gault method) is < 50 mL/min*, this calculation should be repeated within one week. If the calculated creatinine clearance remains < 50 mL/min, TDF must be held until an underlying etiology for the renal insufficiency is determined. If no alternative etiology is determined, the renal insufficiency improves with holding TDF, or in the presence of hypophosphatemia or any other signs of renal tubular acidosis/tubular dysfunction, permanently stop TDF. ABC may be substituted for TDF if its use is feasible/not contraindicated.

If another etiology is determined and after renal function has stabilized, TDF may be re-instituted with careful monitoring after discussion with the START Project Director and/or START PI, but with appropriate dose reduction for the level of renal function.
In the event of treatment-limiting toxicity, the following substitutions are allowed at any time in either Phase I or Phase II:

**Table 15: Potential Side Effects of First-Line ART Medications and Recommended Alternatives**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Suspect Drug</th>
<th>Recommended switch during TB Treatment</th>
<th>Recommended switch post TB Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neurologic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness, inability to concentrate</td>
<td>EFV</td>
<td>NVP* or SQV + RTV</td>
<td>NVP* or LPV/r</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>ddl or ddl-EC</td>
<td>TDF (first choice) ABC (second choice)</td>
<td>TDF (first choice) ABC (second choice)</td>
</tr>
<tr>
<td><strong>Dermatologic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>EFV</td>
<td>NVP* for Grade 1-2 rash or SQV + RTV (first choice) ABC (second choice)</td>
<td>NVP* for Grade 1-2 rash or LPV/r (first choice) ABC (second choice)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SQV + RTV or ABC for Grade 3-4 rash</td>
<td>LPV/r or ABC for Grade 3-4 rash</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia, Nausea/Vomiting</td>
<td>ddl or ddl-EC</td>
<td>TDF (first choice) ABC (second choice)</td>
<td>TDF (first choice) ABC (second choice)</td>
</tr>
<tr>
<td></td>
<td>EFV</td>
<td>NVP* or SQV + RTV</td>
<td>NVP* or LPV/r</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>ddl or ddl-EC</td>
<td>TDF (first choice) ABC (second choice)</td>
<td>TDF (first choice) ABC (second choice)</td>
</tr>
<tr>
<td></td>
<td>EFV</td>
<td>NVP* or SQV + RTV</td>
<td>NVP* or LPV/r</td>
</tr>
<tr>
<td>Hepatitis (Grade 3/4)</td>
<td>EFV</td>
<td>SQV + RTV (first choice) ABC (second choice)</td>
<td>LPV/r (first choice) ABC (second choice)</td>
</tr>
<tr>
<td></td>
<td>ddl/ddl-EC</td>
<td>TDF</td>
<td>TDF</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>ddl or ddl-EC</td>
<td>TDF (first choice) ABC (second choice)</td>
<td>TDF (first choice) ABC (second choice)</td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactic Acidosis</td>
<td>ddl or ddl-EC</td>
<td>TDF (first choice) ABC (second choice)</td>
<td>TDF (first choice) ABC (second choice)</td>
</tr>
</tbody>
</table>

* NVP should not be used in females with CD4+ cell counts > 250 cells/µL, in males with CD4+ cell counts > 400 cells/µL, in participants co-infected with HIV and HBV and/or HCV, in participants with underlying liver disease of any severity, and in participants with elevated hepatic transaminases at the time of NVP initiation. If a participant falls within the criteria described above and there are no other options for ART, NVP may be allowed with permission from the START Project Director and/or START PI after a risk/benefit analysis on whether to use NVP given the participant’s entire clinical
presentation. The use of protease inhibitors instead of NVP will be allowed in participants without the criteria listed above at the study clinician’s discretion since there is a continuum of risk. For all participants starting NVP, LFTs will be measured at the time NVP is initiated weekly for the first 6 weeks, at week 8, and then monthly until week 20 of NVP treatment, and every 3 months thereafter. In addition to these timeframes, LFTs will be measured when any symptoms of rash or hepatitis develop.

8.0 CRITERIA FOR DISCONTINUATION

8.1 Criteria for Treatment Discontinuation

Reasons for treatment discontinuation include:

- Drug-related toxicity requiring discontinuation of ART (see Section 7.0 - Toxicity Management).
- Requirement for prohibited concomitant medications resulting in the discontinuation of all ART (see Section 5.5).
- Participant is failing ART and there are no other alternative drugs available.
- Request of the primary care provider if s/he thinks the study treatment is no longer in the best interest of the participant.
- Clinical reasons believed life-threatening by the study clinician, even if not addressed in the toxicity management of the protocol.

If study drugs are permanently discontinued, and the participant has not withdrawn informed consent, the participant will continue to be followed according to the schedule of evaluations in Section 6.0.

8.2 Criteria for Study Discontinuation

Reasons for study discontinuation include:

- Request by the participant to withdraw.
- Participant judged by the study clinician to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results.
- Request of the primary care provider if s/he thinks the study is no longer in the best interest of the participant.
- At the discretion of the National Institute of Allergy and Infectious Diseases (NIAID), Medicines Control Council (MCC), or IRB/IEC.
9.0 CLINICAL MANAGEMENT ISSUES

9.1 Recommendations for Management in Case of “HIV-Related Clinical Deterioration” in the Sequential Arm

9.1.1 Participants assigned to the sequential treatment arm may initiate ART prior to their otherwise-scheduled initiation date, if indicated, based on deterioration of their TB/HIV disease state. The decision will be based on the clinical judgment of the study clinician and will include an assessment of the changes in the participant’s functional capability. ART must be considered prior to end of TB treatment for participants presenting with signs of HIV-related clinical deterioration including:

- Definitive or presumptive diagnosis of AIDS-defining condition (Appendix II).
- Hospital admission.

Participants admitted to hospital for an AIDS-related condition should be assessed during the admission by the study team in consultation with the hospital medical staff. If the Karnofsky Performance Score fails to return to the baseline ± 10 value within one month, commencement on ART should be considered.

- In the event a participant develops symptoms, signs, or conditions which, in the opinion of the study clinician, indicate clinical progression of HIV disease requiring initiation of ARV therapy, the case will be referred to a clinical meeting for a decision on whether ART should be initiated. Examples indicating progression of HIV disease are:
  - Unexplained weight loss, > 10% of body weight
  - Unexplained chronic diarrhea, >1 month
  - Unexplained prolonged fever (intermittent or constant), > 1 month

9.1.2 For participants who meet the criteria in Section 9.1.1 above, the decision to commence ART will be made at a clinical meeting convened by the START Project Director or the START PI, with the exception of participants presenting with an AIDS-defining condition. In such cases, the study clinician may commence ART immediately. The participant’s study clinician will present the clinical case and the reasons for deciding to commence or withhold ART at the clinical meeting. The decision and the reasons will be documented by the study clinician in the case notes which are part of the source documentation.
9.2 Procedures in the Event of Pregnancy and Breastfeeding

A supplemental consent form will be provided to participants who become pregnant and/or who are breastfeeding.

No changes in ART will be made to women who are breastfeeding. Women who are breastfeeding will be managed as all other study participants while on ART. Women who are breastfeeding will be referred to an available mother-to-child transmission (MTCT) program for counseling on feeding choices and related support.

Female participants who become pregnant while on study will be referred to the KEH clinics for prenatal and newborn care.

For women who become pregnant while receiving ART treatment, EFV will be discontinued immediately and may be replaced with NVP 200 mg once daily for 14 days and then 200 mg twice daily or with protease inhibitors for the full course of pregnancy. It will be at the discretion of the study clinician to determine whether a woman should remain on NVP following pregnancy or return to EFV.

Nevirapine should not be used in females with CD4+ cell counts > 250 cells/µL, in participants co-infected with HIV and HBV and/or HCV, in participants with underlying liver disease of any severity, and in participants with elevated hepatic transaminases at the time of NVP initiation.

If a participant falls within the criteria for restriction of NVP use described above and there are no other options for ART, NVP may be allowed with permission from the START Project Director and/or START PI after a risk/benefit analysis on whether to use NVP given the participant’s entire clinical presentation. The use of protease inhibitors instead of NVP will be allowed in participants without the criteria listed above at the study clinician’s discretion since there is a continuum of risk.

For all participants starting NVP, LFTs will be measured at the time NVP is initiated weekly for the first 6 weeks, at week 8, and then monthly until week 20 of NVP treatment, and every 3 months thereafter. In addition to these timeframes, LFTs will be measured when any symptoms of rash or hepatitis develop.

After the initial 20-week period, clinical and laboratory monitoring should continue every 3 months thereafter. Pregnant women will receive folic acid supplement (5 mg once daily).

The use of the combination of didanosine and stavudine is prohibited due to the risk of severe lactic acidosis in pregnant women.

Women who become pregnant while receiving ART and TB therapy concomitantly may require a modification or temporary discontinuation of their ART regimen but must not remain on EFV. In these cases, management of the ART regimen is left to the clinical judgment of the study clinician.
9.3 Diagnostic Criteria and Recommendations for Management of IRIS/PR

In this study, we will consider an IRIS/PR when any of the following clinical pictures emerge after the initiation of ART and/or anti-TB therapy in the absence of an identifiable source. IRIS/PR related to other opportunistic infections may also occur after initiation of ART. A general operational definition of IRIS has been developed for this study that may be applied to IRIS/PR episodes associated with any opportunistic infection.

<table>
<thead>
<tr>
<th>Criteria for TB-related Suspected IRIS/PR</th>
<th>Criteria for IRIS/PR related to Other Co-Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>• new persistent fever (temperature $\geq 38.5^{\circ}C$) which develops after the initiation of ART and/or anti-TB therapy OR</td>
<td>• symptoms that are consistent with an infectious/inflammatory condition and temporally related to initiation of ART AND</td>
</tr>
<tr>
<td>• marked worsening or emergence of intrathoracic lymphadenopathy, or pulmonary infiltrates OR</td>
<td>• evidence of an increase in CD4+ cell count and/or a decrease in the HIV-1 RNA viral load in response to starting ART AND</td>
</tr>
<tr>
<td>• worsening or emergence of cervical adenopathy OR</td>
<td>• symptoms that cannot be explained by a newly acquired infection, the expected clinical course of a previously recognized infectious agent, or the side effects of ART or anti-TB therapy itself</td>
</tr>
<tr>
<td>• worsening of other tuberculous lesions or manifestations, such as cutaneous, peritoneal, or CNS inflammatory pathology OR</td>
<td></td>
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<tr>
<td>• new onset seizure OR</td>
<td></td>
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<tr>
<td>• worsening respiratory symptoms OR</td>
<td></td>
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<tr>
<td>• new or worsening neurological symptoms OR</td>
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<tr>
<td>• new or worsening abdominal pain OR</td>
<td></td>
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<tr>
<td>• new onset ascites OR</td>
<td></td>
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<tr>
<td>• new onset hepatosplenomegaly</td>
<td></td>
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</tbody>
</table>
IRIS/PR is a diagnosis of exclusion: The study clinician will need to rule out other possibilities such as drug fever, treatment failure, TB recurrence, drug resistance, and other opportunistic infections or other complications while considering a suspected IRIS/PR. IRIS/PR should be considered once all appropriate evaluations including multiple blood cultures, urine and sputa testing, and other procedures, when clinically indicated, fail to identify an infectious cause of these findings.

9.3.1 Assessment and Management of IRIS/PR

In this study, participants are specifically evaluated during Phase I Weeks 1, 2, and 3, and Months 1, 2, and 3 in both arms and Phase II Weeks 1, 2, and 3 and Months 1, 2, and 3 in the sequential arm for symptoms of suspected IRIS/PR. The IRIS/PR screening assessment includes temperature, assessment for lymphadenopathy, respiratory rate, and lung auscultation.

If any of these assessments represent new or worsening findings, a chest x-ray, blood cultures, urine culture, and additional diagnostic work-up is indicated. Additionally, a laboratory evaluation for immune parameters should be obtained. The laboratory sample involves 30 mL of blood for PBMCs obtained in real time or a stored sample obtained within 14 days of the suspected IRIS/PR. If PBMCs are available within 14 days of the suspected IRIS/PR, additional blood collection is not required.

The immune parameters that may be studied include: CD4+ and CD8+ cell count, CD4+ and CD8+ memory and naïve cells, and cytokine production such as IFN-γ, IL-10, IL-2, and IL-12.

Medical management of a suspected IRIS/PR includes the following options:

- Continue ART and TB treatment.
- Initiate anti-inflammatory agents, initially non-steroidals or corticosteroids at the discretion of the study clinician.
- Provide symptomatic therapy.

Study staff will complete a Paradoxical Reaction Reporting Form within 14 days of the completion of the IRIS/PR workup for the suspected IRIS/PR. All suspected IRIS/PR will be evaluated retrospectively by the Paradoxical Reaction Committee (PRC). The PRC consists of members of the protocol team who are not responsible for clinical evaluations of study participants. The members of the PRC will evaluate each case of suspected IRIS/PR independently. The core members of the PRC will consist of Salim S. Abdool Karim, MD, Ph.D; Gerald Friedland, MD; Gavin Churchyard, MBChB, Ph.D; and Wafaa El Sadr, MD, MPH. Additional members of the PRC will be appointed as needed. The PRC will be responsible for retrospectively evaluating each case of suspected IRIS/PR.
independently and categorizing the suspected IRIS/PR as “probable,” “possible,” or “unlikely.”

The PRC will evaluate suspected cases of IRIS/PR every 6 months. The evaluation by the PRC will occur after all of the results of the tests/diagnostics are completed and the study participant has completed at least 6 months of ART. The PRC will be blinded to participants’ randomized treatment assignments to ensure unbiased assessment.

9.4 Management of TB Treatment Failure and Recurrence

Cases of TB treatment failure and recurrence identified during the study will be referred to the Prince Cyril Zulu CDC clinic for additional needs and/or changes in TB treatment.

9.5 Participant Tracking and Follow Up

An electronic tracking system will be established on enrollment to provide study staff with a means for monitoring and tracking participants who have missed scheduled DOT and/or study visits. A follow-up team (two full-time fieldworkers) will be responsible for ensuring follow-up, conducting home visits when participants do not arrive for their scheduled appointments, and for assisting those who require transport for follow-up.

Daily DOT and study visit schedules will be generated on a weekly basis. At the beginning of each day a list of participants who are scheduled for a study visit will be generated. At the end of each day the study nurse will collate the DOT record cards and cross check them with the list of participants who were scheduled to have DOT. In the event of a participant missing a DOT visit the procedure described below will be followed:

Tracking and Follow Up Plan

Day 1 after missing appointment
  o Attempt telephone contact with the participant

Day 2 after missing appointment
  o Contact persons listed on the locator form

Day 3 after missing appointment
  o Send a field worker to the site identified based on updated locator information

Additional measures that will be in place to assist the study staff with retention and follow-up include:
• A combination of a year planner in site co-ordinator's office, staff meetings in preparation for visits, computer generated reminder list on site and at the data management center, and internal quality assurance (QA)/quality control (QC) reports will be used for tracking purposes.

• Attempts will be made to re-contact and re-schedule missed appointments within 24 hours (preferably on the same day).

• Study staff will pay close attention to the allowable visit window and prioritize retention efforts for participants nearing the end of the window, particularly for quarterly visits at which primary study endpoints are determined. Daily caseloads and work assignments will be organized based on these priorities.

• For those participants who demonstrate a pattern of late or missed appointments, study staff will schedule follow-up visits scheduled at the beginning of the allowable visit window (i.e., up to 14 days before the actual target date) allowing maximum time for re-contact and rescheduling if needed.

• Study staff will emphasise the value of the participant’s involvement in the study during the study informed consent process and subsequently at follow-up visits.

10.0 EXPEDITED ADVERSE EVENT REPORTING

10.1 Adverse Events

The ART drugs proposed for this study are US FDA-approved agents and are not investigational. They have been studied extensively and have well-established safety profiles. Regardless, the definition of an adverse event for this study will be the same as for investigational agents, i.e., an adverse event is defined as any untoward medical occurrence in a clinical research participant administered a product and which does not necessarily have a causal relationship with the product. The current Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events will be used for grading toxicities.

10.2 Expedited Adverse Event (EAE) Reporting to DAIDS

The expedited adverse event (EAE) reporting requirements and definitions for START and the methods for expedited reporting of adverse events (AEs) to the DAIDS Regulatory Compliance Center (RCC) Safety Office are defined in “The Manual for Expedited Reporting of Adverse Events to DAIDS” (DAIDS EAE Manual), dated May 6, 2004 (Appendix IX).

AEs reported on an expedited basis must be documented on the DAIDS Expedited Adverse Event Reporting Form (EAE Form) available in the START MOP and the RCC website at http://rcc.tech-res-intl.com/.
10.3 EAE Reporting Requirements for this Study

10.3.1 EAE Reporting Level

This study uses the standard level of expedited AE reporting as defined in the DAIDS EAE Manual.

10.3.2 Study Agents for Expedited Reporting to DAIDS

The study agents that must be considered in determining relations of AEs requiring expedited reporting to DAIDS are: efavirenz (EFV), didanosine (ddI/ddI-EC), lamivudine (3TC), nevirapine (NVP), tenofovir (TDF), abacavir (ABC), saquinavir (hgc) (SQV-hgc), ritonavir (RTV), and lopinavir/ritonavir (LPV/r).

10.3.3 Grading Severity of Adverse Events

The current Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events must be used for determining and reporting the severity of AEs and is available at the RCC Web site http://rcc.tech-res-intl.com/.

10.3.4 EAE Reporting Periods

AEs must be reported on an expedited basis at the standard level during the protocol-defined EAE Reporting Period, which is: during the entire study duration (from enrollment until the study participant completes or discontinues the study).

After the end of the protocol-defined EAE Reporting Period stated above, the site must report serious, unexpected, clinical suspected adverse drug reactions if the study site staff becomes aware of the even on a passive basis, i.e., from publicly available information.

10.3.5 Additional Adverse Event Reporting Requirements

In addition to submitting EAE information to the DAIDS Safety Office through the RCC, the study clinician is required to submit AE information as required by local regulatory agencies or other local authorities.

11.0 DATA COLLECTION AND MONITORING

11.1 Records to be Kept

CRFs will be provided for each participant. Participants must not be identified by name on any CRFs. Participants will be identified by the patient identification number (PID) provided by the CAPRISA Data Management Center upon randomization.
11.2 **Roles of Data Management**

Instructions concerning the recording of study data on CRFs will be provided by the CAPRISA core dealing with data management and will be included in the START MOP. Completed CRFs must be checked by the designated on-site QA person and upon approval, must be faxed to the CAPRISA DataFax system at the University of KwaZulu-Natal. The data must be verified in the DataFax system, QC reports produced, and approved data then added to the study database according to CAPRISA data management SOPs.

It is the responsibility of the CAPRISA data management core to assure the quality of computerized data for the study. A data QA plan will be specifically defined as part of the CAPRISA data management plan and SOPs.

All CRFs to be used as study source documents will be identified prior to study initiation. Study staff will be trained in source documentation requirements in accordance with the DAIDS SOP for Source Documentation and in proper forms completion techniques.

Database files will be password-protected, and access to the files will be limited to authorized study staff members only. Quality control and validation checks will be performed and data cleaning steps will be undertaken prior to finalizing the study database for analysis. Analyses will be conducted by study statisticians.

11.3 **Data Storage**

Original and DataFax electronic copies of study CRFs and related documents will be stored securely both during and after study completion. During the study, the original completed forms for each participant will be kept on-site at the Prince Cyril Zulu CDC and will be transferred to the KEH Infectious Disease Unit as part of the KEH entry visit. At both sites, the forms will be stored in locked cupboards in a secure room with restricted access. Upon completion of the study, the close-out site monitoring visit and finalization of the database for analysis, the original forms will be bound and kept at an off-campus separate site for long-term storage.

CRF data on the DataFax server will be accessible to the study staff and the statistician in a read-only mode. The data management team will have write-access, with access being restricted by passwords and validation levels. Study staff that has access to the data on the computer systems will be trained in how to access the system and the importance of system security. All information will be backed-up at regular intervals, and backups will be stored in file cabinets or secure areas with limited access.

11.4 **QA/QC of Data**

A QC check of the study forms will be conducted before the forms are datafaxed. The QC procedures will specify the following types of checks:

- There are no illegible handwritten items, spelling errors, etc.
• Responses are clearly within designated spaces.
• All fields are completed with participant data or reason for no data is noted in or near the field.
• The participant's PID is recorded on all pages of the forms.
The designated on-site QA person will initial each page to confirm that the form has been checked.

The CAPRISA laboratory manager will also be responsible for checking that all the laboratories involved in the study are complying with QA procedures. The CAPRISA pharmacist will check that all drug related documentation meets Good Clinical Practice (GCP) requirements for drug accountability.

QA/QC of data will be undertaken according to the SOPs.

11.5 Clinical Site Monitoring and Record Availability

Site monitors under contract to the National Institute of Allergy and Infectious Diseases (NIAID) will visit participating clinical research sites to review the individual participant records, including consent forms, CRFs, supporting data, laboratory specimen records, and medical records (physicians’ progress notes, nurses’ notes, individuals’ hospital charts), to ensure protection of study participants, compliance with the protocol, and accuracy and completeness of records. The monitors will also inspect sites’ regulatory files to ensure that regulatory requirements are being followed and sites’ pharmacies to review product storage and management.

The investigator will make study documents (e.g., consent forms, drug distribution forms, CRFs) and pertinent hospital or clinic records readily available for inspection by the local IEC/IRB, the MCC, the site monitors, the NIAID, or the Office for Human Research Protections (OHRP) for confirmation of the study data.

12.0 STATISTICAL CONSIDERATIONS

12.1 Primary Endpoint

A definitive or presumptive diagnosis of AIDS-defining illness (Stage IV of the Modified WHO Staging System for HIV Infection and Disease as shown in Appendix II) or death during the first 18 months after enrollment in the study.

12.2 Secondary Endpoints

12.2.1 Safety, tolerability and drug interactions defined by:

- Safety - Grades 3 and 4 adverse events.
- Tolerability - defined as an ART or TB treatment interruption for more than 2 weeks due to drug-related adverse effects or treatment discontinuation due to drug-related adverse events.
- Drug Interaction - Rifampicin and efavirenz blood levels measured at the times specified in the Schedule of Events.

12.2.2 Percentage of prescribed anti-TB and ART doses taken, as reported on a 7-day adherence questionnaire administered throughout the study as specified in the Schedule of Events, pill counts, and DOT records.

12.2.3 Biological markers of disease progression (e.g., viral load, CD4+ cell counts) measured at baseline and over the duration of the study.

12.2.4 IRIS/PR and related Immune Markers during the first 6 months follow-up:
- IRIS/PR determined clinically as described in Section 9.3.
- Immune markers of IRIS/PR: Total CD4+ and CD8+ T-cells, CD4+ and CD8+ memory and naïve cells and cytokine production such as IFN-γ, IL-10, IL-2, and IL-12.

12.2.5 ART or TB drug resistance (ART drug resistance will be assessed by detecting the emergence of drug specific resistance mutations).

12.2.6 Patterns of sexual risk behaviors and Quality of Life measures at baseline and Month 6 of each study phase.

12.2.7 TB outcomes, including cure, successful completion, failure, recurrence, and other non-specified TB outcomes as defined under Study Definitions.

12.2.8 Total provider’s cost, defined as the sum of the inpatient and outpatient costs, after 3 months and at the end of the first 12-month follow-up period. Cost effectiveness analysis will be based on 1) number of participants recruited, and 2) cases of AIDS (Stage IV) or deaths avoided.

12.2.9 A definitive or presumptive diagnosis of AIDS-illness (Stage IV of the Modified WHO Staging System for HIV Infection and Disease as shown in Appendix II) or death after enrollment in the study.

12.3 Primary Objective

12.3.1 Sample Size Projection

The primary objective of this study is to assess the effectiveness of integrated TB and HIV care provision, including ART administered through the TB DOT program enhanced with ASP vs. sequential treatment of TB and HIV during the first 18 months after enrollment in the study. This entails comparing the
progression-to-AIDS-defining illnesses/mortality distributions between the two arms.

This is a superiority study and it is assumed that the integrated arm will be superior to the sequential arm. Thus, the following assumptions are made:

1) \( \frac{1}{2} \)-year cumulative Progression-to-AIDS/Mortality (sequential arm) of 10%
2) 1-year cumulative Progression-to-AIDS/Mortality (sequential arm) of 15%
3) 1½-year cumulative Progression-to-AIDS/Mortality (sequential arm) of 20%
4) \( \frac{1}{2} \)-year cumulative Progression-to-AIDS/Mortality (integrated arm) of 5%
5) 1-year cumulative Progression-to-AIDS/Mortality (integrated arm) of 8%
6) 1½-year cumulative Progression-to-AIDS/Mortality (integrated arm) of 12%
7) Accrual duration of 2 years and total study follow-up for the primary endpoint of 3½ years
8) Two-sided type I error level = 5%, 80% power
9) 7.5% loss to follow-up over 18 months
10) Three annual interim reviews and one final analysis

Under these assumptions a total of 592 participants (296 per arm) will be required to determine superiority of the integrated arm over the sequential arm in terms of the time to progression-to-AIDS/mortality distributions. These calculations allow for non-constant risks of failure (Halpern and Brown, 1993).

12.3.2 Sample Size Re-estimation

The \( \frac{1}{2} \)-year and 1-year cumulative probability of progression-to-AIDS/mortality on both arms will be estimated from the accruing data at one year, using the Kaplan-Meier (1959) product limit method. These estimates will then determine whether the sample size needs further adjustment.

12.3.3 Statistical Interim Analyses

Interim efficacy analyses will be conducted annually starting one year after the study has opened. Comparisons of the primary endpoint between the two arms will be done using the logrank test or as described in section 12.6.1. Interim stopping will be based on the O’Brien-Fleming stopping boundary taking into account the information available at the time of the interim analysis. If the sequential logrank summary statistic crosses the stopping boundary, then consideration may be given to stopping the inferior arm.

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1 The estimates of the \( \frac{1}{2} \), 1 and 1½-year cumulative Progression-to-AIDS/Mortality are uncertain and several different choices were explored. From these choices we finally decided on assumptions 1) to 6) above.
12.4 Secondary Objective 2.2.6 (QOL): Detectable Effect Sizes

The minimum effect sizes attainable between the two arms were calculated with 80% power, type I error of 5%, and 296 participants in each arm. The method of Rochon (1991) which provides a 2-group repeated measures calculation taking into consideration both main effects and time by group interactions; the main effect is defined by the distance between parallel group profiles and the interaction is defined by the relative slopes of two lines. Table 16 reflects the minimum detectable main effect and interaction effect sizes (standardized units). These calculations, in addition, assume 4 time points (Phase I baseline, Phase I month 6, Phase II baseline, and Phase II month 6) and an autoregressive model for the growth time series with auto-correlations of 0.1, 0.2, and 0.3.

Table 16: Detectable main and interaction effect sizes (standardized units) with 296 participants per arm (80% power, alpha=0.05), auto-correlation=0.0, 0.1, 0.2, 0.3 and four equidistant time-intervals.

<table>
<thead>
<tr>
<th>Auto-Correlation</th>
<th>0</th>
<th>0.1</th>
<th>0.2</th>
<th>0.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detectable main effect size</td>
<td>0.116</td>
<td>0.125</td>
<td>0.134</td>
<td>0.144</td>
</tr>
<tr>
<td>Detectable interaction effect size</td>
<td>0.386</td>
<td>0.385</td>
<td>0.384</td>
<td>0.380</td>
</tr>
</tbody>
</table>

By the labels of Cohen (1977), the main effect and interaction effect (which Cohen halves) sizes are small to medium in magnitude.

12.5 Randomization and Stratification

Eligible participants will be randomized in one of the two treatment arms (sequential or integrated) in equal proportions (1:1) using stratified permuted block randomization (e.g. blocks of variable sizes 6 or 8). The stratification factor is CD4+ count with 2 levels, 50-200 cells/µL vs. > 200 cells/µL. Permuted blocking limits the ability of study staff to predict sequential assignments. A list of random allocations of participants will be generated in advance. The following displays a hypothetical example of such a list for “50-200.” An analogous list for the other stratum pertains.
Stratum = CD4+ count: 50-200 cells/µL  
A = sequential arm  B = integrated arm

<table>
<thead>
<tr>
<th>Envelope</th>
<th>Participant ID</th>
<th>Randomization Date (MM/DD/YY)</th>
<th>Randomization Time</th>
<th>Allocation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>B</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>A</td>
</tr>
</tbody>
</table>

From such a randomization sheet, a series of sealed opaque randomization envelopes for each CD4+ stratum will be provided to study staff at the Prince Cyril Zulu CDC prior to study start-up. The sealed envelope will contain the assigned treatment group, namely, integrated or sequential for a given CD4+ stratum. The envelopes will be stored in a safe at the Prince Cyril Zulu CDC and opened in sequential order at eligible participants’ enrollment visits by study staff members authorized to perform randomization procedures by the START PI. After opening the envelopes, staff members will record the date and time of opening the envelopes, as well as their names, on the envelopes. This information will then be noted on the randomization sheets. Opened envelopes and their contents will be stored with other participant study records for purposes of study monitoring and QC/QA review. Assigned envelope numbers will also be recorded on the study screening and enrollment log.

12.6 Analysis Plans

All analyses will be based on the ITT principle and all statistical tests will be two-sided.

12.6.1 Primary Objective

The incidence of AIDS-defining illness or death between the two arms will be evaluated. Time to progression or death (Survival curves) will be constructed for each arm using the Kaplan-Meier product limit method and compared using the log rank test. Additional (adjusted) analyses will be used to compare the time to event distributions between arms by means of Cox’s proportional hazards model, which adjusts for the effect of the covariates predictive of progression. These covariates, in addition to treatment arm, would include age, gender, body mass index and CD4+ cell count at baseline. These adjusted comparisons entail score tests that are more powerful than the tests above because of covariate adjustments. The proportional hazards assumption will be checked by plotting the Schoenfeld residuals for significant covariates and interactions. If the proportional hazards assumption is violated, several approaches may be considered. One approach would be to use a stratified proportional hazards model in which the proportional hazards assumption holds within each stratum. Another approach introduces appropriate time-dependent covariates in place of those covariates with hazard
functions non-proportional to the baseline hazard. An appropriate Cox model with time-dependent covariates is then fitted. Results from the proportional hazards regression will include the hazard ratios and their corresponding 95% confidence intervals.

12.6.2 Secondary objectives

12.6.2.1 Secondary objective 2.2.1

**Adverse events:** The incidence of any severe adverse events (Grade 3 and 4) between arms will be compared using the Fisher’s exact test for 2x2 contingency tables for each type of adverse event. In addition, severe drug adverse events will be described by type of event and the highest grade (severe or life-threatening) for that type of event for each participant. Two-way contingency tables of severity grade by arm for each type of adverse event will be constructed. Where appropriate, the adverse event severity grades will be compared between the two arms using the Fisher-Freeman-Halton test, a generalization of the Fisher’s exact test for “RxC” contingency tables.

**Tolerability:** The endpoint is the frequency of treatment interruptions of > 2 weeks for both ART and TB treatment. The frequency of treatment interruptions due to drug-related adverse effects in the integrated and sequential treatment arms or treatment discontinuation due to drug related adverse events will be compared using categorical data analysis, perhaps assuming the frequencies occur according to a Poisson distribution.

**Drug interactions:** Rifampicin blood levels will be measured monthly over 3 months on both arms during Phase I. EFV blood levels will be measured monthly over 3 months in Phase I on the integrated arm and similarly on the sequential arm during Phase II (Schedule of Events).

The mean rifampicin profiles between the integrated and sequential treatment arms will be compared longitudinally using a repeated measures analysis of variance (ANOVA) (Phase I). This analysis will be carried out using mixed effects models (Diggle, Liang and Zeger, 1994).

The mean EFV blood levels during Phases I and II on the integrated arm will be compared using a repeated measures ANOVA with two repeated factors, the first repeated factor being the months and the second the phases of the study, that is pre and post anti-TB treatment.

12.6.2.2 Secondary objective 2.2.2

The adherence questionnaire will be administered throughout the study
to evaluate participant adherence to therapy. Adherence is defined as a binary outcome: Participants who consume at least 90% of their medication are adherent; otherwise, non-adherent. Adherence questionnaires will be administered for both anti-TB and ART drug adherence. Since adherence is defined as a binary outcome we shall use logistic regression (repeated measures) via generalized estimating equations (GEE) to compare adherence between the two arms. GEE is a useful technique for dealing with repeated categorical data and has been used extensively in situations where an identical measurement (adherence) is repeatedly taken on the same participant. Repeated measurements will induce a correlation structure that can be utilized in the analysis. GEE procedures (Zeger and Liang, 1986) allow for general patterns of correlation over time. Pill count proportions will also be analyzed in this framework.

12.6.2.3 Secondary objective 2.2.3

Longitudinal data for biological markers (HIV-1 RNA, CD4+ cell counts) will be collected. For these continuous endpoints a repeated measures ANOVA will be used to compare the mean biological marker values between arms. The analysis will use mixed effects models (Diggle, Liang and Zeger, 1994). For example, the SAS PROC MIXED procedure may be used for this purpose. In repeated measures ANOVA (mixed models) the main effect tests for average differences between the treatment arms over time, while an interaction term evaluates the extent to which the two arms differ over time. Treatment arm will be a fixed effect (other covariates are possible), while participants will be the random effects. Appropriate transformations (Box-Cox) will be applied to these continuous endpoints to achieve approximately normality. It is well-known that the log of HIV-1 RNA is approximately normally distributed.

12.6.2.4 Secondary objective 2.2.4

Immune reconstitution illness will be clinically determined by participant presentation as defined in Section 9.3. The endpoint will be binary and if repeatedly measured, then a similar longitudinal analysis as in Section 12.6.2.2 will be conducted. If a cross-sectional analysis is called for then Fisher’s exact test will be used to compare this endpoint between the two arms. Additionally, immune markers will be measured repeatedly, treated as continuous variables, and evaluated as risk factors for PR using regression models suitable for repeated measures analysis.

12.6.2.5 Secondary objective 2.2.5

The time to development of drug resistance distribution for each arm
will be estimated using the Kaplan-Meier product limit method. The time to development of drug resistance distributions between the two arms will be compared using logrank tests. Additional (adjusted) analyses will be used to compare the time to event distributions between arms by means of Cox’s proportional hazards model, similar to the analysis described in Section 12.6.1. If appropriate, we would simply compare the proportions of participants with drug resistance using Fisher’s exact tests which may be less powerful than a time to event analysis especially for lengthy time durations.

12.6.2.6 Secondary objective 2.2.6

The Sexual Behaviour Survey (Appendix XII) will be administered at baseline and at the 6 month visit of each study phase. Outcome variables include condom use (binary), type of sex (categorical), drinking alcohol (binary) and so on. For the binary outcome variable we shall use logistic regression (repeated measures) via GEE to compare these sexual/risk behaviors between the two arms. For the number of partners over time we shall also use GEE assuming a Poisson distributed outcome. Other repeated categorical outcomes will be compared between the two arms using the polytomous GEE approach of Lipsitz et al. (1994).

The Functional Assessment of HIV Infection (FAHI) quality of life (QOL) instrument (See Appendix VII) will be used and QOL data will be collected repeatedly (baseline and at the 6 month visit of each study phase, and at months 12 and 18 of Phase II). In order to explore the changes in total FAHI scores, a repeated measure ANOVA model will be used. However, it is important to stress that attempting to collect longitudinal data at so many time points may result in the occurrence of missing data. Missing data arising in longitudinal studies can seriously affect the analysis.

There are several approaches to the analysis of longitudinal QOL data (Fairclough, 1998; DL Fairclough, personal communication, 1998) which depend primarily on the research hypothesis of interest. The most common views the study as a repeated measures design. The analyses will be done using mixed effects models (Diggle, Liang and Zeger, 1994) as in the SAS Proc Mixed procedure. A linear contrast statement in Proc Mixed can be used to compare changes in QOL from baseline to each of the subsequent follow-up times.

The types of analyses will be affected by the type and amount of missing data. We stress that every effort should be made to ensure that the amount of missing data is kept at a minimum since their presence complicate the statistical analyses.
In general, multivariate analyses require complete data vectors or that the proportion of participants with missing assessments should be small (less than 5%) and missing completely at random (MCAR). That is, “missingness” is completely unrelated to the participant’s QOL measurement and covariates. The MCAR assumption is strong and, if violated, the estimates of treatment effect could be biased. In missing at random (MAR), a weaker assumption than MCAR, “missingness” depends on covariates and the non-missing outcomes (QOL) but is independent of the value of the missing outcomes (QOL). In both MAR and MCAR the missing data are ignored and one can simply perform the standard repeated measures analysis as outlined above. Fortunately, mixed effects models are sufficiently robust in the presence of up to 20% missing outcomes, even if the outcomes are MAR (Fairclough, 1998). The reasons for any missing data will be investigated as the study proceeds, which should enable us to check whether the MAR assumption is tenable.

In the worst case scenario, the missing outcomes are not missing at random (NMAR). In NMAR, “missingness” depends on the value of the missing observation. For example, the missing observations arise when participants do not return for follow-up, due to death or severity of illness. The remaining participants may appear healthier (also known as informative censoring) because the sample is shrinking down to an even smaller complement of healthier participants. We therefore propose to use imputation schemes if missing data are NMAR. The motivation for imputation is that balanced statistical data methods such as multivariate analysis of variance (MANOVA) can be used to analyze the imputed data sets. Multiple imputation (Rubin, 1987 and 1996; Rubin and Schenker, 1991) can deal with both NMAR and MAR by imputing non-randomly missing values using a statistical model for the outcome given the missing value indicator.

12.6.2.7 Secondary objective 2.2.7

Time-to-TB recurrence distributions will be constructed using the Kaplan-Meier product limit method. TB recurrence distributions between the two arms will be compared using logrank tests. If appropriate, adjusted analyses will be used to compare the relapse distributions between arms by means of Cox’s proportional hazards model (see Section 12.6.1). Covariates may include age, gender, body mass index (BMI), etc.

TB therapy completion rates will be compared at 2 and 6 months between the two arms using a GEE longitudinal approach (see Section 12.6.2.2).

Time-to-TB treatment failure distributions will be constructed using
the Kaplan-Meier product limit methods. Time-to-TB treatment failure distributions between the two arms will be compared using logrank tests.

The proportions of participants deemed cured of TB, the proportion of participants with other non-specified TB outcomes, and the proportion of participants deemed to have successfully completed TB treatment between the two arms will be compared using Fisher’s exact test.

12.6.2.8 Secondary Objective 2.2.8

Cost data for the economic analysis will be collected using an activity based approach. For each arm of the study the cost of the following activities will be estimated: recruitment of clients, routine out-patient visits for treatment, other out-patient visits, per day cost of drug related in-patient visits and per day cost of non-drug related in-patient visits. Economic cost data will be collected as opposed to financial data only. Economic costs include resources used but not paid for, such as donations, volunteer time, use of existing resources. Financial costs are a subset of economic costs including only items that are paid for as a direct result of implementation.

For each activity cost data will be collected from a provider and client perspective. Provider costs will be estimated based on interviews with staff involved in the delivery of services, observations of facilities used to provide services, facility records and secondary data sources. Data collection for provider costs will be conducted at three months and repeated after the first year to examine the resources implications of learning, as the efficiency of providing services may improve over time.

Client costs will be based on interviews with participants in regard to costs incurred, including expenses, and work time lost. Work time will be valued at a constant cost regardless of individual characteristics. Five percent of participants from each arm will be interviewed in regard to the cost of routine and other out-patient care. Cost data from all participants requiring in-patient care will be collected until data from twenty participants from each of the four groups (two arms by drug related and non-drug related) has been collected.

The total cost of each arm, over the study period, will be estimated by combining the cost per activity (out-patient and in-patient visits) with recorded activity levels which will be generated from the study database.

The estimation of the total provider cost of each arm can be summarized as follows:
Total provider cost of arm = In-patient costs + Out-patient costs

1. In-patient costs = drug-related in-patient costs + non-drug-related in-patient costs
   a. Drug-related in-patient costs = No. of day in-patient care* avg. cost per day for drug-related
   b. Non-drug-related in-patient costs = No. of day in-patient care* avg. cost per day for non-drug-related

2. Out-patient costs = regular treatment cost + other out-patient costs
   a. Regular treatment costs = No. of treatment visits*avg. cost per visit for regular treatment
   b. Other out-patient costs = No. of visits*avg. cost per visit for other out-patient care

For each of the average costs the financial and economic only elements will be identified allowing for the presentation of results in terms of financial costs only and total economic costs.

Cost effectiveness analysis and incremental cost effectiveness analysis will be conducted, in hindsight, using two outcome measures: number of participants recruited and AIDS (Stage IV) or deaths avoided. The number of participants recruited will be combined with cost data to estimate the cost per participant recruited, this will be conducted twice, once after 3 months and a second time at the end of the first year. Each time the average number of participants from the preceding 3 months of recruitment will be combined, in the analysis, with the cost per month of recruitment efforts. The analysis is repeated to investigate improvements in efficiency associated with learning.

Data will be captured in a spreadsheet based cost model. Sensitivity analysis will be conducted to determine the implications of variations in key variables.
12.7 Periodic Summary Adverse Experience Safety Reviews

12.7.1 Monitoring Committee Reviews

Interim monitoring reports will be generated by the study statisticians and data managers for review by the designated NIAID Data Safety Monitoring Board (DSMB). An interim administrative report will be generated after the first 30 participants are enrolled. This administrative report will be reviewed by DAIDS and the DSMB for the sole purpose of ensuring that data are being captured adequately and that the data management system is functioning according to the standards. Detailed descriptions of all report contents will be described in the overall Study Monitoring Plan. A full interim review will be performed at least annually to allow the DSMB to review the overall study progress for feasibility, safety issues, losses to follow-up, and evidence of efficacy.

The NIAID DSMB could provide a recommendation to alter the design or stop the trial if unacceptable safety results emerge.

12.7.2 Additional Periodic Safety Monitoring Reviews

Reports with cumulative adverse experiences not sorted by treatment arm will be sent to study teams for review at quarterly for the first year and then bi-annual intervals. If appropriate, these reports may include adverse experiences sorted by treatment arms for review by the designated DAIDS medical officer (and possibly a member of the DSMB depending on results of discussion with the committee.). The detailed contents of the reports will be described in the Study Monitoring Plan.

13.0 HUMAN SUBJECT PROTECTION

13.1 Informed Consent

Written informed consent will be obtained from each study participant prior to screening and prior to enrollment. A separate informed consent will be obtained for participants who become pregnant while on study. Written informed consent will also be obtained for long-term specimen storage and possible future testing. However, consent for specimen storage is not a pre-condition for study participation. Participants will be provided with a copy of their informed consent forms if they wish to receive them.

Study informed consent forms will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. The informed consent forms will also be translated into Zulu and the accuracy of the translation will be verified through independent back-translation.

As there is currently very limited access to ART through the public sector in South Africa, extra efforts will be taken to minimize coerced participation. The study consent process will include an assessment of each potential participant’s understanding of the
study and the risks and benefits of study participation, which are essential for an informed decision. Participants who are not able to demonstrate adequate understanding of key concepts will not be enrolled in the study.

13.1.1 Justification for Exclusion of Minors

It is difficult to obtain parental consent for adolescents in the South African setting. Enrollment of adolescents requires both the consent of the parent/guardian and independent individual assent by the minor. Parental knowledge of HIV status of the minor may place the adolescent at risk with his/her parent(s) due to these issues of disclosure.

In addition, anecdotal evidence suggests that many adolescents do not reside with their parents either due to parental death or because many parents work and reside in different localities, leaving their children in the care of others. These guardians are not legally recognized or appointed as legal guardians. In these instances, seeking parental consent for study enrollment or determining whom, if anyone, is the legal guardian is practically difficult. Ethics committees in South Africa have been reluctant to approve the enrollment of adolescents in research studies without seeking parental consent.

13.2 Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Informed Consent

This protocol and the informed consent documents (Appendix I) and any subsequent modifications will be reviewed and approved by the IRB or IEC responsible for oversight of the study.

13.3 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the IRB/IEC, the NIAID, the OHRP, MCC, or the sponsor’s designee.

13.4 Study Discontinuation

This study may be discontinued at any time by the IRB/IEC, the NIAID, or other government agencies as part of their duties to ensure that research participants are protected.

14.0 PUBLICATION OF RESEARCH FINDINGS

Presentation and publication of the results of this study will be governed by CAPRISA publication policy (available at www.CAPRISA.org). All presentations, abstracts, and
manuscript will be made available to the CAPRISA Publications Sub-Committee for review prior to submission.

15.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood-borne pathogens and TB can occur through contact with contaminated needles, blood, blood products, and sputum, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the National Institutes of Health.

All infectious specimens will be transported using packaging mandated in the Federal Code of Regulations, 42 CFR Part 72. Please also refer to individual carrier guidelines, e.g., FedEx, Airborne, for specific instructions.
16.0 REFERENCES


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APPENDIX IB

17.0 APPENDICES

APPENDIX IA
SAMPLE SCREENING INFORMED CONSENT FORM

Title of the Study:
The START (Starting Tuberculosis and Anti-Retroviral Therapy) Trial: A Randomized Controlled Trial to Assess the Effect of Integrated Tuberculosis and HIV Care on the Incidence of AIDS-Defining Conditions or Mortality in participants Co-Infected with Tuberculosis and HIV.

Short Title: START: Starting Anti-Retroviral Therapy

Sponsored by: The National Institute of Allergy and Infectious Diseases
Division of AIDS (DAIDS)
6700B Rockledge Drive
Bethesda, Maryland 20852
United States

Principal Investigator: Professor Salim Abdool Karim, MBChB, PhD

INTRODUCTION

You are being asked to take part in a series of lab tests and medical evaluations to find out if you meet the requirements for joining the START research study. This is called screening. The START study will see whether it is safe and effective to give TB and HIV medicines to people who have active TB and HIV at the same time. The START study will compare two groups of people. One group will start HIV medicines almost at the same time as TB medicines are started. The other group will start HIV medicines after they have completed their TB medicines.

YOUR PARTICIPATION IN THE START STUDY SCREENING PROCEDURES IS VOLUNTARY

This consent form gives you information about the START screening. The research staff will talk with you about this information. Ask questions and discuss any concerns you have with the research staff. If you agree to take part in the screening process, you will be asked to sign your name or make your mark on this form. You will be given a copy to keep.
Before you learn more about the screening process, it is important that you know the following:

- Your participation in the START screening process is entirely voluntary.
- You may decide not to have the screening procedures done, or to withdraw from the screening process at any time, without losing the benefits of your routine medical care.
- If you decide not to undergo the screening process for the START study, you can still join another research study later, if one is available and you are eligible.
- You are only being asked to take part in the screening procedures at this time. Even if you complete all the necessary tests, you do not have to join the START study.

WHY ARE THESE SCREENING PROCEDURES BEING DONE?

The purpose of the screening procedures is to identify people who meet the requirements for the START study.

WHAT DO I HAVE TO DO IF I AM HAVING SCREENING PROCEDURES?

You will need to come into the clinic for physical examinations, interviews, and laboratory tests. There will be at least two to three visits. Visits will take about 1 hour.

HIV Confirmatory Testing

You have been diagnosed as having TB and HIV. You were tested for HIV by having 2 Rapid Tests for HIV. The Rapid Tests for HIV that you had are accurate. There is only a very small chance that both of these tests will be negative if you have HIV. As part of the HIV testing to see if you can enter the START Study, a third test is also done to confirm your HIV infection.

This confirmatory HIV test checks your blood for viral load (the amount of HIV virus in your blood). The test cannot tell you the date when you were infected, or by whom you were infected. A 5 mL blood sample will be sent to a laboratory for viral load testing. In the very unlikely event that this test is negative, you will not be eligible to enter the study. This test will confirm the results of your earlier HIV tests.

The results of your HIV confirmatory test will be available in approximately 5 working days from the day you had your blood drawn.

Pre-Test and Post-Test Counseling

You were given all the required information about HIV testing during the counseling you recently received before and after the Rapid Tests for HIV. If you agree to have the confirmatory HIV test, you will receive similar counseling before and after receiving the confirmatory HIV test. The study staff will discuss the test with you, what it means to be HIV positive, and the reason that this test is needed.
CD4+ Cell Count Testing

You will have about 5 mL of blood drawn for CD4+ T cell counts (immune cells that help fight infection such as HIV). You will be given the results of these tests. Some doctors recommend that people with lower CD4+ cell counts start antiretroviral drugs.

Routine Laboratory Tests

You will have about 20 mL of blood drawn for routine laboratory tests. You will be given the results of these tests. If you are a woman and able to become pregnant, you will be asked to provide some urine for a pregnancy test. You will get the result of the pregnancy test as soon as it is available. If you are pregnant, you may not enter the START study. You will be told where you can go for further care.

Your blood that is leftover after all required screening testing is done will be discarded.

Medical Evaluations

You will be asked questions about your medical history and any medicines that you have taken and will have a physical examination.

Contact Information

You will be asked to provide contact information so that we can locate you in case you miss a visit or if there are ever problems with your lab test results.

TB Treatment and HIV Testing Records

In addition, the results of your initial sputum tests, HIV rapid tests, and chest X-rays done at the time you were diagnosed with TB will be reviewed by the research staff. If you join the START study, these results will be used in the study.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 592 people will take part in the START research study.

RISKS AND/OR DISCOMFORTS

You may feel some discomfort, pain or lightheadedness during the blood sample collection. Some people get a bruise or swelling where the needle is put in your arm to draw blood. In rare cases, the blood drawing procedure can cause fainting or infection.
Many people do not understand the facts about infection with the AIDS virus. Being HIV positive can be a very stressful experience, especially in the beginning. You may feel worried or anxious while waiting for your test results. In addition, you may be treated badly by friends and family if you are HIV positive and your HIV status becomes known to others.

ARE THERE BENEFITS TO HAVING THE SCREENING PROCEDURES DONE?

You may have no direct benefit from agreeing to be screened for the START study. Knowing the results of the HIV test will allow you to seek treatment for HIV infection. Taking part in screening for this study may help identify health problems you would not have known about otherwise.

WHAT OTHER CHOICES DO I HAVE BESIDES SCREENING FOR THIS STUDY?

If you choose not to be screened for the START study, you will still be able to receive standard TB drug treatment and care as part of the Tuberculosis Control Programme. You may also choose to be screened for other studies. The clinic staff will talk to you about these and other choices available to you and will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

Your medical records, personal information, and the results of your HIV tests and other medical and laboratory evaluations will be kept strictly confidential within the extent of South African law. Only your doctor and/or nurse will know the results of your tests. Your records will be identified by a study code. Any publication of this study will not use your name or identify you personally.

Every effort will be made to protect your confidentiality but we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Your records may also be reviewed by regulatory authorities, such as the Medicines Control Council (MCC), the Ethics Committees, the U.S. National Institutes of Health (NIH), study staff and study monitors.

WILL I RECEIVE ANY PAYMENT?

You will receive payment for transportation and one meal per visit until we find out if you meet the requirements for the START study.

WHAT ARE THE COSTS TO ME?

There is no cost to you for being seen by the research staff for medical evaluations or for the laboratory tests that you will receive.
WHAT HAPPENS IF I AM INJURED?

It is unlikely that you will be injured as a result of completing the screening procedures. If you are injured, the study staff will give you immediate treatment for your injuries. The study will pay for your medical management. There is no program for compensation for research-related injuries through the U.S. National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the screening evaluations or a research-related injury, contact any of the following persons:

Clinic Manager at Prince Cyril Zulu Communicable Disease Clinic:
Dr. Nesri Padayatchi
Tel: (031) 260-4574

Clinic Manager at King Edward VIII Clinic:
Dr. Kogieleum Naidoo
Tel: (031) 260-4687

Project Director:
Dr. Kogieleum Naidoo
University of KwaZulu-Natal
King George V Avenue
Durban 4001
Tel: (031) 260-4687

Principal Investigator:
Prof. Salim Abdool Karim
University of KwaZulu-Natal
King George V Avenue
Durban 4001
Tel: (031) 260-2381

For questions about your rights as a research participant, you may contact:

Ms. Cheryl Borresen
Postgraduate Administration Office
University of KwaZulu-Natal
Tel: (031) 260 4495

Prof. Ames Dhai
Chairperson of the Research Ethics Committee
University of KwaZulu-Natal
Tel: (031) 260-4604
SCREENING INFORMED CONSENT SIGNATURES PAGE

I have read this form, or had it read to me, and voluntarily agree to have the screening tests. The purpose of the study, the procedures, and the risks and benefits have been explained to my satisfaction. My signature, thumbprint or mark indicates that I consent to the screening tests, have received a copy of this consent form, and that I understand the consequences of having the screening tests.

____________________       __________________
Signature of Participant                            Date

___________________                    __________________
Signature of Researcher                         Date

For illiterate participants:

Mark or thumbprint:______________________________

Independent Witness:___________________________ Date:____________

Title and Name:_______________________________

Telephone Number:____________________________
APPENDIX IB

SAMPLE STUDY INFORMED CONSENT FORM

Title of the Study: The START (Starting Tuberculosis and Anti-Retroviral Therapy) Trial: A Randomized Controlled Trial to Assess the Effect of Integrated Tuberculosis and HIV Care on the Incidence of AIDS-Defining Conditions or Mortality in participants Co-Infected with Tuberculosis and HIV.

Short Title: START: Starting Tuberculosis and Anti-Retroviral Therapy

Sponsored by: The National Institute of Allergy and Infectious Diseases
Division of AIDS (DAIDS)
6700B Rockledge Drive
Bethesda, Maryland 20852
United States

Principal Investigator: Professor Salim Abdool Karim, MBChB, PhD

INTRODUCTION

You are being asked to take part in this research study because you are infected with the HIV virus and tuberculosis (TB). This study is sponsored by the US National Institutes of Health (NIH). The doctor in charge of this study at this site (CAPRISA) is Prof. Salim S. Abdool Karim, MBChB, PhD. Before you decide if you want to be a part of this study, we want you to know about the study.

This consent form gives you information about this study, which will be done at Prince Cyril Zulu Communicable Disease Centre (CDC) and King Edward VIII Hospital (KEH). The research staff will talk to you about this information. Ask questions and discuss any concerns you may have with the research staff. If you agree to take part in this study, you will be asked to sign this consent form. You will be given a copy of this consent form to keep.

Please note that:

- Your participation in this study is entirely voluntary. You do not have to participate in the START study. You may decide to obtain your HIV care through your own medical provider.
• You may stop taking part in the study at any time without losing your standard health care.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to learn whether it is safe and effective to give TB and HIV medicines at the same time to people who have active TB and HIV. The study will also see how well people who take TB and HIV medicines at the same time are able to stay on the medicines without serious side effects.

The best time to start HIV medicines, called antiretroviral therapy or ART, in people who have TB and HIV infection is not known. There is little information about the best way to treat people who are infected with both HIV and TB.

All of the drugs used in this study are approved by the US Food and Drug Administration (FDA) for treating HIV/AIDS. These drugs do not cure HIV/AIDS. These are the same drugs that you would receive from the South African government, although not all of the study drugs may be available.

OVERVIEW OF THE STUDY

If you agree to participate in this study and tests show that you can enter the study, you will be randomized (assigned by chance, like flipping a coin) to one of two treatment groups. This means you will have an equal chance of being in one of the two groups listed below. You will not be able to choose which group you are in, but both you and your doctor will know which group you are in.

EARLY group: This group will start ART about 2 to 4 weeks after starting TB treatment.

LATER group: This group will begin ART soon after the TB treatment is finished (about 6 to 9 months later).

Both groups will receive the standard TB medicines as part of the Tuberculosis Control Programme. TB treatment usually lasts for about 6 to 9 months. You will come to the Prince Cyril Zulu Communicable Disease Centre (CDC) to receive and be observed while taking your TB medicines. If you are in the EARLY group you will receive ART at the same time at the CDC and be observed and on weekends take ART on your own until your TB treatment is finished. After you finish TB treatment, you will take ART on your own. If you are in the LATER group, you will start taking ART on your own soon after you have completed your TB treatment. Both groups will be seen at KEH for all study visits after TB treatment is finished. You will receive ART there until the end of the study (2 years after you enter the study).
APPENDIX IB

WHAT DO I HAVE TO DO IF I PARTICIPATE IN THIS STUDY?

If you enroll in this study, you will need to come into the clinic for examinations, interviews, and laboratory tests frequently; at least 28 times during the 2 years of the study depending on when you complete your TB treatment. Weekly visits will take about 30 minutes and most other visits will take about 1 to 1½ hours. Three visits will take up to 3 hours to measure the amount of TB and HIV drugs in your blood. Site staff will pay close attention to whether you have kept appointments since they want to keep track of your health. If you miss appointments, the persons you named will be contacted or field workers will be sent to your home.

Any time that results of exams and laboratory tests such as viral load (which measures how much HIV virus is in your blood), CD4+ T cell counts (immune cells that help fight infection such as HIV), and safety tests are known, they will be given to you. There may be times that you must come for additional visits if these exams or tests are abnormal. Some of the blood drawn throughout the study can be stored. You will be asked for your permission to store the blood for future research and asked to sign a separate consent form if you agree to do this. You may still participate in the study if you do not agree to have blood stored.

Study Entry Visit

If the results from screening showed you can be in the study, you will return to the clinic to enter the study within 28 days after starting TB medicines. This visit will take about 2 hours.

You will be asked questions about your medical history and any medicines that you have taken. You will be asked how to be contacted in case you miss a visit or there are ever problems with your lab results. You will be given a physical exam and have about 60 mL of blood drawn for routine tests, CD4 + cell counts, and to check for hepatitis (infection of the liver). You will be told your test results throughout the study. Some of your blood will be stored (with usual protectors of identity) for future HIV-related testing including a test for HIV resistance (to see if the HIV is able to respond to the ART). If you are a woman and able to become pregnant, you will be asked to provide some urine for a pregnancy test. You will be asked questions about your sexual activities. Some of these questions may cause you to be embarrassed. You do not have to answer these questions in order to be in this study.

After you complete the entry tests, you will be assigned to one of the two study groups as described above. If you are in the EARLY group, you will meet with a counselor for about 30 minutes to discuss the ART and how to take the medicines properly. The ART will then be started.
Follow up Visits

Both groups will have weekly visits for a month and then monthly visits at the CDC until TB treatment is complete (usually 6 months but up to 1 year for people who need more treatment).

After completion of TB therapy, all your visits will be at the KEH in Phase II. If you are in the LATER group, you will be seen weekly for the first month of ART and then monthly until the end of the study. At the first visit, you will have tests to see if you can start ART safely at that time. If you can, ART will begin at the next visit. If you cannot safely start ART then, these tests will be repeated at later visits until you can start ART. The EARLY group will continue ART and will have visits monthly until the end of the study.

During the Follow Up visits, you will be asked about any medicines you are taking, be given a physical exam, and at some of these visits will have about 30 to 40 mL of blood drawn for routine tests, CD4 counts, and HIV viral load. If you are a woman and able to become pregnant, at every visit while you are taking HIV drugs you be asked to provide urine for a pregnancy test. At some monthly visits, you will be asked about your health, receive your next study drug supply, and women will be asked to provide urine for a pregnancy test. At 6 visits, about 10 mL of blood will be taken to measure the amount of TB or HIV drugs in your blood. At 3 of these visits, the blood to measure your TB medicines will be drawn about 2½ hours after you take your TB medicine. If you agree and sign a separate consent form, at some visits about 35 mL of blood will be drawn, stored, and used for research in the future. You may still participate in the study if you do not agree to have blood stored.

Sputum will be collected at least twice during the study. Sputum will be collected and you will have a chest x-ray at 2 months and any time the doctors think you have TB after finishing TB treatment.

Once you start ART, you will complete a questionnaire about taking your study medicines. This will take about 30 minutes. In addition, if you are in the EARLY group, you will meet with a counselor three times for about 15 to 30 minutes to discuss ART and how to continue the medicine after TB treatment.

Four times during the study, you will be asked questions about your sexual behavior, general health as well as other questions related to your lifestyle. This will take about 30 minutes to one hour.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 592 people will take part in this study.
HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for about 2 years after you enter the study. If you need to stop study drugs permanently for any reason, you will still be asked to continue with study visits. Once you have finished the study, the study will no longer provide you with ART drugs. After the study is over, we anticipate that you will receive ART drugs from the South African rollout program for antiretroviral therapy or another HIV treatment or research program.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:

- the study is canceled by the US NIH, the Medicines Control Council, or the Ethics Committee (EC). An EC is a committee that watches over the safety and rights of research participants.
- a Data Safety Monitoring Board (DSMB) recommends that the study be stopped early. A DSMB is a group of experts who are not involved in the study that monitors the results of the study.

If you decide that you do not want to participate in the study anymore, you may leave the study at any time.

The study doctor may also need to take you off the study drugs without your permission if:

- continuing the study drugs may be harmful to you,
- you need a treatment that you may not take while on the study;
- you are not able to take the study drugs as required by the study or you are not able to attend the study visits as required by the study; or
- these medicines are not working well enough against the HIV virus and no other effective drugs are available.

If you must stop taking the study drug(s) before the study is over, the study doctor may ask you to continue to be part of the study and return for your regularly scheduled study visits.

WHAT ARE THE RISKS OF THE STUDY?

Risk of Early versus Later HIV Treatment for People with TB

The South African government is starting an ART rollout program to provide HIV treatment. Current guidelines suggest that people with HIV who have a very weak immune system (CD4+ cell count of less than 200 cells/µL) should begin taking ART.
On this study, even if your immune system is weak (CD4+ cell count from 50 to 199 cells/µL), you may have to wait 6 to 12 months before you start ART if you are randomized to the LATER group. If you have advanced HIV disease, you are at risk for developing HIV-related infections until after you start ART. While treatments are available for most of them, some of these infections can be very serious and can result in death. During this time the study staff will watch your health very carefully. If you are becoming increasingly sick from HIV, the study doctors may decide to begin ART before you finish your TB treatment. It is also possible that if you do not start taking ART until AFTER TB treatment is completed (6 months or more), you may not respond as well to treatment for TB as if you started ART within the next few weeks.

If you do not want to take a chance with the study, the study staff will try to help you find other ways to get ART, including treatment from the government or other research programs. People who start HIV treatment at the government rollout sites need to meet certain requirements. The study staff will tell you if you meet these requirements.

The HIV drug combination that we use in this study, is different from the one used by the government hospitals. All the drugs are accepted worldwide to treat HIV but the SA government uses them in a different order from what we will. There is a possibility that if you develop resistance or problems with any of our drugs during the study period and require alternate drug regimens that your choices of drugs on transitioning to the government ARV roll-out programme will be limited

Possible Risks of Starting ART During TB Treatment

The risks of ART while receiving TB treatment may include added side effects from the medications, either from the drug used against HIV or from the TB drugs. Interactions between these two kinds of drugs may also cause trouble. There may also be an increase in the chance of getting IRIS. (See below)

Risk of Immune Reconstitution Inflammatory Syndrome (IRIS)

While being treated with ART, your improving immune system's strong response to TB or other HIV/AIDS-related infections may also cause illness. This is called Immune Reconstitution Inflammatory Syndrome (IRIS). Usually, it causes a return or worsening of at least some of the symptoms.

Some examples of what could happen are that your lymph nodes (small organs in your body that help filter disease germs from the blood) could swell up, you could get a high fever, and you might have worsened cough and shortness of breath. While some of these reactions can be serious, they usually last for a short time and can be treated without stopping the ART. If this reaction happens to you, you will be treated for the problem and asked to have some additional blood drawn for testing of your immune system at that time.

DRUG RISKS
Anti-HIV Drugs:

There are many drugs available to treat HIV and AIDS. The study doctor will determine the best combination of these drugs to treat you. It is possible that the study drugs will make you feel sick or will affect your blood tests, in which case the study doctor may either switch you to different drugs, or stop them all together. It is very important for you to return to the clinic whenever you feel sick. Feeling sick may be due to the drugs or it may be due to a sickness caused by your HIV infection. Either way, we want to see you when you feel sick so we can take care of you.

All anti-HIV drugs can cause side effects, which can be more serious or severe with long-term use. Some of these side effects are mild and may go away after you have taken the drugs for a few weeks. Examples of these types of side effects include upset stomach, vomiting, headache, and changes in your mood, sleep, or concentration. Other side effects are severe and may require treatment or hospitalization. Examples of these types of side effects include rash, liver problems, severe depression or psychosis, and pancreas problems. Rarely, some people taking HIV drugs can develop a condition called “lactic acidosis.” Some symptoms that might be caused by lactic acidosis include: unexplained weight loss, stomach upset, nausea, vomiting, fatigue, weakness, and shortness of breath. Lactic acidosis, along with an enlarged and fatty liver, may result in problems such as liver failure. In some cases, the condition results in death. The liver problems and death have been seen more in women on these drug regimens.

The use of anti-HIV drug combinations may be associated with an abnormal placement of body fat and wasting. Some of the body changes include: increase in fat around the waist and stomach area; increase in fat on the back of the neck; thinning of the face, legs, and arms; and breast enlargement. The use of anti-HIV drug combinations may also be associated with altered fat metabolism including elevated triglycerides and/or elevated cholesterol.

Most people who agree to participate in this study will receive the medicines listed below to begin their HIV treatment: Efavirenz (EFV) + didanosine (ddl/ddI-EC) + lamivudine (3TC) once a day.

Below are the risks for the initial anti-HIV drug combination that you could be given.

**Risks of Didanosine (Videx®, ddl/ddI-EC)**
- Pancreatitis (inflammation of the pancreas), which may cause death. If you develop pancreatitis, you may have one or more of the following: stomach pain, nausea, and vomiting.
- Deaths from liver failure have been reported in pregnant women receiving the combination of didanosine and stavudine with other anti-HIV drugs.
- Numbness, tingling, and pain in the hands or feet
• Abnormal vision changes
• Upset stomach, vomiting and loose or watery stools
• Headache
• Abnormal pancreatic function blood tests or abnormal liver function blood tests
• Increase in uric acid in the bloodstream

When didanosine is used with other medicines with similar side effects, these side effects may be seen more often and may be more severe than when didanosine is used alone. People who take didanosine together with stavudine, with or without hydroxyurea, may be at greater risk for pancreatitis or liver problems or both. These conditions may result in death.

Risks of Efavirenz (Sustiva®, Stocrin, EFV)
Effects on mental function include:
• Dizziness
• Trouble sleeping such as inability to sleep, abnormal dreams, and drowsiness
• Confusion
• Difficulty concentrating
• Hallucinations
• A feeling of strangeness and losing touch with reality
• An exaggerated feeling of well-being
• Agitation or anxiety

If alcohol or mind- or mood-altering drugs are used with efavirenz, it is possible that the above symptoms could become worse.

Serious psychiatric problems include:
• Depression, which may be severe
• Suicidal thoughts or attempts (rarely)
• Aggressive behavior
• Psychosis-like symptoms, such as abnormal thinking, paranoia, and delusions

People with a history of psychiatric problems may be at greater risk for these serious psychiatric problems.

Other risks include:
• Rash
• Upset stomach
• Loose or watery stools
• Headache

Increases in substance in the blood which can mean problems with the pancreas, such as inflammation or swelling of the pancreas with abdominal pain
• Increase in cholesterol
• Increase in triglycerides
• Abnormal liver function tests and inflammation of the liver (hepatitis)
• Abnormal vision
• Fever
• An abnormal or unusual distribution of body fat

Studies using efavirenz in pregnant monkeys have shown newborn monkeys with birth defects. Three out of twenty monkeys had birth defects. One monkey had a defect in the roof of the mouth, another had small eyes, and another was missing a brain and missing one eye. The monkeys in this study received doses of efavirenz similar to those that are being studied in humans. It is not known what this information means or whether this could happen in humans; therefore, you should not become pregnant while taking efavirenz.

A false-positive urine screening test for marijuana has been seen with one particular test brand and has not been seen when using other screening tests or with tests used to confirm results for marijuana.

Risks of Lamivudine (Epivir®, 3TC)
• Headache
• Feeling of vague overall discomfort
• Feeling tired
• Dizziness
• Depression
• Upset stomach
• Vomiting
• Loose or watery stools
• Decrease in appetite
• Abdominal cramps
• Sleeplessness
• Rash
• Numbness, tingling, and pain in the hands or feet
• Decrease in the number of white blood cells that help fight infection
• An increase in a substance in the blood (a type of a pancreatic enzyme) which could mean a problem with the pancreas
• Increased liver function tests, which could mean liver damage

Participants who are infected with both Hepatitis B and HIV should be warned that their liver function tests may increase, and symptoms associated with hepatitis (an acute inflammation of the liver) may worsen after lamivudine has been stopped. Although most of these cases have resolved without treatment, some deaths have been reported.

At the end of this consent form, there is a table that describes the side effects for other anti-HIV drugs that may be provided to you by the study if you need to switch anti-HIV drugs. These drugs include nevirapine (NVP), tenofovir (TDF), abacavir (ABC),
saquinavir and ritonavir (SQV + RTV), or lopinavir and ritonavir (LPV/r). When the study doctor gives you the study drugs, he or she will discuss the possible side effects with you. Throughout the study, these side effects will be told to you, particularly if you receive a new anti-HIV drug. If the study doctor gives you an anti-HIV drug that is not listed in the table, he or she will make sure that you understand the side effects of the drug. If you have questions concerning study drug side effects, please ask the study staff.

After you begin taking the anti-HIV drugs, do not stop taking any of them unless you discuss it with the study doctor. Suddenly stopping your treatment can cause an increase in the amount of HIV in your blood, and the virus can become resistant to HIV, which means that the drugs will no longer work.

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with study drugs. For your safety, you must tell the study doctor or nurse about all medications, herbs, or home remedies you are taking before you start the study and also before you take any treatment. You must also tell the study doctor or nurse before taking any nonstudy medications, herbs, or home remedies while you are on the study. In addition, you must tell the study doctor or nurse before enrolling in any other clinical trials while on the study.

**Risks of Blood Draws**

You may feel some discomfort, pain or lightheadedness during the blood sample collection. Some people get a bruise or swelling where the needle is put in your arm to draw blood. In rare cases, the blood drawing procedure can cause fainting or infection.

**ARE THERE RISKS RELATED TO PREGNANCY?**

It is not known if the drug or drug combinations in this study harm unborn babies. Tests in pregnant animals do show some risks for some drugs. If you are having sex that could lead to pregnancy, you must agree not to become pregnant or make a woman pregnant. Some drugs in this study and some of the TB drugs make some hormonal birth control methods less effective. Breastfeeding mothers are allowed in the study.

- If you are on a drug combination that includes EFV, you and your partner must use two methods of birth control that you discuss with the study staff. You must continue to use both methods until 6 weeks after stopping EFV. (If you are a woman and are unable to use two methods, your doctor will talk with you about taking another ART drug rather than EFV.) You may choose two of the birth control methods listed below:
  1. Birth control drugs that prevent pregnancy given by pills, shots, or placed on or under the skin.
  2. Male or female condoms with or without a cream or gel that kills sperm
  3. Diaphragm or cervical cap with a cream or gel that kills sperm
  4. Intrauterine device (IUD)
• If you are not taking EFV or rifampicin, you must use one method of birth control listed below that you discuss with the study staff:
  1. Male or female condoms with or without a cream or gel that kills sperm
  2. Diaphragm or cervical cap with a cream or gel that kills sperm
  3. Intrauterine device (IUD)

**ARE THERE SPECIAL RISKS RELATED TO BREASTFEEDING?**

A mother who is infected with HIV may infect her baby through breast milk. HIV-infected mothers who are able to obtain baby formula and clean water should not breastfeed their babies. It is unknown whether the study medicines pass through the breast milk and cause harm to your infant. It is also unknown whether study drugs may reduce the chances that HIV can pass to your baby through your breast milk.

**WHAT HAPPENS IF I BECOME PREGNANT?**

If you think you may be pregnant at any time during the study, tell your study staff right away. The study staff will talk to you about your choices and refer you to a provider of prenatal care at the King Edward VIII Hospital clinics. If you decide to continue in the START study, you will be asked to sign another consent form. This study will not provide or pay for care related to your pregnancy or the delivery of your baby.

**ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?**

If you participate in this study, there may be a direct benefit to you, but no guarantee can be made. Your health will be followed more closely than usual while you are on the study, which may help you to feel better. Laboratory tests to monitor the effects of these drugs will be provided by the study. It is also possible that you may receive no benefit from being in this study.

Information learned from this study may help others who have HIV/AIDS by identifying whether it is safe and effective to start HIV medications while being treated for TB.

**WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?**

Instead of being in this study you have the choice of:
  • treatment with ART through the South African national rollout program once this program begins (which is expected to begin in 2005), if you qualify
  • treatment with experimental drugs, if you qualify
  • no treatment

Antiretroviral medications, laboratory tests to monitor the effectiveness of these medications, and quality medical care for HIV/AIDS may or may not be available to you outside the study. The clinic staff will discuss with you other treatment choices in your
area and the risks and the benefits of all the choices.

If you choose not to join this study, you can still receive TB treatment through the Tuberculosis Control Programme at CDC.

WHAT ABOUT CONFIDENTIALITY?

Your medical records, personal information, and the results of your HIV tests and other medical and laboratory evaluations will be kept strictly confidential within the extent of South African law. Only your doctor and/or nurse will know the results of your tests. Your records will be identified by a study code. Any publication of this study will not use your name or identify you personally.

Every effort will be made to protect your confidentiality but we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Your records may also be reviewed by regulatory authorities, such as the Medicines Control Council (MCC), the Ethics Committees, the US National Institutes of Health (NIH), study staff, and study monitors.

WILL I RECEIVE ANY PAYMENT?

You will receive reimbursement for transportation and one meal when you attend study visits.

WHAT ARE THE COSTS TO ME?

The HIV treatment (ddI/ddI-EC, EFV, 3TC, TDF, NVP, ABC, SQV + RTV, LPV/r) will be provided free of charge while you are on study. If you require HIV treatment that does not include these drugs, you will receive this care from a local authority and/or provincial health facility. Provincial hospitals may ask you to pay a fee, depending on your income.

The TB treatment is provided free of charge to you by the Tuberculosis Control Programme at the CDC.

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries at KEH. The study will pay for your medical management at the hospital. There is no program for compensation for research-related injuries through the U.S. National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.
WHAT ARE MY RIGHTS AS A VOLUNTEER IN A RESEARCH STUDY?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. You will be treated the same no matter what you decide.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact any of the following persons:

Clinic Manager at Prince Cyril Zulu Communicable Disease Clinic:
Dr. Nesri Padayatchi
Tel: (031) 260-4574

Clinic Manager at King Edward VIII Clinic:
Dr. Kogieleum Naidoo
Tel: (031) 260-4687

Project Director:
Dr. Kogieleum Naidoo
University of KwaZulu-Natal
King George V Avenue
Durban 4001
Tel: (031) 260-4687

Principal Investigator:
Prof. Salim Abdool Karim
University of KwaZulu-Natal
King George V Avenue
Durban 4001
Tel: (031) 260-2381

For questions about your rights as a research participant, you may contact:

Ms. Cheryl Borresen
Postgraduate Administration Office
University of KwaZulu-Natal
Tel: (031) 260 4495

Prof. Ames Dhai
Chairperson of the Research Ethics Committee
STUDY INFORMED CONSENT SIGNATURES PAGE

I have read this form, or had it read to me, and voluntarily agree to take part in the study. The purpose of the study, the procedures, and the risks and benefits have been explained to my satisfaction. My signature, thumbprint or mark indicates that I consent to take part in the study, have received a copy of this consent form, and that I understand the consequences of taking part in the study.

____________________________________  __________________
Signature of Participant                            Date

____________________________________  __________________
Signature of Researcher                         Date

For illiterate participants:

Mark or thumbprint: ____________________________

Independent Witness: __________________________ Date: _____________

Title and Name: ________________________________

Telephone Number: ____________________________
Here is a table that describes the side effects for other anti-HIV drugs that may be provided to you by the study if you need to switch anti-HIV drugs. When the study doctor gives you the study drugs, he or she will discuss the possible side effects with you. Throughout the study, these side effects will be told to you, particularly if you receive a new anti-HIV drug. If the study doctor gives you an anti-HIV drug that is not listed in the table, he or she will make sure that you understand the side effects of the drug. If you have questions concerning study drug side effects, please ask the study staff.

<table>
<thead>
<tr>
<th>Anti-HIV Drug</th>
<th>Side Effects</th>
</tr>
</thead>
</table>
| Abacavir [Ziagen®, ABC] | • An allergic reaction which may include many different symptoms, such as: fever, rash, feeling tired, upset stomach, vomiting, loose or watery stools, abdominal pain, cough, sore throat, shortness of breath, aching, or a general feeling of illness.  
  • These symptoms usually appear within the first six weeks after starting this drug but can occur at any time during treatment. This reaction can be severe and could even lead to death if abacavir is not stopped. The severe form of allergic reaction can also recur if abacavir is restarted after it has been stopped and can even lead to death.  
  
  IF YOU THINK YOU MIGHT BE DEVELOPING A REACTION TO ABACAVIR, DO NOT TAKE ANY MORE DOSES AND CONTACT THE DOCTOR AT THE CLINIC IMMEDIATELY.  
  
  NOTE: Severe or fatal allergic-type reactions can occur within hours after abacavir is restarted in participants who have interrupted abacavir therapy. Allergic-type reactions to abacavir can occur in patients who have had no prior identified history or whose symptoms were previously unrecognized. If you interrupt abacavir for any reason, immediately contact the medical staff at the site. If your doctor decides to restart, you may need to be monitored more closely in the clinic or in the hospital.  
  • Upset stomach  
  • Vomiting  
  • Vague overall feeling of discomfort  
  • Feeling tired  
  • Decrease in appetite  
  • Loose or watery stools  
  • Inflammation or swelling of the pancreas with abdominal pain  
  • Headache  
  • Increased triglycerides  
  • Lactic acidosis. The signs of lactic acidosis that you may notice are: unexplained weight loss, stomach ache, upset stomach, throwing up, tiredness, weakness, and shortness of breath. Lactic acidosis can cause death |
## APPENDIX IB

### Anti-HIV Drug Side Effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Side Effects</th>
</tr>
</thead>
</table>
| **Lopinavir/ritonavir**<br>[Kaletra®, LPV/r] | - Pancreatitis (inflammation of the pancreas), which may cause death. If you develop pancreatitis, you may have one or more of the following: stomach pain, nausea, vomiting or abnormal pancreatic function blood tests  
- Abnormal bowel movements (stools), including loose or watery stools, upset stomach and stomach pain  
- Large increases in triglycerides and cholesterol in the blood  
- Liver problems and worsening liver disease, which may result in death. People with these conditions may have abnormal liver function blood tests  
- Feeling weak and tired  
- Headache  
- Rash (seen in children)  
- The use of protease inhibitors may be associated with the development of or the worsening of elevations in blood sugar and diabetes  
- There have been reports of increased bleeding in HIV-infected persons with hemophilia who were treated with protease inhibitors. It is not known if protease inhibitors were the cause of these bleeding episodes. |
| **Nevirapine**<br>[Viramune®, NVP] | - Severe liver damage that can cause death may occur. People with higher CD4 cell counts are at increased risk for developing liver damage, which is often associated with a rash. Women with CD4 cell counts greater than 250 cells/µL, including pregnant women receiving chronic nevirapine therapy, are at even higher risk for developing liver damage. People who have abnormal liver function tests before starting nevirapine and people with active Hepatitis B or C infection are also at higher risk for liver damage  
- If you are developing liver damage, you may have one or more of the following: Tiredness, general feeling of illness, loss of appetite, nausea, pale stools, dark urine, yellowing of the skin or whites of your eyes, liver tenderness or abnormal liver function tests  
- Rash is the most common side effect associated with nevirapine. Rash occurs more often in women. Most rashes occur early during treatment. The rash may be severe and rarely may cause death. One of the risk factors for developing serious skin reactions includes failure to take nevirapine properly during the first 14 days of treatment.  
- Hypersensitivity reactions (HSR), which can rarely be fatal, may occur. Symptoms associated with an HSR include rash, fever, fatigue, muscle or joint aches, blisters, mouth sores, facial swelling, red eyes and irritation of the eyes, general feeling of discomfort, hepatitis, kidney problems, and/or changes in white blood cell levels.  
- The risk of people developing any of the serious side effects listed above is greatest during the first few months of treatment, but these side effects also can occur later. If you develop any of the side effects listed above, no matter how long you have been receiving nevirapine, you must contact your health care provider right away and try to be seen by the medical staff at your site before your next dose. If you and your doctor then decide to stop your treatment because of symptomatic hepatitis, hypersensitivity or severe skin reactions, you should never take Nevirapine again.  
- Other risks include: Fever, headache, upset stomach |
### APPENDIX IB

| Ritonavir [Norvir®, RTV] | • Stomach and bowel problems including abdominal pain, upset stomach, vomiting, abnormal stools, and loose or watery stools  
• An increase in triglycerides  
• Numbness and tingling in the arms, legs and around the mouth  
• Rash  
• Abnormal liver function tests  
• Fever  
• A change in the sense of taste  
• The use of protease inhibitors may be associated with the development of or the worsening of elevations in blood sugar and diabetes  
• There have been reports of increased bleeding in HIV-infected persons with hemophilia who were treated with protease inhibitors. It is not known if protease inhibitors were the cause of these bleeding episodes. |
| Saquinavir [Fortovase®, SQV] | • Loose or watery stools  
• Upset stomach  
• Abdominal discomfort/pain  
• Heartburn  
• Gas  
• Feeling tired  
• Headache  
• Increased CPK (an enzyme found in the heart)  
• Abnormal liver function tests  
• Low blood sugar  
• Decrease in the number of white blood cells that help fight infection  
• The use of protease inhibitors may be associated with the development of or the worsening of elevations in blood sugar and diabetes  
• There have been reports of increased bleeding in HIV-infected persons with hemophilia who were treated with protease inhibitors. It is not known if protease inhibitors were the cause of these bleeding episodes. |
APPENDIX IB

<table>
<thead>
<tr>
<th>Tenofovir [Viread®, TDF]</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Upset stomach, vomiting, gas, loose or watery stools</td>
</tr>
<tr>
<td>• Dizziness</td>
</tr>
<tr>
<td>• Abdominal pain</td>
</tr>
<tr>
<td>• Lack of energy</td>
</tr>
<tr>
<td>• Kidney damage or failure</td>
</tr>
<tr>
<td>• Inflammation or swelling and possible damage to the pancreas</td>
</tr>
<tr>
<td>• Shortness of breath</td>
</tr>
<tr>
<td>• Rash</td>
</tr>
<tr>
<td>• Low phosphate, a chemical in the blood</td>
</tr>
<tr>
<td>• Increase of liver functions tests in children</td>
</tr>
<tr>
<td>• Allergic reaction, which may include fever, rash, upset stomach, vomiting, loose or watery stools, abdominal pain, achiness, shortness of breath or a general feeling of illness</td>
</tr>
<tr>
<td>• Changes in bone growth and strength were seen in study animals given tenofovir. It is unknown if taking tenofovir for a long time will cause bone abnormalities in adults. In children, some decrease in bone thickness (density) has been seen.</td>
</tr>
<tr>
<td>• If you are infected with both Hepatitis B and HIV, you should be aware that your liver function tests may increase, and symptoms associated with hepatitis (an acute inflammation of the liver) may worsen if tenofovir is stopped.</td>
</tr>
<tr>
<td>• Because there is only a small amount of information on tenofovir in pregnant women, tenofovir should be used during pregnancy only if clearly needed.</td>
</tr>
<tr>
<td>• Lactic acidosis. The signs of lactic acidosis that you may notice are: unexplained weight loss, stomach ache, upset stomach, throwing up, tiredness, weakness, and shortness of breath. Lactic acidosis can cause death.</td>
</tr>
</tbody>
</table>
APPENDIX IC

SAMPLE STUDY INFORMED CONSENT FORM FOR WOMEN WHO BECOME PREGNANT WHILE ON STUDY

Title of the Study: The START (Starting Tuberculosis and Anti-Retroviral Therapy) Trial: A Randomized Controlled Trial to Assess the Effect of Integrated Tuberculosis and HIV Care on the Incidence of AIDS-Defining Conditions or Mortality in participants Co-Infected with Tuberculosis and HIV.

Short Title: START: Starting Anti-Retroviral Therapy

Sponsored by: The National Institute of Allergy and Infectious Diseases
Division of AIDS (DAIDS)
6700B Rockledge Drive
Bethesda, Maryland 20852
United States

Principal Investigator: Professor Salim Abdool Karim, MBChB, PhD

INTRODUCTION

Because you are now pregnant, you are being asked if you want to continue taking part in this research study. This study was designed so that women who were pregnant could not join the study. However, because you were already in the study when you became pregnant, you will be allowed to stay in the study and come for the same study visits whether or not you continue study medicines during your pregnancy.

This is a consent form. It gives you information about how participating in this study may affect your pregnancy and your baby. The research staff will talk with you about this information. You may also talk with your own doctor about what is best for you and your baby, if you should remain on study medicines or choose other anti-HIV medicines. If you agree to stay in this study, you will be asked to sign this consent form. You will get a copy to keep. You are free to ask questions of the research staff at any time.

Please note that:
- Your participation in this study is entirely voluntary.
- You may stop taking part in this study at any time without losing your standard health care.
WHAT DO I HAVE TO DO IF I STAY IN THIS STUDY?

It is not known if the drug or drug combinations in this study harm unborn babies. Tests in pregnant animals do show some risk for some drugs. The risks to unborn babies for each drug are listed in the section called “What Are the Risks of the Study?” in the main study’s consent form for START. If you become pregnant while taking efavirenz (EFV), your doctor will tell you to stop taking it and replace it with another safer anti-HIV medicine. Additional blood tests may be done if nevirapine is used to replace EFV.

This study will not provide care related to your pregnancy, the delivery of your baby or the care of your baby. You must arrange for your care and your baby’s care outside of this study. The most likely place that you will get this care is a government antenatal clinic close to the study site.

WHAT ARE THE RISKS RELATED TO STAYING IN THE STUDY?

Now that you are pregnant, there are some possible risks you should know. These possible risks to you and your baby are in addition to the risks that are described in the study consent you already signed.

Risks to You if You Stay on Study Medicines

- Different side effects or more severe side effects may occur in pregnant women taking anti-HIV medicines. This may make it more difficult for you to take your study medicines. Not taking anti-HIV study medicines as directed may cause the medicines not to work on the HIV in your blood.
- The amount of medicine in the blood may change during pregnancy. This possibly means that your level of anti-HIV medicines may decrease and not work as well or cause the HIV to become resistant to the medicines.
- It is not known if some risks of pregnancy might be made worse by study medicines or may result in death.

Risks to Your Baby if You Stay on Study Medicines

- It is not known if some study medicines may cause you to have a baby that is born early or dead.
- It is not known if some study medicines may cause your baby to be sick or have birth defects. Not all birth defects are seen at birth. Some birth defects are seen later as the baby grows.
- In the U.S., only zidovudine (ZDV, Retrovir) is approved by the FDA to decrease the risk of passing HIV from mother to baby. The U.S. Public Health Service recommends that women discuss with their doctor the use of ZDV alone and with other anti-HIV drugs to decrease the risk of passing HIV to their baby. Zidovudine will not be provided by the study.
APPENDIX IC

- Please look at the main study’s consent form for START that you read and signed relating to the specific risks of the drugs you are taking.

BREASTFEEDING

After delivery, if you decide to breastfeed your baby you may continue taking study medicines. Researchers know that HIV can pass through breast milk. Taking anti-HIV medicines has not been proven to decrease the chance of passing HIV through your breast milk to your baby. If the HIV becomes resistant to your anti-HIV medicines, there is the chance that you may pass this resistant HIV virus through breast milk to your baby. This may make it more difficult to treat the HIV in your baby.

If you decide to breastfeed, it will not stop you from being on the study.

ARE THERE BENEFITS TO STAYING IN THIS STUDY?

Use of anti-HIV medicines during later pregnancy significantly decreases the chance that the baby will become HIV-infected during pregnancy. However, if you continue to take part in this study no guarantee can be made of a benefit to you or your baby. It is also possible that you and your baby will receive no benefit from continuing in this study. Information learned from this study may help others who have HIV.

WHAT OTHER CHOICES DO I HAVE BESIDES STAYING ON STUDY DRUGS?

Instead of staying on the study medicines you have the choice of:

- Treatment with prescription medicines available to you from the Department of Health Treatment Plan.
- Interrupt your study treatment for the first three months of pregnancy, during which most of the development of the baby occurs and the danger of treatment problems is the highest, and then you may be able to receive study treatment again.
- Treatment with experimental drugs being studied for use during pregnancy, if you qualify.
- No treatment during pregnancy, however this carries a higher risk of your baby being HIV-positive.

Please talk to your doctor about these and other choices available to you. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

The results of your HIV tests and other medical and laboratory evaluations will be kept strictly confidential within the extent of South African law. Only your doctor and/or nurse will know the results of your tests. Your records will be identified by a study code. Any publication of this study will not use your name or identify you personally.
Every effort will be made to protect your confidentiality but we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Your records may also be reviewed by regulatory authorities, such as the Medicines Control Council (MCC), the Ethics Committees, the US National Institutes of Health (NIH), study staff and study monitors.

WHAT ARE THE COSTS TO ME?

As stated in the study consent you already signed, there are no costs to you for study-related visits or study medicines. This study will not cover any cost related to your pregnancy, delivery of your baby, or care of your baby.

WILL I RECEIVE ANY PAYMENT?

You will continue to receive reimbursement for transportation and one meal when you attend study visits.

WHAT HAPPENS IF MY BABY OR I AM INJURED?

If your baby or you are injured as a result of being in this study, you will both be given immediate treatment for your injuries at KEH. The study will pay for your medical management at the hospital. There is no program for compensation for research-related injuries through the U.S. National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Continuing to take part in this study is completely voluntary. You may choose not to continue in this study or leave this study at any time. You will be treated the same no matter what you decide.

We will tell you about new information from this or other studies that may affect your health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact any of the following persons:

Clinic Manager at Prince Cyril Zulu Communicable Disease Clinic:
Dr. Nesri Padayatchi
Tel: (031) 260-4574
Clinic Manager at King Edward VIII Clinic:
Dr. Kogieleum Naidoo
Tel: (031) 260-4687

Project Director:
Dr. Kogieleum Naidoo
University of KwaZulu-Natal
King George V Avenue
Durban 4001
Tel: (031) 260-4687

Principal Investigator:
Prof. Salim Abdool Karim
University of KwaZulu-Natal
King George V Avenue
Durban 4001
Tel: (031) 260-2381

For questions about your rights as a research participant, you may contact:

Ms. Cheryl Borresen
Postgraduate Administration Office
University of KwaZulu-Natal
Tel: (031) 260 4495

Prof. Ames Dhai
Chairperson of the Research Ethics Committee
University of KwaZulu-Natal
Tel: (031) 260-4604
STUDY SIGNATURES PAGE FOR PREGNANT WOMEN

I have read this form, or had it read to me, and voluntarily agree to continue taking part in the study. The risks and benefits have been explained to my satisfaction. My signature, thumbprint or mark indicates that I consent to continue taking part in the study, have received a copy of this consent form, and that I understand the consequences of continuing in the study during my pregnancy.

____________________       __________________
Signature of Participant                            Date

___________________                    __________________
Signature of Researcher                         Date

For illiterate participants:

Mark or thumbprint:_____________________________

Independent Witness:___________________________     Date:___________

Title and Name:_______________________________

Telephone Number:____________________________
APPENDIX ID

SAMPLE INFORMED CONSENT FORM FOR SPECIMEN STORAGE

Title of the Study: The START (Starting Tuberculosis and Anti-Retroviral Therapy) Trial: A Randomized Controlled Trial to Assess the Effect of Integrated Tuberculosis and HIV Care on the Incidence of AIDS-Defining Conditions or Mortality in participants Co-Infected with Tuberculosis and HIV.

Short Title: START: Starting Anti-Retroviral Therapy

Sponsored by: The National Institute of Allergy and Infectious Diseases
Division of AIDS (DAIDS)
6700B Rockledge Drive
Bethesda, Maryland 20852
United States

Principal Investigator: Professor Salim Abdool Karim, MBChB, PhD

INTRODUCTION

If you decide to participate in the START research study, blood and other biological samples will be taken from you for testing. Some of these samples may be kept for future research relating to the study of HIV. This consent form gives you information about this storage and use of samples. You are being asked to consent to the storage of your blood and other samples. The study staff will discuss this with you. Please ask if you have any questions. If you agree to the storage of your blood and other samples, you will be asked to sign this consent form. You will be given a copy of this form to keep.

BLOOD AND BIOLOGICAL SAMPLES

At each of your clinic visits, blood and other biological samples (sputum, urine) will be taken from you. Some of the blood and biological samples obtained during the study will be stored. As with your other samples, only a number, not your name, will be used to identify these samples. These samples may provide valuable information in the future when different immune system and HIV tests become available.
USE OF STORED SAMPLES

The stored samples may be used for future research, to confirm test results, or to do additional testing. Your samples will not be sold or used in products that make money for the researchers. Any studies that use your samples will be reviewed by the Ethics Committee of the Nelson R. Mandela School of Medicine.

The researchers do not plan to contact you or your regular doctor with any results that are done on the stored samples after the study has been completed. This is because research tests are often done with experimental procedures so the results from one study are generally not useful for making decisions on managing your health. Should a rare situation come up where the researchers decide that a specific test result would provide important information for your health, the researchers will notify the study doctor who will try to contact you or your regular doctor. If you wish to be notified of this type of test result, you need to make sure that you contact the study nurse or doctor with any changes to your phone number or address. If you want your regular doctor to be told about this kind of test result, you need to provide the study team with the contact details of your regular doctor.

STORAGE OF SAMPLES

Your samples will be stored at laboratories that are specially designed to keep stored samples safely. Only approved researchers working on this project and related projects will be able to access your samples. The people who work at these laboratories will have access to your samples when they store them and keep track of them, but they will not know who you are as your samples will be stored by number. There is no time limit on how long your samples may be stored.

BENEFITS

There is no direct benefit to you through having your samples stored and tested later. Information learned from stored samples may help others who have HIV/AIDS.

RISKS

There is very little risk to you when you have your samples stored. There is a small risk that others may find out information about your HIV status from stored samples. This risk is reduced as your sample is stored under a study number, and not your name. You are entitled to the same protections of confidentiality and privacy for stored samples as you are for the samples that are drawn and used during the study. It is possible that tests that have yet to be developed may tell us things about your health we cannot currently test for. Results from these tests may cause distress to you.
CONFIDENTIALITY

The results of future tests of your samples will not go into your medical record. Although every effort is made to make sure that your samples are stored confidentially (by number and not name), we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Your records may also be reviewed by regulatory authorities, such as the Medicines Control Council (MCC), the Ethics Committees, the U. S. National Institutes of Health (NIH), study staff and study monitors.

PARTICIPANT RIGHTS

The decision to allow your samples to be stored is completely voluntary. If you do not allow your samples to be stored, you may still participate in the main study. You may decide not to allow your samples to be stored after the tests that are needed for this study have been done or you decide to stop participating in the study. If you do decide to allow your samples to be stored, you can change your mind at any time and still participate in the main study. You must contact the study doctor or nurse and let them know that you do not want your samples to be stored any more. If you decide to do this, your samples will no longer be stored. You will then be asked if you want all stored samples to be destroyed. In this case, any samples that have been stored will be destroyed. You will then be asked to sign this form again under the section, “Withdrawal of Consent” so that there is a record of your decision. At the end of the study you will also be given the opportunity to review your consent for the storage of your samples.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

If you have any questions about the storage of samples for this study, or would like to know more about the storage of blood, contact any of the following:

Clinic Manager at Prince Cyril Zulu Communicable Disease Clinic:
Dr. Nesri Padayatchi
Tel: (031) 260-4574

Clinic Manager at King Edward VIII Clinic:
Dr. Kogieleum Naidoo
Tel: (031) 260-4687

Project Director:
Dr. Kogieleum Naidoo
University of KwaZulu-Natal
King George V Avenue
Durban 4001
Tel: (031) 260-4687
Principal Investigator:
Prof. Salim Abdool Karim
University of KwaZulu-Natal
King George V Avenue
Durban 4001
Tel: (031) 260-2381

For questions about your rights as a research participant, you may contact:

Ms. Cheryl Borresen
Postgraduate Administration Office
University of KwaZulu-Natal
Tel: (031) 260 4495

Prof. Ames Dhai
Chairperson of the Research Ethics Committee
University of KwaZulu-Natal
Tel: (031) 260-4604
Please read the statement below and think about your choice. No matter what you decide, it will not affect your care.

I agree to allow some of my biological samples to be stored and used for testing and future research in HIV studies (please tick only one).

_______ Yes
_______ No

I am aware that I may withdraw my consent at any time without prejudice to further care.

Signature of Participant ____________________________ Date ____________________________

Signature of Researcher ____________________________ Date ____________________________

For illiterate participants:

Mark or thumbprint: ____________________________ Date: ____________________________

Independent Witness: ____________________________ Date: ____________________________

Title and Name: ____________________________ Telephone Number: ____________________________
Withdrawal of Consent

I hereby withdraw my consent for the storage of my biological samples. It is my wish that (please tick only one):

_____ Samples that have already been stored may continue to be stored and used.

_____ All samples that have already been stored must be destroyed.

____________________       __________________
Signature of Participant                            Date

___________________                    __________________
Signature of Researcher                         Date

For illiterate participants:

Mark or thumbprint*: ____________________________ Date: ____________

Independent Witness: __________________________   Date: ____________

Title and Name: ________________________________

Telephone Number: ____________________________
## AIDS-DEFINING ILLNESSES
(Modified WHO Stage IV criteria)

<table>
<thead>
<tr>
<th>Sign/Symptom/Disease</th>
<th>Definitive Diagnostic Methods</th>
<th>Presumptive Diagnostic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV wasting syndrome, as defined by the Centers for Disease Control and Prevention</td>
<td>Findings of profound involuntary weight loss &gt; 10% of baseline body weight plus either chronic diarrhea (at least three loose stools per day for &gt; 30 days) or chronic weakness and documented fever (for &gt; 30 days, intermittent or constant) in the absence of a concurrent illness or condition other than HIV infection that could explain the findings (e.g. cancer, tuberculosis, cryptosporidiosis, or other specific enteritis)</td>
<td>A history of dyspnea on exertion or non-productive cough of recent onset (within the previous 3 months); and Chest radiograph evidence of diffuse bilateral interstitial infiltrates or gallium scan evidence of diffuse bilateral pulmonary disease; and No microbiological evidence of a bacterial pneumonia or tuberculosis or a pneumonia due to any other known pathogen</td>
</tr>
<tr>
<td>Pneumocystis carinii pneumonia</td>
<td>Microscopy (histology or cytology)</td>
<td>(1) Recent onset of a focal neurological abnormality consistent with intercranial disease or a reduced level of consciousness; and either (2) Brain imaging evidence of a lesion having a mass effect (on computerized tomography or nuclear magnetic resonance) or the radiographic appearance of which is enhanced by injection of contrast medium; or (3) Successful response to therapy for toxoplasmosis</td>
</tr>
<tr>
<td>Toxoplasmosis of the brain</td>
<td>Microscopy (histology or cytology)</td>
<td></td>
</tr>
<tr>
<td>Cryptosporidiosis with diarrhoea &gt; 1 month</td>
<td>Microscopy (histology or cytology)</td>
<td></td>
</tr>
<tr>
<td>Cryptococcosis, extrapulmonary</td>
<td>Microscopy (histology or cytology), culture, or detection of antigen in a specimen obtained directly from the tissues affected of fluid from those tissues</td>
<td>Meningitis with positive serum cryptococcal antigen (CRAG)</td>
</tr>
<tr>
<td>Sign/Symptom/Disease</td>
<td>Definitive Diagnostic Methods</td>
<td>Presumptive Diagnostic Criteria</td>
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<tr>
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</tr>
<tr>
<td>Cytomegalovirus disease of an organ other than liver, spleen or lymph nodes</td>
<td>Microscopy (histology or cytology)</td>
<td>Cytomegalovirus retinitis: A characteristic appearance of serial ophthalmoscopic examination (e.g. discrete patches of retinal whitening with distinct borders, spreading in a centrifugal manner, following blood vessels, progressing over several months, frequently associated with retinal vasculitis, haemorrhage, and necrosis). Resolution of active disease leaves retinal scarring and atrophy with retinal pigment epithelial mottling.</td>
</tr>
<tr>
<td>Herpes simplex virus infection, mucocutaneous &gt;1 month, or visceral any duration</td>
<td>Microscopy (histology, cytology, DFA test, PCR test) culture, or detection of antigen in a specimen obtained directly from the tissues affected or fluid from those tissues</td>
<td></td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy</td>
<td>Microscopy (histology or cytology), culture, or detection of antigen in a specimen obtained directly from the tissues affected or fluid from those tissues</td>
<td>Characteristic signs and symptoms + compatible CT scan</td>
</tr>
<tr>
<td>Any disseminated endemic mycosis (i.e. histoplasmosis, coccidioidomycosis)</td>
<td>Microscopy (histology or cytology), culture, or detection of antigen in a specimen obtained directly from the tissues affected or fluid from those tissues</td>
<td></td>
</tr>
</tbody>
</table>
| Candidiasis of the esophagus | Gross inspection by endoscopy or autopsy or by microscopy (histology or cytology) on a specimen obtained directly from the tissues affected (including scrapings from the mucosal surface), not from a culture | (1) Recent onset of retrosternal pain on swallowing; and  
(2) Oral candidiasis diagnosed by the gross appearance of white patches or plaques on an erythematous base or by the microscopic appearance of fungal mycelial filaments in an uncultured specimen scraped from the oral mucosa; and  
(3) Successful response to anti-fungal therapy |
| Atypical mycobacteriosis, disseminated | Blood or tissue culture | Microscopy of a specimen from stool or normally sterile body fluids or tissue from a site other than lungs, skin or cervical or hilar lymph nodes, showing acid-fast bacilli of a species not identified by culture |
| Non-typhoid Salmonella septicaemia | Blood or tissue culture | CT scan with characteristic lesions, plus failure to respond to treatment for toxoplasmosis. |
| Lymphoma | Microscopy (histology or cytology) | CT scan with characteristic lesions, plus failure to respond to treatment for toxoplasmosis. |
| Kaposi’s sarcoma | Microscopy (histology or cytology) | A characteristic gross appearance of an erythematous or violaceous plaque-like lesion on skin or mucous membrane. (Note: presumptive diagnosis of Kaposi’s sarcoma should not be made by clinicians who are not familiar with it) |
### APPENDIX II

<table>
<thead>
<tr>
<th>Sign/Symptom/Disease</th>
<th>Definitive Diagnostic Methods</th>
<th>Presumptive Diagnostic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV encephalopathy, as defined by the Centers for Disease Control and Prevention.</td>
<td>Clinical findings of disabling cognitive and/or motor dysfunction interfering with occupation or activities of daily living, or loss of behavioral developmental milestones affecting a child, progressing over weeks to months, in the absence of a concurrent illness or condition other than HIV infection that could explain the findings. Methods to rule out such concurrent illnesses and conditions must include cerebrospinal fluid examination and either brain imaging (computerized tomography or nuclear magnetic resonance) or autopsy.</td>
<td></td>
</tr>
<tr>
<td>Isosporiasis (&gt;1 month duration)</td>
<td>Microscopy (histology or cytology)</td>
<td></td>
</tr>
</tbody>
</table>

**SOURCES:**

1. ANNEX 1. WHO staging system for HIV infection and disease in adults and adolescents
APPENDIX III

KARNOFSKY PERFORMANCE SCALE

100%  Normal, no complaints, no evidence of disease
90%   Able to carry on normal activity: minor symptoms of disease
80%   Normal activity with effort: some symptoms of disease
70%   Cares for self: unable to carry on normal activity or active work
60%   Requires occasional assistance but is able to care for needs
50%   Requires considerable assistance and frequent medical care
40%   Disabled: requires special care and assistance
30%   Severely disabled: hospitalization is indicated, death not imminent
20%   Very sick, hospitalization necessary: active treatment necessary
10%   Moribund, fatal processes progressing rapidly
0%    Dead
APPENDIX IV

APPENDIX IV

ADHERENCE SUPPORT PROGRAM

Adherence Support Program (ASP)
For the CAPRISA START Study

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   A. Objectives
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II. Personnel Responsibilities for ASP
ADHERENCE SUPPORT PROGRAM (ASP)

CAPRISA START Study

The primary aim of the CAPRISA START study is to compare the clinical effectiveness of two strategies for use of ART agents (ART) in participants with HIV-related TB; integrated provision of ART during TB treatment (ART/DOT arm) or initiation of ART after completion of TB treatment. The START Adherence Support Program (ASP) is a central feature of the ART/DOT strategy. It is comprised of five interrelated components, all with the goal of promoting patient adherence to the dual HIV/TB treatment regimen.

I. Intervention Components for Participants Assigned to Experimental ART-DOT Arm of the START study

A. OBJECTIVES

The objectives of the ASP for participants assigned to ART-DOT arm are:

- To identify deficits in information, motivation, and behavioral skills that inhibit consistent and correct self-administration of ART medications.
- To ensure daily attendance (Mondays through Fridays) at the Cyril Zulu Communicable Disease Clinic (Prince Cyril Zulu CDC) for receipt of anti TB and ART medications via DOT.
- To provide information and assist in the development of motivation and behavioral skills necessary for daily attendance of Prince Cyril Zulu CDC and self-administration of ART medications on weekends (Saturdays and Sundays).
- To ensure transition to successful self-administration of ART medications and continuing care at the HIV Clinic at KEH upon completion of the TB treatment phase and ART-DOT.

B. DESIGN

The design of the specific components of the ASP is based on the Information-Motivation-Behavioral Skills Model, a theoretical model previously used with HIV-infected participants to enhance ART medication adherence. In addition, a modified version of the counseling style called Motivational Interviewing (MI) will be used as a strategy to provide most of the components of the ASP. The ASP is comprised of five interrelated components:

1. Development and maintenance of an educational and supportive milieu at the Prince Cyril Zulu CDC by the study health educators.

2. A four-session education, support, and skills building program, with each session scheduled at key times throughout the participants’ TB and ART-DOT course. These will be provided by the study health educators.
3. The provision of a defined set of information during TB and ART-DOT visits.

4. A pre-weekend planning session by the study health educators on the first three Fridays after ART-DOT is initiated to promote participants’ utilization of pre-planned medication adherence strategies every Saturday and Sunday.

5. A post-weekend medication adherence debriefing session by the study health educators on the first three Mondays after ART-DOT is initiated.

Each component of the ASP will be conducted at the Prince Cyril Zulu CDC and is described below.

C. COMPONENTS OF THE ASP

i) Component 1: Development and Maintenance of an Educational and Supportive Milieu

Efforts will be made by the study health educators to establish a comfortable, educational, and supportive environment at the Prince Cyril Zulu CDC where they can meet both formally and informally with participants. Within this context, participants will receive the four one-on-one educational sessions and their pre-weekend planning and post-weekend debriefing sessions. Whenever possible, the study health educators will initiate informal discussions with participants to encourage open dialoguing among participants and with the health educators.

A separate room will be made available for exclusive use of the ASP. This room will have educational materials available at all times, and be a comfortable area for participants to relax and socialize with one another during the course of their time at the Prince Cyril Zulu CDC, if they so desire. If a study participant wants additional support from the health educator, then an appointment can be made for that purpose. Likewise, if a study researcher thinks an individual would benefit from an additional appointment with the health educator, which will be accommodated within the set schedule noted below.

ii) Component 2: Provision by Study Health Educators of Four Structured Education and Support, and Behavioral Skills Sessions

The educational, support, and behavioral skills sessions have been adapted from a new ART medication adherence program that is part of the MTCT-Plus training program initiative (ref. MTCT Plus Training Manual). This component is composed of four, one-on-one interactive sessions that will be conducted by the health educators. The sessions will take place at four important times during participants TB and ART-DOT:

- 24 – 72 hours prior to commencement of ART-DOT
- 2 weeks after starting ART-DOT
- 2 months after starting ART-DOT
• 1-3 weeks before the end of TB and ART-DOT

The content matter (key educational, support and skills points/messages) for the sessions will be conveyed by the study health educator using a specially designed storyboard; the front side will face the participant and the backside will face the health educator. The storyboard will be divided into four-panels. Key points/messages for each session will be displayed on the front side of each panel along with culturally appropriate images that depict each point/message. When indicated, instructional guidelines and/or key teaching points for each session will be displayed on the backside of each panel.

The first panel will display key points/messages and images related to the basic information, motivation and behavioral skills that participants must have in order to begin self administering ART medications during the coming weekend. Each session after that will display key points/messages and images that elaborate on the previous session’s points/messages. As each session is about to begin, the health educator will unfold the storyboard to reveal the previous session’s panel in order that key points/messages can be reviewed and reinforced. At the conclusion of the fourth session, all requisite information, motivation and behavioral skills points/messages and images will be displayed and discussed so that participants can self administer daily ART medications consistently and correctly and continue HIV care at KEH.

The other important educational, motivation and skills building tool that will be developed and used during the four sessions and throughout other program components will be a double-sided Adherence Problem Solving Pocket Card. This tool will list/describe/depict commonly occurring medication adherence problems on the front side and practical solutions/strategies on the back side. Additional materials for participants to take home and to use elsewhere will be developed based upon the key points/messages of the four education, support, and behavioral skills sessions.

Session 1 (24-72 Hours Prior to Commencement of ART-DOT) - 30 Minutes

Title: Preparing to Take ART Medications

Key Instructional Guidelines and/or Teaching Points

• Identify deficits in participant’s information, motivation and behavioral skills related to attending the Prince Cyril Zulu CDC on weekdays and self administering ARVs on weekends (Ask the participant the Motivational Interviewing Screening questions in Appendix IV-A. Then tailor subsequent instruction/discussions based on these findings).

• Review key study procedures and requirements

• Begin to address critical deficits focusing mostly on information (i.e. transportation issues, Prince Cyril Zulu CDC policies and procedures and ART medication)

• Jointly identify examples of potential barriers to attending the Prince Cyril Zulu CDC and self administering weekend ART medications
APPENDIX IV

- Ask participant how he/she plans to anticipate and address these barriers

**Key Educational and Support Points/Messages**

**Information**

- HIV is a virus that weakens the body’s ability to fight infections
- HIV can be treated, but not cured
- This treatment is made up of 3 powerful medications (ddl/ddI-EC, EFV, and 3TC)
- Adherence means taking all 3 medications together every day at the same time
- The HIV germ can become stronger than the medicines if all three of the ARVs are not taken together
- Do not share your medicines with anyone
- Side Effects (i.e., nausea, vomiting, diarrhea, vivid dreams, trouble sleeping, dizziness, and rash) can occur when you first start taking the 3 medications. This often becomes better over time. Always make sure to tell your nurse or health educator about these

**Motivation**

- You need to really want to take the medicines every day
- Staff at Prince Cyril Zulu CDC and family/loved ones can help you with your medicines
- Your body is going to take time to adjust to the 3 medications. Sometimes you can even feel worse before you start to feel better. Don't be discouraged

**Behavior/Skills**

- Find a time that is most convenient for you to take your medicines
- You will need to keep the medicines in a secure place
- If you are not at home, then you need to plan how you will take your medicines on the weekends
- When you receive your weekend supply of ddl/ddI-EC, EFV, and 3TC on Friday, please remember the following:
  - You should take the 3 medications at the same time each day
  - All 3 medicines have to be taken together at least one hour before you eat
  - Always make sure to tell your nurse or health educator about any problems you are having with coming to clinic or taking your medicines
- As mentioned above, there will be take-home material for those participants who want it. This will be a combination of START developed products and previously developed products

- Session 2 (2 weeks After Starting DOT-ART) - 15 minutes

**Title: Adjusting to Taking ART Medications**
Key Instructional Guidelines and/or Teaching Points:

- Assess the participant’s experience over the last two weeks coming to the Prince Cyril Zulu CDC every day and self-administering weekend ART medications over the last 2 weeks
- Assist participant to identify and solve any problems/difficulties
- Review and reinforce the key points/messages from Session 1 (panel 1)
- Referring to panel 2, continue to address critical deficits focusing mostly on motivation and skills. (e.g. costs and benefits of attending the Prince Cyril Zulu CDC every weekday and taking ART medications, what’s needed to do this)

Key Educational and Support Points/Messages:

Information
- Brief review of Session 1 information

Motivation
- Adherence to medication plans is difficult for many people. Don’t get discouraged. If you are having difficulty, you are not alone.
- It is tempting to share medications. But, you should not share your ddl/ddI-EC, EFV or 3TC with anyone. If you share medications you could hurt both yourself and your friend/family member
- Brief review of Session 1 motivation

Behaviors/Skills
- Learn and do what works best for you in order to take your medicines
- Adherence is the most important part of improving your health – Taking medicines every day is your new "job"
- Share the successes and difficulties you are facing with your provider or health educator
- Brief review of Session 1 behaviors/skills

Session 3 (2 Months After Starting ART-DOT) - 15 minutes

Title: Feeling Good and Staying Healthy Taking ART Medications

Key Instructional Guidelines and/or Teaching Points

- Assess the participant’s experience over the last 2 months coming to the Prince Cyril Zulu CDC every day and self-administering weekend ART medications over the last 2 months
- Assist participant to identify and solve any problems/difficulties
- Review and reinforce the key points/messages from Sessions 1 and 2 (panels 1 and 2)
• Continue to address critical deficits focusing mostly on behavioral skills (e.g. securing transportation money, storing ART medications) displayed on panel 3

Key Educational and Support Points/Messages

Information

- You have reached an important goal in your treatment – 2 months of ART!
- You will continue to get stronger with the help of the ARVs – If taken every day at the same time you will be stronger than the virus.
- If you want to stop one or all medicines for any reason (like side effects, other) then tell me or talk to a study researcher, and we can work together to solve the problem – don't let the virus get stronger than you by stopping your medications by yourself.

Motivation

- HIV/AIDS is a life-long illness, but you can be very healthy for many, many years if you continue to take all your medications the way you are suppose to (together at the same time every day).
- Your energy and mental focus should be directed toward staying well/healthy - not only for yourself but also for your children, family, and friends.

Session 4 (1-3 Weeks Before the End of TB and ART-DOT) - 30 minutes

Title: Planning for Ongoing HIV Care and Daily ART Medication Taking

Key Instructional Guidelines and/or Teaching Points

- Review and reinforce the key points/messages from Sessions 1-3 (panels 1-3)
- Finish addressing critical deficits focusing on behavioral skills (e.g. self administration for a whole month at a time, securing transportation money, storing ART medications) displayed on panel 4 necessary for participant to transition to KEH and self administer daily ART medications.

Key Educational and Support Points/Messages

Information

- In ___ days you will end the first part of your treatment at the Prince Cyril Zulu CDC and start going to a new clinic at KEH to continue your HIV treatment.
  - We will arrange for a visit to see the clinic and meet the staff.
  - Provide information on the location of the clinic and how to get there
- You will have a different doctor and nurse. Their names are (NAMES HERE)
- Procedures at the HIV clinic will be new/different and will take time to adjust to.
- When you start this new phase, you will be taking all the ART medicines on your own, every day.
Motivation

- Praise participant for the accomplishments s/he has made over the last ____ months noting particular instances where s/he overcame particular barriers to daily attendance at the Principle Cyril Zulu CDC everyday and weekend self-administration of ART medications.
- Acknowledge with participant that changing the way s/he is use to receiving ART may not be comfortable at first but assure participant that you are confident that s/he is ready to make this change and able to self-administer ART medications safely for many years.
- Review and reinforce the two key motivational messages from session 3, panel 3.
- Remind participant of important people s/he has met in the bi-weekly support group meetings and encourage her/him to keep up these relationships.

Behaviors

- Help the participant construct a plan for daily self-medication.
- Help the participant construct a plan to contain/store a month’s worth of ARVs.
- Discuss concretely what the participant plans to do if s/he has a problem between monthly visits and how s/he will contact the clinic.
- Always share any problems (medical or otherwise) with the HIV clinic staff.

[Operational note: the visit to the HIV clinic should be arranged in advance with study participants and research staff. In addition, a provision for 2 weeks worth of ARTs should be given to the integrated arm participants on their last visit to the Prince Cyril Zulu CDC – such that they have 2 weeks to make their next appointment at the HIV clinic at KEH Infectious Disease Unit]

iii) Component 3: The Provision of Set Information During TB and ART-DOT Visits by Clinic DOT Nurse

The clinic DOT nurse will administer TB and ART-DOT to each participant Mondays through Fridays. The nurse will make sure s/he gives medications in the following way:

1) Asks the participant if s/he is experiencing any problems. If necessary, s/he will refer the participant to the study nurse or physician
2) Points to each ART medication as it is dispensed and quietly names it
3) Reminds the participant of the importance of coming to the Prince Cyril Zulu CDC every weekday for treatment

After giving weekend ART medication supply on the first 3 Fridays, reminds the participant to go to the second floor to see the health educator(s) for the pre-weekend planning sessions.

iv) Component 4: The Pre-Weekend ART Medication Planning Session

In order to develop strategies for weekend medication adherence that are useful, tailored, and efficacious, each participant will meet with one of the study health educators for the first three Fridays after ART-DOT is initiated. The health educator will reinforce key messages from the ASP and ask a number of questions (specified
below) related to skills building and planning for safe and correct self-administration of weekend ART medications including:

1. Where at home (or elsewhere) are you planning to put your medications to make sure that they are safe and will remind you to take your medications?

2. What problems could develop that could interfere with you taking your Saturday or Sunday medications?

3. What could you do about each problem? (The health educator begins to help the participant problem-solve using the ADHERENCE PROBLEM SOLVING POCKET CARD.)

4. Please remember the following things:
   - Before you leave the clinic, put your ART medications in a safe place like your pocket or purse.
   - As soon as you get home, transfer your medications to the place that is safe and will help remind you to take your medications.
   - On Saturday and on Sunday, remember to take all of your medications at the same time-the time that you feel would be best.
   - Do not share any of your ART medications.

5. What are your plans for the weekend?
   
   If the participant’s plans necessitate being away from home the health educator will ask:
   - Do you think these plans could interfere with your ability to take your ART medications on either Saturday or Sunday?

   If the participant indicates yes, the health educator will then help the participant use general problem-solving strategies using Motivational Interviewing to develop medication-taking plan for the weekend.

6. Have a good weekend and I’ll see you on Monday before you go for your TB and ART-DOT.

v) Component 5: The Post-Weekend ART Medication Debriefing Session

In order to receive constructive feedback and positive reinforcement regarding weekend self-administration of ART medications, participant will meet briefly with one of the study health educators for the first three Mondays after initiating ART-DOT before going to the Clinic DOT nurse for TB and ART-DOTS. The health educator will welcome each participant back to the clinic and ask the following questions:

1. How was your weekend?

2. Did you have any problems taking your Saturday or Sunday ART medications?
   
   Encourage participant to describe exactly what s/he did in terms of taking medications over the weekend.

   If the participant says no, the health educator will ask………. 
APPENDIX IV

a. Were you able to take your Saturday and Sunday medications when you thought you would?

   i. If the participant says yes, the health educator will praise the participant and wish her/him a good week and remind her/him to come to clinic daily this week.

   ii. If the participant says no, the health educator will, in a non-judgmental way, investigate the nature of the problems. S/he then will investigate with the participant possible ways these problems can be avoided during the coming weekend.

   iii. Do you think that you can fix this problem? How?

The health educator will provide the participant with positive reinforcement for coming to the Prince Cyril Zulu CDC and successfully self administering ART medications on the weekend
## II. Personnel Responsibilities for Adherence Support Program (ASP)
Participants Assigned to ART-DOT Arm

<table>
<thead>
<tr>
<th></th>
<th>Clinic DOT Nurses*</th>
<th>Study Health Educators**</th>
</tr>
</thead>
</table>
| **Mondays – Fridays**  | ▪ Ask about possible medication side effects  
                          ▪ Refer to physicians when necessary  
                          ▪ Administer TB and ART-DOT according to protocol  
                          ▪ Stress importance of adherence to visits at Prince Cyril Zulu CDC |
|                        | ▪ Conduct one-on-one education and support sessions  
                          ▪ Meet with participants who have additional health education questions or adherence issues on an ad hoc basis |
| **Fridays**            | ▪ Give weekend supply of ART medications  
                          ▪ Remind participants to go to study health educators for pre-weekend planning sessions and for post-weekend debriefing for first 3 weeks of ARVs |
|                        | ▪ Reinforce key educational and support messages for first 3 weeks of ARVs  
                          ▪ Conduct pre-weekend adherence planning sessions for first 3 weeks of ARVs |
| **Saturdays and Sundays** | None  | None |
| **Mondays**            | ▪ Ensure participants have seen study health educators for first 3 weeks of ARVs |
|                        | ▪ Reinforce key educational and support messages for first 3 weeks of ARVs  
                          ▪ Conduct post-weekend medication adherence debriefing session for first 3 weeks of ARVs |
| **Every other week**   | ▪ Facilitate participants support groups |
| **1-3 weeks Prior to End of TB Treatment** | ▪ Remind participants that transition is upcoming |
|                        | ▪ Conduct final (4th) one-on-one education and support session re: transition and complete self-administration of ARVs |

*The clinic DOT nurse will either be 1) a dedicated RN for START Participants only or 2) one of the team of rotating nurses at the Prince Cyril Zulu CDC who will see the participants. Either way, the DOT nurse responsible for the START participants will be hired by the Prince Cyril Zulu CDC and part of the larger Prince Cyril Zulu CDC staff.

**The Health Educator will be either: 1) an RN with experience in patient education, or 2) a person who is not an RN, but who has considerable experience as a Health Educator for the City DOH.
Appendix IV-A

Session 1 IMB/ Motivational Interviewing Screening Questions

Information

1. How does HIV make you sick?
2. What is a "side effect" of a medication?
3. What does "adherence to medication" mean to you?

Motivation

4. Do you think that medication for HIV works?
5. Do you know anyone who can help you with taking your medications?
6. Are you afraid of getting sick on the medications?

Behavior/Skills

7. What do you find difficult about taking your TB/other medication?
8. Do you have a safe place to keep your medication?
9. How do you get to clinic and back home?
## APPENDIX V

### SPECIMEN COLLECTION AND PROCESSING GUIDELINES

**Version 5, 3 September 2004**

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## APPENDIX V

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Transport heparin sample on ice; separate at 3000rpm within 1 hour. Ship in dry ice.

1 X Serum at -70°C.
1 X PBMCs in liquid nitrogen.
EDTA plasma from Viral Load at -70°C.
Heparin plasma at -70°C.
ACD plasma from PBMC preps at -70°C.

All the rest.

1 X Plain SST
1 X EDTA
1 X Heparin

Lancet
Lancet
UCT Pharm
## APPENDIX V

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**Micro** = UKZN Medical Microbiology  
**Lancet** = Lancet Laboratories  
**UCT Pharm** = University of Cape Town Pharmacology  
**CDC** = Prince Cyril Zulu Communicable Diseases centre  

- When specimens are collected for Lancet Laboratories, a separate specimen is required for each discipline (e.g. serology, biochemistry etc).
- 1 X Plain SST is sufficient for Liver Function Tests, Lipase and Creatinine (i.e. all Lancet biochemistry).
- After Screening and Enrolment HIV resistance testing to be performed whenever clinically suspected.
- * Obtained 2 months after initiation of TB therapy.
- † Obtained 6 months after initiation of TB therapy.
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<td>Pregnancy test T.BIL/AST/ALT Creatinine FBC Viral Load CD4/CD8 count Store serum Store PBMCs Store Plasma</td>
<td>KEH Lancet Lancet Caprisa Caprisa Caprisa Caprisa</td>
<td>Urine Plain SST Plain SST EDTA EDTA EDTA Plain SST EDTA</td>
<td>1 X Urine 2 X Plain SST 3 X EDTA 3 X ACD</td>
<td>47.5</td>
<td>No</td>
<td>1 X Serum at -70°C. 1 X PBMCs in liquid nitrogen. ACD plasma from PBMC preps at -70°C.</td>
<td>N/A</td>
<td>1 X Plain 1 X EDTA</td>
<td>Lancet Lancet</td>
</tr>
<tr>
<td></td>
<td>Sequential</td>
<td>Store serum Store PBMCs Store Plasma</td>
<td>Caprisa Caprisa</td>
<td>Plain SST ACD ACD</td>
<td>1 X Plain SST 3 X ACD</td>
<td>30.5</td>
<td>N/A</td>
<td>1 X Serum at -70°C. 1 X PBMCs in liquid nitrogen. ACD plasma from PBMC preps at -70°C.</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Month 1</td>
<td>Pregnancy Store serum Store Plasma Efavirenz pk level</td>
<td>KEH Caprisa Caprisa UCT Pharm</td>
<td>Urine Plain SST EDTA Heparin</td>
<td>1 X Urine 1 X Plain SST 1 X EDTA 1 X heparin</td>
<td>13</td>
<td>Transport heparin sample on ice; separate at 3000rpm within 1 hour. Ship in dry ice.</td>
<td>1 X Serum at -70°C. EDTA plasma at -70°C. Heparin plasma at -70°C.</td>
<td>N/A</td>
<td>1 X Heparin</td>
<td>UCT Pharm</td>
</tr>
</tbody>
</table>
### APPENDIX V

<table>
<thead>
<tr>
<th>Sequential</th>
<th>Pregnancy T.BIL/AST/ALT Creatinine FBC Store serum Store PBMCs Store Plasma Efavirenz pk level</th>
<th>KEH Lancet Lancet Caprisa Caprisa Caprisa UCT Pharm</th>
<th>Urine Plain SST Plain SST EDTA Plain SST ACD ACD Heparin</th>
<th>1 X Urine 2 X Plain SST 1 X EDTA 1 X Heparin 3 X ACD</th>
<th>43.5 Transport heparin sample on ice; separate at 3000rpm within 1 hour. Ship in dry ice.</th>
<th>Heparin plasma at -70°C. 1 X Serum at -70°C. 1 X PBMCs in liquid nitrogen. ACD plasma from PBMC preps at -70°C.</th>
<th>Rest</th>
<th>1 X Plain 1 X EDTA 1 X Heparin</th>
<th>Lancet Lancet UCT Pharm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integrated</td>
<td>Pregnancy Store serum Store Plasma Efavirenz pk level</td>
<td>KEH Caprisa Caprisa UCT Pharm</td>
<td>Urine Plain SST EDTA Heparin</td>
<td>1 X Urine 1 X Plain SST 1 X EDTA 1 X heparin</td>
<td>13 Transport heparin sample on ice; separate at 3000rpm within 1 hour. Ship in dry ice.</td>
<td>1 X Serum at -70°C. EDTA plasma at -70°C. Heparin plasma at -70°C.</td>
<td>N/A</td>
<td>1 X Heparin</td>
<td>UCT Pharm</td>
</tr>
<tr>
<td>Month 2</td>
<td>Pregnancy T.BIL/AST/ALT Creatinine FBC Store serum Store PBMCs Store Plasma Efavirenz pk level</td>
<td>KEH Lancet Lancet Lancet Caprisa Caprisa Caprisa Caprisa UCT Pharm</td>
<td>Urine Plain SST Plain SST EDTA Plain SST ACD ACD Heparin</td>
<td>1 X Urine 2 X Plain SST 1 X EDTA 1 X Heparin 3 X ACD</td>
<td>43.5 Transport heparin sample on ice; separate at 3000rpm within 1 hour. Ship in dry ice.</td>
<td>Heparin plasma at -70°C. 1 X Serum at -70°C. 1 X PBMCs in liquid nitrogen. ACD plasma from PBMC preps at -70°C.</td>
<td>Rest</td>
<td>1 X Plain 1 X EDTA 1 X Heparin</td>
<td>Lancet Lancet UCT Pharm</td>
</tr>
<tr>
<td>Sequential</td>
<td>Pregnancy T.BIL/AST/ALT Creatinine FBC Viral Load CD4/CD8 count Store serum Store Plasma Efavirenz pk level</td>
<td>KEH Lancet Lancet Lancet Caprisa Caprisa Caprisa Caprisa UCT Pharm</td>
<td>Urine Plain SST Plain SST EDTA EDTA Plain SST EDTA Heparin</td>
<td>1 X Urine 2 X Plain SST 4 X EDTA 1 X Heparin</td>
<td>30 Transport heparin sample on ice; separate at 3000rpm within 1 hour. Ship in dry ice.</td>
<td>1 X Serum at -70°C. EDTA plasma at -70°C. Heparin plasma at -70°C.</td>
<td>Rest</td>
<td>1 X Plain SST 1 X EDTA 1 X Heparin</td>
<td>Lancet Lancet UCT Pharm</td>
</tr>
<tr>
<td>Month 3</td>
<td>Integrated</td>
<td>KEH Caprisa Caprisa Caprisa UCT Pharm</td>
<td>Urine Plain SST Plain SST EDTA EDTA Plain SST EDTA Heparin</td>
<td>1 X Urine 2 X Plain SST 4 X EDTA 1 X Heparin</td>
<td>30 Transport heparin sample on ice; separate at 3000rpm within 1 hour. Ship in dry ice.</td>
<td>1 X Serum at -70°C. EDTA plasma at -70°C. Heparin plasma at -70°C.</td>
<td>Rest</td>
<td>1 X Plain SST 1 X EDTA 1 X Heparin</td>
<td>Lancet Lancet UCT Pharm</td>
</tr>
</tbody>
</table>

- **Sequential**
- **Integrated**
- **Month 2**
- **Month 3**
<table>
<thead>
<tr>
<th>Month 4 and 5</th>
<th>Integrated</th>
<th>Pregnancy</th>
<th>KEH</th>
<th>Urine</th>
<th>KEH</th>
<th>Urine</th>
<th>1 X Urine</th>
<th>0</th>
<th>N/A</th>
<th>N/A</th>
<th>N/A</th>
<th>N/A</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 6</td>
<td>Both</td>
<td>Pregnancy</td>
<td>KEH</td>
<td>Urine</td>
<td>KEH</td>
<td>Urine</td>
<td>1 X Urine</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Month 7 and 8</td>
<td>Both</td>
<td>Pregnancy</td>
<td>KEH</td>
<td>Urine</td>
<td>KEH</td>
<td>Urine</td>
<td>1 X Urine</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Month 9</td>
<td>Both</td>
<td>Pregnancy</td>
<td>KEH</td>
<td>Urine</td>
<td>KEH</td>
<td>Urine</td>
<td>1 X Urine</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Months 10 and 11</td>
<td>Both</td>
<td>Pregnancy</td>
<td>KEH</td>
<td>Urine</td>
<td>KEH</td>
<td>Urine</td>
<td>1 X Urine</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Month 12</td>
<td>Both</td>
<td>Pregnancy</td>
<td>KEH</td>
<td>Urine</td>
<td>KEH</td>
<td>Urine</td>
<td>1 X Urine</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Months 13 and 14</td>
<td>Both</td>
<td>Pregnancy</td>
<td>KEH</td>
<td>Urine</td>
<td>KEH</td>
<td>Urine</td>
<td>1 X Urine</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
## APPENDIX V

| Month 15 | Both | Pregnancy | T.BIL/AST/ALT | Creatinine | FBC | Store serum | Store Plasma | KEH | Lancet | Lancet | Lancet | Lancet | Caprisa | Caprisa | Urine | Plain SST | Plain SST | EDTA | Plain SST | Plain SST | EDTA | Store serum | Store Plasma | 1 X Urine | 2 X Plain SST | 2 X EDTA | No | 1 X Serum at -70°C. EDTA plasma at -70°C. | All the rest. | 1 X Plain SST | 1 X EDTA | Lancet | Lancet |
|----------|------|-----------|---------------|------------|-----|-------------|--------------|-----|--------|--------|--------|--------|---------|---------|-------|-----------|-----------|------|-----------|-----------|------|----------------|----------------|--------|----------------|-------------|------|-------------------------------|----------|--------|-------|
| Months 16 and 17 | Both | Pregnancy | KEH | Urine | 1 X Urine | 0 | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | No | 1 X Serum at -70°C. EDTA plasma at -70°C. | All the rest. | 1 X Plain SST | 1 X EDTA | Lancet | Lancet |
| Final Study Visit or Month 18 | Both | Pregnancy | KEH | Urine | 1 X Urine | 4 X EDTA | 2 X Plain SST | 26 | No | 1 X Serum at -70°C. EDTA plasma at -70°C. | N/A | 1 x Plain | 1 x EDTA | Lancet | Lancet |
APPENDIX VI

ADHERENCE QUESTIONNAIRE

Instructions:
Complete this form as part of the WEEKLY and MONTHLY medication review and adherence check.

7 – DAY ADHERENCE CHECK

Visit or contact date: 

Record in a Part A the requested information for each medication in the participant’s prescribed regimen. Ask the participant if he/she missed over the last 7 days for each drug recorded as yes or no. If participant took only part of the dose, please record that the dose as being missed.

Part A

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Drug Picture</th>
<th>Yesterday</th>
<th>2 days ago</th>
<th>3 days ago</th>
<th>4 days ago</th>
<th>5 days ago</th>
<th>6 days ago</th>
<th>7 days ago</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>DAY</td>
<td>DAY</td>
<td>DAY</td>
<td>DAY</td>
<td>DAY</td>
<td>DAY</td>
<td>DAY</td>
</tr>
<tr>
<td>DATE</td>
<td>DATE</td>
<td>DATE</td>
<td>DATE</td>
<td>DATE</td>
<td>DATE</td>
<td>DATE</td>
<td>DATE</td>
<td>DATE</td>
</tr>
<tr>
<td>1. EFV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. DDI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. 3TC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Part B

I’m going to read some reasons why people MISS taking their medication. Please answer “YES” or “NO” to indicate whether or not each of the following reasons describes why you MISSED taking your medicine.

<table>
<thead>
<tr>
<th>#</th>
<th>Reason</th>
<th>Yes</th>
<th>No</th>
<th>#</th>
<th>Reason</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I was confused or uncertain about how to take the medication</td>
<td></td>
<td></td>
<td>11</td>
<td>I did not want others to notice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>I was too depressed</td>
<td></td>
<td></td>
<td>12</td>
<td>I don’t think I need the medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>There was too much medication to take</td>
<td></td>
<td></td>
<td>13</td>
<td>I did not want to mix medicines with alcohol or other drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>I forgot to take the medication</td>
<td></td>
<td></td>
<td>14</td>
<td>Felt that the drugs were toxic or harmful</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>I slept through a dose</td>
<td></td>
<td></td>
<td>15</td>
<td>I shared my medication with others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>I was away from home</td>
<td></td>
<td></td>
<td>16</td>
<td>My medication was stolen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>I was too busy</td>
<td></td>
<td></td>
<td>17</td>
<td>Felt sick or ill</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>I had a change in my routine</td>
<td></td>
<td></td>
<td>18</td>
<td>Ran out of pills</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>I felt worse when I took the medication How did you feel worse?</td>
<td></td>
<td></td>
<td>19</td>
<td>Felt good</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Had problems taking pills at specified times</td>
<td></td>
<td></td>
<td>20</td>
<td>Other reason</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX VII

FUNCTIONAL ASSESSMENT OF HIV INFECTION (FAHI) AND BEHAVIORAL RISK ASSESSMENT QUESTIONNAIRE

Below is a list of statements that other people with your illness have said are important. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

<table>
<thead>
<tr>
<th>PHYSICAL WELL-BEING</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Some-what</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have a lack of energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have nausea</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Because of my physical condition, I have trouble meeting the needs of my family</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am bothered by side effects of treatment</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel ill</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am forced to spend time in bed</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>*I have been short of breath</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am bothered by a change in weight</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I get tired easily</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel fatigued</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel weak all over</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>*I have been coughing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

* Items are not scored in current FAHI version.
By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I feel sad</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel nervous</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I worry about dying</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I worry that my condition will get worse</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am unhappy with my appearance</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>It is hard to tell other people about my infection</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I worry about spreading my infection</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am concerned about what the future holds for me</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I worry about the effect of stress on my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am embarrassed by my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

<table>
<thead>
<tr>
<th>FUNCTIONAL AND GLOBAL WELL-BEING</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I am able to work (include work at home)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>My work (include work at home) is fulfilling</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am able to enjoy life</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have accepted my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am sleeping well</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am enjoying the things I usually do for fun</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am content with the quality of my life right now</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am satisfied with how I am coping with my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am losing hope in the fight against my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel sexually attractive</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have a good appetite</td>
<td>0</td>
<td>1</td>
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<tr>
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**APPENDIX VII**

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

### SOCIAL WELL-BEING

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<th>Some-what</th>
<th>Quite a bit</th>
<th>Very much</th>
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### COGNITIVE FUNCTIONING

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</table>
APPENDIX VIII

TB CLINICAL AND DIAGNOSTIC TREATMENT GUIDELINES

Tuberculosis - Clinical Guidelines - Launched October 2000 (South Africa)

Author: Dr. Harry Hausler

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1) BACKGROUND

Target audience

These guidelines are for the use of doctors and nurses who provide clinical care to tuberculosis (TB) patients and to patients living with HIV/AIDS. It should be feasible to implement the recommendations, at all levels of the health system including primary care level.

Purpose

Practical advice is offered on how to deliver care to patients with the symptoms of TB and HIV/AIDS and when to refer patients for more specialised care. For more comprehensive guidelines, refer to *TB/HIV: A Clinical Manual* which is published by the World Health Organisation and is available from the Department of Health.

Interaction of TB and HIV/AIDS

- TB is the most common disease and the leading cause of death in people living with HIV/AIDS.
- It is caused by *Mycobacterium tuberculosis*, also known as TB bacilli.
- HIV, by attacking the immune system, makes a person who is infected with TB bacilli more likely to get sick with TB.
- TB can occur at any time, but often occurs early in the course of HIV disease.
- TB probably accelerates the progression of HIV disease.
- In the absence of HIV infection, only about 10% of people infected with TB bacilli get sick with TB during their lifetime. In people who are infected with HIV, about 50% may get sick with TB.
- About 40% of TB patients in South Africa are infected with HIV and this proportion is increasing rapidly.
- TB can be prevented in people living with HIV/AIDS using isoniazid prophylaxis.

**TB can be cured**, whether a patient is infected with HIV or not, using Directly Observed Treatment, Short-Course (DOTS), with the same drugs for the same amount of time.

### SUMMARY

- TB is the most common disease and the leading cause of death in people living with HIV/AIDS.
- HIV increases the risk of progressing from TB infection to TB disease.
- TB can be prevented in people living with HIV/AIDS using isoniazid prophylaxis.
- TB can be cured, whether a patient is infected with HIV or not, using Directly Observed Treatment, Short-Course (DOTS), with the same drugs for the same amount of time.
2) THE DOTS STRATEGY

The elements of DOTS

"DOTS" means "Directly Observed Treatment, Short-course". It is an internationally recommended strategy for controlling TB. It has been effective in such diverse settings as China, Botswana and New York City. South Africa has been implementing DOTS since 1996.

The elements are:

- Political commitment - direct resources towards TB control including appointment of district coordinators.
- Identify infectious patients with sputum smear microscopy.
- Directly observe treatment and provide patient-centred care.
- Ensure drug supply and use of standardised anti-TB treatment regimens.
- Monitor treatment outcomes with the TB recording and reporting system (e.g. TB register).

Patient-centred care

- An important factor in whether or not the patient will complete treatment is their relationship with their health worker.
- Patient-centred care requires:
  - Addressing each patient's needs.
  - Always being friendly, courteous and encouraging.
  - Explaining the importance of completing treatment.
  - Discussing the patient's feelings, expectations and potential barriers that will prevent success from the outset. Most patients will be able to predict their own adherence accurately, taking their lifestyle, habits and past experience into account.
  - Trying to ensure that the same health worker listens to the patient, monitors, encourages and provides feedback on progress. This will allow a bond to develop which may help to ensure completion of treatment.
  - Should more than 2 doses of treatment be missed, making an extra effort to help the patient mobilise support to manage any problems.
  - Making your services as convenient as possible for the patient, by keeping clinic waiting times short and making treatment accessible outside normal working hours.

SUMMARY

- The DOTS strategy is effective in curing TB.
- Completing TB treatment is difficult - address patients' needs to help them complete their treatment.

3) DIAGNOSIS OF TB IN ADULTS

Diagnosis of pulmonary TB: Symptoms and history

More than 85% of people with TB in South Africa have TB of the lungs (pulmonary TB). The symptoms of this TB are the same whether patients are infected with HIV or not:
TB of other organs (extrapulmonary TB) may also occur and is more frequent in people infected with HIV (see "Extrapulmonary TB" section).

In a patient with symptoms of TB, a careful history should be taken. The following are risk factors for TB:

- known or suspected HIV infection
- exposure to a pulmonary TB case, especially a sputum smear-positive case
- industrial silica dust exposure (e.g. in underground miners)

**Physical examination**

The physical signs of TB are non-specific and do not help to distinguish TB from other chest diseases.

**Investigations**

**New patients**

New patients are patients who have never had more than 4 weeks of TB treatment in the past. For these patients, do:

**Sputum for smear microscopy** – The best way to diagnose pulmonary TB is by sending the patient’s sputum for smear microscopy (stained for acid-fast bacilli or AFB). Two sputum samples should be examined.

- If 2 sputum smears are positive, then treat as a new patient.
- If only one sputum smear is positive, then do a chest x-ray. If it is too difficult to obtain a chest x-ray, TB treatment may be initiated for a patient with a single positive sputum smear.
- If both sputum smears are negative, then give a one-week course of antibiotics and reassess.

**Sputum collection** – In an outpatient setting, ask the TB suspect to give a sputum sample as follows:

- Label the container first with the patient’s name, TB register number, clinic/hospital name, and “TB specimen”.
- Bring the patient to a well-ventilated area, preferably outside without others watching. Sputum collection indoors without good ventilation increases the risk of transmitting TB to others.
- Demonstrate a deep cough, beginning with 3 deep breaths.
- Give the patient the container without the lid.
- Hold the lid yourself, ready to replace it immediately.
• Stand behind the patient.
• Ask the patient to cough up material from deep in the lungs and spit the sputum into the container.
• Instruct the patient to be very careful not to contaminate the outside of the container.
• Take the container from the patient and screw on the lid tightly.
• Send the container as quickly as possible to the laboratory. If the sample can not be sent immediately, then store it in the cold, preferably in a fridge.
• If results can be obtained the same day, ask the patient to wait for the results.
• Give the patient a container with instructions to cough up another sample into the container when they wake up the next morning, and to return the next day.
• In hospital, 2 early morning sputum samples should be collected.

**SUMMARY**

- Sputum smear microscopy is the best way to diagnose pulmonary TB.
- Collect 2 sputum samples.
- Proper sputum collection is crucial for TB diagnosis.
- Ensure that lids are tightly screwed onto sputum containers after sputum collection.
- If 2 sputum smears are positive, then treat as a new patient.

**Course of antibiotics** - If the patient has 2 negative sputum samples, provide a 7-day course of broad-spectrum antibiotics (e.g. amoxicillin 250 mg three times per day). Reassess the patient after the course.

**Chest x-ray** - Do a chest x-ray if the patient has:
- only one positive sputum smear or
- 2 negative sputum smears and continues to cough after a course of antibiotics.

If the patient has one positive sputum smear and a chest x-ray suggestive of TB, then treat as a new patient.

No chest x-ray pattern is absolutely typical of TB. Chest x-ray changes in TB/HIV patients reflect the degree of immunocompromise. In early HIV disease (mild immunocompromise), the appearance is classical:
- upper lobe infiltrates
- bilateral infiltrates
- cavitation
- pulmonary fibrosis and shrinking
- In late HIV disease (severe immunocompromise), the appearance is atypical:
  - interstitial infiltrates (especially lower zones)
  - no cavitation

**SUMMARY**

- Do a chest x-ray if the patient has only one positive sputum smear OR if the patient has 2 negative sputum smears with no response to a course of antibiotics.
APPENDIX VIII

- No chest x-ray pattern is absolutely typical of TB.
- Chest x-ray patterns in TB/HIV patients with severe immunocompromise are often atypical.
- If a patient has one positive sputum smear and a chest x-ray suggestive of TB, then treat as a new patient.

**TB culture** - If a patient has 2 negative smears, has not improved on a course of antibiotics and has a normal chest x-ray, reassess the diagnosis. If the chest x-ray is compatible with TB, collect 2 sputa and send one for sputum smear microscopy and one for TB culture.

- If either the sputum smear or the sputum culture is positive, then treat as a new patient.
- If a patient is severely ill, with 2 negative sputum smears and chest x-ray abnormalities consistent with extensive pulmonary TB (interstitial or miliary) then a medical officer may take the decision to treat for TB before culture results are available.
- Once the decision to treat has been taken, treatment should continue for the entire 6 months. No trials of therapy should be given.

**SUMMARY**

- Ideally, TB treatment should only be started if there is a positive sputum smear or culture.
- People living with HIV/AIDS are more likely to have smear-negative, culture-positive pulmonary TB.
- A medical officer may take the decision to treat a TB patient who is severely ill, with 2 negative sputum smears, with chest x-ray abnormalities consistent with extensive pulmonary TB.

**Retreatment patients**

Retreatment patients are patients who have been treated for TB for more than 4 weeks in the past. They are more likely to have resistance to one or more of the anti-TB drugs, so their sputum should be sent for culture and susceptibility testing. People living with HIV/AIDS have an increased risk of recurrence of TB after completing TB treatment.

**Sputum for TB smear microscopy**

- Collect one sputum sample for smear microscopy as described above.
- Give the patient 2 containers with instructions to cough up 2 samples into the container when they wake up the next morning.
- Send one of the 2 samples for smear microscopy.
- If 2 sputum smears are positive, then treat as a retreatment patient.
- If only one sputum smear is positive, then do a chest x-ray. If it is too difficult to obtain a chest x-ray, TB treatment may be initiated for a patient with a single positive sputum smear.
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- If both sputum smears are negative, then give a one-week course of antibiotics and reassess.

**Sputum for TB culture and susceptibility**

- Send the second early morning sputum sample for TB culture and susceptibility testing, if possible.
- If the culture is positive, then start on TB retreatment regimen.
- If there is resistance to anti-TB drugs, then refer to a medical officer.

**Course of antibiotics** - If 2 sputum smears are negative, then give a 7-day course of broad-spectrum antibiotics (e.g. amoxicillin 250 mg three times per day). Reassess the patient after a course of antibiotics.

**Chest x-ray** - Do a chest x-ray if the patient has:

- only one positive sputum smear or
- 2 negative sputum smears and continues to cough after a course of antibiotics.
- If the patient has one positive sputum smear and a chest x-ray suggestive of TB, then treat as a retreatment patient.
- If a patient is severely ill, with 2 negative sputum smears and chest x-ray abnormalities consistent with extensive pulmonary TB (interstitial or miliary) then a medical officer may take the decision to treat for TB before culture results are available. If there is no positive sputum smear or culture, then the patient should be treated with the new treatment regimen.

**SUMMARY**

- People living with HIV/AIDS are more likely to have a recurrence of TB after completing TB treatment
- All retreatment TB suspects should have sputum sent for culture and susceptibility testing
- The retreatment regimen should only be given to patients with a positive sputum smear or culture
- A medical officer may take the decision to treat a TB patient who is severely ill, with 2 negative sputum smears, with chest x-ray abnormalities consistent with extensive pulmonary TB. This patient should be treated with the new treatment regimen.

**Multidrug resistant TB (MDR TB)**

Multidrug resistant TB (MDR TB) refers to TB which is resistant to at least isoniazid and rifampicin. It is difficult and expensive to treat. Currently, the cure rate of MDR TB patients is less than 50%. It is therefore essential to prevent its development.

- MDR TB is only diagnosed by TB culture and susceptibility testing.
- MDR TB can be prevented by treating TB patients with appropriate TB regimens (see "Treatment of TB" section), ensuring patient adherence to treatment by providing DOT (see "Directly Observed Treatment" section) and obtaining drug susceptibility tests when indicated (see "Monitoring TB Treatment" section).
- Refer MDR TB patients to a MDR TB unit where experienced clinicians can treat the patient according to the 'Guidelines for the Management of Drug-resistant Tuberculosis Patients in South Africa' which are available from the Department of Health. If you are unsure of which facility is designated as a MDR TB unit in your
province, contact your Provincial TB Coordinator (a list of Provincial TB Coordinators is attached in Annex 4).

**SUMMARY**

- Multidrug resistant TB (MDR TB) is TB which is resistant to isoniazid and rifampicin.
- MDR TB patients should be referred to a MDR TB unit.

**Diagnosis of extrapulmonary TB**

Common forms of extrapulmonary TB associated with HIV are: lymphadenopathy, pleural effusion, pericardial disease, miliary, meningitis.

- Extrapulmonary TB is common in HIV-positive patients.
- Many patients with extrapulmonary TB also have pulmonary TB so they should also be investigated for this (see "Pulmonary TB" section).
- Diagnosis of extrapulmonary TB is often difficult, so diagnosis may be presumptive, after excluding other conditions.
- The treatment of extrapulmonary TB is the same as the treatment for pulmonary TB (see "Treatment of TB" section).

**TB meningitis**

TB meningitis is life threatening if not treated promptly.

- Patients present with gradual onset of headache and decreased consciousness.
- Examination reveals neck stiffness and positive Kernig's sign (flex one of the patient's legs at hip and knee with the patient lying on back, and then straighten the knee. Resistance to straightening the knee and pain in the lower back and posterior thigh suggest meningeal inflammation).
- Diagnosis rests on clinical grounds and lumbar puncture to examine cerebrospinal fluid (CSF) (elevated CSF white cells with predominance of lymphocytes, increased protein, decreased glucose and sometimes the presence of acid-fast bacilli).
- Always exclude cryptococcal meningitis by cryptococcal antigen test, if possible. If cryptococcal antigen test is not available, do CSF microscopy (India ink stain) and, if available, fungal culture.
- Patients with TB meningitis should be hospitalised.

**Tuberculous lymphadenopathy**

- Persistent generalised lymphadenopathy (PGL) develops in up to 80% of HIV-infected individuals and requires no treatment. In PGL, lymph nodes are non-tender, <2 cm in size and symmetrical.
- Lymph node disease, including tuberculous lymphadenopathy, should be suspected if lymph nodes are tender, painful, nonsymmetrical, matted, fluctuant, rapidly growing or associated with fever, night sweats or weight loss.
- If clinical features suggest a cause of lymphadenopathy other than PGL, refer to a doctor who will do a needle (18G or 19G) aspirate of the lymph node (TB is diagnosed if the aspirated material is caseated and a smear of the aspirate reveals acid-fast bacilli).
• If no diagnosis is made after a needle aspirate, a lymph node biopsy should be done.
• Tuberculosis may also cause mediastinal or intra-abdominal lymphadenopathy that may be detected by X-ray, ultrasound or computerised axial tomography (CT scan). This may be treated empirically, unless the nodes are accessible to aspiration at a tertiary health facility where the process may be guided by CT scan, fluoroscopy or ultrasound.

Miliary TB

Miliary TB results from widespread blood borne dissemination of TB bacilli ("miliary" means "like small millet seeds").

• Miliary TB is an under-diagnosed cause of end stage wasting in HIV-positive individuals.
• Patients present with fever, night sweats and weight loss and may have an enlarged liver and spleen (hepatosplenomegaly).
• Chest x-ray shows diffuse, uniformly distributed, small miliary nodules.
• Full blood count may show pancytopenia (this may also be seen as a result of HIV).
• Bacterial confirmation of the diagnosis is sometimes possible from sputum, CSF or bone marrow.

Tuberculous serous effusions

Inflammatory tuberculous effusions may occur in any of the serous cavities of the body, i.e. pleural, pericardial or peritoneal cavities. They are a common form of TB in HIV-positive patients.

• Patients usually have systemic and local features.
• Microscopy of the aspirates from tuberculous serous effusions rarely show AFB because the fluid forms as an inflammatory reaction to TB lesions in the serous membrane.
• TB culture is of no immediate help because a culture result takes three weeks.
• The aspirate is an exudate (the protein content is more than 30g/L). A biochemistry lab is not required to diagnose an exudate. Let the aspirated fluid stand for while. If it clots, it is an exudate.
• In populations with a high prevalence of HIV, TB is the commonest cause of an exudative serous effusion.

Tuberculous pleural effusion

• Typical clinical features are chest pain, breathlessness, tracheal and mediastinal shift away from the side of the effusion and decreased chest movement.
• Chest x-ray shows unilateral, uniform white opacity, often with a concave upper border.
• Diagnosis is done by pleural aspiration. The fluid is an exudate and is usually straw coloured. The white cell count is high (1 000 - 2 500 per mm3).
• If facilities are available, a closed pleural biopsy can be done with an Abrams needle for histological diagnosis. The yield is about 75% positive for TB.
• Differential diagnosis includes malignancy, post-pneumonic effusion and pulmonary embolism.
APPENDIX VIII

SUMMARY

• In a hospital or clinic serving a population with a high prevalence of TB you should treat a patient with a unilateral exudative pleural effusion with anti-TB drugs.

Tuberculous empyema

• The physical signs are the same as those of a pleural effusion.
• If pleural aspiration reveals pus, it indicates an empyema. Send the pus to the laboratory for examination for TB, Gram stain and bacterial culture. The main differential diagnosis is bacterial empyema.
• A succussion splash is a splashing sound heard with the stethoscope while shaking the patient's chest. It indicates a pyopneumothorax (pus and air in the pleural space). After chest x-ray confirmation, insert a chest drain with underwater seal.

Tuberculous pericardial effusion

• Diagnosis usually rests on suggestive systemic features and ultrasound.
• Cardiovascular symptoms include: chest pain, shortness of breath, cough, dizziness and weakness due to low cardiac output, leg swelling, right hypochondrial pain (liver congestion), abdominal swelling (ascites).
• Cardiovascular signs include: tachycardia, low blood pressure/pulsus paradoxus, raised jugular venous pressure, impalpable apex beat, distant heart sounds, pericardial friction rub, signs of right-sided heart failure (e.g. hepatosplenomegaly, ascites, oedema).
• Chest x-ray may show a large globular heart, clear lung fields, pleural effusion.
• ECG may show tachycardia, flattening of ST and T waves, low voltage QRS complexes.
• Treatment is the same as for all types of TB (see "Treatment of TB" section) but corticosteroids can be added. Treatment without pericardiocentesis usually results in resolution of tuberculous pericardial effusion.
• In cases of cardiac tamponade the effusion should be aspirated by a specialist.

SUMMARY

• In high TB/HIV prevalence populations, TB is the most likely treatable cause of pericardial effusion. It may be safer for the patient to start presumptive anti-TB treatment than to undergo diagnostic pericardiocentesis.

Tuberculous ascites (TB peritonitis)

• Clinical features include systemic features and ascites. There may be palpable abdominal masses (mesenteric lymph nodes). Bowel obstruction may develop from adhesion of nodes to bowel; and fistulae between bowel, bladder and abdominal wall.
• Always do a diagnostic ascitic tap. The aspirated fluid is usually straw coloured, but is occasionally turbid or blood stained. The fluid is an exudate, usually with more than 300 white cells per mm3. White cells are predominantly lymphocytes.
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(polymorphs predominate in spontaneous bacterial peritonitis which is a common complication of cirrhosis).

- Do a chest X-ray to look for pulmonary TB.
- Diagnosis is usually presumptive - in doubtful cases, a peritoneal biopsy may be considered at a hospital if a mini-laparotomy or laparoscopy can be performed.

**Tuberculosis of bones and joints**

When primary TB occurs during childhood, bacilli often spread to the vertebrae and ends of long bones. Disease may either rapidly develop there or months or years later. The infection may spread locally causing arthritis.

- Weight-bearing bones and joints are the most commonly affected, with the spine most frequently affected, then the hip, the knee and the bones of the foot.
- In the spine, TB starts in the intervertebral disc, spreads along the ligaments and involves the adjacent vertebral bodies.
- Clinical features of spinal TB include: pain and swelling locally, sometimes an obvious lump or bend of the spine, stiff back, reluctance to bend the back, a child that refuses to walk, paralysis or weakness of the lower limbs due to pressure on the spinal cord.
- X-rays of the spine show disc space narrowing and erosion of the adjacent vertebral bodies.
- A well-fitted orthopaedic brace is sometimes needed to immobilise the affected area.
- Surgical treatment is necessary if there is compression of the spinal cord and the patient has weakness or paraplegia of the lower limbs. These patients should be referred to a specialist urgently.

**4) TREATMENT OF TB IN ADULTS**

**Directly observed treatment (DOT)**

The best way to ensure that a TB patient completes TB treatment is with Directly Observed Treatment (DOT).

DOT means that every dose of treatment is seen to be swallowed by a treatment supporter. Every TB patient should have DOT. It is required for all smear-positive (infectious) TB patients.

DOT is organised as follows:

- Discuss with the patient who they would like as a treatment supporter.
- Treatment supporters can be any responsible person who the patient trusts such as a health worker, colleague, employer, traditional healer, friend, community member or family member.
- Explain to the treatment supporter how to give the correct doses of TB drugs, refer the patient to the clinic if they develop side effects, and how to fill in the Patient Treatment Card.
- Provide monthly supplies of drugs and review the Patient Treatment Card to make sure that treatment is going smoothly.
- Provide ongoing support to the patient and treatment supporter and follow up all problems and concerns.
• Trace the patient and ensure appropriate treatment supervision if the patient interrupts treatment.

The treatment supporter's responsibilities:
• Observing the TB patient as s/he swallows the daily dose of medication.
• Liaising with the health worker to ensure an uninterrupted supply of TB drugs.
• Advising the patient to attend the clinic if side effects develop, and reminding the patient of clinic appointments.
• Checking off the appropriate box on the Patient Treatment Card each time a dose of TB drugs is taken.
• Supporting and motivating the patient to complete treatment.
• Visiting the patient or informing the health worker on the second day if the patient did not show up to receive treatment.
• Informing the health worker if the patient moves or is unable to receive TB treatment for any reason.

The TB patient's responsibilities:
• Swallowing each dose of TB medication, reporting side effects and any other problems promptly to the supporter or health worker and attending the clinic for appointments.
• Informing the health worker or supporter if moving or unable to receive TB treatment for any reason.

The employer's responsibilities (for DOTS in the workplace):
• Supporting and encouraging DOTS in the workplace.
• Allowing time off for employees to meet with health workers about how to provide DOTS in the workplace.
• Allowing time off for employees to go to clinic and attempting to provide a private space where a TB patient can receive TB treatment.

SUMMARY
• Directly Observed Treatment (DOT) means that every dose of treatment is seen to be swallowed by a treatment supporter.

TB treatment regimens
TB treatment is the same for those who are infected with HIV and those who are not. Treatment is given five times per week in the intensive phase (the first 2 months of treatment in new patients and the first 3 months of treatment in retreatment patients).

Hospitalised TB patients can receive the same dosages 7 days per week. For continuation phase treatment (the last 4 months of treatment for new patients and the last 5 months of treatment for retreatment patients) can be given five times or three times a week. Ensure that you give the correct doses.
APPENDIX VIII

SUMMARY

- TB treatment is the same whether a patient is infected with HIV or not.

New adult patients (Regimen 1)

New smear or culture-positive and other serious pulmonary and extrapulmonary tuberculosis

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>2 Months Initial Phase (treatment given 5 times a week)</th>
<th>4 Months Continuation (treatment given 5 times a week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Weight</td>
<td>Combination tablet RHZE 120/60/300/200 mg*</td>
<td>Combination tablet RH 150/100 mg</td>
</tr>
<tr>
<td></td>
<td>4 tabs</td>
<td>3 tabs</td>
</tr>
<tr>
<td>&lt;50 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;50 kg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Ethambutol 225 mg in combination is also acceptable
R=rifampicin; H=isoniazid (INH); Z=pyrazinamide; E=ethambutol; S=streptomycin

Retreatment adult patients (Regimen 2)

Smear or culture positive retreatment cases

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>2 Months Initial Phase (treatment given 5 times a week)</th>
<th>3rd Month (5 times a week)</th>
<th>5 Months Continuation Phase (5 times a week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Weight</td>
<td>RHZE 120/60/300/200 mg*</td>
<td>RHZE</td>
<td>RH 50/100 mg</td>
</tr>
<tr>
<td></td>
<td>4 tabs</td>
<td>4 tabs</td>
<td>3 tabs</td>
</tr>
<tr>
<td>&lt;50 kg</td>
<td></td>
<td></td>
<td>2 tabs</td>
</tr>
<tr>
<td>&gt;50 kg</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Streptomycin should be reduced to 750 mg per day to those older than 45 years and not be given to those over 65 years.* Ethambutol 225 mg in combination is also acceptable.

Three times per week regimens

Three times per week regimens have been shown to be as effective as daily regimens. To avoid mistakes, the regimen should be applied to all patients at particular facilities. Furthermore, since different packaging is involved, the use and packing of 3 times per week regimens should be approved and co-ordinated at provincial level.
New adult regimen with 3 times per week continuation phase

<table>
<thead>
<tr>
<th>Pretreatment Body Weight</th>
<th>2 Months Initial Phase (treatment given 5 times a week)</th>
<th>4 Months Continuation (treatment given 3 times a week)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Combination tablet RHZE 120/60/300/200 mg</td>
<td>Combination tablet RH 150/100 mg</td>
</tr>
<tr>
<td>&lt;50 kg</td>
<td>4 tabs</td>
<td>3 tabs</td>
</tr>
<tr>
<td>&gt;50 kg</td>
<td>5 tabs</td>
<td></td>
</tr>
</tbody>
</table>

Retreatment adult regimen with 3 times per week continuation phase

<table>
<thead>
<tr>
<th>Pretreatment Body Weight</th>
<th>2 Months Initial Phase (treatment given 5 times a week)</th>
<th>3rd Month (5 times a week)</th>
<th>5 Months Continuation Phase (3 times a week)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RHZE 120/60/300 /200 mg streptomycin RHZE 150/10 0 mg</td>
<td>H100 mg</td>
<td>RH 300/150 mg H100 mg E 400 mg</td>
</tr>
<tr>
<td>&lt;50 kg</td>
<td>4 tabs 750 mg</td>
<td>4 tabs 3 tabs 1 tab</td>
<td>2 tabs 3 tabs 4 tabs</td>
</tr>
<tr>
<td>&gt;50 kg</td>
<td>5 tabs 1000 mg</td>
<td>5 tabs</td>
<td></td>
</tr>
</tbody>
</table>

**SUMMARY**
- New adult TB patients are treated for 6 months.
- Retreatment adult TB patients are treated for 8 months.

**Cotrimoxazole prophylaxis**

Cotrimoxazole is highly effective in preventing pneumocystis carinii pneumonia and toxoplasmosis. It also has activity against pneumococcus, Salomonella and Nocardia.

The 'HIV/AIDS Clinical Care Guidelines for Adults' recommends cotrimoxazole 960 mg (either 3 times per week or 5 times per week) to all HIV-positive patients (whether they have TB or not) who:

- have a CD4 count less than 200 cells/cubic mm or
- have clinical signs of advanced immune deficiency (e.g., oropharangeal candidiasis)
- have already had pneumocystis carinii pneumonia or toxoplasmosis

A study in Abidjan, Cote d'Ivoire (Sassan-Morokro et al., 12th World AIDS Conference, Geneva 28 June-3 July 1998, Abstract #12461) found that daily cotrimoxazole (960 mg) prophylaxis among HIV-infected TB patients started one month into anti-TB treatment...
decreased mortality by 48% from 21.6 per 100 person-years to 11.3 per 100 person-years. It also decreased hospitalisation by 44%.

The spectrum of HIV-related opportunistic infections in South Africa may be different from the spectrum in Cote d'Ivoire. It is therefore not known whether providing cotrimoxazole prophylaxis to HIV-infected TB patients in South Africa will also decrease mortality and hospitalisations. However, cotrimoxazole prophylaxis is being recommended for any HIV-positive people with advanced immune deficiency and TB is a sign of immune deficiency in people living with HIV. It is therefore recommended that all HIV-positive TB patients be offered cotrimoxazole prophylaxis as follows:

- Wait until the patient has completed one month of TB treatment - this is to be able to differentiate between side effects from anti-TB drugs and side effects from cotrimoxazole.
- Counsel patients on the effectiveness and side effects of cotrimoxazole (i.e., explain to patients that cotrimoxazole can help prevent pneumonia and other infections, that it is only effective while the patient takes it so that it should be taken for the rest of their lives and that it can cause a rash and other side effects).
- If a patient chooses to accept it, provide cotrimoxazole 960 mg either 3 times per week (Monday, Wednesday, Friday) or 5 times per week (daily from Monday to Friday).

5) CONTACTS

Contact tracing

Contacts are people who were living in the same house as a TB patient while the patient was smear-positive. Contacts are at risk of becoming infected with TB.

- Advise patients to bring any contacts under 5 years old to the clinic for assessment.
- Advise patients to tell contacts who are older than 5 years old to come to the clinic if they develop TB symptoms.
- Put contacts up to 5 years old on TB prophylaxis.
- Contacts of any age who are known to be HIV-positive should be asked to come to the clinic to assess if they should start TB preventive therapy (see "Eligibility for TB Preventive Therapy" section).
- Your first priority is to cure new smear-positive (infectious) TB patients. Contact tracing is a lesser priority.

SUMMARY

- Contacts up to 5 years old should be put on TB prophylaxis.
- Contacts of any age who are known to be HIV-positive should be asked to come to the clinic to assess if they should start TB preventive therapy.
Prophylaxis for child contacts up to 5 years old

**TB prophylaxis for children < 5 years old**

<table>
<thead>
<tr>
<th>Pretreatment Body weight</th>
<th>3 months (5 times a week)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RH60/30 mg</td>
</tr>
<tr>
<td>3-4 kg</td>
<td>1/2 tablet</td>
</tr>
<tr>
<td>5-7 kg</td>
<td>1 tablet</td>
</tr>
<tr>
<td>8-9 kg</td>
<td>1 ½ tablets</td>
</tr>
<tr>
<td>10-14 kg</td>
<td>2 tablets</td>
</tr>
<tr>
<td>15-19 kg</td>
<td>3 tablets</td>
</tr>
<tr>
<td>20-24 kg</td>
<td>4 tablets</td>
</tr>
<tr>
<td>25-29 kg</td>
<td>5 tablets</td>
</tr>
</tbody>
</table>

R = rifampicin  H = isoniazid

6) **MONITORING PROGRESS IN ADULT PULMONARY TB**

During TB treatment, all pulmonary TB patients should be monitored by sputum smear microscopy. In some cases, sputum culture and susceptibility testing is necessary. Monitoring TB is done the same way whether a patient is infected with HIV or not.

**SUMMARY**

- Monitoring TB is done the same way whether a patient is infected with HIV or not.

**New patients**

**Sputum microscopy at 2 months**

- At 2 months, send 2 sputum samples for smear microscopy for all new patients.
- If both smears are negative, then start the continuation phase of treatment (see "Treatment of TB - New Adult Patients" section).
- If one or both of the 2-month smears is positive, then give a third month of intensive phase treatment.

**Sputum investigations at 3 months**

- Send 2 sputum samples for smear microscopy at 3 months only if one or both of the 2-month smears was positive.
- If both 3-month smears are negative, then the continuation phase of treatment should be given for 3 months (not 4 months), so that a total of 6 months of treatment is given.
- If one or both of the smears is positive, then a sputum sample should be sent for TB culture and susceptibility and the continuation phase should be started.
• If the TB bacilli are susceptible to all anti-TB drugs, the continuation phase should be continued.
• If the TB bacilli are resistant to any of the anti-TB drugs, the patient should be referred to a medical officer.

Sputum investigations at 5 months

• Send 2 sputa for smear microscopy for all new patients.
• If both smears are negative and the patient is clinically well continue treatment until 6 months and register the patient as cured.
• If one or both of the 5 month smears is positive, then register the patient as a treatment failure, send sputum for culture and susceptibility, re-register the patient as a retreatment patient and start the retreatment regimen (see "Treatment of TB - Retreatment Adult Patients" section).

SUMMARY

- Send 2 sputa for smear microscopy at 2 months and at 5 months for all new patients.
- If a patient has a positive sputum smear at 2 months, give an extra month of intensive phase treatment and send 2 sputa for smear microscopy at 3 months.
- If a patient has a positive sputum smear at 3 months or at 5 months, send sputum for culture and susceptibility testing.

Retreatment patients

Sputum investigations at 3 months

• Send 2 sputa for smear microscopy at 3 months for all retreatment patients.
• If both smears are negative, start continuation phase (see "Treatment of TB - Retreatment Adult Patients" section).
• If one or both smears are positive, send sputum for culture and susceptibility and start continuation phase.
• If the TB bacilli are susceptible to all anti-TB drugs, continue continuation phase.
• If the TB bacilli are resistant to any of the anti-TB drugs, refer to a medical officer.

Sputum investigations at 7 months

• Send 2 sputa for smear microscopy at 7 months for all retreatment patients.
• If both smears are negative, continue treatment until 8 months and register the patient as cured.
• If one or both of the smears are positive, register the patient as a treatment failure and refer to a medical officer.
SUMMARY

- Send 2 sputa for smear microscopy at 3 months and at 7 months for all retreatment patients.
- If a patient has a positive smear at 3 months, send sputum for culture and susceptibility testing.
- If a patient has a positive smear at 7 months, refer the patient to a medical officer.

7) TB PREVENTIVE THERAPY

TB Preventive Therapy and Health Services

TB can be prevented in people living with HIV/AIDS by offering isoniazid prophylaxis (TB preventive therapy). In these individuals, TB preventive therapy decreases the risk of TB disease and should be part of a package of care for people living with HIV/AIDS.

TB preventive therapy should only be offered in the following situations:

- Voluntary HIV counselling and testing by appropriately trained staff is available.
- Patients can be followed monthly to exclude active TB disease and side effects.
- The provision of preventive therapy does not interfere with the detection and cure of infectious (smear-positive) pulmonary TB cases.
- The local AIDS programme takes responsibility for implementation and there is strong collaboration with the TB programme.

Practically, this means that TB preventive therapy will not be offered initially in all public health services. It can be considered in services which have staff who can be trained in HIV counselling, where TB services are functioning well, and where monthly follow up is possible. It will be piloted in HIV/TB pilot districts and may be considered in occupational health services (including mines), in prison health services, and for health care workers.

If your health service is interested in offering TB preventive therapy, then contact your Provincial HIV/AIDS/STD Coordinator and your Provincial TB Coordinator to ensure proper co-ordination and monitoring.

SUMMARY

- TB preventive therapy should only be offered by a health service if it does not interfere with the detection and cure of infectious pulmonary TB cases and if patients can be followed monthly to exclude active TB disease.

Eligibility for TB Preventive Therapy

TB preventive therapy has been proven to prevent TB in HIV-positive patients with greater benefit seen in those who have positive tuberculin skin tests. An HIV-positive individual should be counselled on TB preventive therapy. The counselling should explain that TB
preventive therapy decreases the risk of getting TB but that TB may still occur despite it. It should also explain that there is a small risk of hepatitis as a side effect of taking isoniazid. If the individual would like to receive TB preventive therapy, the following steps should be followed:

**Screen for TB symptoms**

Determine if the patient has symptoms of TB. The symptoms of pulmonary TB are the same whether patients are infected with HIV or not:

- cough
- night sweats and fever
- loss of appetite and weight
- tiredness and weakness
- chest pain
- coughing up blood (haemoptysis)
- TB of other organs (extrapulmonary TB) may also occur and is more frequent in people infected with HIV
- If the patient does have TB symptoms, investigate for TB (see "Diagnosis of TB in Adults" section) or refer to health services which diagnose and treat TB.
- If the patient does not have TB symptoms do a chest x-ray, if possible.

**Chest x-ray**

- If possible, a chest x-ray should be done to rule out TB lung disease in asymptomatic patients.
- If the chest x-ray shows abnormalities consistent with TB, do not start TB preventive therapy and investigate further for TB.

**Tuberculin testing**

The World Health Organisation (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) have recommended that in areas where the prevalence of TB infection is greater than 30%, tuberculin testing is not required for screening for TB preventive therapy. However, clinical trials have shown that the benefit of TB preventive therapy is only significant in HIV-positive people with positive tuberculin skin tests.

In South Africa, the prevalence of TB infection is approximately 60%. Although tuberculin testing is suggested, it is not required for screening for TB preventive therapy. If your health service chooses to use tuberculin skin testing to screen for TB preventive therapy, then do the following:

- If the patient does not have symptoms of TB and has a normal chest x-ray, do a tuberculin skin test. If there is induration greater than or equal to 5 mm (tuberculin test positive) and there are no TB symptoms, start TB preventive therapy.
- If the tuberculin skin test is negative, do not start TB preventive therapy.
SUMMARY

- TB preventive therapy should be offered to HIV-positive patients with no symptoms of TB and a normal chest x-ray.
- If tuberculin testing is done, TB preventive therapy should be offered to tuberculin-positive people living with HIV with no symptoms of TB and a normal chest x-ray.

TB Preventive Therapy Regimen

Before starting TB preventive therapy, and on a regular basis, the patient should be counselled on HIV, the symptoms of side effects of isoniazid (particularly hepatitis), the symptoms of active tuberculosis and the importance of seeking care if they develop those symptoms while on preventive therapy.

For HIV-positive patients with no TB symptoms:

- Give isoniazid (INH) 5 mg/kg (maximum 300 mg) daily for 6 months.
- Give 1 month supply to the patient at a time. Ask the patient to return on a monthly basis.
- Advise the patient to return immediately if TB symptoms develop.
- At each monthly visit, monitor adherence and determine if the patient has symptoms of TB or is experiencing side effects to isoniazid (major: jaundice, or vomiting and confusion from hepatitis; minor: burning sensation in feet from peripheral neuropathy).
- If, at any time during the 6 months of preventive therapy, the patient develops TB symptoms, stop TB preventive therapy and investigate for TB.
- If the patient develops peripheral neuropathy, give pyridoxine 10-25 mg once daily.
- If the patient develops hepatitis, stop TB preventive therapy and refer to a medical officer.
- If the patient interrupts therapy, they should be counselled on the importance of adherence and may be restarted with the aim of providing at least 6 months of isoniazid during a one year period.
- If the patient interrupts therapy twice, despite counselling, then preventive therapy should be stopped.
- Maintain individual patient records and record the following: attendance at scheduled appointments, adherence (proportion of doses taken), toxicity and withdrawals from therapy due to toxicity.
- Maintain a TB preventive therapy register and monitor the following:
  - number of persons started on TB preventive therapy.
  - number of persons interrupting TB preventive therapy, for which reasons.
  - number of persons completed preventive therapy.
  - Keep track of the number of suspected TB cases in screening, the number of suspected TB cases during preventive therapy, and the number of individuals presenting to TB services who have previously taken preventive therapy.
APPENDIX VIII

SUMMARY

- Give isoniazid 5 mg/kg (maximum 300 mg) **once daily** for 6 months.
- See the patient on a monthly basis.
- If TB symptoms develop, stop TB preventive therapy and investigate for TB.
- If the patient develops hepatitis, stop TB preventive therapy and refer to a medical officer.

8) PREVENTION AND TREATMENT OF OTHER HIV-RELATED OPPORTUNISTIC INFECTIONS

See *'HIV/AIDS Management Guidelines'*.

See cotrimoxazole prophylaxis in the *'Treatment of TB in Adults'* section.

9) PROTECTION FROM TB INFECTION

Health care workers who are in contact with TB patients are at increased risk for TB infection and TB disease. Those involved in autopsies, drainage of TB abscesses and cough-inducing procedures (bronchoscopy, aerosolised pentamidine treatment) are at high risk. HIV-infected health care workers have a particularly high risk of TB.

In order to limit transmission of TB in health facilities and to protect health care workers, these measures should be followed:

Consider HIV counselling and testing

- Any health care worker in TB wards, general medical wards, outpatient clinics or laboratories which do TB microscopy should seriously consider seeking voluntary confidential HIV counselling and testing. If HIV-positive, they should be moved or given other responsibilities to minimize your contact with TB suspects or TB patients.
- In settings where there is stigmatisation of HIV-infected individuals, health care workers may be unwilling to be tested for HIV. Help decrease stigma through ongoing education and counselling.
- Many health care workers may be concerned that confidentiality of a positive test result will be difficult to maintain, because people will assume they are HIV-infected if they are moved away from contact with TB patients. This is a difficult issue to resolve. One possibility is to also offer such a move to other health care workers with increased risk for TB, such as diabetics and people on corticosteroids.

Seek care if TB symptoms develop

- Any health worker should seek care and be investigated for TB as soon as they develop TB symptoms. If they delay, they will increase the severity of the disease and will increase the risk of infecting others.

Rapidly diagnose and treat infectious TB patients

- Rapidly diagnose and treat infectious TB patients. The sooner they are diagnosed and started on treatment the sooner they will become non-infectious.
- Instruct patients to cover their mouths when coughing.
• Collect sputum properly outdoors (see "Diagnosis of Pulmonary TB - Sputum collection" section).
• Decrease delays in sputum collection and delivery. If possible, sputum samples should be transported to a microscopy centre daily, and the results should be sent back from the laboratory on the same or the next day.
• In hospitals, assign a staff member the responsibility of "cough officer" to collect sputum, deliver results back to the ward and ensure that smear-positive pulmonary TB patients are registered and started on treatment as soon as a diagnosis is made.
• As soon as spuza results are received at a clinic, trace smear-positive patients and ask them to return to the clinic to start treatment.
• Ensure directly observed treatment. If patients interrupt treatment, they may become infectious.

Isolate TB suspects and patients
• Separate coughing patients from others in waiting rooms.
• Triage coughing patients to be assessed by a health care worker quickly.
• Do not admit TB suspects for investigation in hospital if they can be investigated as outpatients. This will decrease the number of potentially infectious patients who are admitted.
• Isolate TB suspects who are admitted to hospital from other patients, especially other TB patients and immunocompromised patients (patients who are known or suspected to have HIV, diabetics, patients on systemic corticosteroids). If isolation rooms are not available, TB suspects could be kept in one area of a ward which is screened off from other sections of the ward.
• Give at least 2 weeks of sick leave to smear-positive TB patients. If patients are still coughing or are too ill to return to work then their sick leave should be extended. There is almost no increased risk of TB disease among family contacts of patients treated at home.
• Isolate smear-positive pulmonary TB patients from other patients (especially immunocompromised patients) for at least 2 weeks or until their cough resolves. Establishing a TB ward best does isolation of TB patients. Smear-negative and extrapulmonary TB patients need not be isolated, but they can also be treated in a TB ward.
• If possible, isolate TB patients who are infected with HIV in single rooms to limit their exposure to air-borne pathogens.

Implement environmental controls
• Isolation rooms, TB wards, general medical wards, outpatient clinics and rooms in which sputum induction procedures are carried out should have windows that open to the outside and doors to other parts of the hospital which are kept closed most of the time. Exhaust fans which move air from inside to outside should also be installed. Isolation rooms should ideally be located on higher floors.
• Hospital TB wards should have large windows to let plenty of sunlight in. The latter is a cheap form of ultraviolet light, which has a germicidal effect on TB bacilli.
• Ultra-violet lights are not currently recommended because, although there is experimental evidence that ultra-violet lights can kill TB bacilli, there is no evidence
of their effectiveness in reducing TB transmission in practice. UV lights are expensive, difficult to maintain and potentially harmful if not installed properly.

- Guidelines for laboratory safety are covered in the "Training Manual for Tuberculosis Microscopy Centres" available from the Department of Health.

**Ensure proper disinfection**

- Wash hands with an appropriate disinfectant or alcohol rub if your hands have contacted the patient without gloves.
- All equipment used on TB/HIV patients should either be autoclaveable or disposable. None of the equipment should be reused except sphygmomanometers or other equipment which is applied to the unbroken skin of the patient.
- Clean thermometers with soap and water and then soak in 70% alcohol for 10 minutes after each use.

**Use protective clothing**

- The effectiveness of high efficiency particulate air-filter (HEPA) respirators (masks which filter particles 1 micron in size with 95% efficiency) in preventing TB transmission has not been quantified. These masks are very expensive (US$5-7) and are therefore not affordable for most health facilities in South Africa.
- If HEPA respirators can be provided, they should be used by staff who are involved in high risk situations, such as procedures which produce respiratory aerosols (autopsies, draining TB abscesses, bronchoscopy, administering aerosolized pentamidine, endotracheal suction), working with multidrug resistant TB patients and ambulance staff who are transporting coughing TB patients.
- Masks should be discarded after being used in a high risk procedure and should generally not be worn for more than 10 minutes.
- Masks are not currently recommended for use in outpatient clinics or TB wards with drug-susceptible TB patients.
- Surgical masks are less than 50% effective in preventing the inhalation of droplet nuclei containing TB bacilli and are therefore not recommended for staff or visitors to TB wards.
- The use of surgical masks by TB patients with a productive cough who are being transported to other areas of the hospital for investigations may help to reduce TB transmission.
- Wear gloves when handling objects contaminated by sputum.

**BCG vaccination may be considered but is not recommended**

- Most people in South Africa receive BCG vaccination at birth.
- BCG revaccination is not recommended.
- BCG should not be given to HIV-positive individuals because it may cause disseminated BCG infection.
- If a health care worker who works with TB patients did not receive BCG at birth, counselling could be offered on its possible benefits and risks. If the health care worker is interested in receiving BCG vaccination, then a tuberculin skin test should be done. If the skin test is negative, then BCG could be administered.
Screening of health care workers working with TB patients

- No regular screening is required.
- Pre-employment tuberculin skin test may be done to detect past infection and a baseline chest x-ray may be done.
- Serial tuberculin testing is not recommended. The only situation in which it should be considered, is in HIV-positive health care workers in settings where decisions for provision of TB preventive therapy are based on tuberculin results (see "TB Preventive Therapy" section).
- Regular questionnaires on symptoms of TB and regular weighing to detect unexplained weight loss could also be considered, although these have not been proven to be effective.
- Annual chest x-ray screening is not recommended. A few early lesions may be detected by chest x-ray, but in the absence of symptoms, it is difficult to determine the significance of the x-ray findings.
- Tuberculin skin tests may be done on termination of employment. If the test is positive, and the pre-employment test was negative, and if the health care worker subsequently gets sick with TB, they are eligible for compensation according to the Compensation for Occupational Injuries and Diseases Act. A chest x-ray may be done on termination of employment to compare to the pre-employment chest x-ray.

SUMMARY

- HIV-positive health care workers should avoid contact with TB patients.
- Health care workers should seek care if they develop TB symptoms.
- The best way to prevent TB transmission is to rapidly diagnose and treat infectious TB patients.
- Isolation of TB patients prevents TB transmission to other patients.
- TB wards should have large windows with good ventilation and sunlight.
- If available, HEPA masks should be used by health care workers in high risk situations.

10) CONTINUITY OF CARE

A major problem which is faced by health care workers and TB/HIV co-infected patients is the lack of continuity of care in South Africa. It is important for the following reasons:

- For the patient, it helps maintain health and relieves anxiety.
- For health care workers, it assists in the provision of high quality care.
- For communities, it limits the spread of disease - e.g. adequate follow up of TB patients will prevent TB transmission, improve TB cure rates and prevent the development of multidrug resistant TB.
- Ensuring continuity of care should be a shared responsibility of patients, health care workers and communities:
- Patients should learn the symptoms of HIV/AIDS/STD/TB, seek care if they develop them, and follow health care workers' recommendations on when to come for appointments and go to referral facilities.
• Health care workers should provide high quality services, and should communicate
well with patients, and staff from other facilities.
• Communities should ensure that appropriate services are available for their members
who require care and support.
• Continuity of care for patients co-infected with HIV and TB can be improved in the
following ways:

Follow admission and discharge criteria for TB patients

The National TB Control Programme has developed admission and discharge criteria for TB
patients (see Annex 1) which incorporate several important principles for referral as follows:

• Priority for admission should be given to new smear-positive pulmonary TB patients.
• Only patients who are sick enough to require hospital care or who do not have access
to community-based care should be admitted to hospital
• Patients referred for admission should be accompanied by a completed TB transfer
form (see Annex 2).
• The decision to admit an HIV-infected TB patient should be made in the same way as
for any other TB patient, but staff who work with HIV-infected patients require
ongoing training and support to deal with the medical and social implications of
AIDS, and patients require counselling.
• Discharge planning should be started on admission and completed within 2 weeks of
admission and should include recruitment of a treatment supporter, health education
of the patient and the treatment supporter, and communication with the patient's
chosen outpatient clinic to ensure continued treatment and monitoring.
• Patients should be discharged as soon as the patient is medically stable and either able
to care for himself or has access to family or community-based care and is willing
and able to access treatment and to be monitored either by going to a clinic or by
receiving visits from a treatment supporter.

Create resource lists of services and facilities for referral

• Obtain a copy of the resource list for HIV/AIDS and STD services, 'South African
AIDS Network: A Directory of the National AIDS Database, 1997' from the
Department of Health.
• Collaborate with other role players (government departments, community based
organisations, non-governmental organisations, private organisations) to create a
district level resource list for HIV/AIDS/STD/TB which lists the type of service, the
name of a contact person, the telephone number, and how to refer a person to the
service.

Encourage formation of community support services

• Encourage the formation of community support services (directly observed TB
treatment, home based care, palliative care, counselling, nutritional assistance,
spiritual support and economic support) and provide them with technical assistance.

Use available transfer forms

• For TB patients, whether they are infected with HIV or not, use the 'Patient Transfer
Form' (GW 20/14) (see Annex 2) which is available from the Department of Health.
• Give this transfer form to the patient and send a duplicate to the referral facility on discharge to ensure that health care workers there receive all the information they need to provide continuing care.
• If you feel that the form does not provide sufficient space or information, add a referral letter with more details.
• For HIV-infected patients, consider giving the following information with the patient's consent: the date of the patient's first positive HIV test, the history of opportunistic infections, the current immune status (lymphocyte count, +/-CD4, +/- viral load), current medications for prophylaxis and treatment, and details on the patient's support network (with whom there is shared confidentiality of the patient's HIV status).
• Consider measuring the proportion of patients who are lost to follow up after being discharged from hospital using the "Loss to follow up form" (see Annex 3).
• Improve co-ordination between services
• Ensure good communication and collaboration when referring patients between community services, clinics, hospitals, districts and provinces.
• Organise monthly meetings of key role players (district coordinators, health care workers from public and private hospitals and clinics, laboratories, community-based organisations, non-governmental organisations) to improve communication and co-ordination.
• If possible, telephone the referral facility to tell them when a patient is being transferred to their care.

Plan for high patient mobility
• When a patient is started on TB treatment or the management of other HIV-related diseases, ask the patient about their current employment and social circumstances. Try to determine if it is likely that the patient will move in the near future.
• Provide all TB patients with the "Patient Treatment Card" (GW 20/15) and encourage them to carry it at all times. This card has most of the information required for any facility to continue providing appropriate TB treatment to the patient.
• Counsel patients on the importance of continuity of care and encourage them to come to the clinic before moving so that they can receive a transfer form and a sufficient supply of medications.

Communicate well with patients and provide health education
• Good communication with patients is essential to provide them with adequate information and support. Listening to a patient's concerns is time well spent.
• Improved communication will increase trust, relieve anxiety and increase the likelihood that a patient will report any problems which may interfere with treatment.
• Provide health education on the symptoms of AIDS, STDs, TB and other opportunistic infections and encourage patients to seek care if those symptoms develop. If patients present to health facilities at an early stage they have a better chance of being cured.

Make a home visit and verify contact details
• If possible, conduct a home visit to verify the patient's address and to assess the patient's home environment and support network.
• Home visits may be done by anyone on the health management team including doctors, nurses, social workers, health educators or community health workers.

**Ensure adequate staff and transport**

• Ensure adequate staff and drug supplies in clinics so patients can confidently seek care at primary health care level instead of going directly to hospitals.
• When possible, transport discharged patients from hospitals to the referral clinics to decrease loss to follow up.

**SUMMARY**

• Continuity of care can be improved through following admission and discharge criteria, creating resource lists, using available transfer forms, improving communication with patients and between service providers.

**11) HOSPITAL ADMISSION AND DISCHARGE CRITERIA FOR TUBERCULOSIS PATIENTS**

**Aim**

To ensure that TB hospital beds in South Africa are used optimally by:

• Ensuring successful completion of the intensive phase of TB treatment in new smear-positive TB patients, where access to clinic or community-based treatment support (direct observation) is difficult.
• Providing appropriate and effective care for TB patients who are sick enough to require hospitalisation, until they are well enough to be treated at the clinic or in the community.
• Ensuring that patients who are referred to and from hospitals are not lost to follow up by implementing appropriate referral mechanisms.

**Choice of Hospital for Referral**

TB patients who are critically ill and who require continuous supervision by a medical officer should be stabilised at a hospital which has the staff and equipment to provide adequate intensive care before being transferred to a hospital which does not have that capacity. In practice, this means that most clinics should refer critically ill TB patients to a general hospital for stabilisation before the patient can be transferred to a TB hospital.

**Admission Criteria**

**Referral requirements**

Patients referred for admission should be accompanied by a completed TB referral form (GW 20/14). This must include the names, telephone numbers and addresses of the referring doctor, clinic nurse, patient and patient's family, and a proposed discharge plan.

**Pulmonary TB patients**

Patients with pulmonary TB who require daily medical and nursing care which cannot be provided in the community should be admitted only after bacteriological diagnostic
APPENDIX VIII

investigations are done according to the 'South African Tuberculosis Control Programme Practical Guidelines' or the 'Tuberculosis and HIV/AIDS Clinical Guidelines'.

**New smear-positive TB patients**

At this stage of the TB epidemic in South Africa, priority for admission should be given to new smear-positive pulmonary TB patients who have limited access to TB treatment support (direct observation) at a clinic or in the community. Patients should be admitted for the full intensive phase and discharged with a smear-negative sputum result. The patient should be discharged on smear conversion even if direct observation cannot be guaranteed, provided the patient has access to a weekly or monthly supply of treatment. Discharge planning for these patients must start on admission.

The proportion of patients who convert at 2 and at 3 months should be noted in the quarterly report. At 2 months, a patient with 2 positive smears should have a culture and sensitivity done, as well as two repeat smears at 3 months. This result should also be noted in the quarterly report.

**Retreatment pulmonary TB patients**

Retreatment pulmonary TB patients can be admitted for the two months that they receive intramuscular streptomycin injections if outpatient treatment can not easily be arranged.

**Extrapulmonary TB patients and smear-negative pulmonary TB patients**

Extrapulmonary TB (e.g. TB meningitis, TB pericarditis, miliary TB, TB spine, TB peritonitis) patients and smear-negative pulmonary TB patients should be admitted if daily nursing care is required and can not be provided in the community.

**Multiple drug resistant TB**

Multiple drug resistant pulmonary TB cases should be admitted only to hospitals which are able to provide appropriate treatment.

**HIV-infected TB patients**

The decision to admit an HIV-infected TB patient should be made in the same way as for any other TB patient. All staff who work with TB patients require ongoing training and support to deal with the medical, social and other implications of HIV/AIDS and they should be encouraged to counsel and support patients are living with HIV.

**Concomitant disease**

TB patients with concomitant disease (e.g. cardiac failure, cor-pulmonale, chronic lung sepsis, diabetes mellitus, epilepsy, severe hypertension, liver disease, psychiatric illness) should be admitted if they can not be managed on an outpatient basis.

**Complications of TB**

TB patients with severe complications of TB (e.g. pneumothorax, large effusions, haemoptysis) should be admitted.
APPENDIX VIII

Adverse drug reactions
TB patients who develop severe adverse drug reactions (e.g. hepatitis/jaundice, persistent vomiting, severe rash) should be admitted.

Children
Children with serious forms of TB (e.g. TB meningitis, miliary TB, gross lymphadenopathy with ulceration) or who are not improving on out-patient TB treatment should be admitted.

Adherence problems
Sputum smear-positive pulmonary TB patients who are at risk of having adherence problems (e.g. alcohol or drug dependent patients, previous treatment interrupters, patients who refuse therapy) may be admitted. Discharge planning should include a social worker, if possible.

On the recommendation of a Medical Officer of Health or legal equivalent, a magistrate may issue a detention order and enforce admission until a patient is rendered non-infectious (Regulation 2438 article 17, under the Health Act of 1977). This is difficult to enforce and should only be undertaken with the co-operation of, and in consultation with the family and local community. This regulation has rarely been found to be useful.

Breastfed babies
Breastfed babies of mothers with TB can be admitted if the mother is unable or unwilling to arrange for the baby to be taken care of by someone else. Such babies should receive TB prophylaxis for at least 3 months (see 'The South African Tuberculosis Control Programme Practical Guidelines').

Discharge planning
Discharge planning should be started on admission and completed within 2 weeks of admission. It should include recruitment of a treatment supporter, health education of the patient and the treatment supporter, and communication with the patient's chosen outpatient clinic to ensure continued treatment and monitoring.

Reporting
A quarterly report should be provided on the smear conversion rates at 2 and 3 months of all TB patients who are hospitalised for more than 2 months.

Discharge Criteria
Large studies have conclusively shown that patients treated for TB outside of hospital respond to treatment as well as those treated in hospital. Furthermore, their contacts are at no increased risk of contracting TB. The challenge is to ensure adherence through provision of community-based, directly observed TB treatment.

Clinical criteria
A patient should not be routinely kept in hospital for a specific period of time but should be discharged as soon as the patient is:
• medically stable (e.g. not dyspneic, no haemoptysis, afebrile, not emaciated) and
• either able to care for himself or has access to family or community-based care and
• willing and able to access treatment and to be monitored either by going to a clinic or
   by receiving visits from a treatment supporter.

**Intensive phase completed**

If directly observed treatment cannot be reasonably assured at a clinic or in the community, patients should be discharged when smear conversion takes place.

**HIV-infected TB patients**

The decision to discharge an HIV-infected TB patient should be made in the same way as for any other TB patient. However, special effort should be made to ensure community-based care for such a patient and the family.

**Nutritional support**

If a patient is not severely emaciated (at least 15% less than expected mass for height), they should not be kept in hospital only for nutritional support. If possible, outpatient nutritional support should be arranged for patients with the Department of Welfare or a non-governmental organisation working in the area.

**Multiple drug resistant TB**

Multiple drug resistant TB cases should have at least three consecutive monthly negative sputum cultures prior to discharge.

**Discharge planning and referral**

A discharge plan should be completed within 2 weeks of admission and should include recruitment of a treatment supporter, health education of the patient and the treatment supporter, personal communication with the patient's chosen outpatient clinic to ensure continued treatment and monitoring, and a completed transfer form.
APPENDIX IX

MANUAL FOR EXPEDITED REPORTING OF ADVERSE EVENTS TO DAIDS

Manual for Expedited Reporting

Of

Adverse Events to DAIDS

Final

May 6, 2004
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1.0 PURPOSE OF MANUAL

1.1 Purpose

The purpose of this Manual is to describe the criteria and method for expedited reporting of certain serious and other reportable adverse events to the Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), through the DAIDS Safety Office.

1.2 Scope

This Manual applies only to those clinical studies/trials requiring expedited reporting of adverse events to the DAIDS Safety Office as stated in the protocol.

This Manual applies to all study agents specified in the protocol as requiring expedited reporting to DAIDS. Although not covered under this Manual, note that DAIDS may require MedWatch reporting (using e.g., Form FDA 3500A or CIOMS I Form) to the Food and Drug Administration (FDA) and/or DAIDS for some studies. MedWatch reporting may only be applied to studies/trials of US FDA-approved study agents. Any requirements for MedWatch reporting will be identified in the study/trial protocol.

1.3 Introduction

For adverse events requiring expedited reporting to DAIDS, sites must follow the general reporting requirements and procedures described in this Manual. In order to fully define the expedited adverse event reporting requirements that apply to an individual study/trial, the protocol will specify:

- One of three Levels of Adverse Event Reporting (Section 3.1) and any other adverse events to be reported on an expedited basis (Section 3.2).
- The duration of the protocol-defined expedited reporting period.
- The name or category of each study agent (US FDA-approved or investigational) that requires expedited reporting of adverse events to DAIDS. This may include study agents in addition to those provided by the study/trial.

2.0 DESCRIBING AN ADVERSE EVENT BY SERIOUSNESS, SEVERITY, RELATIONSHIP TO STUDY AGENT, AND EXPECTEDNESS

The criteria for expedited reporting of adverse events to the DAIDS Safety Office include the seriousness of the outcome of the event, the severity (intensity) of the event, its relationship to study agent, and (only for the Targeted Level) expectedness, i.e., whether the adverse event is expected or unexpected.
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2.1 Seriousness

The first consideration for expedited reporting of adverse events to DAIDS is the seriousness of the outcome of the event. The April 1996 International Conference on Harmonisation (ICH) guidance, “Good Clinical Practice: Consolidated Guidance,” (ICH E6) defined a serious adverse event (SAE) as “any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.”

“Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above” may also be considered to be serious. (October 1994 ICH guidance (E2A), “Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.”)

2.2 Severity (Intensity)

The second consideration for expedited reporting of adverse events to DAIDS is the severity (intensity) of the event. In order to maintain consistency among studies/trials and sites, DAIDS has developed a list of common clinical and laboratory adverse events and defined grade 1 – 5 severity parameters to generate the Division of AIDS Tables for Grading Adult and Pediatric Adverse Experiences (also known as “the toxicity tables”). These tables are located on the DAIDS Safety Office website at http://rcc.tech-res-intl.com.

Unless stated otherwise in the protocol, study staff is required to use the Division of AIDS Tables for Grading Adult and Pediatric Adverse Experiences to determine the intensity of adverse events in order to establish consistency in adverse event reporting to DAIDS. Specific protocols may include additional or modified criteria for grading adverse events that are not included in the current versions of the Division of AIDS Tables for Grading Adult and Pediatric Adverse Experiences.

2.3 Seriousness vs. Severity (Intensity) of Adverse Events and Reporting Criteria

For expedited reporting to DAIDS, the term “severity” (or “intensity”) is described as the grade for a specific event, i.e., mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4). This is not the same as “serious,” which is based on participant/event outcome or action criteria usually associated with events that pose a threat to a participant’s life or functioning (ICH E2A).

2.4 Relationship to Study Agent

The third consideration for expedited reporting of adverse events to DAIDS is the judgment of causal association (relationship) between an adverse event and the study agent. The protocol must specify by name or category each study agent (either approved or investigational) that
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requires expedited reporting of adverse events to DAIDS. The research clinician/investigator makes the site’s final assessment of the causal association based upon the temporal relationship to administration of the study agent(s), the pharmacology of the study agent(s), and his/her clinical judgment.

The terms used in DAIDS studies/trials to assess relationship of an event to study agent are:

- **Definitely Related.** The adverse event and administration of study agent are related in time, and a direct association can be demonstrated.

- **Probably Related.** The adverse event and administration of study agent are reasonably related in time, and the adverse event is more likely explained by study agent than other causes.

- **Possibly Related.** The adverse event and administration of study agent are reasonably related in time, and the adverse event can be explained equally well by causes other than study agent.

- **Probably Not Related.** A potential relationship between study agent and the adverse event could exist (i.e., the possibility cannot be excluded), but the adverse event is most likely explained by causes other than the study agent.

- **Not Related.** The adverse event is clearly explained by another cause not related to the study agent.

- **Pending.** Pending may be used as a temporary relationship assessment only for death and only if data necessary to determine relationship to study agent are being collected. The site is required to submit a final assessment within 3 business days after reporting the death. If no final assessment is made within 3 business days after the date of submission, the event will be assessed as possibly related to study agent. Any additional information received at a later time, including an autopsy report, should be submitted as a Follow-up Report.

A **suspected adverse drug reaction (SADR)** is an adverse event that could potentially have a causal relationship to the study agent (definitely, probably, possibly, probably not related, or for deaths, pending).

### 2.5 Expectedness (Expected vs. Unexpected)

Expected refers to the perspective of events previously observed, not on the basis of what might be anticipated from the pharmacological properties of the study agent. (ICH E2A)

Unexpected refers to events whose nature or severity (intensity) is not consistent with those included in the package insert/summary of study agents that have been approved by the US FDA or in the Investigator’s Brochure. (ICH E2A)
3.0 ADVERSE EVENTS REQUIRING EXPEDITED REPORTING AND THE STUDY/TRIAL REPORTING PERIOD

3.1 Levels of Adverse Event Reporting

The protocol will specify one of three Levels of Adverse Event Reporting. The Level of Adverse Event Reporting chosen for expedited reporting is based primarily upon the degree of risk that may be associated with the study agent.

3.1.1 Standard Level

Report all adverse events following any exposure to study agent that:

- Result in death regardless of relationship to study agent.
- Are congenital anomalies, birth defects, or fetal losses regardless of relationship to study agent.
- Result in persistent or significant disabilities or incapacities regardless of relationship to study agent.
- Are a suspected adverse drug reaction, i.e., definitely, probably, possibly, and probably not related, to a study agent that requires or prolongs existing hospitalization, or requires intervention to prevent significant/permanent disability or death.
- Are life-threatening (including all Grade 4 adverse events) suspected adverse drug reactions, i.e., definitely, probably, possibly, and probably not related to a study agent.

3.1.2 Intensive Level

In addition to all adverse events reported for the Standard Level, also report all Grade 3 suspected adverse drug reactions, i.e., definitely, probably, possibly, and probably not related to a study agent. (The Intensive Level includes reporting Grades 3 and 4 SADRs.)

3.1.3 Targeted Level

Use of the Targeted Level of reporting is limited to non-IND studies/trials of US FDA-approved agents and doses for approved indications and populations. Report only the following adverse events:

- All events that result in death regardless of relationship to study agent.
- All congenital anomalies, birth defects, or fetal losses regardless of relationship to study agent.
- All persistent or significant disability or incapacity regardless of relationship to study agent.
- Unexpected* suspected adverse drug reactions, i.e., definitely, probably, possibly, and probably not related to a study agent, that require or prolong existing hospitalization, or require intervention to prevent death or significant/permanent disability.
• **Unexpected** life-threatening clinical suspected adverse drug reactions, i.e., definitely, probably, possibly, and probably not related to a study agent. **DO NOT report** Grade 4 laboratory values that are not associated with a life-threatening clinical event.

*Unexpected events are events whose nature or severity is not consistent with the package insert/summary of product characteristics for a US FDA-approved study agent.*

### 3.2 Additional Protocol-Required Expedited Reporting Requirements

In addition to specifying one of the reporting levels above, a protocol may require other adverse events to be reported on an expedited basis. In this case, the protocol will explicitly state the additional adverse events to be reported to DAIDS. For example, in rare instances a protocol may specify use of the Intensive Level and also require Grades 1 and 2 SADRs to be reported, or a protocol may require reporting of a specific type of adverse event regardless of grade.

### 3.3 Additional Adverse Events That Should Be Reported for Any Study/Trial Requiring Expedited Reporting to DAIDS

In addition to the reporting requirements described above, sites should report any of the following adverse events on an expedited basis:

- Suspected adverse drug reactions, i.e., definitely, probably, possibly, and probably not related to a study agent, that do not meet the protocol-required reporting criteria, but the Investigator believes are of sufficient concern to be reported on an expedited basis to DAIDS. This includes adverse events that, based upon appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent a serious adverse event. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm or blood dyscrasias or convulsions that do not result in hospitalization.

- Unexpected, serious suspected adverse drug reactions, i.e., definitely, probably, possibly, and probably not related to a study agent, that occur at any time after the protocol-defined expedited reporting period if the study staff become aware of its occurrence. These events include deaths, permanent disabilities, congenital anomalies, hospitalizations, and life-threatening clinical events. (Do not report Grade 4 laboratory values unless associated with a life-threatening clinical event.)

- Serious adverse events that are not related to a study agent, but could be associated with study participation or procedure (e.g., pulmonary embolism secondary to an intravenous catheter placed for study agent administration).
3.4 Protocol-Defined Expedited Adverse Event Reporting Period

The protocol-specified reporting level continues throughout the study/trial period (from enrollment of a participant through the end of study follow-up visits for that participant). The protocol may also require the same level of adverse event reporting to be continued beyond the end of study follow-up for each participant, and if so, the protocol must specify the duration of this additional reporting period.

4.0 METHOD AND TIMEFRAME FOR EXPEDITED REPORTING OF INDIVIDUAL ADVERSE EVENTS

All information requested on the DAIDS Expedited Adverse Event Reporting Form must be provided and the form submitted to the DAIDS Safety Office. This form can be found at the web site for the DAIDS Safety Office. Contact information for the DAIDS Safety Office is provided in Appendix B.

The timeframe for expedited reporting of individual adverse events begins when the site recognizes that an event fulfills the criteria outlined in this Manual for expedited reporting to DAIDS. Sites must submit adverse events requiring expedited reporting to the DAIDS Safety Office as soon as possible, but no later than 3 business days, after the site’s recognition that the event fulfills the criteria for expedited reporting.

5.0 ADDITIONAL EXPEDITED REPORTING REQUIREMENTS

5.1 Follow-up Reporting of Adverse Events

5.1.1 Submitting Follow-Up Information on Adverse Events

For the circumstances listed below, the site is required to submit follow-up information when it becomes available on a new Expedited Adverse Event Form as a Follow-up Report.

- Requests by DAIDS for additional information.
- A change in the relationship between the adverse event and study agent by the research clinician/investigator.
- Additional significant information that becomes available for a previously reported adverse event. This is particularly important for new information addressing cause of death if the initial assignment was “pending.”
- Results of rechallenge with the study agent(s), if performed.

5.1.2 Outcome of Adverse Events

The site must follow each reported adverse event and record eventual outcomes in the source documentation. However, report of the outcome of a reported adverse event to the DAIDS Safety Office is not required unless specifically requested by DAIDS.
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5.2 Reporting Recurrent Adverse Events

For events that have been previously reported to the DAIDS Safety Office, if the event has fully resolved and then re-occurs to a level requiring expedited reporting, the adverse event must be reported as a New Report to the DAIDS Safety Office.

5.3 Reporting Change in Severity of Adverse Events

Any ongoing event that increases in severity to a higher grade than previously reported must be reported again as a New Report on a new DAIDS Expedited Adverse Event Reporting Form.

Ongoing events that improve, but are not resolved, and then increase in severity to the same or lower severity grade than previously reported do not have to be reported again to the DAIDS Safety Office. Resolution is the normalization or return to baseline (i.e., prior to study agent exposure) of laboratory values, signs, or symptoms related to the event.

5.4 Study Physician Assessment and Signature

A study physician listed on the Form FDA 1572 for IND studies or the DAIDS Investigator of Record Agreement (IoR) for non-IND studies must review and verify the data on the DAIDS Expedited Adverse Event Reporting Form for accuracy and completeness. This physician also makes the site’s final assessment of the relationship between the study agent and the adverse event. This physician must sign the completed DAIDS Expedited Adverse Event Reporting Form. If necessary to meet timely reporting requirements, sites can submit an expedited adverse event report without a completed signature page. However, the completed signature page, and necessary corrections or additions, must be submitted within the next 3 business days.
APPENDIX IX

6.0 APPENDICES

6.1 Appendix A: Definition of Terms

Adverse Event (AE): An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (ICH E6) (Synonym: Adverse Experience)

DAIDS Safety Office: The Office to which adverse events requiring expedited reporting are submitted. (DAIDS)

Division of AIDS Tables for Grading Adult and Pediatric Adverse Experiences (Toxicity Tables): Lists of common terms and severity (intensity) parameters used to describe adverse events occurring in DAIDS-sponsored clinical studies/trials. (DAIDS)

IND: An investigational new drug application. (21 CFR 312.3)

Investigator’s Brochure: A compilation of the clinical and nonclinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human participants. (ICH E6)

Non-IND Study/Trial: A study/trial for which there is no IND filed with the US FDA.

Package Insert: The approved package circular in marketed drug packaging containing the drug description, clinical pharmacology, indications and usage, contraindications, warnings, precautions, adverse reactions, drug abuse and dependence, dosage and administration, how drug is supplied, “clinical studies,” and “references.” (21 CFR 201.57)

Serious Adverse Event (SAE): Any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. This includes important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. (ICH E6 and E2A)

Study Agent: Drugs, biological products, or combination of drugs and biological products (approved or investigational) defined in the protocol as requiring expedited reporting to DAIDS. (DAIDS)

Study Physician: A physician listed on the Form FDA 1572 for IND studies or on the DAIDS Investigator of Record Agreement (IOR) for non-IND studies. (DAIDS)
Suspected Adverse Drug Reaction (SADR): An adverse event that could potentially have a causal relationship to a study agent (definitely, probably, possibly, probably not related or for deaths, pending). (DAIDS)

Toxicity: An adverse event that has an attribution of possibly, probably, or definitely related to a study agent. (DAIDS) NOTE: This term should not be used for expedited reporting of adverse events to DAIDS.

Unexpected Event: An adverse event, the nature or severity (intensity) of which is not consistent with the applicable product information (Investigator’s Brochure, package insert, or summary of product characteristics for a US FDA-approved study agent. (DAIDS)
6.2 Appendix B: Contact Information for DAIDS Safety Office

All completed DAIDS Expedited Adverse Event Forms are submitted to the DAIDS Safety Office.

For questions or other communication, please note the following:

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<thead>
<tr>
<th>Website:</th>
<th><a href="http://rcc.tech-res-intl.com">http://rcc.tech-res-intl.com</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>Office Phone*:</td>
<td>1-800-537-9979 (US only) or +1-301-897-1709</td>
</tr>
<tr>
<td>Office Fax*:</td>
<td>1-800-275-7619 (US only) or +1-301-897-1710</td>
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<tr>
<td>Office Email:</td>
<td><a href="mailto:RCCSafetyOffice@tech-res.com">RCCSafetyOffice@tech-res.com</a></td>
</tr>
<tr>
<td>Office Hours:</td>
<td>Monday through Friday, 8:30 AM to 5:00 PM (US Eastern Time)</td>
</tr>
<tr>
<td>Mailing Address:</td>
<td>DAIDS Safety Office</td>
</tr>
<tr>
<td></td>
<td>6500 Rock Spring Drive</td>
</tr>
<tr>
<td></td>
<td>Suite 650</td>
</tr>
<tr>
<td></td>
<td>Bethesda, MD 20817</td>
</tr>
</tbody>
</table>

*Office phone and fax are accessible 24 hours per day.
### 6.3 Appendix C: Summary Chart for Expedited Reporting of Adverse Events to DAIDS for Protocol-Specified Study Agents

<table>
<thead>
<tr>
<th></th>
<th>Standard Level</th>
<th>Intensive Level</th>
<th>Targeted Level</th>
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</thead>
<tbody>
<tr>
<td><strong>Deaths</strong></td>
<td>All Events</td>
<td>All Events</td>
<td>All Events</td>
</tr>
<tr>
<td><strong>Congenital anomalies, birth defects, fetal losses</strong></td>
<td>All Events</td>
<td>All Events</td>
<td>All Events</td>
</tr>
<tr>
<td><strong>Disabilities/Incapacities</strong></td>
<td>All Events</td>
<td>All Events</td>
<td>All Events</td>
</tr>
<tr>
<td><strong>Hospitalization</strong></td>
<td>All Suspected Adverse Drug Reactions&lt;sup&gt;2&lt;/sup&gt;</td>
<td>All Suspected Adverse Drug Reactions&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Unexpected Suspected Adverse Drug Reactions&lt;sup&gt;2,3&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Other events</strong></td>
<td>All Grade 4 Suspected Adverse Drug Reactions&lt;sup&gt;2&lt;/sup&gt;</td>
<td>All Grades 3 and 4 Suspected Adverse Drug Reactions&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Unexpected Life-Threatening Clinical Suspected Adverse Drug Reactions&lt;sup&gt;2,3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup>This category includes hospitalization, prolongation of hospitalization or requirement of intervention to prevent permanent disabilities or death.

<sup>2</sup>Suspected adverse drug reactions are adverse events that are assessed as definitely, probably, possibly, probably not related to a study agent (or for deaths, pending).

<sup>3</sup>Unexpected events are adverse events, of a nature or severity (intensity) that is not consistent with the applicable product information (package insert/summary of product characteristics) for a US FDA-approved study agent.

**Timeframe for Expedited Reporting of Individual Adverse Events:**

Adverse events requiring expedited reporting are to be reported to the DAIDS Safety Office no later than 3 business days after the site’s recognition that the event fulfills the criteria for expedited reporting.

**Protocol-Defined Expedited Adverse Event Reporting Period**

The protocol-specified reporting level continues throughout the study/trial period (from enrollment of a participant through the end of study follow-up visits for that participant). The protocol may also require the same level of adverse event reporting to be continued beyond the end of study follow-up for each participant.
WHO CLINICAL STAGE III CONDITIONS (MODIFIED) (excluding pulmonary tuberculosis)

These conditions may be used to assist in the evaluation of HIV-1 Treatment Failure (Table 10).

1. Weight Loss >10% of body weight
2. Unexplained chronic diarrhea, >1 month
3. Unexplained prolonged fever (intermittent or constant), >1 month
4. Oral candidiasis (thrush)
5. Oral hairy leukoplakia
6. Severe bacterial infections (i.e. pneumonia, pyomyositis)

And/or performance scale 3: bedridden < 50% of the day during last month
APPENDIX XI

APPENDIX XI

ZIAGEN® MEDICATION GUIDE/WARNING CARD

WHAT YOU SHOULD KNOW ABOUT ZIAGEN® TABLETS AND ZIAGEN® ORAL SOLUTION

This leaflet tells you about ZIAGEN® Tablets and ZIAGEN® Oral Solution. Please read it carefully before you start taking the medicine. This leaflet describes the main points relating to ZIAGEN® Tablets and ZIAGEN® Oral Solution. For more information or advice please ask your doctor or pharmacist.

THE PROPRIETARY NAME OF YOUR MEDICINE

ZIAGEN® Tablets and ZIAGEN® Oral Solution

COMPOSITION

What is in your medicine

ZIAGEN Tablets and Oral Solution contain abacavir as the active ingredient. Each tablet contains 300mg abacavir while each milliliter of oral solution contains 150mg abacavir.

The tablets contain the following active ingredients: microcrystalline cellulose, sodium starch glycolate, magnesium stearate, colloidal anhydrous silica, talc, titanium dioxide, magnesium stearate, polyethylene glycol and yellow and red colour.

The oral solution contains the following active ingredients: sorbitol, saccharin sodium, sodium chloride, citric acid, sodium hydroxide, methyl parahydroxybenzoate propyl parahydroxybenzoate, propylene glycol, artificial strawberry and banana flavour. Proprietary water.

ZIAGEN Tablets are yellow, film-coated, capsule-shaped tablets, engraved with "OX 623" on one side. The tablets are supplied in blister packs containing 60 tablets.

ZIAGEN Oral Solution is a clear to yellowish with strawberry/banana flavouring. The solution is supplied in cartons containing a 250ml white polyethylene bottle, with a child-resistant cap. The pack includes a 10ml oral dosing syringe and a plastic syringe adapter for the bottle.

INDICATIONS

How your medicine works and what it is used for

ZIAGEN belongs to a group of medicines called antiretrovirals, and is used to treat Human Immunodeficiency Virus (HIV) infection.

ZIAGEN is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infected adults and children.

ZIAGEN in combination with other antiretrovirals reduces HIV viral load, and keeps it at a low level. It also increases CD4 cell count. Response to treatment with ZIAGEN varies between patients. Your doctor will be monitoring the effectiveness of your treatment.

BEFORE TAKING THIS MEDICINE

If you answer 'yes' to any of the following questions, please consult your doctor before taking this medicine.

Are you or have you been told that you are allergic to any of the ingredients of ZIAGEN Tablets and Oral Solution?

Are you pregnant, trying to become pregnant or are you breastfeeding?

If you are pregnant or breastfeeding your baby while taking this medicine, please contact your doctor, pharmacist or other health care professional for advice.

The safety of ZIAGEN in human pregnancy has not been established. It is likely that abacavir will be found in human breast milk. As there is currently no information on the use of ZIAGEN in babies under three months of age, it is recommended that you do not breastfeed your baby while taking this medication.

Do you suffer from an hereditary fructose intolerance? ZIAGEN Oral Solution contains sorbitol as a sweetening agent.

Are you taking any other medication?

It is important to tell your doctor about all the medicines you are taking, including those you have bought yourself. If you are taking other medicines on a regular basis, concurrent use of this medicine may cause undesirable interactions. Please consult your doctor or pharmacist.

Please take note of the following special warnings:

- An allergic reaction: a small number of patients (about 3 in every 1000) who are treated with ZIAGEN, develop an allergic reaction to the active ingredient abacavir. Please consult your doctor immediately should you develop the following symptoms:
  - high temperature
  - nausea
  - vomiting
  - diarrhoea
  - abdominal pain
  - shortness of breath, sore throat or cough
  - skin rash
  - tiredness.

  These symptoms usually occur in the first six weeks of treatment with ZIAGEN and worsen with continued treatment. ZIAGEN treatment will have to be stopped should an allergy be diagnosed. YOU MUST NOT take ZIAGEN again, as a more serious allergic reaction may occur which could be fatal.

- ZIAGEN helps to control your condition but is not a cure for HIV infection. You will need to take it every day. Do not stop taking your medicine without first talking to your doctor.

- Treatment with ZIAGEN has not been shown to reduce the risk of passing HIV infection on by sexual contact or by blood transfusion. You should continue to use appropriate precautions to prevent this.

- You may continue to develop other infections and other illnesses associated with HIV disease. You should therefore keep in regular contact with your doctor while taking ZIAGEN.

- ZIAGEN is unlikely to affect your ability to drive or operate machinery. Please consult your doctor should you have any concerns in this regard.

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HOW TO TAKE THIS MEDICINE

Take your medicine as your doctor has advised you. If you are unsure about how to take it, ask your doctor or pharmacist.

Dose in adults and adolescents over 12 years of age. 300 mg (one tablet) twice a day. Should you be unable to take tablets this dose equals to 15 ml of oral solution twice a day.

In children 3 months to 12 years of age the recommended dose is 8 mg/kg body weight twice daily up to a maximum dose of 600 mg (30 ml) daily. The oral solution is available for the treatment of children.

To accurately measure your dose of oral solution use the oral dosing syringe supplied with the pack as follows:

1. Remove the bottle cap.
2. Push the plastic adapter into the neck of the bottle, while holding the bottle firmly.
3. Insert the syringe firmly into the adapter.
4. Turn the bottle upside down.
5. Pull out syringe plunger until the correct amount is withdrawn.
6. Turn the bottle the correct way up and remove the syringe from the adapter.
7. Replace and tighten the bottle cap.
8. Administer the dose into the mouth by placing the tip of the syringe against the inside of the cheek. Slowly depress the plunger, allowing time to swallow. Forceful squirting to the back of the throat may cause choking.

After use the syringe must not be left in the bottle and should be washed thoroughly in clean water.

If you forget to take your medicine, take it as soon as you remember, and then continue as before.

WHAT TO DO IF YOU TAKE TOO MUCH (an overdose)

Accidentally taking too much of your medicine is unlikely to cause any serious problems. However, you should tell your doctor or your pharmacist, or contact your nearest hospital emergency department for further advice.

SIDE EFFECTS

All medicines may cause some undesirable effects. When treating HIV infection it is not always possible to tell whether any undesirable effects that occur are caused by ZIAGEN, by other medicines you are taking at the same time or by HIV disease.

Not all side effects reported for these medicines are included in this leaflet. If your general state of health worsens while taking this medicine, please consult your doctor.

The following side effects are thought to be related to treatment with ZIAGEN: nausea, vomiting, lethargy and fatigue. Other effects that have been seen are: loss of appetite, fever, headache and diarrhea.

In general, most of these have only lasted a short time, been mild or moderate in severity and got better without stopping treatment with ZIAGEN.

An allergic response has been reported in about 3 in every 100 patients who have been treated with ZIAGEN. It is important that you read and understand the information about the allergic response – this information is provided in the “Before taking this medicine” section of this patient information leaflet.

Always tell your doctor or pharmacist about any undesirable effect, even those not mentioned in this leaflet.

STORAGE AND DISPOSAL INFORMATION

Tablet: Store at or below 30°C.
Oral Solution: Store at or below 30°C. Discard oral solution two months after first opening.
Do not take the medicine after the expiry date shown on the tablet pack or bottle.
Do not share medicines prescribed for you with others.
Store all medicines out of reach of children.

WHO MAKES YOUR MEDICINE

This medicine is supplied by: Glaxo Wellcome South Africa (Pty) Limited,
Qld Pretoria Road, Midrand, South Africa.

REMEMBER

This leaflet is for your information. Please keep it and refer to it as often as is necessary.

The information contained in this leaflet applies to ZIAGEN Tablets and ZIAGEN Oral Solution only. If you have any questions or are not sure about anything, please ask your doctor or pharmacist.

HIV/AIDS Helpline: 0800 110 605
APPENDIX XII
SEXUAL BEHAVIOUR SURVEY

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<th>Baseline Survey - Sexual Behaviour</th>
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<td>Visit Date dd MMM yy</td>
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</table>

Sexual Behaviour Survey

I will be asking you personal questions during this interview. The interview will take about 30 minutes. The questions that follow will be about your experience with relationships. If you have any questions at any point during the course of the interview, you are welcome to interrupt. I will make every effort to answer and clarify anything that you find unclear. If you ask questions I do not have an answer to at the time of the interview, I will record your question and provide you with information either by phone or at your next visit.

1. How many sexual partners have you had in your entire life?  
2. How old were you when you first engaged in sex (vaginal, anal, and/or oral sex)?  
   - Vaginal  
   - Anal  
   - Oral  
3. Do you currently have a steady partner? A steady partner is one who you have sex with and who you consider your 'darling/sweetheart'.  
   - Yes  
   - No  
   - Go to Question 7
4. How long have you been without a steady sexual partner?  
   - Days  
   - Weeks  
   - Months  
   - Years  
5. Did you have sex during this period (in Question 4)?  
   - Yes  
   - No  
   - Go to Question 8
6. If yes, did you use a condom?  
   - Always  
   - Sometimes  
   - Rarely  
   - Never  
7. Are any of your current partner(s) your first sexual partner?  
   - Yes  
   - No  
8. Did you have drinks containing alcohol in the last four weeks?  
   - Yes  
   - No  
   - I don’t remember  
9. If yes, how often did you have drinks containing alcohol in the last four weeks? Would you say?  
   - At least once a day  
   - At least once a week  
   - Less than once a week  

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Baseline Survey - Sexual Behaviour

10. (Men Only) Are you circumcised?
   - Yes
   - No

11. (Women Only) Did you have sex during menstruation with any of your partners in the past 6 months?
   - Yes
   - No

12. Did you know your HIV positive status before participating in this study?
   - Yes
   - No

13. How long have you known your HIV positive status before this study?
   - Weeks
   - Months
   - Years

14. Did your partner(s) (at the time) test for HIV?
   - Yes
   - No
   - No partner

15. If you tested HIV positive, did you share your status with your partner(s) at the time?
   - Yes
   - No
   - No partner

16. Were your partner(s) supportive and accepting?
   - Yes
   - No
   - No partner

17. Have you ever had an STI in the past?
   - Yes
   - No

18. If yes, how many times did you have an STI in your lifetime?
   - I don't remember

19. When did you have your last STI?
   - Less than 3 months ago
   - 3-6 months ago
   - 6-12 months ago
   - More than 12 months ago

20. When was your last sexual act?
   - dd
   - MMM
   - yy

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- MMM
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Baseline Survey - Sexual Behaviour

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Visit Code: Phase | Visit | Interim #

Sexual Behaviour Survey

21. Did you use a condom during your last sex act?
(Emphasise ALL ROUNDs of sex. If during the last sex act the participant begins using a condom and then removes the condom, but continues another round of sex without a condom, you must check the “No” box for this question. Only if a condom was used throughout the last sex act should the “Yes” box be checked.)

☐ Yes ☐ No ☐ I don't remember

22. How many steady and casual partners have you had over the past 6 months? (A steady partner is one you have sex with and who you consider to be your “darling/sweetheart” and a casual partner is one you have sex with but is not your “darling/sweetheart”)

☐ Steady ☐ Casual

Now I would like you to tell me a little bit about each of these partners. We can start with anyone of the partners you included above. I will ask you to give each partner a “nickname” that is unique and familiar to you. This is just a way to remember the partner as we talk. It will not be used in any other way.
## Partner Questionnaire

I will now ask you questions about your current partner(s) over the past 6 months.
(One questionnaire must be filled in for each current partner)

<table>
<thead>
<tr>
<th>Partner Nickname</th>
<th>Steady</th>
<th>Casual</th>
<th>Partner #</th>
</tr>
</thead>
</table>

1. Age of partner

2. Do you and your partner live:
   - Together
   - Separate, but same city/location
   - Separate, but other city/location

3. Does your partner(s) have other sexual partners?
   - Yes
   - No
   - I suspect
   - Don’t know

4. How long have you been in a relationship with this partner? What I mean is how long approximately was it between the first time you had sex together and the last time?
   - Less than a month
   - Months
   - Years

5. Do you use condoms with this partner?
   - Always
   - Sometimes
   - Rarely
   - Never

6. What type of sex do you engage in with this partner?
   a. Oral
   b. Anal
   c. Vaginal
   d. Thigh Sex

   - Yes
   - No
   - Don't remember

7. Do you receive/give money, food, shelter in exchange for sex with him/her?
   - Always (everytime)
   - Sometimes (50%)
   - Rarely (less than 50%)
   - Never

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Baseline Survey - Sexual Behaviour - Partner

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Participant ID

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Visit Date

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Partner Questionnaire

Partner Nickname

Partner #

8. How often do you see your partner in the course of a week?
   - At least once a day
   - At least once a week
   - Less than once a week

9. Have you shared your HIV status with your partner?
   - Yes
   - No

   Go to Question 12

10. When did you share your status with this partner?

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<th>yy</th>
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</thead>
</table>

11. If yes, what was his/her response? (Check all that apply)

   - Anger
   - Disbelief
   - Shame
   - Blaming
   - Supporting
   - Accepting
   - Abuse (verbal and physical)
   - Ended relationship
   - Continuing relationship

12. Has your partner been tested for HIV?

   - Yes, I know his/her HIV status
   - Yes, but I don’t know his/her HIV status
   - No, she/he has not been tested
   - I don’t know

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</table>
## Sexual Behaviour Follow-up

1. Do you currently have a partner?  
   - Yes  
   - No  
   Go to Question 4

2. Is your current steady partner your first sexual partner?  
   - Yes  
   - No

3. How many steady and casual partners have you had over the past 6 months? (A steady partner is one you have sex with and is considered to be your “darling/sweetheart” and a casual partner is one you have sex with but is not your “darling/sweetheart”.)  
   - Steady  
   - Casual  
   Go to Question 8

4. How long have you been without a sexual partner?  
   - Days  
   - Weeks  
   - Months  
   - Years

5. Did you have sex during this period?  
   - Yes  
   - No  
   Go to Question 7

6. Did you use a condom?  
   - Always  
   - Sometimes  
   - Rarely  
   - Never

7. Have you chosen to abstain from sex?  
   - Yes  
   - No

8. Have you been treated for an STI in the past 6 months?  
   - Yes  
   - No

9. When was your last sex act?  
   - dd  
   - MMM  
   - yy

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Follow-up Survey - Sexual Behaviour

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<th>Participant Number</th>
<th>Visit Code</th>
<th>Phase</th>
<th>Visit</th>
<th>Interim #</th>
</tr>
</thead>
</table>

Sexual Behaviour Follow-up

10. What type of sex did you engage in during your last sex act? Check all that apply
   - Oral
   - Anal
   - Vaginal

11. Did you use a condom during your last sex act?
   (Emphasise ALL ROUNDS of sex. If during the last sex act the participant begins using a condom and then removes the condom, but continues another round of sex without a condom, you must check the “No” box for this question. Only if a condom was used throughout the last sex act should the “Yes” box be checked.)
   - Yes
   - No
   - I don’t remember

12. Did you have drinks containing alcohol in the last four weeks?
    - Yes
    - No
    - Go to Question 14

13. If yes, how often did you have drinks containing alcohol in the last four weeks?
    - At least once a day
    - At least once a week
    - Less than once a week

14. (Women) Did you have sex during menstruation (with any of your partners) in the past 6 months?
    - Yes
    - No

15. Have you shared your HIV status with any of your past partners in the past 6 months?
    - Yes
    - No

16. Has your partner been tested for HIV?
    - Yes
    - No
    - I don’t know
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Follow-up Survey - Sexual Behaviour - Partner

<table>
<thead>
<tr>
<th>CAPRISA 001</th>
<th>Plate 034</th>
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</table>

Participant ID

Site | Participant Number

Visit Date

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Partner Follow-up Questionnaire

Partner Nickname

[ ] Steady [ ] Casual [ ] Partner #

1. What is your status with this partner?

[ ] Together [ ] Partner Deceased [ ] No longer a partner

[ ] Other

Specify:

2. Have you shared your HIV status with this partner(s) over the past 6 months?

[ ] yes [ ] no

Go to Question 5

3. When did you share your status with your partner?

dd | MMM | yy

4. What was his/her response? (Check all that apply)

[ ] Anger [ ] Disbelief [ ] Shame

[ ] Blaming [ ] Supporting [ ] Accepting

[ ] Abuse (verbal and physical) [ ] Ended relationship [ ] Continuing relationship

5. Has your partner been tested for HIV?

[ ] Yes, I know his/her HIV status

[ ] Yes, but I don't know his/her HIV status

[ ] No, she/he has not been tested

[ ] I don't know

6. Do you have any other/new partners that we have not included here?

[ ] yes [ ] no

(If there is a partner(s), use the baseline partner questionnaire first.)

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