

CAPRISA 003

**A Study to compare three existing starting points of ART Initiation in
HIV/TB co-infected patients**

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Schema

- Design: This is a randomized, open-label pilot study comparing three existing treatment strategies of ART initiation in HIV/TB co-infected patients:
Group 1: early initiation of ART with TB treatment,
Group 2: initiation of ART upon completion of the intensive phase of TB treatment,
Group 3: initiation of ART upon completion of the continuation phase of TB treatment
- Sample Size: Approximately 519 patients will be enrolled.
- Population: Men and women ≥ 18 years of age with documented HIV infection and smear-positive pulmonary TB.
- Treatment Programme: TB/HIV co-infected patients at the CDC are routinely offered ART in this treatment programme funded by PEPFAR and the Global Fund. The treatment programme includes extensive counselling and adherence support and detailed clinical and laboratory assessment for initiation of ART. At present, the clinicians arbitrarily decide when to start ART – this is the only aspect of the treatment programme which will be changed – patients will now be randomised into one of three ART starting points. All other care and monitoring received by all the patients in the treatment programme is standard.

1 INTRODUCTION

1.0 Background

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).

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 testing and CD4+ cell count assays are cost-efficient in this group since most TB patients are HIV positive and most HIV positive TB patients will have CD4+ counts at or below the threshold for treatment initiation. Hence HIV positive TB patients are the most readily identifiable and accessible group that fulfil the criteria for ART. Initiating ART in HIV positive TB patients will lead to the inclusion of the majority of HIV/AIDS patients fulfilling the criteria for therapy.

The approved START study aims to answer the research question of 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. However, funding for the START study has been delayed by a few months providing an opportunity to address a related but separate treatment question through an existing ART programme at the CDC. We are requesting ethics approval to randomize patients into one of three ART treatment starting points which have evolved over time in the course of the implementation of an existing ART programme at the CDC. The proposed research component, viz randomisation to

one of the three starting points will help us to determine when to initiate ART in patients co-infected with TB and HIV. There are no published studies addressing this specific question even though it is important in settings like South Africa where the TB and HIV epidemics coincide.

1.2 Study setting

The Centre for the AIDS Programme of Research in South Africa has a PEPFAR-funded treatment programme which aims to initiate HIV infected patients onto a package of HIV care including ART. Access to ART is provided using two models of ART provision, i.e. ART provision in an urban setting attached to the TB treatment clinic and ART provision in a rural setting associated with the Primary Health Care Clinic in the rural area of Vulindlela in KwaZulu-Natal. This project will be undertaken in our urban facility only.

2 A) PRIMARY OBJECTIVE

To determine the optimal time to start ART in patients on TB treatment by comparing clinical status (CD4 count, viral load, mortality rates and Opportunistic Infections) at 18 months of HIV/TB co-infected patients who initiated ART with TB treatment, at the end of the intensive phase of TB treatment or upon completion of TB treatment.

B) SECONDARY OBJECTIVES

- i)* To assess the impact of the three times of starting HIV care relative to TB treatment on the TB treatment outcomes (cure, treatment success, treatment interruption and treatment failure other non-specified TB outcomes).
- ii)* To assess the impact of the three times of starting HIV care relative to TB treatment on the emergence of ART or TB drug resistance
- iii)* To assess the cost-effectiveness of TB and HIV care across the three arms.

3. STUDY POPULATION

3.1 Description of population

Patients who attend the Prince Cyril Zulu CDC for services comprise a cross-section of different races, ages, and genders. Patients from throughout the greater Durban area who may have TB are routinely evaluated at this health centre and are routinely offered voluntary counselling and testing. Patients who test positive for HIV are offered HIV specific care through the CAPRISA AIDS Treatment programme.

3.2 Inclusion Criteria

The CAPRISA AIDS Treatment Programme's inclusion criteria are broad in order to make treatment available to most patients who need it:

1. HIV infected patients co-infected with TB
2. Receiving any one of the standard anti-TB therapy regimens
3. All patients must agree to use contraception since they will be on efavirenz.

3.3 Exclusion Criteria

Entry into the treatment programme is based on a clinical assessment and should patients not be clinically eligible to maintain a treatment regimen, their entry may be deferred or precluded.

4 STUDY PROCEDURES

4.1 Randomization

Patients will be randomized in one of the three starting points for ART within the same treatment programme in equal proportions (1:1:1) using stratified permuted block randomization (e.g. blocks of variable sizes 6 or 9).

The randomization will be done by a statistician and the randomization codes will not be available to study staff until the moment a participant is randomized. This will be done by providing sealed opaque randomization envelopes to the treatment programme staff at the CAPRISA – eThekweni TB/HIV Research Unit at the Prince Cyril Zulu CDC. The envelopes will be stored in a safe and opened in sequential order by staff members authorized to perform randomization procedures by the CAT Programme Director. 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.

1.0 Link with the CAPRISA AIDS Treatment Programme

All patients entering the CAPRISA AIDS Treatment programme, whether they are in or out of this study, and regardless of which treatment initiation point they are randomized to, will receive the standard care package. For those patients who consent to participation in this pilot study, they will be randomized to one of the three ART starting points. In the event that a patient shows signs of clinical or lab parameter deterioration, the clinician will be at liberty to initiate ART based on their judgement of the best interests of the patients – such patients who may start their ART earlier or later than they would have according to their random allocation will still be included in the intention to treat analysis. For those who do not consent to randomisation, it will be left to the clinicians to decide on when to commence ART. All patients in the CAT Programme see a CAT clinician monthly for clinical and laboratory follow-up. The clinical monitoring includes a history, physical examination and assessment of any adverse events with detailed documentation. All patients are offered the standard first line ART regimen, regardless of when they start; ddl, 3TC and Efavirenz. TB management will be done routinely at the Durban Chest Clinic and in accordance with the South African National TB control programme.

2.0 ART initiation

Group 1: Patients will start ART within a month of starting TB treatment.

Group 2: Patients will start ART within a month of completing the intensive phase of TB treatment (ie. generally, this will mean initiation of ART within 3 months of TB treatment initiation)

Group 3: Patients will start ART within a month of completing the continuation phase of TB treatment (ie. generally, this will mean initiation of ART within 6-7 months of TB treatment initiation)

If there is evidence of clinical deterioration, regardless of the randomisation, patients will be started on ART and will be carefully monitored clinically. Laboratory monitoring will include monitoring of clinical status and safety assays.

3.0 Primary endpoint

The primary analysis will be a comparison of routine clinical and laboratory information documented in the treatment programme including clinical condition, mortality, CD4 count and viral load at 18 months post-randomisation.

5 HUMAN SUBJECTS CONSIDERATIONS

5.1 Regulatory and Ethical Review

The study has thus far been conducted under the oversight of the University of KwaZulu-Natal's Nelson R Mandela School of Medicine Research Ethics Committee (EC) Ref: E107/05. The amended study protocol will be submitted to the EC by the Principal Investigator and reviewed and approved by the EC prior to study initiation. The Investigator will provide progress reports and all other information required by the EC to conduct its reviews.

5.2 Informed Consent

Informed consent forms for randomization into one of the three treatment arms, as well as for specimen storage is attached.

5.3 Risks

Both anti-retroviral agents as well as anti-TB treatment are associated with drug toxicities which range from mild, and self limiting to being potentially life-threatening. Guidelines for the detection and management of these toxicities have been developed, and will be followed. The use of highly active anti-retroviral therapy has led to a profound reduction in the morbidity and mortality due to opportunistic infections among HIV positive individuals. Despite this, a small sub-group of patients will exhibit a paradoxical worsening of their clinical status despite an improvement in their CD4 count and good virological suppression.

Immune reconstitution inflammatory syndrome or a paradoxical reaction, is an unusual inflammatory reaction to an opportunistic infection that occurs in a small group of HIV positive patients with profound immunosuppression during the reconstitution of the immune system during the initial months of anti-retroviral therapy.

5.4 Benefits

1. Clinical care

Patients participating in the CAPRISA AIDS treatment programme will have access to ARV treatment which is only available at a limited level in the public sector at present. They will also have access to comprehensive medical care through the

programme staff, resources and referral systems. Note that this is available to the patients even if they reject participation in the pilot study.

2. Public health

The critical question of when to initiate ART in patients co-infected with TB and HIV could be answered and could assist decision making at a provincial, and national level.

3. Long-term plans for patients in the CAPRISA AIDS Treatment Programme.

Since this is part of the KZN DOH's Global Fund Programme, those receiving their ART from this treatment programme will be transitioned into the National ARV rollout Programme when the Pefpar Programme ends. Discussions have already commenced for the transitioning of stable CAT patients into DoH rollout facilities. If shown to be successful, the intervention could readily be available to local populations. The outcomes of this randomized procedure in the treatment programme may influence policy and treatment guidelines when managing HIV positive people co-infected with TB worldwide. Currently the best levels of evidence in this setting are largely anecdotal.

5.5 Confidentiality

Patient information is stored securely at the treatment programme sites. All patient information is stored in lockable file cabinets in areas with access limited to study staff. Medical data collection, administrative forms, laboratory specimens, and other reports are identified by a coded number only, to maintain patient confidentiality.

6.0 REFERENCES

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