HIV-1 Subtype C Infection:

Response to Treatment as a Function of Disease Progression

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Study Purpose and Rationale

According to 2005 UNAIDS/WHO estimates there are 38.6 million people living with HIV in the world and this number will continue to grow. The worldwide impact of the HIV/AIDS pandemic is well recognized with over 25 million people dying of AIDS since 1981. However, despite a slowing down of the global AIDS infection rate, new infections are continuing to increase in specific regions. Of the 38.6 million people currently infected with HIV, 24.5 million or 63% live in Africa. In 2005 alone 2.7 million people in Sub-Saharan Africa became infected with HIV and there are currently 12 million African children who are now orphans as a result of AIDS.

South Africa in particular carries one of the highest HIV infection rates in the world with prevalence of HIV infection estimated to be 28-29% of the general population. More specifically, data from a study conducted by the South African Department of Health in 2005 reveals that the district of KwaZulu-Natal in the city of Durban has the highest HIV levels in South Africa with prevalence rates reported to be 39.1% in pregnant women.

However, despite these alarmingly high rates of infection, currently there is only limited HIV/AIDS research that has been performed on African populations. Instead, the vast majority of research in HIV/AIDS has been gathered from populations in more developed countries such as the United States and various European countries. Consequently, there remains much to be determined about the patterns of HIV infection and immunological response in African populations. By studying populations who are experiencing increased rates of HIV infection, such as the high-risk groups in the KwaZulu-Natal district of South Africa, valuable information can be gained about the characteristics of HIV infection in these patients to contribute to the overall goal of helping to create more effective HIV treatment and infection prevention strategies for people worldwide.

It is widely accepted in the literature that spread of HIV in South Africa is predominantly linked to heterosexually transmitted HIV-1 Subtype C infection.

Although a few studies have characterized some of the viral dynamics and immunological response in individuals infected with the HIV-1 Subtype C virus in South Africa, there is little to no data on a specific sub-population of individuals known as rapid progressors. Limited studies have revealed that, as compared to the rates predicted by previous studies on non-African populations, the high-risk populations in Uganda, Kenya and India progress at a faster rate when infected with the HIV-1 subtype C virus. In these Africa-based studies the average time to diagnosis of AIDS or AIDS-related death has been reported to occur in less than five years after initial infection. These studies in particular have not identified specific risk factors for rapid progression or calculated treatment effect; however, it has been hypothesized that concurrent infections or access to healthcare may play a role in HIV disease progression. Furthermore, some researchers believe that individuals in this population may respond less to standard of care treatment strategies.

In the South African District of KwaZulu-Natal preliminary data from studies examining high-risk individuals confirms the existence of this population of rapid progressors, with characteristics similar to the rapid progressors in the studies in Uganda, Kenya and India. While there are studies underway which aim to identify the characteristics causing one to rapidly progress after seroconversion, there are no studies examining this population's response to treatment.

Our project, therefore, aims to characterize this population's response to initiation of antiretroviral therapy (ART) as compared to a control population of chronically infected patients who are initiating ART. By studying this population's response to treatment we aim elucidate the relationship between rate of disease progression and response to initiation of ART to gain a clearer understanding of HIV pathogenesis.

Study Design

This study is a prospective cohort study examining the response to initiation of ART in both rapid progressors and chronically infected normals initiating treatment. Patients will be identified from a high-risk population of men and women in the KwaZulu-Natal District of South Africa who are currently receiving treatment at clinics

located in Durban or who are enrolled participants in microbicide trials in Vulindlela. Patients will be screened by clinic personnel and then referred to the study if eligible.

Once enrolled patients will be screened for HIV seroconversion every six months in addition to filling out questionnaires on a regular basis to determine their current health status and risk for HIV infection. At the time of HIV diagnosis baseline CD4 cell counts, HIV RNA viral load levels and CD8 cell counts will be collected. These levels will subsequently be monitored on a regular basis every six months for the duration of the study. Laboratory specialists who will be blinded to all patient identifiers and clinical data will perform analysis of specimens. Participants will also be categorized according to WHO clinical staging criteria at time of diagnosis and each visit thereafter.

Subjects will be offered the chance to initiate treatment with triple drug antiretroviral therapy when their CD4 counts fall below 350 cells/mm3. Subjects will also receive prophylactic medications for all other infections in accordance with current standard of care treatment.

Additionally, data on chronically infected controls will also be gathered from clinic records, which have been gathered in a prospective fashion using the same parameters as our current study guidelines specify. Data from these records will be included in the study if all study requirements are met.

Diagnosis of HIV Infection

Time of HIV infection will be defined as the median time between most recent negative and first positive HIV antibody test. HIV antibodies will be detected via recombinant HIV-1/2 ELISA assay with positive results to be confirmed by western blot analysis. Viral loads will be determined by bDNA (version 3.0; Bayer) and lymphocyte subsets will be measured on fresh samples by use of FACscount (Becton Dickinson).

Staging of Disease Progression and Defining of Rapid Progressors

Once seroconversion has been confirmed participants will be staged in accordance with the clinical and performance scale of the WHO staging system. Subjects' initial stage will be the stage at time of first HIV-1 positive result.

Rapid progressors will be those participants who develop HIV-related symptoms within the one-year after diagnosis – with these symptoms most commonly reported to be weight loss, mucocutaneous manifestations, bacterial infections, chronic fever and chronic diarrhea. Normal/slow progressors will be all those participants who have not developed HIV-related symptoms at one and a half year post HIV diagnosis. Those participants who develop HIV-related symptoms in the intermediate period will be excluded from the final analyses in an attempt to reduce potential overlap between the two groups.

<u>Study Outcomes</u>

The primary outcome will be measured as mean increase in CD4 cell count at 6, 12 and 18 months following treatment initiation. We will also assess for significant differences in two secondary outcomes – mean HIV RNA viral load and mean CD8 cell count – also measured at 6, 12 and 18 months after initiation of treatment.

Statistical Analysis

The primary outcome measure will be increase in CD4 cell counts after initiation of treatment. In previous studies the CD4 cell count has increased an average of 134, 184 and 220 at 6, 12 and 18 months respectively. In past studies, the resultant change in CD4 cell count has been skewed in distribution and, if this occurs, we will use a transformation to normalize the distribution.

It is predicted that the rapid progressor population compromises 5-10% of the entire study population of 250 patients, thus it is likely that the study will involve 220 normal progressors and 20 rapid progressors. In order to detect the presence of a significant difference in CD4 cell count response to treatment analysis of CD4 cell count increase will be performed using an unpaired t-test. This statistical approach will enable a CD4 cell count difference of 50 cells/mm3 to be detected at a p value of less than 0.05 with a rapid progressor population of 20 individuals enrolled in the study.

$$n = 1 + 16 \text{ (st dev/effect)}^2$$

Further analysis will involve multiple regression models as needed.

Study Drugs or Devices

Participants meeting requirements for ART as stated above will be given a standard triple drug therapy regimen (Stavudine, Lamivudine, and Efavirenz or Nevirapine) as well as prophylaxis against opportunistic infections and/or treatment for other illnesses as needed.

No medical devices will be used in this study.

Study Questionnaires

Subjects will complete questionnaires regarding lifestyle and diet habits at time of diagnosis as well as at 6, 12 and 18 months following diagnosis. The importance of this record is to control for various confounding factors that could contribute to variation in response to ART. Questionnaires will be verbally translated as necessary.

Subjects

Participants will be identified from three separate populations – female sex workers in KwaZulu-Natal, participants in a Phase II/IIb microbicide trial in Durban as well as female and male research participants in Vulindlela.

Inclusion Criteria:

1. 18 years of age or older
2. Naïve to Antiretroviral Therapy
3. Participant deemed high-risk

Exclusion Criteria:

1. Unwillingness or inability to provide informed consent
2. Any contraindication to antiretroviral therapy or regular blood draws
3. Most recent negative HIV test more than 6 months prior to first positive result
4. Inability to comply with regular physician visits
5. AIDS defining illness at time of initial HIV infection diagnosis

Confidentiality of Study Data

Confidentiality will be protected using standard CUMC clinical protocol procedures outlined by the CUMC IRB and HIPAA in compliance with the procedures outlined by the IRB of the Nelson R Mandela School of Medicine of Natal University.

Compensation

Participants will not be financially compensated for their participation in this study.

Potential Risks

Participants taking ART are at risk for developing side effects from the treatment. Potential risks also include psychological and/or emotional distress as a result of finding out their HIV status. Participants will receive counseling and education in an attempt to minimize this potentially harmful effect.

Potential Benefits

Participants in this study are at an increased risk of contracting HIV and, therefore, monitoring their HIV status will enable them to obtain treatment and educate themselves about their disease at an earlier time point. The subjects will have access to triple regimen antiretroviral therapy and access to medical care at the clinic as a result of their participation in this study.

Apart from the direct potential benefits to the participants, the results from this study will help to clarify the pathogenesis of HIV infection and contribute to clarification of the immune response and various immunological factors that effect disease progression. This information will help to elucidate HIV viral function and potentially contribute to better treatment and prevention strategies.

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