HSV-2 and HIV-1 subtype C set point in a group of women in KwaZulu-Natal, South Africa

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A. Study Purpose & Rationale

Worldwide HIV-1 Infection

Current estimates of worldwide HIV-1 infection is approximately 37 million adults, 66% of whom reside in sub-Saharan Africa, and approximately 2.5 million children below age 15. UNAIDs estimates that in 2003 there were approximately 5 million new cases of infection worldwide and approximately 3 million deaths attributable to AIDS making AIDS 4th on the list of the leading causes of worldwide mortality.[4] There is heterogeneity of the HIV-1 virus and it exists as a number of subtypes depending on viral sequence variations. Subtype B is the most common in the US, Canada, Western Europe, Australia and certain areas of South America. Subtype C is the most common worldwide and is prevalent in Africa, India and parts of Asia.[4]

HIV-1 set point

A number of trials have elucidated prognostic factors associated with HIV-1 viral set point in patients with subtype B infection. Studies of patients with acute infection with subtype B have shown that steady state levels of viral replication are achieved approximately four months following infection and remain at this level during the early infection period (approximately first two years).[7,8] Studies have also shown that this level or "set point" is lower in women.[8] Set point levels have been shown to be in independent predictor of risk to progression of AIDS in both women and men.[8]

Few studies have been completed examining set points and likelihood of progression to AIDS in patients with subtype C infection. A recent study using data from a prospective cohort of female sex workers in Kenya followed from 1993 to 2004 showed that higher set point viral load was predictive of death. Median set point was 4.67 log copies/ml in this group. Women with a set point viral load of >5 log copies/ml had median duration of survival of 7.1 years. Those with set point of 4-5 log copies/ml had median duration of survival of 8.7 years.[7]

HIV-1 & HSV-2

Recent studies have focused on the overlap of the HIV-1 and HSV-2 epidemics and how the infections influence each other. Seroprevalence of HSV-2 among pregnant women in the US ranges from 20-35% with rates in Europe approaching those in the US.[3] Seroprevalence of HSV-2 in sub-Saharan Africa is estimated to be higher – greater than 40% among women in prenatal clinics and rates as high as 60-90% among female sex workers have been shown in a number of small studies.[3] HSV-2 has been shown to both increase the rate of acquisition of HIV-1 in patients who are HSV-2 positive and the rate of transmission of HIV-1 from an HSV-2 positive person to an HIV-1 negative partner.[2,3] Studies have shown that many HIV-1 patients are also coinfected with HSV-2 and experience frequent subclinical reactivations of their HSV-2 infections.[2,3] Some studies have shown an increase in HIV-1 viral load in patients experiencing a subclinical HSV-2 reactivation.[2,3,6] Total HSV shedding has been shown to be correlated with HIV-1 viral load.[6] Given the higher transmission rates associated with HSV-2, the overlap of the two epidemics is relevant in HIV-1 endemic areas and has raised the question as to whether treatment of HSV-2 should be included in WHO recommendations of patients with genital ulcer disease.

HSV-2 & set point

Few studies have looked at whether coinfection with HSV-2 influences HIV-1 set point. Gray et all have shown a 0.5 log increase in the HIV-1 viral load of recently infected HIV-1 positive men & women in Rakai, Uganda who have HSV-2 coinfection in a paper presented at the International Conference on Sexually Transmitted Disease Research; 2003.[3] In a poster presented at the February 2006 Conference on Retrovirus and Opportunistic Infections, HSV-2 coinfection was shown not to influence viral set point in a group of HIV-1 subtype B positive men in an acute infection cohort in San Diego, California.[1]

This study proposes to examine the relationship between coinfection with HSV-2 and viral set point of HIV-1 subtype C in a high risk group of women in KwaZulu-Natal, South Africa. Patients will be enrolled from the existing acute infection protocol following their conversion to HIV-1 seropositivity and entry into phase II of the trial.

B. Study Design and Statistical Procedures

The primary outcome for this study will be log of the HIV-1 viral load measured at 12 months following suspected infection date in both patients who are HSV-2 positive and negative. Log of the HIV-1 viral load will be used as viral load is not normally distributed but normal distribution of the data can be approximated by using the log values. The study hypothesizes that there will be a 0.5 log higher level of HIV-1 viral load at 12 months in patients who were HSV-2 positive at the time of infection vs. patients who are HSV-2 negative.

Based upon estimates of HSV-2 seropositivity in Africa, we will assume that HSV-2 seropositivity among the HIV-1 infected members of the acute infection group is approximately 65%. We will also assume that standard deviation of the log of viral set point at twelve months is no higher than 0.5 log HIV-1 viral load copies/ml. The study will be powered to detect a difference of 0.5 log HIV-1 viral load copies/ml between the two groups with a power of 80% and a p value of 0.5 using the unpaired t-test for continuous variables as follows:

$$n_{\text{(in each group)}} = 1+16\left(\frac{\text{Standard Deviation}}{\text{Effect}}\right)^2$$

$$= 1+16\left(\frac{0.5}{0.5}\right)^2$$

$$= 17 \text{ per group}$$

$$\text{Power} = 80\% \qquad p=0.5$$

We will enroll 20 patients per group. Potential confounders include age and CD4 count – additional analysis may be necessary to account for this.

C. Study Procedures
Following entry into the study, participants will undergo testing for HSV-2 seropositivity using HSV-2 EIAs with Western blot confirmation of borderline results at the time of scheduled blood draw for the Acute Infection protocol. Testing for HSV-2 will require drawing an additional small amount of blood at this time. Patients who were HSV-2 negative at enrollment will be retested using the same method at their one-year post infection blood draw. HIV-1 viral load is already tested using PCR one-year post infection as part of the acute infection protocol – this data will be used as the primary outcome.

D. Study Drugs or Devices
No drugs or devices will be used in the study.

E. Study Questionnaires
No study questionnaires will be used in the study.

F. Study Subjects
Patients enrolled in the Acute Infection Protocol who enter phase II (HIV+) will be eligible for enrollment in the study.

G. Recruitment
Patients will be recruited from the patients enrolled in the Acute Infection study at the Centre for the AIDS Program of Research in South Africa (CAPRISA) who become HIV+ and enter phase II of the protocol. CAPRISA was founded by the Universities of Natal, Cape Town, and the Western Cape, the Trustees of Columbia University in the City of New York, and the National Institute for Communicable Diseases. Over 200 high risk HIV-1 negative women have been enrolled from Durban and Vulindlela (a small village in the district of KwaZulu-Natal) and followed for conversion to HIV+. Patients who seroconvert to HIV-1 positive and enter phase II of the trial will be asked to enroll in the study.

H. Confidentiality of Study Data
Confidentiality will be maintained using standard methods of the Columbia and University of KwaZulu-Natal IRBs and HIPAA. Study participants will be assigned a number and data will be stored securely at CAPRISA headquarters.

I. Potential Risks
Potential risks of the study are minimal but include potential stigma following HIV-1 & HSV-2 diagnosis. All efforts will be extended to ensure confidentiality.

J. Potential Benefits
Study participants will be carefully followed per the Acute Infection protocol and will access the clinic system. They will receive physical exams at each visit and if HIV treatment is required they will be referred to the CAPRISA Antiretroviral Treatment program.

K. Alternatives

Participants may choose to enroll only in the Acute Infection protocol without enrollment in this additional study. Patients may discontinue their enrollment at any time.

References

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