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Research Proposal:

Clinical Signs and Symptoms of Acute Retroviral Syndrome among women infected with HIV-1 subtype C virus

a.Specific Aims

Objective 1:

To describe the clinical signs and symptoms seen among women presenting with the Acute Retroviral Syndrome (ARS). To describe the prevalence of six symptoms: fever, rash pharyngitis, diarrhea, lethargy and thrush among women with and without acute HIV infection

Hypothesis 1: Women with acute HIV-1 infection have a higher frequency of clinical signs and symptoms than women who are seronegative

Objective 2: Describe symptoms most predictive of ARS

Hypothesis 2: Fever and diarrhea are more likely to be associated with ARS than any other symptom

b. Background and Significance:

The devastating toll taken by the HIV/AIDS epidemic in Africa, where over 25 million inhabitants are infected with the virus, has been well documented. Yet, our knowledge of clinical and virologic characteristics of HIV-1 subtype C infection, the subtype most prevalent in sub-Saharan Africa, is lacking and lagging behind our understanding of the subtype B HIV infection prevalent in the western world.

In light of this knowledge gap and in an effort to characterize acute infection of women infected with HIV-1 subtype C, the Centre for the AIDS Programme of Research in South Africa initiated an Acute HIV Infection Study in August of 2004. This study recruited and enrolled a cohort of women at high risk for contracting HIV in spite of counseling and access to condoms.

It is well known that the period of acute and early HIV infection is characterized by high levels of viral replication (and high HIV-1 RNA level) in the absence of HIV specific antibodies. It has been shown that acutely infected individual is most infectious in this time period. Studies of subtype B virus have demonstrated that 30-80% of individuals with acute infection present with acute retroviral syndrome (ARS) characterized by flu-like symptoms such as fever, rash, pharyngitis, diarrhea. In subtype B infection, number of symptoms reported has been associated with more rapid progression to AIDS or CD4 cells below 200.

Therefore, the ability to detect acute and early phases of HIV-1 infection is of paramount importance to mitigate the transmission as well subsequent course of the illnessMoreover, identifying acute HIV infection may allow for earlier treatment, which could potentially alter the virologic and immunologic course of the disease (Rosenberg, 2000).

Challenges in recognizing and diagnosing acute HIV infection rest in having a high index of suspicion to obtain an HIV RNA test antibody tests can remain negative until approximately 22 days after infection. Further compounding the difficulty of detection is the fact that the symptoms of ARS could be easily confused with a more benign infection (Busch, 2001).
In a setting were RNA testing is not available, or not routinely performed for economical reasons, the ability to develop a clinical checklist of signs and symptoms most likely associated with ARS would be of benefit.

For this reason, researchers have set out to delineate symptoms that may raise clinical suspicion and lead clinicians to use HIV RNA testing (Pilcher 2004). A study conducted in UCSF studied this in the case of acute infection with HIV-1 subtype B. This prospective cohort study showed that the symptoms most strongly associated with acute retroviral infection included fever (OR 5.2%) and rash (OR 4.8%). Further, they showed that combination of rash and fever had high specificity but limited sensitivity for primary HIV infection in this particular cohort. Other symptoms they identified included oral ulcers, arthralgia, pharyngitis, loss of appetite, weight loss, malaise and myalgia. This paper also suggests that considering this data on symptoms along with potential risk of exposure can be used to estimate pre-test probability of ARS (Hecht, 2002).

Because this study was conducted in the United States, where the viral subtype is different and where potentially confounding diseases may be different, its generalizability to the population of high-risk African women is limited. A prospective cohort study of female sex workers was conducted in Mombasa, Kenya. This study also showed fever as the most common symptom with an OR of 2.8. Vomiting and diarrhea were the second and third most prevalent symptom, respectively. In contrast to the study in UCSF, however, skin rash was not seen in any of those who became HIV positive (Lavreys, 2000). Inguinal adenopathy was shown to be a statistically significant sign in both the study on women in Mombasa and in a cross-sectional study of men in Malawi who were diagnosed as having ARS (Pilcher, 2002).

The cohort study that is taking place in South Africa has shown a seroincidence rate of 8.8 per 100 person years. The screening of the larger population of the larger group of high risk women from which the cohort was taken yielded an HIV prevalence of 59.6%. Although the number of new infections is smaller than that of chronic infection, the transmission of HIV-1 is thought be greatest at the time of acute infection. Thus, identifying the symptoms of acute infection in this particular high risk population may be

important in identifying women who should undergo RNA testing to detect acute or early HIV infection.

c. Study Design and Statistical Analysis

This study will be a retrospective analysis of data gathered in the CAPRISA Acute Infection Study. This study was a cohort study of 245 HIV-uninfected women who were accrued between August 2004 and 2005 and followed for a >2 year period. Study volunteers returned to the clinic on a monthly basis where they underwent HIV antibody testing and RNA-PCR testing. At every visit, women were asked about 6 symptoms associated with the acute retroviral syndrome they may have experienced since the last visit: fever, rash, pharyngitis, diarrhea, lethargy and thrush. The monthly evaluations also included: HIV pre & post-test counseling, HIV/STI risk reduction counseling, provision of condoms and prevention education supplies, a routine clinical evaluation.

Acute infection was defined as having a positive HIV-RNA test in the absence of HIV antibodies.

Of the HIV-negative women who enrolled into the study, 53 of them seroconverted during a 2.5 year follow up. In this study, we will determine the prevalence of 6 signs and symptoms among women who were diagnosed with acute HIV-1 infection. Categorical variables will be compared using chi-square or Fisher's exact test (presence or absence of symptom among women with and without acute HIV).

Multivariate logistic models will be used to describe the independent predictors of having acute HIV infection. Variables included in the final model will include demographic variables (age, number of partners) and sign/symptoms that were associated with acute infection on univariate analysis. Seroconverters will be matched to non sero-converters for the purpose of multivariate analysis.
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Strengths and Weaknesses:
One of the strength of this study lies in the fact that the information was gathered prospectively. The women did not know their HIV status when reporting their symptoms. If indeed fever and diarrhea are associated with primary HIV infection, this information can be applied to a similar population of women in order to assess the pre-test probability of infection.

A potential limitation of this study is that symptom reports included times in between the monthly visits. This will increase the number of clinically significant symptom reports. In a study that aims to follow the natural history of HIV-1 in high risk women, it is more likely that women who come in with symptoms will test positive for the virus and this may lead to increased sensitivity of symptoms. Another weakness lies in the overall generalizability of the study. It is unclear whether these findings will be broadly applicable to women who are at a decreased risk for HIV and possibly have different

diseases risks. Nevertheless, it is reasonable to believe that the results will be applicable to women who are at high risk of contracting and transmitting the virus given similar prevalence rates of HIV and other possible confounding infections. Broader question remain to be explored in further studies about women who work as sex workers. To what extent they are able to protect themselves and others from infections with the use of condoms. If they do seroconvert, what challenges do they face before receiving treatment and accessing proper care?

d. Study Procedure and Data Collection:
We will use the data that has already been collected through the Acute Infection study. We will then perform statistical analysis on this data as outlined above.

e. Study Drugs:
There are no drugs being investigated in this study.

f. Medical Device
No medical devices were used in this study

g. Study Questionnaires
. Study participants were asked to complete questionnaires at every visit asking if they experienced any of specified symptoms in the past 7 days. Please see attached questionnaire. Questionaires were translated into isiZulu

h. Study Subjects
Prior to beginning study, ten community liason persons were selected from previously identified sex worker sites to assist with study recruitment and retention efforts.
Inclusion Criteria: Women who were at least 18 years old and self identified as female sex workers or who reported > 3 partners n the preceding 3 months
Exclusion: Women who were pregnant at time of screening or who were planning to travel away from site for more than 3 months

i. Recruitment of Subjects
Women were recruited by word of mouth through the ten community liason person

j. Confidentiality of Study Data

k. P*otential Conflict of Interest*
There is no apparent conflict of interest for this study

l. Location of Study
Study was located at Doris Duke Medical Research Institute (DDMRI) at the Nelson R Mandela School of Medicine at the University of KwaZulu-Natal, South Africa

m. Potential Risks
Potential of stigma in community if discovered to have
HIV

n. Potential Benefits
Regular HIV testing,
Clinical evaluation,
HIV/STI risk reduction counseling
Condoms
Treatment for Sexually transmitted Infections
Travel compensation

o.Alternative Therapies
None

p. Compensation of Subjects
The subjects will not be compensated for participation in this study.

q. Minors as Research Subjects
This study will not involve the participation of minors

r. Radiation or Radioactive Substances
This study will not involve radioactive substances.

References:

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