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An observational study to compare acute HIV infection detection rates in STD clinics to detection rates in all other clinics combined over 12 months in northern Manhattan and Chelsea

A. Study Purpose and Rationale

Acute infection with human immunodeficiency virus (HIV) occurs in the first weeks-to-months after a person has contracted the virus, and is associated with high HIV viral replication without detectable antibodies. Because persons with acute HIV infection (AHI) test negative for HIV via standard testing methods that look for antibodies, it is very difficult to diagnose AHI. Currently, the only ways to detect acute HIV infection is to do nucleic acid amplification or test for HIV (p24) antigen in the blood. These methods are not commercially available at this time for diagnosis. As a result, nearly all cases of AHI are not detected[1].

There is evidence that identifying patients with AHI may have positive therapeutic, public health, and research implications. For example, it is possible that treating patients aggressively during the acute phase may have long-term benefit. Acute infection is associated with a massive loss of CD4+ T cells, particularly in mucosa-associated lymphoid tissues, with a corresponding dramatic increase in viral load in plasma, often to levels over 1 million RNA molecules per milliliter[2,3]. During this phase, the cellular immune system mounts a vigorous attempt to control HIV replication and 40 to 90 percent of patients experience a viral-like syndrome characterized by fever, maculo-papular rash, fatigue, pharyngitis and other symptoms. Eventually – from a few days to 10 weeks – the CD4+ count recovers, symptoms abide, and viral load is suppressed to a set-point that is specific for each patient. At this time, the patient enters the asymptomatic chronic phase of HIV infection. Higher viral loads are associated with more rapid progressions to acquired immunodeficiency syndrome (AIDS) and death. Therefore, it is theorized that treating patients aggressively during the acute phase would lead to establishing a more favorable viral set-point and thus slower disease progression.

Identifying patients with acute HIV infection also creates opportunities to block secondary transmission[4]. Acutely infected persons are considered highly infectious as they have extremely high viral loads and increased viral shedding in mucosa in particular. Moreover, these persons are usually currently engaged in high risk behavior. In fact, there may be a 20-fold greater risk of transmission from an individual with AHI compared to an individual with chronic infection[1]. By identifying these individuals, public health agencies could then target the social networks of these persons, including sexual partners. This could potentially lead to direct prevention of person-to-person HIV transmission, as well as improved outbreak identification and HIV surveillance.

An additional benefit to identifying patients with acute HIV infection is improved vaccine development. The pathogenesis of HIV infection during the acute phase is not well-understood, and studies have largely been done on the SIV-macaque model. This phase is of great interest to vaccine development, as it may provide new directions for research in a currently disappointing field.

Efforts to systematically identify acute HIV infection have been thwarted by the vague nature of the symptoms and lack of access to viral load testing for diagnostic purposes. Many strategies to detect persons with AHI have been targeted at recognizing the symptoms of the acute phase, but these have not been successful to date [1,5,6]. Though there is a cluster of symptoms that is specific for AHI – namely, fever and rash – these symptoms are sufficiently vague that other diagnoses are often suspected[7]. However, strategies that have targeted routine screening for AHI have been more successful[8,9,10]. Recent studies have suggested that testing for acute HIV infection at the same time as standard HIV antibody tests would increase the number of cases identified without being prohibitively expensive. These studies use a strategy of pooled nucleic acid amplification testing (NAAT). In this method, blood specimens are pooled into lots and each lot is tested; if a lot is positive it is broken into smaller lots until the positive individual sample is identified.

A study in North Carolina by Pilcher et al. in the *New England Journal of Medicine* in 2005 demonstrated the feasibility of this approach. In this study, all persons in North Carolina who consented for routine HIV testing at state-funded sites also received concomitant acute HIV testing via pooled nucleic acid amplification. Over the course of one year, 109,250 persons were tested: 583 had positive HIV tests using standard methods and 23 were positive using NAAT. All subjects with AHI were notified of infection: 20 of the subjects began antiretroviral drug therapy, including 1 pregnant woman. Forty-eight sexual partners of subjects with AHI were notified, 30 of which were HIV negative. The total extra cost of NAAT was $3.63 per processed specimen, and $17,515 per additional diagnosed case of AHI. One significant finding from the North Carolina study was that 70 percent of acute HIV infections were detected at STD clinics, as compared to all other sites. Other sites included prenatal and family planning clinics, prisons, drug treatment clinics and general medicine clinics, among others. If only STD clinics were targeted the cost would have been $10,070 per detected case but 7 cases would be missed.

The findings from the North Carolina study suggest that acute HIV infection screening using NAAT is feasible, and may be more cost-effective if focused only on STD clinics. This theory is supported by a recent study in *Journal Acquired Immune Deficiency Syndrome* in 2006 which showed that adding HIV RNA screening to routine HIV antibody testing in several STD clinics in California identified a substantially increased proportion of cases of AHI. In this study, however, the cost of screening was higher than in North Carolina: $12 per additional specimen and $34,800 per additional diagnosed case of AHI. This study suggests that the true cost of screening will surely vary from city to city.

Currently, New York City does not have an acute HIV infection screening program, despite having six times the number of new HIV cases annually than North Carolina (3800 vs. 583). Such a program would likely identify a substantial number of AHI cases, and could potentially make an impact on disease transmission. However, it would also be an expensive undertaking, the true cost of which is unknown. Prior research also suggests that AHI screening should only be targeted to STD clinics, but these results may not apply to New York City. Therefore, a pilot screening program in New York City is indicated.

The primary objective of this study is to compare acute HIV infection detection rates in STD clinics to detection rates in all other clinics combined over a 12-month period in northern Manhattan and Chelsea.

B. Study Design and Statistical Analysis

Over one year, all consenting persons who present for routine HIV counseling and testing in all testing sites in northern Manhattan and Chelsea will submit serum to be tested by standard HIV antibody testing and pooled nucleic acid amplification testing (NAAT). The site of testing will be categorized and recorded. All testing will be confidential and linked to patient information using unique identifiers. Persons who test positive via either method will be contacted as usual and given post-test counseling and access to HIV care. Partner notification will also proceed as usual. Persons identified with AHI will receive an additional survey regarding risk behaviors, symptoms, and partnerships, and will be offered entry into current experimental protocols for treatment of AHI.

The acute HIV infection detection rate from testing at STD clinics will be compared to the rate from testing at all other sites combined. In addition, the added cost of testing per sample and per diagnosed case of AHI will be compared between STD sites and all other sites.

The study will enroll 50,000 subjects among STD clinics and 50,000 subjects among all other clinics in northern Manhattan and Chelsea[*]. In these neighborhoods in 2005 there were 619 new cases of HIV diagnosed using standard methods[11]. Using North Carolina data, this translates to roughly 138,754 HIV tests done in these areas, 40 percent of which were done at STD clinics (i.e. 55,501). (The actual data could not be obtained secondary to lack of access to information). In North Carolina, less than 1.5 percent of patients who requested HIV testing either did not qualify or did not consent for enrollment in the study. With a similar rate in this study, more than 50,000 people would still enroll in each group.

Results will be analyzed using the Chi-Square test to compare proportions in two groups. A sample size of 50,000 tests in each group should have 80 percent power to detect a statistically significant ($p < 0.05$) difference between STD sites and all other sites combined, based on the different detection rates reported in the North Carolina study

[*] These neighborhoods include Washington Heights, Inwood, Central and Eastern Harlem, Morningside Heights, Upper West Side, Upper East Side, Chelsea and Clinton.

(0.0004 vs. 0.0001). The study is expected to detect 20 cases of AHI from STD clinics as compared to 5 cases from everywhere else.

C. Study Procedures

All subjects in the study will undergo standard HIV antibody testing as well as pooled nucleic acid amplification testing (NAAT). Standard HIV testing involves initial enzyme immunoassay testing and confirmatory Western blot analysis. Pooled NAAT is a method to cut down on the expense of HIV viral load testing, which can cost more than $100 per test. In this method, aliquots of serum samples are combined into several master pools. These master pools are screened with qualitative NAAT and positive pools are broken down into sub-groups and then individual specimens until the positive sample is identified. The process takes one to two weeks. All positive samples are re-tested with NAAT and standard methods. In this study (following the numbers from North Carolina), aliquots from serum samples will be combined into 90 distinct pools.

D. Study Drugs

None

E. Study Questionnaires

Questionnaires will be given to all subjects who test positive for acute HIV infection. The questionnaire is under development. However, topics to be discussed in the questionnaire include symptoms of AHI, risk behaviors, and information regarding sexual partners for intense social network targeting. The questionnaire will be administered by trained study personnel.

F. Study Subjects

Inclusion criteria include all persons who present to a clinic that offers HIV testing and counseling in northern Manhattan or Chelsea.

Exclusion criteria include anyone who has a known diagnosis of HIV or AIDS.

G. Recruitment of Subjects

Subjects will be approached about enrollment during routine pre-test counseling. HIV counselors and physicians at study sites will be educated concerning the study with on-site visits by study personnel.

H. Potential Conflict of Interest

None

I. Location of Study

The study will be conducted at all clinics where HIV testing is offered in Washington Heights, Inwood, Central and Eastern Harlem, Morningside Heights, Upper West Side, Upper East Side, Chelsea and Clinton.

J. Potential Risks and Benefits

There is a risk that some subjects will experience psychological distress in the event that they are diagnosed with acute HIV infection. Study personnel will be trained at evaluating this distress and referring subjects to appropriate counseling as necessary.

The benefits of participating in the study are that subjects diagnosed with AHI will have immediate access to specialized treatment centers and may enroll in a treatment study. Subjects will also be able to protect their sexual partners from secondary transmission.

K. Compensation

There is no compensation for subjects except for travel vouchers in the event that a subject needs to complete a questionnaire.

L. Costs

There are no additional costs to subjects except for the small proportion of subjects identified with acute HIV infection. These subjects will need to spend more time completing a questionnaire and receiving confirmatory testing.

M. Minors

Minors will be invited to participate if they are also offered routine HIV antibody testing.

N. Radiation or Radioactive Substances

None used in study.

O. References

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