

Identifying Acute HIV Infection In Rhode Island

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Acute HIV Infection is the earliest stage of HIV disease, immediately following the acquisition of the HIV virus. During this time the body is viremic but has not yet developed a detectable antibody response to the infection. In the absence of antibodies, standard HIV tests such as enzyme immunoassays and Western blot analysis will not detect the virus. The acute phase can last from a few weeks up to two months, and is characterized by peaking viral loads and increased viral shedding in the genital tract.^{1,2,3} Newly infected individuals, typically unaware of their infection, are likely to engage in risky behaviors that increase the chance of transmission to uninfected individuals. Coupled together, increased viral loads and an unknown status significantly increase the public health risk of further transmission during the first two months following infection.^{4,5} Up to 50% of new HIV infections may be attributed to transmission by individuals with acute HIV infection.^{6,7}

The diagnosis of acute HIV infection has enormous implications for HIV prevention. Studies have shown that completing HIV counseling and testing, regardless of serostatus, correlates with a reduction in risk behavior.^{8,9} In one study, almost 50% of **men who have sex with men (MSM)** receiving an HIV test reported a reduction in risk behaviors following the test.⁹ Receipt of a positive HIV test has an even stronger impact on risk reduction.¹⁰ Instituting educational and behavioral risk reduction programs at the earliest stage of HIV infection when transmission risk is greatest could have a large impact on subsequent transmission rates. Additionally, ongoing investigations are evaluating the impact of initiating antiretroviral therapy during the acute stage, with the dual goals of preventing the progression of disease within the infected individual and reducing subsequent transmission by lowering viral loads.¹¹⁻¹⁵

Acute HIV infection is under-diagnosed in part because of nonspecific symptoms and a lack of awareness amongst clinicians. Symptoms of acute retroviral syndrome commonly include

fever, fatigue, rash, pharyngitis, myalgia, headache, weight loss, and gastrointestinal discomfort.^{1,14} The significance of symptoms during the acute stage is not fully understood, but studies suggest a possible correlation between the number, severity, and duration of symptoms and the rate at which disease progression occurs.¹⁴ However, not all newly infected patients are symptomatic. Between 40 and 90% of acute HIV infection cases have the associated symptoms referred to as the acute retroviral syndrome.^{4,16} Unfortunately, the inconsistent and nonspecific nature of these symptoms, combined with the reluctance of clinicians to ask about risky sexual and drug use behaviors, results in the frequent failure to diagnose acute HIV infection. In a retrospective analysis of serum from 563 patients evaluated for mononucleosis, which has similar symptoms, undiagnosed acute HIV infection was identified in seven patients (1.2%).¹⁷ Improving awareness amongst clinicians of the link between symptoms of acute viral infections in sexually active individuals and HIV infection is critical for increasing the diagnosis of acute HIV infection.

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Identifying acute HIV infection largely depends upon the timing of presentation of the infected individual and the type of HIV testing completed. Following infection, the virus rapidly replicates, reaching peak viral levels within approximately 3-4 weeks before declining to a steady state.⁴ However, not until approximately four weeks after infection

are antibodies detectable with standard assays including ELISA and Western blot.¹⁶ This discrepancy between the time of infection and detection with conventional HIV tests is referred to as the “window period.” During this period, acute HIV infection can be identified through nucleic acid testing. When a test for plasma HIV RNA yields a positive result and antibody testing is negative or indeterminate, a diagnosis of acute infection is made. Several studies have utilized HIV RNA testing with pooling techniques to create a cost-effective model for screening for acute HIV infection. In North Carolina, pooled HIV RNA tests were performed on serum samples with negative or indeterminate antibody results at state-funded testing sites. The HIV RNA testing resulted in identification of 23 cases of acute HIV infection, which increased overall diagnosis of HIV infection by 3.9%.¹⁶ Pooled HIV RNA testing at STD clinics in Los Angeles and San Francisco increased diagnosis of HIV by 7.1% and 10.5%, respectively.¹⁸ Both studies reported that pooling of samples allowed for cost-effective testing.

In 2006, the National Institute of Mental Health launched a multisite study to assess the feasibility of identifying acute HIV infection and risk behaviors surrounding recent HIV transmissions, with the goal of developing effective prevention interventions for acutely infected individuals. Among other sites, the **Lifespan/Tufts/Brown Center for AIDS Research (CFAR)** collaborated with the Yale University Center for Interdisciplinary AIDS Research to form a study site in New England. We report our experience with identifying cases of acute HIV infection in select high-risk populations in Rhode Island.

METHODS

Two strategies to identify acute HIV infection were employed over a 15-month study period.

First, HIV RNA testing was incorporated into established HIV testing pro-

Table 1: Characteristics of participants with acute or recent HIV Infection.

Pt #	Screening/Referral Site	Gender/Race	Age	Risk behaviors reported	Symptoms Reported	Diagnosis
1	Immunology Center	M White	52	Unprotected anal sex and other risky sexual activities with multiple HIV+ men	Dermatological problems	Recent
2	Immunology Center	F Latina	37	Unprotected sex with a male partner suspected of having outside sexual relationships	None; voluntarily sought HIV testing	Acute
3	Primary Care Physician	M White	45	Unprotected oral and anal sex with multiple male partners of unknown HIV status	Flu symptoms, chills, fever, malaise, headache	Acute
4	Megaplex Bathhouse	M Latino	39	Unprotected anal sex with a male partner of unknown HIV status	Myalgia, sore throat, fatigue	Acute
5	Whitmarsh STD Clinic	M White	32	Unprotected anal sex with multiple male partners of unknown HIV status	Syncope, shortness of breath, sore throat, headache	Recent
6	Immunology Center	M Cape Verdean	34	Unprotected sex with a female sex worker on a single occasion	Dysuria	Recent

grams at two locations. MAP Drug and Alcohol Rehabilitation Services provides substance abuse treatment and HIV education and prevention services to minority populations in the Providence area and conducts an HIV testing program one day per week. The Gay Megaplex, the largest bathhouse in New England, catering to men who have sex with men, has provided an environment conducive to risky sexual practices among men for more than a decade. An HIV and sexually transmitted infection testing program has operated at the bathhouse two to four times a month since 2000, staffed by local clinicians and health educators. Both the MAP and Megaplex testing programs utilize rapid HIV antibody testing, which provides results within 20 minutes. Individuals requesting an HIV test at either of these locations were informed of the limitations of antibody testing with respect to acute infection and invited to participate in the study. Persons with negative rapid antibody test results had serum samples collected for HIV RNA testing that was conducted at the Lifespan/Tufts/Brown CFAR laboratory. HIV RNA testing was performed using the Versant HIV-1 RNA 3.0 [bDNA] signal amplification nucleic acid probe assay using a pooling algorithm to reduce costs.

In a second strategy to identify acute HIV infection, clinicians at The Miriam Hospital Immunology Center, Miriam and Rhode Island Hospital Emergency Departments, and Whitmarsh STD clinic were educated regarding the clinical symptoms of acute retroviral syndrome. Patients presenting with appropriate symptoms who also reported recent sexual activity were informed of and offered referral to the study. If the patient agreed, an appointment with a study researcher was made within 72 hours. If standard HIV antibody test results were not available from the referring provider, a rapid test was performed. If this test was negative, serum samples were collected for HIV RNA testing.

Participants with a negative rapid test, or a negative or indeterminate ELISA or Western blot, followed by a positive HIV RNA test, were considered to have acute infection. Individuals with confirmed positive antibody testing but a documented negative antibody test within the previous six months were considered to have recent HIV infection and were also eligible for the study. Individuals with confirmed HIV infection were linked to the Miriam Hospital Immunology Center and invited to complete two interviews that examined behaviors surrounding acute infection.

RESULTS

Three cases of acute HIV infection and 3 cases of recent HIV infection were identified in this study. All six individuals were between the ages of 30-55 years; five were male. All six reported unprotected sex with a partner of unknown or positive HIV status. Five of the six reported symptoms attributed to HIV infection. (Table 1)

Screening: One hundred thirteen participants from the community testing sites were screened with pooled HIV RNA testing; 65 from the Megaplex and 48 from MAP. Of these, one case of acute HIV infection was identified from the Megaplex. (Table 1, Pt# 4)

Referrals: Five suspected cases of acute HIV infection were referred to the study for evaluation; 3 from the Miriam Hospital Immunology Center, one from the Whitmarsh STD Clinic, and one from a primary care physician in the community. Of these five, two cases of acute and three cases of recent HIV infection were diagnosed. (Table 1)

CONCLUSIONS

We identified six individuals with acute or recent HIV infection within Rhode Island. Five were identified through referrals and one individual out

of 113 screened for acute infection with pooled HIV RNA testing was found to have acute infection. Considering screening programs in other states have pooled thousands of specimens for HIV RNA testing to identify one person with acute infection,¹⁶ our testing yield was quite high in this study. Pooled HIV RNA testing is both feasible and appropriate to identify acute HIV infection in screening settings, especially in those with high background HIV prevalence and where there is a reasonable throughput of persons who can provide specimens for testing. Five of the six individuals diagnosed with acute or recent HIV infection were referred to the study by local clinicians, reinforcing the importance of stepping up identification of suspected acute HIV infection by providers in the community. Providers need to recognize the symptoms of acute retroviral syndrome and be cognizant of the need to ask patients about sexual and other HIV risk behaviors. Ongoing education of community providers is warranted in order to maintain appropriate levels of awareness. Improved provider awareness must be supported with the development and implementation of efficient identification and referral systems in order to expedite diagnosis treatment, and prevention counseling for those with acute or recent HIV infection.

Acknowledgements

This project was funded by the National Institute of Mental Health (NIMH) grant number P30 MH62294-05-S1, and the Lifespan/Tufts/Brown Center for AIDS Research: P30 AI042853. In addition, we would like to acknowledge our collaborating NIMH Multisite AHI Study sites: Center for AIDS Prevention Studies, University of California San Francisco; HIV Center for Clinical and Behavioral Research, New York State Psychiatric Institute and Columbia University; HIV Neurobehavioral Research Center, University of California San Diego; Center for AIDS Intervention Research, Medical College of Wisconsin; and Center for HIV Identification, Prevention and Treatment Services, University of California Los Angeles. Dr. Beckwith is supported by the National Institute on Drug Abuse 5K23DA021095 and P30DA01386.

REFERENCES

- Pilcher CD, et al. Brief but efficient. *J Infect Dis* 2004; 189:1785-92.
- Chakraborty H, et al. Viral burden in genital secretions determines male-to-female sexual transmission of HIV-1. *AIDS* 2001; 15: 621-7.
- Pilcher CD, et al. Amplified transmission of HIV-1. *AIDS* 2007; 21:1723-30.
- Zetola NM, Pilcher CD. Diagnosis and management of acute HIV infection. *Infect Dis Clin North Am* 2007; 21:19-48.
- Schwarcz S, et al. Late diagnosis of HIV infection. *J Acquir Immune Defic Syndr* 2006; 43:491-4.
- Brenner BG, et al. High rates of forward transmission events after acute/early HIV-1 infection. *J Infect Dis* 2007; 195:951-9.
- Pao D, et al. Transmission of HIV-1 during primary infection: relationship to sexual risk and sexually transmitted infections. *AIDS* 2005; 19:85-90.
- Amaro H, et al. Heterosexual behavioral maintenance and change following HIV counseling and testing. *J Health Psychol* 2005; 10:287-300.
- MacKellar DA, et al. Recent HIV testing among young men who have sex with men. *Sex Transm Dis* 2006; 33:183-92.
- Colfax GN, et al. Sexual risk behaviors and implications for secondary HIV transmission during and after HIV seroconversion. *AIDS* 2002; 16:1529-35.
- Goujard C, et al. CD4 cell count and HIV DNA level are independent predictors of disease progression after primary HIV type 1 infection in untreated patients. *Clin Infect Dis* 2006; 42:709-15.
- Berrey MM, et al. Treatment of primary human immunodeficiency virus type 1 infection with potent antiretroviral therapy reduces frequency of rapid progression to AIDS. *J Infect Dis* 2001; 183:1466-75.
- Hare CB, et al. Seroreversion in subjects receiving antiretroviral therapy during acute/early HIV infection. *Clin Infect Dis* 2006; 42:700-8.
- Rosenberg ES, et al. Immune control of HIV-1 after early treatment of acute infection. *Nature* 2000; 407:523-6.
- Granich RM, et al. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission. *Lancet* 2009; 373:48-57.
- Pilcher CD, et al. Detection of acute infections during HIV testing in North Carolina. *NEJM* 2005; 352:1873-83.
- Rosenberg ES, Caliendo AM, Walker BD. Acute HIV infection among patients tested for mononucleosis. *NEJM* 1999; 340:969.
- Patel P, et al. Detection of acute HIV infections in high-risk patients in California. *J Acquir Immune Defic Syndr* 2006; 42:75-9.

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Disclosure of Financial Interests

Curt G. Beckwith, MD. Grant support: Gilead Sciences

Alexandra H. Cornwall, Robert Dubrow, MD, PhD, Kimberle Chapin, MD, Robert Ducharme, Irma Rodriguez, BS, MT, Lavinia Velasquez, MS, Michael H. Merson, MD, Kathleen J. Sikkema, PhD, Kenneth Mayer, MD, have no financial interests to disclose.

Discussion of off-label usages of drug or product: Versant HIV-1 RNA 3.0 [bDNA] signal amplification nucleic acid probe assay

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