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A Conceptual Model of Interventions to Increase Diagnosis of Acute HIV Infection and Reduce Forward Transmission

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Introduction

Approximately 56,000 individuals in the US acquire HIV annually [1,2]. Newly-infected persons are highly infectious during the first 2–4 months following HIV acquisition—a period known as acute HIV infection (AHI)—and consequently contribute disproportionately to HIV transmissions. In this paper, we discuss a conceptual model that incorporates interventions specifically targeting AHI that have the potential to greatly decrease new HIV infections.

Two important properties distinguish acute HIV infection from the later, chronic stage of HIV infection. First, AHI is characterized by exceptionally high levels of virus circulating in the blood and in the genital tract [3–9]. Plasma and genital tract viral load levels are positively correlated with the risk of sexual transmission [4,5,10]. The high-level viremia observed during acute infection results in greatly increased risks of HIV transmission during sexual or syringe-sharing activities.

The risk of transmission during acute HIV infection is approximately 8–22 times greater, on a per-act basis, than it is during the subsequent period of chronic infection [5,11]. Consequently, and despite the relatively brief period during which persons are acutely-infected, the acute period of infection plays a disproportionate role in fueling nascent epidemics and sustaining more mature epidemics [12–16]. Simulation and mathematical models of the mature epidemics in the UK and US suggest that between 10 and 20% of sexually-transmitted infections can be attributed to acute-phase transmission [12,17]. Moreover, phylogenetic analyses of persons with recent infection in England and Quebec suggest that 25–50% of recently-acquired infections are due to transmission during the early or acute-phase of HIV infection [13,16].

The second distinguishing characteristic of AHI is that antibodies against HIV are not detectable during much of the acute period of infection. Formation of HIV antibodies usually occurs 2–4 weeks after HIV is acquired [7,18]. Antibody levels detectable by

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standard enzyme-linked immunoassay (EIA, ELISA) screening tests are not reliably present until 4–8 weeks after infection. As a consequence, acutely-infected individuals usually have negative or indeterminate antibody test results [3,18]. Current HIV screening strategies mainly rely on HIV antibody tests. Unfortunately, even the most aggressive antibody-based testing strategy will fail to identify HIV-infected individuals during AHI, when the risk of onward transmission is greatest.

The annual incidence of new HIV infections in the US has remained relatively constant for more than a decade [1]. To reduce HIV incidence below the current plateau, innovative HIV prevention strategies are needed, including interventions to increase AHI diagnoses and prevent transmission of the virus during AHI. Currently, accurate diagnosis of AHI requires the use of HIV nucleic acid amplification tests that detect the presence of HIV RNA, rather than antibodies against the virus. We have developed a conceptual model of potential targets of AHI-specific interventions to increase AHI diagnoses and to reduce HIV transmission through a combination of increased RNA testing in both public health and clinical settings; education of at-risk individuals, health care providers, and HIV counselors; and implementation of timely and efficient partner notification programs.

Current Interventions Targeting Acute HIV

Increasing acute HIV diagnoses and preventing transmission during the brief, but extremely infectious period of acute infection should be a key component of comprehensive HIV prevention strategies.

To-date, few intervention approaches have been proposed to increase AHI detection. One notable exception is North Carolina's utilization of pooled-sample RNA testing to identify acute infection, combined with aggressive partner notification and testing [19]. In this protocol, blood specimens from individuals who test negative for HIV antibodies are pooled, then tested for the presence of HIV RNA. When a pooled-sample tests positive for HIV RNA, the test then is repeated with successively smaller pools until a single person (or possibly multiple persons) with acute HIV infection can be identified. Acutely-positive individuals are then contacted and informed of their diagnosis and partner notification services are initiated. Several other states and municipalities have enacted similar HIV RNA testing protocols within public health or community-based settings. These programs have yielded acute infection detection rates of between 0.2 and 3.6 positive results per 1,000 individuals tested [20–22].

A Multi-Faceted Conceptual Model to Target AHI

To further increase AHI diagnoses and to help prevent forward transmission of the virus during acute infection, additional interventions are needed. Our conceptual model of potential targets of AHI-specific interventions is presented in Fig. 1. The conceptual model augments public health-based RNA testing with increased clinical diagnosis of AHI, achieved through enhanced education and training of at-risk individuals, health care providers, and HIV counselors. Figure 1 illustrates how these multiple interventions (labeled A–D) could enhance current HIV testing and prevention strategies (shown with dotted arrows) by creating additional routes to HIV prevention and earlier diagnosis of HIV infection (shown with dashed arrows). We describe below how these multiple interventions—individually and synergistically—could help increase AHI diagnoses and prevent secondary HIV transmission.

Individuals At-Risk for HIV Acquisition

Educational campaigns are needed to increase at-risk persons' awareness and understanding of AHI, its symptoms, and its associated elevated risk of transmission (Fig. 1a). Most acutely-infected persons have symptoms that commence 1–4 weeks after HIV is acquired. The most common symptoms include fever, rash, fatigue, pharyngitis, weight loss, muscle aches, and lymphadenopathy [3,23–25]. In the only direct examination of AHI knowledge of which we are aware, 30% of at-risk men who have sex with other men (MSM) could not identify a single symptom associated with AHI [26]. When asked whether they would seek medical attention if they developed “flu-like” symptoms after having unprotected intercourse with an anonymous sex partner, fewer than half reported that they would do so. Similarly, many participants in the NIMH multisite acute HIV infection study reported that they had experienced symptoms prior to being diagnosed with acute infection, but very few had associated these symptoms with the possibility that they might recently have acquired HIV [27].

Individuals at-risk for HIV acquisition also should be educated that some individuals with recently-acquired HIV experience no symptoms. Persons with a recent high-risk (potential) exposure to HIV—with or without symptoms of acute infection—should be encouraged to seek prompt medical care for AHI evaluation. The potential benefits of early HIV diagnosis, including improved medical outcomes and reduced transmission to others, should be highlighted.

Finally, at-risk individuals should be made aware of the greatly increased risk of transmission during AHI and the need to refrain from transmission risk activities if they believe they might recently have acquired HIV. No published studies have evaluated at-risk persons' knowledge of the heightened risk of transmission during AHI. There is, however, evidence of behavior change following an AHI diagnosis. After being diagnosed with AHI, men in the NIMH multisite acute HIV infection study significantly decreased the number of sex partners per week, decreased unprotected sex acts with partners thought to be seronegative, and preferentially engaged in unprotected sex with partners they believed were HIV-infected [28]. Educational campaigns should encourage persons who suspect that they might recently have acquired HIV to abstain from unprotected intercourse or syringe-sharing activities until the possibility of infection can be ruled out. Knowledgeable health care providers could help reinforce this message (see below).

Health Care Providers

Increasing AHI diagnoses and reducing AHI-related transmission will require increased awareness of AHI on the part of health care providers who may encounter acutely-infected individuals. To our knowledge, there are no published studies of physicians' knowledge of AHI, or how often front-line care providers consider acute HIV infection when a patient reports recent sexual or injection risk behaviors and physical symptoms associated with AHI. Many people with acute HIV infection are seen by health care professionals each year [29]. As many as 0.7–1% of patients seen in primary or urgent care settings with “viral” symptoms are acutely-infected with HIV [20,30,31]. These encounters represent an important opportunity for early HIV diagnosis. However, correctly diagnosing AHI requires knowledge of the associated symptoms, coupled with timely consideration of this diagnosis during the patient encounter. It further requires that the provider understand the strengths and limitations of currently-available HIV tests with regard to diagnosing acute HIV.

Professional education should be made available to all health-care providers who might potentially encounter acutely-infected individuals, including primary care and emergency medicine providers (Fig. 1b). Providers should be trained to recognize the symptoms

associated with AHI, to inquire about patients' recent sexual and drug injection histories, and should be educated about the appropriate use of diagnostic tests for AHI. Further, these providers should be aware of the heightened risk of HIV transmission during AHI and should counsel patients at-risk for AHI about the importance of decreasing risk behaviors until a definitive diagnosis is obtained.

HIV Counselors

Increased awareness of AHI among HIV testing counselors could further enhance AHI diagnosis and decrease secondary transmission during the acute period of infection (Fig. 1c). HIV counselors also encounter at-risk individuals at particularly opportune times. Some individuals with very recent, potential exposures to HIV present for testing before the development of HIV antibodies.

During post-test counseling of persons with a recent exposure and an antibody-negative or indeterminate test result, counselors should raise the possibility of AHI, inform clients that an antibody test cannot reliably detect very recent HIV infection, and advise them to seek medical care for a definitive evaluation (if RNA testing is unavailable within the counseling setting). Clients also should be advised to abstain from unprotected intercourse or other transmission risk activities while uncertain of their HIV status. At present, little is known about HIV counselors' knowledge of AHI or the content of the educational messages, if any, provided to clients regarding AHI.

Partner Notification

An important cornerstone to our model is the expedient notification to all sexual and needle-sharing contacts of newly diagnosed individuals, especially those diagnosed with AHI, since their contacts are more likely to be experiencing AHI themselves (Fig. 1d). All contacts must be efficiently contacted to allow for immediate delivery of appropriate counseling that can reduce HIV transmission risk behaviors. In addition, the contacts need immediate rapid HIV antibody testing, and, if negative, HIV RNA testing to evaluate for AHI. Efficient partner notification, counseling, and testing are essential to break chains of acute HIV transmission.

Discussion

The acute HIV infection detection and secondary transmission prevention strategy outlined above focuses on increasing knowledge about AHI among potentially affected individuals, accurate diagnosis of AHI, and short-term risk reduction by at-risk persons with a recent, potential exposure to HIV. This approach complements the use of pooled-sample RNA testing to identify persons with acute infection, but goes beyond this approach by proposing interventions that would: (1) utilize clinical and HIV testing encounters as counseling opportunities to reduce secondary transmission; (2) educate at-risk persons about the symptoms and elevated transmission risk during AHI, and the importance of seeking medical care and reducing risk behaviors after a potential exposure to HIV; (3) expand the use of RNA testing in clinical settings and increase referrals to clinical settings when RNA testing is not available in nonclinical settings; and (4) utilize maximally efficient partner notification to break chains of acute HIV transmission. To be successful, the proposed HIV prevention strategy will require augmenting AHI-related knowledge and skills within several different groups, including at-risk persons, health care providers, and HIV testing counselors.

Research is needed to identify current levels of AHI knowledge in these groups and to design effective interventions to increase knowledge and change behaviors. Nevertheless,

here we offer initial suggestions regarding potential interventions to target AHI. Educational interventions for at-risk persons should be broad-based and targeted, to reach as many at-risk persons as possible. Broad-based approaches could include public service announcements on radio or television, and advertising on public transit and internet sites. More targeted intervention approaches might include advertisements in gay newspapers; educational materials at gay events; educational campaigns on internet sites used by individuals seeking sex partners; needle-exchange venues; and, drug treatment centers. Acute HIV-related educational information can also be communicated to at-risk individuals by incorporating it into standard messages delivered by HIV counselors.

Information about AHI could be provided to front-line health care professionals efficiently through online continuing education modules, review articles in journals, and through inclusion in the content evaluated by board certification examinations. Educational efforts could be supported by the development of concise AHI diagnosis guidelines (current guidelines discuss only the diagnosis of chronic HIV infections) [32–34].

To improve HIV counselors' knowledge of AHI, educational modules could be developed, disseminated, and be required by the governmental bodies that train and certify HIV counselors. The varying availability of HIV RNA testing will require that counselors have a thorough knowledge of locally available resources to assist with AHI diagnosis.

Although we have focused on RNA testing as the “gold standard” for detecting acute HIV infection, combination assays that test both for HIV antibodies and for p24 antigen currently are being evaluated and could provide an alternative to RNA testing as a means of detecting early HIV infection [35–39]. Notably, although combined antibody/antigen tests offer the potential to shorten the period between HIV acquisition and diagnosis compared to antibody-only tests, these tests cannot detect the very first stages of infection. Nevertheless, when these tests become commercially available, it will become even more important for at-risk individuals, health care providers, and HIV counselors to understand the utility of different types of tests with regard to acute HIV diagnosis.

Although advances in antiretroviral medications have greatly decreased AIDS-related mortality [40] and extended healthy life-years among HIV-positive persons with access to medical care, there remains no substitute for primary prevention. A multi-modal approach to AHI detection and prevention of HIV transmission during acute infection could help reduce the incidence of HIV in the US in several ways: by decreasing risk behaviors of individuals at-risk for infection and individuals with undiagnosed acute (or chronic) infection; by helping infected persons learn their HIV status as early as possible so they can take precautions to prevent secondary transmission; and by ensuring that infected persons are started on antiretroviral therapy—which reduces the likelihood of transmission—as soon as medically indicated. In addition, earlier diagnosis and entry into HIV care would benefit HIV-infected individuals, especially in light of current treatment guidelines, which recommend initiation of antiretroviral therapy earlier in the course of HIV infection [41,42]. Novel AHI-related interventions, at multiple levels, are needed to fully realize these benefits.

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Fig. 1.
Potential pathways of interventions to increase AHI diagnoses and reduce transmission risk