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EDITORIAL

How can we detect HIV during the acute or primary stage of infection?

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1. Expert view

Primary HIV infection describes the first three to four months following HIV transmission, and incudes the earliest stage – acute HIV infection (AHI) – which is characterized by a negative or indeterminate HIV antibody (Ab) test in the presence of detectable HIV-1 RNA. The acute phase of HIV infection is associated with high titer plasma viremia, dissemination of virus to anatomic reservoirs such as the brain, and establishment of a long-lived HIV reservoir in memory CD4 T cells [1]. Transient high titer viremia during AHI is also associated with an increased risk of HIV transmission, with estimates suggesting that approximately half of all HIV transmissions occur from persons with acute HIV infection [2]. The appearance of HIV Ab marks the transition to early phase HIV infection and a more stable level of plasma viremia (i.e. 'setpoint' viremia) that serves as a prognosticator of subsequent disease progression in the absence of antiretroviral treatment (ART). In persons who are HIV Ab-positive, HIV infection can be readily identified by a variety of point-of-care (POC) assays, though differentiation of early (i.e., recent; generally less than 6 months) and established (i.e. nonrecent) HIV infection is more challenging, relying on a variety of noncommercial assays, none of which is currently recommended for clinical use [3].

Current HIV treatment guidelines recommend immediate ART in all HIV-infected persons, including those with AHI [4]. Individuals receiving early ART demonstrate more rapid and robust immunologic recovery, lower inflammation, and reduced viral reservoir size compared to persons starting ART later [5]. In addition to these individual benefits, ART initiated during acute and very early HIV infection rapidly decreases viral load and infectivity [6], thus reducing HIV transmission. Immediate ART provided to persons with AHI may, however, alter evolution of HIV biomarkers over time, resulting in nonreactivity of antibody responses (rates depend on sensitivity of immunoassay used) and seroreversion (loss of reactivity to HIV Ab testing) in approximately 50% of persons initiating ART during AHI [7]. AHI diagnosis may also reduce transmission risk in the absence of biomedical interventions, as evidence suggests that individuals generally reduce their risk behavior after being diagnosed with HIV [8].

While diagnosis of AHI has been shown to be cost-effective in populations of at-risk men who have sex with men (MSM) where the proportion of AHI diagnoses among all HIV diagnoses is 10% or higher [9], it is not inexpensive. Routine AHI screening requires infrastructure support for current fourth-generation screening assays or use of more expensive qualitative or quantitative viral load assays. Efforts to limit AHI screening to those at greatest risk are limited by the absence of specific signs, symptoms, or behavioral risks associated with AHI. The nonspecific signs and symptoms that frequently accompany AHI include transient (most often lasting 2–4 weeks) fever, malaise, myalgias, headache, rash, etc. [10] and are absent altogether in an estimated 10–20% of persons. In a recent study occurrence of symptoms during the prior 14 days was reported by 80% of individuals diagnosed with AHI, while ongoing symptoms at the time of presentation for HIV testing were reported by only 50% [10]. The type and frequency of risk behaviors may also help to prioritize AHI testing resources. Our group developed the San Diego Early Test Score (freely available at http://sdet.ucsd.edu), which uses sexual risk variables reported by MSM presenting for AHI testing to generate a score, shown to be significantly associated with acute and recent HIV diagnosis in this population [11]. In settings where risk behavior is not evaluated, also repeated voluntary HIV testing or stimulant substance use may be used as a proxy of increased risk behavior [12,13]. Evaluation of risk behaviors alone, however, may be unreliable in settings where underlying sexual network factors (individual, contextual, and social factors that affect exposure to HIV) drive the HIV epidemic (e.g. having sex with one partner from a high risk sexual network may be more risky than having sex with multiple partners from a low risk sexual network) [14,15]. Therefore, the reliability of risk behavior as a predictor of HIV risk may vary between settings and populations.

The recognition that persons with AHI contribute disproportionately to population-level HIV transmission and that symptoms of acute retroviral syndrome and risk behaviors may be unreliable indicators of AHI support the updated recommendations for laboratory diagnosis of HIV infection in health-care settings, using routine fourth-generation immunoassays to detect HIV-1/HIV-2 Ab and HIV-1 p24 Ag [16]. While neither of the recommended HIV Ag/Ab combo differentiates HIV-1 Ag from Ab, both assays will reliably detect persons with AHI [sensitivity for seronegative and nucleic acid testing (NAT)-positive AHI

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is around 80% for both assays] [9,16]. Thus, even routine use of a fourth-generation HIV Ag/Ab assay may fail to detect acute HIV in about 20% of persons with AHI.

An estimated 40% of new HIV infections in the United States are identified in community HIV testing programs [17] where the main barriers to AHI screening include elevated costs, need for venipuncture, delayed turnaround time for test results, and lack of laboratory capacity. Absence of POC tests that reliably detect AHI may represent the greatest limitation, as loss to follow-up remains a major concern in these settings. The one commercially available POC test to detect HIV Ag and Ab (i.e. to identify persons with AHI) is limited by unacceptably low sensitivity for HIV Ag detection (below 50%) and is thus not recommended for AHI screening [9,18,19]. Several POC viral load detection assays are in development and may provide major advances to community and field-based HIV screening programs in the future.

The need to provide immediate test results (i.e. POC) currently precludes AHI screening in most community-based HIV screening programs. To identify the optimal testing algorithm for each community-based setting, local HIV prevalence and incidence data are needed, particularly in populations at greatest risk. Routine or symptom-based quantitative viral load testing, for example, may only be cost-effective for diagnosing HIV in very high risk groups, and likely misses the cost-effectiveness threshold when performed for all annual HIV tests in MSM [19]. In contrast, a recently published comprehensive cost analysis showed that 'cheaper' qualitative individual donation, NAT, may provide a cost-effective community-based screening technology for AHI in high-risk MSM populations with HIV prevalence rates above 0.4–1% [9]. In a high-risk population with a HIV prevalence of 2.7%, an established community-based testing program utilizing qualitative individual donation NAT may prevent between 5 and 45 transmissions per year for excess costs of about 120,000$ per year when compared to HIV antibody testing alone [20]. These results indicate that community-based AHI testing among high-risk MSM in the United States can pay for itself over the long run. P24 Ag-based tests may be cost-effective in other at-risk populations with HIV prevalence rates above 0.1–0.3% but below 0.4–1.0%. Only in populations with very low HIV prevalence rates (below 0.1–0.3%) POC Ab testing alone may still be the method of choice [9]. While it is important to mention that cost items for that analysis (e.g. costs for testing assays, personnel, data notification systems) were derived from a setting in the United States and may therefore not reflect actual costs at other locations, results clearly point out the importance of knowing the underlying HIV prevalence when deciding which testing algorithm to use.

2. Five-year view

Development of POC HIV viral load assays has the potential to provide rapid, inexpensive, sensitive, and mobile strategies to routinely detect AHI and seroprevalent HIV in both community and health-care settings. POC AHI screening algorithms may be further optimized to reliably differentiate early HIV infection from nonrecent infection. Currently at least 10 diagnostic companies are in the process of developing POC HIV NAT test systems, some of which may broadly detect various HIV-1 subtypes. The immediacy of AHI and HIV Ab test results are expected to support more rapid initiation of ART, ideally within the first few days of HIV diagnostic testing. Improved AHI diagnostic testing methods and ART uptake are also expected to reduce HIV transmission rates, with the ultimate goal of improving the HIV treatment continuum and reducing HIV population incidence.

Key issues

- Detection of seronegative acute HIV infection (AHI) is critical for preventing HIV transmission.
- Very early ART initiated during AHI may profoundly alter evolution of HIV biomarkers over time, causing delayed antibody seroconversion and seroreversion due to viral suppression in up to 50% of individuals.
- Updated guidelines for laboratory diagnosis of HIV infection in healthcare-settings recommend universal fourth generation immunoassays to detect HIV antibody and p24 antigen (Ag) as the first test in the HIV screening algorithm. These HIV Ag/Ab combo tests will detect a significant proportion of AHI.
- Most community-based settings today still rely on rapid HIV antibody testing only (i.e. less expensive, POC results), with targeted testing for AHI in those with indicators.
- Indicators of AHI that may be used for targeted testing, such as signs and symptoms or reported risk behaviors are not very reliable.
- Knowledge of regional HIV prevalence and incidence is necessary to determine which testing algorithm (HIV NAT or p24 Ag versus HIV Ab only) should be chosen.
- POC tests that reliably detect AHI are expected to revolutionize HIV testing in community and field based settings in the near future.

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Declaration of interest

M Hoenigl has served in the past on the speakers' bureau of Merck. SJ Little reported grant funding from Gilead Sciences, Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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