

# Early HIV Infection: Recognizing the not so obvious with no time to lose

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Acute HIV infection (AHI) refers to the brief period after HIV infection when HIV RNA first appears in the blood but before HIV specific antibodies are detectable. Individuals with AHI have increased HIV transmissibility due to the increased viral load in both blood and genital secretions, making it centrally important for prevention of secondary HIV transmission<sup>1</sup>. While some patients with acute infection have a viral syndrome (known as acute retroviral syndrome or primary HIV); the mild and non-specific nature of acute retroviral syndrome complicates effective screening<sup>2</sup>. A significant barrier to diagnosis of AHI is the non-specific nature of the signs and symptoms associated with the acute retroviral syndrome. Unless a clinician entertains the diagnosis in the differential and orders an appropriate diagnostic test, the diagnosis will be missed. It is vital to have clinicians consider AHI in young adults with fever and diffuse lymphadenopathy and that clinicians also know to include a viral specific test and not just an HIV antibody as diagnostic tests. Methods to incorporate HIV RNA screening of all HIV antibody negative bloods for testing populations may reduce the number of missed diagnosis for AHI. Specimen pooling and nucleic acid amplification methodologies have proven to be a feasible and effective method of acute HIV infection screening of at risk populations such as individuals seen in Sexually Transmitted Disease clinics, Emergency Departments, and at other locations where HIV testing is routinely provided or individuals at risk for HIV infection may seek care<sup>3</sup>.

Diagnosing AHI is of benefit at the level of the individual patient and at the level of the general public as part of HIV disease control efforts. Early HIV therapy presents a potential window of opportunity to improve immune function and slow the progression to AIDS, and more trials are underway now to determine the clinical benefits of early HIV therapy<sup>4,5</sup>. Transmission of HIV is principally driven by the quantity of the HIV inoculum in either blood or genital secretions. This brief period of extremely high HIV viral load and uncontrolled viral replication in AHI last for less than eight weeks. Therapy with ARV can precipitously drop the serum and genital secretion viral load and potentially render the individual "non-infectious" should the viral load drop below detection. Additional pub-

lic health benefits include epidemiologic information about incidence rates in communities<sup>6</sup>, case clustering<sup>7</sup>, information on trends in drug resistance<sup>8</sup>, identification of high risk periods and places<sup>9,10</sup>, molecular characterization to better define core populations and sexual risk<sup>11</sup>, identification of marginalized and otherwise hidden high risk groups<sup>12</sup>, and a unique opportunity to disrupt active HIV transmission networks.

The kinetics of HIV transmission and diagnosis has profound implications for disease control efforts<sup>13,14</sup>. The biological progression and behavioral characteristics leading to AHI as well as concomitant sexually transmitted infections exacerbate the risk of secondary HIV transmission<sup>15</sup>. As higher viral loads correlate to greater risk of HIV transmission, the increased viral burden in blood and genital secretions associated with AHI increase the probability of transmission<sup>1,16</sup>. "Look-back" studies investigating transmission rates<sup>17</sup>, case series showing rapid secondary transmission<sup>18</sup>, and prospective sero-discordant couple studies<sup>19</sup> all strongly suggest a greater likelihood of transmission per sex act during acute HIV infection. Our own data from the North Carolina AHI program (STAT) suggest transmission of HIV during acute infection occurred > 1:13 to 1:18 unprotected coital acts. Beyond the increased risk of transmission from an individual with AHI, the partners subsequently infected during this period are also at an increased risk of transmitting HIV, creating a chain of secondary transmission among core populations<sup>20</sup>.

In addition to this heightened biological risk of HIV derived from increased viremia among specific populations, increased behavioral risk has also been suggested during the AHI. Studies analyzing MSM who recently seroconverted revealed behaviors during the period of acute HIV infection which likely facilitated HIV transmission, and declined soon after diagnosis<sup>21</sup>. This behavioral component of HIV risk is independent of viremia, but importantly seems to correspond to a similar period of high risk behavior. Recall bias interferes with locating active HIV transmission networks since it tends to increase as time elapses from sexual encounter<sup>22</sup>. Finding individuals with AHI at the earliest time following infection is urgent both for the public health and individual wellbeing.

Sued et al, in their paper describe the epidemiologic and clinical characteristics of cohort of patients with AHI whom they followed prospectively. This represented nearly 3% of all new HIV infections diagnosed during a seven year time period. The symptoms were nonspecific with only fever and asthenia being nearly universal (98% and 86% respectively)<sup>23</sup>. Prior studies suggest symptoms of an acute retroviral syndrome occur in 40-90% of patients<sup>13</sup>.

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Our own experience in North Carolina found that 70% of individuals developed an acute retroviral illness but that less than 50% had symptoms at the time of diagnosis. The development of symptoms is associated with high-level viremia and the initial immune response to HIV. Much is unknown regarding the prognostic significance of the acute retroviral syndrome but the severity of illness may reflect difficulty of the host immune response to control viral replication and has been correlated with a more rapid progression of disease<sup>13</sup>. Sued, et al provide further support for this conclusion with the more rapid progression of disease reported in those who did not receive ART (42.3% vs. 12.3%)<sup>23</sup>. It is, for this reason, disturbing that the percentage of individuals starting on ART decreased during the observed period from 79% to 49%. The high rate of dyslipidemia and lipodystrophy may be attributable to the choice of ART or reflect a "defect" in the host immune response with poor response to viral replication since the majority of the individuals in the cohort had an acute retroviral syndrome.

The timing of HIV diagnosis is central to subsequent public health response and preventing unknowing transmission of HIV. Depending on the threshold used for a true positive, nucleic acid amplification testing (NAAT) used for acute HIV surveillance can be positive within the first week of infection. Some third generation ELISA tests may be positive as early as three weeks following HIV infection, compared to the two weeks needed for positive p24 antigenemia<sup>16</sup>. The sensitivity of assay used to detect either HIV or HIV specific antibody response is only one factor in diagnosing acute HIV. The frequency of repeat HIV testing in high risk groups will also impact the ability to diagnosis individuals during the AHI period. Clinician awareness of the presentation of AHI as well as a high index of suspicion is also critical since detectable antibodies levels may not be present at the maximal height of viremia and the onset of symptoms. Appropriate clinical history such as sexual risk factors reported intravenous drug use coupled with physical signs and symptoms of an acute retroviral illness should prompt the ordering of appropriate diagnostic tests. Sued and colleagues looked for evidence of AHI in this high risk population and therefore were able to recognize and diagnose AHI.

The University of North Carolina Hospitals recently implemented routine HIV RNA screening of all HIV ELISA antibody negative or Western Blot indeterminate blood as a way of reducing clinician oversight of AHI. When used with specimen pooling, HIV NAAT offers a sensitive and specific method for detection of acute HIV infection before the period of greatest transmissibility<sup>3,23</sup>. North Carolina's STAT program illustrates how acute HIV surveillance is critically time dependent. During the period November 2002 to November 2005, 63 patients from 110 public counseling and testing sites were RNA positive and antibody negative. Finding individuals with acute HIV infection and their recent sexual partners provides insight about HIV sexual networks at the leading edge of the epidemic. From a public health perspective, the evidence to support increased HIV transmissibility during acute infection justifies closely related case finding and prevention activities.

The clinical presentation of AHI is, at best, non-specific and can closely resemble a host of other "viral-like" illness.

A history of recent unprotected sexual intercourse or injecting drug use coupled with characteristic signs/symptoms such as fever, rash or lymphadenopathy should alert clinicians to consideration of the diagnosis. Education of clinicians and patients concerning acute retroviral syndrome and access to frequent HIV testing is critical for identification of AHI.

Closing the window period between acquisition and diagnosis of HIV infection via routine acute HIV infection screening is a major public health opportunity that demands further study and consideration. Case interviewing needs to be better connected to HIV prevention, given what we know about the increased HIV transmissibility associated with acute HIV infection. In most parts of the world, physicians fail to diagnose acute HIV infection; case interviewing is underutilized; and disease control based on acute HIV surveillance remains a theoretical benefit. Since the increased HIV transmissibility associated with acute HIV infection is supported by North Carolina's STAT program<sup>3</sup> and transmission data, identifying acute HIV infections and tracing their partners should be further considered. Analyzing the high-risk people/places/periods involved in active HIV transmission needs to be considered in other locations, as a complementary strategy alongside the sensitive-less sensitive HIV testing. Despite support from the US CDC and work in the field, routine detection of acute HIV infection and case interviewing has not yet been broadly applied.

Some have persistent doubts about acute HIV centered testing and disease control. Limitations to the proposed approach include higher testing costs, NAAT test performance issues, and a requisite venous blood draw. In addition, the need for follow-up Western Blot confirmation for presumably positive clients makes anonymous testing difficult. Given the increased uptake associated with rapid HIV testing, the longer follow-up and potentially greater refusal of blood draws required for acute HIV screening, strategies to incorporate AHI screening seems justified. North Carolina's STAT program has shown that identification of acute HIV infections and disease control can be implemented on a very large scale while preserving test performance and low cost. Sued and associates demonstrate an additional approach by prospective following of high risk groups with the hope of recognizing AHI. Even with the increased cost and potentially higher refusal rate associated with this strategy, the public health advantages demand further study and consideration of these new approaches.

Extensive public health experience with syphilis control suggests that disease control focused epidemiologic investigations linked to active transmission among core high risk groups may be a more effective public health approach to HIV control than merely recommending universal HIV testing. While traditional HIV surveillance systems provide broader estimates of overall HIV incidence, such surveys are very unlikely to adequately sample either populations that deny high risk behaviors or high morbidity areas to provide the type of detailed information essential to stopping active transmission networks.

Acute HIV infection detection and disease control systems allow clinicians and public health authorities to get a more detailed and comprehensive understanding of the when, where, why, and who of new HIV infections. Rou-

tine detection of acute HIV and disease control offers a new blueprint for organizing HIV testing, bringing HIV acquisition and diagnosis closer, and expanding potential prevention programs. Several lines of evidence support a new paradigm of acute HIV detection and disease control, but more investigation and further replication are necessary.

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