

Published in final edited form as:

*Curr Opin HIV AIDS*. 2010 July ; 5(4): 277–282. doi:10.1097/COH.0b013e32833a0d3a.

## The Role of Acute and Early HIV Infection in the Sexual Transmission of HIV

William C. Miller<sup>1,2</sup>, Nora E. Rosenberg<sup>2</sup>, Sarah E. Rutstein<sup>3</sup>, and Kimberly A. Powers<sup>2</sup>

<sup>1</sup> Division of Infectious Diseases, Department of Medicine, School of Medicine, University of North Carolina at Chapel Hill

<sup>2</sup> Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill

<sup>3</sup> Department of Health Policy and Management, School of Public Health, University of North Carolina at Chapel Hill

### Abstract

**Purpose of Review**—Acute HIV infection (AHI), the earliest period after HIV acquisition, is only a few weeks in duration. In this brief period, the concentration of HIV in blood and genital secretions is extremely high, increasing the probability of HIV transmission. Although a substantial role of AHI in the sexual transmission of HIV is biologically plausible, the significance of AHI in the epidemiological spread of HIV remains uncertain.

**Recent Findings**—AHI is diagnosed by detecting viral RNA or antigen in the blood of persons who are HIV seronegative. Depending on the setting, persons with AHI represent between 1% and 10% of persons with newly diagnosed HIV infection. The high concentration of virus during AHI leads to increased infectiousness, possibly as much as 26 times greater than during chronic infection. In mathematical models, the estimated proportion of transmission attributed to AHI has varied considerably, depending on model structure, model parameters and the population. Key determinants include the stage of the HIV epidemic and the sexual risk profile of the population.

**Summary**—Despite its brief duration, AHI plays a disproportionate role in the sexual transmission of HIV infection. Detection of persons with AHI may provide an important opportunity for transmission prevention.

### Keywords

acute HIV infection; mathematical models; HIV transmission

### Introduction

Acute HIV infection (AHI) is the earliest phase of HIV infection, immediately following acquisition of the virus and prior to seroconversion. The period of acute infection generally lasts 3–4 weeks, during which both HIV RNA and p24 antigen (Ag) are present [1]. In the absence of a developed immune response, AHI is further characterized by unfettered viral replication, resulting in high concentrations of HIV recovered from blood and genital secretions [1–8]. The concentration of HIV remains markedly elevated for up to 10–12 weeks post-infection, at which point it gradually declines to the levels observed in established infection. The duration of the pre-seroconversion period and the magnitude of the peak in viral load are variable. Seroconversion indicates a transition out of the acute

phase and into the stage of early or recent infection in which antibodies are present and viral load begins to decline [1, 4].

The high concentration of HIV in the genital tract during AHI leads to very efficient sexual transmission [5, 7]. Consequently, AHI has a disproportionate role in HIV transmission, despite the short duration of AHI. The significance of AHI in HIV transmission depends on the stage of the epidemic and the characteristics of the underlying population. Despite this potentially substantial role in sexual transmission, detection of AHI has not become routine, primarily because of the challenges in diagnosis.

## Diagnosis of Acute HIV Infection

The diagnosis of AHI is complicated by the absence of detectable HIV-specific antibodies. In the window period, ranging from a few weeks to roughly 2 months in duration, a person with AHI will test negative or indeterminate with traditional HIV antibody assays [4, 9–10]. Therefore, diagnosis of acute infection relies on the direct detection of the virus, typically plasma HIV RNA detected with nucleic acid amplification tests (NAAT). Pooling samples for RNA testing is a cost-containment strategy, significantly reducing per-patient costs for this otherwise expensive assay [11]. Pooling also contributes to the feasibility of identifying the relatively rare acute infection among the thousands of individuals who test negative for HIV antibodies [3, 9, 12–14].

Many patients with AHI have symptoms of acute retroviral infection, but these symptoms are often mild and non-specific. Targeted testing based on a combination of factors, including reported risk behaviors, symptoms of acute retroviral infection, or STI syndromes, such as genital ulcer disease, may facilitate identification of HIV-seronegative persons who are most likely to benefit from testing for AHI [15–16]. The type of clinic and geographical location may be important criteria for targeted testing in large programs [16]. The targeted approach reduces resource utilization for population-level AHI screening.

Financial, technical, and logistical challenges impede widespread utilization of NAAT in many high-prevalence, low-resource settings. The window period can be shortened by using third- and fourth-generation indirect enzyme immunoassays (EIAs) that are sensitive to both IgM and IgG, leading to detection of the host immune response earlier in the course of infection [9]. Fourth-generation combination immunoassays are sensitive to p24 antigen and IgM/IgG antibodies. Fourth-generation tests correctly identify 60–77% of acute infections, generally missing persons with lower viral loads and very early infections [9, 17]. Combining standard rapid antibody tests with an “ultrasensitive” p24 antigen assay is another alternative, detecting up to 90% of acute infections [12], but this procedure is difficult to implement in practice. Point-of-care combination antibody/antigen tests are under evaluation and could offer the benefit of same-day results.

AHI testing has been incorporated into routine testing procedures in several settings. Given the short duration of AHI, persons with AHI generally represent a small proportion of persons with negative HIV antibody tests. However, persons with AHI represent a substantial proportion of all persons diagnosed with HIV infection, approximately 1–10% [7, 9–11, 15–16, 18–20]. This proportion varies by setting. In the general counseling and testing setting, the prevalence is often lower, as is the prevalence of established HIV infection. [11, 16, 18] Enriching the population for higher risk persons, such as men who have sex with men or persons attending STD clinics, increases the yield [10, 16, 18]. Targeted efforts in an STD clinic in Malawi and among febrile patients in Mozambique have yielded substantial numbers of persons with AHI [15, 20–21].

## Biological Plausibility of AHI role in Transmission

Persons with AHI often exhibit markedly elevated viral loads, often exceeding 1 million copies/milliliter [1–8]. Virus can be detected within the internal iliac lymph nodes within two days of infection, with systemic viral dissemination occurring shortly thereafter [22]. The rapid consumption of target cells by HIV during AHI allows for significant viral replication, leading to markedly elevated viral loads [6, 21]. In addition to host-specific genetic factors that influence viremia during acute infection, viral factors may also play a significant role [23]. The viremia expands exponentially for 2–3 weeks after infection, unregulated in the absence of HIV-specific antibodies [2]. Among a cohort of Malawian men with newly diagnosed HIV infection, the median blood viral burden among those with AHI was  $>10^6$  copies/ml, compared to  $10^{4.5}$  copies/ml observed among men with chronic infection [21].

The heightened viral load in infected blood during AHI is mirrored in genital secretions [6–8]. In men, the peak viral load is estimated to occur at 17 days in plasma and at 30 days in semen [6]. Increased viral concentrations are also observed in female genital secretions during the acute stage [8]. Cervical viral loads are strongly correlated with plasma viral loads for the first 6 months of infection, and are significantly higher than levels in chronic infection, approximately  $0.7 - 1.1 \log_{10}$  copies/ml above set point [8].

The elevated viral load in genital secretions in men and women provides the biological mechanism for efficient sexual transmission of HIV during AHI [3, 6–7, 24–26]. Other biological factors, including concomitant STI, also contribute to enhanced viral transmissibility [7, 27]. As the majority of new HIV infections worldwide are acquired through sexual transmission, the peak viremia and associated risk of onward transmission make AHI a potential target for transmission prevention.

## Empirical Evidence for the Role of AHI in Sexual Transmission

Despite the clear biological plausibility of a meaningful role of AHI in sexual transmission, determining the proportion of transmission events attributable to AHI and estimating the transmission rate by stage of infection have been difficult. The relative lack of empirical data linking AHI to increased transmission reflects the dual challenges of identifying individuals during or just after the brief acute stage and linking them to HIV-uninfected sexual partners who subsequently seroconvert.

In the study of monogamous HIV serodiscordant couples in a population-based cohort in Rakai, Uganda, the rates of transmission per coital act varied considerably by stage of infection [28]. The rates per coital act were markedly higher during early infection (8.2/1000 within 2.5 months of seroconversion) decreasing to 1.5/1000 within 16 months of seroconversion and 0.7/1000 during established infection. Rates increased again during late stage infection (2.8/1000 within 6–24 months of death). The unadjusted rate of infection was 8.3 times higher in the first five months of infection than in established infection (95% CI: 3.4, 20.2). Adjustment for age and genital ulcer disease reduced the rate ratio slightly to 7.3 (95% CI 3.1, 17.3) [28].

The data from this cohort were reanalyzed with improved assumptions about sexual behavior and transmission timing [29]. During AHI, the hazard rate of transmission was estimated to be 26 times the rate during established HIV infection.

In a European cohort of discordant heterosexual couples, the probability of transmission per coital act was significantly higher for penile-anal sex (126/1000 acts) in the first three months following infection [30]. However, a change in the probability of transmission per

coital act across stages was not observed for penile-vaginal sex, possibly because of limited statistical power. A meta-analysis incorporating these and the Rakai data found per coital act probabilities to differ by 2.5/1000 in early versus established infection [15].

Phylogenies reconstructed from sampled viral gene sequences can be used, cautiously, to identify probable transmission clusters. In Quebec, reconstructed phylogenies were used to identify likely transmission clusters among persons who seroconverted in the previous six months [31]. Persons with treated or untreated established infection were also included. Approximately half of the persons who seroconverted in the previous six months cosegregated into 75 transmission clusters, while the remaining individuals had unique sequences, suggesting that early HIV infection was responsible for approximately half of HIV transmission events. Elsewhere, approximately 30–35% of persons with primary HIV infection cosegregated into phylogenetically related clusters [27, 32]. However, these data may overestimate the proportion of transmission events attributable to AHI [33].

## Mathematical Models

With limited empirical data, mathematical models have been a key tool for evaluating the role of AHI in HIV epidemiology. Mathematical models have addressed two issues – the relationship between viral load and male-to-female transmission probabilities and the impact of AHI on predicted evolution of the HIV epidemic.

As one would expect, HIV RNA concentration in genital secretions has a profound effect on predicted HIV transmission. In a probabilistic model, transmission was assessed as a function of viral load based on HIV cell free viral concentrations in seminal plasma. The probability of transmission was described with a  $\log_{10}$  exponential function of viral load with transmission probabilities of 0.3/1000 with 1000 copies of HIV RNA and 10/1000 with 100,000 copies [24]. The latter estimate is consistent with peak seminal viral burdens during AHI [6–7].

Mathematical models to describe epidemic spread have used a variety of model structures in varying populations and settings with differing parameter estimates (Table 1). Early mathematical modeling studies supported a role of early HIV infection as a critical driving force in the HIV epidemic [36]. In more recent studies, however, the impact of AHI in mathematical models has varied considerably, due in part to the varying approaches used [37, 39, 41, 43, 45].

The epidemic phase appears to be a critical determinant of the importance of AHI in sexual transmission of HIV. In the early phase of an epidemic, acute/early HIV infection appears to be responsible for a considerable share of transmission [34, 37, 43]. This observation is logical, as a relatively larger proportion of infected persons have acute or early infection and relatively few have progressed to late-stage disease [43]. In contrast, in models of endemic HIV disease, the importance of AHI has been remarkably variable, with estimates ranging from <1% to 82% [34, 36–37, 39, 41, 43, 45].

The characteristics of the population also greatly influence the potential role of acute/early HIV infection. In contexts of high sexual partner concurrency or very high rates of partner change, the role of AHI is substantially increased [29, 39]. Given its short duration, the potential transmission due to AHI is limited to one person if the index case is in a monogamous relationship for the duration of AHI. However, if the index case has concurrent sexual partners, the risk of onward transmission is substantially increased. In North Carolina, individuals with AHI named 2.5 times (95% CI: 2.1–3.0) as many current sexual partners as individuals diagnosed with established HIV infection [46]. Importantly,

concurrency operates not only as an individual factor for increased transmission, but also by connecting multiple sexual dyads and clusters to one another at the population level [47].

Although mathematical models have been useful tools for assessing the role of AHI in HIV sexual transmission, the quality of available data for use as model parameters is limited. Mathematical models developed in the future would benefit greatly from more accurate data about the relationship between disease state and transmissibility, as well as valid, reliable, setting-specific data regarding sexual contact patterns.

## Opportunities for Prevention Interventions

The challenges in the design of a prevention intervention targeted to persons with AHI are numerous. First, as with any intervention dependent on testing, the success of the intervention would hinge on persons' decisions to seek HIV testing or aggressive population-based programs (such as door-to-door testing). Second, the intervention would undoubtedly require additional testing procedures, such as NAAT or antigen testing, to detect AHI. Finally, the brief window period of AHI limits the proportion of persons who would be identified with any testing program.

The potential benefits of an AHI testing program with a transmission prevention intervention are substantial. In traditional testing, persons with AHI who present for HIV testing will be informed that they are likely HIV-uninfected, and in most settings, will be asked to return for repeat testing after several weeks or months. Such persons have little incentive to alter behavior and may continue to contribute to onward HIV transmission.

Persons with unknown HIV status are believed to be responsible for a substantial proportion of HIV transmission [48–49]. Indeed, test and treat has been suggested as a key approach for HIV prevention [50]. Efforts to detect AHI are especially poignant in this context. AHI reflects the earliest possible period of intervention after infection. Persons with AHI who are informed of their status will know their HIV status from the earliest possible moment – within a few days of HIV acquisition. The potential impact on transmission through “positive prevention” may be substantial, even if the impact is primarily realized in the latter phases of established HIV infection.

An intervention after AHI diagnosis is likely to require both behavioral and treatment components. A behavioral intervention would need to be administered quickly and must emphasize risk reduction, including partner notification, limiting new partner acquisition, condom use, and possibly, abstinence during the acute phase. Treatment may also be beneficial from a public health perspective. The treatment goal would be rapid reduction of the viral load, especially in the genital tract, to limit the potential for onward transmission. Other potential aspects of AHI treatment are discussed elsewhere in this volume [Fidler].

## Conclusion

Persons with AHI contribute disproportionately to the onward sexual transmission of HIV infection. While the magnitude of the proportion of HIV transmission attributable to persons with AHI (or early HIV infection) is uncertain and variable, it is undoubtedly greater than the prevalence of AHI. AHI represents a brief window of time and consequently, the prevalence of AHI is low at any given time. However, the “hyperinfectious state” of persons with AHI increases the likelihood of transmission to others.

The role of AHI in sexual HIV transmission varies with the epidemic stage and the characteristics of the population. AHI appears to be especially important in populations with newly introduced HIV infection. The significance of AHI also appears to increase in

populations with high prevalence of concurrent partnerships and frequent partner change. Even in a well-established HIV epidemic where the role of AHI generally appears to be less, detection of persons with AHI provides an opportunity to intervene at the earliest possible stage of infection.

Persons with AHI will continue to play an important role in the sexual transmission of HIV for the foreseeable future. Improved awareness of AHI and implementation of routine testing programs are needed. In addition, rapid, point-of-care diagnostics capable of detecting a high proportion of persons before seroconversion would greatly facilitate diagnosis. Currently, diagnosis of AHI is extremely challenging. But, ignoring AHI may have substantial consequences for the future of the HIV epidemic.

## Acknowledgments

This work was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health to William C. Miller and Audrey Pettifor (NIAID - R01 AI083059). We wish to thank Drs. Audrey Pettifor, Myron Cohen, Joseph Eron, Jr., Susan Fiscus, Christophe Fraser, Azra Ghani, and Sarah Fidler for comments on the grant identified above, which served as the primary basis for this work.

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Proportion new HIV infections attributable to early index cases in mathematical modeling studies

Table 1

Author, year	Population/Setting <sup>1</sup>	Model type <sup>2</sup>	Early HIV infection duration (months)	% new cases due to early HIV	Factors varied
Jacquez, 1994 [34]	MSM/USA	Mixing	2	25% – 51% <sup>3</sup>	Number of sexual activity groups; Sexual contact rates; Early transmission probability
Pinkerton, 1996 [35]	MSM/USA	Linear	2	25% – 90%	Early transmission probability; Number of acts per partner
Koopman, 1997 [36]	MSM/USA	Mixing	1.5	20% – 47% <sup>3</sup>	Aging process; Number of sexual activity groups
Kretzchmar, 1998 [37]	Hypothetical	Mixing, Pair	1–2	65% – 82% <sup>3</sup>	Model type (mixing/pair); Pair separation rate
Coutinho, et al. 2001 [38]	Mixed	Linear	1.5	2% – 89%	Aging process; Sexual contact patterns; Relationship: viral load, infectiousness
Xiridou et al., 2004 [39]	MSM/Amsterdam	Hybrid	1 – 5	<1% – 39% <sup>3</sup>	Partnership type (casual/steady); Ratio of partnership to AHI length
Hayes & White, 2006 [40]	Heterosexuals/Uganda	Mixing, Pair	5	23% – 41%	Sexual contact patterns
Pinkerton, 2007 [41]	Mixed/USA	Linear	1.5 – 2	3% – 17%	Duration of AHI; Transmission rate ratio (AHI:EHI)
Pinkerton, 2008 [42]	Heterosexuals/Uganda	Linear	1.5 – 2	85% – 93%	Durations of latent period & AHI
Abu-Raddad & Longini, 2008 [43]	Heterosexuals/Kenya & Cameroon	Mixing	2.5	~7% – ~15% <sup>3</sup>	Sexual mixing patterns and risk behaviors
Salomon & Hogan, 2008 [44]	Heterosexuals/Uganda	Linear	5	~20% – 40%	Sexual contact patterns; ART patterns
Hollingsworth et al., 2008 [29]	Heterosexuals/Uganda	Mixing, Pair	2.9	9% – 31% <sup>3</sup>	Model type (pair vs. mixing)
Prabhu, et al. 2009 [45]	Mixed/USA	Linear	1.5	11%	N/A

<sup>1</sup> Either directly used in modeling or for source of parameter values.

<sup>2</sup> Linear models do not include the non-linear dependency of HIV incidence on HIV prevalence. Mixing models assume that HIV transmission can only occur during instantaneous contacts between susceptible and infected individuals. Pair models assume that HIV transmission can only occur within monogamous, serodiscordant couples. Hybrid models combine the transmission routes of mixing and pair models to allow transmission both within and outside of steady partnerships; therefore, hybrid models are likely to capture transmission dynamics more realistically than a pure mixing model or pure pair model.

<sup>3</sup> When HIV at endemic equilibrium.