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# Lessons Learned about Behavioral Science and Acute/Early HIV Infection. The NIMH Multisite Acute HIV Infection Study: V

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## Abstract

Acute/early HIV infection is a period of heightened HIV transmission and a window of opportunity for intervention to prevent onward disease transmission. The NIMH Multisite Acute HIV Infection (AHI) Study was an exploratory initiative aimed at determining the feasibility of recruiting persons with AHI into research, assessing their psychosocial and behavioral characteristics, and examining



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short-term changes in these characteristics. This paper reports on lessons learned in the study, including: (1) the need to establish the cost-effectiveness of AHI testing; (2) challenges to identifying persons with AHI; (3) the need to increase awareness of acute-phase HIV transmission risks; (4) determining the goals of behavioral interventions following AHI diagnosis; and (5) the need for "rapid response" public health systems that can move quickly enough to intervene while persons are still in the AHI stage. There are untapped opportunities for behavioral and medical science collaborations in these areas that could reduce the incidence of HIV infection.

### Keywords

Acute HIV infection; HIV prevention; Public health

## Introduction

It has long been known that the greatest spike in viral load occurs during acute HIV infection (AHI), the brief period of weeks to about 2 months between the time when an individual first contracts infection and the completion of seroconversion (Pilcher et al. 2004a). Due to the high viral load, individuals are unusually infectious to others during this acute phase (Quinn et al. 2000; Pilcher et al. 2004b). Furthermore, although acute HIV shedding is over about 10 weeks post-infection, elevated onward transmission likely extends through the period of early infection (defined as the 6 month period after seroconversion) due to ongoing high-risk behaviors, associated sexually transmitted diseases (STDs) that increase transmission risk, and transmission amplification through high-risk sexual and drug-use networks. Transmissions during acute/early infection may account for as many as half of new infections (for more detailed arguments and references, see Kerndt et al. 2009, the first paper of this series in this issue of the journal).

Although the proportion of onward transmissions attributable to acute/early HIV infection undoubtedly depends on HIV epidemic stage, population risk practices, and sexual mixing patterns, these initial stages afford an extremely important window of opportunity for intervention to prevent onward HIV transmission to others and, potentially, to initiate treatment for the infected individual (Pilcher et al. 2004a).

Great public health benefits could accompany the development of systems to identify persons with AHI in particular and to engage them in prevention and care services. Because AHI occurs *before* an antibody response is mounted, conventional antibody tests cannot detect infection at this phase; acutely-infected persons "test negative" or have indeterminate results on standard antibody tests. From 40 to 90% of persons with AHI experience nonspecific influenza-like symptoms (Panel on Antiretroviral Guidelines for Adults and Adolescents 2008). However, these symptoms, if present, are transient and often mistaken for many common and benign viral infections.

AHI can be detected by testing for HIV RNA in the blood. The main barrier to the routine use of HIV RNA testing is its cost, which is much higher than antibody testing. However, and apart from testing procedure issues, there are important and yet-unstudied questions concerning the social, relationship, behavioral, and mental health characteristics of persons who are diagnosed with AHI. If the aim of diagnosing AHI is to quickly engage persons into prevention and care, more must be learned about their psychosocial functioning, needs, distress levels, and behavioral characteristics.

This is the last in a series of five papers in this issue of the journal that describe results from the National Institute of Mental Health (NIMH) Multisite Acute HIV Infection Study (see

Kerndt et al. 2009 for the overall aims of the study). Companion articles by Kerndt et al. (2009), Remien et al. (2009), Steward et al. (2009), and Atkinson et al. (2009) describe substantive findings related to the identification of persons with acute/early infection as well as behavioral and mental health characteristics that accompany the acute/early phase in the HIV disease spectrum. The purpose of this concluding paper is not to recount these findings but instead to discuss lessons learned from this study that bear on both public health policy with respect to HIV prevention and care, and also future mental health research on acute/early infection. We will organize the current paper around five major lessons learned from this initiative.

## Lesson 1: More Data are Needed to Inform Funders and Agencies Concerning the Cost-effectiveness of HIV RNA Testing Programs That Will be Needed to Detect AHI

Given what is known about the high transmission efficiency that characterizes AHI, one might wonder why all HIV screening programs do not routinely test antibody-negative or indeterminate blood specimens for HIV RNA. Such a dual test policy would detect both chronic and also acute HIV infections. The main deterrents appear to be the cost of HIV RNA testing of individual samples and uncertainty about whether a sufficient number of acute infections would be detected to justify that cost and effort.

Advances in test methodology have overcome some of these concerns. Pilcher et al. (2005) reported favorable outcomes of a HIV RNA testing approach used in North Carolina that pooled together blood samples from a large number of persons and performed HIV RNA testing on the pool. Because of its sensitivity, the single test could determine whether *any* of the individual samples in the pool showed the presence of HIV RNA. If so, the samples were then grouped into smaller pools, each smaller pool was tested. The division and retesting process was repeated until the reactive specimen was isolated. Because pooled testing requires fewer tests than separate HIV RNA testing of each individual sample, the approach was economical. Pilcher et al. (2005) reported that the additional cost per specimen tested in North Carolina using the pooled sample method was only $3.63.

Such innovations in HIV RNA testing methodologies and future testing technology developments can reduce the cost and make routine HIV RNA testing feasible in the HIV screening setting. However, test methodology and availability is not the only critical issue. The detection of AHI also requires that persons with very recently-contracted HIV present to providers for testing early in the AHI phase. In this sense, more widescale availability of HIV RNA testing alone is necessary but insufficient for successful screening to detect acute infections. To have maximum impact, incorporation of HIV RNA testing into screening protocols must be accompanied by community intervention, by provider and patient education, and by behavioral campaigns to encourage at-risk persons to quickly seek HIV RNA testing if they believe they were recently exposed or may have AHI symptoms.

Systematic research is needed to determine the cost-effectiveness of AHI testing programs. Cost-effectiveness analyses can delineate circumstances—including population segments, disease incidence and prevalence, and behavioral risk in domestic and international populations—where AHI testing is warranted from a cost-effectiveness perspective. Such analyses can guide policymakers, service agencies, and public health funders in determining whether and with whom to adopt HIV RNA testing policies. These analyses can also mathematically model the number of incident HIV infections that would be prevented by the adoption or expansion of AHI testing. Even if cost-effective, additional public health resources for AHI detection will undoubtedly be needed, and this will require policy-maker and funder priority-setting.

Furthermore, prevention of onward transmission will require providing prevention services to persons with AHI as well as notification of their partners (Pilcher et al. 2005). Third-party/government reimbursement for HIV RNA testing of individuals suspected of having AHI and for populations characterized by high HIV incidence will also be critical.

## Lesson 2: It is Difficult to Quickly Identify Persons with AHI

Efforts to conduct research or provide prevention services related to AHI require the very rapid identification of persons following the event when HIV was contracted and before HIV antibodies have developed, an interval usually lasting several weeks to several months. This process can occur only if: (1) an acutely-infected person presents for HIV testing very quickly following an exposure event or is referred by a provider following presentation with AHI illness symptoms; (2) the blood sample is tested not only for HIV antibodies but also for HIV RNA; and (3) AHI is diagnosed, the individual is informed, and research protocols are initiated or services are provided, all within the brief AHI window. The potential public health benefits of AHI surveillance and intervention are greatest when this process is completed during the *initial* stages of the acute/early disease phase while efficient onward disease transmission to others can still be averted.

As might be expected under these circumstances, the greatest challenge in the NIMH AHI Study was the identification of persons with AHI (see Kerndt et al. 2009). Extensive efforts were made to recruit participants in two ways: (1) through sites such as STD clinics, MSM HIV testing venues, and drug rehabilitation facilities that routinely performed HIV RNA testing of pooled serum samples that had yielded negative or indeterminate results on standard antibody tests (Pilcher et al. 2005); and (2) through referrals from clinical colleagues including HIV providers, primary care providers for high-risk persons, and several established AHI clinical research programs. Study sites located in cities with AHI clinical research programs or where HIV RNA testing was already routinely performed by HIV testing providers were more successful in identifying and recruiting newly-identified acute infections; sites without these resources were much less successful.

On a practical basis, future research and services for persons with AHI are likely to be fruitful when very recently-infected individuals can be more successfully identified. Surveillance and identification of AHI will be more feasible: (1) when HIV RNA testing is routinely performed following a recent high-risk exposure event, whether using individual or potentially more cost-efficient pooled testing methods (Pilcher et al. 2005); (2) with HIV RNA testing of persons who report symptoms that could be indicative of AHI, especially when there was also recent suspected disease exposure; (3) with routine HIV RNA testing for members of populations characterized by high HIV incidence, especially MSM, IDUs, STD clinic patients, and—in some cases—pregnant women (Busch and Hecht 2005; Patterson et al. 2007); and (4) through the use of screening algorithms that combine the presence of AHI illness symptoms, a recent high-risk exposure event, and other demographic variables or characteristics to refine decision-making concerning when HIV RNA testing is warranted and likely to prove cost-effective (Shargi et al. 2005). When these or other strategies are more widely used by HIV testing programs and health care providers, it will be possible to systematically screen for AHI and to identify cases while persons are still in the acute infection phase.

## Lesson 3: Although AHI has Received Substantial Recent Attention in the Scientific Literature, Awareness of AHI Diagnostic Issues and Acute/Early-

## phase HIV Transmission Risk Issues is Low in Communities Affected by AIDS and Among Primary Health Care Service Providers

It is well-known to HIV service providers that there is a brief period of time following the point of contracting HIV when a newly infected individual has not yet produced antibodies and will not yet have a positive HIV antibody test. However, in spite of recent attention in the public health research literature, there is less awareness among primary care service providers and also in the community that infectiousness is dramatically higher during the brief period of AHI than during chronic infection, and that a disproportionately high proportion of new HIV transmissions are attributable to efficient acute/early phase transmission.

Efforts are needed to increase awareness of AHI as a diagnostic entity and the transmission risk implications of acute/early HIV infection among primary care service providers and HIV testing programs. A retrospective study in the United Kingdom found that approximately 50% of HIV-infected persons who had earlier AHI symptoms sought care at the time of those symptoms from their health care providers. Of these, only about half were diagnosed with AHI at first presentation (Sudarshi et al. 2008). In another study, Seattle MSM seeking medical care for febrile illnesses were infrequently tested for HIV (Stekler et al. 2006). Although HIV and infectious disease specialists are typically aware of AHI and its symptoms, *primary* care providers—the professionals most likely to treat persons without known HIV infection—are often not sensitized to the possibility of this diagnosis and must be trained to include AHI in the differential diagnosis for patients who present with symptoms that could be indicative of AHI, particularly seronegative patients with possible recent HIV exposure. Building of provider skills to elicit accurate sex and drug use histories is also essential.

If HIV RNA testing is not performed, the posttest counseling of persons with negative or indeterminate HIV antibody tests should take into account the possibility of undiagnosed AHI, especially when there is a history of recent high-risk exposure. Although HIV testing programs typically recommend antibody re-testing in about 2 months and counsel clients to practice safer sex during the interval before re-testing, we are uncertain how emphatically this advice is given or how often it is heeded. The field's knowledge about elevated transmission risk likelihood during AHI has advanced, and the strength of these precautionary counseling recommendations must be raised.

Sites in the NIMH Multisite AHI Study found very little evidence of community awareness concerning the greatly-elevated HIV transmission risk associated with acute/early-phase HIV infection, even in AIDS-saavy mainstream gay communities (Remien et al. 2009). The antibody test mentality that “HIV-negative = uninfected, HIV-positive = infected” has been the basis for sexual decision-making for 25 years. The notion that persons with negative HIV antibody test results—for at least a brief interval—may be very efficient transmitters of HIV to others is a concept not yet well-understood even in gay communities that are highly-sensitized to the threat of AIDS. It is likely to be even less understood by women, injection drug users, and adolescents, and in disadvantaged minority communities.

Population-level campaigns are needed to raise awareness of AHI as well as understanding of its risk ramifications, especially in communities with high HIV incidence. Community-based AIDS service agencies should also take up this cause. Education of vulnerable communities about AHI should: (1) emphasize the heightened transmission potential during acute/early infection; (2) increase awareness about illness symptoms that often accompany AHI and encourage vigilence for these symptoms following a recent high-risk exposure; (3) encourage persons with very recent high-risk exposure to refrain from unprotected sexual practices and to request HIV RNA testing by their providers; (4) stress that a negative HIV antibody test result does not signal absence of infection during the potential AHI period; and (5) caution

against reliance on serosorting by concordant negative HIV status when based on a single recent antibody test alone. Some of these issues are complex and difficult to clearly convey in public education campaigns. Further, messages about AHI must not generate confusion or lead to fatalism concerning the meaning of all HIV tests. Behavioral research is needed to determine how best to communicate with vulnerable communities around risk issues related to acute/early HIV infection.

## Lesson 4: Challenges in Determining the Goals, Structure, and Delivery Mechanisms of Intervention Following the Diagnosis of AHI

When conceptualizing the NIMH Multisite AHI Study, we anticipated that the delivery of feedback that one had very recently contracted HIV infection would precipitate very strong emotional distress. In fact, psychosocial responses at the time of participant recruitment to our study were varied and heterogeneous. The study usually recruited participants several weeks following initial test result notification, so their immediate transient emotional upheaval—if present—may have already abated. Depression and anxiety were only mildly elevated in most participants, although a substantial number had a recent or lifetime history of more clinically significant mental disorders or substance use disorders (Atkinson et al. 2009). Although the study sample was too small to permit definitive conclusions concerning the prevalence, severity, and nature of mental health disorders among persons with recently-diagnosed acute/early HIV infection, our findings suggest the possibility that psychopathology and substance abuse—if present—may have historically preceded the onset of infection. These included individuals with serious mental illness including bipolar disorder, suggesting a need for prevention efforts in this vulnerable population.

Further, a number of persons diagnosed with acute/early infection appeared to try to make efforts to avoid disease transmission to others following notification. There was evidence of a spontaneous shift among MSM diagnosed with acute/early infection toward serosorting, selecting other HIV-positive men as sexual partners following notification of their own disease status (Steward et al. 2009). These are similar to patterns long known to follow notification of a positive HIV antibody test result (Rotheram-Borus et al. 2001b; Crepaz and Marks 2002).

Risk reduction behavior change efforts to protect others are unlikely to be perfect. Some persons aware of their positive antibody status continue to engage in high-risk sexual practices with nonconcordant partners (Crepaz and Marks 2002; Kalichman et al. 2000; Vanable et al. 2000). High-risk behaviors during acute/early infection have even more serious public health implications given the greater transmission efficiency during this period. A public health priority must be the development of “rapid response” prevention case management services for persons diagnosed with AHI. Beyond ensuring that persons are aware of their elevated likelihood of onward HIV transmission during and immediately after this phase, such services should include assistance in developing the skills needed to refrain from activities that could transmit HIV to others; assistance in serostatus disclosure and handling disclosure consequences; the provision of mental health and substance abuse treatment when needed; and rapid entry into medical care (Hecht et al. 2006).

Several reports have described favorable outcomes of behavioral interventions in these domains among persons living with chronic HIV infection (Healthy Living Project Team 2007; Kalichman et al. 2001; Rotheram-Borus et al. 2001a). Although not specifically undertaken with persons in the acute/early phase, culturally-tailored, client-centered cognitive-behavioral and skills development-focused intervention models constitute an appropriate “starting point” for developing approaches to counsel newly-infected persons. A main difference is the much greater time-urgency of intervention and counseling delivery needed for persons diagnosed with AHI where a special aim is to prevent further disease transmission

during the short period of heightened infectivity. This urgency requires the development of brief, individually-tailored interventions that can be quickly delivered.

## Lesson 5: Can the "System" be Made to Move Quickly Enough to Permit Intervention with Persons While Still in the Acute/Early Phase of Their HIV Infection?

Approximately 55,000 persons in the United States contract HIV infection each year (Hall et al. 2008). Worldwide, approximately 2.5 million new HIV infections are contracted annually (UNAIDS and WHO 2007). Many newly-infected persons each year could potentially have been reached through AHI testing and rapid intervention, and a large number of subsequent transmissions to others could also have been averted. Intervention during the acute/early phase constitutes a public health strategy with the potential to reduce HIV incidence below current levels in the US and to curb rapidly-advancing epidemics in much of the world.

By its nature, AHI in particular is very transitory. Consequently, identification, referral, and intervention delivery must all move very rapidly. With the exception of rapid-response investigations into urgent outbreaks of infectious disease—events such as quickly tracking those who may have been exposed to drug-resistant tuberculosis on an airplane flight—public health systems are rarely designed for the kind of rapid but sustained action that is required to provide intervention on a wide scale for acutely-infected persons. AHI could remain—as it is now—a phenomenon that will only occasionally be diagnosed under fortuitous circumstances. Alternatively, it may be possible to develop rapid response systems that can significantly reduce new HIV incidence in the US and in the world.

Achieving the latter goal will require allocation of resources and coordination of efforts in the areas of community member education, the involvement of AIDS community-based organizations, the education of primary health care providers, and the development of HIV testing programs and policies that support AHI testing, prevention, counseling, and care. It will also require the allocation of resources for the campaigns to heighten community awareness of AHI and to support behavioral and psychosocial interventions for persons affected by it. It may well be the case that countries, states, or cities with high HIV incidence will assign greater priority to more intensive and comprehensive services related to AHI than areas with lower disease burden or threat. However, it is difficult to foresee circumstances where community and provider education concerning AHI, at the minimum, should not be improved.

## Intervention Related to Acute/Early HIV Infection and Primary Prevention: New Opportunities for Medical and Behavioral Science Collaboration

The field's new knowledge about heightened HIV transmission efficiency during the period of acute/early infection provides important new opportunities for medical, behavioral, and social science collaboration to achieve primary disease prevention public health aims. The use of direct HIV RNA testing to detect AHI in individuals not yet antibody-positive is a medical cornerstone of these efforts. However, the full public health impact of available testing methods can only be achieved when vulnerable community members become much more aware of AHI, understand its transmission risk implications, and take steps to refrain from further unprotected acts and seek AHI testing immediately following either a suspected exposure or symptom onset. These issues are largely behavioral and call for the development of community-level interventions. Similarly, primary health care providers are likely to be the first professionals to see patients with illness symptoms that could be indicative of AHI. Behavioral interventions directed toward primary care health service providers—especially those who serve patients in high-incidence communities—should seek to increase interview screening of patients for

recent risk behaviors in cases of potential AHI, to perform HIV RNA testing when warranted, and to provide patient counseling or referral for risk reduction behavioral intervention. Interventions directed to frontline primary health care providers constitute an important objective for the prevention of acute-phase transmission.

In addition to challenges in producing uptake of efforts to detect AHI, there are opportunities to develop and evaluate the effects of psychosocial and behavioral interventions for persons whose AHI has been diagnosed. Research findings of the NIMH AHI Study, while preliminary in nature, suggest that a significant number of persons with AHI have psychiatric or substance abuse disorders, possibly predating when HIV was contracted (Atkinson et al. 2009). It will be important to conduct outcome trials of brief interventions designed to reduce transmission risk behaviors, promote psychosocial coping, and ensure medical treatment access for individuals who are diagnosed with AHI. Such behavioral intervention research can provide an evidence basis for programs that will later be carried out by providers of services to this population. More extended interventions that span beyond the acute/early infection window will be needed for persons with substantial mental health or substance abuse problems.

## Conclusions

It has become increasingly clear in the HIV prevention field that the greatest public health impact will be achieved by approaches that combine together multiple prevention components rather than rely on a single type of intervention. This benefit is especially likely when prevention interventions are combined in a coordinated manner and when prevention efforts are focused on population segments at very high risk for contracting or transmitting HIV infection. Developments in the field's understanding of virological, medical, and epidemiological aspects of acute/early HIV infection provide a picture of how a brief illness stage can have major impact on the course of an epidemic, and underscore the need for interventions to reduce HIV transmission at this critical stage. Prevention of transmission associated with acute/early HIV infection can carry significant public health benefits. These benefits will best be achieved through well-coordinated medical, behavioral, social, policy, and community intervention efforts. Integrating these interdisciplinary perspectives creates new opportunities to advance the development of interventions that bring together medical and behavioral service with the aim of reducing incidence of HIV infection.

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