Characteristics of People with
Acute and Recent Human Immunodeficiency Virus
in North Carolina

By

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Abstract

Background: The prevalence of HIV continues to increase, even in persons with relatively few sexual partners or risk factors. Acute HIV infection is increasingly recognized as a period of HIV infection during which an individual may be highly contagious. An ever increase proportion of HIV transmissions are attributed to individuals who are in the acute stage of HIV. Still, acute HIV is under-diagnosed, even in people who may be aware of their high risk of infection.

Objective: To describe the characteristics of people diagnosed with acute or recent HIV in NC including demographic profile (sex, age, race, sexual orientation, education), sexual and drug use risk behaviors, HIV testing history, symptoms of acute retroviral syndrome, and medical use and access.


Participants: 32 adults (26 men and 6 women) diagnosed with acute or recent HIV infection through voluntary HIV screening at one of NC’s publicly funded tested sites.

Methods: North Carolina screens for acute HIV infection among people who test negative of standard HIV antibody tests. Standardized interviews were conducted with consenting participants. Descriptive, univariate statistics were calculated to describe the study population.

Results: Median numbers of lifetime sexual partners were 9 for straight women, 20 for straight men, 12 for bisexual men, and 50 for gay men. No participants reported intravenous drug use. A very large proportion of the population engaged in sexual activities with men. Most experienced symptoms indicative of acute retroviral syndrome, most commonly fever and loss of appetite or weight loss, and most sought medical care for these symptoms. Providers suggested acute HIV infection as a possible cause of symptoms in 25% of these cases.

Conclusion: While characteristics of people with AHI may vary widely depending on geographical location, social situation, and medical access, close epidemiologic investigation into populations with AHI can facilitate the early detection of and intervention into outbreaks as well as help design the most effective HIV transmission prevention strategies.
Introduction

Over 60 million people are living with the human immunodeficiency virus / acquired immunodeficiency syndrome (HIV/AIDS) worldwide. More than 1 million individuals in the United States (US) are living with HIV/AIDS and, despite widespread HIV education and prevention efforts, the rate of newly acquired HIV infections in the US has remained relatively constant for the last several years at an estimated 40,000 new infections occurring each year in the US. In fact, after a period of decline in the US, the incidence rate of sexually transmitted HIV infection has recently increased, and an estimated 25% of people with HIV are unaware of their infection. Unfortunately, the increasing prevalence of HIV among women and racial minorities and a resurgence of infections among men who have sex with men (MSM) painfully reveals that our current HIV prevention efforts are insufficient. As of 2003, fewer than 1,000 cases of HIV had been diagnosed worldwide during the first month of infection because, in the recent past, it was difficult to identify persons with acute HIV infection (AHI).

AHI, also known as primary HIV infection (PHI), is the stage of HIV from initial infection until a complete set of antibodies to HIV can be produced by the immune system. HIV antibodies can usually be detected in the plasma or serum 3 to 8 weeks after infection with the virus, an event known as seroconversion, upon which the diagnosis of HIV is usually based. In this stage of disease when detectable HIV antibodies have not yet appeared, massive amounts of viral replication and shedding occur. AHI must be semantically distinguished from acute retroviral syndrome (ARS) which is the predicable constellation of mononucleosis-like symptoms and clinical signs that frequently occur between 1 to 4 weeks after initial HIV infection in up to 90% of people. Early or recent HIV infection are terms generally used to indicate the first 6 to 12 months of HIV infection; a time span rather than a stage of infection,
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and thus should not be used interchangeably for AHI. During early or recent infections, antibody responses have reduced concentration or avidity but are detectable in the blood by standard antibody tests.\textsuperscript{1, 17}

Importance of Diagnosing HIV during the Acute Stage

During AHI, a peak in HIV viral replication and shedding occurs\textsuperscript{8} resulting in a very high viral load in both blood and genital secretions.\textsuperscript{18-22} In the first few weeks after infection, the plasma viral load can quickly escalate to greater than 1,000,000 copies/ml.\textsuperscript{10, 23} Such a high magnitude of viremia is closely correlated with an increased risk of HIV transmission.\textsuperscript{3, 24} In fact, the level of the viral load is purported to be the most important factor determining the probability of HIV transmission among untreated serodiscordant couples.\textsuperscript{24} The timely initiation of antiretroviral therapy (ART) can control genital tract shedding and decrease the level of plasma viremia in primary infection.\textsuperscript{21, 25} It may therefore be possible to decrease a person’s infectiousness through early diagnosis and therapeutic intervention in AHI.\textsuperscript{10} Furthermore, the HIV-specific antibodies found in genital secretions during latent infection that might neutralize some of the infectious genital viral shedding are not yet present.\textsuperscript{26}

Overall, AHI, and the 1 or 2 months following, are associated with a significantly high probability of transmitting HIV to another individual.\textsuperscript{15} AHI is considered the most infectious period of HIV, even compared with advanced AIDS during which the viral load is also quite high. A study among homosexual men found that HIV transmission is 100-3,000 times more likely to occur with an episode of unprotected anal sex during AHI than during latent HIV and 10-300 times more likely to occur during AHI than during advanced HIV/AIDS.\textsuperscript{27} Several studies have been conducted among monogamous, heterosexual, serodiscordant couples.\textsuperscript{3, 22, 28} One found that HIV transmission during a coital act was 5-12 times more likely to occur during early HIV than latent HIV and was 3 times more likely to occur during early HIV than advanced HIV/AIDS.\textsuperscript{3} Another reported that 20 days after infection with HIV, men with average viral loads and no
concurrent sexually transmitted infections (STIs) are 8-10 fold more likely to transmit HIV when engaging in heterosexual coitus than after 2 months of infection.\textsuperscript{22} Yet another study investigating heterosexual, serodiscordant partners found that male-to-female transmission by penile-anal sex was 13 times greater for men with early or advanced infection than men with latent HIV. However, no differences transmission by HIV stage were noted for penile-vaginal sex or female-to-male transmission.\textsuperscript{28} One study estimated that AHI may carry a risk of transmission up to 20-fold greater per exposure compared to the latent HIV infection.\textsuperscript{26} These estimates can vary a great deal based upon individual characteristics, type of intercourse, and use of protection.

While the exact proportion of HIV infections transmitted by those who are in the acute stage of infection is unknown, it is estimated that approximately 17,000 new infections may be transmitted by persons with acute HIV each year in the US, which is 42.5\% of all estimated infections each year.\textsuperscript{3} Data indicate that about 50\% of HIV transmission occurs during the first 5 months following seroconversion,\textsuperscript{6} and 43\% of partners are likely to be infected during the first 5 months of HIV infection.\textsuperscript{5,17} Between 25 to 47\% of new HIV infections transmitted by MSM networks are estimated to occur during the first few months of HIV infection.\textsuperscript{18,27} During the first 2 months of infection, men without concurrent sexually transmitted infections (STIs) with average viral loads would be expected to infect 7-24\% of susceptible female partners depending on the frequency and type of coitus.\textsuperscript{22}

By diagnosing AHI, several important public health actions can be realized. In the past, HIV surveillance has been limited to populations living with latent or advanced HIV disease due to the use of standard HIV antibody tests. Determining HIV incidence by the cross-sectional sampling of populations with only latent or advanced HIV has not proven accurate enough to guide clinical management or epidemiologic investigation.\textsuperscript{29,30} By adding tests to detect AHI to the HIV testing regimen, HIV incidence will become a more precise and accurate estimate, without adding misclassification error. Increased accuracy and precision of incidence estimates
can result in improved passive and active HIV surveillance. This information can be used to monitor trends prospectively within testing populations defined by varying demographic or risk factors.

Historically, it has been difficult not only to monitor HIV incidence, but also to identify high-incidence populations accurately or to access patients early in infection. North Carolina (NC) incorporated AHI screening into their public HIV testing algorithm and witnessed a variety of public health benefits in result, including increased HIV case identification, additional prevention opportunities, and found new local patterns of viral transmission that led to the detection of new risk populations. Public health officials can now map transmission networks and thereby investigate HIV-transmission events systematically through early diagnosis of AHI and partner notification strategies. Tracing source patients and their exposed partners is of use in helping to characterize sexual, social, and injecting drug user (IDU) networks of active HIV transmission with new details that might better facilitate targeted interventions and emergent prevention activities. This approach has been useful in identifying epidemiologic trends and hidden populations at risk for HIV infection and providing early detection of ongoing outbreaks. Hence, the identification of newly infected individuals and contact tracing should be considered an important public health measure to reduce HIV transmission.

Epidemiologists and mathematical modelers often hypothesize that there must be behavioral as well as biologic forces driving AHI to play such a large role in the HIV epidemic. Newly infected people with AHI, have very high viral loads, are especially infectious, and are usually unaware of their HIV status or have been misdiagnosed as HIV-negative. Further, they are likely to be in a period of life in which they are engaging in similar high-risk sexual behaviors to those which were responsible for acquiring their own infection. Such actions likely contribute substantially to the efficient spread of HIV during this stage. This combination of forces is likely to greatly increase the number of potentially preventable infections that occur due
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Therefore, identifying individuals with AHI affords an important opportunity to prevent further HIV transmission.

Clearly, from a public health perspective, interventions to interrupt ongoing viral transmission are especially needed during the acute stages of infection. The priorities of HIV prevention programs should be placed on identifying persons with AHI as early as possible and counseling them about strategies to reduce transmission such as abstinence and safer sex. Most standard voluntary counseling and testing practices do not identify most HIV-positive patients until they have established infection and after most sexual transmission has already occurred thus limiting the effectiveness of existing HIV testing strategies as preventative.

Identifying and interviewing individuals with AHI can help in the design of effective prevention interventions as recently infected individuals can more easily pinpoint the risk behaviors in which they were engaging at the time of HIV acquisition.

Studies have shown that counseling interventions at the time of the receipt of an HIV-positive test result were associated with a significant reduction in risk behavior. Even just identifying individuals with HIV and alerting them as to their HIV-positive status has been demonstrated to reduce the prevalence of high-risk sexual behavior substantially. A meta-analysis of 11 studies showed that once a person knows he or she is HIV-positive, he reduces his rate of unprotected intercourse (vaginal or anal) by 53%. After adjusting to account only for partners who are not known to be HIV-positive, the reduction in unprotected intercourse is even greater at 68%. Of note, it has not, however, been conclusively proven that counseling induces more behavior change than notification of a HIV-positive test result alone. It does seem reasonable to expect that identification and counseling people with AHI would have a similar effect on decreasing risky behavior to the identification and counseling of people with latent HIV. Yet, the former allows for a much greater impact on subsequent virus transmission as the majority of new HIV infections may be transmitted during AHI. Therefore, considerable
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Efforts and resources should be directed at implementing identification, counseling, and partner prevention services of persons with AHI to decrease overall HIV incidence.

Identifying and targeting prevention efforts toward acutely infected people may also help to prevent the spread of drug-resistant viral strains. Drug-resistant viruses are becoming increasingly common and are being transmitted more often to uninfected individuals. Therefore, acutely infected people are at high risk not only for secondary spread of infection but also for having primary drug resistance. Analyzing the patterns of drug-resistance among networks of individuals with AHI can help prospectively identify emerging patterns of disease transmission.

Clearly, diagnosing those with highly infectious AHI is important in preventing transmission of HIV and reducing the spread of the epidemic. Public health programs can play a more effective role in HIV prevention by detecting cases of AHI. Substantial benefits also occur on an individual level when people are notified of their serostatus, and no drawbacks to individuals being informed of their AHI status have yet been found. When people are tested for AHI in addition to latent HIV, they not only receive more accurate test results, but, if positive, will receive access to appropriate clinical management, drug therapy, and partner counseling and referral services within days after testing.

Identifying People with AHI

Diagnosis of AHI has been problematic for a number of reasons, chief among them being that, until recently such diagnoses were dependent upon the clinical recognition of ARS, which is characterized by nonspecific signs and symptoms also present with common bacterial or viral syndromes, such as infectious mononucleosis, influenza, streptococcal pharyngitis, and cytomegalovirus. Several studies have found that no individual symptom, combination of symptoms, or physical findings can reliably distinguish patients with AHI from those who are HIV negative. Also, HIV acquisition can result in sub-clinical infection. Consequently, ARS is under-diagnosed and often misdiagnosed, even in persons enrolled in programs of...
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routine surveillance for HIV infection. The failure of clinicians to assess patients for HIV risks, the lack of knowledge regarding proper diagnostic testing, and the lack of awareness of the potential benefits of early diagnosis exacerbate the under-diagnosis of AHI still further. The symptoms of AHI may be one of the only prompts for infected individuals to seek diagnosis and medical care during the initial years of HIV infection. If AHI is overlooked by clinicians when people present with ARS, many will not be diagnosed until years later when they develop AIDS. Also, the lack of diagnosis until recently was due to the lack of affordable, efficient testing during this phase before antibodies are produced.

Routine diagnostic tests for HIV infection are known as enzyme linked immuno-soribent assays (ELISAs) or just enzyme immuno-assays (EIAs) and are confirmed by a Western blot assay analysis. As ELISAs/EIAs and Western blots depend on the detection of antibodies to HIV to yield a positive result, they are negative during the first weeks to months (usually the first four to five weeks) of HIV infection, thereby creating a “window period” during which persons with AHI have negative test results on routine HIV tests. The window period can vary from weeks to months depending on the type and generation of HIV test performed and the rapidity of a person’s antibody response to the virus. The specificity of the third-generation EIA has been reported as ranging from 97% to over 99%. The sensitivity of the currently used standard EIAs are 96.2% (95% CI, 94.4 to 97.6) which is improved from the second-generation EIA sensitivity of 94.3% (95% CI, 86.2 to 97.8). The cost-effectiveness of broad HIV screening with routine antibody testing has long been justified.

The window period can be shortened and AHI diagnosed by also using assays for HIV antigens such as p24 or HIV nucleic acids such as ribonucleic acid (RNA). Measuring the CD4 cell count of the blood has not been proven to be a useful way to test for HIV seroconversion. p24 antigen testing is less expensive than RNA assays and has a better specificity, reported as 99.5% to 99.96% or higher. Unfortunately, there are substantial limitations in the sensitivity of p24 antigen testing, which is only around 79%-87% in referral populations — a population
likely to have a much higher prevalence rate of AHI than a general screening population. One study found that 13% of the people with AHI were not identified when using the p24 antigen assay. Another drawback of the p24 antigen assay is the possibility of a period during which immune system activity can make the p24 antigen undetectable before antibody tests are positive.

Using a more sensitive third-generation antibody test in combination with the p24 antigen assay can eliminate the window period. However, the additional infections detected by the sensitive EIA would not be recognized as being recent. This oversight could lead to missed opportunities for contact tracing, secondary prevention, and crucial clinical follow-up.

HIV RNA assays, also known as nucleic acid amplification tests (NAATs), are the gold standard and the most sensitive test to date for the detection of AHI and so most commonly used when testing or screening for acute HIV. Blood banks have routinely used NAATs to protect the blood supply for several years due to their high sensitivity, and it has been long recommended that all high-risk patients who present with symptoms compatible with AHI have a HIV NAAT. NAATs that can detect 50 HIV RNA copies per milliliter of blood will positively identify HIV infection approximately 6 to 11 days before an IgM/IgG-sensitive EIA and 26 to 31 days before an IgG-sensitive EIA alone. NAATs may even be positive several days before the p24 antigen is detectible and positive when testing peripheral blood only a few days after infection. Unfortunately, HIV RNA tests can be too expensive to use in routine testing and are vulnerable to false-positive readings from low levels of contamination. One study found a false-positive rate of 2.6% for HIV RNA testing in patients referred for evaluation of possible AHI.

Individuals presenting with ARS typically have high levels of HIV RNA in their blood. As a person seroconverts, his viral load usually decreases to a set point. As a result, if a person's HIV RNA level is less than 10,000 copies/ml, he may have progressed beyond AHI. False-positive tests occur almost exclusively with results of less than 2,500 HIV RNA copies/ml.
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To ensure the least number of errors possible, HIV RNA levels that are less than 5,000 copies/ml are regarded as potential false-positives. While HIV DNA NAAT can serve as an alternative to HIV RNA assays when testing for AHI, DNA testing may be less sensitive as RNA levels are higher than proviral DNA levels in early infection. In addition, RNA testing is more widely available and provides clinically useful information as to disease progression.

While there is agreement that NAAT is an important tool for public health prevention, surveillance, and management of AHI and should be used as a standard tool in clinical settings to identify AHI even in the absence of ARS symptoms, the use of it in routine screening and testing has not been feasible due to cost. However, systems have recently been developed based on the use of algorithms to incorporate multistage specimen pooling before NAAT. Blood banks were the first to use group testing approaches to decrease the number of samples tested by NAAT. Recently, several programs have used algorithms to incorporate multistage specimen pooling and NAAT into routine HIV EIA testing. Blood specimens that have a negative HIV EIA are pooled together before screening for HIV RNA. Then several groups may be pooled together into a larger group. If a large group screen is positive, its smaller group components can be tested and then the specimens from a NAAT positive small group are individually tested. Pooling in this fashion increases throughput, decreases cost, dramatically reduces false-positive results, and enhances overall testing accuracy as only very few individual specimens are tested for HIV RNA. These screening strategies have been found to be a feasible, accurate, and cost-effective method for detecting AHI on a population basis.

The addition of pooled NAAT to standard antibody testing algorithms can significantly improve HIV testing performance especially in urban settings, where the HIV burden is high and concentrated in specific populations. The positive predictive value (PPV) of combined antibody testing and NAAT with pooling is 0.997 (95% CI, 0.988 to >0.999). The PPV of nucleic acid amplification testing (NAAT) with pooling alone is 0.920 (95% CI, 0.740 to 0.990).
specificity of NAAT with pooling is greater than 0.999 (95% CI, 0.999 to >0.999). The PPV and specificity of the combined EIA, Western blot, and a NAAT pooling algorithm is 100%.6

Fortunately, the advancements in laboratory tests to detect HIV infection before seroconversion and the invention of a cost-effective screening protocol have enabled some to begin on the path to routine AHI screening. As the benefits and cost-effectiveness of screening for AHI are more widely recognized, an increasing number of HIV screening programs are adding NAAT to their testing algorithm. However, for screening programs to be successful, laboratories must be sure to use adequate quality controls and interpret very low-level positive test results as potential false-positives.30,39 The remarkable increases in cost efficiency and predictive value seen with pooling makes this a clinically and economically feasible public health screening program for acute HIV.1

Importance of Knowing Characteristics of Acutely HIV Positive People

People who experience ARS often undergo extensive clinical evaluation including serological tests, blood cultures, imaging studies, and hospitalization before arriving at the correct diagnosis. While awaiting diagnosis, many patients with ARS receive needless antibiotics contributing to the overuse of these vital drugs and the microbial development of antibiotic-resistance. Also importantly, the recognition of AHI allows appropriate clinical management and therapy to be initiated which has been hypothesized could slow the progression to AIDS.26,30 Not only are there the costs of inappropriate tests and therapies used to evaluate and treat ARS, but there is also the incalculable expense of treating more advanced HIV/AIDS once it is diagnosed and the immeasurable expense associated with transmission of HIV to others. An early and accurate assessment and diagnosis of AHI could eliminate much of this.28

It may also be important to avoid unnecessary HIV testing in uninfected persons. Diagnostic tests for AHI do have some limitations in accuracy and the resulting errors in
diagnosis can be psychologically distressing. Therefore, the clinical suspicion of health care providers when considering testing for AHI in a patient can become particularly important.\textsuperscript{13} Unfortunately, it is quite difficult to identify people with a substantial probability of having AHI on the evaluation of risk behaviors alone.

The highest HIV risk exposures, unprotected receptive anal intercourse or sharing injection drug equipment with an HIV-infected partner, are estimated to have a risk of HIV transmission that is less than 3\% per exposure. Other risk behaviors, such as unprotected vaginal or insertive anal intercourse, carry a lower risk of viral transmission.\textsuperscript{52} However, even the lowest-risk exposures such as unprotected receptive oral sex with a male partner have been responsible for documented cases of HIV transmission. Although aspects such as high partner viral load and the presence of other STDs can substantially increase the per contact risk of HIV transmission, these factors are frequently unknown to both the patient and physician and so are difficult to assess, much less quantify.\textsuperscript{13}

Substantial variations have been found in the prevalence of AHI among different types of testing sites, categories of risk, and demographic characteristics.\textsuperscript{30} Still, additional studies investigating characteristics of all people in a population with AHI, such as demographic profiles, risk behaviors, access to health care, and place of presentation, are needed to explore whether such criteria might help identify target populations for AHI screening.\textsuperscript{30} A cohort with a higher prevalence of AHI might be identifiable on the basis of risk factors, but there are no data on the use of these risk factors in screening for AHI.\textsuperscript{53, 54} Targeting screening to particular high-risk groups with pooling NAAT algorithms would allow for great cost-effectiveness. Determining the behavioral and biological risk factors of people diagnosed with AHI through cross-sectional studies can contribute to our understanding of the transmission and the natural history of AHI\textsuperscript{55} and may yield more efficient forms of AHI detection.
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We will explore relationships between the characteristics such as demographics, risk factors, and health care access of people diagnosed with AHI that we might better target prevention and screening activities. We will attempt to summarize the social and epidemiological factors leading to the acquisition of HIV to guide the use of supplemental NAAT. The results of this study can be used to help the clinician’s working at different locations with comparable source populations to more accurately select patients for laboratory AHI testing by giving data to yield a more accurate estimation of the pre-test probability of AHI when combined with subjects’ individual HIV risk exposure. An additional use the study results will be to assess the feasibility of timely intervention in networks of social and sexual contact. This study aims to describe the demographics, risk factors, and health care access among people with AHI in NC to better characterize this group and summarize any social and epidemiological factors that may have lead to the acquisition of HIV. The information obtained from these analyses will be used to better guide the use of supplemental NAAT by enhancing the ability of assessing pretest probability of AHI. First, I will present a systematic review of the literature to conclusively establish what is known about the epidemiology of other populations with AHI. Second, I will describe the methods used to complete the data analysis and present the quantitative results of that analysis which will describe people diagnosed with AHI in NC through voluntary, publicly funded HIV testing. Next, I will discuss the relationship between the results of the systematic review and that of the analysis conducted here. Last, I will discuss the impact these finding could have in the future on the prevention of HIV transmission.

Systematic Review of the Literature
I conducted a systematic review of the literature to identify previous studies that screen broad populations for AHI and described characteristics of populations with AHI being diagnosed in the US, including age, gender, race, risk behaviors, ARS symptoms, medical site of presentation for AHI diagnosis, medical care needed to receive AHI diagnosis and medical follow-up care, ART use, and the cost-effectiveness of AHI screening.

**Selection of Articles**

The Medline/Pubmed database was searched for the MeSH term “Acute Disease” combined with either “HIV Infections/diagnosis,” “HIV Infections/epidemiology,” “HIV Infections/prevention and control,” “HIV Infections/transmission,” or “HIV Infections” and “Risk Factors.” The Acute HIV Infection and Early Disease Research Program (AIEDRP) literature database was reviewed in entirety. Searches were limited to English language articles with human subjects and published from 1985 to March 2007.

All titles and/or abstracts of the 1,064 articles yielded by these searches were reviewed and were excluded for clearly being of the wrong subject matter or if not conducted in the general population (i.e. performed in psychiatric or pediatric populations). Articles with patient populations other than the US were included. Articles examining treatment for AHI were excluded unless data was also reported about the population with AHI who did not receive treatment. Of these articles, 92 appeared relevant so were reviewed in greater detail. Bibliographies of all articles included in the systematic review as well as those of relevant editorials, reviews, or commentaries were hand-searched, and an additional 48 articles that appeared to be relevant to the study question were identified and reviewed in entirety. Case reports, non-systematic review articles, and editorials were excluded. Articles that limited the study population to one single demographic group, most commonly observed with either MSM or heterosexual, monogamous couples, were excluded due to their poor external validity for this descriptive, population-based study. Studies were excluded if the same cohort was used in an
Characteristics of People with AHI in NC included study that had a more complete reporting of methods and results. Studies that did not report the age, sex, race, and probable mode of HIV exposure of the participants with AHI were excluded. Eleven articles, summarized in Table 1, were found to be relevant and fit the above criteria.

**Appraisal of Literature**

**Internal Validity Ratings**

Table 2 presents quality ratings for each of the articles. The articles identified by the search were assigned quality ratings using a 0 to 3-point scale (0=poor, 1=fair, 2=good, 3=excellent) for each of the categories in Table 2 including source and study populations, measurement methods and data collection, statistical analysis, and overall reporting of results. Unfortunately, these quality ratings were not able to be validated. I used standardized methods to assess each study with predefined criteria for different categories of quality.

**Selection of the Study Population**

Selection of the study population was evaluated according to whether the source population was adequately described and whether the study population was representative of the source population. Five studies received excellent ratings on describing the source population, four of which, as well as one additional study, also received excellent ratings on whether the study population represented the source population. An excellent rating for describing the source population was obtained if the description provided enough detail to prove external validity, and the inclusion/exclusion criteria were clearly reported. An excellent rating for accurate representation of the source population with the study participants was earned for clearly detailing how the participants were selected in text and/or a flow chart. Further, studies garnering an excellent rating elucidated clear and logical inclusion/exclusion criteria as well as participant referral and recruitment procedures. In the
above mentioned studies, the demographics and HIV risk data of the study population were compared to and found to be similar to that of the source population and any differences were clearly described. Two studies had one technician enroll all participants in order to minimize the inclusion of repeat testers into the study population.\(^5,39\)

Two studies received a good quality rating for describing the source population\(^10,35\) as the authors reported the number, location, and type of clinics that served as study sites from which to recruit all clinic attendees for AHI screening. However, additional information about the inclusion/exclusion criteria was not provided nor any demographic details of the source population. Three studies received fair quality ratings and\(^26,55,57\) one study received a poor quality rating for describing the source population.\(^25\) A fair quality rating was given for a brief, non-systematic definition of the source population. These studies provided inclusion/exclusion criteria but failed to report the breadth (such as the number of study sites) or the characteristics (such as the type of clinics serving as study sites) of the source population. These studies also failed to report how people were identified or recruited for study participation. Celum, et al.\(^55\) used the participants of a different study as their source population. A poor quality rating was given to the study that did not describe the source population beyond naming the city in which the study sites were located.\(^25\)

While no study was rated as good quality for representing the source population accurately with the study population, two studies received a fair quality rating\(^35,55\) and four studies received a poor quality rating.\(^25,26,56,57\) A fair quality rating was assigned when the derivation of participants from the source population was explained but potential selection biases were not addressed, and no data was provided to prove that the study population was representative of the source. A poor quality rating was obtained when no information about how the study population was derived from or related to the source population was provided leading to the potential for selection bias toward those who proactively seek medical care, have greater
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medical access, and volunteer for medical research. It is unknown how people who were identified as eligible but chose not to participate relate to the study participants.

Measurements

Measurements were evaluated based on the description of the tool used for data collection and the identification of the data collectors. No study received an excellent score for either measurement category but six studies received a good quality score for the description of their data collection method. All of the studies that received a good quality rating utilized interviews or written questionnaires to assess demographics, social history including risk behaviors, and medical history. A good quality score was awarded for an adequate description and definition of the variables in the survey or interview and the data collection process. However, no study provided a description of methods used to develop the questionnaire or the process of evaluating the instrument for social desirability, reliability, and construct validity. No data collection method was reported as having been tested in another population, so all methods have uncertain accuracy and precision. Weintrob, et al. verified patient data through a review of clinic and hospital records but did not state how the patient data was obtained. Daar, et al. was able to assess the effect of recall bias upon symptom reporting in 70% of participants by comparing the concordance of symptoms reported prospectively during screening and retrospectively upon learning of their positive HIV test results. Pincus, et al. had an investigator review clinical data within 1 week of participant enrollment to ensure comprehensiveness and internal consistency. Schacker, et al. corroborated the sexual contact history from a standardized administered questionnaire on subsequent visits and reviewed recent medical records.

Three studies received fair quality scores for the description of measurement tools, and two studies received a poor quality score. Two of the studies that obtained a fair quality rating collected data through chart reviews but gave no indication that this process was
characteristics of people with AHI in NC Shaw validated in any way. The other study to receive a fair quality rating collected defined information from participants during routine HIV counseling and testing procedures but failed to define the exact method of data collection or if the process was validated. A poor quality rating for data collection tools was received by studies that did not define any of the contents of the questionnaire or its validity. Yerly, et al. only reported the method of data collection for a portion of the participants with AHI, allowing potential for unequal measurement bias in addition to the bias of unknown reliability and validity of their data collection tool.

One study received a good quality rating for the identification of the data collectors as the training and type of clinician that collected the data was reported. Two studies received a fair quality rating for identifying the data collectors. Yerly, et al. reported that the clinician in charge collected the data but did not define the training, type, or identity of that clinician, and Hecht, et al. identified the investigators who reviewed the data but not who collected it. All remaining eight studies received poor quality ratings for this category as they failed to identify the data collectors or elaborate on the training or position these investigators had. The data collectors were not blinded for any of the studies reviewed. While there is a concern for the potential of incorrect or manipulated data, we expect data coding and entry errors to be randomly distributed. Also, most studies consisted of only one cohort and lacked a control group.

Overall, in synthesizing the quality scores for data collection, only one study received a quality rating of good. Five studies received a quality rating of fair, and five studies received a quality rating of poor because of measurement bias that could weaken the internal validity of the studies. Reliability and validity of instruments was an important factor in measurement quality score assignment which is why none of the studies received an excellent score for measurement ratings.

Statistical Analysis
Quality ratings of the analysis were based on the use of appropriate statistical methods and the potential for confounding of results. Two studies received an excellent quality score for the analysis as both thoroughly explained the statistical tests used for each type of data. One study also reported their construction of variables for bivariate analysis and the other assessed recall bias among symptom reporting using the McNemar test. The analysis conducted in six studies was rated as good because the appropriate statistical tests were used and p values or confidence intervals were reported. One study used regression models of the symptoms of AHI to see if any one symptom was independently associated with AHI and so controlled for the symptoms associated with a diagnosis of AHI by a p value <0.2.

Two studies were ranked as fair because the analysis was not adequately described and therefore could not be fully evaluated, and one did not report p values. One study received a poor quality rating as the statistical analysis conducted was not described at all.

Results

Defining Acute HIV Infection

Five studies limited their population to those only with AHI as defined by a negative or indeterminate EIA or Western blot and positive NAAT. The other six studies used recently-infected populations with estimated dates of infection ranging from days to 3 years earlier. All required documentation of a previous HIV-negative test within the last 7 months to 3 years although most studies required the documentation to be within a year prior to study entry. One study had a documented HIV-negative test in the prior 7 months as its only inclusion criteria. Two studies included participants with evolving EIAs and/or Western blots, and two studies required (some) participants to have had documented symptoms of ARS within the past 3 months. Three studies included patients with a positive NAAT and a negative EIA and/or Western blot, the current standard for the diagnosis of AHI, and three studies included patients with a negative less-sensitive EIA (LS-EIA) and a
positive sensitive-EIA. These five studies had either an evolving EIA and/or Western blot or a positive NAAT and a negative EIA and/or Western blot and either a negative less-sensitive EIA (LS-EIA) and a positive sensitive-EIA or documented symptoms of ARS within the past 3 months as inclusion criteria. Schacker, et al. compared the demographic characteristics of patients with classic AHI (positive NAAT with negative EIA) with those of patients with recent HIV (HIV negative in the previous year and symptoms of ARS in the prior 3 months) and found no differences between the two groups.\(^{10}\)

**Age**

The average age of study participants ranged from 24\(^{6}\) to 38\(^{57}\) years of age, and the range of ages in the studies varied widely from 17 to 71 years.\(^{25}\) Seven studies had participants ranging in age from the early 20's to late 40's.\(^{13, 25, 26, 39, 55-57}\) Three studies did not report the range of ages of participants.\(^{10, 30, 35}\) In a population-based NC study, 70% of people with AHI were over 24 years old\(^{30}\) which is quite similar to a referral-based University of Washington study which found that 72% of participants were over 24 year old.\(^{10}\) One study looked at age by probable mode of HIV transmission and gender and found that MSM (32 years) were significantly younger than male IDUs (40 years) or women in general (40 years).\(^{55}\)

**Gender**

In all eleven studies,\(^{6, 10, 13, 25, 26, 30, 35, 39, 55-57}\) the majority of participants were men ranging from 65%\(^{30}\) to 100%.\(^{35}\) Pincus, et al. noted that women were more likely to decline enrollment in their study and thereby be tested for AHI.\(^{39}\)

**Race**

The race/ethnicity of the study participants varied widely and was mostly determined by that of the source population. In six studies,\(^{10, 13, 25, 26, 55, 56}\) the majority of participants were
Characteristics of People with AHI in NC

Caucasian ranging from 56% to 98% while in studies in which Caucasians were minorities they ranged from 22% to 41%. Three studies had African-Americans as the majority of participants ranging from 55% to 75% while in the other eight studies, African-Americans were in the minority ranging from 3% to 40%. Some studies also had smaller numbers of minority groups such as Hispanic/Latino (4% to 67%), Native American (3% to 4%), Haitian (20%), and Asian (27%).

Pilcher, et al. observed that at publicly funded testing sites in NC, 45% of the HIV testing population was African-American, but 70% of the people with AHI were African-American. While African-Americans were clearly more likely to have AHI in this testing population, Caucasians and Hispanics were less likely as they made up 32% and 15% of the testing population but 22% and 4% of the AHI population respectively. Patel, et al. found that while non-Hispanic whites, Hispanics, and Asians made up equal proportions of the study participants with AHI (27% each), Asians with HIV were far more likely to be detected in the acute stage (30%) compared to the proportion of Hispanics (9%) and non-Hispanic whites (6%) that were in the acute stage. Pincus, et al. noted that Haitians were more likely to decline enrollment in their study and thereby not be tested for AHI.

Probable Mode of HIV Transmission

In every study, the most common HIV risk factor was MSM intercourse. Participants that identified as MSM ranged from 30% to 91% and in eight studies, MSM made up more than half of the participants. In the Pilcher, et al. study, 47% of male participants with AHI reported that they had sex with men on a self-administered questionnaire, but during in-depth interviews with disease-intervention specialists 73% reported having male sexual partners.

In one study, 68% of MSM with AHI reported having unprotected anal intercourse in the 3 months before diagnosis, and another study corroborated that 65% of MSM with AHI
Characteristics of People with AHI in NC

reported unprotected receptive anal intercourse with an HIV-positive or unknown partner and most reported multiple episodes. In the latter study, 14% of MSM reported unprotected receptive oral sex as their greatest risky behavior. Oral sex is a mode of HIV transmission. Among MSM, most men who report unprotected receptive oral sex also report protected anal sex. Compared to people with AHI in other risk groups, MSM reported having a higher median number of sexual partners, particularly those of unknown HIV status. This study also found that 5% of MSM shared drug injection equipment and MSM were more likely to be white, have attained higher education, and have private health insurance compared to male IDUs and women in general (p<0.001).

From 5% to 42% of participants identified as heterosexual, although in a study with only four participants, 1 man and 1 woman were heterosexually infected. Of all the men in the Patel, et al. study, only one male self-identified as heterosexual but this person still reported having oral sex with men as well as oral and vaginal sex with women. One study population consisted of 14% women of whom slightly over half reported heterosexual activity as their only risk factor.

In population-based California (CA) study, 10% of MSM with HIV were in the acute stage and 17% of heterosexuals with HIV were detected during AHI. The population-based NC study found that while only 3% of people who voluntarily HIV tested identified themselves as MSM, 30% of people with AHI were MSM. MSM are clearly at very high risk for AHI while heterosexuals with no other risk factors were at much lower risk as this group made of 33% of the testing population but just 4% of those diagnosed with AHI. Two percent of the testing population identified as heterosexual and reported being an IDU and these people made of 4% of the population diagnosed with AHI.

In the Patel, et al. study, 67% of people with AHI had more than 5 sex partners in the past year, 27% reported having had 20 or more sex partners in the past year, and 36% reported having had sex with anonymous partners. In one study, the participants with AHI had an
average of 2.4 sexual partners in the 2 months before study enrollment; with MSM having an average of 2.7 sexual partners and heterosexuals having an average of 2 sexual partners in the 2 months before study enrollment. This difference was not statistically significant. Of the MSM with a HIV-positive, steady partner, 25% reported consistent condom use. 40% of participants with AHI attested that in the 2 months prior to study enrollment, they used a condom most of the time. All of these participants were MSM. The other 60% reported using a condom all of the time prior to diagnosis and study enrollment. In the Celum, et al. study, 16% of those with AHI reported only protected sexual and injection exposures, and just 9% of people with AHI had a single HIV-positive partner in the 9 months before testing HIV-positive. A larger proportion of subjects, particularly MSM, had multiple potential exposures. In contrast, Schacker, et al. found that most seroconverters had a single positive partner during the transmission period. One study found that 9% of people with AHI had a sex partner at risk of having HIV and 9% of people used non-injection drugs and had a sex partner at risk of having HIV. The entire study population for both Schacker, et al. and Pilcher, et al acknowledged having a sexual activity before seroconversion. In the Pilcher, et al. study, nearly half of all participants were monogamous in the month before seroconversion, while 12% had more than 5 partners in the month before. Schacker, et al. found that the male patients had had a median of 3 sexual partners with whom they had 51 sexual contacts (average of 2.1 per week) in the 6 months prior to HIV acquisition with a median of 1 sexual partner in the month prior. For men with AHI, unprotected oral-genital contact was the most frequently reported sexual activity with receptive oral sex being more common. Only 3.6% of oral-genital contacts and 42% of genital-rectal contacts were protected. In the Schacker, et al. study, 83% of people who had unprotected sex that led to the transmission of AHI had had a single sexual encounter with a known HIV-positive partner, and 33% had only unprotected oral-genital contact. Of note, Celum, et al. found that participants with AHI were equally divided between frequent, occasional, and rare exposure to high risk behaviors. About one-third of
seroconverters reported frequent high-risk exposures (≥9 weeks with episodes of unprotected vaginal or anal sex or shared injection equipment during the seroconversion period), one-third had occasional high-risk exposures (2-8 weeks with such exposures), and the remaining third of seroconverters reported rare high-risk activities (0 or 1 week with such exposures).

The amount of IDUs in all the studies was comparatively low. Self-reported IDU exposure ranged from none to 15%. Celum, et al. noted that while 6% of study participants were women IDUs, high-risk sexual activity was more common than IDU (6%) among women. Pilcher, et al. noted that 4% of men with AHI were heterosexuals and IDUs, while Schacker, et al noted that 75% of IDUs were homosexual or bisexual men.

One study looked at 23 index cases of AHI in North Carolina and found that possible social factors contributing to the risk of transmission included recent prison release (22%), sex work (22%), multiple anonymous sexual partnerships (17%), and heavy drug or alcohol use (43%). Seventeen percent were college students, 4% were a victim of sexual assault and 3% reported a needlestick injury. One study found that 6% (3 of the subjects) had intentionally engaged in high-risk sexual behavior in attempts to become infected with HIV.

**STIs**

The presence of a concurrent STI at the time of AHI diagnosis was fairly common in the four studies that reported this information, ranging from 8% to 75%. In the Celum, et al. study, early infectious syphilis, rectal gonorrhea and/or chlamydia infections in MSM, and trichomonal vaginitis in women were all equally prevalent. In the Priddy, et al. study, all two African-American men had concurrent gonococcal urethritis, and the one woman diagnosed with AHI, also African-American, reported a history of a recent STI. The Caucasian MSM with AHI did not have any clinical findings reported. Patel, et al. tested all participants for early syphilis at the time of HIV testing and found no one with the disease concurrently. Pilcher, et al. found the presence of an STI to be an equally common risk factor as MSM and more
participants reported having symptoms related to a STI (35%) than actually had STIs (30%). The amount of participants reported previously having a STI ranged from 0 to 27%, most commonly being genital herpes or anogenital sores. In the Hecht, et al. study, 5% of people with AHI reported sores on their anus and 2.4% reported sores on their genitals. There was no significant or clinically important difference in the prevalence of anal or genital sores in those with and without AHI. However, genital ulcers did last significantly longer in persons with AHI (27 days) compared to persons without AHI (9.5 days). Thirty-seven percent of people with AHI reported oral ulcers or mouth sores (n=15) which compared to 15% of participants without AHI (n=33); OR 3.1 (95% CI 1.5-6.6).

Symptoms

The symptoms associated with the diagnosis of AHI were fever, fatigue, pharyngitis, myalgias, weight loss, headache, nausea, rash, oral ulcers, arthralgias, loss of appetite, night sweats, diarrhea, vomiting, and lymphadenopathy. Schacker, et al. found the median reported fever was 38.9°C and the median weight loss was 5 kg.

In the Schacker, et al. study, 89% of participants had symptoms associated with HIV seroconversion. Of people with AHI at study entry, 94% had signs or symptoms of ARS while 86% of the participants with recent HIV at study entry retrospectively reported ARS symptoms. Eighty-seven percent of people who HIV tested routinely before diagnosis with AHI prospectively reported ARS symptoms. Although no one with AHI in the Pilcher, et al. study was clinically suspected to have AHI at the time of HIV testing, ARS symptoms were recognized in 56% of participants once the AHI diagnosis was made. Retrospectively, 85% of subjects reported one or more ARS symptoms lasting for 3 or more days. In the Priddy, et al. study, only 1 participant (25%) presented with any symptoms of ARS and he was not recognized by the HIV counselor at the time of testing as potentially having ARS.
Celum, et al. found that participants were significantly more likely to remember experiencing the non-specific viral symptoms of fever, sweats, headache, nausea, lymphadenopathy, and myalgias after learning of their HIV-positive status rather than report them prospectively during screening. Whether this is due to recall bias or the under-reporting of non-specific symptoms during seroconversion is unknown. Weight loss was significantly under reported by participants compared with clinical records.55

The most frequently reported ARS symptoms were fatigue (57%) and fever (56%), and the most frequent symptom lasting 7 or more days was fever (23%).55 A rash was reported by 21% of participants with AHI and lasted more than 3 days in 16%.55 Interestingly, in referral-based cohorts the rates of rash are much higher at 30% to 68%.8,10,38,55 Of patients who sought medical help for ARS symptoms, 66% had clinical signs of ARS including postural hypotension, exudative pharyngitis, thrush, oral, genital, or rectal ulceration, lymphadenopathy, and neuropathy, and 24% had signs and symptoms of aseptic meningitis including fever, headache, photophobia, and stiff neck.10 The median time from sexual encounter to the development of symptoms was 15 days in participants who could pinpoint the date of HIV acquisition. The median duration of symptoms for both acute and recent HIV was 14 days.10 Providers in the Celum, et al. study were more likely to presumptively diagnose AHI among MSM, particularly those with fever of 7 days or more or a rash of 3 days or more, than among other symptomatic subjects.55

The symptoms most sensitive for the diagnosis of AHI were fever (80%) and malaise (68%). The most specific symptoms for AHI are weight loss (86%) and oral ulcers (85%). The best independent predictors of AHI are fever (OR 4.0 (95% CI 1.4-9.3)) and rash (OR 3.4 (95% CI 1.6-7.3)).13 The sensitivity of specific individual symptoms or combination of symptoms is relatively low in predicting AHI.55 In fact, both Daar, et al. and Pincus, et al. found that no symptom, combination of symptoms, or sign could reliably distinguished patients with AHI from those who were HIV negative,12,39 and the percentage of patients with 3 or more symptoms or
signs was not significantly different between people with AHI and HIV-negative people (100% vs. 75%; p > .05).  

Site of Patient Presentation

Of people who routinely tested for HIV and sought medical evaluation of ARS symptoms, 48% went to their own primary care provider, 31% went to an emergency department, and 21% went to a walk-in clinic. A diagnosis of AHI was considered at these medical encounters in only 26% of those patients. In the Weintrob, et al. study, 45% of patients initially presented to an emergency department, 28% to a primary care provider, and 28% to an urgent care clinic. Interestingly, 41% of Caucasian persons were seen initially by a primary care provider compared to just 8% of nonwhite persons. However, 83% of the diagnoses of AHI were made by infectious disease specialists. While this is a shocking revelation, we are left to wonder if this is an artifact of this prospective cohort study as the path from source to study population was not well defined. If this finding is in fact not due to selection bias, its implications are unfortunate as very few patients with the relatively nonspecific presentation of AHI are referred to infectious disease physicians. Differences in the frequency of AHI were significant (p < 0.001) across different types of confidential HIV testing sites. Seventy percent of persons with AHI were identified at STI clinics whereas only 41% of all people presented for testing at these sites. The other 30% of participants were detected at prenatal-obstetrical clinics (17%), family-planning clinics (16%), freestanding HIV testing sites (11%) or jails (3%).

Another prospective study demonstrated that 1.0% of patients receiving urgent care in an urban medical center in the northeastern US for a viral syndrome actually had AHI.

Path to Diagnosis
Eighteen percent of MSM and none of the other risk groups who sought medical care reported that their provider suspected AHI.\textsuperscript{55} In one study, of the people with AHI at study entry and symptoms, 94% sought medical assistance, and 80% of those were eventually tested for HIV infection during their illness.\textsuperscript{10} Weintrob, et al. noted that 52% of all patients were seen by clinicians at least 3 separate times before AHI was diagnosed. The number of visits until diagnosis did not differ based upon sexual orientation or site of initial presentation but it did differ by race. Seventy-one percent of Caucasian patients had 3 or more visits before diagnosis while 75% of nonwhite persons were diagnosed at the first or second visit.\textsuperscript{26}

Of all the people with AHI at study entry, 66% sought medical help, 8% were hospitalized, and 31% were HIV tested during ARS. Of the participants with recent HIV at study entry and a history of ARS symptoms, 88% sought medical care for those symptoms, and 41% of those who sought medical care had HIV testing at the initial medical encounter, and 23% referred themselves for testing shortly after the illness developed. Of all the people with recent HIV at study entry, 94% sought medical help, 29% were hospitalized, and 71% were HIV tested during the ARS period. Frequency of hospitalization was the only significant difference noted in the clinical presentation of patients who entered the study with AHI compared with those with recent HIV.\textsuperscript{10} While 17% of participants were diagnosed with AHI at the initial presentation for their ARS symptoms, 80% of these people were admitted to the hospital for an unknown febrile illness for a median of 11 days (range 7-14) prior to diagnosis. The other 20% requested HIV testing at the first visit to an infectious disease clinic due to concern over a sexual contact with a person with AHI. Fourteen percent of patients were diagnosed as having AHI within one week of presentation but 17% were not diagnosed until greater than one month later. Overall, the average time from presentation to diagnosis was 14 days (range 1-60 days).\textsuperscript{26}

Eighty-nine percent of participants had a definable illness that prompted medical attention and hospitalization was needed to manage symptoms in 15% of patients. Most patients came to the attention of a health care provider during the acute illness, but only 25% of
Characteristics of People with AHI in NC

persons received a correct diagnosis at the initial medical encounter. Patients with AHI are frequently given alternative diagnoses before HIV is detected. In one study, 31% were diagnosed with nonspecific viral syndrome, 17% with Rocky Mountain Spotted Fever, and 10% with streptococcal pharyngitis. Pincus, et al. found that of people with ARS symptoms who presented to an urban urgent care center connected to a teaching hospital, 60% were diagnosed with a viral syndrome, 20% with acute pharyngitis, and 20% with fever and headache before they were diagnosed with AHI. Other presumptive diagnoses included upper respiratory infections, "flu" and viral syndromes, sinusitis, and streptococcal pharyngitis. Patients were treated with doxycycline (21%), ceftriaxone (10%), azithromycin (7%), amoxicillin (7%), and amantadine (3%).

In one study, 68% of participants reported that their ARS symptoms were so severe that they had to change their daily activities and 57% missed work. Almost half sought medical care for their symptoms, which was strongly associated with a fever lasting more than 3 days.

HIV Testing Patterns

In one study, 82% of participants with AHI had a previous HIV-negative test result. One study found that 50% of patients were participating in routine surveillance programs for HIV, testing every 6 months.

Insurance, Education, and Employment

In the Celum, et al. study of 103 patients, 37% of participants with AHI had private insurance, 14% had Medicare/Medicaid, 6% had other insurance, and 25% had no insurance. Ten percent of study participants with AHI had less than a high school education, 20% were high school graduates or had their GED, and 70% had more than a high school education. In another study, 76% of participants were employed.
Follow-Up

In the Pincus, et al. study, 4 of the 5 AHI-positive individuals returned to obtain their results. In the Pilcher, et al. study, 100% of people who tested positive for AHI were notified of their HIV-positive status, and 74% were alerted within 3 days after test results were available. Specially medical care was begun by 91% of participants. Forty-eight sexual partners of subjects with AHI received counseling for risk reduction, and 10% of these partners were newly diagnosed with HIV. Eleven partners were identified who were the likely source of the infection. Ten of these partners were aware of their HIV infection, but only three had disclosed their status to the study participants. Three of the infected partners had been previously named in surveillance records as a potential source of infection in at least three other cases. Participants did not report any adverse events (e.g., psychological trauma, violence against or from partners, violation of confidentiality, or inappropriate HIV therapy) from being notification of their acute HIV status during follow-up.

Medication

Antiretroviral use was reported by 55% to 70% of participants. In the latter study, HAART was begun a median of 9.4 months after the AHI diagnosis. MSM were significantly more likely than woman to begin therapy and initiate it sooner after seroconversion. None of the male IDUs used antiretroviral medication during the study follow-up period. Pilcher, et al. found that 87% of people with AHI in NC who tested at publicly funded sites, including one pregnant woman, began antiretroviral therapy. In the Pincus, et al. study, all participants who returned to receive their AHI diagnosis began antiretroviral therapy a mean of 10 days (range 8-14 days) after enrollment.

Cost-effectiveness
Cost-effectiveness calculations vary widely in their results. In NC, the pooled HIV NAAT cost has been calculated as $2 to $3.63 per specimen for the RNA assay cost in a low-prevalence AHI setting in addition to the original cost of the EIA and specimen processing. Another study calculated that cost of NAAT as $2.82 per patient screened. However, in CA, the total cost of HIV and pooled NAAT screening was $12.78 per specimen. EIA and Western blot testing cost $11.79 per patient screened. The cost of antibody screening alone is $2.14 per specimen. The average cost of the more sensitive IgM/IgG HIV antibody test is approximately $8 per specimen.

However, EIA and Western blot testing only cost $395 per additional case identified. A screening study in an urban hospital calculated the screening costs to be $16,000 per case of AHI diagnosed. In CA, the costs ranged from $2,314 to $4,950 per case of HIV identified depending on the protocol used. In one NC study, costs were $17,515 per additional index case of HIV infection diagnosed by NAAT which is dramatically greater than the $1,560 per additional case identified by NAAT calculated in another study.

One study found that the total cost of diagnosing each case of AHI (which includes NAAT, ELISA, and Western blot assay) was $16,000 per case of AHI. The cost for the identification of AHI can vary according to the size of the master pool. In populations in which the prevalence of AHI is 1.0%, whether screening for AHI is cost-effective depends not only on the cost of screening but also on the efficacy of therapy for AHI and the probability that the diagnosis and treatment of AHI will decrease subsequent transmission. Given that the lifetime costs of HIV infection exceed $200,000, only 1 case prevented for 40 cases identified would justify the costs for HIV RNA screening.

Summary of Internal Validity

The overall quality of the articles analyzed in this systematic review was fair to good. The most significant problem affecting internal validity of these studies was selection bias. A
Table 1. Summary of evidence from selected studies.

<table>
<thead>
<tr>
<th>Study Authors, Year</th>
<th>Study Design</th>
<th>Source Population</th>
<th>Study Population</th>
<th>Measurements</th>
<th>Significant Results</th>
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<tbody>
<tr>
<td>Celum, Buchbinder, Donnell, et al. 2001</td>
<td>Prospective cohort</td>
<td>Participants in HIVNET VPS cohort in Boston, Chicago, Denver, New York, Philadelphia, Providence, San Francisco, and Seattle and other HIVNET-approved cohort studies who became infected with HIV and had a documented HIV-negative test in the prior 7 mo from a HIVNET study or other approved cohort study during 4/95-8/98</td>
<td>103 recent seroconverters</td>
<td>Interviewed about symptoms, STDs, and risk behaviors; physical exam, routine STD testing at enrollment. Flu 1 mo after enrollment and then every 3 mo for &lt;3 years for interviews about risk behaviors, STDs, symptoms, opportunistic infections, and ART use.</td>
<td>33 yo; 85% male, 14% female; 85 MSM, 4 Male IDUs, 6 female IDUs, 7 homosexually active females; 56% (56) white, 15% (15) African American, 21% (22) Hispanic, 8% (8) Other; 37% have private insurance, 14% have Medicare/Medicaid, 6% have other insurance, 25% have no insurance; 10% have less than high school education, 20% are high school graduate/GED, 70% are more than high school</td>
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<tr>
<td>Hecht, Busch, Rawal, et al. 2002</td>
<td>Prospective Cohort</td>
<td>18 yo (216 if emancipated minor), no prior ART; pts w/ HIV exposure within past 3 mo + sx of ARS or unprotected receptive anal sex or shared IDU with a partner known to be HIV + in past 3 mo or neg ELISA in past yr and recent + ELISA or hx of neg ELISA and HIV exposure within past 6 mo presenting to UCSF between 6/1/96-12/31/99</td>
<td>40 pts w/ PHI: 22 w/ pre-seroconversion (acute HIV); 18 w/ recent seroconversion (early HIV); excluded if prev hx of known HIV + or equivocal LS-EIA on screen</td>
<td>Standardized questionnaire – self-administered for first 44% (178) pts screened for PHI and interviewer-administered for other 56%.</td>
<td>32 yo; 92% male, 8% female; 3% African American, 10% Latino, 74% white, 13% other; 90% MSM, 5% heterosexual, 3% IDU, 3% occupational</td>
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<tr>
<td>Pao, Fisher, Hue, et al. 2005</td>
<td>Prospective cohort</td>
<td>1235 HIV+ pts at a genitourinary clinic in UK from 1999-2003; 86% Caucasian, 69% men, 79% MSM</td>
<td>103 pts w/ acute HIV or recent HIV</td>
<td>Collected from clinic case notes</td>
<td>36 yo; 96% male, 101 caucasian; 91% MSM, 6% IDU; Of MSM, 66% had unprotected anal intercourse; Of 89 with Information available, 38.2% had concurrent STIs</td>
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<tr>
<td>Patel, Klausner, Bacon, et al. 2006</td>
<td>Observational / cross-sectional</td>
<td>People seeking voluntary HIV testing at San Francisco City Clinic (SFCC) from Oct 2003 to July 2004 or at 3 STD clinics in LA or the MSM unit of the LA county Men's Central Jail from Feb to April 2004</td>
<td>SFCC: 3041 screened, 97% HIV-neg, 105 HIV- pos, 11 HIV-RNA pos LA: 2170 screened, 99% HIV-neg, 22 HIV-pos, 1 HIV-RNA pos</td>
<td>HIV antibody EIA, pooled HIV RNA, age, race/ethnicity, occupation, income, zip code, syphilis history, HIV testing history, other STD diagnoses at time of testing, STD history, reasons for testing, behavioral risk factors, HIV status of partners, use of condoms, types of intercourse, and substance use</td>
<td>SFCC: Acute HIV + were mean age 34; all male; 27% white, 27% Hispanic, 27% asian, 18% black; 91% were MSM, 9% heterosexual, 82% HIV tested prev, 27% &gt;5 partners in past yr, none had STDs in past years, none had syphilis at presentation</td>
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<tr>
<td>Pilcher, Fiscus, Nguyen, et al. 2005</td>
<td>Observational / prospective cohort</td>
<td>People receiving HIV testing at one of 110 state-funded sites in NC between 11/1/02-10/31/03</td>
<td>23 cases of acute HIV</td>
<td>HIV ELISA, HIV RNA NAAT Testing forms with characteristics of testing sites, demographics, reasons for testing, HIV-testing history, lifetime risk factors. Interview for information about symptoms, risk behavior, and partnerships</td>
<td>15 men, 8 women; 16 &gt;24 yo, 7 ≤24 yo; 5 white, 16 black, 1 Hispanic, 1 Native American; 1 heterosexual, 7 have STD, 2 have sex partner at risk, 2 had sex partner and use non-injecting drugs, 7 MSM, 1 heterosexual and IDU, 1 victim of a sexual assault, 0 have acknowledged sex partner; 70% presented to STD clinics</td>
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<td>Study Authors, Year</td>
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<td>Study Population representative of source population?</td>
<td>Description of Measurement tool?</td>
<td>Data collectors identified, blinded?</td>
<td>Appropriate analysis?</td>
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<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
second problem was the potential for measurement bias. Lack of blinding of data collectors and lack of description and validity of the measurement tools used were common problems. Finally, all studies had high potential for confounding as a result of study design (cross-sectional, descriptive cohorts).

External Validity of Findings from the Systematic Review

Quality ratings for external validity were not assigned. The majority of the articles appraised in this systematic review concern characteristics of people and populations with AHI or recent HIV. The relevance of some of these studies to undiagnosed patients with acute HIV is uncertain, since the risk habits of people can vary widely depending upon local customs, expectations, and peer groups. For instance, a population with AHI in San Francisco\textsuperscript{13,35} is likely to have a very different risk profile and behaviors than a population with AHI in Uganda or Switzerland.\textsuperscript{25} A higher incidence of AHI at sites serving a primarily MSM may be expected partly due to more frequent testing in the MSM population. Studies in the developing world may not be fully applicable in the developed world, as the frequency of risk exposures and cultural difference may differ. The characteristics of the population will also vary markedly upon whether the source population was based upon a geographical population or a referral population. While this population is not likely to be biologically different from others, it is very possible that the risk factors, demographics, and health care access, all the main areas of interest, differ dramatically between source populations.

Methods

Study Design

A cross-sectional observational study was conducted over 24 months to describe people in NC who are acutely or recently infected with HIV and are diagnosed by routine HIV testing at any publicly funded NC test site. This study protocol was approved by the Institutional Review
Characteristics of People with AHI in NC

Shaw

Board of the University Of North Carolina School Of Medicine. This study presented here is a secondary analysis of the data collected. The objectives of this analysis is to describe new details about the demographics, sexual HIV risk factors, HIV testing history, and health care access among the populations that were acquiring and transmitting HIV in NC.

Study Subjects

The NC Department of Health and Human Services (DHHS) HIV/STD Prevention and Care Branch's current Screening and Tracing for Active HIV Transmission (STAT) Program screens all consenting individuals who present for HIV counseling and testing at 110 publicly funded testing sites in NC for HIV first by EIA. All specimens with a negative or intermediate EIA are screened by NAAT using a group algorithm which pools specimens into groups of 9 and then pools 10 of the groups of 9 so that 90 specimens are screened by one NAAT. If a positive NAAT occurred, each of the 10 groups of 9 was tested by NAAT. Then, the specimens from any positive group of 9 were tested by NAAT individually.

Approximately 120,000 blood samples are screened annually from people requesting routine HIV testing. All testing was confidential and was linked to patient information with unique identifiers, according to state public health statutes. Anonymous, unlinked HIV testing is not available in NC. Written informed consent for all HIV testing and for the use of personal information in evaluation research was obtained during pretest counseling.30 As the Figure illustrates, 79 people were diagnosed with AHI or recent HIV between January 1, 2003 and December 31, 2004. Persons for whom the HIV antibody status was negative or indeterminate but had a positive NAAT were defined as having AHI. Persons with a documented negative antibody test and then a positive antibody test within 6 months were classified as recent. Four participants were excluded for an inability to speak English or being less than 18 years of age. The 75 eligible subjects with acute or recent infection were asked for permission to be contacted by the study coordinator regarding this cross-sectional study. Twenty-six people refused to
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participate in the study, and 17 people could not be located. All remaining 32 study participants were confirmed to have HIV upon seroconversion and were interviewed (Figure).

Study Procedures

All participants were interviewed for approximately 60 minutes face-to-face by trained study technicians (the principle investigator, a research assistant, and several investigators from the Centers for Disease Control and Prevention (CDC)), all who used a standardized questionnaire developed in collaboration between researchers from the University of North Carolina and the CDC. The questionnaire used in this study was based upon a questionnaire developed by the CDC to investigate an outbreak of syphilis among MSM in New York. Other components of the questionnaire used in this study were drawn from other validated surveys. The questionnaire was piloted on co-investigators and support staff in "mock-fashion" prior to use. Demographics, reasons for testing, HIV-testing history, and lifetime HIV risk factors, as well as detailed information about health care access, use of health services, health care delivery, and any acute illness consistent with ARS, were the primary constructs about which data were gathered at the interview. HIV/STD transmission risk factors, such as types of sexual partners, sexual activity, and drug use, were assessed in the year prior to AHI diagnosis by informing the participant of the time period of interest prior to each group of questions.

Verbal consent to be contacted by a study coordinator was obtained at time of delivery of HIV test results, and verbal consent was also obtained over the phone by the study coordinator prior to study participation. Written informed consent for participation and for the use of personal but non-identifiable information in research was obtained at the study interview. Unfortunately, the precise amount of time between AHI diagnosis and study interview is not known but all took place within less than 1 year from the time of diagnosis.

Analyses
Unlinked data from the 32 interviews were entered into a secure database for analysis. Accurate data entry was confirmed by a quality control investigator for reliability. Descriptive, univariate statistics, as well as comparative analyses assessing differences in age and number of sexual partners by gender and self-reported sexual orientation, were generated using statistical software (STATA version 9.2; StataCorp, College Station, TX). Differences in means of sexual contact history were evaluated using Student’s t-test for two groups (e.g. gender) and ANOVA for more than two groups (e.g. race, sexual orientation). All reported p values are 2-tailed. For highly skewed data, medians were also reported. Participants were excluded from analyses for which data were missing.
Figure: Selection of the Study Population

79 Acute Infections Identified

- 4 Did not meet inclusion criteria (5.1%)
- 26 Refused participation (32.9%)
- 17 Could not be located (21.5%)
- 32 Interviewed (40.5%)

26 Men

6 Women
Results

Demographic Characteristics of the Study Sample

In this study, 81% of participants were men and 19% were women. The sample was diverse in terms of race/ethnicity with 59% of participants being African-American (n=19) and 28% Caucasian (n=9). Most people were single and had never been married (63%). The highest level of education obtained for most was some college or trade school (34%) closely followed by those a high school degree (31%). Seventy-two percent of participants were currently employed, and, of the 69% that had health insurance in the year prior to their HIV diagnosis, 59% obtained in from their employer. These characteristics are further described in Table 3.

Fifteen participants (46.9%) were over 24 years of age. The men were slightly older than the women; the mean age of the men was 29.6 years (range, 19 to 63) and the mean age of the women was 27.3 years (range, 21 to 28) but this different is not statistically significant. The mean age of the men who self-identified as straight (n=6) was 38.3 years old (range, 19 to 63), but the actual distribution was bimodal with 50% being 19 to 22 years of age and 50% 50 to 63 years of age. The men who identified as bisexual were a mean of 22 years of age (range, 19 to 25), and the men who identified as gay were a mean of 29.8 years of age (range, 19 to 51). None of the differences in average age by gender of sexual orientation were statistically significant.

All women (n=6) identified as straight and only reported male sexual partners. Twenty-two men (84.6%) reported having male sexual partners, and 42.3% of men reported having female sexual partners. Of the 6 men who identified as straight, 100% had female sexual partners, and 2 (33.0%) also had male sexual partners. Of the 7 men who identified as bisexual, 5 (71.0%) had female sexual partners and all 7 (100%) had male sexual partners.
the 13 men who identified as gay, none had female partners and all had male partners. Neither males nor females reported having transgender sexual partners.

**HIV Transmission Risk Behaviors of the Study Sample**

The mean number of lifetime sexual partners of participants was 67 but the median number was 20 (range, 1 to 1,000). Men and women who identified as straight had a mean of 17 and a median of 11 lifetime sexual partners (range, 1 to 72); straight identified men had a mean of 26 and a median of 20 partners (range, 1 to 72), and straight identified women had a mean and median of 9 partners (range, 1 to 19). Bisexual men had a mean of 22 and a median of 12 partners (range, 1 to 54), and gay identified men had a mean of 137 and a median of 50 partners (range, 2 to 1000). The difference between the means of lifetime sexual partners based upon gender or sexual orientation is not statistically significant.

No participant reported that they had injected any nonprescription drugs in the year prior to HIV diagnosis. All details on types of sexual activity are reported by sexual orientation and gender in Table 4. While no gay men reported any sexual acts with female partners, at least a third of straight men reported sexual acts with steady and casual male partners. No straight men reported having insertive anal sex with another man but several reported having receptive anal sex with a male partner. More bisexual men reported sexual acts with male partners (29-71% reported various sexual acts with a male partner) than with female partners (14-29% reported various sexual acts with a female partner). All gay men reported having unprotected oral sex with a steady male partner and 85% of gay men reported unprotected receptive anal sex with a steady male partner. No men reported having anal sex with women. No woman reported vaginal or anal sex with a casual male partner (Table 4). For all, it was unclear whether the study participant was the receptive or performing partner for the oral sex acts reported.
Sexually Transmitted Infections

Eight participants (25%) reported that at some point in their life, a doctor or health department official informed that they had gonorrhea. Five participants (16%) had been told that they had chlamydia at some point and another 5 people had been informed that they had hepatitis. Four people (13%) reported that they had syphilis at one time. The incidence of these and other STIs are reported in Table 5.

History of HIV Testing

Of the 32 participants, 4 (12.5%) had only ever tested once for HIV and at that test was diagnosed with HIV and 5 people (15.63%) had tested twice. Eleven people (34.4%) had tested 3 to 4 times, and 8 people (25%) had tested 5 to 10 times. Four people (12.5%) had tested more than 10 times for HIV (range 12 to 25). One person (3.13%) said that they voluntarily tested for HIV yearly, twelve people tested for HIV every 6 months (37.5%) and 2 people (6.25%) tested every 3 months.

These reasons people reported for HIV testing, which are not mutually exclusive, are reported in Table 6. Seventy-five percent of the participants reported their own personal reasons for being tested for HIV. Fifty-six percent of participants tested because they had had unprotected anal sex with a man and 56% tested because they wanted the reassurance that they were HIV negative. Ten people (31%) report having a HIV tested because they were having ARS symptoms. Other reasons frequently reported include that the HIV test was part of a routine medical exam (25%), symptoms of another STI were present and so decided to be evaluated for all STIs (16%), and their sex partner is HIV-positive (16%).

ARS and Medical Evaluation

Of the 32 participants in the study, 25 (78.1%) reported being sick at some point in the 3 months prior to their first positive HIV test. Of these 25 people, 20 (80.0%) sought medical
attention for the illness. The 5 people who felt ill but did not seek medical attention named several non-mutually exclusive reasons for this. Three (60.0%) reported that they did not seek medical attention because of the cost of medical care or insurance issues and 3 (60.0%) reported that their symptoms were not severe enough to warrant it. Two people (40.0%) did not seek medical care because the symptoms resolved on their own. Only 6 participants (18.8%) reported that they had ever heard of AHI. Of the 20 people who sought medical care for their illness, 5 (25.0%) reported that at that visit the provider suggested the possibility that the patient had AHI.

Of those that experienced symptoms, the most common symptoms reported were fever (80%), loss of appetite/weight loss (76%), gastrointestinal upset (68%), and sore throat (64%). The incidences of various symptoms of ARS are further described in Table 7.

Medical Care for HIV

Twenty-one of the participants (65.6%) said that they already had a routine provider who is managing their HIV infection at the time of their interview and all these people’s provider is a specialist in HIV/AIDS. Five (23.8%) of these patients have routine follow-up visits with their HIV provider every month and 6 (28.6%) follow-up every 1-3 months. Thirteen of the participants (40.63%) reported that they were already currently on ART.
Table 3. Demographic Characteristics of People with Acute HIV Infection in NC during 1/2003 - 12/2004

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (%) (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>26(81.3)</td>
</tr>
<tr>
<td>Female</td>
<td>6(18.8)</td>
</tr>
<tr>
<td><strong>Age, mean years [SD] (range)</strong></td>
<td>29 [12] (19, 63)</td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>19 (59.4)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>9 (28.1)</td>
</tr>
<tr>
<td>Latino</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td><strong>Relationship Status</strong></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>3 (9.4)</td>
</tr>
<tr>
<td>Single, never been married</td>
<td>20 (62.5)</td>
</tr>
<tr>
<td>Long-term relationship with a partner</td>
<td>5 (15.6)</td>
</tr>
<tr>
<td>Divorced</td>
<td>3 (9.4)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>5 (15.6)</td>
</tr>
<tr>
<td>High school or obtained GED</td>
<td>10 (31.3)</td>
</tr>
<tr>
<td>Some college or technical trade school</td>
<td>11 (34.4)</td>
</tr>
<tr>
<td>4 year college degree</td>
<td>3 (9.4)</td>
</tr>
<tr>
<td>Graduate or professional school</td>
<td>3 (9.4)</td>
</tr>
<tr>
<td><strong>Employed</strong></td>
<td>23 (71.9)</td>
</tr>
<tr>
<td><strong>Sexual Identity of Men</strong></td>
<td>n=26</td>
</tr>
<tr>
<td>Straight</td>
<td>6 (23.1)</td>
</tr>
<tr>
<td>Bisexual</td>
<td>7 (26.9)</td>
</tr>
<tr>
<td>Gay</td>
<td>13 (50.0)</td>
</tr>
<tr>
<td><strong>Any Kind of Health Care Coverage in Yr Prior to HIV+ Test</strong></td>
<td>n=22 (68.8)</td>
</tr>
<tr>
<td>Private Health Insurance Plan from Employer or Workplace</td>
<td>13 (59.1)</td>
</tr>
<tr>
<td>Private Health Insurance Plan Purchased Directly</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Medicare</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Medicaid/Medical Assistance/Other State Program</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>On Parents Insurance Plan</td>
<td>7 (31.8)</td>
</tr>
</tbody>
</table>
Table 4. HIV Risk Factors in Year Prior to HIV Diagnosis By Gender and Sexual Orientation

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Women (n=6)</th>
<th>All Men (n=26)</th>
<th>Straight Men (n=6)</th>
<th>Bisexual Men (n=7)</th>
<th>Gay Men (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With a steady female partner</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral Sex</td>
<td>0</td>
<td>4 (15.4%)</td>
<td>3 (50.0%)</td>
<td>1 (14.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Protected Vaginal Sex</td>
<td>NA</td>
<td>4 (15.4%)</td>
<td>2 (33.0%)</td>
<td>2 (28.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Unprotected Vaginal Sex</td>
<td>NA</td>
<td>6 (23.0%)</td>
<td>4 (66.7%)</td>
<td>2 (28.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Protected or Unprotected Anal Sex</td>
<td>NA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>With a casual female partner</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral Sex</td>
<td>0</td>
<td>3 (11.5%)</td>
<td>2 (33.0%)</td>
<td>1 (14.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Protected Vaginal Sex</td>
<td>NA</td>
<td>3 (11.5%)</td>
<td>2 (33.0%)</td>
<td>1 (14.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Unprotected Vaginal Sex</td>
<td>NA</td>
<td>3 (11.5%)</td>
<td>3 (50.0%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Protected or Unprotected Anal Sex</td>
<td>NA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>With a steady male partner</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protected Oral Sex</td>
<td>0</td>
<td>2 (7.7%)</td>
<td>0</td>
<td>2 (28.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Unprotected Oral Sex</td>
<td>5 (83.3%)</td>
<td>20 (76.9%)</td>
<td>2 (33.0%)</td>
<td>5 (71.4%)</td>
<td>13 (100%)</td>
</tr>
<tr>
<td>Protected Vaginal Sex</td>
<td>2 (33.3%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Unprotected Vaginal Sex</td>
<td>4 (66.7%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Protected Receptive Anal Sex</td>
<td>0</td>
<td>15 (57.7%)</td>
<td>2 (33.0%)</td>
<td>4 (57.1%)</td>
<td>9 (69.2%)</td>
</tr>
<tr>
<td>Unprotected Receptive Anal Sex</td>
<td>1 (16.7%)</td>
<td>16 (61.5%)</td>
<td>1 (16.7%)</td>
<td>4 (57.1%)</td>
<td>11 (84.6%)</td>
</tr>
<tr>
<td>Protected Insertive Anal Sex</td>
<td>NA</td>
<td>12 (46.1%)</td>
<td>0</td>
<td>4 (57.1%)</td>
<td>8 (61.5%)</td>
</tr>
<tr>
<td>Unprotected Insertive Anal Sex</td>
<td>NA</td>
<td>12 (46.1%)</td>
<td>0</td>
<td>4 (57.1%)</td>
<td>8 (61.5%)</td>
</tr>
<tr>
<td>With a casual male partner</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protected Oral Sex</td>
<td>0</td>
<td>3 (11.5%)</td>
<td>0</td>
<td>3 (42.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Unprotected Oral Sex</td>
<td>2 (33.3%)</td>
<td>16 (61.5%)</td>
<td>2 (33.0%)</td>
<td>4 (57.1%)</td>
<td>10 (76.9%)</td>
</tr>
<tr>
<td>Protected Receptive Anal Sex</td>
<td>0</td>
<td>15 (57.7%)</td>
<td>2 (33.0%)</td>
<td>4 (57.1%)</td>
<td>9 (69.2%)</td>
</tr>
<tr>
<td>Unprotected Receptive Anal Sex</td>
<td>0</td>
<td>10 (38.5%)</td>
<td>1 (16.7%)</td>
<td>3 (42.9%)</td>
<td>6 (46.1%)</td>
</tr>
<tr>
<td>Protected Insertive Anal Sex</td>
<td>NA</td>
<td>11 (42.3%)</td>
<td>0</td>
<td>3 (42.8%)</td>
<td>8 (61.5%)</td>
</tr>
<tr>
<td>Unprotected Insertive Anal Sex</td>
<td>NA</td>
<td>9 (34.8%)</td>
<td>0</td>
<td>3 (42.9%)</td>
<td>6 (46.1%)</td>
</tr>
</tbody>
</table>

Table 5. Lifetime Incidence of STIs

<table>
<thead>
<tr>
<th>History of STI</th>
<th>Number of People (%) (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes</td>
<td>2 (6.3%)</td>
</tr>
<tr>
<td>Genital Warts</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>5 (15.6%)</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>8 (25.0%)</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>5 (15.6%)</td>
</tr>
<tr>
<td>Syphilis</td>
<td>4 (12.5%)</td>
</tr>
</tbody>
</table>
Characteristics of People with AHI in NC Shaw

Table 6. Reasons for Voluntarily Seeking an HIV Test

<table>
<thead>
<tr>
<th>Reasons for HIV testing at time of + test</th>
<th>Number of people (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Had Unprotected Vaginal Sex with a Woman (n=26)</td>
<td>3 (11.5%)</td>
</tr>
<tr>
<td>Had Unprotected Anal Sex With a Man</td>
<td>18 (56.3%)</td>
</tr>
<tr>
<td>Shared Needles or Syringes</td>
<td>0</td>
</tr>
<tr>
<td>Undefined High Risk Exposure</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Contacted By DIS Regarding Exposure</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Sex Partner is HIV-Positive</td>
<td>5 (15.6%)</td>
</tr>
<tr>
<td>Sex Partner may be HIV-Positive</td>
<td>2 (6.3%)</td>
</tr>
<tr>
<td>Sex Partner Asked You To</td>
<td>4 (12.5%)</td>
</tr>
<tr>
<td>Part of a Routine Physical Examination or Medical Check-Up</td>
<td>8 (25.0%)</td>
</tr>
<tr>
<td>Wanted Reassurance, Make Sure You Were Negative</td>
<td>18 (56.3%)</td>
</tr>
<tr>
<td>Symptoms of ARS</td>
<td>10 (31.3%)</td>
</tr>
<tr>
<td>Symptoms of Other STI</td>
<td>5 (15.6%)</td>
</tr>
<tr>
<td>Routine Practice</td>
<td>3 (11.5%)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Any Other Reasons</td>
<td>24 (75.0%)</td>
</tr>
</tbody>
</table>

Table 7. Incidence of ARS Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number of people (%) (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>25 (78.1%)</td>
</tr>
<tr>
<td>Fever</td>
<td>20 (62.5%)</td>
</tr>
<tr>
<td>Sore Throat</td>
<td>16 (50.0%)</td>
</tr>
<tr>
<td>Skin Rash</td>
<td>10 (31.3%)</td>
</tr>
<tr>
<td>Stomach Complaints (diarrhea, nausea/vomiting)</td>
<td>17 (53.1%)</td>
</tr>
<tr>
<td>Loss of appetite/weight loss</td>
<td>19 (59.4%)</td>
</tr>
<tr>
<td>Sores/ulcers on genitals</td>
<td>2 (6.3%)</td>
</tr>
<tr>
<td>Other</td>
<td>16 (50.0%)</td>
</tr>
</tbody>
</table>

Discussion

Comparison of Findings in Present Study and the Systematic Review

Our cohort was younger than previous cohorts in NC as we had 47% of participants were over 24 years of age where as Pilcher, et al. found that 70% of the NC population was over 24 years of age. Pao, et al. found that a younger age, high rate of unprotected anal intercourse, and high rate of sexual partner change was more likely to transmit HIV during the AHI stage.

The population in this study consists of very few women and this trend was seen throughout the systematic review as well. While it is feasible that fewer women present with
HIV due to the large amount of virus transmission that occurs in MSM networks, the low numbers of women detected could also be exacerbated perhaps by women not seeking HIV testing until later stages of the virus. Alternatively, women could be seeking testing from private physicians. Perhaps a future research could analyze the incidence of AHI among women strictly at alternative sites where women may seek care more frequently such as family planning, STD clinics, or private physicians. The fact that MSM may test more than heterosexuals due to perceived risk of HIV infection, and therefore be more likely to be diagnosed earlier in infection, could also begin to explain the large number of men present in these studies.

Despite the trend that HIV-positive MSM have fewer sexual partners than did MSM a decade ago, HIV acquisition continues to occur with increasing incidence. This trend may be because people at risk for HIV have oral-genital contact more frequently than anal-genital contact. Oral-genital contact is receiving more attention as an important risk factor for HIV acquisition and appears to be warranted. Unprotected oral-genital contact is a safer form of sex and not very efficient for HIV transmission compared with unprotected receptive anal sex but many reports of HIV transmission by oral-genital transmission have now been detected. But because oral-genital contact is a common unprotected sexual activity, increased attention to oral-genital contact as a risk factor for HIV is warranted. Therefore, although there may be less likelihood of transmission per act of oral-genital contact compared to anal-genital contact, oral-genital contact is so much more frequent than anal-genital contact that the actual rate of transmission for the acts may be closer than originally suspected. Also, people with AHI who report mainly protected vaginal/anal sex and unprotected oral sex may not have recognized or reported condom breakage or slippage. Therefore, people who report oral sex as their only route of exposure to HIV may have actually been unknowingly been exposed to HIV through the vaginal or anal canal by the improper use of condoms.
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The potential inclusion of all people undergoing state-funded HIV testing performed over two years in this study helps ensure that this research accurately reflects most people who are diagnosed with AHI in public health practice. The validity of our findings to other states or to private medical-practice settings is less clear, although other preliminary data strongly suggest that many other testing populations, such as people who are diagnosed at an urgent care, emergency department, or a high-risk clinic, are expected to harbor a similar if not greater numbers of people with AHI.

Study Limitations

Our study population certainly could have been biased by volunteerism, as well as care-seeking and testing behaviors. Also, we had no way of confirming the self-reported data of the participants. Among groups with high risk behaviors there are often high rates of anonymous sexual partners and a difficulty in obtaining a reliable sexual history. If collection of sexual histories had been more anonymous, we might have obtained different data on the frequency of unprotected high-risk sexual behaviors in our cohort, but the case reports and consistency of our observations suggest that the reported information is valid. Unfortunately, the small sample size makes it possible that real differences might not have been detected or found to be statistically significant. The power to detect a difference across groups of potential interest is quite limited here. Also, because we did not have a control group, we could not calculate the relative risk of risk behaviors for transmission of HIV.

In addition, the data entry did not occur until several years after the data collection. This led to some ambiguously recorded or contradictory responses and could contribute to measurement bias. A decision rule was created but in some cases the true response was unable to be assessed or recorded.

AHI Diagnosis and Prevention
The prevalence of HIV is increasing and efforts to create a vaccine or medical cure for HIV have been unsuccessful. Therefore, in order to halt the spread of HIV, innovative prevention programs are essential. Fortunately, new, more effective public health approaches to HIV are being created, many due to our increased understanding of the infectiousness of AHI and HIV transmission during this stage. The early diagnosis of HIV infection has long been recognized as an essential component in the reduction of HIV transmission. Epidemiologic investigation into AHI, such as was presented here, helps efficiently interrupt ongoing HIV transmission by identifying settings and populations where AHI interventions or educational efforts could yield substantial number of new diagnoses and prevented infections. Any prevention programs aimed at controlling AHI transmission must intervene during the first month or two after infection as well as be sustained for long-term risk reduction in order to have maximal effect. However, intervening in AHI first requires that first an AHI diagnosis is made in a timely and accurate manner. For an AHI intervention to be truly successful and achieve substantial results quickly, it must be based upon early testing and rapid, efficient, and active results notification procedures all aimed at the earliest possible time point.

Clinical Case Finding

For many reasons, AHI is rarely diagnosed in clinical settings, and when people present with ARS, and they often do, that is often misdiagnosed. These diagnostic errors would be less likely to occur if sexual and risk behavior histories were obtained more frequently. A comprehensive history is essential for quality medical care, and a sexual history should be taken for every person who presents with fever, sore throat, lymphadenopathy, or symptoms of viral meningitis. AHI should be in the differential diagnosis for patients presenting with any viral symptoms as the benefits of AHI detection and diagnosis to individuals and society is so large. It is staggering to think of the number of missed opportunities for HIV diagnosis that occur among people presenting to emergency rooms or outpatient clinics with the nonspecific
symptoms of ARS and are not questioned about HIV risk factors and testing. One study found that almost 1% of the samples taken for EBV tests had unrecognized AHI when screened with group NAAT.\(^6\) Even among people at high risk for acquiring HIV and who are enrolled in routine HIV surveillance programs, AHI is often not diagnosed. In a study of homosexual men in the Netherlands who were undergoing routine serologic HIV testing every 4 to 6 months and were diagnosed with HIV, ARS was correctly diagnosed in only 26%\(^6\). Several studies have clearly shown that clinicians do not frequently include ARS in the differential of acutely ill outpatients with viral symptoms, especially during the initial workup.\(^10,26\) Unfortunately, no practical way to routinely and confidently exclude AHI as a cause of ARS symptoms on a clinical basis alone exists. Therefore, to make the appropriate diagnosis, specific laboratory testing must ensue.\(^63\)

Some people advocate that HIV testing should be conducted on a voluntary basis as a part of routine medical care by all primary care providers similar to other diagnostic and screening tests such as Pap smears and cholesterol screens. The CDC recommends offering HIV testing to all patients in all high HIV-prevalence clinical settings and in clinical settings serving populations at increased risk as well as to all those at risk for HIV no matter the HIV-prevalence. The CDC states that prevention counseling, while recommended, should not be a barrier to testing and so is no longer required prior to HIV testing.\(^5\)

There are many reasons that ARS may not be recognized by clinicians. People may undergo voluntary HIV testing anonymously at a site different from where they would seek medical care for viral-like ARS symptoms. This may be due to a desire that their sexual and drug use history not be included in their formal medical record.\(^62\) Especially in the past, a large amount of stigma has been connected with a positive HIV diagnosis, even in high risk networks, vigorous, which can hinder public health HIV prevention interventions.\(^17\) Also, ARS symptoms are nonspecific and similar to those of other common, self-limited viral infections. These testing
realities must be remembered when doing epidemiologic studies and incorporated into public health interventions for reducing HIV transmission.\textsuperscript{62}

Currently, most clinicians test for AHI somewhat arbitrarily, by making educated guesses, rather than by being systematic\textsuperscript{63} which leaves many missed opportunities for early treatment and prevention of HIV transmission.\textsuperscript{55} Providers should become more liberal in testing for AHI and HIV.\textsuperscript{63} Clinicians need to have a high index of suspicion for AHI whenever appropriate and be more proactive about obtaining accurate risk histories, especially from patients who might present to emergency departments or walk-in clinics with ARS-like symptoms.\textsuperscript{10} Clinicians must remember that they may be ignorant of their patients HIV risk factors and testing habits. Clearly, additional efforts to improve clinical recognition of AHI are needed in order to increase the sensitivity and timeliness of diagnosis. Perhaps educational efforts should target health care providers and stress the need to ask about risk behaviors and to consider the diagnosis of ARS in persons at risk, even if symptoms widely vary.\textsuperscript{55}

\textbf{AHI Screening}

A recent public health HIV transmission prevention strategy implemented is AHI screening.\textsuperscript{6} Perhaps the biggest impact of AHI screening is that individuals who consider themselves at risk for HIV and seek testing can also be tested for AHI without the requirement of physician intervention or special request.\textsuperscript{6} Targeting AHI testing only to people who clinicians suspect have ARS can be counterproductive compared to population based screening. One study found that only 30\% of patients had ARS at the time they had a positive NAAT test.\textsuperscript{30} HIV testing outside of the traditional medical setting, such as in correctional facilities, could reach many more individuals.\textsuperscript{5}

The current HIV screening system fails to detect AHI at multiple points beginning at the failure to recognize ARS symptoms, initial HIV antibody-based testing, the standard recommendation to retest in a few months, and by failure to achieve follow-up of high risk
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In order to improve the diagnosis of this deadly disease, it is essential that the public health AHI actions are an integrated approach involving medical and community service providers as well as public health leaders. The same principles necessary for HIV prevention interventions, acute case finding and network intervention, have been also used to interrupt the spread of other STIs such as syphilis. Public health actions to eliminate syphilis have been notoriously successful in recent years and have broad political and community support despite its sexual transmission. Unfortunately, unlike syphilis, HIV cannot be cured once one is infected and high risk networks are notoriously hard to identify.

AHI screening, if done on a population basis, can facilitate epidemiologic investigation into risk networks leading to the early detection of HIV infection outbreaks. In NC, young black MSM were involved in an ongoing HIV outbreak and detected by epidemiologic analysis of people with AHI detected by screening. As this network was detected early, it serves as a good example of the sensitivity that AHI identification can have in pinpointing epidemiologic trends even in hidden populations and the effective public health interventions that can result. AHI screening for individuals presenting for routine, voluntary HIV testing at publicly funded sites has been so effective that it has been permanently funded in NC.

Prevention Strategies

The CDC funds health departments and community-based organizations (CBOs) to provide prevention programs that aim to reduce sexual and drug-using risk behavior. Historically, all prevention efforts have been mainly targeted at HIV-negative people at risk for infection. Over the past 25 years, a wide variety of effective strategies to motivate people to protect themselves from acquiring HIV have been created.

Brief, focused, risk-reduction counseling techniques have been demonstrated effective for some. Clinical counseling, even when delivered only once, can result in significant behavioral changes, especially if conducted in “teachable moments” such as when people
present for STI/HIV testing or are receiving the test results as people are more likely to be motivated and attentive when they feel that they or their loved ones are truly at risk.

The CDC conducted a study, Project RESPECT, that demonstrated that two 20 minute HIV risk reduction counseling sessions with HIV testing in the context of STD clinic services reduces risk behavior and recurrent STI treatment as four session enhanced counseling. The reduced counseling utilized a personal risk assessment in addition to risk education and a established relationship between the counselor and client to form an individualized risk reduction plan. This reduced counseling resulted in a 30% reduction in new STIs over the following 6 months and a 20% reduction over a year in people who tested HIV-negative compared to people who received only educational, informational messages – a meaningful reduction.

HIV testing does not necessarily have to occur for risk reduction counseling to be conducted in at-risk populations. Risk reduction counseling could be adapted to the field work involved in network notification efforts which could have a more direct effect on AHI. Other prevention strategies are educational campaigns to promote awareness of HIV and the ARS symptoms targeted to high risk groups which encourage people to seek HIV testing. While knowledge of risk behaviors is helpful, if only people in the highest-risk groups were tested for HIV, the majority of infected individuals would be missed as people in every risk group have a chance of being infected. Physicians must remember that even a single episode of unprotected oral sex or sexual intercourse could be responsible for transmitted HIV infection. In fact, the highest rates of new infections are in people who are not easily defined as very high-risk. Almost any person who was ever sexually active is at risk for being HIV-positive and any person who is currently sexually active is at risk for having AHI. One study found that even people who presented to an urgent care center for an unrelated medical concern were generally amenable to being tested for HIV. However, this urgent care center did have HIV counseling and testing immediately available at that site which is easy to believe might be more likely to
influence patients to accept testing rather than having to make a later appointment or travel to a different location.\textsuperscript{5}

The recent development of new methods of AHI detection may greatly improve our ability to identify and intervene in risk networks. Prevention strategies are now being appropriately developed to identify AHI networks and diagnose AHI, complete partner counseling and referral services in a timely manner, efficiently convince individuals with AHI to reduce their risk behavior, and manage disease. This is all done with the goal of blocking transmission networks in this crucial stage of HIV.\textsuperscript{32,56} Existing HIV prevention programs now need to strongly think about incorporating AHI intervention strategies as well to be more efficient and comprehensive. To truly establish an AHI intervention as necessary, more research is needed into the health outcomes of interventions with modeling exercises and intervention trials.\textsuperscript{17} Overall, an emphasis on greater access to testing and on providing prevention and care services for persons infected with HIV can reduce new infections and lead to reductions in HIV-associated morbidity and mortality.\textsuperscript{4,5}

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