

Assessing the Need for Acute HIV Testing in the Emergency Department

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Abstract

Background: Acute HIV Infection (AHI) is a period during which patients are at their most infectious during a time when, by routine HIV antibody test, they are diagnosed as uninfected [1]. While there have been advances in HIV detection a significant portion of patients remain undiagnosed. This is most frequently the case in countries where antigen testing is still not widely available or not widely chosen by the institution as the preferred method of testing. Many of these undiagnosed patients are acutely infected. A contributing factor is that patients do not always present with complaints of STI exposure or flu-like symptoms of acute infection, and even when they do, these symptoms can be easily misinterpreted or completely missed in the Emergency Department (ED). Even when patients are diagnosed there are still significant delays in linkage-to-care (LTC). The proportion of HIV-infected individuals who are misdiagnosed will increase unless sensitive tests are used to mitigate the expected greater number of false-negative antibody test results during acute and early infection [2]. Once identified more robust LTC needs to be implemented.

Hypothesis: We hypothesize that there have been a significant number of patients presenting to the ED with symptoms of Acute HIV Infection but, due to limitations in testing methods, receive a negative HIV test result.

Methods: This is a retrospective chart review of the medical records of all ED patients that received a first-time diagnosis of HIV using the Oraquick™ screening test and a positive Western Blot confirmatory test during the twelve-month period prior to initiation of acute testing in our ED. Patients were included in the study if they had a minimum of one non-reactive HIV screening test in the ED in the three months prior to the time of HIV diagnosis. Patients with previously documented HIV disease were excluded from the study. One hundred and twenty-five patients were confirmed HIV positive during the study period and 20 met the inclusion criteria. Nineteen patients were stratified into groups based on the chief complaint at the time of the first visit (viral symptoms or other) and interval visits between the visit on which the negative test result and the visit on which the positive test result was obtained. There was incomplete data on the first visit for one of the patients in the cohort. We recorded the laboratory studies that were ordered at the time of those visit(s).

Results: 15.2% of patients who were diagnosed with HIV in a one-year period had made a previous visit to the ED during which they received a negative result on an HIV antibody assay. 40% of the cohort were seen in the ED with viral symptoms prior to their HIV positive result. Males, individuals who self-identify as Black, and patients between the ages of 20 - 40 were more likely to present to the ED with viral syndrome at some point prior to a positive HIV antibody test.

Conclusion: It is impossible to determine how many patients may have presented in the acute phase of infection but did not represent to our ED after the initial visit. This limitation would underestimate the number of cases of acute HIV that are missed each year, and thus lends support for the need for fourth generation HIV testing in the ED. It can be inferred that the availability of antigen-based testing during the “window period” will result in an increase in detection of Acute HIV infection, and thus a decrease in forward transmission of the virus. Even fourth generation HIV testing the LTC rate are still suboptimal.

Keywords: Acute HIV; HIV Testing; HIV Screening; Testing Modalities; Emergency Department

Abbreviations

AHI: Acute HIV Infection; STI: Sexually Transmitted Infection; LTC: Linkage-To-Care; ED: Emergency Department; HIV: Human Immunodeficiency Virus; AIDS: Acquired Immunodeficiency Syndrome; NHAS: National HIV/AIDS Strategy; CDC: Centers for Disease Control and Prevention; LSU: Louisiana State University; CI: Confidence Interval; CD4: Cluster Differentiation 4; NAAT: Nucleic Acid Amplification Test

Introduction

Background

The public health burden created by infection with the Human Immunodeficiency virus (HIV) remains substantial. Medical and social determinants mandate that the needs of four distinct groups be addressed if we are to impact the pandemic. These groups are the known infected who are in care, the known infected who are out of care, the undiagnosed, and the uninfected in whom disease must be prevented. The undiagnosed population in the United States remains significant. At the end of 2020, an estimated 1.2 million persons aged 13 and older were living with HIV infection in the United States and an estimated 14.0% remained undiagnosed [3].

Among the undiagnosed, those who are acutely infected pose the greatest risk for transmission of infection. A Centers for Disease Control and Prevention report found that acute HIV infection constituted nearly half of the undetected HIV cases in low to moderate risk settings [12]. Despite progress in implementation of ED screening for chronic HIV, it is likely that thousands of acute HIV infection cases go undetected in US emergency departments every year [12].

Previous studies have demonstrated that timely linkage to care (LTC) following initial HIV diagnosis is associated with delayed HIV-related complications, decreased cost of care, and possibly decreased risk of disease transmission in the community [13,14]. And yet, early recognition of acute HIV infection remains a significant challenge within the medical community globally. The emergency department (ED) is an important venue for routine HIV screening because it is often used by persons in medically underserved populations with limited access to or use of health care in other settings and with high rates of new HIV diagnoses [15,16]. For more than a decade EDs have successfully identified thousands of previously unrecognized infected individuals (principally by dedicated HIV testing Programs) [17]. Studies focusing on missed diagnosis of acute HIV infection have shown that undiagnosed patients often present to the ED with complaints of acute viral symptoms before serum antibodies are detectable [4]. During this early stage of disease, both viral load and viral shedding are at their highest levels, and persons are extremely infectious [5]. Diagnosis of HIV infection at this stage could facilitate early treatment that would reduce mortality and prevent further transmission by reduction of risk behaviors [6].

While 4th generation tests are more common in the first world, there are significant delays in LTC. A substantial proportion (15% to 30%) of those newly diagnosed in the ED have delayed initial entry into care after being diagnosed or fail to enter into care at all [18,19]. In 2009, the national linkage-to-care (LTC) rate was estimated at 66% [7]. In 2010, the National HIV/AIDS Strategy (NHAS) set a linkage-to-care (LTC) rate goal of 85% within 90 days of HIV diagnosis [20]. Yet, in 2018, only 76% of diagnosed patients were linked to care and only 58% of those linked are retained in care [3].

In 2016 Menon, *et al.* published a review of data from 37 U.S. adult ED HIV testing programs that performed over 200,000 HIV tests and identified approximately 1,800 HIV-infected individuals. They found an overall rate of 74% compared to 76% found in a systematic review and meta-analysis by Marks, *et al.* [20,21].

With delays in the recognition of HIV infection those acutely infected are actively replicating virus without an antibody response. This six-to-eight-week period is traditionally referred to as the window period. During this stage, the high viral load causes a symptomatic viral syndrome in many individuals. The symptoms are vague and non-specific, like those exhibited with other viral infections. These

symptoms include fever, muscle and joint ache, rash, sore throat, nasal congestion, night sweats and headache. These acutely infected patients, testing negative for antibodies, represent a missed opportunity for early detection, education, and treatment referral. Failure to diagnose HIV in these patients poses a potential public health risk since they are discharged from care, having been told that their HIV status is negative. Acutely infected patients thus leave the ED with a false sense of security and lack the knowledge that they can spread the virus to others. Diagnosis of infection is important because persons aware of their infection tend to be less likely to engage in risky sexual behaviors than unaware person [11].

New HIV screening tests are available to detect HIV infections prior to antibody response but are not universally available in all countries. These fourth generation HIV tests detect viral antigen and are recommended by the CDC [8]. We hypothesized that there were a significant number of patients who present to the ED with symptoms of acute viral syndrome and received a negative HIV screening result due to limitations in antibody-based testing methods at the time of this study. Today utilization of fourth generation HIV test in EDs has increased in the first world, however significant delays in LTC among the acutely infected remain [3].

The Centers for Disease Control and Prevention (CDC) key strategies to control the HIV epidemic include routinizing HIV testing and linking newly diagnosed patients to care in healthcare settings, including emergency departments [12].

Materials and Methods

Study design

This was a retrospective chart review of the medical records of all ED patients that received a first time diagnosis of HIV using the Oraquick™ screening test during the twelve month period preceding transition to fourth generation antibody testing. The electronic medical records of these patients were reviewed to determine whether they had a previously negative Oraquick™ and/or a previous ED visit for symptoms of acute viral syndrome, and to determine which laboratory studies were ordered at the time of those visit(s). Patients were included in the study if they received a reactive Oraquick™ screening HIV test in the ED during the study period and had a positive confirmatory Western Blot AND had a minimum of one non-reactive HIV screening test in the three months prior to the time of HIV diagnosis OR had an ED visit in the preceding three months for a complaint of viral symptoms. Patients with previously documented HIV disease were excluded from the study.

Using this method, we identified 125 patients who tested positive during the study period. Twenty patients met the inclusion criteria (Table 1). The narrative record for the first visit was missing from the chart of one patient. We divided the remaining 19 patients in the cohort into four groups (Table 2):

1. **Group A:** Prior to the visit on which they tested positive, were seen in ED for viral symptoms and had a negative result.
2. **Group B:** Prior to the visit on which they tested positive, were seen in ED for other complaints unrelated to viral syndrome and had a negative result.
3. **Group C:** Prior to the visit on which they tested positive, had a negative result followed by an ED visit(s) for symptoms unrelated to viral syndrome.
4. **Group D:** Prior to the visit on which they tested positive, had a negative result followed by an ED visit(s) for viral symptoms.

Descriptors	n = 20	Percentage (%)
Sex		
Male	18	90
Female	2	10
Age		
20 - 29	9	45
30 - 39	5	25
40 - 49	2	10
> 50	4	20
Race		
African American	14	70
White	6	30

Table 1: Study population.

Note: Study conducted in a large, urban public teaching hospital in a city with a high prevalence of HIV.

Groups	Criteria	
Group A	Prior to the visit on which they tested positive, were seen in ED for viral symptoms and had a negative result.	More likely AA (CI = 95%, 0.857 - 1.661); Female (CI = 95%; 0.657 - 11.519), Age 20 to 40 (CI = 95%; 0.41 - 1.43)
Group B	Prior to the visit on which they tested positive, were seen in ED for other complaints unrelated to viral syndrome and had a negative result.	Less likely AA (95%; CI = 0.603 - 1.167), male (95%; CI = 0.775 - 3.453). No significance with age
Group C	Prior to the visit on which they tested positive, had a negative result followed by an ED visit(s) for symptoms unrelated to viral syndrome.	More likely AA (CI = 95%; 0.568 - 1.942), Male (CI = 95%; 0.568 - 1.942), No significance with age
Group D	Prior to the visit on which they tested positive, had a negative result followed by an ED visit(s) for viral symptoms.	More likely AA (CI = 95%; 0.568 - 1.942), Male (CI = 95%; 0.568 - 1.942), No significance with age

Table 2: Cohorts.

Population

The study was conducted in a large, urban public teaching hospital located in a city with a high prevalence of HIV infection and was approved by the Institutional Review Board. Interim LSU Hospital was the only hospital in the city of New Orleans operating as a public charity hospital at the time of the visits included in this study. Internal surveillance by our Laboratory Department and Infection Control indicated that 1.8% of all tests performed in our ED were positive during the testing period.

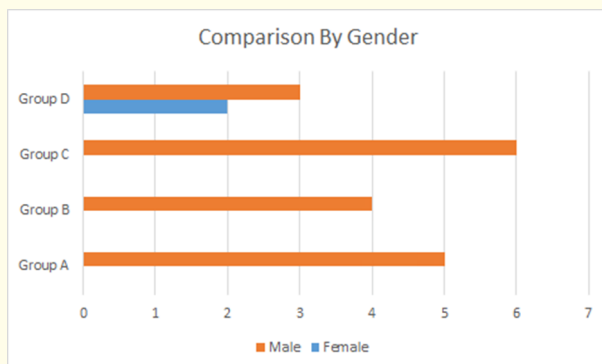
Data analysis

For binary data, simple percentages were calculated, and chi squared test analysis was performed. For descriptive data, estimates and 95% confidence intervals were calculated. Analysis of continuous variables as compared to published population data in these categories were performed using the unpaired t-test.

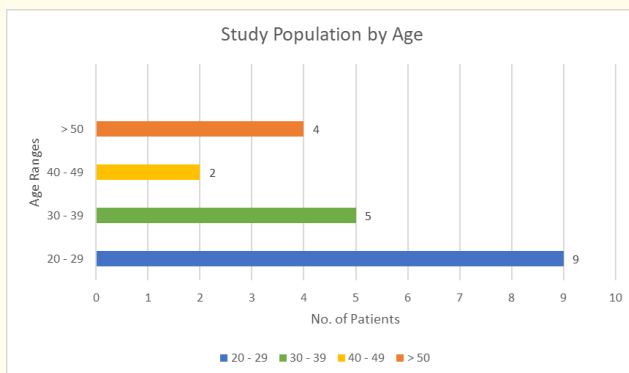
Results

A total of 20 patients met the inclusion criteria for the study. There was incomplete data on the first visit of one patient. She is included in the demographic data for the cohort, but not in the analysis of the groups. Of the cohort of 20 patients, 70% were African American and

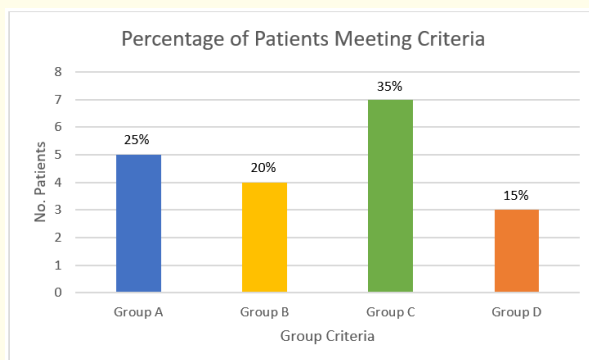
90% were males (Graph 1). Forty five percent were between the ages of 20 and 29 years, 25% were between 30 and 39 years, 10% were between 40 and 49 years, and 20% were over the age of 50 years (Graph 2). Of the cohort of 19 patients, 25% met the inclusion criteria for Group A, 20% for Group B, 35% for Group C, and 15% for Group D (Graph 3).



Graph 1: Comparison of groups by gender.



Graph 2: Study population by age.



Graph 3: Patients meeting criteria.

Group A patients had no interval visits between the visit on which they complained of viral symptoms and received a negative result and the visit on which they received a positive result. Group A patients were more likely to be African American (CI = 95%, 0.857 - 1.661), female (CI = 95%, 0.657 - 11.519), and to be between the ages of 20 to 40 years old (CI = 95%, 0.41 - 1.43).

Group B patients, those who were seen for non-viral symptoms and had no interval visits between the visit on which they tested negative and the visit on which they tested positive, were less likely to be African American (95% CI = 0.602 - 1.167) and less likely to be male (95% CI = 0.775 - 3.453). There was no statistically significant relationship with age.

Forty percent of the cohort (Groups A plus D) were seen for viral symptoms prior to the visit on which they tested positive. Half of these were African American, and all were males. Their ages were evenly distributed among the four groups (twenties, thirties, forties and > 50 years). On the visit(s) on which they tested negative, 100% had a chest radiograph, liver function tests, and a complete blood count and 25% of the had a CD4 count sent.

Patients who had an interval visit (Groups C plus D) were more likely to be African American (CI = 95%, 0.568 to 1.942) and male (CI = 95%, 0.568 to 1.942). Age was not a statistically significant factor.

Group D patients had an interval visit for viral symptoms between a visit with a negative result and a visit with a positive result. All of these patients were African American and one third of them were males. Two thirds were 35 to 39 years of age and one third were between 50 - 54 years. All these patients had a chest radiograph, liver function tests, and a complete blood count. Two thirds of them had a repeat HIV antibody screening test. One third had a CD4 count sent.

Discussion

During the past decade, there have been advances in technology that allow for rapid detection of acute HIV infection, but this technology is not globally available [22]. One of the most significant limitations to the antibody assay still in use in many countries remains the decreased ability to detect acute HIV infection [9]. Fourth generation testing modalities provide real-time results and are well suited to an emergency department environment where patient follow up is limited. Assays which detect p24 antigen in addition to IgM and IgG HIV antibodies using the third-generation techniques, and nucleic acid amplification test (NAAT) can detect persons with acute HIV infection (AHI) [11]. The current CDC guidelines for HIV screening in adults were established in 2006 and have not changed for the general population. They recommend routine screening in populations where the prevalence is 0.1% or greater [23]. Testing recommendations for gay, bisexual and other men who have sex with men were revised in 2017. Despite the fact that general testing recommendations have not been revised, recent CDC data reports that the United States has still not succeeded in meeting targeted testing benchmarks [24]. Review of the literature suggests many of those undiagnosed are acutely infected and this poses a significant public health risk. For this retrospective analysis, we attempted to determine if cases of acute HIV were going undiagnosed because of the use of antibody only testing technology in our ED.

Over the course of one year, we identified 20 patients with documented seroconversion within a three month period. Each of these patients had at least two ED visits in this time, which demonstrates the existence of a population of patients seeking care in the ED during the months leading up to HIV seroconversion. Of those 20 patients, those in groups A and D presented with acute viral symptoms prior to the visit where they tested positive. This suggests that patients may be presenting to our emergency department with symptoms of acute HIV yet are being misdiagnosed due to the limitations of our then current testing modality. Those in group D had an interim visit during an identifiable period of seroconversion and tested HIV negative on an antibody screening assay. These cases may represent syndromic acute HIV infection and raise concern that antibody testing was not robust enough to detect a significant number of HIV cases presenting to this

emergency department. Furthermore, one third of the patients in group D had a CD4 count ordered by the clinician. This suggests a very high level of clinical suspicion for HIV by the ordering physician, and an attempt to make the diagnosis in the absence of antigen testing.

In 2011 New Orleans had the second highest estimated rate of HIV infection in the United States, behind Miami [10]. While our data does suggest that patients presenting to the ED with acute viral symptoms are more likely to be African American and male, our significant rate of infection argues against the idea of a testing model based on risk stratification. Our demographic data does include both males and females, as well as subjects from multiple racial and ethnic backgrounds. This lends support for a testing protocol that will capture all patients.

On June 27, 2014 the CDC published updated guidelines for laboratory testing for the diagnosis of HIV infection. These guidelines recommended an HIV 1/2 antigen/antibody combination immunoassay as the initial test of choice in the current algorithm [8]. The data from this retrospective analysis supported the need for wider adoption of the CDC's most current laboratory guidelines.

Limitations of the Study

The major limitation to this study is our inability to discern if these patients were truly in the acute phase of HIV infection and if they would have tested positive using a fourth-generation system. This study is also limited by our inclusion of only patients for whom a window of seroconversion is known. It is impossible to determine how many patients may have presented in the acute phase of infection but did not re-present to our ED after the initial visit. This limitation would underestimate the number of cases of acute HIV that are missed each year, and thus still lends support for the need for fourth generation HIV testing in the ED.

This study was conducted at an urban teaching hospital in a city with a high incidence and prevalence of HIV. The results may not be generalizable to non-academic, non-safety net hospitals or to areas where HIV incidence and/ or prevalence is low. Another limitation is the small cohort size. Although 20 patients is a significant number to meet the inclusion criteria in a 12 month period, increasing the scope of the study to include additional time periods would certainly result in a larger cohort. While data from New Orleans may not generalize to all populations, we believe that the potential impact of early diagnosis in the window period will be of universal benefit and most impactful in populations with higher than average prevalence. These conclusions would also be generalizable to nations with a moderate to high incidence and prevalence of the disease and should indicate the need for the introduction of antigen identifying testing technology globally.

Conclusion

Nineteen of the 125 patients (15.2%) who tested positive for HIV antibodies during the 12 month study period had a previous negative HIV antibody test in the months prior to seroconversion. At the time of or shortly after those negative tests, 40% of these patients were evaluated in the ED for viral symptoms and were most likely in the acute phase of HIV infection. Males, individuals who self-identify as Black and patients between the ages of 20 - 40 are more likely to present to the ED at some point with viral syndrome. The interval negative HIV antibody test represents a missed opportunity for early intervention and treatment, as well as a public health risk to the partners of patients under the mistaken impression that they cannot transmit HIV. When exclusively using HIV antibody testing systems, a significant number of HIV cases are likely remaining undiagnosed despite large-scale screening. It is reasonable to assume that if antigen testing were available and patients were diagnosed in the acute phase ("window period"), transmission of HIV would be reduced. Having introduced opt out universal fourth generation testing in our ED, we look forward to assessing the impact on the incidence and prevalence of disease in our community.

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Conflict of Interest

We have no financial interests or conflicts of interest.

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