

Acute Human Immunodeficiency Virus Infection in Patients Presenting to an Urban Urgent Care Center

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Acute infection with human immunodeficiency virus (HIV) is often accompanied by a flu-like illness, and early identification and treatment may help control the infection and prevent transmission. We enrolled patients who presented to an urban urgent care center with any symptoms of a viral illness and any recent potential risk for HIV infection, and we tested them for acute HIV infection using enzyme-linked immunosorbent and RNA assays. Of 499 patients enrolled over a 1-year period, acute HIV infection was diagnosed in 5 (1.0%; 95% confidence interval [CI], 0.1%–1.9%), and chronic HIV infection was diagnosed in 6 (1.2%; 95% CI, 0.2%–2.2%). There were no false-positive results of the RNA assay. No signs or symptoms reliably distinguished patients with acute HIV infection from those who were HIV uninfected. Given the importance of this diagnosis, testing for acute HIV infection using RNA and antibody assays should be offered to all patients in similar settings with viral symptoms and any risk factors for HIV infection.

The majority of the estimated 40,000 new HIV infections in the United States each year are associated with an acute HIV syndrome [1, 2]. This self-limited, flu-like illness, which is characterized by fever, myalgias, arthralgias, lymphadenopathy, pharyngitis, diarrhea, and/or rash, is similar to other, more common viral and bacterial infections, including infectious mononucleosis, streptococcal pharyngitis, and cytomegalovirus infection [2–5]. Although most of these patients present for medical evaluation, acute HIV infection is rarely diagnosed [2, 6]. During the acute phase of infection, patients have high blood concentrations of HIV RNA and negative or indeterminate results of tests for HIV antibodies [7].

The diagnosis and treatment of acute HIV infection may have important clinical and public health benefits. Treatment of patients during the acute phase of HIV infection may improve the rate of response to therapy, decrease the pool of latently infected T cells, and improve HIV-specific immune function [8–12]. If acute HIV infection is not diagnosed, many patients will not be identified until years later, when they develop AIDS [13]. From a public health perspective, identification of patients during this phase of infection can decrease their high-risk behavior, and, because the majority of new HIV infections may be transmitted during primary HIV infection, this could have a substantial impact on subsequent transmission [14–17]. Because this important clinical syndrome is often misdiagnosed as a non-specific viral syndrome, we sought to determine the prevalence of acute HIV infection among patients with symptoms of a viral illness who presented to an urgent care center at an urban teaching hospital.

METHODS

Study population. From 30 March 2000 through 30 March 2001, we enrolled patients who presented to the Urgent Care Center at Boston Medical Center, an urban

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teaching hospital, with viral symptoms and ≥ 1 risk factor for HIV infection, and we tested them for acute HIV infection. Consecutive patients (age, ≥ 18 years) who presented during study hours (weekdays between 9 A.M. and 5 P.M. and some nights and weekends) were screened by a triage nurse for any 1 of the following complaints: rash, myalgias/arthralgias, headache, sore throat, night sweats, oral ulcerations, fatigue, diarrhea, and fever (temperature, $>37.8^{\circ}\text{C}$). Patients with ≥ 1 of these signs or symptoms were invited to speak with an investigator regarding a study of patients with flu-like symptoms. Those who agreed were referred to a research assistant, given a detailed explanation of the study (i.e., that it involved HIV infection), and, if interested, screened for eligibility. Patients were eligible if they had ≥ 1 of the signs or symptoms listed above and ≥ 1 potential risk factor for HIV infection (broadly defined as sexual contact [oral, vaginal, or anal; protected or unprotected] or injection drug, crack cocaine, or alcohol use) within the prior 2 months. Patients were excluded if they were unable to give informed consent in English, had known HIV infection, had previously enrolled in the study, or did not complete the enrollment process. The study protocol was approved by the Human Subjects Committee at Boston Medical Center, and written informed consent was obtained from all subjects.

Clinical assessment of patients. Each patient was interviewed after enrollment to obtain data on demographic characteristics, symptoms of current illness, history of HIV testing and sexually transmitted diseases, and history of alcohol use, drug use, and sexual activity during the prior 2 months. A standardized physical examination was performed by a study physician and included determination of vital signs; presence or absence of rash, lymphadenopathy, pharyngitis, and oral ulcers; and any other notable physical findings.

Laboratory studies. After formal pretest HIV counseling, blood samples were obtained for performance of HIV antibody ELISA (Organon Technica), Western blot (HIV Immunoblot; BioRad), and an HIV-1 RNA assay (Roche Amplicor HIV-1 Monitor 1.0 [Roche Diagnostics Systems]; range of detectability, 400–750,000 copies/mL) and were sent to a clinical laboratory (Quest Diagnostics; Cambridge, MA). Subjects with a negative HIV ELISA result and an HIV RNA level of >2000 copies/mL were considered to have acute HIV infection [18, 19]. Those with a positive HIV ELISA result and confirmatory Western blot finding were considered to have chronic HIV infection, and those with negative results of both HIV ELISA and the HIV RNA assay were considered to be HIV negative.

Follow-up and linkage to care. All subjects made an appointment to return in 1 week to obtain test results and for posttest counseling. Study participants received \$5 for the initial screening visit and \$10 for the follow-up visit. Participants who did not keep their follow-up appointments were contacted by phone and asked to return for their results. Those who tested

positive for either acute or chronic HIV infection were seen by a physician and/or HIV clinical nurse at the time that they received their results and were referred to the HIV Diagnostic Evaluation Unit at Boston Medical Center in accordance with HIV counseling and testing procedures at that institution [20].

Statistical analysis. Clinical data were reviewed by an investigator within 1 week after enrollment to ensure comprehensiveness and internal consistency. Statistical analyses were performed using SAS software, version 8.1 (SAS Institute). Ninety-five percent CIs around prevalence estimates were calculated using the normal approximation of the binomial distribution. The χ^2 test was used to examine the association of specific signs and symptoms with the risk of acute HIV infection, with statistical significance indicated by a 2-sided P value of $<.05$.

RESULTS

Characteristics of the study cohort. During the 1-year study, 1366 patients presenting for urgent care with ≥ 1 symptom of a viral illness were screened for study participation. Of these, 831 (61%) declined participation before speaking with an investigator, were not seen by an investigator, did not speak English, declined participation after speaking to an investigator, or were ineligible (figure 1). Of the 535 fully screened and eligible patients, 36 declined enrollment, and 499 patients were enrolled (table 1). Although demographic data were not available for all patients who declined participation in the study, the data that were available (for 520 patients) suggested that women and Haitians were more likely to decline enrollment (for declining vs. enrolling in the study: women, 53% vs. 42%; Haitians, 10% vs. 5%; $P < .05$).

Prevalence of HIV infection. Among the 499 patients enrolled, 5 (1.0%; 95% CI, 0.1%–1.9%) had acute HIV infection and 6 (1.2%; 95% CI, 0.2%–2.2%) had chronic HIV infection, for a total prevalence of HIV infection of 2.2% (95% CI, 0.9%–3.5%). There were no indeterminate Western blot findings or false-positive HIV RNA assay results (negative ELISA result and detectable RNA level of <2000 copies/mL). Throughout the study, the rate of enrollment of subjects and identification of patients with acute HIV infection was consistent, without seasonal variation.

The characteristics of the patients with acute and chronic HIV infection are shown in table 2. No single symptom or physical finding reliably distinguished patients with acute HIV infection from those who were HIV negative, and the percentage of patients with ≥ 3 symptoms or physical findings was not significantly different between these 2 groups (100% vs. 75%; $P > .05$).

Follow-up and linkage to care. Overall, 359 (72%) of all 499 subjects and 10 (91%) of 11 of those with positive test results returned to obtain their results. Among those with acute

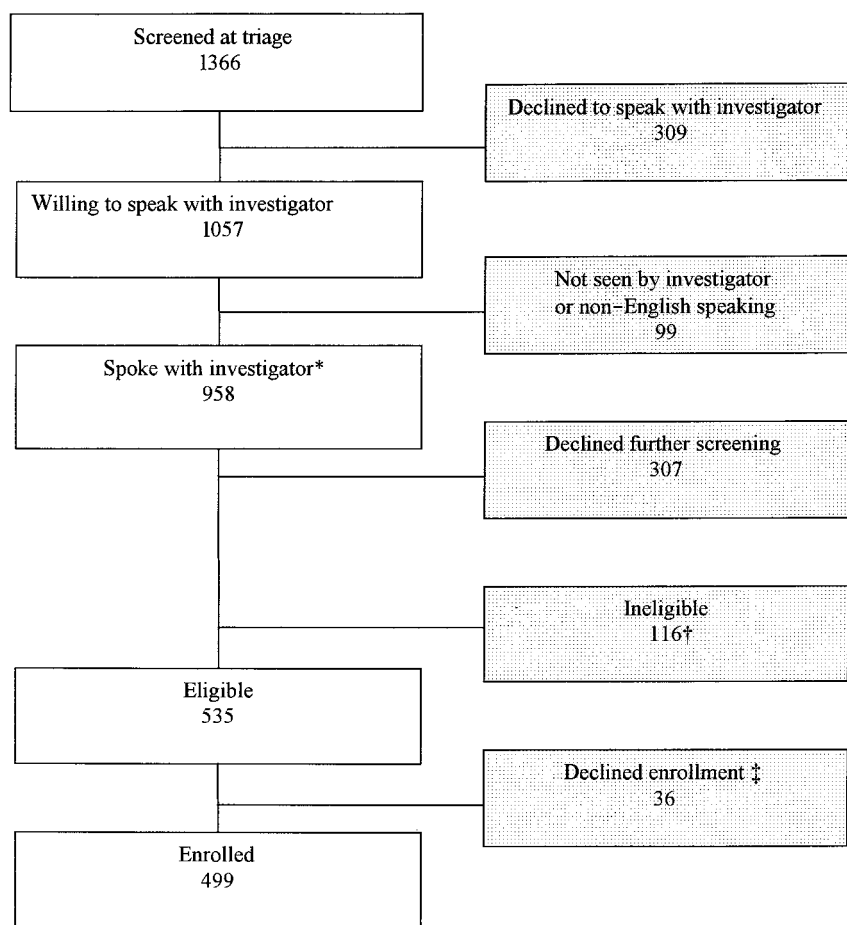


Figure 1. Study enrollment procedure. *First time that subjects were informed that the study was about acute HIV infection. †Includes 2 patients with previously diagnosed HIV infection and 114 patients with no reported risk factors in the past 2 months. ‡Includes 1 patient who was eligible but left before a blood sample was obtained.

HIV infection, 4 of 5 returned to obtain their results and started antiretroviral therapy a mean of 10 days (range, 8–11 days) after enrollment. One patient (patient A4) could not be located for follow-up, despite an extensive effort. All patients with chronic HIV infection received their results, and 4 of 6 returned for clinical care and started antiretroviral therapy.

DISCUSSION

Viral syndrome is a common but nonspecific diagnosis among patients receiving urgent care and includes a wide spectrum of illnesses. We found that, in 1.0% of patients receiving urgent care in an urban medical center in the northeastern United States, the viral syndrome was acute HIV infection. We used very broad entry criteria to determine a lower prevalence estimate for our population, a cohort of lower risk than those in previous studies of acute HIV infection from referral populations [6, 18, 21]. As in prior studies, no individual symptom, combination of symptoms, or physical findings reliably distinguished patients with acute HIV infection from those who were

HIV negative [18, 22]. Although a cohort with a higher prevalence of acute HIV infection might be identifiable on the basis of risk factors, such assessments have proven to be unreliable for guiding testing for chronic HIV infection, and there are no data on their use in screening for acute HIV infection [23, 24].

The Centers for Disease Control and Prevention (CDC) advocates routinely recommending HIV antibody testing to patients in risk groups with a 1.0% prevalence of chronic HIV disease, and a recent CDC initiative recommends an increase in the use of routine, voluntary testing for HIV in areas with a high prevalence of HIV infection [25, 26]. It has also been argued that the 1.0% prevalence represents a higher threshold than that used for many other widely accepted screening tests [27]. The US Preventive Services Task Force recommends screening for colorectal cancer in patients aged >50 years and for breast cancer in women aged 50–69 years; these diseases have an annual incidence in the sixth decade of life of 0.7% and 1.4%, respectively, and the screening tests used have a lower sensitivity and specificity than do HIV antibody and RNA tests

Table 1. Characteristics of the 499 subjects from an urban urgent care center enrolled in a study of acute HIV infection.

Characteristic	Value
Sex	
Male	290 (58)
Female	209 (42)
Age, median years (range)	33 (18–64)
Race/ethnicity	
African American	225 (45)
White	105 (21)
Latino	84 (17)
Haitian	27 (5)
Other	58 (12)
Risk factor/group for HIV infection ^a	
Sex other than with men who had sex with men	397 (80)
Men who had sex with men	23 (5)
Injection drug use	30 (6)
Alcohol and/or crack cocaine use only	50 (10)
Sex with commercial sex workers	16 (3)
Sex with known HIV-infected partner	8 (2)
Any prior sexually transmitted disease	236 (47)
No. of sex partners	
0	55 (11)
1	309 (62)
2–3	76 (15)
>3	59 (12)
No. of new sex partners ^b	
0	317 (72)
1	77 (17)
2–3	31 (7)
>3	19 (4)
Reported condom use ^b	
Never	206 (46)
Most of the time	82 (19)
Sometimes	88 (20)
Always	68 (15)

NOTE. Data are no. (%) of patients, unless otherwise indicated.

^a During the 2 months before enrollment

^b For 444 patients who reported sexual activity during the 2 months before study entry.

for acute HIV infection [28–31]. Furthermore, identifying patients with acute HIV infection may have a public health benefit that cancer screening does not, because it can reduce transmission.

We used the HIV RNA assay to screen for acute HIV infection because it is the most sensitive test for detection of acute HIV infection [18]. Although the p24 antigen assay can also be used to screen for acute HIV infection, the p24 antigen may not be detectable until several days after HIV RNA is detectable [32]. In referral populations, the p24 antigen assay has a sensitivity of only 79%–87% [18, 21], and in a study by Daar et al. [18], 13% of patients with acute HIV infection were not identified using the p24 antigen assay, compared with the HIV RNA assay.

One concern about the use of the more sensitive HIV RNA assay for screening has been the risk of false-positive test results [18, 19, 33]. Daar et al. [18] reported a rate of false-positive results of 2.6% for HIV RNA testing in patients referred for evaluation of possible acute HIV infection. Brambilla et al. [34] found rates of false-positive results of 1.4% and 2.6% using the standard and ultrasensitive Roche HIV Monitor assays, respectively, when evaluating 28 different laboratories, but there was significant variation among laboratories, and the median RNA levels among patients with false-positive results of the standard and ultrasensitive assays were only 924 and 89 copies/mL. We used an HIV RNA assay (lower limit of detection, 400 copies/mL) and did not have any false-positive results among 499 samples obtained from patients at the time of their initial symptomatic presentation. Although caution must be taken to ensure that laboratories use adequate quality controls and that very low-level positive test results are correctly interpreted as false-positive results, we believe that the standard HIV RNA test should be used when screening for acute HIV infection, rather than the less sensitive p24 antigen assay.

Cost has also been cited as an argument against the use of HIV RNA testing to diagnose acute HIV infection [18, 33]. Using a commercial laboratory, our total laboratory costs to screen 499 patients were \$80,140 (\$145 per RNA assay, \$15 per ELISA, and \$50 per Western blot assay) or approximately \$16,000 per case of acute HIV infection diagnosed and \$7300 per case of acute or chronic HIV infection diagnosed. Using p24 antigen testing (\$109 per test at Quest Diagnostics [Cambridge, MA]) would reduce the cost to \$14,300 per case of acute HIV infection diagnosed, but 13%–21% of cases would have been missed [18]. Furthermore, in a recent study using pooled RNA testing to diagnose acute HIV infection in a low-prevalence setting, Pilcher et al. [35] found an RNA assay cost of \$2 per specimen. Whether screening for acute HIV infection in groups in which the prevalence is 1.0% is cost-effective depends not only on the cost of screening but also on the efficacy of therapy for acute HIV infection and the probability that the diagnosis and treatment of acute HIV infection will decrease subsequent transmission [36].

We found that most patients were agreeable to HIV testing even though they had come to the urgent care center for an unrelated concern. Of the 958 patients who were informed about the nature of the study, 651 (68%) agreed to enter the study and to be tested for HIV. Seventy-two percent of tested patients returned to obtain their results, and all patients with acute HIV infection who obtained their results were linked to care, elected to start antiretroviral therapy, and began treatment within 2 weeks after presentation.

In addition to the patients with acute HIV infection, we found that 1.2% of the cohort had chronic HIV infection, and all of those who returned for care (4 of 6 patients) had CD4

Table 2. Characteristics of study patients with acute or chronic HIV infection.

HIV infection status, patient	HIV RNA level, copies/mL	CD4 cell count, ^a cells/mm ³ (%)	Age, years/ sex	Race/ethnicity	Risk behavior or group ^b	No. of sex partners ^b	Condom use ^b	Urgent care center diagnosis
Acute ^c								
A1	407,000	223 (23)	36/M	White	MSM	3	Most of the time	Viral syndrome
A2	>750,000	570 (32)	27/M	White	MSM	3	Most of the time	Viral syndrome
A3	>750,000	294 (5)	29/M	Haitian	MSM	2	All of the time	Fever, headache
A4	>750,000	ND	18/F	African American	Heterosexual	3	All of the time	Acute pharyngitis
A5	>750,000	324 (23)	46/M	African American	Heterosexual	1	All of the time	Viral syndrome
Chronic								
C1	>750,000	0 (0)	30/M	African American	Heterosexual	1	None of the time	Epididymitis
C2	312,000	16 (1)	40/M	Latino	Alcohol use	0	NA	Esophageal candidiasis
C3	5464	37 (3)	39/F	African American	Heterosexual	1	Most of the time	Oral candidiasis
C4	8487	ND	27/F	African American	Heterosexual	1	All of the time	URTI
C5	16,900	26 (2)	51/M	African American	Heterosexual	1	Some of the time	Esophageal candidiasis
C6	2000	ND	39/M	African American	Heterosexual	1	None of the time	Viral URTI

NOTE. On the basis of the CD4 cell counts of patients with chronic HIV infection, the majority of these patients were determined to have been probably infected many years before enrollment, and their risk factors at that time may have been different. MSM, men who have sex with men; NA, not applicable; ND, not determined; URTI, upper respiratory tract infection.

^a CD4 cell counts were not measured as part of the study and are only available for patients who had documented clinical follow-up after the study.

^b Data are for the 2 months before study enrollment and are thus risk factors for acute but not necessarily chronic HIV infection.

^c Acute HIV was defined as a negative result of HIV antibody ELISA and an HIV RNA level of >2000 copies/mL.

cell counts of <50 cells/mm³. Most of these patients had multiple prior hospital visits (median, 7 visits; range, 0–22 visits) for conditions that may have been related to HIV infection, including thrush, pelvic inflammatory disease, chlamydia, and weight loss. In most cases, recommendations for HIV testing had been documented in the medical record at least once, but testing had not been done. The on-site availability of voluntary HIV counseling and testing may have been influential in patients' decisions to get tested in this study during their urgent care visits [26, 37].

This study has several limitations. First, it was performed in a single urgent care center at an urban teaching hospital. Although other studies are needed to determine the prevalence of acute HIV infection in different populations, 72 hospitals in the United States have demographic characteristics similar to the study center in terms of size and percentage of Medicaid patients [38]. In addition, we found a prevalence of acute and chronic HIV infection similar to that found in other reported cohorts [37, 39–41]. Second, only consenting patients were tested. We are aware of 2 patients who declined study participation for whom acute HIV was later diagnosed during their regular clinical care, making the lowest possible prevalence of acute HIV infection in our cohort 0.6% (7 of 1250 patients, where 1250 is the 1366 triaged patients minus the 116 who were known to be ineligible). Third, patients may present repeatedly with viral syndromes. Five patients in this study presented with a second, otherwise eligible viral syndrome during the year of the study. Although these patients were not enrolled

twice, 4 of the 5 consented to additional laboratory studies, and all 4 tested negative for acute HIV infection on both visits. We also employed a full-time research assistant to enroll patients and perform pre- and posttest counseling in the urgent care center. For acute HIV infection case-finding to work optimally, we believe that dedicated staff are needed, although del Rio et al. reported that HIV counseling and testing can be incorporated into a busy academic urgent care center without additional staff [37].

We found that 1.0% of patients presenting to an urban urgent care center with viral symptoms and ≥1 potential risk factor for HIV infection had acute HIV infection, and 1.2% had chronic HIV infection. These were both easily diagnosed using commercially available HIV RNA tests and ELISAs without any false-positive results and with high patient acceptance. Given the potential benefits to individuals and society, acute HIV infection should be considered in the differential diagnosis for patients presenting with viral symptoms, and on-site counseling and HIV testing using HIV RNA and antibody assays should be routinely recommended for patients like this in similar settings.

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