

Prevalence of Primary HIV Infection in Symptomatic Ambulatory Patients

Andrew Coco, MD, MS¹

Emily Kleinbans²

¹Health Research Center, Lancaster General Hospital, Lancaster, Penn

²Goucher College, Baltimore, Md



MORE ONLINE
www.annfammed.org

ABSTRACT

PURPOSE Recognizing primary human immunodeficiency virus (HIV) infection is important for public health. The prevalence in outpatient settings is largely unknown but would be useful in developing testing guidelines. The objective of this study is to estimate the national prevalence of primary HIV infection in symptomatic ambulatory patients regardless of risk factors.

METHODS Patients 13 to 54 years old with each of 17 primary HIV infection symptoms, as well as other reported reasons for their visit consistent with primary HIV infection, were identified from the 2000 National Ambulatory Medical Care and National Hospital Ambulatory Medical Surveys to provide the denominator for the prevalence estimate. These survey data can be extrapolated to represent 90% of all US ambulatory care visits, including those to physician's offices, emergency departments, and hospital clinics. Patients with symptoms and diagnoses inconsistent with a viral illness were excluded. The estimate for the numerator was derived from Centers for Disease Control and Prevention estimates and the medical literature.

RESULTS Patients complaining of fever and other visit reasons consistent with primary HIV infection had a disease prevalence of 0.66% (0.57%-1.02%), those with rash had a prevalence of 0.50% (0.31%-0.82%), and those with pharyngitis had a prevalence of 0.16% (0.11%-0.22%). Patients with other symptoms represented numbers of visits insufficient for reliable estimates of their prevalence.

CONCLUSIONS These estimates of the prevalence of primary HIV infection in ambulatory patients with fever, rash, and pharyngitis can aid with development of clinical testing guidelines and clinical decisions around testing for acute HIV infection.

Ann Fam Med 2005;3:400-404. DOI: 10.1370/afm.376.

INTRODUCTION

Ninety percent of the estimated 40,000 new HIV infections in the United States each year are associated with the acute HIV syndrome.^{1,2} One to 4 weeks after infection, patients with the acute HIV syndrome experience symptoms of a viral illness, such as fever, fatigue, pharyngitis, myalgias, rash, and weight loss, as well as other non-specific symptoms.¹⁻⁵ Most of these patients seek medical care, but seldom do they have primary HIV infection diagnosed.^{1,2,6}

The diagnosis of primary HIV infection has important clinical and public health implications. Patients who do not have their condition diagnosed at this early stage of infection will often seek care much later for acquired immunodeficiency syndrome (AIDS), when treatment may not be as effective.⁷ Diagnosis of primary HIV infection represents an important opportunity to prevent transmission to others, because in the early stages of the disease, patients have high levels of viremia, which, coupled with a lack of awareness of their diagnosis, can lead to transmission through sexual activity.^{8,9}

The prevalence of primary HIV infection in patients visiting outpatient facilities in the United States is largely unknown. One recent prospective

Conflicts of interest: none reported

CORRESPONDING AUTHOR

Andrew S. Coco, MD, MS
Health Research Center
Lancaster General Hospital
555 N Duke St
Lancaster, PA 17604
ascoco@lancastergeneral.org

study determined a prevalence of 1% for patients with viral symptoms and at least 1 risk factor seeking care at an urban urgent care center, a setting in which a high prevalence of HIV infection is expected.¹⁰ Other studies have concluded that no symptom is sufficiently sensitive and specific to allow for targeted testing.^{4,5} It is difficult to determine which persons have a substantial probability of primary HIV infection when evaluating risk factors alone.¹¹ Furthermore, patients may not be aware of their risky behavior.¹²

An estimate of the national prevalence of primary HIV infection in patients seeking care at ambulatory settings, regardless of risk factors, would be important for clinical care in developing testing guidelines. Our objective for this study was to calculate a national estimate of the prevalence of primary HIV infection for patients visiting physician's offices, emergency departments, and hospital outpatient clinics with symptoms consistent with primary HIV infection regardless of risk factors.

METHODS

This study is an analysis of the 2000 National Ambulatory Medical Care Survey (NAMCS) and the 2000 National Hospital Ambulatory Medical Survey (NHAMCS) to identify ambulatory patients with symptoms and diagnoses consistent with primary HIV infection to develop a denominator for a national ambulatory prevalence estimate. The numerator for the prevalence was derived from the Centers for Disease Control and Prevention (CDC) estimate of annual new cases of HIV infection and modified by reports in the medical literature regarding the percentage of patients newly infected with HIV who have specific symptoms, as well the percentage that seek medical care during the phase of acute infection.

Target Population

The target population is US patients with symptoms of primary HIV infection seeking care at physician offices, hospital emergency departments, and hospital outpatient clinics. This population is represented in the 2000 NAMCS and 2000 NHAMCS. These surveys are national probability samples of nonfederal office-based physicians, hospital emergency departments, and hospital outpatient departments.^{13,14} The NAMCS includes only visits to physician offices. The NHAMCS includes 2 separate databases: 1 for emergency departments and 1 for hospital outpatient clinics. Both surveys are conducted annually by the

National Centers for Health Statistics and use a multistage probability sample design that is stratified and weighted to allow for population estimates of annual visits. Selected entities complete a survey form for visits during a randomly selected 1-week period. Combined, the surveys represent about 90% of US ambulatory visits with the exception of federal, veterans, and military outpatient facilities. The analysis is restricted to patients aged 13 through 54 years, inclusive, as they account for 95.2% of new HIV cases based on surveillance data from 25 states.¹⁵

Prevalence Estimate: Denominator

A list of 17 symptoms consistent with primary HIV infection was generated from 3 US studies by including any symptom reported by more than 25% of patients with a diagnosis of primary HIV infection (Table 1).^{2,4,5} Both the NAMCS and NAMHCS include variables for up to 3 reasons for the visit. The NAMCS and the hospital outpatient clinic file in the NHAMCS contain a variable that allows for designation of acute visits. Emergency department visits in the NHAMCS are assumed to be for acute problems. The databases were analyzed separately for each of the 17 primary HIV infection symptoms listed in Table 1 to generate the total number of annual patients with an acute problem and each symptom as 1 of the 3 reasons for their visit. The total number of patients reporting each symptom was refined to include only those for whom the other 2 of their top 3

Table 1. Primary HIV Infection Symptoms

Symptom Reported in the Literature	NAMCS/NHAMCS Equivalent Reason(s) for Visit
1. Fever	Fever, chills, feeling hot
2. Pharyngitis	Throat soreness, throat pain, tonsillitis
3. Lymphadenitis	Sore glands, swollen or enlarged glands
4. Myalgia	Unspecified muscle pain, ache, soreness, discomfort
5. Athralgia	Unspecified joint pain, ache, soreness, discomfort
6. Fatigue	Tiredness, fatigue
7. Night sweats	Excessive sweating
8. Nausea	Nausea
9. Vomiting	Vomiting
10. Diarrhea	Diarrhea
11. Rash	Skin rash
12. Weight loss	Weight loss
13. Oral ulcer	Mouth ulcer
14. Headache	Headache, pain in head
15. Neck stiffness	Limitation of movement, neck stiffness
16. Loss of appetite	Decreased appetite
17. Malaise	General ill feeling

Note: Symptoms reported by more than 25% of patients in Schacker et al,² Hecht et al,⁴ and Daar et al.⁵

HIV = human immunodeficiency virus; NAMCS = National Ambulatory Medical Care Survey; NHAMCS = National Hospital Ambulatory Medical Care Survey.

symptoms were also consistent with primary HIV infection. For example, patients reporting fever as their first reason for the visit would be included in the estimate for that symptom if their second and third reasons for the visit were fatigue or pharyngitis or other symptoms consistent with primary HIV infection as listed in Table 1. Whereas, if fever was their second or third reason for the visit, then the first and third or first and second other 2 reasons for the visit would need to be for symptoms consistent with primary HIV infection. A few other visit reasons not listed in Table 1 but considered consistent with a viral illness were also considered inclusion variables. These were enlarged glands, difficulty swallowing (as a symptom of throat pain), and unspecified pain.

NAMCS and NHAMCS contain data for up to 3 diagnoses for each visit. Primary diagnoses, but not secondary or tertiary ones, considered inconsistent with any of the constellation of primary HIV infection symptoms in Table 1 were excluded to further define the estimate.

The data were analyzed with the Statistical Export and Tabulation System (SETS 2.0), US National Center for Health Statistics. Relative standard errors, the measure of the sampling variability that occurs by chance, were calculated based on National Center for Health Statistics' coefficients and formulas as reported in the NAMCS and NHAMCS.

Prevalence Estimate: Numerator

The numerator for disease prevalence was derived from the CDC estimate of the annual number of new HIV infections of 40,000 per year.^{16,17} In addition to the 13- to 54-year age restrictions (95.2% of new HIV diagnoses), this number was further decreased by 3 other factors. First, the 40,000 new HIV infections estimate was reduced by 10%, because the NAMCS and NHAMCS represent only 90% of US annual ambulatory visits. Second, an estimate of the percentage of patients with primary HIV infection reporting each symptom was derived from 127 patients who had primary HIV infection diagnosed from 3 US studies.^{2,4,5} Percentage estimates were calculated from all patients with primary HIV infection, regardless of whether acute HIV syndrome was reported, and included 95% confidence intervals. Third, the numerator estimate needed to be decreased by the percentage of patients with primary HIV infection who sought medical treatment. Only 2 studies, both of predominately urban gay men, reported findings for patients with primary HIV infection symptoms who were seeking care.^{1,2} Both studies reported rates close to 90%. Our analysis used the lower rate of 50% because of limited data on care-seeking rates for patients from other segments of the population, such as persons of low socioeconomic status, who may be less likely to seek medical care.

RESULTS

Prevalence Denominator Estimates

The annual number of patients with symptoms of fever, rash, and pharyngitis, as well as other symptoms and diagnoses consistent with primary HIV infection symptoms, is displayed in Supplemental Tables 1, 2, and 3 (available online only at <http://www.annfammed.org/cgi/content/full/3/5/400/DC1>). Data detailing exclusionary diagnoses and symptoms in the 3 practice settings represented by NAMCS and NHAMCS are available from the authors. The analysis of the other 14 symptoms from Table 1 showed an inadequate number of patient visits to allow for accurate annual estimates. The combined total number of patient visits for fever and other primary HIV infection symptoms and diagnoses consistent with an acute viral illness from these 3 settings was 2,175,551; there were 6,415,111 such patient visits for pharyngitis and 1,344,060 visits for patients with a rash.

The analysis provided data on which diagnoses were most likely to cause patients to report primary HIV infection symptoms. For example, 46% of patients visiting physician's offices with complaints of fever and other primary HIV infection symptoms had streptococcal sore throat, acute pharyngitis, or influenza diagnosed, whereas in the emergency department unspecified viral infection, acute pharyngitis, and pyrexia of unknown origin accounted for 55% of the annual qualified visits. In the hospital clinic population, 75% of qualified visits were for unspecified upper respiratory tract infections, acute pharyngitis, and streptococcal sore throat.

Prevalence Numerator Estimates

Estimates for the annual number of patients aged 13 to 54 years with primary HIV infection seeking care in physician offices, emergency departments, and hospital clinics with complaints of fever, rash, or pharyngitis are listed in Supplemental Table 4 (available online only at <http://www.annfammed.org/cgi/content/full/3/5/400/DC1>). An estimated combined total of 14,394 patients newly infected with HIV who had fever, 8,568 who had pharyngitis, and 7,540 who had rash were seen in these 3 settings in 2000.

Prevalence Estimates

The prevalence estimates for patients aged 13 to 54 years with symptoms of fever, rash, and pharyngitis, as well as other symptoms and diagnoses consistent with primary HIV infection, are displayed in Table 2. Patients with fever had the highest rate of primary HIV infection, 0.66% or 6.6 cases per 1,000; the rate for those with rash was 0.56%, or 5.6 cases per 1,000; and for those with pharyngitis the rate was 0.13%, or 1.3 cases per 1,000. Prevalence estimates include a range

Table 2. Primary Human Immunodeficiency Virus Infection Estimates

Symptom	Numerator Estimate (95% CI)	Denominator Estimate (95% CI)	Prevalence Estimate (Range)
Fever	14,394 (13,880-15,936)	2,175,551 (1,723,031-2,628,071)	0.66 (0.53-0.92)
Rash	7,540 (5,998-9,082)	1,344,060 (966,721-1,721,399)	0.56 (0.35-0.94)
Pharyngitis	8,568 (7,026-10,436)	6,415,111 (5,528,853-7,301,369)	0.13 (0.10-0.19)

Note: Prevalence estimates were obtained by dividing the numerator estimate by the denominator estimate. The low range estimate was obtained by dividing the low numerator estimate by the high denominator estimate, and the high range estimate by dividing the high numerator estimate by the low denominator estimate.

CI = confidence interval.

of values based on the relative standard error of the denominator estimate and the 95% confidence interval for the numerator estimate.

Sensitivity Analysis

Sensitivity analysis involves recalculating results when assumptions about variable estimates are altered because of uncertainty. In this analysis the most uncertain estimate was the percentage of patients with primary HIV infection who sought care. The baseline analysis assumed that 50% of patients with primary HIV infection would seek medical care. Data are lacking, however, outside the urban, gay, male populations, for which the rate is 90%.^{1,2} If this assumption were varied from 25% to 90%, then for patients with fever the prevalence would vary from 0.33% to 1.19%; for rash from 0.28% to 1.01%; and for sore throat from 0.07% to 0.23%.

DISCUSSION

This analysis provides an initial estimate of the national prevalence of primary HIV infection in patients visiting ambulatory settings with complaints of fever, rash, or sore throat and a diagnosis consistent with an acute viral illness. A national prevalence estimate of primary HIV infection provides a useful starting point for policy decisions regarding early detection and referral programs, as emphasized in a recent CDC initiative.¹⁸ For instance, although current counseling, testing, and referral guidelines recommend routine HIV testing in populations with a prevalence of 1%,¹⁹ a more recent cost-effectiveness analysis has shown that in the era of highly active antiretroviral treatment, testing may be cost-effective when the prevalence is as low as 0.05%,²⁰ ie, rates lower than those found in this study for patients with fever or rash or pharyngitis. The only previous study to develop a prevalence estimate was a prospective study of 499 patients visiting an urban urgent care center in Boston.¹⁰ The prevalence was 1%

for patients complaining of viral symptoms who had at least 1 risk factor for HIV. The prevalence in that population would be expected to be higher than a national estimate based on patients from all settings with similar symptoms regardless of risk factors and thus corroborates these results.

This study has several limitations because of assumptions made in the analysis. The most uncertain estimate involves

the percentage of patients that actually seek medical care during the symptomatic phase of primary HIV infection. Although the baseline assumption of 50% is reasonable because patients with primary HIV infection are ill for 10 to 14 days, and previous reports of care-seeking behavior are 90% for urban gay males, the true percentage is largely unknown.¹⁻⁵ Poor, disenfranchised, injection drug users who acquire HIV infection through needle-sharing behavior, for instance, may be less likely to seek care because they lack insurance or transportation. This issue was addressed through a sensitivity analysis that lowered the rate of those seeking care to 25%, more one third less than that reported in the literature.

Several factors could have affected the denominator estimate. Excluding primary diagnoses that included a patient presenting with primary HIV infection symptoms could decrease the denominator and falsely increase the prevalence estimate. To minimize this potential source of error, all diagnoses possibly construed as viral (Supplemental Tables 1, 2 and 3 (available online only at <http://www.annfammed.org/cgi/content/full/3/5/400/DC1>) were included in the denominator. Additionally, other diagnoses unlikely to represent viral infections but not entirely inconsistent with primary HIV infection symptoms, such as tension headache, migraine headache, unspecified abdominal pain, and gastroesophageal reflux, were included as well.

Another factor that could affect the denominator estimate is the restriction of the analysis to primary diagnoses. The analysis was concerned with only acute problems. In line with this study assumption, diagnostic coding guidelines specify that the primary diagnosis should reflect the patient's main reason for the visit. It is possible, however, especially in private offices with familiar patients, that a chronic problem was coded first even though the patient was seeking care for an acute illness. Missing these visits would decrease the denominator estimate. To assess the impact of this source of

potential error, the data were analyzed for visits to physician's offices for patients reporting fever. A total of 17,824 patients, or 1.75% of the 1,017,573 patients included from this data file, had secondary or tertiary diagnoses consistent with primary HIV infection. Increasing the denominator estimate by 1.75% would minimally decrease the prevalence for febrile patients from 0.66% to 0.65%.

Last, although an attempt was made to include the correct codes for the primary HIV infection symptoms reported in the literature and their likely synonyms, it is possible that some symptoms were coded for visit reasons not included in the analysis, whereas some of the inclusion symptoms, such as chills and feeling hot as possible synonyms for fever, could have overestimated the denominator estimates.

In conclusion, this study is the first to estimate the national prevalence of primary HIV infection. Prevalence estimates were developed from national ambulatory databases for patients aged 13 to 54 years regardless of risk factors who sought care for fever, rash, or sore throat and had an acute illness consistent with a viral infection. We believe these estimates will be useful in developing national testing guidelines that could ultimately aid in decreasing HIV transmission rates and improving the health of those infected through early entry into medical care.

To read or post commentaries in response to this article, see it online at <http://www.annfammed.org/cgi/content/full/3/5/400>.

Submitted January 30, 2005; submitted, revised, April 28, 2005; accepted May 10, 2005.

Key words: Primary HIV infection/epidemiology; prevalence studies; disease frequency surveys

Funding support: This study was supported by a Claire Weaver Scholarship for Research in Family Medicine.

References

- Tindall B, Barker S, Donovan B, et al. Characterization of the acute clinical illness associated with human immunodeficiency virus infection. *Arch Intern Med.* 1988;148:945-949.
- Schacker T, Collier AC, Hughes J, Shea T, Corey L. Clinical and epidemiologic features of primary HIV infection. *Ann Intern Med.* 1996;125:257-264.
- Kahn JO, Walker BD. Acute human immunodeficiency virus type 1 infection. *N Engl J Med.* 1998;339:33-39.
- Hecht FM, Busch MP, Rawal B, et al. Use of laboratory tests and clinical symptoms for identification of primary HIV infection. *AIDS.* 2002;16:1119-1129.
- Daar ES, Little S, Pitt J, et al. Diagnosis of primary HIV-1 infection. Los Angeles County Primary HIV Infection Recruitment Network. *Ann Intern Med.* 2001;134:25-29.
- Weintrob AC, Giner J, Menezes P, et al. Infrequent diagnosis of primary human immunodeficiency virus infection: missed opportunities in acute care settings. *Arch Intern Med.* 2003;163:2097-2100.
- Samet JH, Freedberg KA, Savetsky JB, Sullivan LM, Stein MD. Understanding delay to medical care for HIV infection: the long-term non-presenter. *AIDS.* 2001;15:77-85.
- Cates W, Jr, Chesney MA, Cohen MS. Primary HIV infection—a public health opportunity. *Am J Public Health.* 1997;87:1928-1930.
- Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med.* 2000;342:921-929.
- Pincus JM, Crosby SS, Losina E, et al. Acute human immunodeficiency virus infection in patients presenting to an urban urgent care center. *Clin Infect Dis.* 2003;37:1699-1704.
- Royce RA, Sena A, Cates W, Jr, Cohen MS. Sexual transmission of HIV. *N Engl J Med.* 1997;336:1072-1078.
- MacKellar DA, Valleroy LA, Secura GM, et al. Unrecognized HIV infection, risk behaviors, and perceptions of risk among young men who have sex with men: opportunities for advancing HIV prevention in the third decade of HIV/AIDS. *J Acquir Immune Defic Syndr.* 2005;38:603-614.
- National Ambulatory Medical Care Survey. Centers for Disease Control and Prevention Web site. Available at: <http://www.cdc.gov/nchs/SurveyInstrumentNAMCS>.
- National Hospital Ambulatory Medical Care Survey. Centers for Disease Control and Prevention Web site. Available at: <http://www.cdc.gov/nchs/SurveyInstrumentNHAMCS>.
- Diagnosis and reporting of HIV and AIDS in states with HIV/AIDS surveillance—United States, 1994-2000. *MMWR Morb Mortal Wkly Rep.* 2002;51:595-598.
- Vu MQ, Steketee RW, Valleroy L, et al. HIV incidence in the United States, 1978-1999. *J Acquir Immune Defic Syndr.* 2002;31:188-201.
- Karon JM, Fleming PL, Steketee RW, De Cock KM. HIV in the United States at the turn of the century: an epidemic in transition. *Am J Public Health.* 2001;91:1060-1068.
- Advancing HIV prevention: new strategies for a changing epidemic—United States, 2003. *MMWR Morb Mortal Wkly Rep.* 2003;52:329-332.
- Revised guidelines for HIV counseling, testing, and referral. *MMWR Recomm Rep.* 2001;50:1-57; quiz CE51-19a51-CE56-19a51.
- Sanders GD, Bayoumi AM, Sundaram V, et al. Cost-effectiveness of screening for HIV in the era of highly active antiretroviral therapy. *N Engl J Med.* 2005;352:570-585.