The Rational Clinical Examination

# Does This Adult Patient Have Early HIV Infection?
## The Rational Clinical Examination Systematic Review

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**IMPORTANCE** Timely identification of human immunodeficiency virus (HIV) infection in adults can contribute to reduced mortality and likelihood of further HIV transmission. During the first 6 months after infection, known as early HIV infection, patients often report a well-described constellation of symptoms and signs. However, the literature examining utility of the clinical examination in identifying early infection has not been systematically assessed.

**OBJECTIVE** To assess the accuracy of symptoms and signs in identifying early HIV infection among adults.

**DATA SOURCES** We searched MEDLINE and EMBASE (1981-May, 2014) for articles investigating symptoms and signs of early HIV infection in adults and searched reference lists of retrieved articles.

**STUDY SELECTION** We retained original studies that compared symptoms and signs among patients with early HIV infection in comparison to HIV-negative individuals.

**DATA EXTRACTION AND SYNTHESIS** Data were extracted and used to calculate sensitivity, specificity, and likelihood ratios (LRs), and meta-analysis was used to calculate summary LRs.

**RESULTS** Of 1356 studies, 16 studies included data that were eligible for meta-analysis and included a total of 24 745 patients and 1253 cases of early HIV infection. Symptoms that increased the likelihood of early HIV infection the most included genital ulcers (LR, 5.4; 95% CI, 2.5-12), weight loss (LR, 4.7; 95% CI, 2.1-7.2), vomiting (LR, 4.6; 95% CI, 2.5-8.0), and swollen lymph nodes (LR, 4.6; 95% CI, 1.3-8.0). No symptoms had an LR that was 0.5 or lower, but the absence of recent fever (LR, 0.74; 95% CI, 0.64-0.84) slightly decreased the likelihood of early HIV infection. The presence of lymphadenopathy on physical examination was the most useful sign (LR, 3.1; 95% CI, 1.0-5.2). No sign had an LR of 0.5 or less, but the absence of lymphadenopathy slightly decreased the likelihood of early HIV infection (LR, 0.70, 95% CI, 0.49-0.92). Using data from studies that considered combinations of findings (range of possible findings, 4-17), the summary LR for individuals with 0 findings was 0.47 (95% CI, 0.38-0.58).

**CONCLUSIONS AND RELEVANCE** The limited utility of the clinical examination to detect or rule out early HIV infection highlights the importance of routine testing for HIV infection among adults.

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## Clinical Scenario

A 31-year-old heterosexual woman was seen in the emergency department with a 2-week history of an influenzalike illness, including fever, vomiting, and weight loss and had a generalized maculopapular rash on her chest and neck. She has no significant past medical history and works at a children's day care where she reports regular contact with sick children. Her social history is noteworthy for regular tobacco and heavy weekend alcohol use, and she reports several recent casual sex partners. How does the presence of symptoms affect the likelihood of human immunodeficiency virus (HIV) infection?

## Why Is This Question Important?

Globally, an estimated 35 million individuals are infected with HIV, with an estimated 2.5 million new infections annually.[1] In the United States, approximately 1.1 million individuals are currently infected with HIV, approximately 15% of whom may be unaware that they have HIV.[2] Each year, there are 50 000 new infections.[3,4]

Early identification of HIV infection is important for several reasons. First, the majority of new HIV infections in the United States result from high-risk behaviors among individuals who are unaware of their HIV status.[5] Second, receiving an HIV diagnosis is associated with reduced HIV-risk behaviors.[6] Third, initiating HIV treatment with highly active antiretroviral therapy prior to the development of immunosuppression and life-threatening opportunistic infections prolongs life.[7,8] Fourth, through its ability to reduce plasma HIV RNA to undetectable levels, highly active antiretroviral therapy dramatically reduces the risk of HIV transmission.[9-11] Thus, recognition of symptoms and signs suggesting early HIV infection facilitates early case identification, reducing HIV-associated morbidity and mortality and lowering HIV transmission rates.[7,12-14]

Human immunodeficiency virus disease evolves in several phases. *Early HIV infection* is the first 6-month phase after HIV acquisition as defined by the US Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents. During the early phase, recently infected individuals often experience an "acute retroviral syndrome" of generalized symptoms suggesting an acute viral illness.[15,16] The *latent phase* of HIV is characterized by a period of approximately 10 years during which patients may be asymptomatic. During the *final phase* of HIV infection, immunodeficiency progresses, resulting in opportunistic infections and development of AIDS.[17] This article summarizes evidence regarding the presence or absence of symptoms and signs during the early phase of the disease, facilitating establishment of an HIV diagnosis. Over half of patients with early HIV infection experience symptoms.[18] For example, in a cohort of 155 patients from the Southeastern United States with acute HIV infection referred from emergency departments, urgent care centers, student health centers, primary care clinics, and the North Carolina State Screening and Tracing for Active HIV-1 Transmission program, 138 (89%) reported symptoms, although the diagnosis of HIV infection was identified at the time of first contact with the medical system in only 62 (40%) cases.[19]

Based on the benefits of timely (ie, earlier) case identification, the US Centers for Disease Control and Prevention published guidelines in 2006 recommending opt-out HIV testing for all adolescents and adults in medical care settings where the prevalence of undiagnosed HIV infection is estimated to be greater than 0.1%, and at least annual retesting for persons who continue to engage in behaviors associated with HIV risk such as intravenous drug use or unsafe sex.[20] The US Preventive Services Task Force also recently recommended that, in settings where undiagnosed HIV infection is greater than 0.1%, all adolescent and adult patients be screened for HIV regardless of risk behaviors, although they did not provide optimal screening interval recommendations.[21]

Early signs of HIV infection, including the "acute retroviral syndrome" occurring within weeks of acquiring HIV, are frequently missed by clinicians. Despite screening recommendations, routine testing for HIV remains low.[15,22] For instance, in a recent survey of 376 US hospitals in areas with 0.1% or more of HIV prevalence, less than 10% of hospitals reported universal screening of inpatients and outpatients and less than 35% reported screening some or all adult patients.[23] Possible reasons for low screening rates by physicians include patients not disclosing high-risk behaviors (eg, drug use, unsafe sex) and physicians not recognizing that clinical presentations characteristic of HIV disease (eg, viral illness) may imply a patient is high risk and the physician does not pursue that information.[24] Identification of the signs and symptoms of HIV disease may enhance HIV identification and lead to more referrals for HIV testing.

## Physiologic Origins of Acute Retroviral Syndrome

During the period of early HIV infection, 50% to 90% of patients develop an acute retroviral syndrome characterized by a constellation of symptoms including one or more of fever, nausea or vomiting, weight loss, arthralgia or myalgia, pharyngitis, oral ulcers, rash, and lymphadenopathy.[15,25] These symptoms are similar to other viral infections and are attributable to the immunologic response to the initial burst of viremia, circulating immune complexes of antibodies with viral proteins, acute phase reactants, and the production of inflammatory cytokines.[26] In the absence of antiretroviral treatment, the rate at which HIV disease progresses from initial infection to the development of AIDS is associated with symptom severity during early HIV infection which, in turn, may be related to plasma HIV RNA levels.[27,28]

## How to Elicit Symptoms and Signs of Early HIV Infection

A directed history and physical examination can elucidate a number of symptoms and signs associated with early HIV infection.[15] Additional history information that should be obtained from patients suspected of HIV disease includes assessing the likelihood of possible HIV exposure (ie, sexual and drug use history), the presence of other sexually transmitted infections (eg, genital ulcers), and querying about the presence or absence of recent symptoms of viral infection, including weight loss, vomiting, lymphadenopathy, diarrhea, arthralgia, or fever.

We systematically reviewed and summarized the diagnostic accuracy of symptoms and signs of early HIV infection that clinicians can easily attain at the bedside. These findings have been evaluated primarily in at-risk populations because low-risk populations (prevalence, <1.0%) would not have enough affected patients to generate reliable sensitivity estimates. However, evaluation of the consistency of the sensitivity and specificity across a broad range of prevalence allows an assessment of whether the results could apply to the general population of low-risk patients. This review is intended for clinicians who know the local prevalence of HIV infection and who see patients in primary care clinics or in emergency departments.

**Statistical Definitions**

Likelihood ratio

The odds that a given test result comes from someone with the target condition. Likelihood ratio values greater than 1.0 mean the test result makes the condition more likely, whereas values less than 1.0 make the condition less likely.

$I^2$ Statistic

The $I^2$ statistic is a test of heterogeneity that describes the percentage of variability (0%-100%) that is due to real differences as opposed to random variation. Values on the order of 25% are considered to have low variability, 50% have moderate variability, and 75% have variability that is more likely real rather than random.

$R^2$ Statistic

Quantifies the effect of a covariate on heterogeneity. When a test has heterogeneous results, the $R^2$ statistic quantifies the percentage of variability (0%-100%) between studies that is attributable to the covariate.

## Methods

### Search Strategy and Quality Review

Eligible studies compared patient-reported active or recently experienced (ie, last 6 months in HIV seroconversion studies) symptoms and physical examination findings between patients with early HIV infection and non-HIV-infected patients. We found studies that were constrained to patients with symptoms, and we found studies that reported the results of routine screening of primarily asymptomatic patients (eTable 1 in the Supplement). To identify relevant articles, we searched MEDLINE and EMBASE from 1980 to January 26, 2014. The search strategy used terms including *early*, *acute or primary HIV or HIV-1 infection, HIV seroconversion,* MESH term *HIV infections/diagnosis* as well as terms found to be useful for strategies for retrieving studies of diagnosis (see eAppendix in the Supplement for Search Strategy).[29] We identified additional studies by searching reference lists of original studies and review articles. Studies were not required to be restricted to symptomatic patients. Two reviewers (E.W. and Peter Van, BA, British Columbia Centre for Excellence in HIV/AIDS) independently reviewed abstracts for inclusion and the Rational Clinical Examination levels of evidence. Level 1 indicated the highest quality and was assigned to studies that had independent blinded comparison of the sign or symptom with a valid criterion standard in a large number (for the purposes of this article, >100) of consecutive patients.[30] Level 2 studies were similar to level 1 studies but enrolled fewer than 100 patients. Level 3 studies enrolled nonconsecutive patients. Level 4 studies used nonindependent comparisons among a convenience sample of patients believed to have the condition in question. We evaluated the sources of bias with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool (eTable 3 in the Supplement).[30-32]

### Statistical Methods

We included studies that compared active or recently experienced symptoms derived from medical history or signs assessed on physical examination aimed at detecting early HIV infection in adult patients. We excluded studies that only described symptoms and signs of early HIV infection without comparison to an HIV-negative population as well as review articles that did not include original data. Because prevalence is highly variable and may differ in studies designed to quantify diagnostic accuracy of the clinical examination vs population-based prevalence studies, we describe the disease frequency in the included studies. For population prevalence, we used data reports from the US Centers for Disease Control and Prevention and the World Health Organization.[33,34]

To evaluate the sensitivity, specificity, and likelihood ratios (LRs) we constructed 2 × 2 contingency tables for each sign or symptom. The reliability of symptoms and signs was quantified with the κ statistic. Where necessary, 2 × 2 data were back-calculated from available data using methods described elsewhere.[35] Data were entered into Microsoft Excel spreadsheets predesigned to calculate the sensitivity, specificity, LRs, and their 95% CIs; see Text **Box**. To create summary measures, we used only studies that were of level 1 to 3 by the Rational Clinical Examination criteria.[30] When a symptom or sign was assessed in 3 studies, data were pooled using separate univariate random-effects meta-analysis (*Comprehensive Meta-analysis* version 2.0., Biostat Inc); and when a finding was evaluated in 4 or more studies, data were pooled using bivariate random effects summary measures. SAS version 9.2 (SAS Institute Inc) was used to calculate random effects summary measures and 95% CIs.[36,37]

For all analyses, heterogeneity was assessed with the $I^2$ parameter, with values greater than 50% suggesting real heterogeneity between studies rather than spurious heterogeneity.[38] Because the prevalence of HIV disease varies as a function of the population and study setting, we used metaregression to determine the effect of prevalence on the positive and negative LRs when the finding was evaluated in 4 or more studies and cases for which the $I^2$ was 50% or more. The effect of prevalence on heterogeneity was quantified with the $R^2$ value, which describes the percentage of between-study heterogeneity (quantified by the $I^2$) that is explained by the prevalence (Box).[39]

## Results

### Search Results

The search identified 1356 studies that were systematically reviewed, with 21 articles eligible for qualitative synthesis (eFigure

in the Supplement, flowchart of included studies). These 21 studies all included patients for whom there was a reasonable index of suspicion of early HIV infection, which ranged from 66 to 7727 patients and included research studies of intravenous drug users, sex-trade workers, and men who have sex with men, as well as clinical studies of individuals presenting to general practitioners and sexually transmitted infection clinics. Of these 21 studies, in 19 cases the study quality was level 1 to 3 by the Rational Clinical Examination Quality checklist with bias addressed adequately on most items of the QUADAS tool (eTables 1-3 in the Supplement).[31,32] Full details of study site characteristics are in eTable 1 in the Supplement. Of these 19 studies, 16 studies included measures of signs, symptoms, or both that were eligible for meta-analysis based on being measured in 3 or more eligible studies. These 16 studies included a total of 24 745 patients, 1253 of whom had early HIV infection.

## Prevalence of Early HIV Infection

### Prevalence in Studies That Evaluated Symptoms and Signs

The prevalence of early HIV infection was much higher in the studies designed to assess diagnostic accuracy of symptoms and signs than in population prevalence estimates. Among the 21 diagnostic accuracy studies for which study quality was level 1 through 3, only 6 studies had sufficient data for estimating the prevalence of early HIV infection. The median prevalence was 1.5% and ranged from 0.26% in an unselected sample of men who have sex with men presenting for routine screening at a sexually transmitted infection clinic in San Francisco[40] to 2.18% in a study of HIV-serodiscordant couples from Zambia.[41]

### Population Rates

Recent estimates of US Centers for Disease Control and Prevention estimate an overall incidence rate of 15.8 new HIV diagnoses/100 000 people in 2011. This rate varies with different prevalences of behavioral risk factors (eg, men who have sex with men), race/ethnicity, gender, and region of the country.[33]

The prevalence also varies with health care setting. Among patients presenting to emergency departments, the prevalence of early HIV infection ranged from 0.05% in a study of unselected consecutive patients in San Francisco, California,[42] to 1.0% in a study of symptomatic patients with possible HIV exposure in Boston, Massachusetts.[43] The prevalence of early HIV infection was 0.38% among Londoners presenting to their primary care physicians with an infectious mononucleosislike illness.[44] A study capturing approximately 90% of US ambulatory care visits among those aged 13 through 54 years regardless of HIV risk factors estimated the prevalence of early HIV infection in symptomatic patients to be 0.66% among those with fever, 0.50% among those with rash, and 0.16% among those with pharyngitis.[45]

## Reliability of the History and Physical Examination

Several articles examined physician-patient variation and physician-physician variation when assessing for the presence or absence of symptoms and signs of HIV. In a survey of 315 chronically infected HIV patients and their attending physicians from 34 inpatient and outpatient HIV treatment facilities in France, recognition by physicians of moderately distressing patient symptoms was only fair to poor for assessment of weight loss ($\kappa = 0.50$), fever ($\kappa = 0.58$), and nausea and vomiting ($\kappa = 0.36$).[46] Although interobserver agreement was not reported, in a study of 133 general internists and family practitioners, only 23 physicians (17.3%) correctly identified lymphadenopathy in a patient with prominent diffuse lymphadenopathy.[47] In a prospective study of 32 randomly selected male sexual contacts of men with AIDS, agreement among 3 physicians for the presence or absence of generalized lymphadenopathy was fair ($\kappa = 0.39$-$0.45$).[48]

## Accuracy of Individual Findings From the Clinical History and Physical Examination

### Symptoms

Meta-analysis of 17 symptoms revealed that genital ulcers (sensitivity, 0.08; specificity, 0.99; LR, 5.4; 95% CI, 2.5-12; $I^2 = 83\%$), weight loss (sensitivity, 0.21; specificity, 0.96; LR, 4.7; 95% CI, 2.1-7.2; $I^2 = 77\%$), vomiting (sensitivity, 0.13; specificity 0.97, LR, 4.6; 95% CI, 2.5-8.0; $I^2 = 0\%$) and swollen lymph nodes (sensitivity, 0.11; specificity, 0.98; LR, 4.6; 95% CI, 1.3-8.0; $I^2 = 52\%$) were most closely associated with early HIV infection (**Table**). When we assessed for a possible effect of differing HIV prevalence across studies on heterogeneity, a history of oral ulcers (sensitivity, 0.13; specificity, 0.96; LR, 3.4; 95% CI, 1.2-9.4; $I^2 = 81\%$) was the only finding evaluated in 4 or more studies for which HIV prevalence in the study population accounted for a significant percentage of the heterogeneity ($R^2 = 37\%$; $P = .047$). Studies involving populations that have a higher prevalence of HIV infection found the presence of oral ulcers less useful (lower positive LR) for diagnosing early HIV compared with studies for which the prevalence was lower.

No symptoms had a negative LR that was 0.5 or lower, but the absence of recent fever (sensitivity, 0.33; specificity, 0.90; LR, 0.74; 95% CI, 0.64-0.84; $I^2 = 78\%$) slightly decreased the likelihood of early HIV infection. The prevalence of HIV infection in study populations did not significantly affect the negative LR of fever across studies ($R^2 = 20\%$; $P = .14$).

### Signs

Meta-analysis of 7 signs showed that the presence of any lymphadenopathy (sensitivity, 0.39; specificity, 0.88; LR, 3.1; 95% CI, 1.0-5.2; $I^2 = 91\%$) had the largest positive LR. None of the heterogeneity across studies was attributable to difference in prevalence of disease ($R^2 = 0\%$). The positive LR confidence interval for site-specific lymphadenopathy in the inguinal region (95% CI, 1.5-6.4), neck (95% CI, 1.1-4.3), or axillae (95% CI, 0.70-3.3) showed substantial overlap that added no information beyond the LR for the presence of any lymphadenopathy.

As with symptoms, no sign had a negative LR of 0.5 or less. The absence of lymphadenopathy slightly decreased the likelihood of early HIV infection (LR, 0.70; 95% CI, 0.49-0.92; $I^2 = 88\%$). The prevalence of HIV infection had a large effect on the negative LR ($R^2 = 83\%$; $P < .001$). Studies with higher prevalence of HIV infection found that the absence of lymphadenopathy was more useful (a lower negative LR) compared with studies for which the prevalence was lower.

## Combinations of Symptoms and Signs

Three studies assessed combinations of findings to assist in establishing a diagnosis of early HIV infection.[49,50,52,58] Lavreys et al[58]evaluated 6 symptoms and signs among female sex workers,

Table. Summary Measures for Findings of Early HIV Infection[a]

| Finding | Studies | Sensitivity (95% CI) | Specificity (95% CI) | Likelihood Ratio | | | |
|---|---|---|---|---|---|---|---|
| | | | | Positive Results (95% CI) | $I^2$, % | Negative Results (95% CI) | $I^2$, % |
| **Symptoms** | | | | | | | |
| Genital ulcer[b] | 3[49-51] | 0.08 (0.02-0.24) | 0.99 (0.97-1.0) | 5.4 (2.5-12) | 83 | 0.99 (0.97-1.0) | 43 |
| Weight loss[c] | 7[49,52-57] | 0.21 (0.08-0.34) | 0.96 (0.91-1.0) | 4.7 (2.1-7.2) | 77 | 0.83 (0.72-0.94) | 73 |
| Vomiting[c] | 4[51,54,57,58] | 0.13 (0.05-0.31) | 0.97 (0.94-0.99) | 4.6 (2.5-8.0) | 0 | 0.90 (0.73-0.97) | 76 |
| Swollen lymph nodes[c] | 7[51,54-56,58-60] | 0.11 (0.02-0.21) | 0.98 (0.95-1.0) | 4.6 (1.3-8.0) | 52 | 0.91 (0.83-0.99) | 74 |
| Diarrhea[c] | 10[41,49-55,58,59] | 0.08 (0.02-0.14) | 0.98 (0.96-1.0) | 3.9 (2.3-5.4) | 54 | 0.94 (0.89-0.99) | 70 |
| Arthralgia[c] | 4[49,53,58,60] | 0.16 (0.10-0.24) | 0.96 (0.90-0.98) | 3.7 (1.9-7.4) | 65 | 0.88 (0.81-0.93) | 0 |
| Fever[c] | 12[49,51-54,56-62] | 0.33 (0.21-0.44) | 0.90 (0.86-0.95) | 3.4 (2.4-4.4) | 75 | 0.74 (0.64-0.84) | 78 |
| Oral | | | | | | | |
| Ulcer[c] | 5[49-51,54,57] | 0.13 (0.09-0.19) | 0.96 (0.91-0.98) | 3.4 (1.2-9.4) | 81 | 0.91 (0.84-0.98) | 70 |
| Thrush[b] | 3[41,53,62] | 0.03 (0.01-0.11) | 0.99 (0.98-1.0) | 3.3 (1.2-9.2) | 9 | 0.99 (0.98-1.0) | 3.9 |
| Nausea[b] | 3[49,54,55] | 0.10 (0.03-0.27) | 0.97 (0.92-0.99) | 3.2 (1.5-6.9) | 86 | 0.97 (0.92-0.99) | 29 |
| Pharyngitis[c] | 10[49-54,58,60,62,63] | 0.15 (0.08-0.23) | 0.95 (0.91-0.99) | 3.1 (1.2-5.0) | 79 | 0.89 (0.83-0.96) | 68 |
| Myalgia/arthralgia[c] | 4[50,51,54,59] | 0.29 (0.13-0.51) | 0.90 (0.85-0.94) | 2.9 (2.1-3.8) | 35 | 0.79 (0.57-0.92) | 85 |
| Night sweats[c] | 10[41,49,51-55,57,59,62] | 0.12 (0.06-0.18) | 0.96 (0.94-0.98) | 2.9 (1.4-4.4) | 76 | 0.92 (0.86-0.97) | 69 |
| Fatigue[c] | 8[49-51,54,55,58,59,62] | 0.22 (0.11-0.33) | 0.92 (0.87-0.97) | 2.6 (1.0-4.2) | 89 | 0.85 (0.75-0.96) | 80 |
| Headaches[c] | 9[49-51,54,55,58-60,62] | 0.18 (0.13-0.24) | 0.91 (0.88-0.94) | 2.1 (1.7-2.5) | 35 | 0.90 (0.85-0.93) | 16 |
| Genital wart[b] | 3[50,54,55] | 0.02 (0.01-0.09) | 0.99 (0.96-1.0) | 2.0 (0.68-6.1) | 21 | 0.99 (0.96-1.0) | 30 |
| Rash[c] | 7[49,50,53,55,58-60] | 0.06 (0.03-0.12) | 0.96 (0.95-0.97) | 1.5 (0.67-3.5) | 77 | 0.98 (0.92-1.0) | 56 |
| **Signs** | | | | | | | |
| Any lymphadenopathy[c] | 5[51-53,58,64] | 0.39 (0.10-0.67) | 0.88 (0.72-1.0) | 3.1 (1.0-5.2) | 91 | 0.70 (0.49-0.92) | 88 |
| Inguinal lymphadenopathy[c] | 5[51,53,55,58,65] | 0.25 (0.09-0.52) | 0.92 (0.67-0.98) | 3.1 (1.5-6.4) | 87 | 0.82 (0.69-0.92) | 85 |
| Genital ulcer[c] | 6[51-53,55,58,65] | 0.18 (0.02-0.65) | 0.93 (0.69-0.99) | 2.4 (1.5-3.6) | 52 | 0.89 (0.49-0.99) | 80 |
| Cervical lymphadenopathy[b] | 3[41,51,53] | 0.11 (0.04-0.28) | 0.95 (0.87-0.98) | 2.2 (1.1-4.3) | 71 | 0.95 (0.87-0.98) | 46 |
| Rash[c] | 4[41,51,52,58] | 0.08 (0.00-0.16) | 0.95 (0.90-0.99) | 1.5 (0.45-2.6) | 82 | 0.97 (0.91-1.0) | 74 |
| Axillary lymphadenopathy[b] | 3[41,51,53] | 0.06 (0.02-0.19) | 0.96 (0.90-0.99) | 1.5 (0.70-3.3) | 74 | 0.96 (0.90-0.99) | 82 |
| Genital wart[b] | 3[51,52,58] | 0.04 (0.01-0.16) | 0.98 (0.94-0.99) | 1.4 (0.51-3.6) | 0 | 0.98 (0.94-0.99) | 0 |

[a] See eTable 4 in the Supplement for results from individual studies.

[b] Separate univariate random-effects estimates for sensitivity, specificity, and likelihood ratio, for results that were available for only 3 different studies.

[c] Bivariate random-effects estimates for sensitivity, specificity, and likelihood ratio for results reported for 4 or more studies.

including recent fever, vomiting, diarrhea, being too sick to work, inguinal lymphadenopathy, and vaginal candidiasis. Among this sample, having 4 or more signs or symptoms made HIV much more likely (sensitivity, 0.17; specificity, 0.99; LR, 12; 95% CI, 7.7-20), whereas having no signs or symptoms (sensitivity, 0.79; specificity, 0.55) was associated with an LR of 0.39 (95% CI, 0.27-0.57). Sharghi et al[50] used data from a vaccine preparedness study to identify 4 key clinical factors predicting early HIV infection: recent sexually transmitted infection (chlamydia, nonspecific urethritis, or gonorrhea), recent fever or drenching night sweats, recent exposure to HIV, and any illness lasting 3 or more days. Among this sample, reporting 3 or 4 (sensitivity, 0.19; specificity, 0.97) of these findings gave an LR of 6.9 (95% CI, 4.3-11), whereas no signs or symptoms (sensitivity, 0.62; specificity, 0.65) gave an LR of 0.59 (95% CI, 0.45-0.77). Mlisana et al[49] assessed 17 symptoms and signs of early HIV infection. Among this sample, 4 or more symptoms (sensitivity, 0.14; specificity, 0.99) and signs gave an LR of 11 (95% CI, 5.2-21), whereas having no signs or symptoms (sensitivity, 0.12; specificity, 0.96) gave an LR of 0.91 (95% CI, 0.96-0.97). Using data from the 3 studies that considered combinations of historical features or physical examination findings,[49,50,58] the summary LR for a patient with 0 findings was 0.47 (95% CI, 0.38 – 0.58; $I^2$ = 0%). We did not include 2 studies using rapid HIV test results in their algorithms because these tests are not routinely available to physicians.[51,52]

## Limitations

Variation in HIV prevalence by geography and study setting precluded derivation of a single prior probability estimate. Establishing a diagnosis of early HIV will depend on the clinician knowing the HIV prevalence in his/her practice. For primary care clinicians not working in known higher-HIV-prevalence settings and uncertain of HIV prevalence in their clinical practice, we suggest using a pretest probability of 0.5% for presumed lower-risk patients (eg, outside of a known risk group) and 1.0% among higher-risk patients (eg, men who have sex with men, intravenous drug using).[33] Although the prevalence of disease has geographic variability, the change in prevalence may not affect the value of symptoms and signs because our metaregression statistics ($R^2$) suggested that the HIV prevalence does not affect LRs for most findings.

Symptoms of early HIV infection may be similar regardless of mode of HIV acquisition,[66] but intravenous drug users may report symptoms less frequently.[67] In this context, reviewed studies and studies used to derive prevalence estimates included heterogeneous populations including research studies of intravenous drug users, sex-trade workers, and men who have sex with men and clinical studies of individuals presenting to emergency departments, general practitioners, and sexually transmitted infection clinics. It is possible that groups of patients with different risk exposures (eg, intravenous drug users vs men who have sex with men) could self-report symptoms differently, which would create variability in the sensitivity and specificity. A potential source of a small amount of heterogeneity is that newer, more sensitive HIV testing techniques were not available for the older studies, which often assessed for symptoms and signs during scheduled follow-up periods (eg, every 6 months). Recent studies that used p24 antigen or polymerase chain reaction can identify individuals actively experiencing early or acute HIV infection before HIV antibodies and, in some cases, symptoms develop.[68] This would affect the sensitivity and specificity by classifying some patients with disease who would have been missed in older studies. Finally, many of these studies were done in high-prevalence settings, such as sub-Saharan Africa, where the prevalence of certain identified signs (eg, genital ulcer disease) is also more prevalent (eTable 1 in the Supplement).

## Scenario Resolution

This patient presented to the emergency department with possible HIV exposure through her recent sexual contacts and had findings consistent with a viral illness. Based on this, the physician may estimate the likelihood of early HIV infection at approximately 1%, depending on the baseline prevalence in this setting.[45] Using the results from the Table, the history of recent weight loss has the highest LR of all historical findings (LR, 4.7) and only modestly increases the likelihood of HIV infection to 4.5%. The history and physical examination are not particularly helpful in this case, and the physician should follow guidelines recommending universal HIV testing in this setting.[20,21] Should antibody testing be negative, where available, it would be reasonable to seek out the use of more sensitive testing modalities as described above or serial antibody testing when more sensitive tests are presently unavailable.[68]

## Clinical Bottom Line

Globally, the HIV epidemic remains a significant source of morbidity and mortality with large numbers of new infections in individuals who are unaware of their infection.[5] Because many benefits can result from early case identification, including reduced risk behavior,[6] improved survival,[7,8] and decreased HIV transmission,[9-11] several guidelines now recommend universal screening.[20,21]

Because early HIV infection is commonly associated with a well-described acute retroviral syndrome in the weeks after infection,[26] it could be hoped that the clinical examination could help identify symptoms and signs facilitating establishing the diagnosis of early HIV infection. Unfortunately, the likelihood ratios suggested that there was only limited utility of the clinical examination findings. Specifically, several patient history features, including genital ulcer disease, weight loss, vomiting, and swollen lymph nodes modestly increased the likelihood of early HIV infection being present, whereas the absence of lymphadenopathy on physical examination and the absence of recent fever on history slightly decreased the likelihood of the presence of early HIV infection. Individual studies assessing combinations of symptoms and signs showed that 4 or more findings increase the likelihood of early HIV infection (LR range, 7-12) whereas the absence of findings modestly decreased the likelihood of infection (negative LR, 0.47).[49,50,58]

Based on this evidence, when a physician suspects early HIV infection, a thorough assessment of possible HIV exposure through a sexual and drug use history should be undertaken. It is reasonable to closely examine the patient for genital ulcers and for pharyngeal, cervical, supraclavicular, epitrochlear, and inguinal or femoral lymphadenopathy.[69,70] In addition to HIV, genital ulcers could be caused by genital herpes, lymphogranuloma venereum, chancroid, or primary syphilis.[71]

Importantly, physician assessment of symptoms and signs of HIV infection may be unreliable for identifying findings characteristic for HIV.[46-48] Furthermore, the substantial costs and harms of not diagnosing HIV infection coupled with the limited utility of the LRs for the clinical examination findings means that physicians should not rely on the presence or absence of symptoms or signs to select patients for HIV testing. Instead, routine universal screening for HIV infection among adults is more effective for identifying HIV disease than the clinical examination.[20,21]

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## REFERENCES

**1**. Joint United Nations Programme on HIV/AIDS. Global report: UNAIDS report on the global AIDS epidemic 2013. http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2013/gr2013/UNAIDS_Global_Report_2013_en.pdf. Accessed May 2013.

**2**. Centers for Disease Control and Prevention. HIV in the United States: at a glance; November 2013. http://www.cdc.gov/hiv/pdf/statistics_basics_factsheet.pdf. Accessed May 2013.

**3**. Centers for Disease Control and Prevention. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 US dependent areas—2010. HIV Surveillance Supplemental Report 2012;17(3 part A). http://www.cdc.gov/hiv/pdf/statistics_2010_HIV_Surveillance_Report_vol_17_no_3.pdf. Published June 2012. Accessed June 24, 2014.

**4**. Centers for Disease Control and Prevention. Estimated HIV incidence in the United States, 2007–2010. HIV Surveillance Supplemental Report 2012;17(No. 4):December 2012. http://www.cdc.gov/hiv/surveillance/resources/reports/2010supp_vol17no4/. Accessed June 24, 2014.

**5**. Marks G, Crepaz N, Janssen RS. Estimating sexual transmission of HIV from persons aware and unaware that they are infected with the virus in the USA. *AIDS*. 2006;20(10):1447-1450.

**6**. Dombrowski JC, Harrington RD, Golden MR. Evidence for the long-term stability of HIV transmission-associated sexual behavior after HIV diagnosis. *Sex Transm Dis*. 2013;40(1):41-45.

**7**. Kitahadta MM, Gange SJ, Abraham AG, et al; NA-ACCORD Investigators. Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med*. 2009;360(18):1815-1826.

**8**. El-Sadr WM, Lundgren J, Neaton JD, et al; Strategies for Management of Antiretroviral Therapy (SMART) Study Group. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med*. 2006;355(22):2283-2296.

**9**. Cohen MS, Chen YQ, McCauley M, et al; HPTN 052 Study Team. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. 2011;365(6):493-505.

**10**. Jia Z, Mao Y, Zang F, et al. Antiretroviral therapy to prevent HIV transmission in serodiscordant couples in China (2003-11): a national observational cohort study. *Lancet*. 2013;382(9899):1195-1203.

**11**. Wood E, Kerr T, Marshall BD, et al. Longitudinal community plasma HIV-1 RNA concentrations and incidence of HIV-1 among injecting drug users: prospective cohort study. *BMJ*. 2009;338:b1649.

**12**. Powers KA, Ghani AC, Miller WC, et al. The role of acute and early HIV infection in the spread of HIV and implications for transmission prevention strategies in Lilongwe, Malawi: a modelling study. *Lancet*. 2011;378(9787):256-268.

**13**. Thompson MA, Aberg JA, Hoy JF, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA panel. *JAMA*. 2012;308(4):387-402.

**14**. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet*. 2009;373(9657):48-57.

**15**. Yerly S, Hirschel B. Diagnosing acute HIV infection. *Expert Rev Anti Infect Ther*. 2012;10(1):31-41.

**16**. 2013 Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents: considerations for antiretroviral use in special patient populations acute and Recent (Early*) HIV Infection. http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/glchunk/glchunk_20.pdf. Updated June, 23, 2014. Accessed August 2013.

**17**. Phillips AN, Elford J, Sabin C, Bofill M, Janossy G, Lee CA. Immunodeficiency and the risk of death in HIV infection. *JAMA*. 1992;268(19):2662-2666.

**18**. Richey LE, Halperin J. Acute human immunodeficiency virus infection. *Am J Med Sci*. 2013;345(2):136-142.

**19**. McKellar MS, Cope AB, Gay CL, et al; Duke-Unc Acute HIV Infection Consortium. Acute HIV-1 infection in the Southeastern United States: a cohort study. *AIDS Res Hum Retroviruses*. 2013;29(1):121-128.

**20**. Branson BM, Handsfield HH, Lampe MA, et al Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep*. 2006;55(RR-14):1-17.

**21**. Moyer VA; US Preventive Services Task Force. Screening for HIV: US Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2013;159(1):51-60.

**22**. Daar ES, Pilcher CD, Hecht FM. Clinical presentation and diagnosis of primary HIV-1 infection. *Curr Opin HIV AIDS*. 2008;3(1):10-15.

**23**. Herrin J, Wesolowski LG, Heffelfinger JD, et al. HIV screening practices and hospital characteristics in the US, 2009-2010. *Public Health Rep*. 2013;128(3):161-169.

**24**. Ellis S, Curtis H, Ong EL; British HIV Association (BHIVA); BHIVA Clinical Audit and Standards sub-committee. HIV diagnoses and missed opportunities: results of the British HIV Association (BHIVA) national audit 2010. *Clin Med*. 2012;12(5):430-434.

**25**. Kahn JO, Walker BD. Acute human immunodeficiency virus type 1 infection. *N Engl J Med*. 1998;339(1):33-39.

**26**. Cohen MS, Shaw GM, McMichael AJ, Haynes BF. Acute HIV-1 infection. *N Engl J Med*. 2011;364(20):1943-1954.

**27**. Vanhems P, Lambert J, Cooper DA, et al. Severity and prognosis of acute human immunodeficiency virus type 1 illness: a dose-response relationship. *Clin Infect Dis*. 1998;26(2):323-329.

**28**. Mellors JW, Rinaldo CR Jr, Gupta P, White RM, Todd JA, Kingsley LA. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. *Science*. 1996;272(5265):1167-1170.

**29**. Haynes RB, McKibbon KA, Wilczynski NL, Walter SD, Werre SR; Hedges Team. Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. *BMJ*. 2005;330(7501):1179.

**30**. Simel DL, Rennie D, eds. *Rational Clinical Examination: The Evidence-Based Clinical Diagnosis*. New York, NY: McGraw-Hill; 2008:9-16.

**31**. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol*. 2003;3:25.

**32**. Whiting PF, Weswood ME, Rutjes AW, Reitsma JB, Bossuyt PN, Kleijnen J. Evaluation of QUADAS, a tool for the quality assessment of diagnostic accuracy studies. *BMC Med Res Methodol*. 2006;6:9.

**33**. Centers for Disease Control and Prevention. Diagnoses of HIV infection in the United States and dependent areas, 2011: Surveillance Report, 2011. http://www.cdc.gov/hiv/library/reports/surveillance/2011/surveillance_report_vol_23.html. Published February 2013. Accessed June 24, 2014.

**34**. World Health Organization. Data on the size of the HIV/AIDS epidemic: Prevalence of HIV among adults aged 15 to 49 (%) by country. http://apps.who.int/gho/data/node.main.622?lang=en Accessed September 10, 2013.

**35**. Simel DL, Easter J, Tomlinson G. Likelihood ratios, sensitivity, and specificity values can be back-calculated when the odds ratios are known. *J Clin Epidemiol*. 2013;66(4):458-460.

**36**. Simel DL, Bossuyt PM. Differences between univariate and bivariate models for summarizing diagnostic accuracy may not be large. *J Clin Epidemiol*. 2009;62(12):1292-1300.

**37**. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.

**38**. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558.

**39**. Borenstein MHL, Higgins J, Rothstein H. *Introduction to Meta-Analysis.* Wiley Online Library; 2009.

**40**. Zetola NM, Bernstein KT, Wong E, Louie B, Klausner JD. Exploring the relationship between sexually transmitted diseases and HIV acquisition by using different study designs. *J Acquir Immune Defic Syndr*. 2009;50(5):546-551.

**41**. Sullivan PS, Fideli U, Wall KM, et al. Prevalence of seroconversion symptoms and relationship to set-point viral load: findings from a subtype C epidemic, 1995-2009. *AIDS*. 2012;26(2):175-184.

**42**. Zetola NM, Kaplan B, Dowling T, et al. Prevalence and correlates of unknown HIV infection among patients seeking care in a public hospital emergency department. *Public Health Rep*. 2008;123(suppl 3):41-50.

**43**. Pincus JM, Crosby SS, Losina E, King ER, LaBelle C, Freedberg KA. Acute human immunodeficiency virus infection in patients presenting to an urban urgent care center. *Clin Infect Dis*. 2003;37(12):1699-1704.

**44**. Hsu DT, Ruf M, O'Shea S, Costelloe S, Peck J, Tong C. Diagnosing HIV infection in patients presenting with glandular fever-like illness in primary care: are we missing primary HIV infection? *HIV Med*. 2013;14(1):60-63.

**45**. Coco A, Kleinhans E. Prevalence of primary HIV infection in symptomatic ambulatory patients. *Ann Fam Med*. 2005;3(5):400-404.

**46**. Fontaine A, Larue F, Lassaunière JM. Physicians' recognition of the symptoms experienced by HIV patients: how reliable? *J Pain Symptom Manage*. 1999;18(4):263-270.

**47**. Paauw DS, Wenrich MD, Curtis JR, Carline JD, Ramsey PG. Ability of primary care physicians to recognize physical findings associated with HIV infection. *JAMA*. 1995;274(17):1380-1382.

**48**. Coates RA, Fanning MM, Johnson JK, Calzavara L. Assessment of generalized lymphadenopathy in AIDS research: the degree of clinical agreement. *J Clin Epidemiol*. 1988;41(3):267-273.

**49**. Mlisana K, Sobieszczyk M, Werner L, et al. Challenges of diagnosing acute HIV-1 subtype C infection in African women: performance of a clinical algorithm and the need for point-of-care nucleic-acid based testing. *PLoS One*. 2013;8(4):e62928.

**50**. Sharghi N, Bosch RJ, Mayer K, Essex M, Seage GR III. The development and utility of a clinical algorithm to predict early HIV-1 infection. *J Acquir Immune Defic Syndr*. 2005;40(4):472-478.

**51**. Wahome E, Fegan G, Okuku HS, et al. Evaluation of an empiric risk screening score to identify acute and early HIV-1 infection among MSM in Coastal Kenya. *AIDS*. 2013;27(13):2163-2166.

**52**. Powers KA, Miller WC, Pilcher CD, et al; Malawi UNC Project Acute HIV Study Team. Improved detection of acute HIV-1 infection in sub-Saharan Africa: development of a risk score algorithm. *AIDS*. 2007;21(16):2237-2242.

**53**. Bollinger RC, Brookmeyer RS, Mehendale SM, et al. Risk factors and clinical presentation of acute primary HIV infection in India. *JAMA*. 1997;278(23):2085-2089.

**54**. Hofer CB, Harrison LH, Struchiner CJ, et al; Projecto Praça Onze Study Group. Acute retrovirus syndrome among prospectively identified homosexual men with incident HIV infection in Brazil. *J Acquir Immune Defic Syndr*. 2000;25(2):188-191.

**55**. Lemonovich TL, Watkins RR, Morrison CS, et al Differences in clinical manifestations of acute and early HIV-1 infection between HIV-1 subtypes in African women [published online October 8, 2014]. *J Int Assoc Provid AIDS Care*. 2013.

**56**. Sanchez J, Lama JR, Peinado J, et al. High HIV and ulcerative sexually transmitted infection incidence estimates among men who have sex with men in Peru: awaiting for an effective preventive intervention. *J Acquir Immune Defic Syndr*. 2009;51(suppl 1):S47-S51.

**57**. Marmor M, Titus S, Harrison C, et al. Weight loss associated with HIV seroconversion among injection-drug users. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1996;12(5):514-518.

**58**. Lavreys L, Thompson ML, Martin HL Jr, et al. Primary human immunodeficiency virus type 1 infection: clinical manifestations among women in Mombasa, Kenya. *Clin Infect Dis*. 2000;30(3):486-490.

**59**. Fox R, Eldred LJ, Fuchs EJ, et al. Clinical manifestations of acute infection with human immunodeficiency virus in a cohort of gay men. *AIDS*. 1987;1(1):35-38.

**60**. Morgan D, Mahe C, Whitworth J. Absence of a recognizable seroconversion illness in Africans infected with HIV-1. *AIDS*. 2001;15(12):1575-1576.

**61**. Krämer A, Biggar RJ, Hampl H, et al. Immunologic markers of progression to acquired immunodeficiency syndrome are time-dependent and illness-specific. *Am J Epidemiol*. 1992;136(1):71-80.

**62**. Mientjes GH, van Ameijden EJ, Weigel HM, van den Hoek JA, Coutinho RA. Clinical symptoms associated with seroconversion for HIV-1 among misusers of intravenous drugs: comparison with homosexual seroconverters and infected and non-infected intravenous drug misusers. *BMJ*. 1993;306(6874):371-373.

**63**. Fox PA, Hawkins DA, Boag FC. HIV seroconversion illness following acute hepatitis A. *Sex Transm Infect*. 1999;75(2):133.

**64**. Boyko WJ, Schechter MT, Craib KJ, et al. The Vancouver Lymphadenopathy-AIDS Study: 7. Clinical and laboratory features of 87 cases of primary HIV infection. *CMAJ*. 1987;137(2):109-113.

**65**. Pilcher CD, Price MA, Hoffman IF, et al. Frequent detection of acute primary HIV infection in men in Malawi. *AIDS*. 2004;18(3):517-524.

**66**. Vanhems P, Allard R, Cooper DA, et al. Acute human immunodeficiency virus type 1 disease as a mononucleosis-like illness: is the diagnosis too restrictive? *Clin Infect Dis*. 1997;24(5):965-970.

**67**. Vanhems P, Routy JP, Hirschel B, et al; Collaborative Group. Clinical features of acute retroviral syndrome differ by route of infection but not by gender and age. *J Acquir Immune Defic Syndr*. 2002;31(3):318-321.

**68**. Pilcher CD, McPherson JT, Leone PA, et al. Real-time, universal screening for acute HIV infection in a routine HIV counseling and testing population. *JAMA*. 2002;288(2):216-221.

**69**. Caponetti G, Pantanowitz L. HIV-associated lymphadenopathy. *Ear Nose Throat J*. 2008;87(7):374-375.

**70**. Motyckova G, Steensma DP. Why does my patient have lymphadenopathy or splenomegaly? *Hematol Oncol Clin North Am*. 2012;26(2):395-408.

**71**. Schmid GP. Approach to the patient with genital ulcer disease. *Med Clin North Am*. 1990;74(6):1559-1572.

**72**. UNAIDS. Report on the Global HIV/AIDS Epidemic. Geneva, Switzerland: UNAIDS and World Health Organization; November 2012: http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/20121120_unaids_global_report_2012_with_annexes_en.pdf. Accessed June 24, 2014.