



CLINICAL GUIDELINES PROGRAM

NEW YORK STATE DEPARTMENT OF HEALTH AIDS INSTITUTE | HIV · HCV · SUBSTANCE USE · LGBT HEALTH

Diagnosis and Management of Acute HIV

Medical Care Criteria Committee, September 2015

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Diagnosis and Management of Acute HIV

Introduction

Medical Care Criteria Committee, September 2015

→ WHAT'S NEW—SEPTEMBER 2015 UPDATE

- The Medical Care Criteria Committee recognizes the ongoing need to raise clinical awareness among providers to increase identification and assessment of acute HIV infection. These guidelines emphasize the critical importance of diagnosing acute HIV infection (see Presentation and Diagnosis) and highlight mounting evidence supporting treatment of HIV infection as soon as diagnosed. As indicated in the NYSDOH AI guideline *When to Initiate ART*, the Medical Care Criteria Committee now recommends ART for all patients with HIV.

Editor's Note: In the medical literature, as in this guideline, the terms “acute HIV infection” and “primary HIV infection” both describe the period immediately after infection when the patient is viremic and has detectable p24 antigen and/or HIV RNA without diagnostic HIV antibodies. For consistency, the term “acute HIV infection” is used in these guidelines.

The term “recent infection” is generally used to describe the 6-month period after infection occurs. “Early infection” refers to both acute and recent infection, after which infection is defined as chronic.

In the United States, individuals with acute HIV infection account for less than 1% of all those with HIV. However, the estimated range of incident HIV transmission in the setting of acute infection is 8.6% to 50% [Brenner et al. 2007; Yerly et al. 2001; Wawer et al. 2005; Pinkerton 2007; Powers et al. 2011]. The risk of sexual transmission of HIV during acute or recent infection is significantly higher than during chronic infection [Pinkerton 2008; Pilcher et al. 2004; Hollingsworth et al. 2008; Hollingsworth et al. 2015]. Although estimates are sensitive to modeling assumptions [Bellan et al. 2015], this difference likely correlates with high levels of viremia and is consistent with other routes of transmission. Many challenges are inherent in modeling transmission risk; the refinement of these models will have important implications for HIV treatment as a prevention strategy [Zhang et al. 2012].

Accumulating evidence supports a decision to begin HIV treatment at the time of diagnosis [INSIGHT START Study Group 2015]. Initiation of antiretroviral therapy (ART) during acute infection may have a number of beneficial clinical outcomes, including improved preservation of immunologic function, significantly reduced time to viral suppression, and reduction of the viral reservoir, which could be important for cure strategies [Streeck et al. 2006; Koegl et al. 2009; Le et al. 2013; Pilcher et al. 2015; Pires et al. 2004; Buzon et al. 2012; Ananworanich et al. 2012; Phanuphak et al. 2012; Hocqueloux et al. 2010; Lefeullade et al. 2012; Saez-Cirion et al. 2013; Margolick et al. 2012]. The public health benefit of early initiation of ART is well documented, with a significant reduction of HIV transmission among virally suppressed individuals.

Recognizing and diagnosing acute infection is crucial to linking patients to care early and presents an important opportunity for prevention. Factors that may contribute to the increased risk for transmission during acute infection include:

- Hyperinfectivity associated with both markedly increased viral load levels (often much greater than 10 million viral copies/mm³) and increased infectiousness of the virus [Ma et al. 2009; Quinn et al. 2000]

- Missed HIV diagnosis [Chin et al. 2013] because the nonspecific flu- or mono-like symptoms during acute illness are frequently unrecognized; a diagnosis would prompt providers to recommend treatment and risk-reduction counseling that could reduce both viral load levels and high-risk behavior [Fonner et al. 2012; Steward et al. 2009; Colfax et al. 2002]

For many reasons, detection of acute HIV infection can be a very important link in the chain of prevention. Evidence demonstrates that patients with a recent diagnosis of HIV are more likely to reduce risk behaviors if they are given counseling at the time of testing [Fonner et al. 2012; Steward et al. 2009] and are linked to primary HIV care [Metsch et al. 2008]. In addition, for those who elect to initiate ART, their risk of transmission is significantly diminished [Cohen et al. 2011].

→ RESOURCE

- When a diagnosis of acute infection is made, clinicians should discuss the importance of notifying all recent contacts and refer patients to partner notification services, as mandated by New York State Law. The Department of Health can provide assistance if necessary. See NYSDOH Provider Reporting & Partner Services for more information about required reporting.

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Presentation and Diagnosis

✓ RECOMMENDATIONS

NYS HIV Testing Requirements

- According to New York State Law, physicians must also offer an HIV test to all patients between the ages of 13 and 64 years (or older/younger with risk) if a previous test is not documented, even in the absence of symptoms consistent with acute HIV. Although written consent to HIV testing is no longer required in New York State, patients must be given the opportunity to decline, and verbal consent must be documented in the medical record.

Presentation

- Clinicians should include acute HIV infection in the differential diagnosis for *anyone* (regardless of reported risk) with a flu- or mono-like illness (A3), especially when the patient:
 - Presents with a rash (A2)
 - Requests HIV testing (A3)
 - Reports recent sexual or parenteral exposure to a person with or at risk for HIV infection (A2)
 - Presents with a newly diagnosed sexually transmitted infection (A2)
 - Presents with aseptic meningitis (A2)
 - Is pregnant or breastfeeding (A3)
 - Is currently on pre- or post-exposure prophylaxis (PrEP or PEP) (A3)

When Acute HIV Infection Is Suspected

- A plasma HIV RNA assay should always be used in conjunction with an antigen/antibody combination screening test. (A2)
- A fourth-generation antigen/antibody combination assay is recommended as the initial HIV screening test according to the CDC's Recommended Laboratory HIV Testing Algorithm for Serum or Plasma Specimens. If the screening test is reactive, an HIV-1/HIV-2 antibody-differentiation immunoassay should be performed to confirm HIV infection; Western blot is no longer recommended as the confirmatory test (A2). [Note: When rapid antibody screening is performed, including screening with a rapid fourth-generation test, a laboratory-based fourth-generation immunoassay is recommended in follow-up diagnostic HIV testing.]

Diagnosis

- Detection of HIV RNA with $\geq 5,000$ copies/mL should be considered a presumptive diagnosis of acute infection even if the screening and antibody-differentiation tests are nonreactive or indeterminate. (A2)
- HIV RNA testing should be repeated to exclude a false-positive result when low-level quantitative results (< 5000 copies/mL) from an HIV RNA assay are reported in the absence of serologic evidence of HIV infection. (A2) [Note: The absence of serologic evidence of HIV infection is defined as a nonreactive screening result (antibody or antibody/antigen combination) or a reactive screening result with a nonreactive or indeterminate antibody-differentiation confirmatory result.]
- If a diagnosis of HIV infection is made on the basis of HIV RNA testing alone, a new specimen should be collected 3 weeks later and HIV diagnostic testing should be repeated according to the CDC HIV testing algorithm. (A2)
- If a diagnosis of acute infection is made on the basis of HIV RNA testing, initiation of ART should be recommended while awaiting serologic confirmation. (A2)
- When pregnant women are diagnosed with acute infection by HIV RNA testing, clinicians should *not* wait for results of a confirmatory test to initiate ART; initiation of ART is strongly recommended for pregnant women. (A2)
 - See NYSDOH AI guideline *HIV Testing During Pregnancy and at Delivery*

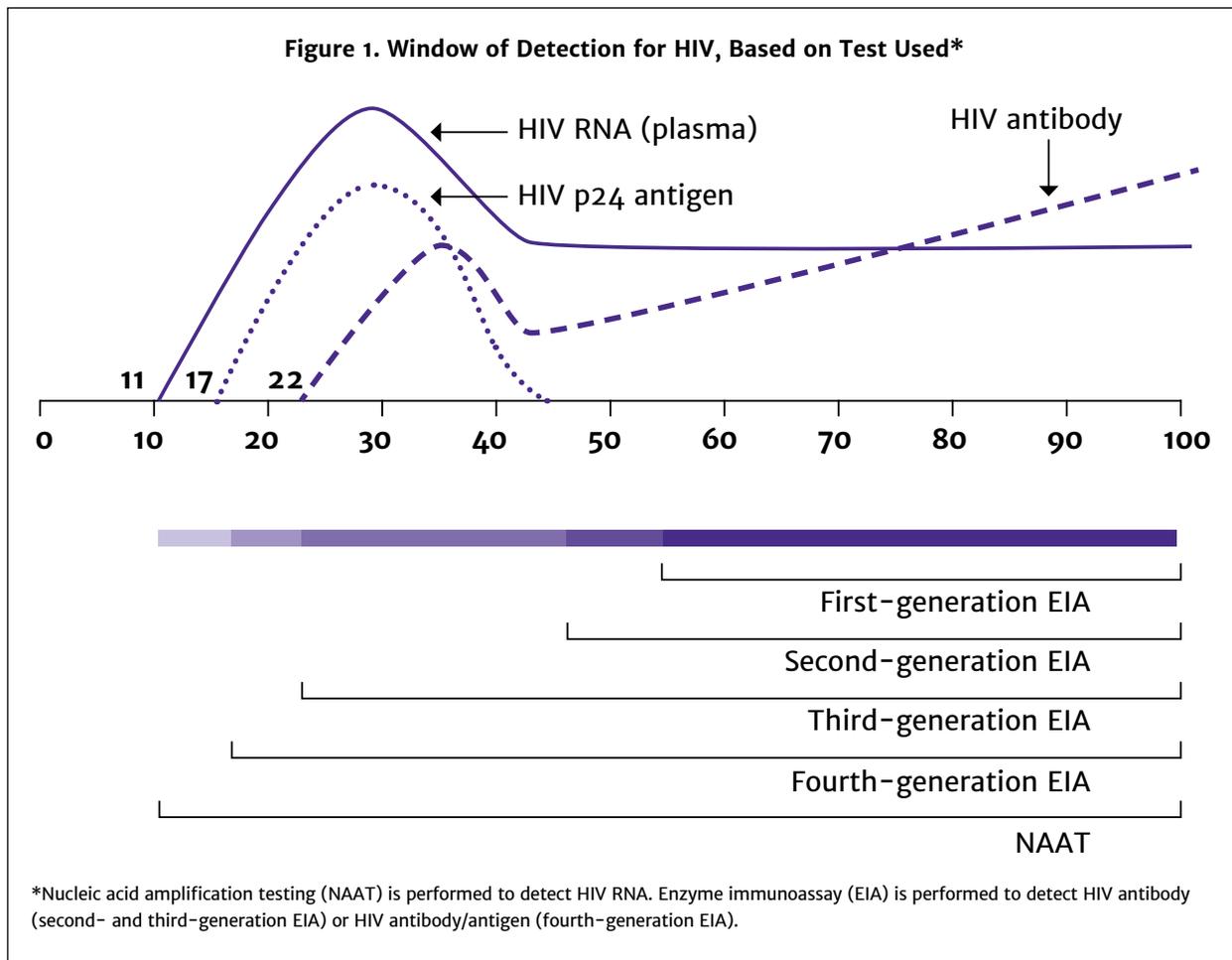
NYS Reporting Requirement and Partner Notification

- Clinicians must report confirmed cases of HIV according to New York State Law (see NYSDOH Provider Reporting and Partner Services for more information about required reporting).
- Clinicians should offer assistance with partner notification and refer patients to other sources for partner notification assistance (Partner Services or CNAP). (A2)

KEY POINTS

- The diagnosis of acute HIV infection requires a high degree of clinical awareness. The nonspecific signs and symptoms of acute HIV infection are often not recognized.
- Diagnostic HIV RNA testing should be considered for patients who present with compatible symptoms (see Acute Retroviral Syndrome), particularly in the context of a sexually transmitted infection [Patel et al. 2006] or a recent sexual or parenteral exposure with a partner known to have HIV or a partner whose HIV serostatus is not known.

The time from HIV infection to detection of the virus depends on the test that is used. Figure 1 illustrates the window of detection of HIV infection according to antibody, antibody/antigen combination, and HIV RNA tests.



Presentation: Patients acutely infected with HIV will often experience at least some symptoms of acute retroviral syndrome. Fever and flu- or mono-like symptoms are common in acute HIV infection but are nonspecific. Rash, mucocutaneous ulcers, oropharyngeal candidiasis, and meningismus are more specific and should raise the index of suspicion. See Acute Retroviral Syndrome for a more extensive list of signs and symptoms. The mean time from exposure to onset of symptoms is generally 2 to 4 weeks, with a range of 5 to 29 days; however, some cases have presented with symptoms up to 3 months after exposure [Apoola et al. 2002]. Theoretically, this time course may be prolonged in patients who become infected while on PEP or PrEP.

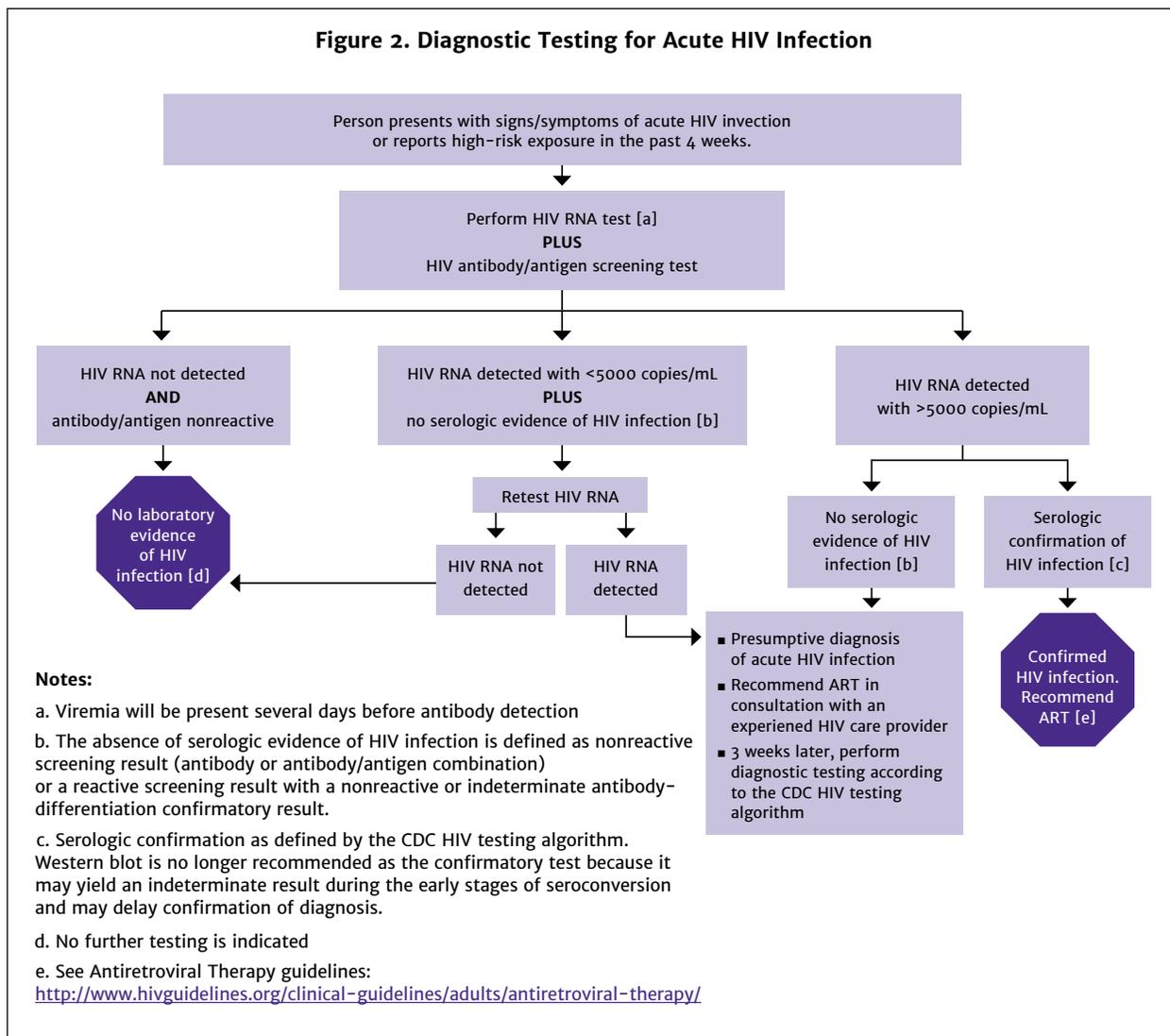
Diagnosis: Acute HIV infection is often not recognized in the primary care setting because the symptom profile is similar to that of influenza, mononucleosis, and other common illnesses. Furthermore, patients often do not recognize that they may have recently been exposed to HIV. Therefore, the clinician should have a high index of suspicion for acute HIV infection in a patient who may have recently engaged in behavior involving sexual or

parenteral exposure to another person’s blood or body fluids and who is presenting with a febrile, flu-, or mono-like illness. Identification of acute HIV infection during pregnancy is particularly important to ensure appropriate steps are taken to prevent mother-to-child transmission [Patterson et al. 2007].

When clinicians suspect acute infection, a test for plasma HIV RNA should be performed. High levels of HIV RNA detected in plasma through use of sensitive nucleic acid amplification testing (NAAT), in combination with a negative or indeterminate HIV screening or type-differentiation test, support the presumptive diagnosis of acute HIV infection.

When low-level viremia is reported by HIV RNA testing (<5000 copies/mL) in the absence of serologic evidence of HIV infection, HIV RNA testing should be repeated to exclude a false-positive result [Hecht et al. 2002]. Repeat HIV RNA testing with a result of low-level viremia may represent true HIV infection, warranting appropriate counseling regarding transmission risk. ART should be recommended in the setting of low-level viremia that has been confirmed by repeat HIV RNA testing.

HIV RNA levels tend to be very high in acute infection; however, a low value may represent any point on the upward or downward slope of the viremia associated with acute infection or could simply represent chronic infection. Plasma HIV RNA levels during acute infection do not appear significantly different in patients who have symptoms versus those who are asymptomatic [Pilcher et al. 2004]. Viremia occurs approximately 2 weeks prior to the detection of a specific immune response. Patients diagnosed with acute infection by HIV RNA testing should always receive follow-up diagnostic testing 3 weeks later to confirm infection (see the CDC HIV testing algorithm) [CDC 2014; CDC 2013]. Figure 2 illustrates diagnostic testing for acute HIV infection.



8 → KEY POINTS IN ACUTE HIV DIAGNOSTIC TESTING

- Patients undergoing HIV testing who are not suspected to have acute infection should receive screening according to the standard protocol (see the CDC HIV testing algorithm). Patients with clinical signs or symptoms of acute retroviral syndrome or who are at high risk for acute infection should receive HIV screening and HIV RNA testing simultaneously.
- A positive HIV RNA assay is a preliminary diagnosis of HIV; ART should be recommended while waiting for confirmatory testing.
- Individual laboratories have internal protocols for reporting HIV tests with preliminary results: *indeterminate*, *inconclusive*, *nondiagnostic*, and *pending validation* are among the terms used when preliminary results cannot be classified definitively. The clinician should contact the appropriate laboratory authority to determine the significance of the nondefinitive results and the supplemental testing that would be indicated. This is of particular importance in tests from patients with suspected acute HIV infection. Clinicians should become familiar with the internal test-reporting policies of their institutions.

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Management, Including While on PEP or PrEP

✓ RECOMMENDATIONS

Managing Acute HIV

- ART should be recommended for all patients with a diagnosis of acute HIV infection. (A2)
- Clinicians should inform patients about the increased risk of transmitting HIV during acute HIV infection. (A2)
- As part of the initial management of patients diagnosed with acute HIV infection, clinicians should:
 - Consult with a provider experienced in the treatment of acute HIV infection (A3)
 - Obtain baseline HIV genotypic resistance testing, regardless of whether ART is being initiated (A2)
- **Patients taking PEP:** When acute HIV infection is diagnosed in a person receiving PEP, ART should be continued pending consultation with an experienced HIV care provider. (A3)
- **Patients taking PrEP:** When acute HIV infection is diagnosed in a person receiving PrEP, a fully active ART regimen should be recommended in consultation with an experienced HIV care provider. (A3)

Initiating ART

- If the clinician and patient have made a decision to initiate ART during acute HIV infection:
 - Treatment should be implemented with the goal of suppressing plasma HIV RNA to below detectable levels (A1)
 - Treatment should not be withheld while awaiting the results of recommended resistance testing; adjustments may be made to the regimen once resistance results are available (A3)
- Clinicians who do not have access to experienced HIV care providers should call the Clinical Education Initiative (CEI) Line at 1-866-637-2342.

Patients are at greatest risk for transmitting HIV during periods of high viremia early in infection. Clinicians should counsel acutely infected patients about the increased risk of transmission during the 6-month period after infection. Partner notification [Golden et al. 2004], safer sex counseling, and screening for other sexually transmitted infections are all important in the management of any new HIV diagnosis.

Consult an Experienced Care Provider

- When choosing an ART regimen for a patient with acute HIV infection, a provider experienced in the treatment of acute HIV infection should be consulted.
- Data are insufficient to support firm recommendations regarding specific regimens for treating acute HIV infection.
- The risks of transmitted resistance should be considered when prescribing ART while awaiting HIV resistance results.

Clinicians who do not have access to experienced HIV care providers should call the Clinical Education Initiative (CEI) Line at 1-866-637-2342.

The rationale for early treatment (CD4 count >500 cells/mm³) in chronic infection has been definitively demonstrated with the release of preliminary results from the START study. The data show a 53% reduction in serious illness or death in the early treatment arm [INSIGHT START 2015]. There is also mounting evidence suggesting that ART during recent infection may have a range of beneficial effects on clinical outcomes, including an increased likelihood of CD4 cell recovery [Streeck et al. 2006; Koegl et al. 2009; Le et al. 2013], significantly reduced time to viral suppression [Pilcher et al. 2015], a decrease in viral reservoir and preservation of gut-associated lymphoid tissue [Pires et al. 2004; Buzon et al. 2012; Ananworanich et al. 2012; Phanuphak et al. 2012], and the small possibility of long-term control of HIV infection after cessation of therapy [Hocqueloux et al. 2010; Lafeuillade et al. 2012; Saez-Cirion et al. 2013; Margolick et al. 2012].

KEY POINT

- If the decision to initiate treatment has been made, therapy should not be withheld while awaiting the results of resistance testing. Adjustments may be made to the regimen once resistance results are available (see the NYSDOH AI guideline *HIV Resistance Assays*).

Three randomized controlled studies compared deferred therapy versus immediate initiation of therapy in acute or recent infection [Fidler et al. 2013; Grijzen et al. 2012; Hogan et al. 2012]. These studies demonstrated that immediate initiation of ART delayed a decrease in CD4 counts to <350 cells/mm³ compared with no therapy. One of the most notable findings across these studies was the high percentage of patients in the deferred-therapy arms who progressed to CD4 counts <350 cells/mm³ within the first year after infection. That finding suggests that if the decision is made to postpone initiation of ART, most patients will experience significant immune decline fairly rapidly.

Although these studies may have over-sampled symptomatic patients, a population that has been shown to progress more rapidly [Lavreys et al. 2006; Vanhems et al. 1998], previous estimates that included more asymptomatic patients nevertheless found an average time of 1.5 years after seroconversion for CD4 counts to decline to <350 cells/mm³ [CASCADE Collaboration 2000]. The findings suggest that the amount of time off therapy gained by deferring initiation will be limited, relative to the need for lifelong treatment.

Notably, these studies not only used an outdated recommended CD4 count threshold (i.e., <350 cells/mm³ versus the current recommendations of early treatment at any CD4 count, including those with CD4 counts >500 cells/mm³), they also investigated various durations of ART followed by treatment interruption [Fidler et al. 2013; Grijzen et al. 2012; Hogan et al. 2012]. With evidence that treatment interruptions carry significant risks of morbidity and mortality [El-Sadr et al. 2006], as well as increased transmission risk during viral rebound [Hamlyn et al. 2012; Rieder et al. 2010], the findings regarding treatment interruption no longer have relevance for individualized treatment decisions in the context of acute or chronic HIV infection.

The clinician and the patient should be aware that the public health benefit of early initiation of ART is well documented despite the difficulty of designing randomized trials of sufficient size and duration that could conclusively demonstrate long-term clinical benefit from therapy for acute HIV infection. Published data increasingly support a decision to begin treatment at the time of diagnosis. There should be a discussion of the potential benefits versus the limited risks (listed below), with an emphasis on current recommendations for when to initiate ART, the short time between infection and CD4 count decline in randomized controlled studies, and the benefits in preventing transmission.

Theoretical rationale for initiating ART during acute infection:

- Reduction in the risk of viral transmission
- Preservation of HIV-specific immune function, including the promotion of the survival of CD4 cells that are involved in the initial response to HIV infection
- Suppression of the initial burst of viral replication with a decrease in the magnitude of viral dissemination, which reduces reservoir size and may preserve gut-associated lymphoid tissue
- Potential reduction in the emergence of viral mutations with the suppression of viral replication
- Potential to reduce the severity and duration of illness during symptomatic acute HIV infection
- Potential to reduce the risk of HIV superinfection (i.e., reinfection with a second strain of HIV) [Redd et al. 2013]

Potential disadvantages of initiating ART during acute infection:

- Development of drug resistance if therapy fails due to nonadherence or insufficient suppression of viral replication
- Adverse effects on quality of life as a result of drug toxicities
- Earlier commitment to lifetime ART

Resistance testing should be obtained to optimize the initial ART regimen. The increasing incidence of transmission of antiretroviral resistance [Kim et al. 2013] argues for resistance testing at baseline in all HIV-infected patients, including those who are acutely infected. Antiretroviral drug resistance mutations are more likely to be detected when genotypic resistance testing is performed at the time of recent infection [Kim et al. 2013]. If information about the possible source person is available, history of antiretroviral drug resistance should be obtained to assist in selection of a regimen. In cases where there are multiple possible sources, as much information should be gathered as possible. All patients should be provided a copy of their baseline resistance test in the event that they defer therapy and initiate treatment later with a different provider.

If therapy is initiated during acute HIV infection, clinicians should continue to treat the patient with ART indefinitely because viremia has been documented to reappear or increase after discontinuation of therapy, and treatment interruptions have been shown to lead to greater morbidity and mortality [El-Sadr et al. 2006].

Regardless of whether or not ART for acute HIV infection is initiated, follow-up for standard HIV testing and HIV primary care should be arranged (see NSYDOH AI guideline *Primary Care Approach*).

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All Recommendations Medical Care Criteria Committee, September 2015

✓ ALL RECOMMENDATIONS

NYS HIV Testing Requirements

- According to New York State Law, physicians must also offer an HIV test to all patients between the ages of 13 and 64 years (or older/younger with risk) if a previous test is not documented, even in the absence of symptoms consistent with acute HIV. Although written consent to HIV testing is no longer required in New York State, patients must be given the opportunity to decline, and verbal consent must be documented in the medical record.

Presentation

- Clinicians should include acute HIV infection in the differential diagnosis for *anyone* (regardless of reported risk) with a flu- or mono-like illness (A3), especially when the patient:
 - Presents with a rash (A2)
 - Requests HIV testing (A3)
 - Reports recent sexual or parenteral exposure to a person with or at risk for HIV infection (A2)
 - Presents with a newly diagnosed sexually transmitted infection (A2)
 - Presents with aseptic meningitis (A2)
 - Is pregnant or breastfeeding (A3)
 - Is currently on pre- or post-exposure prophylaxis (PrEP or PEP) (A3)

When Acute HIV Infection Is Suspected

- A plasma HIV RNA assay should always be used in conjunction with an antigen/antibody combination screening test. (A2)
- A fourth-generation antigen/antibody combination assay is recommended as the initial HIV screening test according to the CDC's Recommended Laboratory HIV Testing Algorithm for Serum or Plasma Specimens. If the screening test is reactive, an HIV-1/HIV-2 antibody-differentiation immunoassay should be performed to confirm HIV infection; Western blot is no longer recommended as the confirmatory test (A2). [Note: When rapid antibody screening is performed, including screening with a rapid fourth-generation test, a laboratory-based fourth-generation immunoassay is recommended in follow-up diagnostic HIV testing.]

Diagnosis

- Detection of HIV RNA with $\geq 5,000$ copies/mL should be considered a presumptive diagnosis of acute infection even if the screening and antibody-differentiation tests are nonreactive or indeterminate. (A2)
- HIV RNA testing should be repeated to exclude a false-positive result when low-level quantitative results (< 5000 copies/mL) from an HIV RNA assay are reported in the absence of serologic evidence of HIV infection. (A2) [Note: The absence of serologic evidence of HIV infection is defined as a nonreactive screening result (antibody or antibody/antigen combination) or a reactive screening result with a nonreactive or indeterminate antibody-differentiation confirmatory result.]
- If a diagnosis of HIV infection is made on the basis of HIV RNA testing alone, a new specimen should be collected 3 weeks later and HIV diagnostic testing should be repeated according to the CDC HIV testing algorithm. (A2)
- If a diagnosis of acute infection is made on the basis of HIV RNA testing, initiation of ART should be recommended while awaiting serologic confirmation. (A2)
- When pregnant women are diagnosed with acute infection by HIV RNA testing, clinicians should not wait for results of a confirmatory test to initiate ART; initiation of ART is strongly recommended for pregnant women. (A2)
 - See NYSDOH AI guideline *HIV Testing During Pregnancy and at Delivery*

NYS Reporting Requirement and Partner Notification

- Clinicians must report confirmed cases of HIV according to New York State Law (see NYSDOH Provider Reporting and Partner Services for more information about required reporting).
- Clinicians should offer assistance with partner notification and refer patients to other sources for partner notification assistance (Partner Services or CNAP). (A2)

Continued next page

✓ ALL RECOMMENDATIONS – CONTINUED**Managing Acute HIV**

- ART should be recommended for all patients with a diagnosis of acute HIV infection. (A2)
- Clinicians should inform patients about the increased risk of transmitting HIV during acute HIV infection. (A2)
- As part of the initial management of patients diagnosed with acute HIV infection, clinicians should:
 - Consult with a provider experienced in the treatment of acute HIV infection (A3)
 - Obtain baseline HIV genotypic resistance testing, regardless of whether ART is being initiated (A2)
- **Patients taking PEP:** When acute HIV infection is diagnosed in a person receiving PEP, ART should be continued pending consultation with an experienced HIV care provider. (A3)
- **Patients taking PrEP:** When acute HIV infection is diagnosed in a person receiving PrEP, a fully active ART regimen should be recommended in consultation with an experienced HIV care provider. (A3)

Initiating ART

- If the clinician and patient have made a decision to initiate ART during acute HIV infection:
 - Treatment should be implemented with the goal of suppressing plasma HIV RNA to below detectable levels (A1)
 - Treatment should not be withheld while awaiting the results of recommended resistance testing; adjustments may be made to the regimen once resistance results are available (A3)
- Clinicians who do not have access to experienced HIV care providers should call the Clinical Education Initiative (CEI) Line at 1-866-637-2342.

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