HIV Antiretroviral Treatment of Adult HIV Infection

OVERVIEW

The objective of this Clinical Practice Guideline (CPG) is to provide evidence-based recommendations for antiretroviral treatment for members diagnosed with HIV. 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. The public health benefit of early initiation of ART is well documented, with a significant reduction of HIV transmission among virally suppressed individuals.1

GUIDELINE HIERARCHY

CPGs are updated every two years or as necessary due to updates made to guidelines and recommendations published by the International Antiretroviral Society USA Panel or the AIDS Institute. When there are differing opinions noted by national organizations, WellCare will default to the member’s benefit structure as deemed by state contracts and Medicaid / Medicare regulations. If there is no specific language pertaining to the antiretroviral treatment for members diagnosed with HIV, WellCare will default (in order) to the following:

- National Committee for Quality Assurance (NCQA);
- United States Preventive Services Task Force (USPSTF), National Quality Strategy (NQS), Agency for Healthcare Research and Quality (AHRQ);
- Specialty associations, colleges, societies, etc. (e.g., American Academy of Family Physicians, American Congress of Obstetricians and Gynecologists, American Cancer Society, etc.).

Links to websites within the CPGs are provided for the convenience of Providers. Listings do not imply endorsement by WellCare of the information contained on these websites. NOTE: All links are current and accessible at the time of MPC approval.

WellCare aligns with the International Antiretroviral Society USA Panel on the topic of antiretroviral treatment for members diagnosed with HIV. The following are highlights from their guidelines and recommendations.

INTERNATIONAL ANTIRETROVIRAL SOCIETY USA PANEL

Highlights International Antiretroviral Society USA (ISA-USA) Panel recommendations on antiretroviral treatment of adult HIV infection were published in 2016. Of note is the addition of a section on initial combination regimens for the antiretroviral-naive patient. The approval of 3 fixed-dose combination products containing tenofovir alafenamide (an oral prodrug of tenofovir) and emtricitabine (TAF/FTC) prompted several changes; key changes include:

- TAF/FTC was added as a 2-NRTI option in several Recommended and Alternative regimens. The addition of TAF/FTC to these recommendations is based on data from comparative trials demonstrating that TAF-containing regimens are as effective in achieving or maintaining virologic suppression as tenofovir disoproxil fumarate (TDF)-containing regimens and with more favorable effects on markers of bone and renal health.

- In the What to Start section, the evidence quality rating “II” was expanded to include “relative bioavailability/bioequivalence studies or regimen comparisons from randomized switch studies.” This evidence rating was broadened because not all recommended regimens were evaluated in randomized, controlled trials in antiretroviral therapy (ART)-naive patients. The Panel on Antiretroviral Guidelines for Adults and Adolescents based their recommendations for some regimens on either data from bioequivalence or relative bioavailability...
studies, or by extrapolating results from randomized “switch” studies that evaluated a drug’s or regimen’s ability to maintain virologic suppression in patients whose HIV was suppressed on a previous regimen. Guidance was also added for clinicians on choosing between abacavir (ABC)-, TAF-, and TDF-containing regimens.

- The lopinavir/ritonavir (LPV/r) plus 2-NRTI regimen was removed from the list of Other regimens because regimens containing this protease inhibitor (PI) combination have a larger pill burden and greater toxicity than other currently available options.

Additional highlights were added pertaining to regimen switching; the Panel simplified the section to focus on switch strategies for virologically suppressed patients. Updated information was included regarding HIV-infected women. The Panel emphasizes that ART is recommended for all HIV-infected patients, including all HIV-infected women. Further, they stressed the importance of early treatment for HIV-infected women during pregnancy and continuation of ART after pregnancy. The section was updated to include new data on interactions between antiretroviral (ARV) drugs and hormonal contraceptives.

The USA Panel also highlighted coinfection of HIV with Hepatitis B (HBV), Hepatitis C (HCV), and Tuberculosis (TB).

- The section on HBV/HIV includes TAF/FTC as a treatment option for patients with HBV/HIV coinfection. Data on the virologic efficacy of TAF for the treatment of HBV in persons without HIV infection and TAF/FTC in persons with HBV/HIV coinfection are discussed. For patients with HBV/HIV, the Panel no longer recommends adefovir or telbivudine as options for HBV/HIV coinfected patients, as there is limited safety and efficacy data on their use in this population. The agents have a higher incidence of toxicities than other recommended treatments.

- Information was added regarding the potential pharmacokinetic (PK) interactions between different ARV drugs and the recently approved drugs daclatasvir for HCV and the fixed-dose combination product of elbasvir and grazoprevir. Peginterferon alfa and ribavirin were removed as they do not have significant PK interactions with ARV drugs.

- Information was added for TB/HIV co-infection and the treatment of latent tuberculosis infection (LTBI) in HIV-infected persons. The Panel notes that a 12-week course of once-weekly rifapentine and isoniazid is an option for patients receiving either an efavirenz (EFV)- or a raltegravir (RAL)-based regimen. The Panel also addresses the data from the TEMPRANO and START studies demonstrating a potential role of ART in reducing TB disease. As rifamycins are potent inducers of P-glycoprotein (P-gp), and TAF is a P-gp substrate, coadministration of TAF and rifamycins is not recommended.

- Infections (Ala) and other opportunistic diseases and AIDS-defining illnesses include all lymphomas and human papillomavirus–related cancers) (Ala-BIII). The optimal timing for patients with cryptococcal meningitis is less certain, but initiating ART early during cryptococcal treatment should be considered when expert management of both cryptococcal and HIV infection is available (BIII).
### Treatment Regimens and Alternatives

**Table 2. Recommended Initial Antiretroviral Regimens**

<table>
<thead>
<tr>
<th>Type of Regimen</th>
<th>Antiretroviral Drug Combination</th>
<th>Rating</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integrase strand transfer inhibitor plus 2 nucleoside reverse transcriptase inhibitors</td>
<td>Dolutegravir(^6) plus tenofovir/emtricitabine (Alan)</td>
<td>AIA</td>
<td>Dolutegravir is dosed once daily. Associated with modest increases in creatinine level due to inhibition of creatinine secretion.</td>
</tr>
<tr>
<td></td>
<td>Dolutegravir(^6) plus abacavir/lamivudine (Alan)</td>
<td>AIA</td>
<td>No evidence that abacavir/lamivudine performs less well at HIV-1 RNA levels &gt;100,000 copies/mL when given with dolutegravir. A fixed-dose combination is in late-stage development.</td>
</tr>
<tr>
<td></td>
<td>Elvitegravir(^9)/cobaltat/tenofovir/emtricitabine (Alan)</td>
<td>AIA</td>
<td>Once-daily fixed-dose combination. Cobicistat is associated with modest increases in creatinine level due to inhibition of creatinine secretion; has similar drug interactions to ritonavir.</td>
</tr>
<tr>
<td></td>
<td>Raltegravir(^11) plus tenofovir/emtricitabine (Alan)</td>
<td>AIA</td>
<td>Raltegravir is taken twice daily.</td>
</tr>
<tr>
<td>Nonnucleoside reverse transcriptase inhibitor plus 2 nucleoside reverse transcriptase inhibitors</td>
<td>Efavirenz(^4)/tenofovir/emtricitabine (Alan)</td>
<td>AIA</td>
<td>Efavirenz central nervous symptoms may persist beyond 2–4 weeks but is no longer contraindicated for use in pregnant women.</td>
</tr>
<tr>
<td></td>
<td>Efavirenz(^4) plus abacavir/lamivudine (Alan)</td>
<td>AIA</td>
<td>Efavirenz central nervous symptoms may persist beyond 2–4 weeks but is no longer contraindicated for use in pregnant women.</td>
</tr>
<tr>
<td></td>
<td>Rilpivirine(^) plus tenofovir/emtricitabine (Alan)</td>
<td>AIA</td>
<td>Once-daily fixed-dose combination. Rilpivirine-based therapy is not recommended in patients with baseline HIV-1 RNA levels &gt;100,000 copies/mL.</td>
</tr>
<tr>
<td>Ritonavir-boosted protease inhibitor plus 2 nucleoside reverse transcriptase inhibitors</td>
<td>Atazanavir(^) plus tenofovir/emtricitabine (Alan)</td>
<td>AIA</td>
<td>Atazanavir is associated with nephrolithiasis, cholelithiasis, and chronic kidney injury.</td>
</tr>
<tr>
<td></td>
<td>Atazanavir(^) plus abacavir/lamivudine (Alan)</td>
<td>AIA</td>
<td>Atazanavir is associated with nephrolithiasis, cholelithiasis, and chronic kidney injury.</td>
</tr>
<tr>
<td></td>
<td>Darunavir(^) plus tenofovir/emtricitabine (Alan)</td>
<td>AIA</td>
<td>Darunavir-based therapy is not recommended in patients with baseline HIV-1 RNA levels &gt;100,000 copies/mL.</td>
</tr>
</tbody>
</table>

\(^1\) The combination of abacavir and lamivudine was less efficacious with baseline HIV-1 RNA level above 100,000 copies/mL than the combination of tenofovir and emtricitabine when these agents were given with efavirenz or ritonavir-boosted atazanavir.

\(^2\) Dolutegravir should be taken with food.

\(^3\) Darunavir-based therapy is not recommended in patients with baseline HIV-1 RNA levels >100,000 copies/mL.

\(^4\) Should be taken on an empty stomach, and preferably at bedtime.
**Clinical Practice Guideline**

**HIV ANTIRETROVIRAL TREATMENT OF ADULT HIV INFECTION**

**HS-1023**

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### Table 3. Alternatives to Recommended Initial Regimens

<table>
<thead>
<tr>
<th>Type of Regimen</th>
<th>Alternative Antiretroviral Drug Combinations</th>
<th>Rating</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Integrate strand transfer inhibitor plus 2 nucleoside reverse transcriptase inhibitors</td>
<td>Raltegravir® plus abacavir®/lamivudine</td>
<td>Bia</td>
<td>No evidence that abacavir/lamivudine performs as well at HIV-1 RNA levels &gt;100,000 copies/mL when taken with raltegravir.</td>
</tr>
<tr>
<td>Nonnucleoside reverse transcriptase inhibitor (NNRTI) plus 2 nucleoside reverse transcriptase inhibitors</td>
<td>Nevirapine® plus 2 nucleoside reverse transcriptase inhibitors</td>
<td>Bia</td>
<td>Severe hepatotoxicity may occur in initial therapy when CD4 cell count is &gt;250/µL in women and &gt;400/µL in men. Severe rash is more common than with other NNRTIs.</td>
</tr>
<tr>
<td>Protease inhibitor plus 2 nucleoside reverse transcriptase inhibitors</td>
<td>Atazanavir®/cobicistat® with 2 nucleoside reverse transcriptase inhibitors</td>
<td>Bla</td>
<td>Atazanavir plus cobicistat as a fixed-dose combination achieves abacavir/lamivudine levels similar to those with ritonavir boosting. As separate agents, they were noninferior to ritonavir-boosted atazanavir, both in combination with tenofovir/emtricitabine.</td>
</tr>
<tr>
<td>Darunavir®/cobicistat® with 2 nucleoside reverse transcriptase inhibitors</td>
<td>Darunavir®/cobicistat® plus darunavir®/cobicistat® with 2 nucleoside reverse transcriptase inhibitors</td>
<td>Blb</td>
<td>Darunavir plus cobicistat as a fixed-dose combination achieves darunavir levels similar to those with ritonavir boosting.</td>
</tr>
<tr>
<td>Lopinavir®/ritonavir® fixed-dose combination with 2 nucleoside reverse transcriptase inhibitors</td>
<td>Lopinavir®/ritonavir® fixed-dose combination with 2 nucleoside reverse transcriptase inhibitors</td>
<td>Blb</td>
<td>Comparative clinical data from a subset of patients from a single, randomized study.</td>
</tr>
<tr>
<td>Nucleoside reverse transcriptase inhibitors limiting or sparing</td>
<td>Darunavir® plus raltegravir®</td>
<td>Blb</td>
<td>Raltegravir taken twice daily, ritonavir-boosted darunavir taken once daily. Less effective at CD4 cell counts of &lt;200/µL and possibly HIV-1 RNA levels &gt;100,000 copies/mL.</td>
</tr>
<tr>
<td>Lopinavir® plus lopinavir®/ritonavir®</td>
<td>Lopinavir® plus lopinavir®/ritonavir®</td>
<td>Bla</td>
<td>Single study: comparator nucleoside reverse transcriptase inhibitor included indinavir (53.9%), tenofovir (36.6%), and abacavir (9.4%), each with lamivudine.</td>
</tr>
<tr>
<td>Lopinavir® plus lopinavir®/ritonavir®</td>
<td>Lopinavir® plus lopinavir®/ritonavir®</td>
<td>Bla</td>
<td>Both medications taken twice daily, single study with relatively small sample size and low baseline plasma HIV-1 RNA level.</td>
</tr>
</tbody>
</table>

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### Monitoring

Readiness of the patient for treatment should be considered prior to initiating ART. ART should be recommended and offered regardless of CD4 cell count. The strength of the recommendation increases as the CD4 count decreases.2

For patients with a CD4 cell count of 500/µL and **below**:  
- Pregnant women  
- Hepatitis B co-infection  
- HIV-associated neuropathy

For patients with a CD4 cell count of 500/µL and **above**:  
- Age 60 years or above  
- Hepatitis C co-infection  
- During the acute phase of primary HIV infection, regardless of symptoms

Plasma HIV-1 RNA levels5 should be monitored frequently when treatment is initiated or changed for virologic failure, until they decrease below detection limits6 and regularly thereafter. Once the viral load is suppressed for a year and CD4 cell counts are stable at ≥350/µL, viral load and CD4 cell counts can be monitored at intervals of up to 6 months in patients with dependable adherence. Baseline genotypic testing for resistance should be performed in all treatment-naive patients and in cases of confirmed virologic failure (A1a). HLA-B*5701 haplotype screening should be performed in patients for whom abacavir is considered. Assessment of viral tropism is recommended before using maraviroc. Therapeutic drug monitoring is not recommended in routine care; selected patients might benefit from this intervention.2

**Notes:**  
1 HIV-1 RNA level should be monitored at about 4 weeks after treatment is initiated or changed, and then every 3 months to confirm suppression of viremia below the limit of quantification of sensitive commercial assays (Ala). CD4 cell count should be monitored at least every 3 months after initiation of therapy, especially among patients with cell counts of <200/µL, to determine the need for initiation or discontinuation of primary opportunistic infection prophylaxis (BIII). Once HIV-1 RNA level is suppressed for 1 year and CD4 cell count is stable at ≥350/µL, viral load and CD4 cell count can be monitored at intervals of 6 months in patients with dependable adherence (CIII).

2 Detection limits (<20-75 copies/mL) should occur by 24 weeks regardless of prior treatment experience.

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Maintenance of regimen potency is the objective when switching ART regimens. Virologic failure of an initial regimen (confirmed measurable viremia) should be identified and treated as early as possible with at least 2 fully active drugs to avoid the accumulation of resistance mutations. For NNRTI failures, the new combination usually should include a PI/r or an agent from a new class if a PI/r is not possible. Etravirine may be a useful component of a new regimen for NNRTI failure but must be supported by a potent combination including a PI/r. Depending on the resistance profile and options available, inclusion of agents from new drug classes (raltegravir or maraviroc) should be considered. Monotherapy with a PI/r should be avoided unless other drugs cannot be considered for reasons of toxicity/tolerability. Design of a new regimen should consider previous drug exposure, previous resistance profile, drug interactions, and history of intolerance/toxicity. Treatment interruptions should be avoided, except in the context of controlled clinical trials. Elective treatment interruptions should consider the different half-lives of the regimen components, with stopping the drugs in a staggered manner when an NNRTI is a component.

AIDS INSTITUTE

Highlights from the AIDS Institute publication Diagnosis and Management of Acute HIV Infection are noted below.

Recommendations for Initiating ART (updated September 2015)

1. ART should be recommended for all patients with a diagnosis of HIV infection.

2. Clinicians should strongly recommend initiation of ART for patients who present with any of the following conditions that increase the urgency of starting ART:
   • AIDS-defining condition
   • Pregnancy
   • Symptomatic from HIV, including any of the following:
     o HIV-associated neurocognitive disorder (HAND)
     o Severe thrombocytopenia
     o HIV-associated nephropathy
     o HIV-related malignancies
   • Chronic hepatitis B or C infection
   • Age 50 or older

3. Patients with seronegative partners should be counseled about the reduction of HIV transmission risk when effective ART is initiated; ART is strongly recommended in patients with seronegative partners.

4. Decisions to initiate ART should be individualized, particularly for the following populations:
   • Long-term non-progressors
   • Elite controllers
   • Patients with potential barriers to adherence

Additional recommendations published by the AIDS Institute include:

- Evaluation and preparation for ART initiation includes each of the following essential components:
  o Discussion with the patient about risks and benefits of ART;
  o Assessment of patient readiness;
  o Identification and amelioration of factors that might interfere with successful adherence to treatment, including inadequate access to medication, inadequate supportive services, psychosocial factors, active substance use, or mental health disorder.

- Clinicians should refer patients for supportive services as necessary to address modifiable barriers to adherence. An ongoing plan for coordination of care should be established.

- Clinicians should involve patients in the decision-making process regarding initiation of ART. The patient should make the final decision of whether and when to initiate ART.

- When the decision to initiate treatment is made, ART should be prescribed and monitored by, or in consultation with, clinicians who have experience in managing ART.
• Obtain baseline HIV genotypic resistance testing, regardless of whether ART is being initiated.¹

  When acute HIV infection is diagnosed in a person receiving pre-exposure prophylaxis (PrEP), a fully active ART regimen should be recommended in consultation with an experienced HIV care provider.¹

• When acute HIV infection is diagnosed in a person receiving post-exposure prophylaxis (PEP), ART should be continued pending consultation with an experienced HIV care provider.¹

**RNA Assay and Testing**

• A positive HIV RNA assay is a preliminary diagnosis of HIV; ART should be recommended while waiting for confirmatory testing.¹

• 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.¹

• 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.¹

**Barriers and Deferring ART**³

In patients with advanced HIV (or AIDS), ART should be initiated even if barriers to adherence are present. In these cases, referrals to specialized adherence programs should be made for intensified adherence support.

Except in cases when initiation of treatment is urgent, clinicians should educate and prepare patients before initiating ART in those with potential barriers to adherence, including active alcohol or drug use; lack of insurance, transportation, or housing; depression; mistrust of medical providers; or a poor social support system.

Decisions to initiate ART in long-term non-progressors and elite controllers should be individualized.

Clinicians should consult with a provider experienced in the management of ART when considering whether to initiate ART in long-term non-progressors and elite controllers.

**Initiating ART Following Acute Opportunistic Infections**³

Clinicians should recommend that patients beginning treatment for acute opportunistic infections (OIs) initiate ART within 2 weeks of OI diagnosis (see next recommendation for exceptions).

Clinicians should not immediately initiate ART in patients with tuberculous meningitis or cryptococcal meningitis.

Consultation with a clinician with experience in management of ART in the setting of acute OIs is recommended.

For all other manifestations of tuberculosis (TB), clinicians should initiate ART in HIV-infected patients as follows:

- For patients with CD4 counts ≥50 cells/mm³: as soon as they are tolerating anti-TB therapy and no later than 8-12 weeks after initiating anti-TB therapy.
- For patients with CD4 counts <50 cells/mm³: within 2 weeks of initiating anti-TB therapy.

**Patient Adherence**³

NOTE: Last updated in July 2004; currently under revision by the AIDS Institute.

A team approach to achieving adherence should be used. Nurses, pharmacists, peer counselors, caseworkers, and others who work in outreach, evaluation, and support of adherence should be involved.

The clinician should assess treatment readiness prior to initiation of treatment, adherence readiness for subsequent regimens, and adherence at every clinical visit.

Interventions should be intensified in times of decreased adherence.
Information about patients' beliefs and attitudes should be communicated with all members of the healthcare team so that each provider can consistently address treatment adherence issues within the context of the overall treatment plan.

If the patient is not fully committed to adhering to therapy, treatment should be delayed, and the clinician should continue to work on abating the patient’s concerns. Appropriate referrals should be provided for support groups, mental health, and drug treatment.

Potential barriers to adherence include:

- Communication difficulties that arise when the patient’s attitude about disease and therapy is different from that of the provider’s. Without open and nonjudgmental communication from the healthcare team, patients may not trust or may misunderstand the prescribed regimen.
- Language or literacy barriers.
- Unstable living situations (including limited or absent social support).
- Discomfort with disclosure of HIV status, which may become known when medications are taken.
- Inability to set long-term goals.
- Inadequate knowledge about disease and effectiveness of medications or healthy living, including a patient’s lack of belief in his/her ability to take medications regularly.
- Difficulty accessing adequate health care.
- Housing, food, lack of childcare, or other immediate life needs, which are viewed as more pressing than taking the medications regularly.

Strict adherence to ART is essential for maintaining treatment benefit and preventing the development of HIV resistance. Study results are clear on the importance of a high level of adherence for good virologic control. Adherence to >95% of PI doses has been correlated with sustained viral suppression in several studies. Good adherence frequently wanes over time, and patients may need significant support the longer the duration of therapy.

Patient Adherence Education

Strategies to encourage patients to adhere to treatment include:

- To foster understanding of the importance of adherence, providers should present easy to understand information, consistent with the patient’s level of education, and free of medical jargon.
- Allow sufficient time to fully educate the patient about the goals of treatment and the need for adherence, both before beginning treatment and frequently during therapy.
- Provide literature and, if available, peer counselors should be enlisted to reinforce education efforts. Attention to language and use of culturally sensitive education materials are essential.
- Adherence tools should be provided. Written schedules, pictures of medications, pillboxes, alarms, and pagers may help patients understand and remember medication schedules. The need for greater adherence support (e.g., support groups, home visits, day treatment programs) should be assessed.
- Review the viral load response to ART in graphic form with the patient to reinforce the efficacy of therapy.
- Advise the patient of events that may interrupt treatment and interfere with patient access to medications (e.g., travel, pharmacy delays in restocking medications, manufacturer shortages, loss of medication, or incarceration). In addition, the patient should be counseled to notify his/her clinician for discussion of alternative options as soon as the patient foresees the occurrence of an interruption.

Patients should be cautioned that if one (or more) drug in their ART regimen is not available for more than several days, all antiretroviral agents should be stopped until the entire ART regimen is again available to avoid the emergence of resistance while using a less suppressive regimen. This issue is of greatest concern when the antiretroviral agent in question is one to which a single point mutation confers a great degree of resistance (e.g., lamivudine and NNRTIs), which appears rapidly in the absence of a fully suppressive regimen.
Substance Use and Adherence

Clinicians should help active substance users plan to decrease or stabilize their use in preparation for initiating ART. Discussion should include how patterns of substance use may affect adherence. Providers should work with other providers experienced with treating this group to encourage reduction in substance use. The link between reducing drug use and engaging in successful HIV treatment should be encouraged.

Patient Monitoring

Periodic laboratory tests are necessary to evaluate the response to ART and its potential related side effects. In the setting of ART failure, viral resistance assays should be used.

Virologic and Immunologic Monitoring (updated June 2015)

Quarterly CD4 count monitoring is no longer recommended for non-pregnant patients receiving ART who have consistently undetectable HIV RNA levels and CD4 counts >200 cells/mm3. Regular monitoring of HIV RNA levels remains the most accurate and meaningful measure of effective ART. The AIDS Institute recommends that clinicians should monitor HIV RNA levels and CD4 counts according to the recommended intervals noted in the full AIDS Institute publication. Follow-up visits should be scheduled more frequently as clinically necessary to address non-HIV-related conditions, secondary prevention, and issues that may affect adherence to ART or retention in care, such as substance use, mental health disorders, unstable housing, or need for supportive services.

Key Point: Quarterly HIV RNA monitoring remains appropriate for patients with a recent history of non-adherence, mental health disorders, substance use, homelessness, poor social support system, or other major medical conditions. Semiannual monitoring may be appropriate for patients with persistently undetectable HIV RNA and none of the above characteristics. Additional information is found in the full update including allergic reactions and monitoring side effects.

HIV Resistance Assays (updated October 2006)

The AIDS Institute recommends that clinicians should perform resistance testing under the following circumstances:
- At baseline, regardless of whether ART is being initiated (genotypic testing)
- In ART-naïve patients before initiation of ART (genotypic testing)
- In patients experiencing treatment failure or incomplete viral suppression while receiving ART (genotypic and/or phenotypic testing)

When resistance testing is indicated, it optimally should be performed while patients are either receiving therapy or have been off therapy for less than 1 year. Clinicians should consult with an expert to interpret the results of resistance assays because the results of resistance assays are often complex.

Failure to Achieve Goals of Initial ART (updated 2006 – under revision)

The AIDS Institute recommends that clinicians address adherence, obtain resistance assays, and consult with a provider with experience in HIV treatment before changing ART regimens that have failed. Clinicians should not change an ART regimen when there is incomplete but significant viral suppression (≥0.5 log reduction, or 3-fold, from baseline viral load value) compared with baseline and a more effective ART regimen cannot be constructed as a result of drug resistance or intolerance.

The goal of ART is to use a regimen that is well tolerated and that will promote maximal viral suppression and immune reconstitution. Failure to demonstrate a >1.5-log drop in viral load within 3 months of treatment and, more importantly, failure to achieve a viral load <50 copies/mL within 6 months (depending on baseline viral load) indicates unsuccessful ART. The initial ART regimen affords the best opportunity to attain maximal viral suppression. Currently, in clinic practice, only 60% to 70% of patients receiving initial ART will achieve sustained viral loads below the limits of detection by ultrasensitive assays. The reasons for this are complex. Low levels of detectable viremia should not be the sole determinant of treatment failure. Treatment failure is best defined by any one of the following:
- Failure of viral load to decrease from baseline
Progressive increase in viral load after initial suppression

Progressive decline of CD4 cell counts

Progression of HIV disease

Management of Treatment Interruption (updated 2006)

The AIDS Institute recommends that patients should be discouraged from stopping ART without first consulting with their clinician. When ART is interrupted, clinicians should inform patients of the potential increased risk of transmitting HIV. Risk-reduction counseling and prevention interventions should be intensified at this time. Before interrupting ART in patients receiving antiretroviral medications with prolonged half-lives, such as NNRTIs, clinicians should consult with a provider with experience in HIV treatment for guidance on how to avoid the emergence of resistance. In addition, clinicians should not interrupt lamivudine, emtricitabine, or tenofovir (or combination pills containing these drugs) in patients who are co-infected with chronic hepatitis B without implementing another HBV treatment option. Strategic treatment interruption (STI) is not recommended in the management of the HIV-infected patient. Some of the scenarios that could result from disrupting ART include:

- Serious adverse drug reactions (e.g., rashes, neuropathy, severe lipoatrophy or fat redistribution, severe nephrolithiasis)
- Lack of access to drugs due to poverty, incarceration, or lack of medical benefits
- Medical/surgical conditions requiring patients to avoid eating or drinking for a specified time period (e.g., pancreatitis, appendicitis)
- Poor adherence (e.g., lack of adherence may be sufficient cause for the clinician to stop treatment while further interventions and education attempts are undertaken)
- Minor drug side effects that mimic disease progression, making it necessary to temporarily interrupt therapy for clinical evaluation of signs and symptoms

In addition, patients may decide to stop therapy due to treatment fatigue, fear of toxicities (e.g., fat redistribution, cardiac disease), traveling overseas for an extended period, perceived ineffectiveness of medications, or pregnancy and fear of teratogenicity.

Referral to Research Studies (updated 2006)

The AIDS Institute recommends that the referral of patients to research protocols should be 1) to provide treatment or diagnostic options that may be otherwise unavailable and that may enhance treatment outcome, and 2) to attempt to answer a relevant research question. In addition, patients should be fully informed of any financial benefit their referral to a research study might have for the referring clinician. Patients should also be informed that research studies often require major commitments of time and effort in addition to potential unforeseeable risk. Finally, the clinician should provide assistance to patients who want to participate in research studies.

TREATMENT AND MANAGEMENT OF HIV

Antiretroviral therapy (ART) refers to the use of pharmacologic agents that have specific inhibitory effects on HIV replication. The use of less than three active agents is not recommended for initiating treatment. These agents belong to six distinct classes of drugs: the nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs, NtRTIs), the non-nucleoside reverse transcriptase inhibitors (NNRTIs), the protease inhibitors (PIs), the fusion inhibitors (FIs), the CCR5 co-receptor antagonists, and the integrase strand transfer inhibitors (INSTIs).

Clinicians should prescribe an ART regimen that is best able to delay disease progression, prolong survival, and maintain quality of life through maximal viral suppression. The clinician should involve the patient in the decision-making process when determining whether to implement ART. The clinician should review the benefits and risks of treatment for each individual patient. Goals of ART include:

- Maximal and durable suppression of viral replication (measured by viral load assays)
- Restoration and/or preservation of immune function
- Reduced HIV-related morbidity and mortality
- Improved quality of life
HIV ANTIRETROVIRAL TREATMENT
OF ADULT HIV INFECTION
HS-1023

- Limitation of the likelihood of viral resistance to preserve future treatment option

Benefits of early ART in asymptomatic HIV-infected patients (initiation at CD4 counts >500 cells/mm³) includes:
- Preservation and/or restoration of immune function and compromise
- Improvement of overall health and the prolongation of life
- Possible lower risk of antiretroviral resistance
- Suppression of viral replication
- Possible decrease in risk of viral transmission to others (including fetal transmission)

Risks of ART include:
- Adverse effects of the medications on quality of life
- Possibility of greater cumulative side effects from ART
- Known, and as yet unknown, long-term drug toxicities, including potential fetal toxicity
- Possibility for earlier development of drug resistance and limitation in future antiretroviral options if adherence and viral suppression are suboptimal
- Development of HIV drug resistance to drugs currently available and possibly to those not yet available, which may limit future treatment options
- Possibility for earlier onset of treatment fatigue
- Higher prescription drug costs for the individual

NOTE: The risk of viral transmission still exists even when the plasma viral load is undetectable; ART is not a substitute for primary HIV prevention measures (e.g., avoiding sharing needles, practicing safer sex).

MEASUREMENT OF COMPLIANCE

CMS has not published a metric for this condition. NCQA has not published a metric for this condition.

REFERENCES


LEGAL DISCLAIMER

Clinical Practice Guidelines made available by WellCare are informational in nature and are not a substitute for the professional medical judgment of treating physicians or other health care practitioners. These guidelines are based on information available at the time and may not be updated with the most current information available at subsequent times. Individuals should consult with their physician(s) regarding the appropriateness of care or treatment options to meet their specific needs or medical condition. Disclosure of clinical practice guidelines is not a guarantee of coverage. Members of WellCare health plans should consult their individual coverage documents for information regarding covered benefits. WellCare does not warrant or guarantee, and shall not be liable for any deficiencies in the information contained herein or for any inaccuracies or recommendations made by independent third parties from whom any of the information contained herein was obtained. Lines of business (LOB) are subject to change without notice; current LOBs can be found at www.wellcare.com – select the Provider tab, then “Tools” and “Clinical Guidelines”.

MEDICAL POLICY COMMITTEE HISTORY AND REVISIONS

<table>
<thead>
<tr>
<th>Date</th>
<th>History and Revisions by the Medical Policy Committee</th>
</tr>
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<tbody>
<tr>
<td>8/19/2016</td>
<td>Approved by MPC. Additions per regulatory review.</td>
</tr>
<tr>
<td>1/7/2016</td>
<td>Approved by MPC. Inclusion of information from the AIDS Institute and updated IAS-USA recommendations.</td>
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<tr>
<td>9/4/2014</td>
<td>Approved by MPC. No changes.</td>
</tr>
<tr>
<td>9/6/2012</td>
<td>Approved by MPC. Added updates for 2012 including new recommendations.</td>
</tr>
<tr>
<td>12/1/2011</td>
<td>New template design approved by MPC.</td>
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<td>12/2010</td>
<td>New. Approved by MPC.</td>
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