U.S. ART Guidelines

WHAT IS ANTIRETROVIRAL THERAPY?

Antiretroviral therapy (ART) for the treatment of HIV infection has improved steadily since the advent of potent combination therapy in 1996. ART has dramatically reduced HIV-associated complications and death and has transformed HIV infection into a manageable chronic condition, with life expectancy approaching that for people without HIV.

ART is also highly effective at preventing sexual transmission of HIV in people who have achieved viral suppression. Unfortunately, in 2018 only 56% of people with HIV in the U.S. had maximally suppressed viral loads. The lack of suppression is mostly due to undiagnosed HIV infection and failure to link or retain people with HIV in care. Read more about HIV in the U.S.

The U.S. ART guidelines are written and updated by the Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents, a working group of the Office of AIDS Research Advisory Council (OARAC). The primary goal of the panel is to provide HIV care practitioners with recommendations based on current knowledge of antiretroviral drugs (ARVs). The guidelines include recommendations on baseline laboratory evaluation, treatment goals, benefits of ART, considerations when initiating therapy, choice of the initial ART regimen, ARV drugs or combinations to avoid, management of treatment failure, optimizing ART regimens, management of adverse effects and drug interactions, and special ART-related considerations in specific populations.

WHY DO THE GUIDELINES KEEP CHANGING?

The guidelines represent current knowledge regarding the use of ARVs. Because the science of HIV evolves rapidly, the availability of new drugs and new clinical data may change therapeutic options and preferences. We keep learning more about the best ways to treat HIV, therefore the panel frequently updates the guidelines. However, updates to the guidelines may not keep pace with the release of new data so the guidelines cannot offer guidance on care for all people with HIV. People with HIV should receive individualized care from a healthcare provider with experience treating HIV infection. This fact sheet reflects the guidelines as of December 2019.

BASELINE EVALUATION

Every person with HIV entering into care should have a complete medical history, physical examination, and laboratory evaluation and should be counseled regarding the implications of HIV infection. The goals of the initial evaluation are to confirm the diagnosis of HIV infection, obtain appropriate baseline historical and laboratory data, ensure that the person understands HIV infection and its transmission, and start HIV treatment as soon as possible.

The initial evaluation also should include a discussion on the benefits of ART for the person's health and to prevent HIV transmission. In the case of previously treated people who present for an initial evaluation with a new healthcare provider, it is critical to obtain a complete ARV history (including drug resistance testing results, if available), preferably through a review of past medical records. Newly diagnosed people should also be asked about any prior use of ARV agents for prevention of HIV infection (also known as pre-exposure prophylaxis or PrEP).

The following laboratory tests performed during initial patient visits can be used to stage HIV disease and to assist in the selection of the initial ART regimen:

- HIV antibody testing
- Viral load
- CD4 cell count
- Complete blood count (CBC), chemistry profile, fasting blood glucose and lipids, blood urea nitrogen (BUN), creatinine, urinalysis, and testing for hepatitis A, B, and C viruses
- HIV drug-resistance testing
- HLA-B*5701 status

Selection of the initial ART regimen should also consider the person's status with regard to:

- Cardiovascular disease (CVD)
- Kidney, liver, and bone disease
- Mental health
- Neurologic disease
- Substance use and treatment
- Pregnancy or pregnancy potential
- Co-infection with hepatitis B virus (HBV), hepatitis C virus (HCV), and tuberculosis (TB)

- Personal preferences and anticipated adherence

VIRAL LOAD

Viral load is the most important indicator of initial and sustained response to ART and should be measured in all people with HIV at entry into care, at initiation of ART, and on a regular basis thereafter.

People who are adherent to their ART regimens and do not have resistance mutations to the component drugs can generally achieve viral suppression* 8-24 weeks after ART initiation.

Recommendations on the frequency of viral load monitoring are summarized below:

- **At the start of HIV care.** This provides a baseline reference value.
- **When starting or changing ART regimens:** Viral load should be measured before starting ART and within 2-8 weeks after starting or changing medications. This shows whether the drugs are working and if you are adherent to the ART regimen. Repeat viral load measurements should be performed every 4-8 weeks until viral load becomes undetectable.
- **In people on a stable, suppressive ART regimen.** Viral load should be repeated every 3-4 months or as needed to confirm continuous viral suppression. Your healthcare provider may extend the interval to 6 months if you are adherent to the treatment regimen and your viral load has been suppressed for more than 2 years.
- **In people who are not achieving viral suppression.** The frequency of viral load monitoring will depend on clinical circumstances, such as adherence and availability of further treatment options. In addition to viral load monitoring, a number of additional factors, such as adherence to prescribed medications, suboptimal drug exposure, or drug interactions, should be assessed. Patients who fail to achieve viral suppression should undergo resistance testing to aid in the selection of an alternative regimen.

* Viral suppression (or "undetectable" viral load) means that there is not enough virus in the body for the test to find and count.

CD4 CELL COUNTS

The CD4 cell count is the most important laboratory indicator of immune function in people with HIV. It is also the strongest predictor of subsequent disease progression and survival. CD4 count should be measured in all people with HIV at entry into care. It is the key factor in determining the need to start treatment for the prevention of opportunistic infections (OIs) (also known as OI prophylaxis) and the urgency to start ART. Although most OIs occur in people with CD4 cell counts less than 200 cells/mm^3, some OIs can occur in people with higher CD4 cell counts. For most people on ART, an adequate response is defined as an increase in CD4 cell count in the range of 50-150 cells/mm^3 during the first year of ART.

Recommendations on the frequency of CD4 count monitoring are summarized below:

- **At the start of HIV care.** This provides a baseline reference value.
- **In people not on ART for any reason.** CD4 counts should be monitored every 3-6 months to assess the urgency of starting ART and the need for OI prophylaxis.
- **After starting an ART regimen.** CD4 counts should be done 3 months after starting ART to assess the magnitude of immune reconstitution.
- **In the first 2 years following ART initiation.** CD4 counts should be monitored every 3-6 months.
- **In people on a stable, suppressive ART regimen.** CD4 count should be repeated every year after 2 years of ART in people whose viral load remains undetectable and the CD4 count is between 300-500 cells/mm^3.
- **In people who are not achieving viral suppression.** CD4 counts should be monitored every 3-6 months.
- **Optional ongoing monitoring.** Continued CD4 monitoring for virologically suppressed people whose CD4 counts are consistently greater than 500 cells/mm^3 for at least 2 years is optional.

HIV DRUG-RESISTANCE TESTING

HIV drug-resistance testing helps healthcare providers choose the most effective drugs and is recommended at entry into care for people with HIV to guide selection of the initial ART regimen. If therapy is deferred for any reason, repeat testing may be considered when ART is started.

In people with acute or recent (early) HIV infection, in pregnant people with HIV, or in people who will start ART on the day of or soon after HIV diagnosis, starting ART should not be delayed while waiting for resistance testing results; the ART regimen can be changed once results are reported.

HIV drug-resistance testing should be done to assist the selection of active drugs when changing ART regimens in the following people:

- People with virologic failure and viral load levels greater than 1,000 copies/mL.

- People with viral load levels greater than 500 copies/mL but less than 1,000 copies/mL (drug-resistance testing may be unsuccessful but should still be considered).
- People with suboptimal viral load reduction.

OTHER LABORATORY TESTS

The guidelines recommend using a viral tropism test before starting therapy with the CCR5 inhibitor maraviroc (Selzentry). In addition, a tropism test should be performed in people who experience virologic failure while taking maraviroc.

The guidelines also recommend screening for HLA-B*5701 before starting on an abacavir-containing regimen to reduce the risk of hypersensitivity reaction. People who have the HLA-B*5701 gene should not be prescribed any abacavir-containing ARVs and their positive status should be recorded as an abacavir allergy in their medical record. When HLA-B*5701 screening is not readily available, the guidelines suggest that people can be prescribed abacavir-containing ARVs with appropriate counseling and monitoring for signs of allergic reaction.

WHEN TO START TREATMENT

ART is recommended for all people with HIV regardless of CD4 count to reduce sickness and death and to prevent the transmission of HIV to others.

Starting ART early is particularly important for people with AIDS-defining conditions, those with acute or recent HIV infection, and people who are pregnant. Delaying therapy in these subpopulations has been associated with high risks of complications, death, and HIV transmission.

The guidelines recommend starting ART immediately (or as soon as possible) after HIV diagnosis in order to increase the uptake of ART and linkage to care, decrease the time to viral suppression, and improve the rate of viral suppression among persons with HIV. Once started on treatment, people with HIV must continue ART indefinitely.

GOALS OF THERAPY

The guidelines list the following goals for HIV therapy. Treatment goals are the same for people starting therapy and those who have been on therapy for a long time:

- Reduce viral load as much as possible for as long as possible
- Restore and preserve the function of the immune system
- Reduce sickness, complications, and death due to HIV
- Prolong the duration and quality of life
- Prevent HIV transmission

The following tools are suggested to help achieve these goals:

- The selection of initial ART regimen generally includes 3 active drugs from 2 or more drug classes. Regimens should be tailored for the individual person to improve adherence and support long-term treatment success.
- Improving adherence to the medication regimen. Suboptimal adherence may result in reduced treatment response. Incomplete adherence can result from:
    - Complex medication regimens
    - Patient-related factors, such as active substance abuse, depression, or the experience of adverse effects
    - Health system issues, including interruptions in access to medication and inadequate treatment education and support.

Conditions that promote adherence should be maximized before and after starting ART.

WHAT DRUGS SHOULD BE USED FIRST?

An ART regimen for people starting ART for the first time generally consists of:

- 2 nucleoside reverse transcriptase inhibitors (NRTIs) administered in combination with a third active ARV drug from one of three drug classes:
    - an integrase inhibitor
    - a non-nucleoside reverse transcriptase inhibitor (NNRTI)
    - a protease inhibitor (PI) with a pharmacokinetic (PK) enhancer (also known as a booster) the two drugs used for boosting are cobicistat (Tybost) and ritonavir (Norvir)

The guidelines recommended 5 ART regimens for people starting ART. They are classified as *Recommended Initial Regimens for Most People with HIV* (in alphabetical order):

- bictegravir / tenofovir AF / emtricitabine (Biktarvy)
- dolutegravir / abacavir / lamivudine (Triumeq) (only for people who are HLA-B*5701 negative and do not have chronic HBV co-infection)
- dolutegravir plus (emtricitabine or lamivudine) plus (tenofovir AF or tenofovir DF)
    - dolutegravir / lamivudine (Dovato)
    - emtricitabine / tenofovir AF (Descovy)
    - emtricitabine / tenofovir DF (Truvada)
    - lamivudine / tenofovir DF (Cimduo)
- dolutegravir / lamivudine (Dovato) (except for people with viral load greater than 500,000 copies/mL, HBV co-infection, or in people whose resistance testing results are not available yet)
- raltegravir plus (emtricitabine or lamivudine) plus (tenofovir AF or tenofovir disoproxil DF)
    - emtricitabine / tenofovir AF (Descovy)
    - emtricitabine / tenofovir DF (Truvada)
    - lamivudine / tenofovir DF (Cimduo)

In addition, the guidelines contain more information about regimens that may be tried based on individual characteristics of the person and among people of childbearing potential. ARV drugs and regimens that are not recommended are discussed and explained as well.

CAUSES OF VIRILOGIC FAILURE

Virologic failure can occur for many reasons. Data from research studies in the earlier era of combination ART suggested that suboptimal adherence and drug intolerance/toxicity are key contributors to virologic failure and people stopping treatment. The presence of pre-existing (transmitted) drug resistance may also lead to virologic failure. Virologic failure may be associated with a variety of factors, including:

Patient/Adherence-Related Factors

- Other conditions that may affect adherence (e.g., active substance abuse, mental health disorders, neurocognitive impairment)
- Unstable housing and other psychosocial factors
- Missed clinic appointments
- Interruption of or intermittent access to ART
- Cost and affordability of ARV drugs (i.e., these factors may affect the ability to access or continue therapy)
- Adverse drug effects
- High pill burden and/or dosing frequency

HIV-Related Factors

- Presence of transmitted or acquired drug-resistant virus documented by current or past resistance test results
- Prior treatment failure
- Innate resistance to ARV drugs
- Higher pretreatment viral load level (some regimens may be less effective at higher levels)

ART Regimen-Related Factors

- Suboptimal response by the body (e.g., variable absorption, metabolism, or penetration into reservoirs)
- Suboptimal virologic potency
- Low genetic barrier to resistance
- Reduced effectiveness due to prior exposure to suboptimal regimens (e.g., monotherapy, dual-NRTI therapy, or the sequential introduction of drugs)
- Food requirements
- Adverse drug-drug interactions with other medications
- Prescription errors

If virologic failure is suspected or confirmed, a thorough assessment of whether one or more of the above factors could have been the cause(s) of failure is important. Often the causes of virologic failure can be identified, but in some cases, they are not obvious. It is important to distinguish among the causes of virologic failure because the approaches to subsequent therapy may differ depending on the cause. Potential causes of virologic failure should be explored in depth. Once virologic failure is confirmed, steps should be taken to improve virologic outcomes.

Medical management of people experiencing ART failure is complex. The guidelines recommend that expert advice be sought. Evaluation of virologic failure should include an assessment of adherence, drug-drug and drug-food interactions, drug tolerability, viral load level and CD4 cell count trends over time, ART history, and prior and current drug-resistance test results.

Drug-resistance testing should be performed while the person is taking the failing ART regimen or within 4 weeks of stopping that particular regimen. Even if more than 4 weeks have elapsed since ARV drugs were discontinued, resistance testing can still provide useful information to guide therapy, although it may not detect previously selected resistance mutations.

The goal of treatment for ART-experienced people with drug resistance who are experiencing virologic failure is to establish virologic suppression, which means viral load levels below the lower limits of detection of currently used assays.

A new regimen should include at least 2, and preferably 3, fully active ARVs. A fully active ARV is one that is expected to have uncompromised activity based on the person's ART history and current and past drug-resistance test results. A fully active ARV may also have a new mechanism of action that has not been tried yet in that particular person.

In general, adding a single ARV agent to a virologically failing regimen is not recommended, because this may risk the development of resistance to all drugs in the regimen.

For some highly ART-experienced people with extensive drug resistance, maximal virologic suppression may not be possible. In this case, ART should be continued with regimens that have the lowest toxicity, preserve CD4 counts, and delay progression to AIDS.

ADHERENCE

Taking ART correctly every day is critical for the medications to work. This is called adherence. The guidelines recommend involving the person with HIV in ART selection, assessing adherence at every clinic visit, and identifying the type and reasons for non-adherence.

OTHER PARTS OF THE GUIDELINES

The guidelines discuss the above topics in much greater detail. In addition, the guidelines discuss other topics, such as taking ART to prevent sexual transmission of HIV (treatment as prevention), management of the treatment-experienced person, special patient populations, considerations for ARV use in people with other infections (such as HBV, HCV, or TB), drug-drug interactions, regimen switching, discontinuation or interruption of treatment, and more.

MORE INFORMATION

Full text of the guidelines: Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV

Downloadable PDF of the guidelines: Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV

Downloadable PDF of just the recommendations

Downloadable PDF of the just the tables

HIVInfo.NIH.gov: Fact Sheets

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