

## Acquired Immunodeficiency Syndrome: DHHS Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV (2021)

### About the Guideline

- This guideline was developed 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.
- The panel is composed of approximately 45 voting members who have expertise in human immunodeficiency virus (HIV) care and research.
- The goal is to provide licensed independent practitioners with guidance on the optimal use of antiretroviral agents (ARVs) in the treatment of HIV in adults and adolescents in the United States.

### Key Clinical Considerations

Become familiar with the recommendations and best-practice statements provided in this guideline, especially if you work in an acute care setting or provide care for patients in this population.

### Clinical Evaluation

- All patients with HIV should undergo a complete medical history and physical evaluation and should be advised of the implications of HIV infection.
- Initial evaluation should include the following:
  - Confirming the diagnosis of HIV infection
  - Obtaining baseline historical and laboratory data
  - Ensuring patient's understanding of HIV infection, transmission, and prevention of opportunistic infections
  - Discussion of the benefits of antiretroviral therapy (ART)
  - Discussion of risk reduction and disclosure to sexual and/or needle-sharing partners
  - Obtaining a complete antiretroviral (ARV) history
  - Education regarding HIV risk behaviors and effective strategies to prevent HIV transmission
  - Assessing the patient's readiness for ART, including the following:
    - Assessment of high-risk behaviors
    - Substance abuse
    - Social support
    - Mental illness
    - Comorbidities
    - Economic factors
    - Medical insurance status and coverage
    - Other factors that are known to impair adherence to ART and increase the risk of HIV transmission

### Laboratory Testing

Laboratory testing is recommended for the initial assessment and the ongoing monitoring of patients with HIV before and after initiation of ART.

- HIV serology
  - On entry into care if HIV diagnosis has not been confirmed

- CD4 T lymphocyte (CD4) cell count (used to assess immune function)
  - On entry into care
  - On ART initiation or modification
  - Every 3 to 6 months during first 2 years of ART, then annually
  - If treatment failure is suspected
  - As clinically indicated
  - Every 3 to 6 months if ART initiation is delayed
- Plasma HIV RNA (viral load) (used to assess the level of HIV viremia)
  - On entry into care
  - On ART initiation or modification
  - 2 to 8 weeks after ART initiation or modification
  - Every 3 to 6 months during first 2 years of ART
  - Every 6 months
  - Treatment failure
  - As clinically indicated
  - Repeat testing is optional if ART initiation is delayed
- Resistance testing (genotype preferred; used to guide the selection of antiretroviral regimen)
  - On entry into care
  - On ART initiation or modification
  - Treatment failure
  - As clinically indicated
  - If ART initiation is delayed
- Viral tropism assay
  - On ART initiation or modification (if considering a CCR5 antagonist)
  - Treatment failure of CCR5 antagonist-based regimen
- HLA-B\*5701 testing
  - On ART initiation or modification if considering abacavir (ABC)
- Hepatitis B serology
  - On entry into care
  - On ART initiation or modification
    - Repeat if patient is nonimmune and does not have chronic Hepatitis B virus (HBV) infection
  - Every 12 months
    - Repeat if patient is nonimmune and does not have chronic HBV infection
  - As clinically indicated
- Hepatitis C screening
  - On entry into care
  - Repeat every 12 months for at-risk patients
  - As clinically indicated
- Basic chemistry
  - On entry into care
  - On ART initiation or modification
  - 2 to 8 weeks after ART initiation or modification
  - Every 3 to 6 months
  - As clinically indicated
  - If ART initiation is delayed, every 6 to 12 months
- ALT, AST, bilirubin

- On entry into care
- On ART initiation or modification
- 2 to 8 weeks after ART initiation or modification
- Every 3 to 6 months
- As clinically indicated
- If ART initiation is delayed, every 6 to 12 months
- CBC with differential
  - On entry into care
  - On ART initiation or modification
  - 2 to 8 weeks after ART initiation or modification if on zidovudine (ZDV)
  - Every 3 to 6 months if on ZDV
  - Every 6 months
  - As clinically indicated
  - If ART initiation is delayed, every 3 to 6 months
- Fasting lipid profile
  - On entry into care
  - On ART initiation or modification
  - Every 6 months if abnormal at last measurement
  - Annually if normal at last measurement
  - As clinically indicated
  - If ART initiation is delayed and baseline measurement is normal, test annually
- Fasting glucose or hemoglobin A1C
  - On entry into care
  - On ART initiation or modification
  - Annually, if normal at last measurement
  - As clinically indicated
  - If ART initiation is delayed and baseline measurement is normal, test annually
- Urinalysis
  - On entry into care
  - On ART initiation or modification
  - Every 6 months if on tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF)
  - Annually
  - As clinically indicated
- Pregnancy test (if appropriate)
  - On entry into care
  - On ART initiation or modification
  - As clinically indicated

#### **Diagnosis of Acute HIV Infection**

- Early diagnosis is important for maximum impact of ART and to reduce the transmission of HIV.
- Test for the presence of HIV-1 RNA or p24 antigen in the setting of a negative or indeterminate HIV-1 antibody test result.
- A reactive HIV antibody test result or antigen/antibody (Ag/Ab) combination test result must be followed by supplemental confirmatory testing.
- A negative or indeterminate HIV-1 antibody test result in a person with a reactive Ag/Ab test result or in whom acute HIV-1 infection is suspected requires plasma HIV-1 RNA testing.

- A positive result on a quantitative or qualitative plasma HIV-1 RNA test in the setting of a negative or indeterminate antibody test result is highly likely to indicate an acute HIV-1 infection.
  - This should be confirmed by the subsequent documentation of HIV antibody seroconversion.

## Antiretroviral Therapy

### Initiation of Antiretroviral Therapy

- ART is recommended for all patients with HIV, regardless of CD4 T lymphocyte cell count.
- ART is also recommended for patients with HIV to prevent HIV transmission.
- When initiating ART, it is important to educate patients regarding the benefits and considerations of ART, and to address strategies to optimize adherence.
- Other comorbidities/co-infections, childbearing risk, initial lab values, potential adverse effects, and the patient's readiness to learn should also be considered when initiating ART.

### Antiretroviral Therapy after Diagnosis of Early HIV-1 Infection

- ART is recommended for all individuals with HIV and should be offered to all patients with early HIV-1 infection.
  - The following conditions increase the urgency to initiate therapy:
    - AIDS-defining conditions, including HIV-associated dementia and AIDS-associated malignancies
    - Acute opportunistic infections (OIs)
    - Lower CD4 counts (that is, less than 200 cells/mm<sup>3</sup>)
    - HIV-associated nephropathy (HIVAN)
    - Acute/early infection
    - HIV/HBV co-infection
    - HIV/hepatitis C virus (HCV) co-infection
- A blood sample for genotypic drug-resistance testing should be obtained before initiation of ART to guide the selection of the regimen (but initiation of ART should be done as soon as possible).
- If no resistance data are available, the recommendation is for a pharmacologically boosted protease inhibitor (PI)-based regimen.
- For patients without transmitted (preexisting) drug-resistant virus, ART should be initiated with one of the combination regimens recommended for patients with chronic HIV-1 infection.
- An antiretroviral (ARV) regimen generally consists of two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a third active ARV drug from one of the following three drug classes:
  - An integrase strand transfer inhibitor (INSTI)
  - A non-nucleoside reverse transcriptase inhibitor (NNRTI)
  - A PI with a pharmacokinetic (PK) enhancer (booster)
- Patients who have not received ART who wish to begin intramuscular therapy should first achieve viral suppression before switching to oral and then injectable forms of the drug.

### HIV-2 Infection

- HIV-2 infection is endemic in West Africa, with little spread outside of this area.
- This infection should be considered when treating patients originating from West Africa, or when treating patients possibly exposed through sexual conduct or through sharing needles with people from this area.

- The clinical course of HIV-2 infection is generally characterized by a longer asymptomatic stage, lower plasma HIV-2 RNA levels, and lower mortality; however, progression to AIDS does occur.
- An optimal treatment strategy has not been defined.
- ART should be initiated before clinical progression has occurred.
- HIV-2 infection is resistant to nonnucleoside reverse transcriptase inhibitors and enfuvirtide, thus these therapies should be avoided.
- Monitoring of HIV-2 RNA levels, CD4 cell counts, and clinical improvements can be used to assess treatment response.

#### Treatment Goals

- Maximal and long-lasting suppression of plasma viremia delays or prevents drug-resistant mutations and maintains or increases CD4 T lymphocyte (CD4) cell numbers.
- Once ART is initiated, it should be continued with the following key treatment goals:
  - Maximal and long-standing suppression of plasma HIV RNA
  - Reestablish and maintain immunologic function
  - Reduce HIV-associated morbidity and prolong the length and quality of survival
  - Prevent HIV transmission
- After initiation of effective ART, viral load reduction to below the limits of assay detection usually occurs within the first 12 to 24 weeks of therapy. Predictors of virologic success include the following:
  - Low baseline viremia
  - High potency of the ARV regimen
  - Tolerability of the regimen
  - Convenience of the regimen
  - Excellent adherence to the regimen

#### Managing Virologic Failure (HIV RNA level less than 200 copies/mL) in Treatment-Experienced Patients

- Key contributors to virologic failure are suboptimal adherence, drug intolerance/toxicity, regimen discontinuation.
- Expert advice is imperative to establish the goal of virologic suppression.
- Assess the following:
  - Adherence to therapy
  - Drug-drug interactions
  - Drug and food interactions
  - Drug tolerability
  - HIV RNA and CD4 T lymphocyte (CD4) cell count trends over time
  - ART history
  - Prior and current drug-resistance testing results
- Drug-resistance testing should be performed while the patient is taking the failing antiretroviral (ARV) regimen or within 4 weeks of discontinuation of treatment.
- A new regimen should include at least two, and preferably three, fully active agents.
- Adding a single ARV agent to a virologically failing regimen is not recommended.
- For some highly ART-experienced patients with extensive drug resistance, maximal virologic suppression may not be possible; however, ART should still be continued.
- In patients who have multidrug resistant HIV and difficulty constructing a viable suppressive regimen, the clinician should consider enrolling the patient in a clinical trial or contacting pharmaceutical companies that may have investigational drugs available.

- Patients who have hepatitis B co-infection (HBV) should receive ARV drugs active against HBV.
- Discontinuing or briefly interrupting therapy may lead to a rapid increase in HIV RNA, a decrease in CD4 cell count, and an increase in the risk of clinical progression; discontinuation is therefore not recommended for virologic failure.

#### Switching ART Regimens in Virologic Suppression

- Reasons to switch ART regimen:
  - Reduce pill burden and dosing frequency
  - Enhance tolerability
  - Decrease short- or long-term toxicity
  - Prevent or mitigate drug-drug interactions
  - Eliminate food or fluid requirements
  - Allow for optimal use of ART during pregnancy or for patients planning pregnancy

#### Discontinuing ART Regimens

- Discontinuation may result in viral rebound, disease progression, or immune decompensation.
- If a patient has an unexpected interruption in therapy and is unable to take oral medications, then all therapy should be stopped simultaneously.
- Planned long-term interruptions in therapy are not recommended.

### **Considerations for Special Populations**

#### Elite HIV Controllers

- This term is used to describe a small group of individuals with HIV who maintain plasma HIV-1 RNA levels below the level of quantification for years without ART.
- Delaying ART for these individuals is strongly discouraged.
- If ART is withheld, controllers should be followed closely, because they may experience:
  - CD4 cell decline
  - Loss of viral control
  - HIV-related complications
- ART is recommended for controllers with evidence of HIV progression, as defined by:
  - Declining CD4 counts
  - Development of HIV-related complications

#### Adolescents with HIV

- Initiate ART early.
  - Some adolescents may not be ready to initiate therapy.
    - Practitioners should offer ART while providing effective interventions to assess and address barriers.
    - To optimize the benefits of ART for adolescents, a multidisciplinary care team should provide psychosocial adherence support.
- To facilitate adherence, treatment regimens must balance the goal of prescribing a maximally potent ART regimen with a realistic assessment of existing and potential support systems.
- All adolescents should be screened for sexually transmitted diseases.
- Transition care programs are beneficial to youths transitioning through the stages of growth and development—from child, to adolescent, to young adult.
  - Successful transition includes the following:
    - An individualized plan

- Communication between the adolescent and adult clinics
- Addressing resistance to care
- Developing life skills (such as appointment management, symptom recognition, medication management)
- Ongoing evaluation and outcome management
- The dosage of ARV drugs should be determined based on the adolescent's sexual maturity rating, not solely based on age.

#### Adherence Concerns in Adolescents

- Adolescents with HIV are vulnerable to specific adherence problems.
- Compared with adults, adolescents have lower rates of viral suppression and higher rates of virologic rebound and loss to follow-up.
- Reasons why adolescents with HIV often have difficulty adhering to the medical regimen include the following:
  - Denial and fear of an HIV diagnosis
  - Misinformation
  - Distrust of the medical establishment
  - Fear of ART and lack of confidence in the effectiveness of medications
  - Low self-esteem
  - Unstructured and chaotic lifestyle
  - Mood disorders and other mental illness
  - Lack of familial and social support
  - Lack of or inconsistent access to care or health insurance
  - Risk of inadvertent disclosure of HIV status if parental health insurance is used

#### Women with HIV

- ART is recommended for all women with HIV.
- For pregnant women, the goal is to keep viral load to undetectable levels throughout pregnancy in order to decrease the risk of transmission to the fetus and newborn.
- The available safety, efficacy, and pharmacokinetic (PK) data on use during pregnancy along with risks and benefits of ARV should be considered and discussed with all women.
- For ARV drugs that have significant PK interactions with hormonal contraceptives, an alternative or additional effective contraceptive method should be utilized to prevent unintended pregnancy.
  - Switching to an ARV drug that does not interact with hormonal contraceptives is recommended.
- Nonpregnant women of childbearing potential should undergo pregnancy testing before the initiation of efavirenz (EFV) and should receive counseling about the potential risk to the fetus.
  - Women on a suppressive regimen containing Efv who become pregnant and present for antenatal care during the first trimester can continue Efv throughout pregnancy.
- Clinicians should consult the most current perinatal guidelines for the most recent guidance in treating this population.
- Health care providers are strongly encouraged to register people who become pregnant while receiving IM INSTI cabotegravir (CAB) and rilpivirine (RPV) with the Antiretroviral Pregnancy Registry.
- Regimens that do not include Efv should be considered in women who are planning to become pregnant or who are sexually active and not using effective contraception.

### Older Patients with HIV

- Antiretroviral therapy (ART) is recommended for all patients.
- Older patients have a greater risk of serious non-AIDS complications and can have a blunted immunologic response to ART.
- Neurocognitive impairment may occur with viral suppressive therapy.
- Adverse drug events from ART and concomitant drugs may occur more frequently in older patients with HIV.
  - The bone, kidney, metabolic, cardiovascular, and liver health of older patients should be monitored closely.
- The risk of drug-drug interactions is higher in this population because polypharmacy is common.
- HIV experts, primary care providers, and other specialists should work together to optimize care.
- Early diagnosis and counseling are important.

### **Considerations for Co-infections**

- HBV/HIV co-infection
  - The severity of HBV should be assessed, and patients with chronic HBV should be tested for hepatitis A.
  - Use TDF or tenofovir alafenamide (TAF) with emtricitabine (FTC) or lamivudine (3TC) whenever possible.
  - If TDF and TAF are contraindicated
    - For treatment of HBV, use FTC or 3TC with entecavir and a suppressive ART regimen.
  - When switching ART regimens because of virologic failure, maintain patients with HBV/HIV co-infection on ARV drugs that are active against HBV.
  - Patients with chronic HBV infection should receive treatment for HBV with NRTIs that are active against both HIV and HBV before starting HCV therapy.
- HCV/HIV co-infection
  - ART should be initiated in all cases, regardless of CD4 cell count.
  - In patients with lower CD4 counts (less than 200 cells/mm<sup>3</sup>), ART should be initiated promptly.
  - Patients with chronic HCV/HIV co-infection should be screened for active and prior HBV infection by testing for the presence of hepatitis B surface antigen (HBsAg) and hepatitis B surface antibodies (HBsAb) and core (HBcAb total or IgG). Patients who are not immune to HBV infection (HBsAb-negative) should receive anti-HBV vaccination.
- Tuberculosis (TB)/HIV co-infection
  - TAF is not recommended with any rifamycin-containing regimen.
  - If rifampin is used
    - Efavirenz (EFV) can be used without dose adjustment.
    - If raltegravir (RAL) is used, increase RAL dose to 800 mg twice daily.
    - Use dolutegravir (DTG) 50 mg twice daily only in patients without selected INSTI mutations. DTG can be prescribed for most people of childbearing age.
    - If using a PI-based regimen, rifabutin should be used in place of rifampin in the TB regimen.

### Strategies to Improve Adherence

- The approach to improve adherence should be tailored to each patient's needs or to barriers to care. Approaches could include the following:
  - Changing ART to simplify dosing or to reduce adverse effects
  - Finding resources to assist with treatment costs to maintain uninterrupted access to both ART and appointments
  - Allowing flexible appointment scheduling
  - Assisting with transportation
  - Linking patients to counseling to overcome stigma, substance use, or depression
  - Multidisciplinary approaches to finding solutions to ART and appointment adherence problems are often necessary and include collaboration with social work and case management (to the extent available). The practitioner's role is to help the patient understand the importance of adherence to the continuum of care; to reveal barriers to adherence; and to link the patient to resources to overcome those barriers.

### Adverse Effects

- The overall benefits of viral suppression and improved immune function as a result of effective ART far outweigh the risks associated with the adverse effects of some ARV drugs.
- Adverse effects are reported with the use of all ARV drugs.
- Newer ARV regimens are associated with fewer serious and intolerable adverse effects.
- To achieve sustained viral suppression over a lifetime, both long-term and short-term ART toxicities must be anticipated and overcome.
- Practitioners must consider the potential adverse effects when selecting an ARV regimen as well as the individual patient's comorbidities, concomitant medications, and prior history of drug intolerances.
- Several factors may predispose individuals to experience adverse effects with ARV medications, such as:
  - Concomitant use of medications with overlapping and additive toxicities
  - Comorbid conditions that increase the risk of or exacerbate adverse effects such as
    - Alcoholism
    - Psychiatric disorders
  - Drug-drug interactions
  - Genetic factors

### Reference

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. (2021). *Guidelines for the use of antiretroviral agents in adults and adolescents with HIV*. Department of Health and Human Services. <https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/whats-new-guidelines>