

Overview of US DHHS Guidelines for the Treatment of HIV in Adults and Adolescents [January 2008 version]

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Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents

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 (OARAC)

Goals of Therapy & Tools to Achieve Goals

- Improved quality of life
- Reduction of HIV-related morbidity and mortality
- Restoration and/or preservation of immunologic function
- Maximal and durable suppression of viral load
- Prevention of vertical transmission
- Prevention of transmission to sexual partners
- Selection of ARV regimen
- Preservation of future treatment options
- Maximizing adherence
- Use of resistance testing

When to Start ART

- Potent ART may improve and/or preserve of immune function in most patients with virologic suppression, regardless of baseline CD4
 - ART indicated for all with low CD4 and/or symptoms
 - Earlier ART may result in better immunologic responses and better clinical outcomes
 - Recommended ARV combinations are considered to be durable, and tolerable
 - Exact CD4 at which to initiate therapy not known, but evidence points to starting at higher CD4 counts
 - Current recommendation: ART for all patients with CD4 <math><350\text{ cells/mm}^3</math>, certain others regardless of CD4

Potential Benefits of Early Therapy (CD4 >350 cells/mm³)

- Maintain higher CD4; prevent irreversible immune system damage
- Decrease risk of HIV-associated complications
 - eg, TB, NHL, KS, peripheral neuropathy, HPV-associated malignancies, HIV-associated cognitive impairment
- Decrease risk of nonopportunistic conditions and non-AIDS associated conditions
 - eg, CV, renal, and liver disease; malignancies; infections
- Decrease risk of HIV transmission

Potential Risks of Early Therapy (CD4 >350 cells/mm³)

- ARV-related side effects and toxicities
- Drug resistance (due to ART failure)
- Inadequate time to learn about HIV, treatment, and adherence
- Increase in total time on ART; greater chance of treatment fatigue
- Current ART may be less effective or more toxic than future therapies
- Transmission of ARV-resistant virus, if incomplete virologic suppression

Indications for Initiating ART: Chronic Infection

Clinical Category and/or CD4 Count	Recommendation
<ul style="list-style-type: none"> ■ History of AIDS-defining illness ■ CD4 <200 cells/mm³ ■ CD4 200-350 cells/mm³ ■ Pregnant women ■ HIV-associated nephropathy ■ Hepatitis B coinfection, when HBV treatment is indicated* 	<p>Initiate ART</p>

*Treat with fully suppressive drugs active against both HIV and HBV.

Indications for Initiating ART: Chronic Infection

Clinical Category and/or CD4 Count	Recommendation
<ul style="list-style-type: none">■ CD4 >350 cells/mm³, asymptomatic, without conditions listed above	Optimal time to initiate ART is not well defined. Consider individual patient characteristics and comorbidities.

Components of Initial ART: DHHS Categories



- Preferred
 - Clinical data show optimal efficacy and durability
 - Acceptable tolerability and ease of use
- Alternative
 - Clinical trial data show efficacy but also show disadvantages in ARV activity, durability, tolerability, or ease of use (compared to “preferred” components)
 - may be the best option in select individual patients
- Other possible options
 - Inferior efficacy or greater or more serious toxicities

Initial Treatment: Preferred Components

NNRTI Option

- **Efavirenz***

OR

PI Options

- **Atazanavir + ritonavir**
- **Fosamprenavir + ritonavir (BID)**
- **Lopinavir/ritonavir (BID)**

+

NRTI Options

- **Tenofovir + emtricitabine****
- **Abacavir + lamivudine*****

*Avoid in pregnant women and women with significant pregnancy potential.

**Emtricitabine can be used in place of lamivudine and vice versa.

*** In patients who have tested negative for HLA B*5701.

Initial Treatment: Alternative Components

NNRTI Option

- Nevirapine*

OR

PI Options

- Atazanavir**
- Fosamprenavir
- Fosamprenavir + ritonavir
(1x/day)
- Lopinavir/ritonavir (1x/day)
- Saquinavir + ritonavir

NRTI Options

- Zidovudine + lamivudine**
- Didanosine + (emtricitabine or lamivudine)

*Nevirapine should not be initiated in women with CD4 counts >250 cells/mm³ or men with CD4 counts >400 cells/mm³

**Atazanavir must be boosted with ritonavir if used in combination with tenofovir

Initial Treatment: Other Possible Options

ARV drugs or regimens

- **Abacavir + lamivudine + zidovudine (coformulated)**
- **Nelfinavir***
- **Stavudine + lamivudine**

Rationale

- Inferior virologic efficacy
- Inferior virologic efficacy
- Significant toxicities

These are considered acceptable but inferior to preferred or alternative components. They may be used in special circumstances.

*Should not be given to pregnant women.

Treatment-Experienced Patients:

- In clinical studies of ART, most patients maintained virologic suppression for 3-7 years
- Patients with suppressed viremia:
 - Assess adherence frequently
 - Simplify ARV regimen as much as possible
- Patients with ARV failure: assess and address aggressively

Treatment-Experienced Patients: ARV Treatment Failure

- Causes of treatment failure include:
 - Patient factors
(CD4 nadir, pretreatment HIV RNA, comorbidities, etc)
 - Drug resistance
 - Suboptimal adherence
 - ARV toxicity and intolerance
 - Pharmacokinetic problems
 - Suboptimal drug potency

Treatment-Experienced Patients: ARV Treatment Failure



- Virologic failure:
 - HIV RNA >400 copies/mL after 24 wks, >50 after 48 wks, or >400 copies/mL after viral suppression
- Immunologic failure:
 - Failure to achieve and maintain adequate CD4 increase despite virologic suppression
- Clinical progression:
 - Occurrence of HIV-related events (after ≥ 3 months on therapy; excludes immune reconstitution syndromes)

Treatment-Experienced Patients: Virologic Failure



- Incomplete virologic response:
 - In patient on initial ART, HIV RNA >400 copies/mL after 24 weeks on therapy or >50 copies/mL by 48 weeks (confirm with second test)
- Virologic rebound:
 - Repeated detection of HIV RNA after virologic suppression (eg, >50 copies/mL)

Treatment-Experienced Patients: Virologic Failure

- Assess drug resistance:
 - Drug resistance test
 - Prior treatment history
 - Prior resistance test results
- Drug resistance usually is cumulative – consider all previous treatment history and test results

Treatment-Experienced Patients: Virologic Failure

- Management:
 - Clarify goals: aim to reestablish maximal virologic suppression (eg, <50 copies/ML)
 - Evaluate remaining ARV options
 - Newer agents have expanded treatment options
 - Base ARV selection on medication history, resistance testing, expected tolerability, adherence, and future treatment options
 - Avoid treatment interruption, which may cause rapid worsening of CD4, HIV RNA, and clinical status

Virologic Failure: Changing an ARV Regimen

General principles:

- Add at least 2 (preferably 3) fully active agents to an optimized background ARV regimen
 - Determined by ARV history and resistance testing
- Consider potent ritonavir-boosted PIs, drugs with new mechanisms of action (eg, fusion inhibitor, CCR5 inhibitor, integrase inhibitor) plus an optimized ARV background
- In general, 1 active drug should not be added to a failing regimen (drug resistance is likely to develop quickly)
- Consult with experts

Treatment-Experienced Patients: Goals of Therapy



- Limited prior treatment and drug resistance, with adequate treatment options:
 - Maximal viral suppression, HIV RNA <50 copies/mL
 - Consider early change to prevent further resistance mutations
- Intermediate prior treatment and drug resistance, with some available treatment options:
 - Maximal viral suppression, if possible (HIV RNA <50 copies/mL)
 - Preservation of immune function and prevention of clinical progression

Treatment-Experienced Patients: Goals of Therapy



- Extensive prior treatment and drug resistance, with some or no adequate treatment options:
 - Viral suppression may be difficult to achieve
 - Preservation of immune function and prevention of clinical progression
 - Balance benefits of partial viral suppression with risk of additional resistance mutations

Web Sites to Access the Guidelines

- <http://www.aidsetc.org>
- <http://aidsinfo.nih.gov>