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Comprehensive Guideline Summary

Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents

May 2014

AETC NRC Slide Set

Guidelines for the Use of Antiretroviral Agents in HIV-1-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 Treatment

- Reduce HIV-related morbidity; prolong duration and quality of survival
- Restore and/or preserve immunologic function
- Maximally and durably suppress HIV viral load
- Prevent HIV transmission

Tools to Achieve Treatment Goals

- Selection of ARV regimen
- Maximizing adherence
- Pretreatment resistance testing

Improving Adherence

- Support and reinforcement
- Simplified dosing strategies
- Reminders, alarms, timers, and pillboxes
- Ongoing patient education
- Trust in primary care provider

Use of CD4 Cell Levels to Guide Therapy Decisions

- CD4 monitoring
  - Check at baseline (x2) and at least every 3-6 months
  - Immediately before initiating ART
  - Every 3-6 months during first 2 years of ART or if CD4 <300 cells/µL
  - After 2 years on ART with HIV RNA consistently suppressed:
    - CD4 300-500 cells/µL: every 12 months
    - CD4 >500 cells/µL: optional
    - More frequent testing if on medications that may lower CD4 count, or if clinical decline

Use of HIV RNA Levels to Guide Therapy Decisions (2)

- RNA monitoring
  - Check at baseline (x2)
  - Monitoring in those not on ART – optional
  - Immediately before initiating ART
  - 2-4 weeks (not more than 8 weeks) after start or change of ART, then every 4-8 weeks until suppressed to <200 copies/mL
  - Every 3-4 months with stable patients; may consider every 6 months for stable, adherent patients with VL suppression >2 years
  - Isolated “blips” may occur (transient low-level RNA, typically <400 copies/mL), are not thought to predict virologic failure
    - ACTG defines virologic failure as confirmed HIV RNA >200 copies/mL

Drug Resistance Testing: Recommendations

RECOMMENDED	COMMENT
Acute HIV infection, regardless of whether treatment is to be started	To determine if resistant virus was transmitted; guide treatment decisions. If treatment is deferred, consider repeat testing at time of ART initiation. Genotype preferred.
Chronic HIV infection, at entry into care	Transmitted drug-resistant virus is common in some areas; is more likely to be detected earlier in the course of HIV infection. If treatment is deferred, consider repeat testing at time of ART initiation. Genotype preferred to phenotype. Consider integrase genotypic resistance assay if integrase inhibitor resistance is a concern.

Drug Resistance Testing: Recommendations (2)

RECOMMENDED	COMMENT
Virologic failure during ART	To assist in selecting active drugs for a new regimen. Genotype preferred if patient on 1st or 2nd regimen; add phenotype if known or suspected complex drug resistance pattern. If virologic failure on integrase inhibitor or fusion inhibitor, consider specific genotypic testing for resistance to these to determine whether to continue them. (Coreceptor tropism assay if considering use of CCR5 antagonist; consider if virologic failure on CCR5 antagonist.)
Suboptimal suppression of viral load after starting ART	To assist in selecting active drugs for a new regimen.

Drug Resistance Testing: Recommendations (3)

RECOMMENDED	COMMENT
Pregnancy	Recommended before initiation of ART or prophylaxis. Recommended for all on ART with detectable HIV RNA levels. Genotype usually preferred; add phenotype if complex drug resistance mutation pattern.

Other Assessment and Monitoring Studies

- HLA-B*5701 screening
  - Recommended before starting ABC, to reduce risk of hypersensitivity reaction (HSR)
  - HLA-B*5701-positive patients should not receive ABC
  - Positive status should be recorded as an ABC allergy
  - If HLA-B*5701 testing is not available, ABC may be initiated after counseling and with appropriate monitoring for HSR
- Coreceptor tropism assay
  - Should be performed when a CCR5 antagonist is being considered
  - Phenotype assays have been used; genotypic test now available but has been studied less thoroughly
  - Consider in patients with virologic failure on a CCR5 antagonist (though does not rule out resistance to CCR5 antagonist)

Recommendations for Initiating ART

ART is recommended for *treatment*:

- "ART is recommended for all HIV-infected individuals to reduce the risk of disease progression."
  - The strength of this recommendation varies on the basis of pretreatment CD4 count (stronger at lower CD4 levels)

Recommendations for Initiating ART (2)

ART is recommended for *prevention*:

- "ART also is recommended for HIV-infected individuals for the prevention of transmission of HIV."

Recommendations for Initiating ART: CD4 Count or Clinical Category

- Recommended for all CD4 counts:
  - CD4 count <350 cells/µL (AI)
  - CD4 count 350-500 cells/µL (AII)
  - CD4 count >500 cells/µL (BIII)

Recommendations for Initiating ART: Prevention

- Perinatal transmission
  - Recommended for all HIV-infected pregnant women (AI)
- Sexual transmission
  - Recommended for all who are at risk of transmitting HIV to sex partners (AI for heterosexuals, AIII for other transmission risk groups)

Potential Benefits of Early Therapy

- Untreated HIV may be associated with development of AIDS and non-AIDS-defining conditions
- Earlier ART may prevent HIV-related end-organ damage; deferred ART may not reliably repair damage acquired earlier
  - Increasing evidence of direct HIV effects on various end organs and indirect effects via HIV-associated inflammation
  - End-organ damage occurs at all stages of infection

Potential Benefits of Early Therapy (2)

- Potential decrease in risk of many complications, including:
  - HIV-associated nephropathy
  - Liver disease progression from hepatitis B or C
  - Cardiovascular disease
  - Malignancies (AIDS defining and non-AIDS defining)
  - Neurocognitive decline
  - Blunted immunological response owing to ART initiation at older age
  - Persistent T-cell activation and inflammation

Potential Benefits of Early Therapy (3)

- Prevention of sexual transmission of HIV
- Prevention of perinatal transmission of HIV

Potential Concerns about Early Therapy

- ARV-related toxicities
- Nonadherence to ART
- Drug resistance
- Cost

Consider Deferral of ART

- Clinical or personal factors may support deferral of ART
  - If CD4 count is low, deferral should be considered only in unusual situations, and with close follow-up
- When there are significant barriers to adherence
- If comorbidities complicate or prohibit ART
- “Elite controllers” and long-term nonprogressors

Current ARV Medications

NRTI

- Abacavir (ABC)
- Didanosine (ddI)
- Emtricitabine (FTC)
- Lamivudine (3TC)
- Stavudine (d4T)
- Tenofovir (TDF)
- Zidovudine (AZT, ZDV)

NNRTI

- Delavirdine (DLV)
- Efavirenz (EFV)
- Etravirine (ETR)
- Nevirapine (NVP)
- Rilpivirine (RPV)

PI

- Atazanavir (ATV)
- Darunavir (DRV)
- Fosamprenavir (FPV)
- Indinavir (IDV)
- Lopinavir (LPV)
- Nelfinavir (NFV)
- Ritonavir (RTV)
- Saquinavir (SQV)
- Tipranavir (TPV)

Integrase Inhibitor (II)

- Dolutegravir (DTG)
- Elvitegravir* (EVG)
- Raltegravir (RAL)

Fusion Inhibitor

- Enfuvirtide (ENF, T-20)

CCR5 Antagonist

- Maraviroc (MVC)

* EVG currently available only in coformulation with cobicistat (COBI)/ TDF/FTC

Initial Therapy: Dual-NRTI Pairs

Preferred: TDF/FTC	▪ Once-daily dosing ▪ High virologic efficacy ▪ Active against HBV ▪ Potential for renal and bone toxicity
Alternative: ABC/3TC	▪ Once-daily dosing ▪ Risk of hypersensitivity reaction if positive for HLA-B*5701 ▪ Possible risk of cardiovascular events; caution in patients with CV risk factors ▪ Possible inferior efficacy if baseline HIV RNA >100,000 copies/mL
Other: ZDV/3TC	▪ Twice-daily dosing ▪ Preferred dual NRTI for pregnant women ▪ More toxicities than TDF/FTC or ABC/3TC

Initial Regimens: Recommended
(Regardless of baseline HIV RNA or CD4 count)

PI based	▪ DRV/r (QD) + TDF/FTC (AI)
INSTI based	▪ DTG/ABC/3TC[3] (AI-Triumeq) ▪ DTG (QD) + TDF/FTC (AI) ▪ EVG/COBI/TDF/FTC[4] (AI-Stribild) ▪ RAL + TDF/FTC (AI)

Notes:

3TC can be used in place of FTC and vice versa; TDF: caution if renal insufficiency

1. Consider alternative to EFV in women who plan to become pregnant or are not using effective contraception.
2. ATV/r should not be used in patients who take >20 mg omeprazole per day.
3. ABC should be used only if HLA-B*5701 is negative; caution if high risk of CV disease.
4. EVG/COBI should be started only if CrCl <70 mL/min.

Alternative Regimen Options

NNRTI based	▪ EFV/TDF/FTC[1] (Atripla-BI) ▪ RPV/TDF/FTC (Complera-BI)
PI based	▪ ATV/r[3] + TDF/FTC (BI) ▪ DRV/r + ABC/3TC[2] (BI)

Notes:

3TC can be used in place of FTC and vice versa; TDF: caution if renal insufficiency

1. Consider alternative to EFV in women who plan to become pregnant or are not using effective contraception.
2. ABC should be used only if HLA-B*5701 is negative; caution if high risk of cardiovascular disease.
3. ATV/r should not be used in patients who take >20 mg omeprazole per day.

ARV Medications: Should Not Be Offered at Any Time

- ARV regimens not recommended:
  - Monotherapy with NRTI*
  - Monotherapy with boosted PI
  - Dual-NRTI therapy
  - 3-NRTI regimen (except ABC + 3TC + ZDV or possibly TDF + 3TC + ZDV)

* ZDV monotherapy is not recommended for prevention of perinatal HIV transmission but might be considered in certain circumstances; see *Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*.

Treatment-Experienced Patients

- The recommended ARV regimens should suppress HIV to below the lower level of detection (LLOD) of HIV RNA assays
- Nonetheless, nearly 25% of patients on ART are not virologically suppressed
  - Virologic rebound or failure of virologic suppression often results in resistance mutations
- Assessment and management of ART failure is complex: expert consultation is recommended

Treatment-Experienced Patients: Virologic Failure (2)

- Failure of current first-line regimens usually caused by suboptimal adherence or transmitted drug resistance

Treatment-Experienced Patients: Causes of Virologic Failure

- Patient factors
  - Higher pretreatment HIV RNA (depending on the ART regimen)
  - Lower pretreatment CD4 (depending on the ART regimen)
  - Comorbidities (eg, substance abuse, psychiatric or neurocognitive issues)
  - Drug resistance
  - Suboptimal adherence, missed clinic appointments
  - Interruptions in access to ART

Treatment-Experienced Patients: Causes of Virologic Failure (2)

- ARV regimen factors
  - Toxicity and adverse effects
  - Pharmacokinetic problems
  - Suboptimal ARV potency
  - Prior exposure to nonsuppressive regimens
  - Food requirements
  - High pill burden and/or dosing frequency
  - Drug-drug interactions
  - Prescription errors

Treatment-Experienced Patients: Management of Virologic Failure (3)

- New regimen should contain at least 2 (preferably 3) fully active agents
  - Based on ARV history, resistance testing, and/or novel mechanism of action
- In general, 1 active drug should not be added to a failing regimen
  (drug resistance is likely to develop quickly)
- Consult with experts

OIs-PRIMARY PROPHYLAXIS

- PCP

  risk: CD4 <200, prior PCP or thrush

  preferred: TMP-SMX qday

  alternatives: dapsone 100 mg qday, weekly dapsone/pyrimethamine, aerosolized pentamidine monthly, atovaquone qday

  immune reconstitution: stop prophylaxis if CD4 >200 for >3 months

- TB

  risk: positive PPD (>5mm) or recent close contact

  preferred: INH x 9 months

OIs-PRIMARY PROPHYLAXIS

- Toxoplasmosis

  risk: CD4 <100 plus positive Toxo serology

  preferred: TMP-SMX qday

  alternatives: dapsone plus pyrimethamine

  immune reconstitution: stop prophylaxis if CD4 >200 for >3 months

- Disseminated MAC

  risk: CD4 <50

  preferred: azithromycin 1200 mg qweek or Biaxin 500 mg BID

  alternative: rifabutin 300 mg qday

  immune reconstitution: stop prophylaxis if CD4 >100 for >3 months

Websites to Access the Guidelines

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