AETC AIDS Education & Training Center Program
National Coordinating Resource Center

Comprehensive Guideline Summary

Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents

July 2016

About This Presentation

These slides were developed using the April 2015 treatment guidelines and were updated in July 2016. The intended audience is clinicians involved in the care of patients with HIV.

Because the field of HIV care is rapidly changing, users are cautioned that the information in this presentation may become out of date quickly.

It is intended that these slides be used as prepared, without changes in either content or attribution. Users are asked to honor this intent.

– AETC NCRC

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults & 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)

Guidelines Outline

- Overview
- Initiation of Antiretroviral Therapy (ART)
- Management of the Treatment-Experienced Patient
- Special Issues

What the Guidelines Address

- Baseline evaluation
- Laboratory testing (HIV RNA, CD4 cell count, resistance)
- When to initiate therapy
- When to change therapy
- Therapeutic options
- Adherence
- ART-associated adverse effects

What the Guidelines Address (2)

- Treatment of acute HIV infection
- Special considerations in adolescents, pregnant women, injection drug users, older patients, HIV-2 infection, and patients coinfected with HIV and HBV, HCV, or TB
- Preventing secondary transmission

Websites to Access the Guidelines

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

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

CD4 Count Monitoring

- CD4 count
  - The major indicator of immune function
  - Most recent CD4 count is best predictor of disease progression
  - A key factor in determining urgency of ART or need for OI prophylaxis
  - Important in determining response to ART
    - Adequate response: CD4 increase 50-150 cells/μL per year

CD4 Count Monitoring
(2)

- 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

HIV RNA Monitoring

- HIV RNA
  - May influence decision to start ART and help determine frequency of CD4 monitoring
  - Critical in determining response to ART
    - Goal of ART: HIV RNA below limit of detection (ie, <20-75 copies/mL, depending on assay)
  - Commercially available assays do not detect HIV-2

HIV RNA Monitoring (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

Testing for Drug Resistance

- Before initiation of ART:
  - Transmitted resistance in 10-17% of HIV-infected patients
  - In absence of therapy, resistance mutations may decline over time and become undetectable by current assays, but may persist and cause treatment failure when ART is started
  - Identification of resistance mutations may optimize treatment outcomes
  - Resistance testing (genotype) recommended for all at entry to care; include INSTI resistance testing if INSTI resistance is suspected
  - Recommended for all pregnant women
- Patients with virologic failure:
  - Perform while patient is taking ART, or ≤4 weeks after discontinuing therapy
  - Interpret in combination with history of ARV exposure and ARV adherence

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 • ART should not be delayed while resistance test results are pending • 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 • Recommended for all on ART with detectable HIV RNA levels • ART should not be delayed while resistance test results are pending; ARV regimen can be modified if needed • Genotype usually preferred; add phenotype if complex drug-resistance mutation pattern

Drug Resistance Testing: Recommendations (4)

NOT USUALLY RECOMMENDED	COMMENT
After discontinuation (>4 weeks) of ARVs	• Resistance mutations may become minor species in the absence of selective drug pressure
Plasma HIV RNA <500 copies/mL	• Resistance assays cannot be performed consistently if HIV RNA is low

Other Assessment and Monitoring Studies

- HLA-B*5701 screening
  - Recommended before starting abacavir (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)

Rationale for ART

- Effective ART with virologic suppression improves and preserves immune function, regardless of baseline CD4 count
  - Earlier ART initiation may result in better immunologic responses and clinical outcomes
    - Reduction in AIDS- and non-AIDS-associated morbidity and mortality
      - Reduction in HIV-associated inflammation and associated complications
  - ART strongly indicated for all patients, especially those with low CD4 count or symptoms
- ART can significantly reduce risk of HIV transmission
- Recommended ARV combinations are effective and well tolerated

When to Start ART

- Evidence supports starting at high CD4 counts
- Current recommendation: ART is strongly recommended for *all*

Rating Scheme for Recommendations

- Strength of recommendation:
  - A: Strong
  - B: Moderate
  - C: Optional
- Quality of evidence:
  - I: ≥1 randomized controlled trials
  - II: ≥1 well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; also randomized switch studies and bioavailability/bioequivalence studies
  - III: Expert opinion

Recommendations for Initiating ART

- ART is recommended for *treatment*:

"ART is recommended for all HIV-infected individuals, regardless of CD4 T lymphocyte cell count, to reduce the morbidity and mortality associated with HIV infection." (A1)

Recommendations for Initiating ART (2)

- ART is recommended for *prevention*:

"ART also is recommended for HIV-infected individuals to prevent HIV transmission." (A1)

Recommendations for Initiating ART: Considerations

- ART should be initiated as soon as possible
  - On a case-by-case basis, ART may be deferred because of clinical and/or psychological factors
- Patients should understand that indefinite treatment is required; ART does not cure HIV
- Address strategies to optimize adherence

Potential Benefits of Early Therapy

- Untreated HIV is associated with development of AIDS and non-AIDS-defining conditions.
  - 2 randomized controlled trials showed significant reductions in both AIDS and non-AIDS events in persons who started ART with CD4 counts >500 cells/μL.
  - Early ART may prevent HIV-related end-organ damage; deferred ART may not reliably repair damage acquired earlier.

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

Consider More-Rapid Initiation of ART

- Pregnancy
- AIDS-defining condition
- Acute opportunistic infection
- Lower CD4 count (eg, <200 cells/μL)
- Acute/early infection
- HIVAN
- HBV coinfection
- HCV coinfection

Considerations When Starting ART

- It is crucial to support adherence and retention in care
  - Mental illness, substance abuse, and psychosocial challenges are not reasons to withhold ART
- Acute opportunistic infections and malignancies
  - Early ART usually indicated
  - For some OIs (eg, cryptococcal and TB meningitis), a short delay in ART initiation may be appropriate
- "Elite controllers"
  - No RTC evaluate benefit of ART
  - Given abnormal immune activation, may have increased risk of non-AIDS diseases

Current ARV Medications

NRTI

- Abacavir (ABC)
- Didanosine (ddI)
- Emtricitabine (FTC)
- Lamivudine (3TC)
- Stavudine (d4T)
- Tenofovir DF (TDF)
- Tenofovir alafenamide (TAF)*
- 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)
- Saquinavir (SQV)
- Tipranavir (TPV)

Integrase Inhibitor (INSTI)

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

Fusion Inhibitor

- Enfuvirtide (ENF, T-20)

CCR5 Antagonist

- Maraviroc (MVC)

Pharmacokinetic (PK) Booster

- Ritonavir (RTV)
- Cobicistat (COBI)

*** TAF available only in coformulations: TAF/FTC, RPV/TAF/FTC, EVG/COBI/TAF/FTC**

Initial ART Regimens: DHHS Categories

- Recommended
  - Easy to use
  - Durable virologic efficacy
  - Favorable tolerability and toxicity profiles
- Alternative
  - Effective but have potential disadvantages, limitations in certain patient populations, or less supporting data
  - May be the optimal regimen for individual patients
- Other
  - Reduced virologic activity; limited supporting data; or greater toxicities, higher pill burden, more drug interactions, or other limiting factors

Initial Treatment: Choosing Regimens

- 3 main categories:
  - 1 INSTI + 2 NRTIs
  - 1 PK-boosted PI + 2 NRTIs
  - 1 NNRTI + 2 NRTIs
- Combination of II, boosted PI, or NNRTI + 2 NRTIs is preferred for most patients
- NRTI pair should include 3TC or FTC
- Few clinical end points to guide choices: recommendations based mostly on rates of HIV RNA suppression and severity of adverse effects
- Advantages and disadvantages to each type of regimen
- Individualize regimen choice

Initial Regimens: Recommended

INSTI based	▪ DTG/ABC/3TC; only if HLA-B*5701 negative (AI) ▪ DTG (QD) + TDF/FTC (AI) or TAF/FTC (AII) ▪ EVG/COBI/TAF/FTC ▪ EVG/COBI/TDF/FTC; only if pre-ART CrCl >70 mL/min (AI) ▪ RAL + TDF/FTC (AI) or TAF/FTC (AII)
PI based	▪ DRV/r (QD) + TDF/FTC (AI) or TAF/FTC (AII)

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

Initial Regimens: Alternative

NNRTI based	▪ EFV/TDF/FTC (BI) ▪ EFV + TAF/FTC (BII) ▪ RPV/TDF/FTC (BI) or RPV/TAF/FTC (BII); only if pre-ART HIV RNA <100,000 copies/mL and CD4 >200 cells/μL (BI)
PI based	▪ (ATV/c or ATV/r) + TDF/FTC (BI) or TAF/FTC (BII) ▪ (DRV/c or DRV/r) + ABC/3TC; only if HLA-B*5701 negative (BIII for DRV/c, BII for DRV/r) ▪ DRV/c + TDF/FTC (BII) or TAF/FTC (BII)

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

Initial Regimens: Other

If HIV RNA <100,000 copies/mL and HLA-B*5701 negative:	▪ (ATV/c (CIII) or ATV/r (CII)) + ABC/3TC ▪ EFV + ABC/3TC (CI) ▪ RAL + ABC/3TC (CII)
Others to consider when TAF, TDF, or ABC cannot be used	▪ DRV/r + RAL (BID) (CI) – only if HIV RNA <100,000 copies/mL and CD4 >200 cells/μL ▪ LPV/r + 3TC (CI)

Note: 3TC can be used in place of FTC and vice versa

Initial Therapy: Dual-NRTI Pairs

ABC/3TC	▪ Once-daily dosing ▪ Cofomulated with DTG in a single-pill regimen ▪ Use only for patients who are negative for HLA-B*5701 (risk of hypersensitivity reaction if positive) ▪ Possible risk of cardiovascular events; caution in patients with CV risk factors ▪ Possible inferior efficacy if baseline HIV RNA >100,000 copies/mL and used with EFV, ATV/r, or RAL

Initial Therapy: Dual-NRTI Pairs

TAF/FTC	▪ Once-daily dosing ▪ In several single-pill regimen coformulations ▪ High virologic efficacy ▪ Active against HBV ▪ Renal and bone toxicity is less common than with TDF/FTC ▪ Approved for eGFR ≥30 mL/min ▪ In some combinations, use supported by bioequivalence/bioavailability studies or randomized switch studies ▪ No randomized comparisons with ABC/3TC

Initial Therapy: Dual-NRTI Pairs

TDF/FTC	▪ Once-daily dosing ▪ In several single-pill regimen coformulations ▪ High virologic efficacy ▪ Active against HBV ▪ Potential for renal and bone toxicity (more than with TAF) ▪ Avoid if CrCl <60 mL/mi

Selecting Initial ART Regimen: Factors to Consider

Patient Characteristics	▪ HIV RNA; CD4 count ▪ HIV resistance test results ▪ HLA-B*5701 status ▪ Patient preferences ▪ Anticipated adherence
Comorbidities or Other Conditions	▪ Cardiovascular disease, hyperlipidemia, renal disease, osteoporosis, psychiatric illness, others ▪ Pregnancy or pregnancy potential ▪ Coinfections: HCV, HBV, TB
Regimen Characteristics	▪ Genetic barrier to resistance ▪ Potential adverse effects ▪ Drug interactions with other medications ▪ Convenience (pill #, dosing frequency, fixed-dose combinations, food requirements) ▪ Cost

Selecting Initial ART Regimen: Selected Clinical Scenarios

CD4 <200	Do not use: higher rate of virologic failure ▪ RPV-based ART ▪ DRV/r + RAL
HIV RNA >100,000	Do not use: higher rate of virologic failure ▪ RPV-based ART ▪ ABC/3TC + EFV or ATV/r ▪ DRV/r + RAL
HLA-B*5701 positive	Do not use ABC: risk of abacavir hypersensitivity
Must treat before resistance test results are known	Avoid NNRTI-based regimens: transmitted resistance more likely than with PI or INSTI Recommended: ▪ DRV/r + TAF/FTC or TDF/FTC ▪ DTG + TAF/FTC or TDF/FTC

Selecting Initial ART Regimen: Selected Clinical Scenarios (2)

One-pill regimen	▪ DTG/ABC/3TC (only if HLA-B*5701 negative) ▪ EFV/TDF/FTC ▪ EVG/COBI/TAF/FTC ▪ EVG/COBI/TDF/FTC ▪ RPV/TAF/FTC (if HIV RNA <100,000 copies/mL and CD4 >200 cells/μL) ▪ RPV/TDF/FTC (if HIV RNA <100,000 copies/mL and CD4 >200 cells/μL)
Food effects	Should be taken with food: ▪ ATV/r or ATV/c ▪ DRV/r or DRV/c ▪ EVG/c/TAF/FTC ▪ EVG/c/TDF/FTC ▪ RPV/TAF/FTC ▪ RPV/TDF/FTC Should be taken on empty stomach: EFV

Selecting Initial ART Regimen: Selected Clinical Scenarios (3)

Chronic kidney disease (eGFR <60 mL/min)	▪ Avoid TDF; use ABC or TAF
	  ▪ ABC not associated with renal dysfunction
	  ▪ TAF has less impact on renal function and proteinuria than TDF; may be used if eGFR >30 mL/min
	▪ Options when ABC or TAF cannot be used:
	  ▪ LPV/r + 3TC
	  ▪ DRV/r + RAL (if HIV RNA <100,000 copies/mL and CD4 >200 cells/μL)

Liver disease with cirrhosis	▪ Some ARVs contraindicated or require dosage modification ▪ Evaluation by expert in advanced liver disease is recommended

Selecting Initial ART Regimen: Selected Clinical Scenarios (4)

Osteoporosis	▪ Avoid TDF: associated with greater decrease in BMD, osteomalacia, urine phosphate wasting
	▪ Use ABC or TAF
	  ▪ Associated with smaller decreases in BMD
	  ▪ ABC may be used if HLA-B*5701 negative (if HIV RNA >100,000 copies/mL, do not use with EFV or ATV/r)

Psychiatric illness	▪ Consider avoiding EFV and RPV: can exacerbate psychiatric symptoms; may be associated with suicidality
HIV-associated dementia	▪ Avoid EFV ▪ Favor DRV- or DTG-based regimens

Selecting Initial ART Regimen: Selected Clinical Scenarios (5)

High cardiac risk	▪ Consider avoiding ABC and LPV/r: increased CV risk in some studies
Hyperlipidemia	Adverse effects on lipids: ▪ PI/r or PI/c ▪ EFV ▪ EVG/c Beneficial lipid effects: ▪ TDF
Pregnancy	▪ See Perinatal Guidelines

Selecting Initial ART Regimen: Selected Clinical Scenarios (6)

HBV	▪ Use TDF or TAF with FTC or 3TC, whenever possible: use 2 NRTIs with activity against both HIV and HBV ▪ If TDF and TAF are contraindicated: treat HBV with FTC or 3TC + entecavir + suppressive ART regimen
HCV	▪ Consult current recommendations

TB	▪ TAF not recommended with rifamycins
	▪ If rifampin is used:
	  ▪ EFV: no dosage adjustment needed
	  ▪ RAL: increase RAL to 800 mg BID
	  ▪ DTG: 50 mg BID (only if no significant INSTI mutations)
	▪ If PI-based regimen: use rifabutin in place of rifampin

ARVs Not Recommended in Initial Treatment

High rate of early virologic failure	▪ ddI + TDF
Inferior virologic efficacy	▪ ABC + 3TC + ZDV as 3-NRTI regimen ▪ ABC + 3TC + ZDV + TDF as 4-NRTI regimen ▪ ddI + (3TC or FTC) ▪ Unboosted ATV, FPV, or SQV ▪ DLV ▪ NFV ▪ TPV/r
High incidence of toxicities	▪ ZDV + 3TC ▪ d4T + 3TC ▪ ddI + TDF ▪ NVP ▪ IDV/r ▪ RTV as sole PI

ARVs Not Recommended in Initial Treatment (2)

Potential for drug-drug interactions	▪ EVG/COBI/TDF/FTC + other ARV drugs
High pill burden/ dosing inconvenience	▪ LPV/r + 2NRTIs ▪ IDV (unboosted) ▪ SQV/r
Lack of data in initial treatment	▪ ABC + ddI ▪ FPV/r ▪ DRV (unboosted) ▪ ENF (T-20) ▪ ETR
No benefit over standard regimens	▪ 3-class regimens ▪ 3 NRTIs + NNRTI ▪ MVC

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*.

ARV Medications: Should Not Be Offered at Any Time (2)

- ARV components not recommended:
  - ddI + d4T
  - ddI + TDF
  - FTC + 3TC
  - d4T + ZDV
  - DRV, SQV, or TPV as single PIs (unboosted)
  - ATV + IDV

ARV Medications: Should Not Be Offered at Any Time (3)

- ARV components not recommended:
  - EFV during first trimester of pregnancy and in women with significant potential for pregnancy (AIII)[1,2]
  - NVP initiation in women with CD4 counts of >250 cells/µL or in men with CD4 counts of >400 cells/µL
  - ETR + unboosted PI
  - ETR + RTV-boosted ATV, FPV, or TPV
  - 2-NNRTI combination

1. Exception: when no other ARV options are available and potential benefits outweigh the risks; consult with expert (BIII)
2. Consult Perinatal Guidelines **(AIII)**

ARV Components in Initial Therapy: Dual-NRTI Pairs

ADVANTAGES

- Established backbone of combination therapy
- Minimal drug interactions

DISADVANTAGES

- Lactic acidosis and hepatic steatosis reported with most NRTIs (rare)

ARV Components in Initial Therapy: INSTIs

ADVANTAGES

- Virologic response noninferior to EFV
- Fewer adverse events than with EFV or PIs
- RAL, DTG have fewer drug-drug interactions than with PIs or NNRTIs (not true of EVG/COBI)
- Single-pill combination regimens available with DTG, EVG/COBI

DISADVANTAGES

- RAL, EVG have lower genetic barrier to resistance than PIs
- COBI has many drug-drug interactions
- COBI may cause or worsen renal impairment
- Myopathy, rhabdomyolysis, skin reactions reported with RAL (rare)

ARV Components in Initial Therapy: PIs

ADVANTAGES

- Higher genetic barrier to resistance
- PI resistance uncommon with failure of boosted PIs

DISADVANTAGES

- Metabolic complications (fat maldistribution, dyslipidemia, insulin resistance)
- GI intolerance
- Potential for drug interactions (CYP450), especially with RTV
- No single-pill combination regimens

ARV Components in Initial Therapy: NNRTIs

ADVANTAGES

- Long half-lives
- Less metabolic toxicity (dyslipidemia, insulin resistance) than with some PIs
- Single-pill combination regimens available with EFV and RPV

DISADVANTAGES

- Low genetic barrier to resistance – single mutation
- High rates of NNRTI resistance in ART-naive patients
- Cross-resistance among most NNRTIs
- EFV: high rate of CNS-related side effects
- RPV: lower efficacy if HIV RNA >100,000 or CD4 <200 cells/μL
- Rash; hepatotoxicity
- Potential drug interactions (CYP450)

Adverse Effects

- Important to anticipate and overcome ART toxicities in order to achieve ART success over a lifetime
- Consider potential adverse effects (AEs) when selecting ARV regimen; also consider patient's comorbidities, other medications, and previous history of ARV intolerance

Adverse Effects: NRTIs

- All NRTIs:
  - Lactic acidosis and hepatic steatosis (highest incidence with d4T, then ddI and ZDV, lower with TDF, ABC, 3TC, and FTC)
  - Lipodystrophy (higher incidence with d4T)

Adverse Effects: NRTIs (2)

- Emtricitabine (FTC)
  - Minimal toxicity
  - Hyperpigmentation
  - In HBV coinfection, exacerbation of HBV if discontinued
- Lamivudine (3TC)
  - Minimal toxicity
  - In HBV coinfection, exacerbation of HBV if discontinued

Adverse Effects: NRTIs (3)

- Abacavir (ABC)
  - Hypersensitivity reaction*
  - Rash
  - Possible increased risk of MI
- Tenofovir alafenamide (TAF), tenofovir disoproxyl fumarate (TDF)
  - Renal impairment (less likely with TAF vs TDF)
  - Decrease in bone-mineral density (less likely with TAF vs TDF)
  - Headache
  - GI intolerance

* Screen for HLA-B*5701 before treatment with ABC; ABC should not be given to patients who test positive for HLA-B*5701.

Adverse Effects: NRTIs (4)

- Didanosine (ddI)
  - GI intolerance
  - Peripheral neuropathy
  - Possible increased risk of MI
  - Pancreatitis
  - Possible noncirrhotic portal hypertension
- Stavudine (d4T)
  - Peripheral neuropathy
  - Lipoatrophy
  - Pancreatitis
- Zidovudine (ZDV)
  - Headache
  - Bone marrow suppression
  - GI intolerance
  - Lipoatrophy

Adverse Effects: INSTIs

- All INSTIs:
  - Rash, hypersensitivity reaction
  - Depression and suicidal ideation (rare; usually in patients with preexisting psychiatric conditions)

Adverse Effects: INSTIs (2)

- Dolutegravir (DTG)
  - Headache
  - Insomnia
- Elvitegravir/cobicistat (EVG/c)
  - Decreased CrCl
  - Increased risk of TDF-related nephrotoxicity
  - Nausea, diarrhea
- Raltegravir (RAL)
  - Nausea
  - Headache
  - Diarrhea
  - CPK elevation, myopathy, rhabdomyolysis

Adverse Effects: PIs

- All PIs:
  - Hyperlipidemia
  - Lipodystrophy
  - Hepatotoxicity
  - GI intolerance
  - Possibility of increased bleeding risk for hemophiliacs
  - Drug-drug interactions

Adverse Effects: PIs (2)

- Atazanavir (ATV)
  - Hyperbilirubinemia
  - PR prolongation
  - Nephrolithiasis, cholelithiasis
- Darunavir (DRV)
  - Rash
  - Liver toxicity
- Fosamprenavir (FPV)
  - GI intolerance
  - Rash
  - Possible increased risk of MI

Adverse Effects: PIs (3)

- Indinavir (IDV)
  - Nephrolithiasis
  - GI intolerance
  - Diabetes/insulin resistance
- Lopinavir/ritonavir (LPV/r)
  - GI intolerance
  - Diabetes/insulin resistance
  - Possible increased risk of MI
  - PR and QT prolongation
- Nelfinavir (NFV)
  - Diarrhea

Adverse Effects: PIs (4)

- Saquinavir (SQV)
  - GI intolerance
  - PR and QT prolongation
- Tipranavir (TPV)
  - GI intolerance
  - Rash
  - Hyperlipidemia
  - Liver toxicity
  - Contraindicated if moderate-to-severe hepatic insufficiency
  - Cases of intracranial hemorrhage

Adverse Effects: Pharmacokinetic Boosters

- Ritonavir (RTV, /r)
  - GI intolerance
  - Hyperlipidemia, hyperglycemia
  - Hepatitis
- Cobicistat (COBI, /c)
  - GI intolerance
  - Increase in serum creatinine

Adverse Effects: NNRTIs

- All NNRTIs:
  - Rash, including Stevens-Johnson syndrome
  - Hepatotoxicity (especially NVP)
  - Drug-drug interactions

Adverse Effects: NNRTIs (2)

- Efavirenz (EFV)
  - Neuropsychiatric
  - Teratogenic in nonhuman primates + cases of neural tube defects in human infants after first-trimester exposure
  - Dyslipidemia
- Etravirine (ETR)
  - Nausea
- Nevirapine (NVP)
  - Higher rate of rash
  - Hepatotoxicity (may be severe and life-threatening; risk higher in patients with higher CD4 counts at the time they start NVP, and in women)
- Rilpivirine (RPV)
  - Depression, insomnia

Adverse Effects: CCR5 Antagonist

- Maraviroc (MVC)
  - Drug-drug interactions
  - Rash
  - Abdominal pain
  - Upper respiratory tract infections
  - Cough
  - Hepatotoxicity
  - Musculoskeletal symptoms
  - Orthostatic hypotension, especially if severe renal disease

Adverse Effects: Fusion Inhibitor

- Enfuvirtide (ENF, T-20)
  - Injection-site reactions
  - HSR
  - Increased risk of bacterial pneumonia

Treatment-Experienced Patients

- The recommended ARV regimens should suppress HIV to below the lower level of detection (LLOD) of HIV RNA assays
- Nonetheless, >20% 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, Definitions

- Virologic suppression:
  - Confirmed HIV RNA below LLOD (eg, <50 copies/mL)
- Virologic failure:
  - Inability to achieve or maintain HIV RNA <200 copies/mL
- Incomplete virologic response:
  - Confirmed HIV RNA ≥200 copies/mL after 24 weeks on ART
- Virologic rebound:
  - Confirmed HIV RNA ≥200 copies/mL after virologic suppression
- Virologic blip:
  - An isolated detectable HIV RNA level that is followed by a return to virologic suppression

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
  - Cost and affordability of ARVs

Treatment-Experienced Patients: Management of Virologic Failure

- Carefully assess causes of virologic failure; management will vary according to cause
- Check HIV RNA, CD4 count, ART history, prior and current ARV resistance test results
  - Resistance test should be done while patient is taking the failing regimen, or within 4 weeks of treatment discontinuation
  - If >4 weeks since ARV discontinuation, resistance testing may still provide useful information, though it may not detect previously selected mutations

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

- Goal of treatment: to establish virologic suppression (HIV RNA <LLOD)
- Treatment interruption is not recommended: may cause rapid increase in HIV RNA, immune decompensation, clinical progression

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

Poor CD4 Recovery and Persistent Inflammation Despite Viral Suppressio

- Morbidity and mortality are higher in HIV-infected individuals than in the general population, even with viral suppression
  - eg, cardiovascular disease, many non-AIDS cancers and infections, COPD, osteoporosis, diabetes, liver disease, kidney disease, neurocognitive dysfunction
  - Likely related to poor CD4 recovery, persistent immune activation, and inflammation, as well as patient behaviors and ARV toxicity

Poor CD4 Recovery and Persistent Inflammation Despite Viral Suppression (2)

- Poor CD4 recovery
  - Persistently low CD4 (especially <200 cells/μL, but also up to at least 500 cells/μL) despite viral suppression on ART is associated with risk of illness and mortality
  - Higher risk of suboptimal response with lower pretreatment CD4 counts

Poor CD4 Recovery and Persistent Inflammation Despite Viral Suppression (3)

- Management:
  - Evaluate for underlying causes (eg, malignancy, infections)
  - If possible, discontinue concomitant medications that may decrease CD4 cells (eg, AZT, combination of TDF + ddI), interferon, prednisone)
  - No consensus on management of patients without evident causes
    - Changing or intensifying the ARV regimen has not been shown to be beneficial

Poor CD4 Recovery and Persistent Inflammation Despite Viral Suppression (4)

- Persistent immune activation and inflammation
  - Systemic immune activation and inflammation may be independent mediators of risk of morbidity and mortality in patients with viral suppression on ART
    - Association with morbidity/mortality is largely independent of CD4 count
  - Immune activation and inflammation decrease with suppression of HIV through ART, but do not return to normal
  - Poor CD4 recovery on ART (eg, CD4 <350 cells/μL) associated with greater immune system activation and inflammation

Poor CD4 Recovery and Persistent Inflammation Despite Viral Suppression (5)

- Causes of persistent immune activation not completely clear: likely include HIV persistence, coinfections, microbial translocation
  - No proven interventions
    - ART intensification or modification: not consistently effective in studies
    - Antiinflammatory medications and others are being studied
    - Clinical monitoring with immune activation or inflammatory markers is not currently recommended
  - Focus on maintaining viral suppression with ART, reducing risk factors (eg, smoking cessation, diet, exercise), managing comorbidities (eg, hypertension, hyperlipidemia, diabetes)

Regimen Switching in Setting of Virologic Suppression

- Changing a suppressive ARV regimen to:
  - Reduce pill burden and dosing frequency to improve adherence
  - Enhance tolerability, decrease toxicity
  - Change food or fluid requirements
  - Minimize or address drug interactions
  - Allow for optimal ART during pregnancy
  - Reduce costs

Regimen Switching in Setting of Virologic Suppression (2)

Principles (cont.)

- Absent drug resistance, switching from a complex regimen, one with higher pill burden, dosing frequency, or more toxic ARVs:
  - Generally improves or does not worsen adherence, maintains viral suppression, and may improve quality of life

Regimen Switching in Setting of Virologic Suppression (3)

Principles:

- Maintain viral suppression and avoid jeopardizing future ARV options
- Review full ARV history, including all resistance test results and adverse effects
  - Previously acquired resistance mutations generally are archived and may reappear under selective drug pressure
  - Resistance often may be inferred from patient's treatment history
    - eg, resistance to 3TC and FTC should be assumed if virologic failure occurred in a patient taking one of these NRTIs, even if the mutation is not seen in resistance test results
- Consult with an HIV specialist if there is a history of resistance

Regimen Switching in Setting of Virologic Suppression (4)

Specific considerations

- Within-class switches:
  - Usually maintain viral suppression if no resistance to other ARVs in the same drug class
- Between-class switches:
  - Usually maintains viral suppression if there is no resistance to the components of the regimen
  - Avoid this type of switch if there is doubt about the activity of any agents in the regimen
- RTV-boosted PI + 3TC or FTC:
  - Growing evidence that boosted PI + 3TC can maintain viral suppression in ART-naive patients with no baseline resistance and those with sustained viral suppression
  - May be reasonable if use of TDF, TAF, or ABC is contraindicated

Regimen Switching in Setting of Virologic Suppression (5)

Switch strategies not recommended:

- RTV-boosted PI monotherapy
  - Less likely to maintain viral suppression
- Switching to maraviroc
  - Insufficient data on use of proviral DNA to determine tropism in virologically suppressed patients
- Other types of switches are under investigation

Regimen Switching in Setting of Virologic Suppression (6)

- Closely monitor tolerability, viral suppression, adherence, and toxicity in first 3 months after regimen switch

Websites to Access the Guidelines

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

About This Slide Set

- This presentation was prepared by Susa Coffey, MD, for the AETC National Resource Center in April 2015 and updated in July 2016 for the AETC National Coordinating Resource Center.
- See the AETC NCRC website for the most current version of this presentation: http://www.aidsetc.org