

# Issues Affecting ART Success: Adherence, ARV Toxicity, Drug Interactions

Guidelines for the Use of Antiretroviral Agents in  
Adults and Adolescents

April 2015

AETC NCRC Slide Set

# About This Presentation

These slides were developed using the April 2015 guidelines and 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the field of HIV care is rapidly changing, users are cautioned that the information in this presentation may become out of date quickly.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

<http://www.aidsetc.org>

# Initiation of Therapy: Contents

- Adherence
- ARV-associated adverse effects
- Drug interactions

# Adherence

- Strict adherence to ART is key to virologic suppression, lower rates of resistance, better quality of life, improved survival, and decreased risk of HIV transmission
- Adherence also encompasses engagement and retention in care
- ART regimens have become much simpler for initial therapy, but suboptimal adherence is common
- Important to assess readiness for ART prior to initiating therapy, and to assess adherence at each clinic visit

# Factors Associated with Adherence Failure

- Regimen complexity and pill burden
- Low literacy or numeracy level
- Younger age
- Some challenges of older age (eg, polypharmacy, vision loss, cognitive impairment)
- Nondisclosure of HIV status
- Stigma
- Psychosocial stressors
- Active drug use or alcoholism
- Mental illness (especially depression)
- Cognitive impairment
- Lack of patient education
- Medication adverse effects
- Treatment fatigue
- Cost and insurance coverage issues

# Factors Associated with Adherence Success

- Regimen simplicity, once-daily dosing
- Low pill burden
- Good tolerability
- Older age
- Multidisciplinary care (eg, with case managers, social workers, pharmacists, psychiatric care providers)
- Directly observed therapy
- Trusting patient-provider relationship
- Use of motivational strategies

# Predictors of Inadequate Adherence

- Age, race, sex, educational level, socioeconomic status, and a past history of alcoholism or drug use do NOT reliably predict suboptimal adherence
- Higher socioeconomic status and education levels and lack of history of drug use do NOT reliably predict optimal adherence

# Measurement of Adherence

- No gold standard
- HIV RNA suppression is one of the most reliable indicators
- Patient self-report may overestimate adherence, but is associated with viral load responses
  - Self-report of suboptimal adherence is strong indicator of suboptimal therapeutic response
- Pharmacy records and pill counts can be helpful



# Improving Adherence

- A continuum of ART support services is needed – team may include providers from many disciplines
- Strengthen early linkage to care and retention in care
- Provide education on HIV disease, treatment, and prevention
- Provide education on importance of adherence, and consequences of poor adherence
- Establish readiness to start therapy
- Individualize treatment, with patient involvement

# Improving Adherence (2)

- Simplify regimen, dosing, and food requirements
- Review potential side effects
- Anticipate and treat side effects
- Identify possible barriers to adherence and address these issues before starting ART
- Use positive reinforcement
- Systematically monitor treatment efficacy and retention in care

# Improving Adherence

(3)

- Use educational aids including pictures, pillboxes, and calendars
- Engage family, friends
- Utilize team approach with nurses, pharmacists, and peer counselors
- Provide accessible, trusting health care team
- Assess adherence at every clinic visit
- Identify type and reasons for nonadherence

# ART-Associated Adverse Effects

- Adverse effects (AEs) are one of the most common reasons for nonadherence, and for switching or stopping ART
- Newer ARV regimens generally result in fewer AEs
- Longer-term complications of ARVs are not well studied
- Risk of certain AEs may be higher in certain groups, eg, in women, those with comorbidities or on interacting medications
- Important to consider possible AEs carefully in selecting ARVs for the individual patient

# ART-Associated Adverse Effects

(2)

- Lactic acidosis/hepatic steatosis
- Hepatotoxicity
- Insulin resistance, diabetes mellitus
- Fat maldistribution
- Hyperlipidemia
- Cardiovascular and cerebrovascular effects
- Increased bleeding in hemophiliacs
- Bone density effects
- Rash

# 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, ZDV)

# 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

- Dolutegravir (DTG)
  - Headache
  - Insomnia
- Elvitegravir/cobicistat (EVG/COBI)
  - 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
  - Renal insufficiency
- 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
  - Hyperlipidemia
  - Teratogenic in nonhuman primates + cases of neural tube defects in human infants after 1st-trimester exposure
- **Etravirine (ETR)**
  - Nausea

# Adverse Effects: NNRTIs

(3)

- 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
  - Headache

# Adverse Effects: CCR5 Antagonist

- Maraviroc (MVC)
  - Drug-drug interactions
  - Rash
  - Abdominal pain
  - Upper respiratory tract infections
  - Cough
  - Hepatotoxicity
  - Musculoskeletal symptoms
  - Orthostatic hypotension

# Adverse Effects: Fusion Inhibitor

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

# ARV-Associated Adverse Effects: Lactic Acidosis/Hepatic Steatosis

- Rare, but high mortality
- Evidently owing to mitochondrial toxicity
- Associated with NRTIs (especially d4T, ddI, ZDV)
- More common in women, pregnancy, obesity
- Clinical presentation variable: have high index of suspicion
- Lactate >2-5 mmol/dL plus symptoms
- Treatment: discontinue ARVs, supportive care

# ARV-Associated Adverse Effects: Hepatotoxicity

- Severity variable: usually asymptomatic, may resolve without treatment interruption
- May occur with any NNRTI or PI, most NRTIs, or MVC:
  - NVP: risk of severe hepatitis in first few months of use (monitor LFTs closely), increased risk in chronic hepatitis B and C, women, and high CD4 count at initiation of NVP (>250 cells/ $\mu$ L in women, >400 cells/ $\mu$ L in men)
  - PIs: especially TPV/r; increased risk in hepatitis B or C, ETOH, other hepatotoxins
  - NRTIs: steatosis (especially AZT, d4T, ddl)
  - ddl; noncirrhotic portal hypertension



# ARV-Associated Adverse Effects: Insulin Resistance, Diabetes

- Insulin resistance, hyperglycemia, and diabetes associated with ZDV, d4T, ddI, some PIs (IDV, LPV/r), especially with chronic use
- Mechanism not well understood
  - Insulin resistance, relative insulin deficiency
- Screen regularly: fasting glucose

# ARV-Associated Adverse Effects: Fat Maldistribution

- Lipoatrophy:
  - Peripheral fat wasting more associated with NRTIs, especially thymidine analogues (d4T > ZDV, ddI > TDF, ABC, 3TC, FTC)
  - May be more likely when combined with EFV (compared with PI/r)
- Lipohypertrophy
  - Central fat accumulation more associated with regimens containing PIs, EFV, RAL; causal relationship not established
  - May be associated with dyslipidemia, insulin resistance, lactic acidosis
  - Monitor closely; intervene early
  - Treatment: switching to other agents may slow or halt progression

# ARV-Associated Adverse Effects: Hyperlipidemia

- ↑ total cholesterol, LDL, and triglycerides
  - Associated with all RTV- or COBI-boosted PIs, EFV, NVP, d4T, ZDV, ABC, TAF > TDF, EVG/COBI/TDF/FTC
- ↑ HDL seen with EFV, RTV-boosted PIs, EVG/COBI
- Concern for cardiovascular events, pancreatitis
- Monitor regularly
- Treatment: consider ARV switch; lipid-lowering agents (caution with PI + certain statins)

# ARV-Associated Adverse Effects: Cardiovascular and Cerebrovascular Effects

- MI and CVA:
  - Risk of MI and CVA associated with PIs in some cohort studies
  - Risk of MI with recent ABC and ddl use in some cohort studies (data are not consistent)
  - Seen especially in patients with traditional cardiovascular risk factors
  - Assess and manage cardiovascular risk factors
  - Consider ARVs with less risk of cardiovascular events, especially in patients at high risk of cardiovascular disease
- Cardiac conduction abnormalities
  - PR prolongation with ATV/r, LPV/r, SQV/r
  - QT prolongation with RPV, SQV/r
  - Avoid if risk factors; baseline and monitoring ECG recommended

# ARV-Associated Adverse Effects: Bone Density Effects

- TDF: greater bone mineral density loss than TAF, ZDV, d4T, or ABC
- Decreases in BMD seen after initiation of any ART regimen
- Other risk factors: low body weight, female, white or Asian ethnicity, older age, alcohol or tobacco use, hypogonadism, vitamin D deficiency, corticosteroid exposure
- Consider assessment by DEXA
- Management: consider alternative to TDF; calcium + vitamin D, bisphosphonate, weight-bearing exercise, hormone replacement

# ARV-Associated Adverse Effects: Rash

- Most common with NNRTIs, especially NVP
  - Most cases mild to moderate, occurring in first 6 weeks of therapy; occasionally serious (eg, Stevens-Johnson syndrome)
  - No benefit of prophylactic steroids or antihistamines (increased risk with steroids)
- PIs: especially ATV, DRV, FPV, LPV/r, TPV
- NRTIs: especially ABC (consider hypersensitivity syndrome)
  - FTC may cause hyperpigmentation
- INSTI: RAL, EVG/COBI/TDF/FTC (uncommon)
- CCR5 antagonist: MVC

# ARV-Associated Adverse Effects: Nephrotoxicity

- Renal insufficiency
  - TDF:
    - ↑ Cr, proteinuria, glycosuria, hypophosphatemia, hypokalemia
    - Concurrent RTV or COBI use may increase risk
  - TAF (vs TDF): less impact on renal biomarkers, lower rates of proteinuria
  - ATV, LPV/r: chronic kidney disease
  - IDV: ↑ Cr, pyuria, hydronephrosis or renal atrophy
  - COBI: nonpathologic ↓ in CrCl; also may increase risk of TDF-related nephrotoxicity
    - ↑ risk in patients with renal disease, low CD4 count
  - Monitor Cr, other renal parameters
  - Management: stop the offending ARV + supportive care
- Nephrolithiasis: IDV, ATV

# Overlapping Toxicities

- Peripheral neuropathy
  - ddl, d4T, ddC, isoniazid
- Bone marrow suppression
  - ZDV, dapsona, hydroxyurea, ribavirin, TMP-SMZ
- Hepatotoxicity
  - NVP, EFV, MVC, NRTIs, PIs, macrolides, isoniazid
- Pancreatitis
  - ddl, RTV, d4T, TMP-SMZ, pentamidine



# Drug Interactions with ARVs

- Certain ARVs, particularly PIs and NNRTIs, and the PK booster COBI have significant drug interactions with other ARVs and with other medications
- Interactions may be complex and difficult to predict
- Coadministration of some ARVs with other ARV or non-ARV medications may require dosage adjustment, and some combinations may be contraindicated
- Check for interactions before prescribing

# Drug Interactions with ARVs

(2)

- Increases in serum drug levels caused by inhibitors of metabolism may increase risk of medication toxicity, whereas decreases in drug levels caused by inducers of metabolism may cause treatment failure
- Some drug interactions may be exploited, eg, low-dose RTV (a strong CYP3A4 inhibitor) may be used as a pharmacokinetic enhancer to increase concentrations and prolong the half-life of other PIs

# Drug Interactions with ARVs

(3)

- All PIs and NNRTIs are metabolized by the hepatic CYP 450 system, particularly the CYP3A4
- PIs
  - All PIs are CYP3A4 substrates, and their serum levels may be affected by CYP inducers or inhibitors
  - Some PIs also are inducers or inhibitors of other CYP isoenzymes or of P-glycoprotein (PGP) or other transporters
- NNRTIs
  - Substrates of CYP3A4, can act as inducer (NVP) or mixed inducer and inhibitor (EFV)
  - ETR is substrate of 3A4, 2C9, and 2C19; inhibitor of 2C9 and 2C19

# Drug Interactions with ARVs

(4)

- NRTIs

- No hepatic metabolism, but some NRTIs may interact via other mechanisms (eg, decrease in ATV concentration if coadministered with TDF, proton pump inhibitors, H-2 receptor antagonists)

# Drug Interactions with ARVs

(5)

## ■ INSTIs

- RAL: eliminated by glucuronidation; inducers of UGT1A1 (eg, rifampin) can reduce RAL concentration
- DTG: eliminated mostly by glucuronidation, minor contribution by CYP3A4; concentrations may be affected by inducers of UGT1A1 and CYP3A inhibitors or inducers; dosage adjustment necessary
- EVG: requires boosting by COBI; many drug-drug interactions, owing to COBI

# Drug Interactions with ARVs

(6)

- CCR5 antagonist
  - MVC: substrate of CYP3A and PGP; concentrations are significantly affected by CYP3A inhibitors or inducers; dosage adjustment necessary
- Fusion inhibitor
  - ENF: no known significant drug interactions

# Drug Interactions with ARVs

(7)

- Cobicistat
  - CYP 3A4 and 2D6 inhibitor, no antiviral activity, used as PK booster of other agents
  - Inhibits PGP-mediated transport
  - Many and complex drug-drug interactions

# Common Drug Interactions with ARVs

The following require dosage modification or close monitoring; some specific combinations should not be used:

- Lipid-lowering agents
- Antimycobacterials, especially rifampin\*
- Antifungals
- Psychotropics – midazolam, triazolam
- Ergot alkaloids
- Antihistamines – astemizole
- Anticonvulsants
- Hepatitis C agents

\* Of NNRTIs and PIs, rifampin may be used only with full-dose RTV or with EFV.



# Common Drug Interactions with ARVs

The following require dosage modification or close monitoring; some specific combinations should not be used:

- Oral hormonal contraceptives, including emergency contraception (Plan B): may require alternative or second method
- Methadone
- Proton pump inhibitors, H2-receptor antagonists (eg, with ATV or RPV)
- Aluminum-, magnesium-, or calcium-containing antacids (with INSTIs)
- Erectile dysfunction agents
- Herbs – St. John's wort

# ARV-ARV Interactions

Require dosage modification or cautious use:

- NNRTIs with PIs
- NNRTIs with INSTIs
- ATV + TDF
- ddi + TDF
- ddi + d4T
- MVC + many PIs
- MVC + EFV or ETR

# ARV-ARV Interactions (2)

- Interactions involving ARVs (or COBI) often require dosage adjustment of the ARV and/or the interacting medication
- Some combinations are contraindicated
- Consider the possibility of interactions whenever adding a new medication
- Consult with expert pharmacists or clinicians

# 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.
- See the AETC National Coordinating Resource Center website for the most current version of this presentation:

<http://www.aidsetc.org>