

HIV/AIDS Guideline Update and Antiretroviral Drug Interactions

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Purpose

- To educate pharmacists on the key changes of the DDHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

Goals and objectives

- Describe benefits of antiretroviral therapy.
- Identify the optimal time to initiate antiretroviral therapy.
- Select an initial antiretroviral regimen.
- Recognize common drug interactions with antiretrovirals.
- List strategies to improve adherence to antiretroviral therapy.

Accessing the guidelines

DHHS

<http://www.aidsinfo.nih.gov>

Updated: December 1, 2009

Treatment goals

- Reduce HIV-related morbidity and prolong survival
- Restore and/or preserve immunologic function
- Improve QOL
- Maximally and durably suppress HIV viral load
- Prevent HIV transmission

Achieving treatment goals

- Selection and initiation of ARV regimen
- Maximizing adherence
- Resistance testing

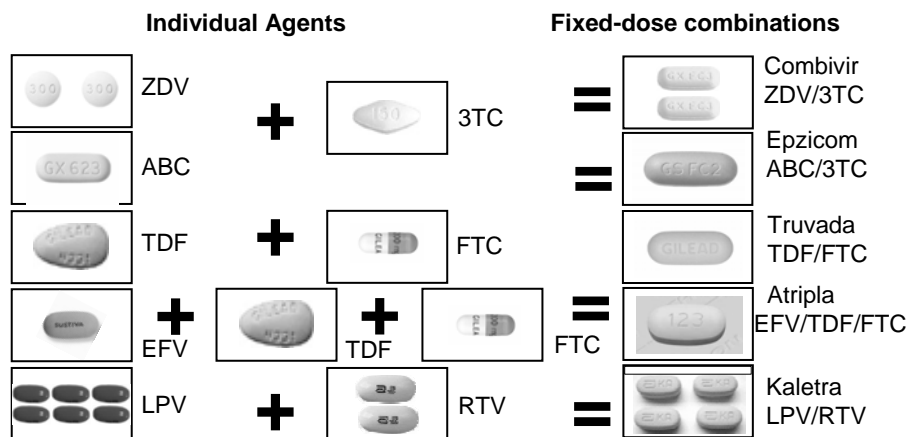
Common abbreviations

- AIDS = Acquired immune deficiency syndrome
- CD4 = CD4+ T Lymphocyte
- HIV = Human immunodeficiency virus
- OI = Opportunistic infection
- VL = Viral load

Common abbreviations

- ARV = Antiretroviral
- ART = Antiretroviral therapy
- INSTI = Integrase inhibitor
- NNRTI = Non-nucleoside reverse transcriptase inhibitor
- NRTI = Nucleos(t)ide analog reverse transcriptase inhibitor
- PI = Protease inhibitor

Fixed-Dose Combinations



Rating scheme for recommendations

Strength of recommendation	Quality of evidence for recommendation
A: Strong recommendation for the statement	I: One or more randomized trials with clinical outcomes
B: Moderate recommendations for the statement	II: One or more well designed, nonrandomized trials or observational cohort studies with LT clinical outcomes
C: Optional recommendation	III: Expert opinion

CD4 cell

- Major indicator of immune function
- Predictor of disease progression
- Guides decision to start HAART or OI prophylaxis
- Important in determining response to ART
- Monitor at baseline, 4 weeks, Q 3-6 months

HIV RNA/Viral Load

- Determines response to HAART
- GOAL: VL below level of detection
- Monitor at baseline, 2-8 weeks, Q 3-6 months

Drug resistance testing

- Initial testing recommended for all persons with HIV infection (AIII)
 - Genotypic assay preferred (AIII)
- Virologic failure (AII)
- Suboptimal virologic response (AIII)
- Pregnant women (AIII)
- Phenotypic testing (BIII)

Resistance

www.iasusa.org/resistance_mutations

<http://hivdb.stanford.edu>

HLA-B*5701 screening

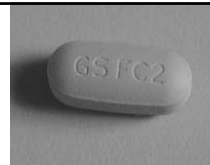
- Abacavir (Ziagen, Epzicom, Trizivir)
- Reduce risk of hypersensitivity reaction (HSR) (AI)
- Positive results = allergy (AII)
- Counseling and monitoring (CIII)

WARNING CARD Ziagen® (abacavir sulfate)



- **Patients taking ZIAGEN may have a serious allergic reaction (hypersensitivity reaction) that can cause death. If you get a symptom from 2 or more of the following groups while taking ZIAGEN, call your doctor right away to determine if you should stop taking this medicine. Symptom(s)**
- **Group 1** Fever
- **Group 2** Rash
- **Group 3** Nausea, vomiting, diarrhea, or abdominal (stomach area) pain
- **Group 4** Generally ill feeling, extreme tiredness, or achiness
- **Group 5** Shortness of breath, cough, or sore throat

Back of warning card

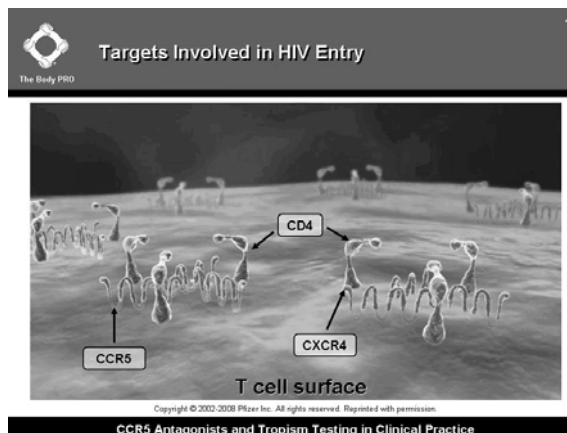


- If you must stop treatment with EPZICOM because you have had an allergic reaction to abacavir, **NEVER take EPZICOM or another abacavir-containing medicine (ZIAGEN® and TRIZIVIR®) again. If you take EPZICOM or another abacavir-containing medicine again after you have had an allergic reaction, WITHIN HOURS you may get life-threatening symptoms that may include very low blood pressure or death.**
- Please read the Medication Guide for additional information on EPZICOM.



Coreceptor tropism assays

- CCR5 antagonist
 - Selzentry (maraviroc) (All)



Indications for initiating ARV

- History of AIDS-defining illness (AI)
- CD4 count <350 (AI)
- Pregnant women (AI)
- Persons with HIV-associated nephropathy (AII)
- Persons coinfectd with hepatitis B virus (HBV), when treatment is indicated (AIII)

Indications for initiating ARV

- Patients with CD4 count between 350-500 (A/BII)
 - 55% strong recommendation (A)
 - 45% moderate recommendation (B)
- Patients with CD4 count >500 (B/CIII)
 - 50% favor/optional (B/C)

Conditions favoring more rapid initiation of therapy

- Pregnancy (AI)
- AIDS-defining conditions (AI)
- Acute OIs
- Lower CD4 counts (AI)
- Rapidly declining CD4 counts (AIII)
- Higher VLs (BII)
- HIV associated nephropathy (AII)
- HBV coinfection when treatment for HBV is indicated (AIII)

Support for earlier therapy

- Report from at least one recent cohort study demonstrating survival benefit with initiation of ART at CD4 >500
- Growing awareness that untreated HIV infection may be associated with development of many non-AIDS defining diseases, including CV, kidney, liver, malignancy

Support for earlier therapy

- Greater efficacy, convenience, tolerability, and safety of current ARV
- Increasing evidence that effective ART reduces HIV transmission (BIII)

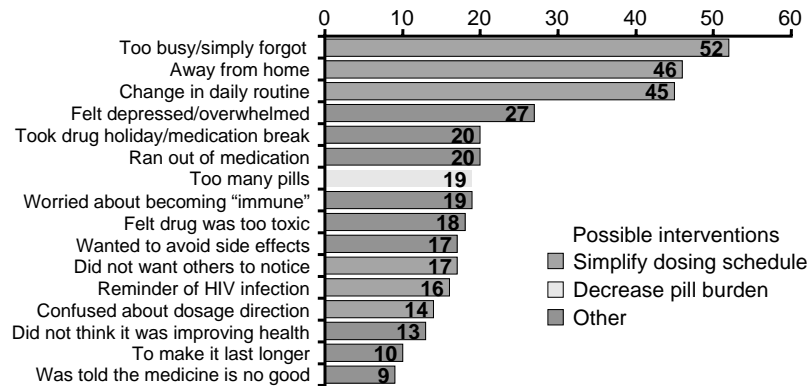
Consider deferral of ART

- Adherence concerns (AIII)
- Clinical or personal factors
- Comorbidities complicate or prohibit
- Cost



Why Do Patients Miss Doses?

Reasons Given for Missing Antiretroviral Doses (Structured Questionnaire) (%)



Gifford AL, et al. J Acquire Immune Defic Syndr. 2000;23:386-395.

Improving adherence

- Support and reinforcement
- Simplified dosing
- Reminders
- Ongoing education
- Trust in PCP

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)

PI

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

Integrase Inhibitor (II)

- Raltegravir (RAL)

Fusion Inhibitor

- Enfuvirtide (ENF, T-20)

CCR5 Antagonist

- Maraviroc (MVC)

Initial ART : DHHS Categories

- Preferred
 - Randomized controlled trials show optimal efficacy and durability
 - Favorable tolerability and toxicity profiles
- Alternative
 - Effective but have potential disadvantages
 - May be the preferred regimen in individual patients
- Acceptable
 - Less virologic efficacy, lack of efficacy data, or greater toxicities
- May be acceptable but more definitive data are needed

Selecting a treatment regimen

- Initiate therapy with 1 of the following 3 types of regimens (AI)
 1. NNRTI + 2NRTIs OR
 2. PI (preferably boosted) + 2NRTIs OR
 3. INSTI + 2 NRTIs

Selecting a treatment regimen

- Individualization based on
 - Virologic efficacy
 - Pill burden
 - Dosing frequency
 - Drug-drug interaction potential
 - Resistance testing results
 - Comorbid conditions

Initial Treatment: Preferred

NNRTI Option

▪Sustiva (efavirenz)*

OR

PI Options

▪Reyataz³/Norvir⁴(atazanavir/r)
▪Prezista/Norvir (darunavir/r)

OR

INSTI Options

▪Isentress (raltegravir)

NRTI Options

▪Truvada
(tenofovir +
emtricitabine^{1,2})

+

* Avoid in pregnant women and women with significant pregnancy potential

¹ Emtricitabine can be used in place of lamivudine and vice versa

² Tenofovir + emtricitabine or lamivudine is preferred in patients with HIV/HBV coinfection

³ Atazanavir/r should not be used in patients that require >20mg omeprazole equivalent QD

⁴ Atazanavir/r is generally preferred over atazanavir

Comparing “Preferred” Initial ART

Recommended Regimen	Total # of Pills/Day	Dosing
Atripla	1	QD
Reyataz + Norvir + Truvada	3	QD
Prezista + Norvir + Truvada	4	QD
Isentress + Truvada	3	BID

Preferred regimen for pregnancy

- Kaletra (lopinavir/r) BID +
- Combivir (zidovudine/lamivudine) (AI)

Recommended Regimen	Total # of Pills/Day	Dosing
Kaletra + Combivir	6	BID

Alternative regimens

- NNRTI-based (BI)
 - Sustiva + Epzicom or Combivir
 - Viramune + Combivir
- PI-based (BI)
 - Reyataz/Norvir + Epzicom or Combivir
 - Lexiva/Norvir + Epzicom or Combivir or Truvada
 - Kaletra + Epzicom or Combivir or Truvada
 - Invirase/Norvir + Truvada

Initial Treatment: Alternative

NNRTI Option

- Sustiva (efavirenz)*
- Viramune (nevirapine)^

OR

PI Options

- Reyataz³/Norvir⁴(atazanavir/r)
- Lexiva/Norvir (fosamprenavir/r)
- Kaletra (lopinavir/r)
- Invirase/Norvir (saquinavir/r)

NRTI Options

- Truvada (tenofovir/emtricitabine^{1,2})
- Epzicom (abacavir⁵/lamivudine)
- Combivir (lamivudine/zidovudine)

+

^ Should not be used in patients with moderate to severe hepatic impairment. NVP should not be started if pre-ARV CD4 >250 in women or >400 in men.

⁵ Should not be used for patients who test HLA-B5701 positive, caution if HIV RNA >100,000 copies/mL, or if high risk of cardiovascular disease.

Comparing “Alternative” Initial ART

Recommended Regimen	Total # of Pills/Day	Dosing
Sustiva + Epzicom or Combivir	2	QD
Sustiva + Combivir	3	BID
Viramune + Combivir	4	BID
Reyataz/Norvir + Epzicom	3	QD
Reyataz/Norvir + Combivir	4	BID
Lexiva/Norvir + Epzicom	4	BID
Lexiva/Norvir + Combivir	5	BID
Lexiva/Norvir + Truvada	4	QD
Kaletra + Epzicom	5	QD
Kaletra + Combivir	6	BID
Kaletra + Truvada	5	QD
Invirase/Norvir + Truvada	7	BID

ARVs not recommended

- High rate of early virologic failure
- Inferior virologic efficacy
- High incidence of toxicities
- High pill burden/dosing inconvenience
- Lack of data as initial treatment
- No benefit over standard regimen

ART that should not be offered

- Monotherapy with NRTI (AII)
- Dual-NRTI (AI)
- Triple NRTI (AI)
- Reyataz + Crixivan (AIII)
- Zerit + Videx (didanosine) (AII)
- 2-NNRTI (AI)
- Sustiva (pregnancy) (AIII)

ART that should not be offered

- Emtriva + Epivir (AIII)
- Intelence + unboosted PI (All)
- Intelence + boosted Reyataz or Lexiva
- Intelence + boosted Aptivus (All)
- Viramune (BI)
 - Women CD4 >250
 - Men CD4 >400
- Unboosted Prezista, Invirase, Aptivus

NNRTI-based

- Advantages
- Disadvantages
- Adverse drug effects
 - Rash
- Sustiva (efavirenz)
 - Neuropsychiatric, teratogenic
- Viramune (nevirapine)
 - Hepatotoxicity

PI-based

- Advantages
- Disadvantages
- Adverse drug effects
 - Hyperlipidemia
 - Insulin resistance and diabetes
 - Lipodystrophy
 - Elevated LFTs
 - Possibility of increased bleeding risk for hemophiliacs

PI ADEs

- Reyataz (atazanavir)
 - Hyperbilirubinemia, PR prolongation, nephrolithiasis
- Prezista (darunavir)
 - Rash, liver toxicity
- Lexiva (fosamprenavir)
 - GI, rash, possible increased risk of MI
- Crixivan (indinavir)
 - Nephrolithiasis, GI

PI ADEs

- Kaletra (lopinavir/ritonavir)
 - GI, PR and QT prolongation, possible increased risk of MI
- Norvir (ritonavir)
 - GI, hepatitis
- Invirase (saquinavir)
 - GI
- Aptivus (tipranavir)
 - Rash, liver toxicity, cases of intracranial hemorrhage

INSTI-based

- Advantages
- Disadvantages
- Adverse drug effects
 - Nausea, headache, diarrhea, CPK elevation

NRTI-based

- Advantages
- Disadvantages
- Adverse drug effects
 - Lactic acidosis and hepatic steatosis (highest incidence with stavudine, then didanosine, lower with tenofovir, abacavir, lamivudine and emtricitabine);
 - lipodystrophy (stavudine)

NRTI ADEs

- Ziagen (abacavir)
 - HSR, rash, possible increased risk of MI
- Videx (didanosine)
 - Peripheral neuropathy, pancreatitis
- Zerit (stavudine)
 - Peripheral neuropathy, pancreatitis

NRTI ADEs

- Viread (tenofovir)
 - Renal impairment, possible decrease in BMD, headache
- Retrovir (zidovudine)
 - bone marrow suppression

Fusion Inhibitor

- Fuzeon (enfuvirtide)
 - Injection site reactions
 - HSR
 - Increased risk bacterial pneumonia

CCR5 antagonist

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

Treatment-experienced

- Treatment goal is to suppress virus below limit of detection (AI)
- Appropriate initial ARV regimens should suppress HIV indefinitely
 - Optimal regimen
 - Adherence
- In patients with suppressed VL <50
 - Assess adherence frequently
 - Simplify regimen
- Patients with ARV failure
 - Assess and address aggressively

ART failure

- Causes of treatment failure include:
 - Drug resistance
 - Suboptimal adherence
 - ARV toxicity and intolerance
 - Pharmacokinetic problems
 - Suboptimal drug potency
 - Provider experience

ART failure

- Virologic failure:
 - HIV RNA >400 copies/mL after 24 weeks or
 - >50 copies/mL after 48 weeks
- Immunologic failure:
 - Failure to achieve and maintain adequate CD4 increase despite virologic suppression
 - Immunomodulator interleukin-2 has not demonstrated clinical benefits (AI)
- Clinical progression:
 - Occurrence of HIV-related events

Management of treatment-experienced patients

- Evaluate remaining ARV options
- Base ARV selection on medication history, resistance testing, expected tolerability, adherence, and future treatment options
- Avoid treatment interruption, which may cause viral rebound, immune decompensation, clinical progression

Regimen simplification

- Changing a suppressive ARV regimen to:
 - Reduce pill burden
 - Reduce dosing frequency
 - Enhance tolerability
 - Decrease food and fluid requirements
- Goals: improve patient's quality of life, improve ART adherence, avoid long-term toxicities, reduce risk of virologic failure

Drug interactions

- Use of 3 or 4 drug ARV regimens
- Multiple agents to treat/prevent OIs
- Chronic diseases
- Pharmacokinetic
- Pharmacodynamic

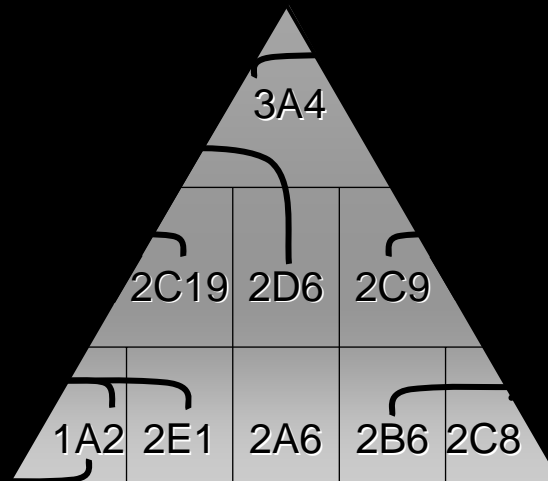
Drug interactions

- ALL PIs and NNRTIs are metabolized by the CYP3A4 enzyme system
- All PIs can inhibit CYP3A4 enzymes
 - Ritonavir (Norvir)
 - Saquinavir (Invirase)
- NNRTIs
 - Nevirapine (Viramune)
 - Efavirenz (Sustiva)

CYP450

- **Substrate:** metabolized by enzyme
- **Inhibitor:** inhibits metabolism of substrate
- **Inducer:** induces metabolism of substrate through increased production of enzyme
 - Interactions involving induction may be delayed since new enzyme must be synthesized

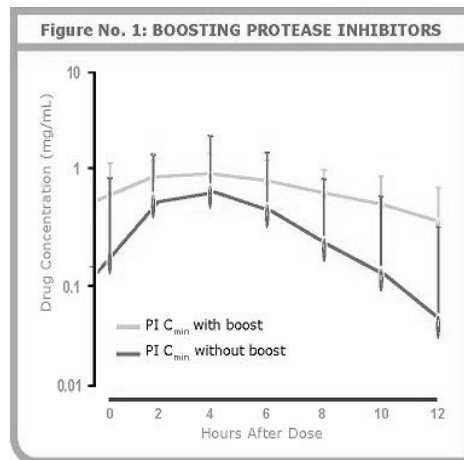
Effect of ARVs on Drug Metabolism



CYP450

- CYP3A4 substrate with narrow margin of safety
- Presence of CYP3A4 inhibitor
 - Prolonged T1/2
 - Toxic drug accumulation
- Ritonavir (Norvir)
 - Inhibitory effect
 - Pharmacokinetic enhancer to increase C_{min} and prolong T1/2

Boosting Protease Inhibitors



- Some PI's can be "boosted" by being used in combination with Norvir.
- Norvir slows down the time it takes the body to get rid of other PI's by interacting with the enzymes responsible for their elimination
- This allows the PI's to be present in the body longer

Drugs that should no be given with PIs

- Simvastatin
- Lovastatin
- Astemizole
- Terfenadine
- Cisapride
- Pimozide
- Bepridil
- St. John's Wort
- Rifampin
- Rifapentine
- Midazolam
- Triazolam
- Ergot alkaloids

Drug interactions: Lipid lowering agents

- Simvastatin and lovastatin are CI with PIs
- Pravastatin and fluvastatin least likely to interact
- Atorvastatin at low doses

Drug interactions

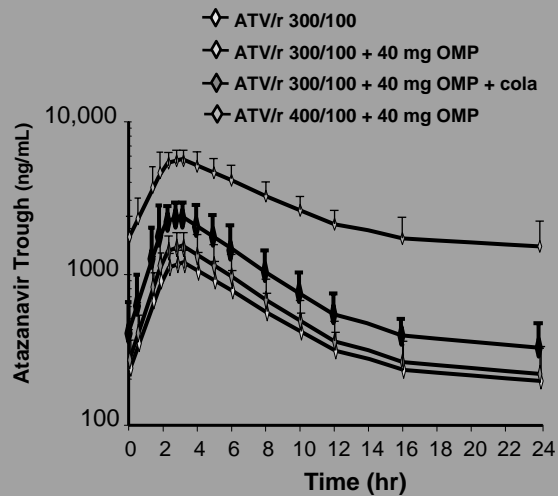
- Fluticasone (3A4 substrate)
- Anxiolytics
 - Safest to use glucuronidated benzodiazepines

Drug interactions OTCs

- St John's Wort
- Acid reducers
 - Traditional antacids
 - H-2 blockers
 - PPIs

Interaction Between Atazanavir + Omeprazole

- N = 48 HIV(-) subjects
- ATV exposures substantially reduced by coadministration with OMP 40 mg
- Not corrected by increased ATV dose or 8 oz cola
- OMP exposures not significantly altered
- Effect of OMP 20 mg (OTC dose) not known
- Do not coadminister



Agarwala S, et al. CROI 2005. Abstract 658.

Dosing requirements

- Renal
- Hepatic
- Weight
- Food

More information

- www.aidsinfo.nih.gov
- www.aidsetc.org
- www.clinicalcareoptions.com
- www.aidsinfo.net
- www.hiv-druginteractions.org
- <http://hivinsite.ucsf.edu>

Additional Questions

Thanks!