NORTHWEST AIDS EDUCATION AND TRAINING CENTER

Initial Anti-Retroviral Therapy

Christian B. Ramers, MD, MPH
Medical Director, NW AETC ECHO
Assistant Professor of Medicine & Global Health, University of Washington

Presentation Prepared by:
Christian B. Ramers, MD, MPH and David Spach, MD
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Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

October 14, 2011

Developed by the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC)

How to Cite the Adult and Adolescent Guidelines:

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. October 14, 2011; 1–167. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed [insert date] [insert page number, table number, etc. if applicable]

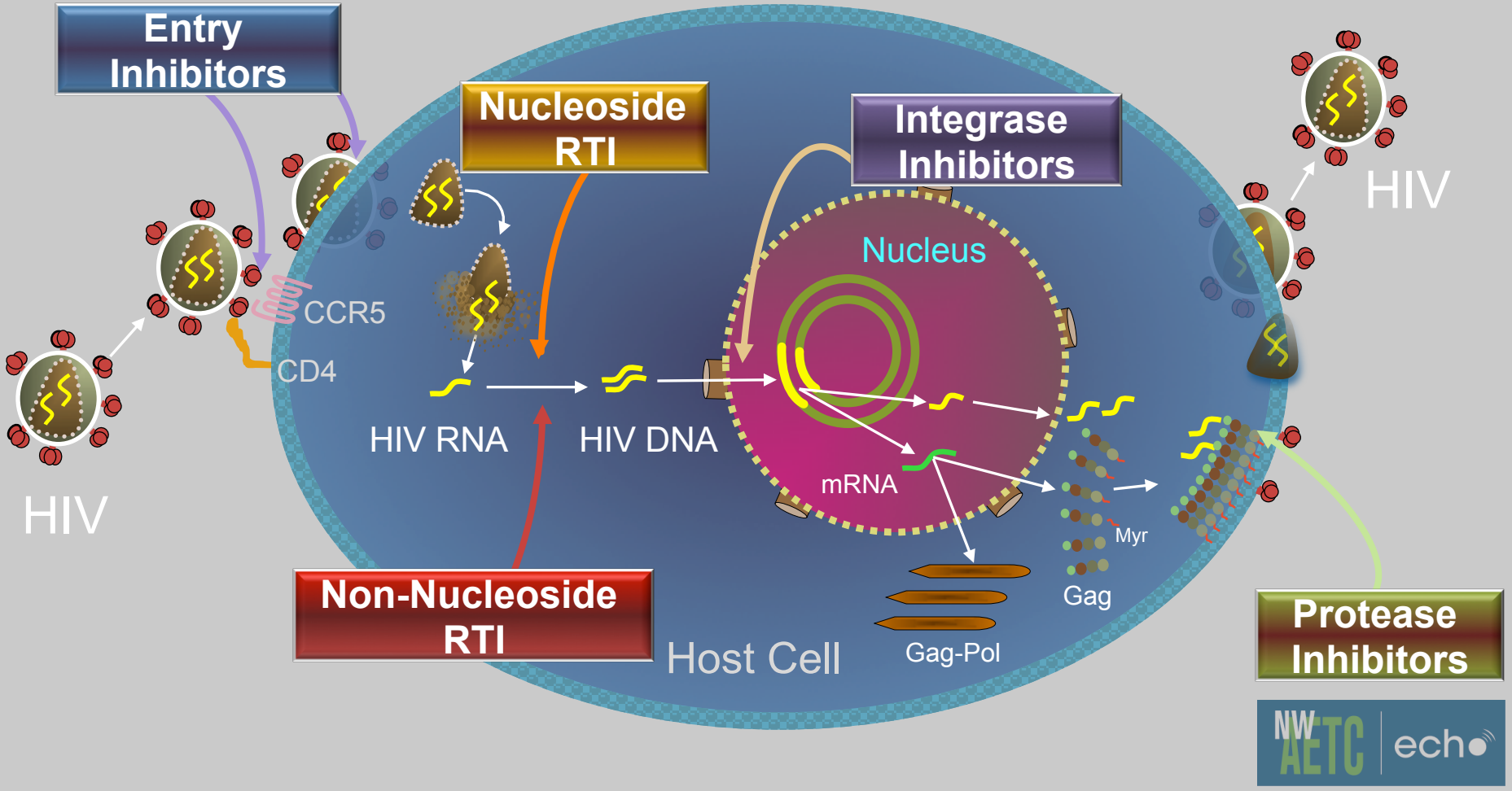
It is emphasized that concepts relevant to HIV management evolve rapidly. The Panel has a mechanism to update recommendations on a regular basis, and the most recent information is available on the AIDS*info* Web site (http://aidsinfo.nih.gov).

access AIDS*info* mobile site

Source: 2011 DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)

SELECTING AMONG 'PREFERRED' REGIMENS

Anti-retroviral drug targets



Anti-retroviral Therapy in 2012

Entry Inhibitors

Enfuvirtide (ENV) Fuzeon®	 90 mg/ml	Administered dose: 90 mg/mL subcutaneously (SQ) 2 times a day (108 mg vial diluted with 1.1 mL sterile water) • Store at controlled room temperature
Maraviroc (MVC) Selzentry®	 150 mg 300 mg	1 x 300 mg tablet 2 times a day (With NRTIs, tipranavir/ritonavir, nevirapine, and weak CYP3A inhibitors or CYP3A inducers) 1 x 150 mg tablet 2 times a day (When given with strong CYP3A inhibitors with or without CYP3A inducers) 2 x 300 mg tablet 2 times a day (With CYP3A inducers including efa-

Combination NRTIs + NNRTI

Tenofovir + Emtricitibine + Efavirenz Atripla®	 TDF 300 mg/FTC 200 mg/ EFV 600 mg	1 tablet once daily at bedtime • Empty stomach recommended

Integrase Inhibitors

Raltegravir (RAL) Isentress®	 400 mg	1 tablet 2 times a day • May be taken with or without food

Combination NRTIs

Abacavir + Lamivudine Epzicom®	 ABC 600 mg/3TC 300 mg	1 tablet once daily • May be taken with or without food
Abacavir + Lamivudine + Zidovudine Trizivir®	 ABC 300 mg/3TC 150 mg/ AZT 300 mg	1 tablet 2 times a day • May be taken with or without food
Zidovudine + Lamivudine Combivir®	 AZT 300 mg/3TC 150 mg	1 tablet 2 times a day • May be taken with or without food
Tenofovir + Emtricitibine Truvada®	 TDF 300 mg/FTC 200 mg	1 tablet once daily • May be taken with or without food

Nucleos(t)ide Reverse Transcriptase Inhibitors (NRTI)

Abacavir (ABC) Ziagen®	 300 mg	1 x 300 mg tablet 2 times a day 2 x 300 mg tablets once daily • May be taken with or without food	Hypersensitivity reaction symptoms may include: fever, rash, nausea, vomiting, malaise or fatigue, respiratory difficulties
Didanosine (ddI) Videx®	 250 mg 400 mg	1 x 400 mg capsule once daily • Reduce dose for weight < 60 Kg • Take on an empty stomach Note: When combined with tenofovir, reduce didanosine to 250 mg once daily; may be taken with food.	Peripheral neuropathy, pancreatitis, nausea, diarrhea
Emtricitabine (FTC) Emtriva®	 200 mg	1 x 200 mg capsule once daily • May be taken with or without food	Headaches, fatigue, nausea
Lamivudine (3TC) Epivir®	 150 mg 300 mg	1 x 150 mg tablet 2 times a day 1 x 300 mg tablet once daily • May be taken with or without food	Headaches, fatigue, nausea
Stavudine (d4T) Zerit®	 30 mg 40 mg	1 x 40 mg capsule 2 times a day • Reduce dose for weight < 60 Kg 1 x 30 mg capsule 2 times a day • May be taken with or without food	Peripheral neuropathy, altered liver function
Tenofovir DF (TDF) Viread®	 300 mg	1 x 300 mg tablet once daily • May be taken with or without food	Renal insufficiency (rare), nausea, upset stomach
Zidovudine (ZDV, AZT) Retrovir®	 100 mg 300 mg	1 x 300 mg tablet 2 times a day • May be taken with or without food	Anemia, neutropenia, headaches, nausea, body aches, insomnia

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

Delavirdine (DLV) Rescriptor®	 200 mg	2 x 200 mg tablets 3 times a day • May be taken with or without food	Rash, headache, altered liver function
Efavirenz (EFV) Sustiva®	 200 mg 600 mg	1 x 600 mg tablet once daily at bedtime 3 x 200 mg capsules once daily at bedtime • Empty stomach recommended	Rash, altered liver function, dizziness, insomnia, impaired concentration, drowsiness
Etravirine (ETR) Intelence®	 100 mg	2 x 100 mg tablet 2 times a day • Take with food	Nausea, headache, rash, Stevens-Johnson syndrome, hypersensitivity reaction, erythema
Nevirapine (NVP) Viramune®	 200 mg	1 x 200 mg tablet 2 times a day (start with 200 mg tablet once daily x 14 days) • May be taken with or without food	Rash, headache, altered liver function

New NNRTI: **Rilpivirine** Co-formulated with Emtricitabine-Tenofovir as **Complera**

Protease Inhibitors (PI)

Atazanavir (ATV) Reyataz®	 150 mg 200 mg 300 mg	2 x 200 mg capsules once daily 1 x 300 mg capsule with ritonavir 100 mg capsule once daily Note: Use ritonavir boosted dose when combined with efavirenz, nevirapine, or tenofovir • Take with light meal • Consult Reyataz prescribing information for use with antacids, H2-blockers and proton pump inhibitors.
Darunavir (DRV) Prezista®	 400 mg 600 mg	Always use with ritonavir 1 x 600 mg tablet 2 times a day with ritonavir 1 x 100 mg capsule 2 times a day 2 x 400 mg tablet once a day with ritonavir 1 x 100 mg capsule once a day • Take with food
Fosamprenavir (FPV) Lexiva®	 700 mg	PI-naïve patients: 2 x 700 mg tablets 2 times a day 2 x 700 mg tablets once daily with 1 or 2 x 100 mg ritonavir capsules once daily Note: Use ritonavir boosted dose when combined with efavirenz or nevirapine, use ritonavir 300 mg once daily when combined with NNRTIs. 1 x 700 mg tablet 2 times a day with ritonavir 1 x 100 mg capsule 2 times a day PI-experienced patients: 1 x 700 mg tablet 2 times a day with 1 x 100 mg ritonavir capsule 2 times a day • May be taken with or without food
Indinavir (IDV) Crixivan®	 400 mg	2 x 400 mg capsules 2 times a day with ritonavir 100-200 mg capsule(s) 2 times a day • Take with food • Drink at least 1.5 liters of fluid per day
Lopinavir/ Ritonavir (LPV/r) Kaletra®	 LPV 200 mg/RTV 50 mg	PI-naïve patients: 2 tablets 2 times a day 4 tablets once daily PI-experienced patients: 2 tablets 2 times a day Once daily not recommended Note: Use 3 tablets 2 times a day when used with nevirapine or efavirenz
Nelfinavir (NFV) Viracept®	 250 mg 625 mg	2 x 625 mg tablets 2 times a day 5 x 250 mg tablets 2 times a day 3 x 250 mg tablets 3 times a day • Always take with food
Ritonavir (RTV) Norvir®	 100 mg	Ritonavir is primarily used in low doses to boost drug levels of other protease inhibitors • Keep refrigerated
Saquinavir (SQV) Invirase®	 200 mg 500 mg	Always take at same time with ritonavir 2 x 500 mg tablets 2 times a day with ritonavir 100 mg capsule 2 times a day 5 x 200 mg capsules 2 times a day with ritonavir 100 mg capsule 2 times a day • Always take with food
Tipranavir (TPV) Aptivus®	 250 mg	Always use with ritonavir PI-experienced patients: 2 x 250 mg capsules 2 times a day with ritonavir 2 x 100 mg capsules 2 times a day • Take with food

Source: www.nwaetc.org

NW AETC | echo

DHHS Antiretroviral Therapy Guidelines: October 2011 Preferred Regimens for ARV-Naïve Patients

Backbone

(2) Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

+

Third Agent

Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)

or

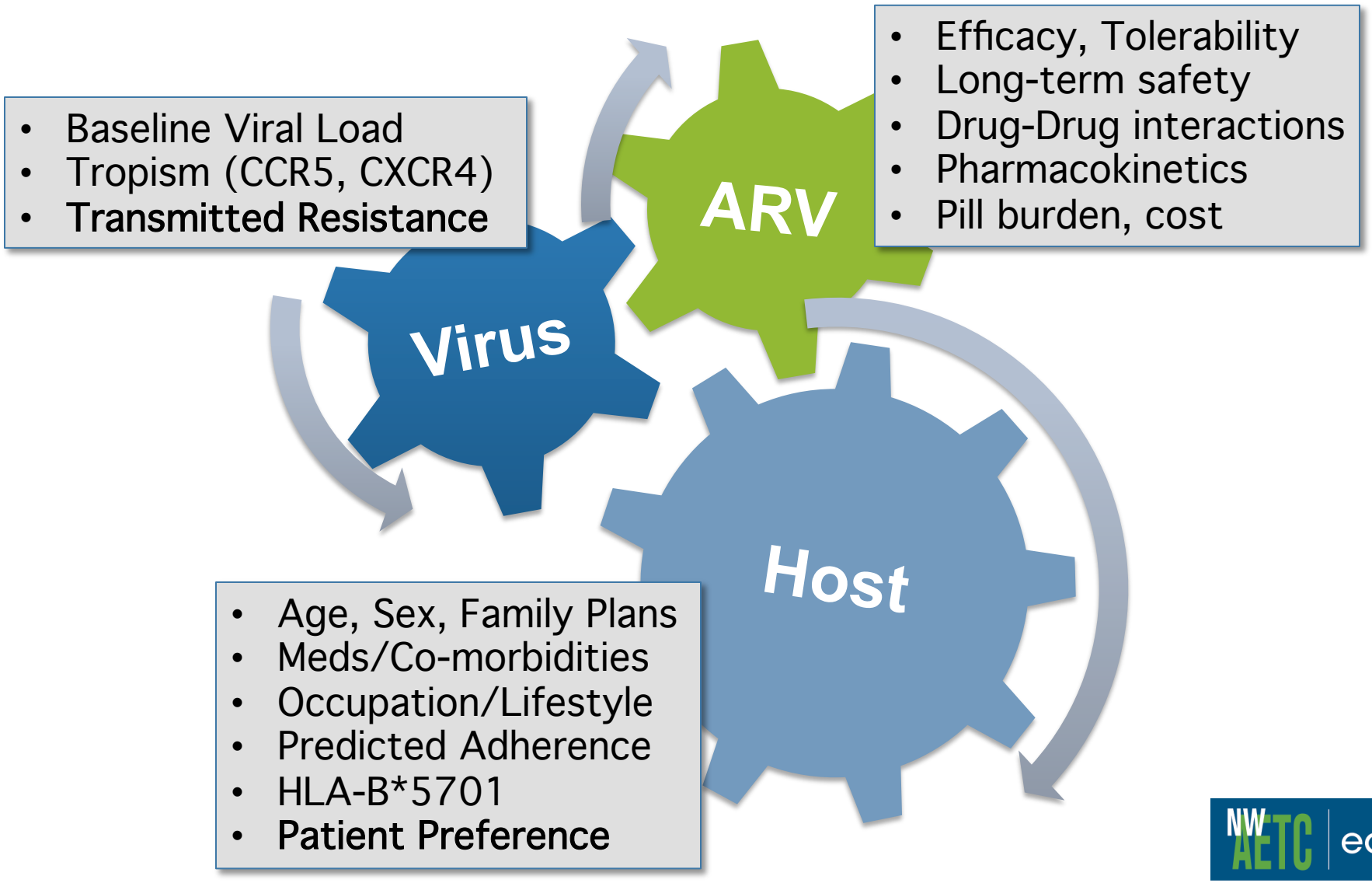
Protease Inhibitor (PI) (ritonavir-boosted)

or

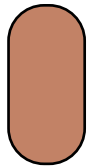
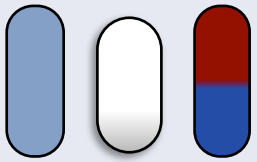
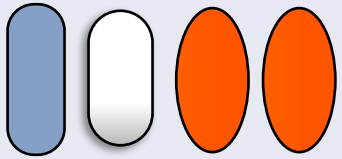
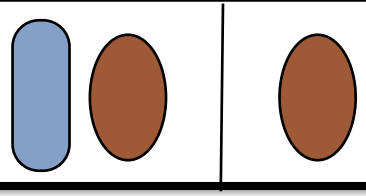
Integrase Strand Transfer Inhibitor (INSTI)

Source: DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)

Key Factors Influencing First-line Regimen

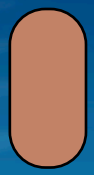


DHHS Antiretroviral Therapy Guidelines: October 2011
Preferred Regimens for ARV-Naïve Patients: Pill Burden

Class	Therapy	Pill Burden
NNRTI-Based	Efavirenz-Tenofovir-Emtricitabine	
PI-Based	Ritonavir + Atazanavir + Tenofovir-Emtricitabine	
	Darunavir + Ritonavir + Tenofovir-Emtricitabine	
INSTI-Based	Raltegravir + Tenofovir-Emtricitabine	

Source: 2011 DHHS Antiretroviral Therapy Guidelines. AIDS Info (www.aidsinfo.nih.gov)

Efavirenz-based Regimens (Atripla)

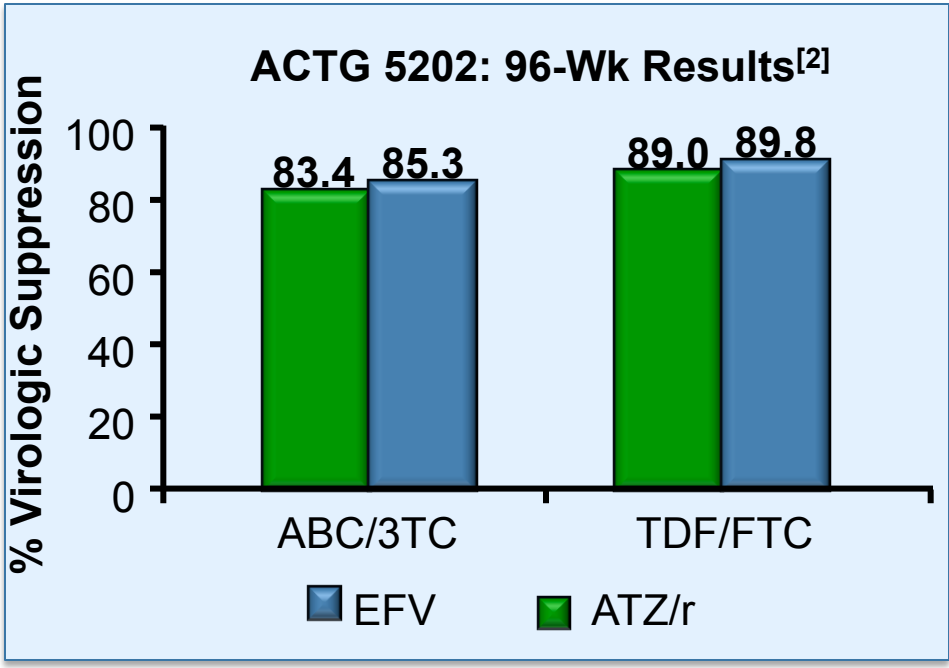


Advantages

- Long history as Gold Standard
- Never lost head-to-head trial
- Only preferred One Pill QD
- Appropriate for TB co-infection

Disadvantages

- Low genetic resistance barrier
- Higher risk of NRTI resistance with NNRTI failure
- CNS adverse effects
- 1st trimester teratogenicity
- Potential drug-drug interactions



1. Lennox JL, et al. Lancet. 2009;374:796-806.
2. Daar ES, et al. Ann Intern Med. 2011;154:445-456.
3. Johnson VA, et al. Top HIV Med. 2010;18:156-163.
4. Riddler SA, et al. N Engl J Med. 2008;358:2095-2106.

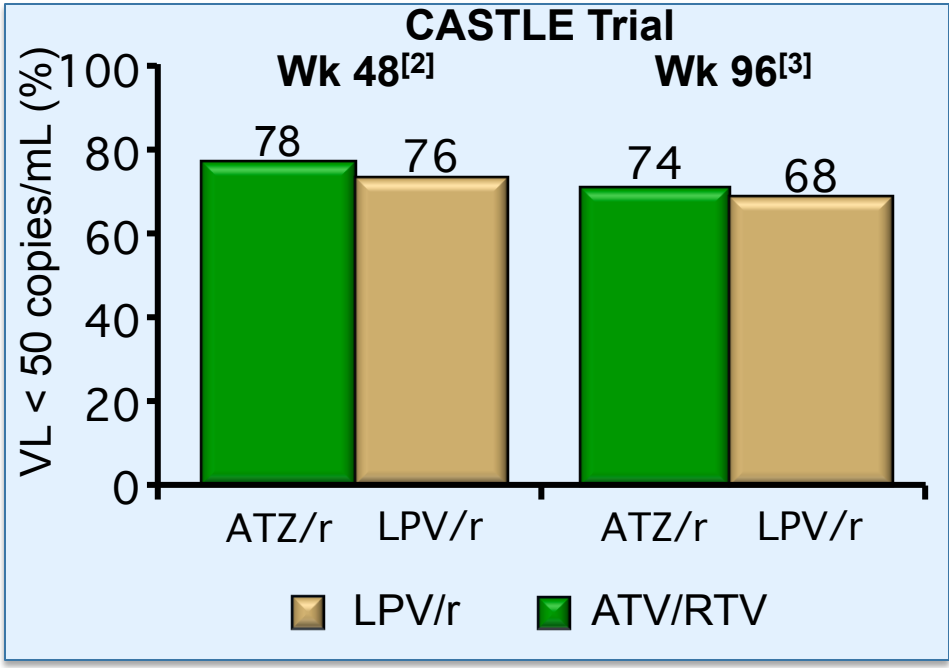
Atazanavir/ritonavir-based Regimens

Advantages

- Equivalent to EFV at 96 weeks[1]
- Favorable lipid effects[2,3]
- Low resistance risk at failure[1-3]
- 3 pills QD, only 100 mg ritonavir

Disadvantages

- Impaired absorption with acid-reducing agents
- Unconjugated hyperbilirubinemia in 4-9% of patients[4]
- Food requirements for dosing
- No co-formulations available
- Requires 100 mg ritonavir



1. Daar ES, et al. Ann Intern Med. 2011;154:445-456.
2. Molina JM, et al. Lancet. 2008;372:646-655.
3. Molina JM, et al. J Acquir Immune Defic Syndr. 2010;53:323-332
4. Atazanavir Package Insert. October 2011

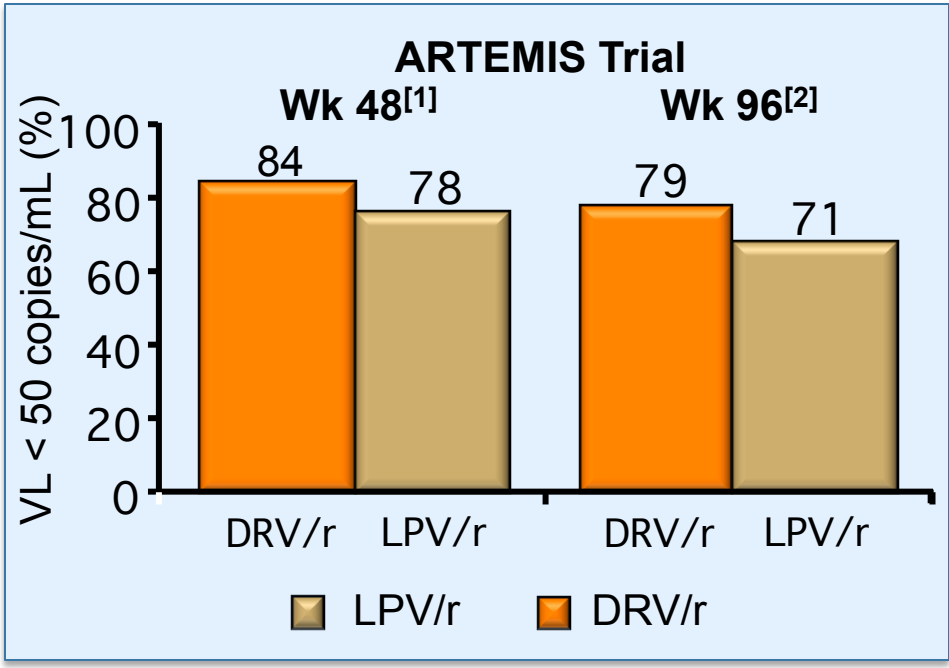
Darunavir/ritonavir-based Regimens

Advantages

- Most potent PI
- Favorable lipid effects[1, 2]
- Low resistance risk at failure[1, 2]
- 4 pills QD, only 100 mg ritonavir

Disadvantages

- Rash in ~6% of patients; caution for use in sulfa-allergic patients[3]
- No co-formulations available
- No head-to-head comparisons with other recommended agents
- Requires 100 mg ritonavir



1. Ortiz R, et al. AIDS. 2008;22:1389-1397.
2. Mills AM, et al. AIDS. 2009;23:1679-1688.
3. Darunavir [package insert]. November 2011.

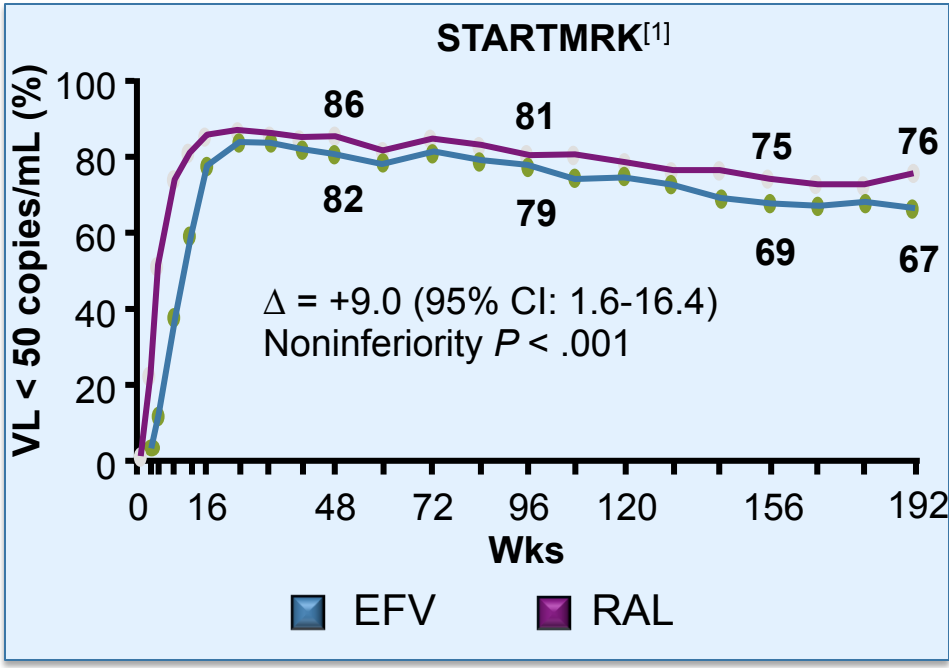
Raltegravir-based Regimens

Advantages

- Comparable to EFV at 4-year follow-up, regardless of baseline CD4/VL[1]
- Very well-tolerated[2]
- Few drug interactions[3]
- Favorable Lipid profile[2]
- Greater CD4+ increase than EFV[2]

Disadvantages

- Requires BID dosing
- Low genetic barrier to resistance[4]
- Risk of NRTI resistance with failure[2]
- No co-formulations w/ other classes
- Potential for skin reactions
- Little data except with FTC/TDF



1. Rockstroh J, et al. EACS 2011. Abstract PS 1/1.
2. Lennox JL, et al. Lancet. 2009;374:796-806.
3. Raltegravir [package insert]. November 2011.
4. Hatano H, et al. J Acquir Immune Defic Syndr. 2010;54:389-393.

Considering Individual Patient Factors

Patient Factors: HIV VL > 100,000

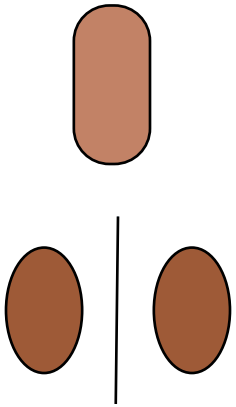
Do all agents perform equally well?

- **Efavirenz** (EFV) – equivalent at all VL strata[1, 2]
- **Atazanavir** (ATZ/r) – similar efficacy to EFV[2] and LPV/r[3]
- **Darunavir** (DRV/r) – superior to LPV/r[4]
- **Raltegravir** (RAL)– similar to EFV[5]
- **Truvada** (FTC/TDF) – superior to Epzicom (ABC/3TC)[2]

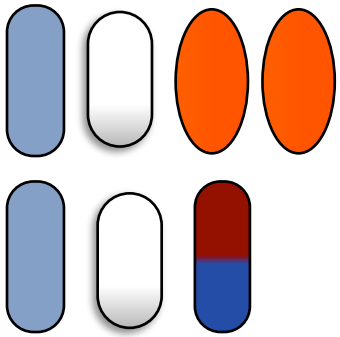
- **Epzicom** (ABC/3TC) – more virologic failures
- **Complera** (FTC/TDF/RPV) – more virologic failures

1. Ribaudo HJ, et al. J Infect Dis. 2008;197;1006-1010, 2. Daar ES, et al Ann Intern Med 2011;154:445-456, 3. Molina JM, et al. Lancet. 2008;372:646-655, 4. Mills A, et al. AIDS. 2009;23:1679-1688. 5. Rockstroh J, et al. EACS 2011. Abstract PS 1/1

Patient Factors: Adherence Concerns



- **Efavirenz** (EFV) and **Raltegravir** (RAL) both have a lower genetic barrier to resistance
- Long half-life of **Efavirenz** (EFV) makes it vulnerable to drug resistance due to shorter half-life of other agents in **Atripla** (FTC/TDF/EFV)



- Protease Inhibitors (**Atazanavir**, ATZ/r and **Darunavir** DRV/r) have a high genetic barrier to resistance and low incidence of drug resistance even on failure

Patient Factors: Viral Hepatitis

Hepatitis B

- **Emtricitabine** (FTC), **Tenofovir** (TDF), **Lamivudine** (3TC) all have activity against Hepatitis B. Preferred to use either FTC/TDF, 3TC/TDF, or 3TC/**Entecavir** in context of ART
- Caution at discontinuation or regimen switch regarding rebound of HBV if any active agents are removed

Hepatitis C

- Drug-induced liver injury more common, but can't specify individual agents (except NVP, d4T,ddI, RTV)
- ART has overlapping toxicity and many drug-drug interactions with new HCV Protease Inhibitors; AVOID ddI, d4T, ZDV; **Truvada** (FTC/TDF) + **Raltegravir** probably has least interactions

Patient Factors: CV disease or Hyperlipidemia

How will ART affect my patient's lipids?

- Protease Inhibitors generally increase lipids but **Atazanavir** (ATZ/r) and **Darunavir** (DRV/r) have mild effects compared to **Lopinavir** (LPV/r) [3, 4]
- **Efavirenz** (EFV) adversely affected cholesterol more than **Atazanavir** (ATZ/r)[2] and **Raltegravir** (RAL)[1]
- **Raltegravir** (RAL) appears to be neutral with respect to lipid changes[1]
- Concern for **Abacavir** (ABC)-related cardiovascular risk

1. Lennox J, et al. Lancet. 2009;374:796-806 2. Daar ES, et al. Ann Intern Med. 2011;154:445-456. 3. Molina JM, et al. Lancet. 2008;372:646-655. 4. Ortiz R, et al. AIDS. 2008;22:1389-1397.

Patient Factors: Renal Function

- Some ARV's require renal dose adjustment making fixed dose combinations (**Truvada** FTC/TDF, **Epzicom** ABC/3TC) problematic
- **Tenofovir** (TDF) has been associated with declining renal function over time in some patients[1], perhaps made worse in presence of boosted PI's[2, 3].
- Cumulative exposure to **Atazanavir** (ATZ/r) was associated with reversible renal dysfunction[4]

1. Tenofovir [package insert]. September 2011. 2. Morlat P, et al. IAS 2011. Abstract WEPDB0104. 3. Gallant JE, et al. AIDS. 2009;23:1971-1975. 4. Mocroft A, et al. AIDS. 2010;24:1667-1678. 5. Raltegravir [package insert]. November 2011.

Patient Factors: Women of Childbearing Age

Must have a candid discussion regarding future plans to initiate pregnancy

- **Efavirenz** (EFV, **Atripla**, FTC/TDF/EFV) felt to be teratogenic in 1st Trimester
- Limited data on **Raltegravir** (RAL) and Darunavir (DRV) in pregnancy
- **Combivir** (AZT/3TC) + **Lopinavir** (LPV/r) preferred agent in pregnancy, however **Truvada** (FTC/TDF) + **Atazanavir** (ATZ/r) acceptable

Patient Factors: Dyspepsia/GERD

- Use of acid-reducing agents is associated with reduction of **Atazanavir** (ATZ/r) and **Rilpivirine** (RPV) concentration
- Can theoretically be overcome by stepping down to H2-antagonists and/or dosing antacid 12 hrs apart from **Atazanavir** (ATZ/r) dose
- **Raltegravir** (RAL) concentrations may be increased by concurrent use of proton-pump inhibitors

Patient Factors: Psychiatric Disease

- **Efavirenz** (EFV) associated with neuropsychiatric side effects such as dizziness, vivid dreams,
- **Atripla** (FTC/TDF/EFV) thus not a great choice for patients significant mental health diagnoses:
  - bipolar disorder
  - Severe PTSD
  - Schizophrenia
- **Complera** (FTC/TDF/RPV) has less neuropsychiatric effects, but more virologic failures than Atripla (FTC/TDF/RPV) and currently not a ‘preferred’ agent

When is it appropriate not to use a 'preferred' regimen?

DHHS Antiretroviral Therapy Guidelines: October 2011
Alternative Regimens for ARV-Naïve Patients

Class	Therapy
NNRTI-Based	Efavirenz + Abacavir-Lamivudine (**BI**)
	Rilpivirine + Tenofovir-Emtricitabine (**BI**)
	Rilpivirine + Abacavir-Lamivudine (**BIII**)
PI-Based	Atazanavir + Ritonavir + Abacavir-Lamivudine (**BI**)
	Darunavir + Ritonavir + Abacavir-Lamivudine (**BIII**)
	Fosamprenavir (1-2x daily) + Ritonavir + Abacavir-Lamivudine (**BI**) Fosamprenavir (1-2x daily) + Ritonavir + Tenofovir-Emtricitabine (**BI**)
	Lopinavir-Ritonavir (1-2x daily) + Abacavir-Lamivudine (**BI**) Lopinavir-Ritonavir (1-2x daily) + Tenofovir-Emtricitabine (**BI**)
INSTI-Based	Raltegravir + Abacavir-Lamivudine (**BIII**)

Source: DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)

DHHS Antiretroviral Therapy Guidelines: October 2011
Acceptable Regimens for ARV-Naïve Patients

Class	Therapy
NNRTI-Based	Efavirenz + Zidovudine-Lamivudine (**CI**)
	Nevirapine + Tenofovir-Emtricitabine (**CI**) Nevirapine + Zidovudine-Lamivudine (**CI**) Nevirapine + Abacavir-Lamivudine (**CIII**)
	Rilpivirine + Zidovudine-Lamivudine (**CIII**)
PI-Based	Atazanavir + Abacavir-Lamivudine (**CI**) Atazanavir + Zidovudine-Lamivudine (**CI**)
	Darunavir + Ritonavir + Zidovudine-Lamivudine (**CIII**)
	Fosamprenavir + Ritonavir + Zidovudine-Lamivudine (**CI**)
	Lopinavir-Ritonavir + Zidovudine-Lamivudine (**CI**)
INSTI-Based	Raltegravir + Zidovudine-Lamivudine (**CIII**)
CCR5 Antagonist-Based	Maraviroc + Zidovudine-Lamivudine (**CI**)
	Maraviroc + Tenofovir-Emtricitabine (**CIII**)
	Maraviroc + Abacavir-Lamivudine (**CIII**)

Source: DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)

Summary: Selecting an Initial ART Regimen

- Four ‘preferred’ regimens all have extensive safety and efficacy experience through many clinical trials.
- ‘Third agents’ (**Efavirenz, Atazanavir, Darunavir, and Raltegravir**) have advantages and disadvantages that must be discussed with the patient
- Patient-level factors (e.g. childbearing potential, co-infections, co-morbidities, medlist) should be considered when selecting the ideal ART regimen
- Occasionally an Alternative regimen may be appropriate
- Respect the patient’s opinion as it will affect adherence.