PAETC HIV LEARNING NETWORK

Didactic Series

Fine Tuning Initial Anti-Retroviral Therapy

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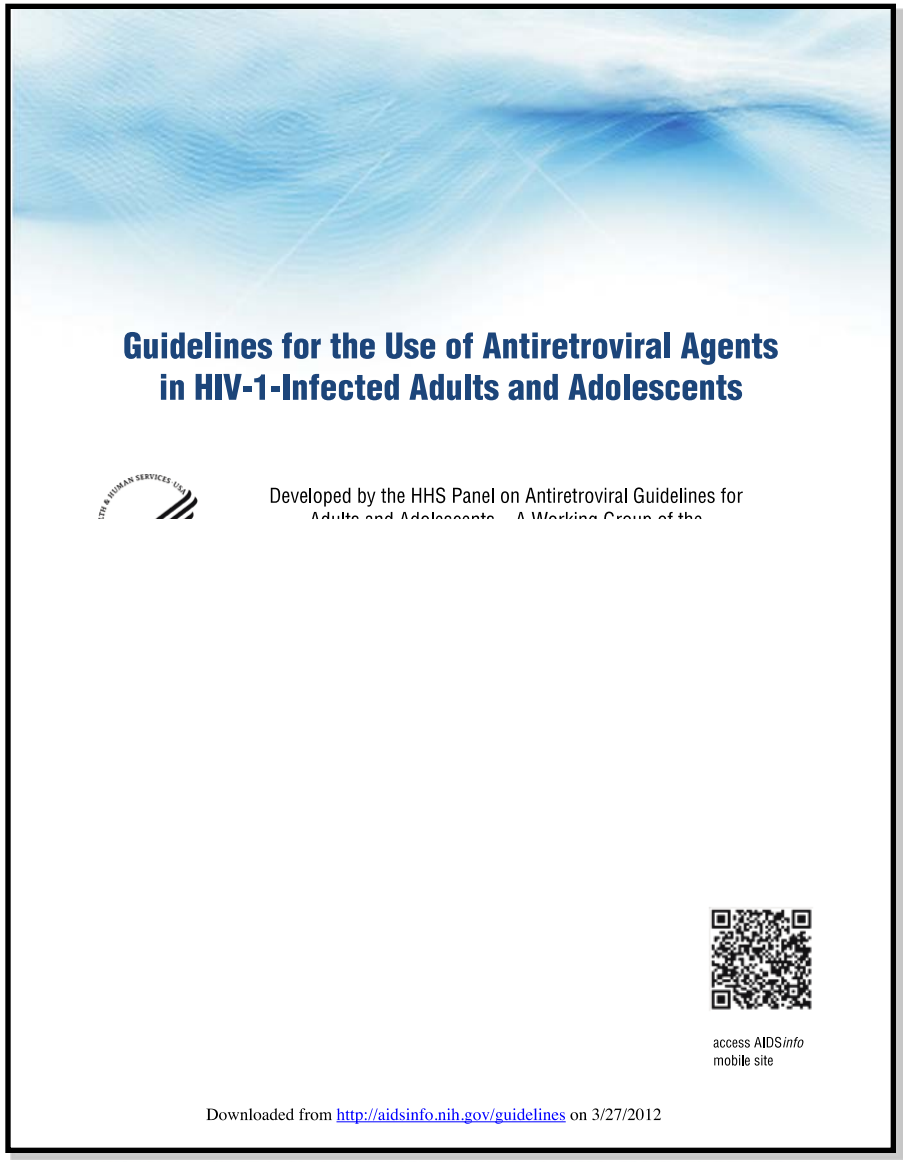
10/25/12

Learning Objectives

1) Review the 3/2012 DHHS criteria to initiate ART in HIV-infected patients
2) List relative contraindications to ‘preferred’ and ‘alternative’ regimens
3) Weigh ARV, viral, and patient factors to provide individualized recommendations on initial ART for treatment naïve patients

US Department of Health and Human Services (DHHS)

March 27, 2012 Antiretroviral Therapy Guidelines



- aidsinfo.nih.gov

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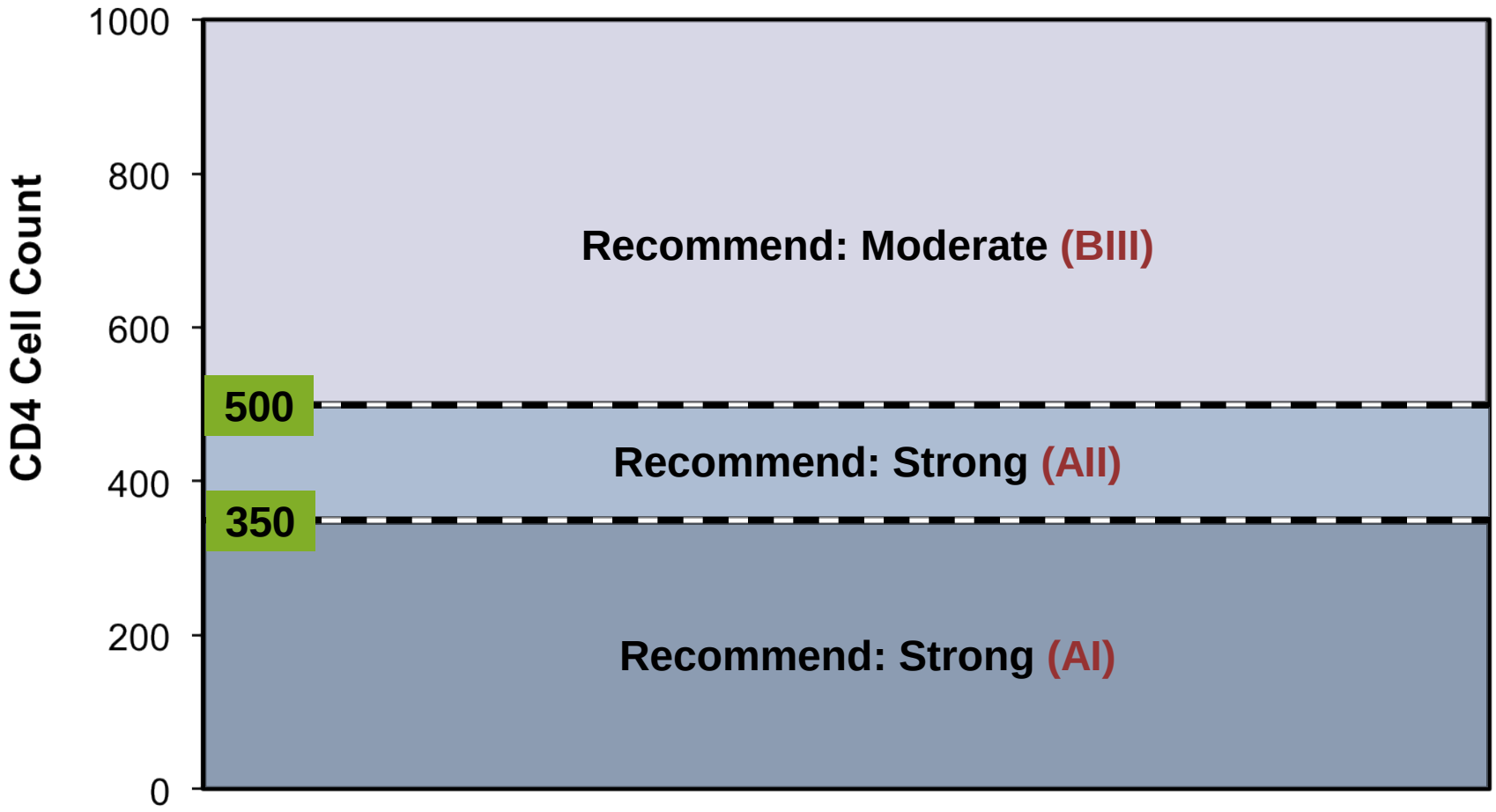
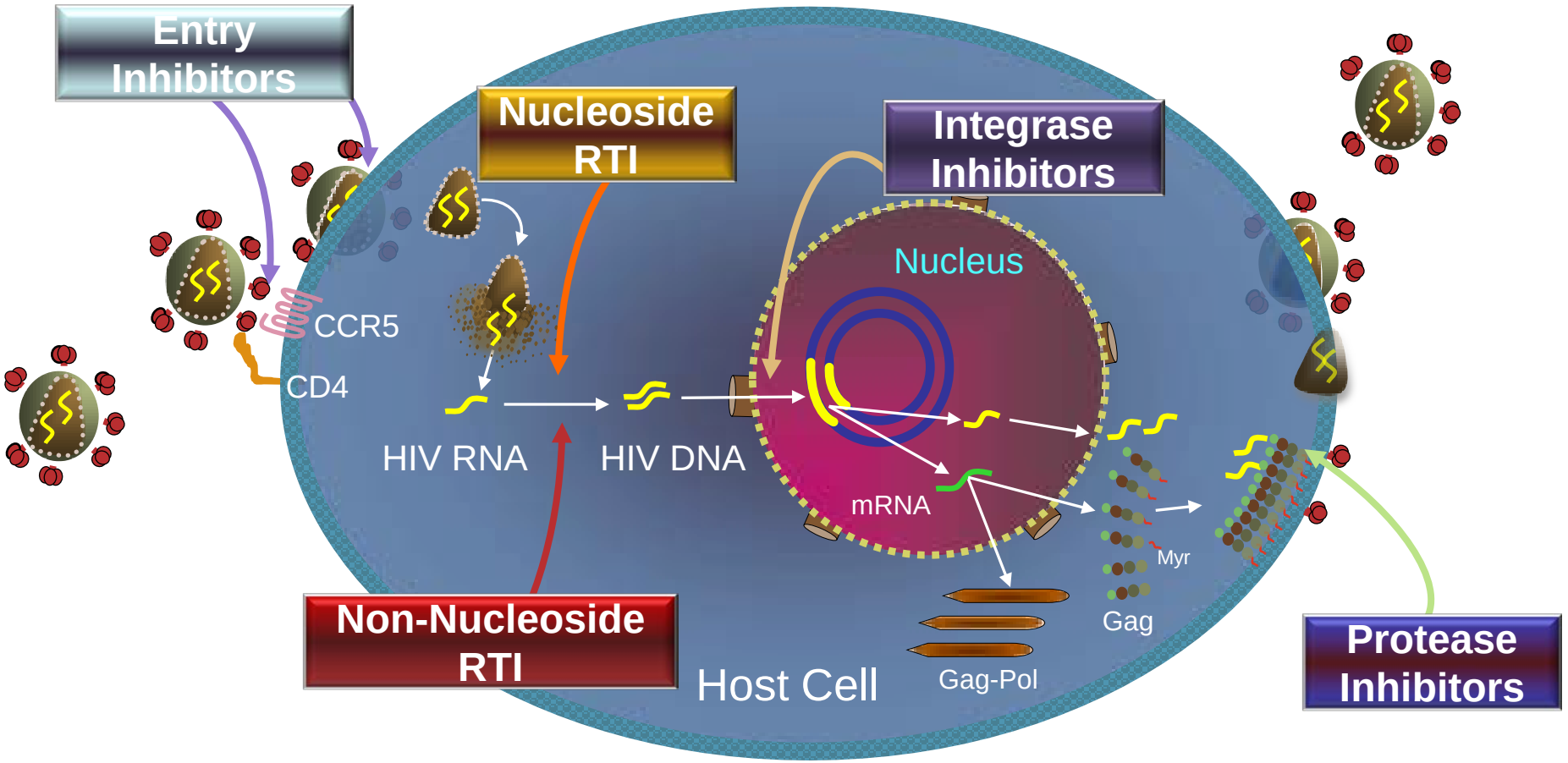
DHHS Antiretroviral Therapy Guidelines: March 2012

Initiating Therapy in Treatment-Naïve Patients



Anti-retroviral drug targets



- Source: David Spach, MD

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, lopinavir/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

Additional STR's:

Complera (FTC/TDF/RPV)

Stribild (FTC/TDF/COBI/ELV)

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

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DHHS Antiretroviral Therapy Guidelines: March 2012

Preferred Regimens for ARV-Naïve Patients

Backbone

(2) Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

+

Third Agent

Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)

or

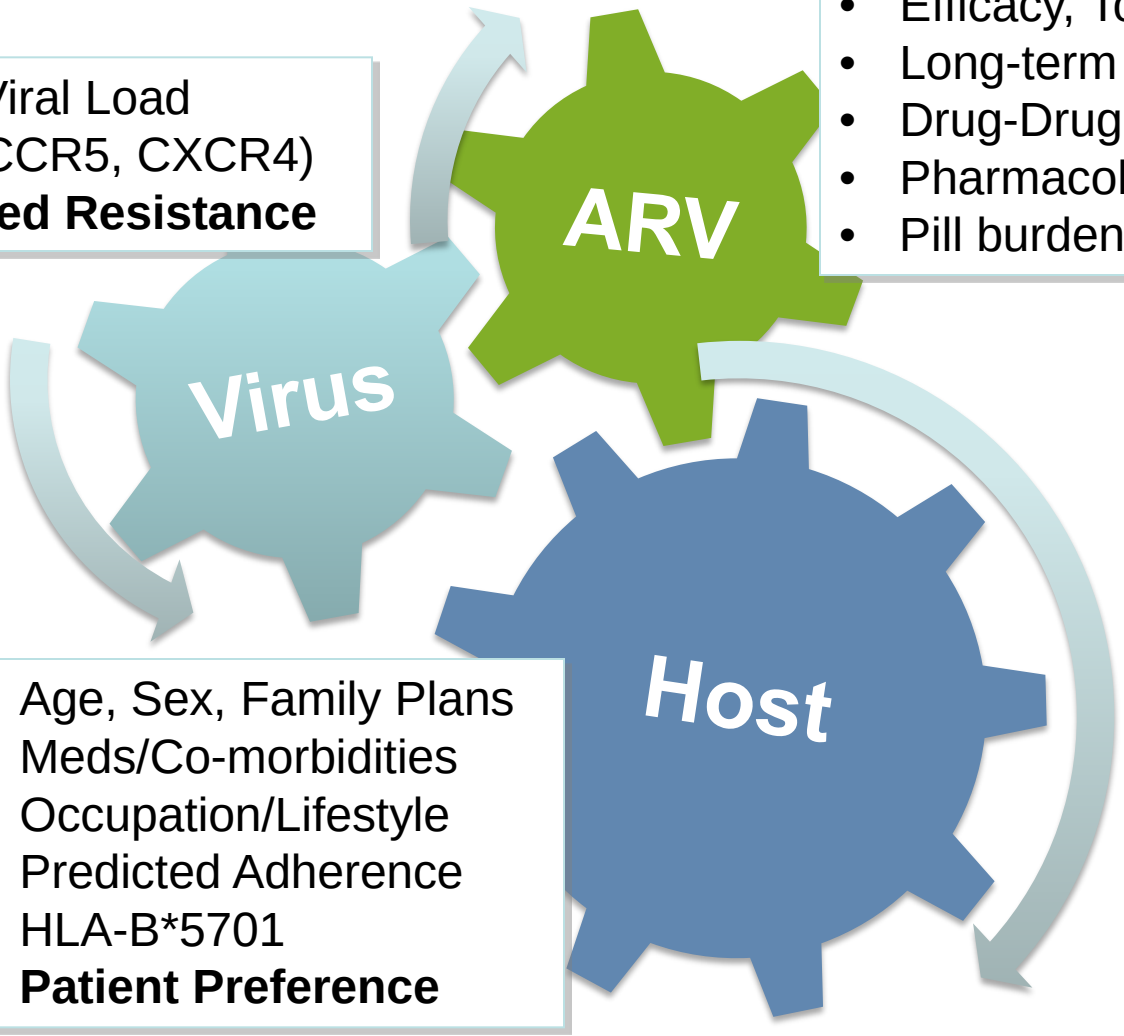
Protease Inhibitor (PI) (ritonavir-boosted)

or

Integrase Strand Transfer Inhibitor (INSTI)

Key Factors Influencing First-line Regimen

- Baseline Viral Load
- Tropism (CCR5, CXCR4)
- **Transmitted Resistance**

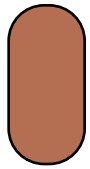
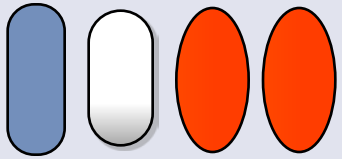
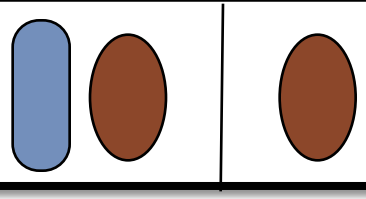


- Efficacy, Tolerability
- Long-term safety
- Drug-Drug interactions
- Pharmacokinetics
- Pill burden, cost

- Age, Sex, Family Plans
- Meds/Co-morbidities
- Occupation/Lifestyle
- Predicted Adherence
- HLA-B*5701
- **Patient Preference**

DHHS Antiretroviral Therapy Guidelines: March 2012

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	

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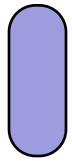
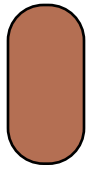
Alternative Regimens for ARV-Naïve Patients

Class	Therapy	Pill Burden
NNRTI-Based	Rilpivirine-Tenofovir-Emtricitabine	
INSTI-Based	Elvitegravir-Cobicistat-Tenofovir-Emtricitabine	

Efavirenz-based Regimens (Atripla)

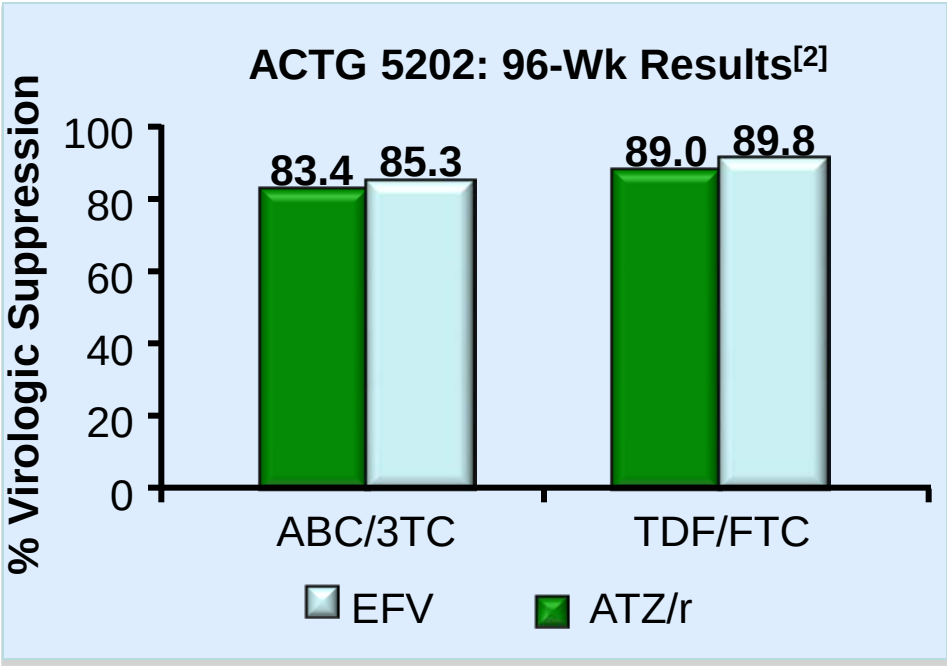


Advantages

- 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
  - Inferior to Dolutegravir in SINGLE trial



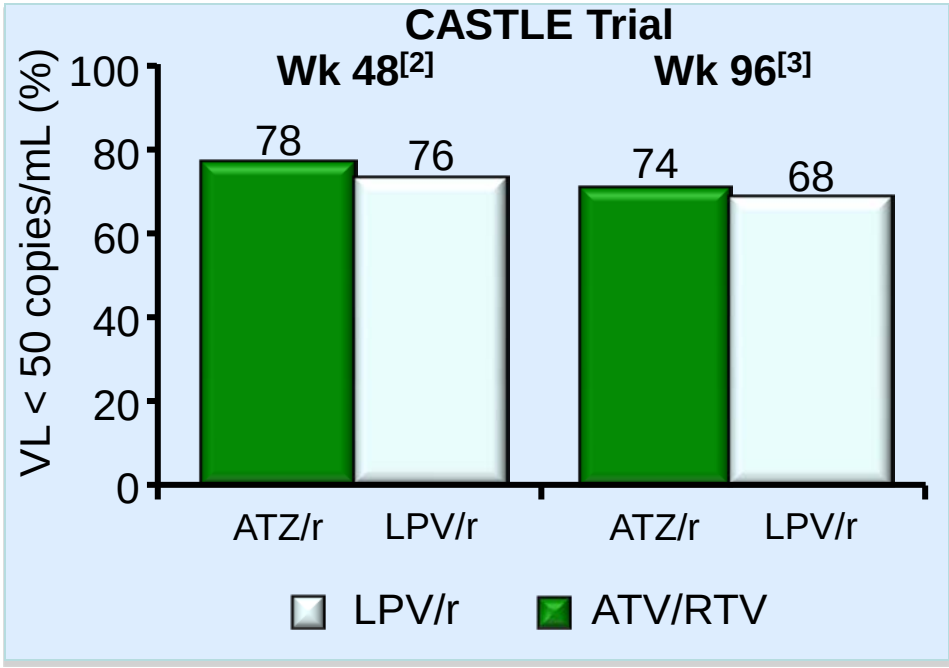
Atazanavir/ritonavir-based Regimens

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
- 4-9% of patients have unconjugated hyper-bilirubinemia[4]
- Food requirements for dosing
- No co-formulations available
- Requires 100 mg ritonavir



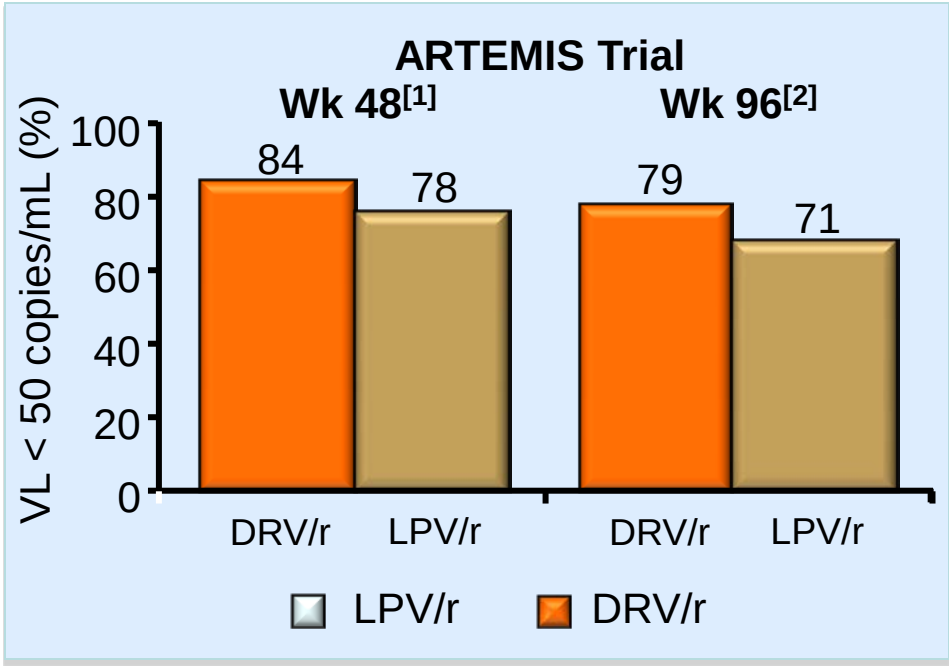
Darunavir/ritonavir-based Regimens

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



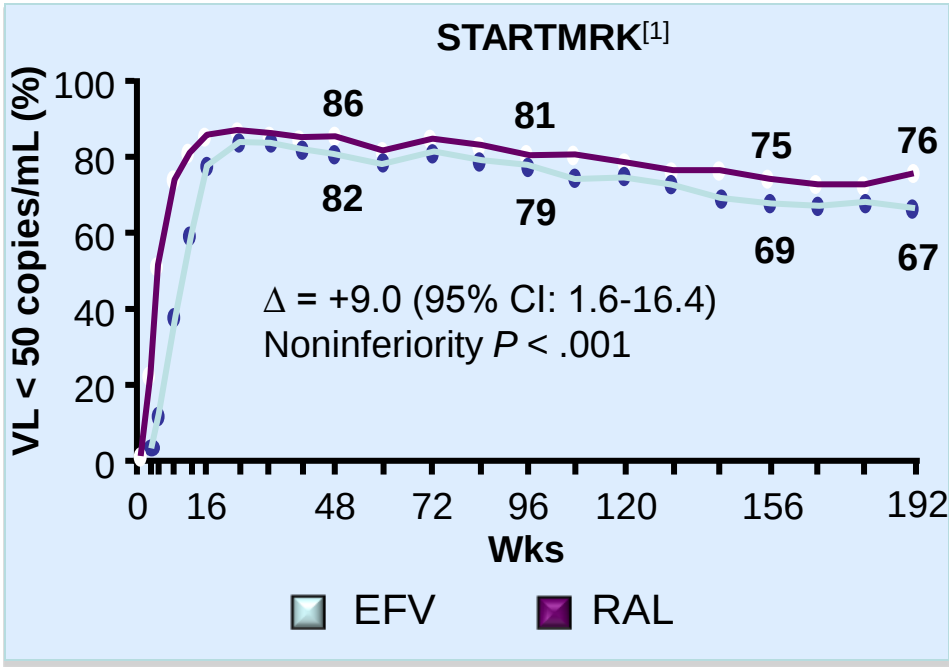
Raltegravir-based Regimens

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
- Potential for skin reactions
- Little data except with FTC/TDF



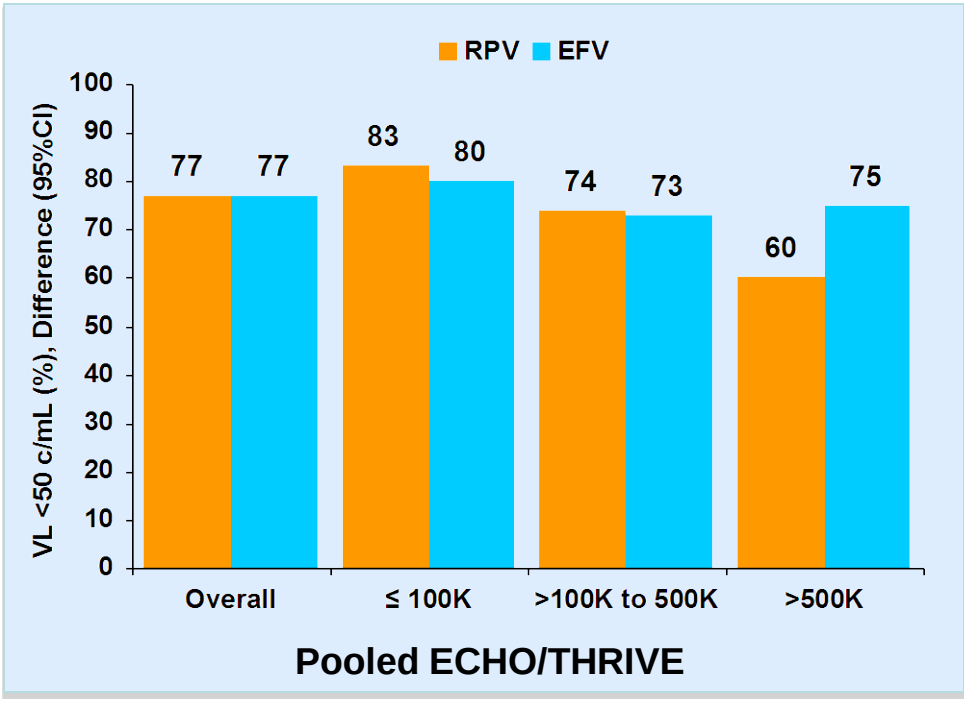
Rilpivirine-based Regimens (Complera)

Advantages

- Single Tablet Regimen
- Comparable to FTC/TDF/EFV through 96 weeks if VL < 100K[1,2]
- Very well-tolerated—less CNS reactions than FTC/TDF/EFV[2]
- Few drug interactions[3]
- Favorable Lipid profile[2]

Disadvantages

- Meal-dependent dosing
- PPI therapy is a contraindication
- Genetic barrier to resistance similar to Efavirenz, but higher NRTI resistance and risk of pan-NNRTI resistance with failure [4]



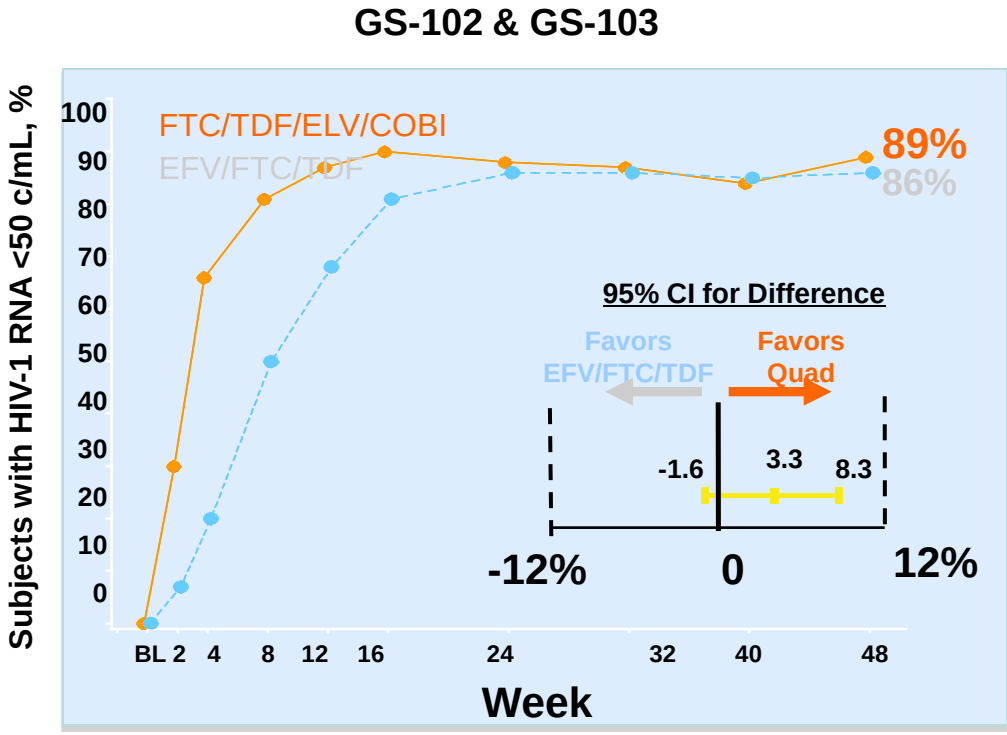
Elvitegravir-based Regimens (Stribild)

Advantages

- Comparable to EFV and ATZ/r regimens at 48 wk follow-up, regardless of baseline CD4/VL[1]
- Lipids = ATZ/r, better than EFV[2]
- INSTI-based regimen, fully active against NNRTI mutants
- Greater CD4+ increase than EFV[2]

Disadvantages

- Considerable drug-drug interactions
- GI side effect profile comparable to ATZ/r (20% nausea, diarrhea)
- Genetic barrier to resistance comparable to NNRTI's, INSTI's[4]
- Risk of NRTI resistance w/failure[2]
- Complex interplay w/ Creatinine



1. Sax, P et al Lancet
2. DeJesus et al Lancet.

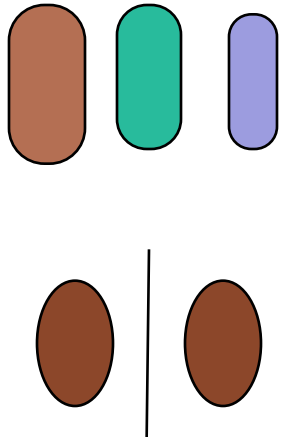
Patient Factors: HIV VL > 100,000

Do all agents perform equally well?

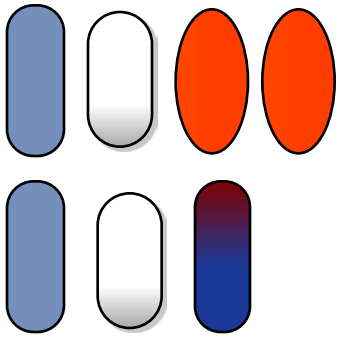
- **Efavirenz** (EFV) – equivalent at all VL strata[1, 2]
- **Atazanavir** (ATZ/r) – similar efficacy to EFV[2] and LPV/r[3]
- **Darunavir** (DRV/r) – superior to LPV/r[4]
- **Raltegravir** (RAL)– similar to EFV[5]
- **Elvitegravir** (ELV) – similar to EFV or ATZ/r [6, 7]
- **Truvada** (FTC/TDF) – superior to Epzicom (ABC/3TC)[2]

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

Patient Factors: Adherence Concerns



- **Efavirenz** (EFV), **Raltegravir** (RAL), **Elvitegravir** (ELV) have lower genetic barrier to resistance
- **Rilpivirine** (RLP) failure may result in E138K
- 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) neutral with respect to lipid changes[1]
- **Elvitegravir** (ELV) roughly equivalent to **Atazanavir** (ATZ/r)[5] , somewhat better than **Efavirenz** (EFV)
- **Rilpivirine** (RPV) significantly better than **Efavirenz** (EFV)
- Concern for **Abacavir** (ABC)-related cardiovascular risk

Patient Factors: Renal Function

- Some ARV's require renal dose adjustment → no fixed dose combinations (**Truvada** FTC/TDF, **Epzicom** ABC/3TC)
- **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]
- **Cobicistat** (COBI) a component of **Stribilid** (FTC/TDF/COBI/ELV) requires eGFR > 70 ml/min

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) or **Atazanavir** (ATZ/r) preferred agent in pregnancy, however **Truvada** (FTC/TDF)

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) less neuropsychiatric effects, but more virologic failures than Atripla (FTC/TDF/RPV) and currently not a 'preferred' agent

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
- Occasionally an Alternative regimen may be appropriate, currently two other ‘Single Tablet Regimens’: **Complera** (FTC/TDF/RPV), **Stribild** (FTC/TDF/COBI/ELV)
- Patient-level factors (e.g. childbearing potential, co-infections, co-morbidities, medlist) should be considered when selecting the ideal ART regimen
- Respect the patient’s opinion as it will affect adherence.