

# HIV/AIDS: ARV Treatment Overview

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# Objectives

- Explain the risks and benefits of HAART
- Understand the strengths and weaknesses of various ARVs, including dosing regimen, AE, and drug interactions
- Recommend guideline-based regimens in ARV-naïve patients
- Recommend appropriate prophylactic medications for patients at risk for opportunistic infections
- Implement ARV regimens that are as effective, tolerable, and simple to take as possible

# HIV/AIDS: Epidemiology

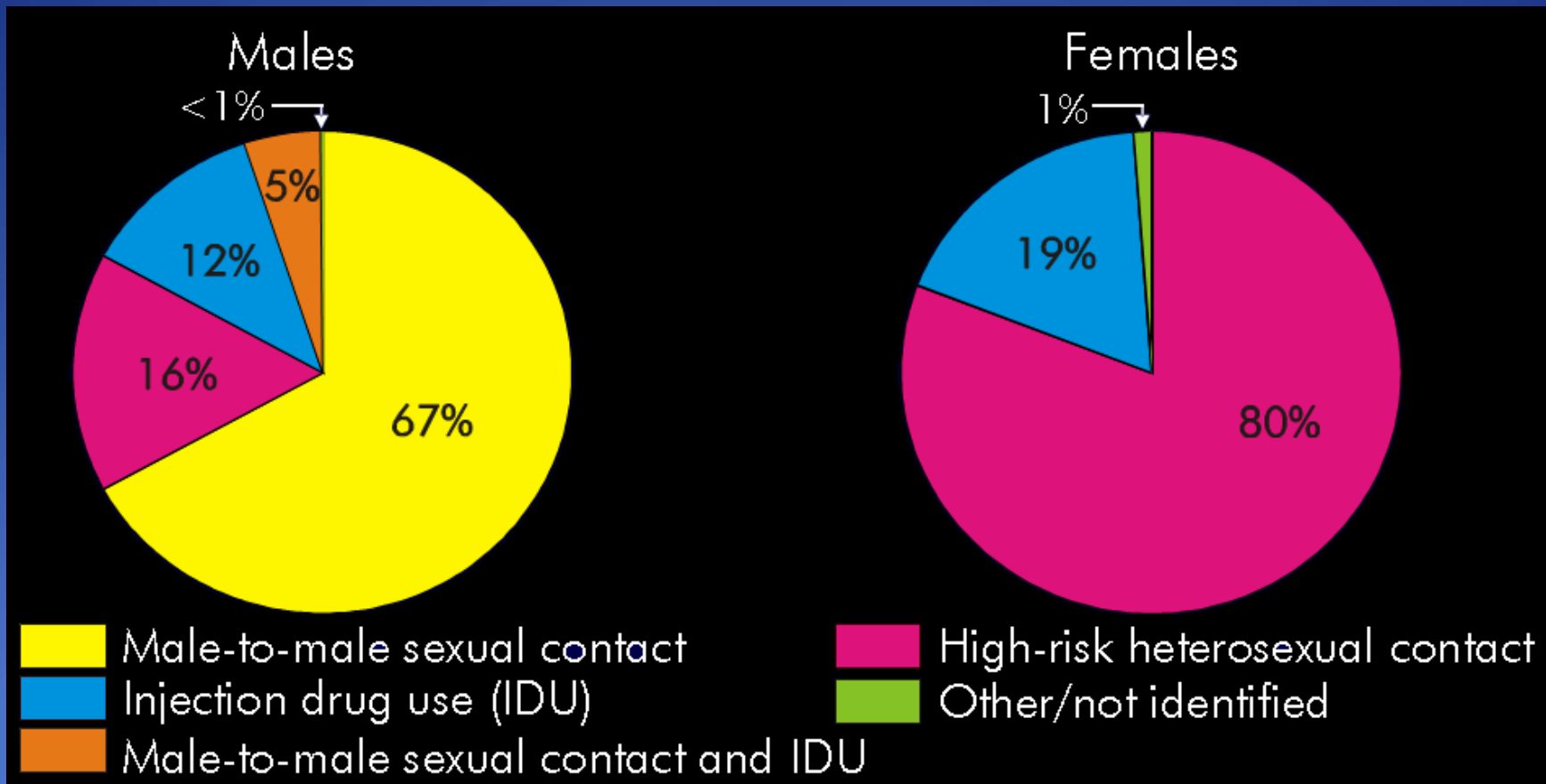
- WHO/UNAIDS: 33.4 million people infected with AIDS worldwide<sup>1</sup>
- 2 million deaths in 2008<sup>1</sup>
- In USA, 1.1 million living with HIV/AIDS at the end of 2008<sup>2</sup>
- >42,000 new diagnoses in the U.S. in 2007<sup>2</sup>
- 3% of Washington D.C. residents have HIV<sup>3</sup>

1) FACTBOX-Africa still worst hit by AIDS. Reuters ; 24 Nov 2009. Accessed 23 Mar 2010. Available at: <http://www.reuters.com/article/idUSGEE5AN0VF>

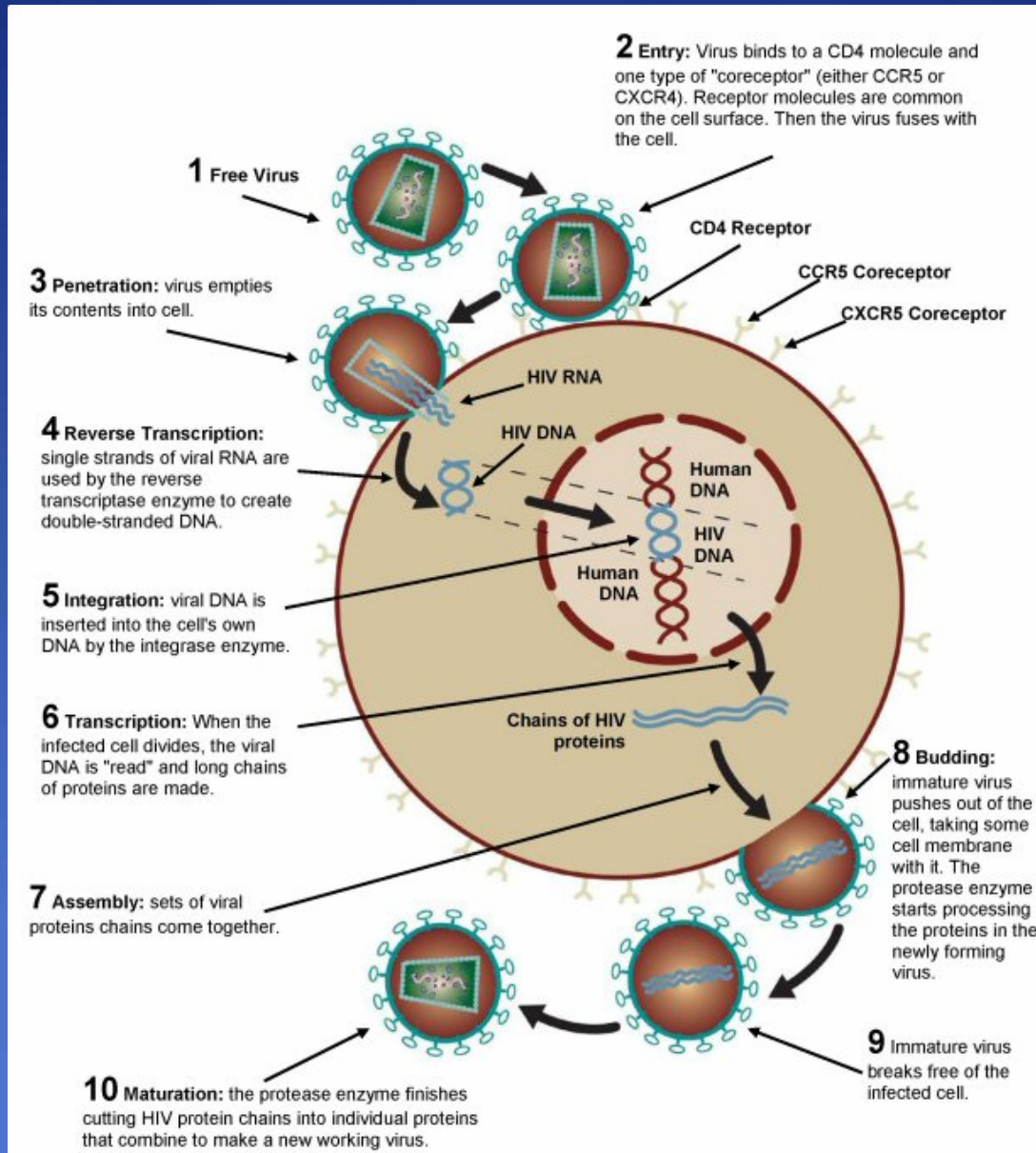
2) HIV/AIDS in the Unites States. CDC website. Accessed 23 Mar 2010. Available at: <http://www.cdc.gov/hiv/resources/factsheets/us.htm>

3) At Least 3 Percent of D.C. Residents Have HIV or AIDS, City Study Finds; Rate Up 22% From 2006. Washington Post; 15 Mar 2010. Accessed 23 Mar 2010. Available at: <http://www.washingtonpost.com/wp-dyn/content/article/2009/03/14/AR2009031402176.html>

# Routes of Transmission (CDC)



# Life Cycle of HIV



# Highly Active Antiretroviral Therapy (HAART)

- Primary treatment for HIV/AIDS
- Goal: to reduce morbidity and mortality
- Benefits include possible reconstitution of immune system, reduction in inflammation, and reduction in transmission
- Recent guidelines recommend starting treatment earlier

# When to start HAART

- History of AIDS-defining illness or CD4+ count of  $<350$  cells/mm<sup>3</sup>
- HIV as well as pregnancy, HIV-associated nephropathy, or HBV coinfection when treatment of HBV is indicated
- CD4+ count between 350 and 500 cells/mm<sup>3</sup>
- CD4+ count  $>500$  cells/mm<sup>3</sup>
- Patients must commit to lifelong treatment, understand benefits/risks, and importance of adherence



# Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

- Inhibit RNA-dependent DNA polymerase (reverse transcriptase) by competing with endogenous deoxynucleotides
- Thymidine analogs (zidovudine and stavudine)
- Cytosine analogs (lamivudine and emtricitabine)
- Inosine analog (didanosine)
- Guanosine analog (abacavir)
- Nucleotide adenosine analog (tenofovir)
- Dual-NRTI backbone is standard in HAART
- Rare class toxicities (lactic acidosis, hepatic steatosis)
- Most require dosing adjustment in renal impairment

# Commonly-Used NRTIs

- Tenofovir disoproxil fumarate (TDF; Viread)
  - Dose: 300 mg daily if CrCl >50; 300 mg q48h if CrCl 30-40; 300 mg 2x/week if CrCl 10-29; 300 mg weekly if on HD
  - Also indicated for chronic HBV
  - Associated with ARF and decreased bone mineral density
  - Most common AE: rash, diarrhea, HA, pain, depression, asthenia, and nausea
  - Coformulated with emtricitabine as Truvada; dosed once daily



# Commonly-Used NRTIs

- Lamivudine (3TC, Epivir)
  - 150 mg BID or 300 mg daily
    - Adjust for renal impairment
  - Generally well-tolerated
  - Also used to treat HBV
  - Preferred in pregnant women
  - Emtricitabine (FTC, Emtriva) is prodrug; considered equal to 3TC



# Commonly-Used NRTIs



- Abacavir (ABC, Ziagen)
  - 300 mg BID or 600 mg daily
    - Adjust dose in liver dx but not in renal impairment
  - Associated with fatal hypersensitivity reactions
    - Must test for HLA-B\*5701 allele
  - Associated with increased risk of MI in D:A:D study but not in others
  - Coformulated with lamivudine for once-daily dosing in Epzicom

# Commonly-Used NRTIs

- Zidovudine (ZDV, Retrovir)
  - The first ARV available
  - 300 mg BID; adjust to once daily if CrCl <15
  - Mitochondrial toxicities: macrocytic anemia, neutropenia
  - GI intolerance, HA, insomnia, asthenia, nail pigmentation
  - Most associated with lactic acidosis/hepatic steatosis of currently-recommended NRTIs
  - Coformulated with lamivudine in Combivir



# Less Commonly-Used NRTIs

- Didanosine (ddI, Videx EC): must take on empty stomach; AE: pancreatitis, peripheral neuropathy, association with noncirrotic portal HTN
- Stavudine (d4T, Zerit): pancreatitis, peripheral neuropathy, lipoatrophy, rare rapidly progressive ascending neuromuscular weakness, highest incidence of lactic acidosis/hepatic steatosis of all the NRTIs

# Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

- Bind noncompetitively to allosteric site on RT to change in shape of enzyme and inhibit activity
- Long half-lives; allow for forgiveness of nonadherence
- Low genetic barrier to resistance; one viral mutation (K103N) causes resistance to 3 of 4 NNRTIs
- All cause rash
- All currently-recommended NNRTIs are CYP3A4 inducers and substrates; CI with St. John's Wort

# Efavirenz (EFV, Sustiva)

- Preferred NNRTI for tx-naïve patients
- 600 mg daily at bedtime on empty stomach
  - Can cause neuropsych effects; usually decrease with time
- Increased liver enzyme levels; lipid abnormalities (though less than most PIs)
- Associated with false-positive results with some cannabinoid and BDZ screening assays
- CI in first trimester of pregnancy
- CI with oral midazolam; must modify doses if used with voriconazole or rifabutin; reduces effect of Plan B



# Nevirapine (NVP, Viramune)

- 200 mg once daily x 2 wks, then increased to BID
- Highest incidence of rash of all NNRTIs
- Associated with serious and sometimes fatal hepatic events
  - CI in Child-Pugh Class B or C
- Fewer trial data; early virologic failure seen when given with Truvada
- CI with rifampin



# Etravirine (ETR, Intelence)

- 200 mg BID taken after a meal
- K103N does not cause resistance (though other mutations do)
  - Not indicated for treatment-naive pts
- Hypersensitivity reactions
- High pill burden
- CI with clopidogrel, carbamazepine, phenobarbital, phenytoin, rifampin



# Delavirdine (DLV, Rescriptor)

- Not recommended as part of initial regimen
- TID dosing
- CYP3A4 inhibitor
- Inferior virologic efficacy
- Less trial data

# Drug Interactions with NNRTIs

- Antimicrobials: Azole antifungals, clarithromycin, rifabutin, rifampin, atovaquone
- Warfarin
- CBZ, phenytoin, phenobarbital
- CCBs, statins
- PDE5 inhibitors
- Some oral contraceptives (including Plan B)
- Methadone, buprenorphine

# Protease Inhibitors (PI)

- Inhibits HIV protease-> inhibits maturation of a new HIV virion via cleaving of polypeptides
- High genetic barrier to resistance
- Cause metabolic AE, GI intolerance (N/V/D)
- Some must be adjusted in liver impairment; some are CI
- Fat redistribution (lipoatrophy, lipodystrophy)
- CYP3A4 inhibitors and substrates



# Atazanavir (ATV, Reyataz)



- Once daily with food; can be given with or without ritonavir
  - 400 mg if unboosted, 300 mg if with 100 mg ritonavir
  - If used concomitantly with tenofovir, must boost with RTV
- Fewer lipid abnormalities than with other PIs
- Can cause indirect hyperbilirubinemia -> physical effects
- May cause PR interval prolongation if given with another drug that produces this effect
- Other AE: nephrolithiasis, rash
- Requires acidic environment in stomach for absorption
- DI with acid-lowering medications

# Dosing Recommendations with ATV and Acid-Lowering Medications

- Antacids: give ATV at least 2 hrs before or one hr after
- H<sub>2</sub>RAs: ATV simultaneously with or at least 10 hrs after H<sub>2</sub>RA
  - If using both TDF and H<sub>2</sub>RA with ATV, dose at 400 mg with 100 mg RTV
- PPIs: not recommended in pts receiving unboosted ATV or PI-experienced pts receiving ATV
  - Daily PPI dose should not exceed omeprazole 20 mg daily

# Darunavir (DRV, Prezista)



- Once-daily or twice-daily dosing with food; must be boosted with ritonavir
- Tx-naïve: **DRV 800 mg + RTV 100 mg daily**
- Tx-experienced: **DRV 600 mg + RTV 100 mg BID**
- Previously used in PI-experienced pts resistant to many other PIs; now rec'd for use in tx-naïve pts
- Contains sulfonamide moiety
- AE: usual PI AE; also HA, nausea, diarrhea, possible increased bleeding in hemophilia

# Lopinavir/ritonavir (LPV/r, Kaletra)

- Coformulated in one pill
- Dose: 400mg/100mg BID; 800mg/200mg daily can be used in PI-naive pts
- Recommended PI in pregnancy (must give BID)
- In one study, had larger CD4+ increase than EFV regimen
- Larger dose of ritonavir (200 mg vs. 100 mg) can cause worse GI and lipid AE
- D:A:D cohort showed higher risk of MI
- Can cause PR and QT prolongation



# Drug Interactions With PIs

- All CI with **rifampin**, triazolam, oral midazolam, St. John's Wort, simvastatin, lovastatin, alfuzosin, salmeterol, sildenafil at PAH doses
- Warfarin
- Carbamazepine, lamotrigine, phenytoin, valproic acid
- Bupropion, sertraline, paroxetine, trazadone (CI with SQV), TCAs
- Azole antifungals (voriconazole CI with RTV), clarithromycin, rifabutin (reduce dose), atovaquone
- "LOT" benzodiazepines safest

# Drug Interactions with PIs

- Inhaled fluticasone: can cause adrenal insufficiency
- Buprenorphine (CI with unboosted ATV)
- PDE5 inhibitors: modify dosing
- Colchicine: lower dose and do not use in renal/hepatic insufficiency
- Atorvastatin and rosuvastatin: use at lowest dose and monitor (except with FPV)
- Pravastatin and fluvastatin safest statins (except pravastatin level increases with DRV/r)
- Digoxin, CCBs

# Less Frequently-Used PIs

- Fosamprenavir (FPV, Lexiva): pill burden, 19% incidence of rash
- Saquinavir (SQV, Invirase): 6 pills/day, PR/QT prolongation
- Nelfinavir (NFV, Viracept): 6 pills/day, inferior virologic effectiveness, high incidence of diarrhea
- Indinavir (IDV, Crixivan): high incidence of nephrolithiasis, must drink at least 1.5 L water daily
- Tipranivir (TPV, Aptivus): eight pills/day, has caused hepatitis, rare intracranial hemorrhages
- **Ritonavir (RTV, Norvir): formerly dosed 12 pills/day; now only for boosting of other PIs due to high pill burden and high incidence of lipid abnormalities and GI intolerance**

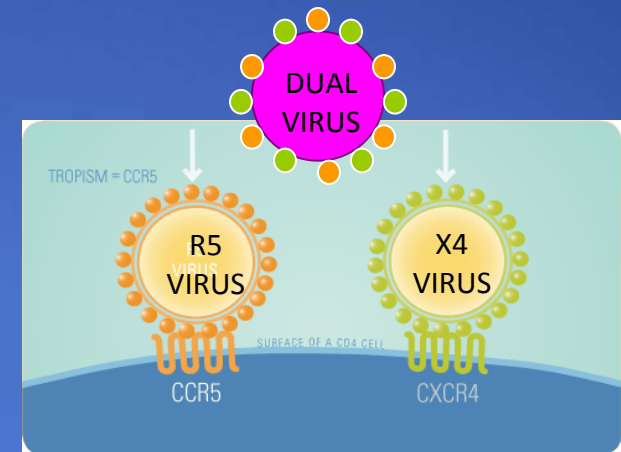
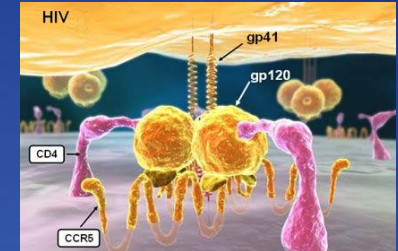
# Integrase Strand Transfer Inhibitor (INSTI)



- Raltegravir (RAL, Isentress)
- Dosing: 400 mg BID
  - 800 mg BID with rifampin
- Well-tolerated (AE: HA, nausea, diarrhea, pyrexia, CPK elevation w/ rare rhabdomyolysis)
- Fewer DDI compared to PIs and NNRTIs
- Low genetic barrier to resistance

# Chemokine Receptors in HIV

- R5 Viruses
  - Use CCR5 preferentially
  - Most common in sexually-transmitted HIV
- X4 Viruses
  - Use CXCR4 preferentially
  - More common in later disease
  - Syncytium-inducing
- R5X4 Viruses- use both receptors
- Mixed-tropic: both R5 and X4 viruses



# CCR5 Antagonist



- Maraviroc (MVC, Selzentry)
- Binds to chemokine receptor CCR5 on human cell membrane
- Must do Trofile test first to see if CCR5-tropic virus
  - Other tropisms (CXCR4, dual, mixed) are not susceptible to MVC
- Dosing: 150 mg BID, 300 mg BID, or 600 mg BID
  - Lower dose with 3A4 inhibitors, higher with inducers
- AE: nausea, HA, ab pain, URI, orthostasis, hepatotoxicity

# Fusion Inhibitor

- Enfuvirtide (T20, Fuzeon)
- Injectable: must be reconstituted and used w/in 24 hrs
- Only approved for treatment-experienced pts
- Dosing: 90 mg BID
- AE: Local injection site reactions in ~100% of patients, increase in bacterial pneumonia, hypersensitivity reaction in <1% pts



# What to Start for an Antiretroviral-Naïve Patient

- One of the following regimens should be used: NNRTI with 2 NRTI, PI + 2 NRTI, or INSTI + 2 NRTI
- Preferred regimens:
  - Efavirenz + tenofovir + emtricitabine
  - Ritonavir-boosted atazanavir + tenofovir + emtricitabine
  - Ritonavir-boosted darunavir + tenofovir + emtricitabine
  - Raltegravir + tenofovir + emtricitabine
  - Low toxicity; all are once-daily except for raltegravir
  - Lamivudine can be substituted for emtricitabine
- For pregnant women: lopinavir/ritonavir (BID) + zidovudine/lamivudine

# Risks/Benefits of Regimens

- EFV/TDF/FTC
  - Coformulated as once-daily pill (Atripla)
  - CNS effects, low barrier to resistance, and CYP3A4 induction with EFV
- ATV/r with TDF/FTC
  - Less lipid abnormalities with ATV vs. other PIs
  - Interactions with acid reducers and CYP3A4; hyperbilirubinemia

# Risks/Benefits of Regimens

- DRV/r with TDF/FTC
  - DRV has higher barrier to resistance than other PIs
  - GI and lipid abnormalities; 4 pills/day
- RAL with TDF/FTC
  - Low toxicity
  - Low barrier to resistance; BID dosing with RAL; regimen has only been compared to EFV/TDF/FTC

# Alternative Regimens

NRTIs	NNRTI	PI
(abacavir or zidovudine) + lamivudine	efavirenz	
zidovudine/lamivudine	nevirapine	
(abacavir or zidovudine) + lamivudine		atazanavir w/ ritonavir boosting
(abacavir or zidovudine) + lamivudine OR tenofovir/emtricitabine		fosamprenavir w/ ritonavir boosting
(abacavir or zidovudine) + lamivudine OR tenofovir/emtricitabine		lopinavir/ritonavir (daily or BID)

# HIV/Hepatitis B Coinfection

- 5-10% of HIV patients
- ARV regimen must include at least two agents active against Hep B:
  - Lamivudine or emtricitabine
  - Tenofovir (if not an option, use entecavir plus full ARV regimen)
- If Hep B tx but not HIV tx is desired, must not use tenofovir, entecavir, or monotherapy with lamivudine or emtricitabine

# Management of Treatment-Experienced Patients

- Assess adherence frequently, simplify regimen when possible, and change drugs to reduce and manage toxicity
- Optimal response: HIV RNA <400 copies/mL after 24 wks, <50 copies/mL after 48 wks
  - Persistent low level viremia such as HIV RNA 50-200 does not require change in treatment
- Two or preferably three active agents should be used when switching

# Evaluation of Treatment Failure

- Assessment of severity of HIV disease
- ARV treatment history
  - Duration, drugs, ARV potency and response, adherence history, drug intolerance/toxicity
- Use of concomitant medications
- HIV RNA and CD4+ counts trends
- Results of prior drug resistance testing

REPLICATION CAPACITY  
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Springfield, VA 22151  
USA

Client: 02336  
Phone: (703)321-2600

Project: 00073  
Fax: (703)321-2603

Patient Name: [REDACTED]	DOB 03/11/1962	Patient ID	Gender M	Monogram Accession # [REDACTED]
Date Collected 04/23/2008 00:01	Date Received 04/26/2008 10:55	Date Reported 05/19/2008 13:14	Mode F.M	Report Status FINAL
Referring Physician John Scott, 8001 Forbes Place Suite 200, Springfield VA 22151 USA			Reference Lab ID	
Comments			HIV-1 Subtype: B	

	DRUG		PHENOSENSE™ SUSCEPTIBILITY		Evidence of Susceptibility		Net Assessment			
	Generic Name	Brand Name	Cutoffs (Lower - Upper)	Fold Change	Increasing	Decreasing			Pheno Sense	Gene Seq
NR1I	Abacavir	Ziagen	(4.5 - 6.5)	4.12	[Bar Chart]	[Bar Chart]	Y	N	Resistant	12
	Didanosine	Videx	(1.3 - 2.2)	7.07	[Bar Chart]	[Bar Chart]	N	N	Resistant	
	Emtricitabine	Emtriva	(3.5)	7.03	[Bar Chart]	[Bar Chart]	N	N	Resistant	
	Lamivudine	Epivir	(3.5)	3.38	[Bar Chart]	[Bar Chart]	Y	N	Resistant	12
	Stavudine	Zerit	(1.7)	7.86	[Bar Chart]	[Bar Chart]	N	N	Resistant	
	Zidovudine	Retrovir	(1.9)	15	[Bar Chart]	[Bar Chart]	N	N	Resistant	1
	Tenofovir	Viroad	(1.4 - 4)	1.01	[Bar Chart]	[Bar Chart]	Y	Y	Sensitive	
NR1I Mutations			D67N, T69D, K70K/R, F116Y, Q151M, T215V, K219Q							

NNRTI	Delavirdine	Rescriptor	(6.2)	>MAX	[Bar Chart]	[Bar Chart]	N	N	Resistant	
	Efavirenz	Sustiva	(3)	>MAX	[Bar Chart]	[Bar Chart]	N	N	Resistant	
	Etravirine	Intenceo™	(2.9)	106	[Bar Chart]	[Bar Chart]	P	N	Partially Sensitive	13
	Nevirapine	Viramune	(4.5)	>MAX	[Bar Chart]	[Bar Chart]	N	N	Resistant	
NNRTI Mutations			V90I, K101P/Q/R, K103N, V108I, Y181C							

PI	Atazanavir	Reyataz	(2.2)	23	[Bar Chart]	[Bar Chart]	N	N	Resistant	
		Reyataz / r*	(5.2)	23	[Bar Chart]	[Bar Chart]	N	N	Resistant	
	Darunavir	Prezista / r*	(10 - 90)	6.18	[Bar Chart]	[Bar Chart]	Y	Y	Sensitive	
	Fosamprenavir	Lexiva	(2)	15	[Bar Chart]	[Bar Chart]	N	N	Resistant	
		Lexiva / r*	(4 - 11)	15	[Bar Chart]	[Bar Chart]	N	N	Resistant	
	Indinavir	Crixivan / r*	(10)	33	[Bar Chart]	[Bar Chart]	N	N	Resistant	
	Lopinavir	Kaletra	(9 - 55)	32	[Bar Chart]	[Bar Chart]	P	N	Partially Sensitive	
	Nelfinavir	Viracept	(3.6)	21	[Bar Chart]	[Bar Chart]	N	N	Resistant	
	Ritonavir	Norvir	(2.5)	95	[Bar Chart]	[Bar Chart]	N	N	Resistant	
	Saquinavir	Invirase	(1.7)	21	[Bar Chart]	[Bar Chart]	N	N	Resistant	
		Invirase / r*	(2.3 - 12)	21	[Bar Chart]	[Bar Chart]	N	N	Resistant	
Tipranavir	Aptivus / r*	(2 - 8)	>MAX	[Bar Chart]	[Bar Chart]	N	N	Resistant		
PI Mutations			L10V, I13V, L33F, M36I, M48I, I54V, Q58E, L63P, A71T, V82T, I84V							

[Lower Clinical Cutoff (in bold)] Hypersusceptibility  
 [Upper Clinical Cutoff (in bold)] Cutoff  
 [Biological Cutoff]

[ ] Sensitive  
 [ ] Partially Sensitive  
 [ ] Resistant

[ ] Evidence of Drug Sensitivity  
 [ ] Evidence of Partial Drug Sensitivity  
 [ ] Evidence of Drug Resistance

For more information on interpreting this report, please visit [www.MonogramHIV.com](http://www.MonogramHIV.com) or call Customer Service at 800-777-0177 between the hours of 6:30am to 5:00pm PST Monday through Friday.

# Prevention of Opportunistic Infections

- Pneumocystis pneumonia: TMP-SMX DS or SS Daily if CD4+ <200 cells/mm<sup>3</sup> or hx of oropharyngeal candidiasis; TMP-SMX 3x/week an alternative
  - Also consider if CD4+ cell percentage <14%
  - Dapsone 100 mg daily
  - Dapsone plus pyrimethamine plus leucovorin
  - Other options: inhaled pentamidine, atovaquone
- Discontinue when CD4+ increases to >200 cells/mm<sup>3</sup> for >3 months

# Prevention of OI (Cont.)

- *Toxoplasma gondii*: prophylaxis indicated if pt is sero(+) and CD4+ <100 cells/mm<sup>3</sup>
  - TMP-SMX DS daily preferred
  - Other options: TMP-SMX DS 3x/week, dapsone-pyrimethamine plus leucovorin, atovaquone with or without pyrimethamine/leucovorin
  - D/c at same time as PCP prophylaxis

# Glucose-6-Phosphate Deficiency (G6-PD)

- Genetic disorder – predisposes to hemolytic anemia when pt receives oxidant drugs
  - Sulfa drugs, dapsone, primaquine
- Most common in African American and Mediterranean men
- Anemia can be mild or life-threatening
  - Lab markers: elevated indirect bilirubin and LDH, decreased haptoglobin, reticulocytosis, bite cells
- Levels can be used for screening or diagnosis after hemolytic event

# Prevention of OI (Cont.)

- Mycobacterium avium complex (MAC): prophylaxis indicated if CD4+ <50
  - 1200 mg azithromycin weekly or clarithromycin 500 mg BID
  - Alternative: rifabutin but r/o TB first
  - Discontinue when CD4+ count increases to >100 cells/mm<sup>3</sup> for ≥3 months

# Patient Case

MV is a 62 y.o. AAM who has PMH of HIV/AIDS x 15 yrs, Hep C, and remote hx of PCP pneumonia. He presents to the ER at WHC c/o inability to swallow. The patient is diagnosed with oropharyngeal candidiasis, and the physician orders the following medications: atazanavir 100 mg daily, ritonavir 600 mg BID, emtricitabine 200mg/tenofovir 300 mg one tablet daily, pantoprazole 40 mg daily, and fluconazole 200 mg daily.

- CD4+: 43
- (+) G6PD
- Scr: 1.5

# Which doses are incorrect?

- Atazanavir: should be 300 mg or 400 mg daily
- Ritonavir: 100 mg daily when given with atazanavir

# Which medication may require renal dosing adjustment?

- Tenofovir:
  - 300 mg daily if CrCl >50
  - 300 mg q48h if CrCl 30-40
  - 300 mg 2x/week if CrCl 10-29
  - 300 mg weekly if on HD

# Which two medications interact?

- Atazanavir and pantoprazole
- Alternative: famotidine- give with atazanavir and/or 10 hours separated

# For which opportunistic infections is this patient at risk?

- PCP pneumonia
- *Toxoplasma gondii*
- Disseminated MAC infection

Which medication can we give the patient to cover both *T. gondii* and PCP?

- Atovaquone 1500 mg PO daily

# Which medication should we give to protect against MAC?

- Azithromycin 1200 mg PO weekly

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Questions?