Sculpting a Better Regimen: The ART of HIV Medications

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For HealthTrust Members

Disclosure

- This program may contain the mention of drugs or brands presented in a case study or comparative format using evidence-based research. Such examples are intended for educational and informational purposes and should not be perceived as an endorsement of any particular supplier, brand or drug.

Learning Objectives

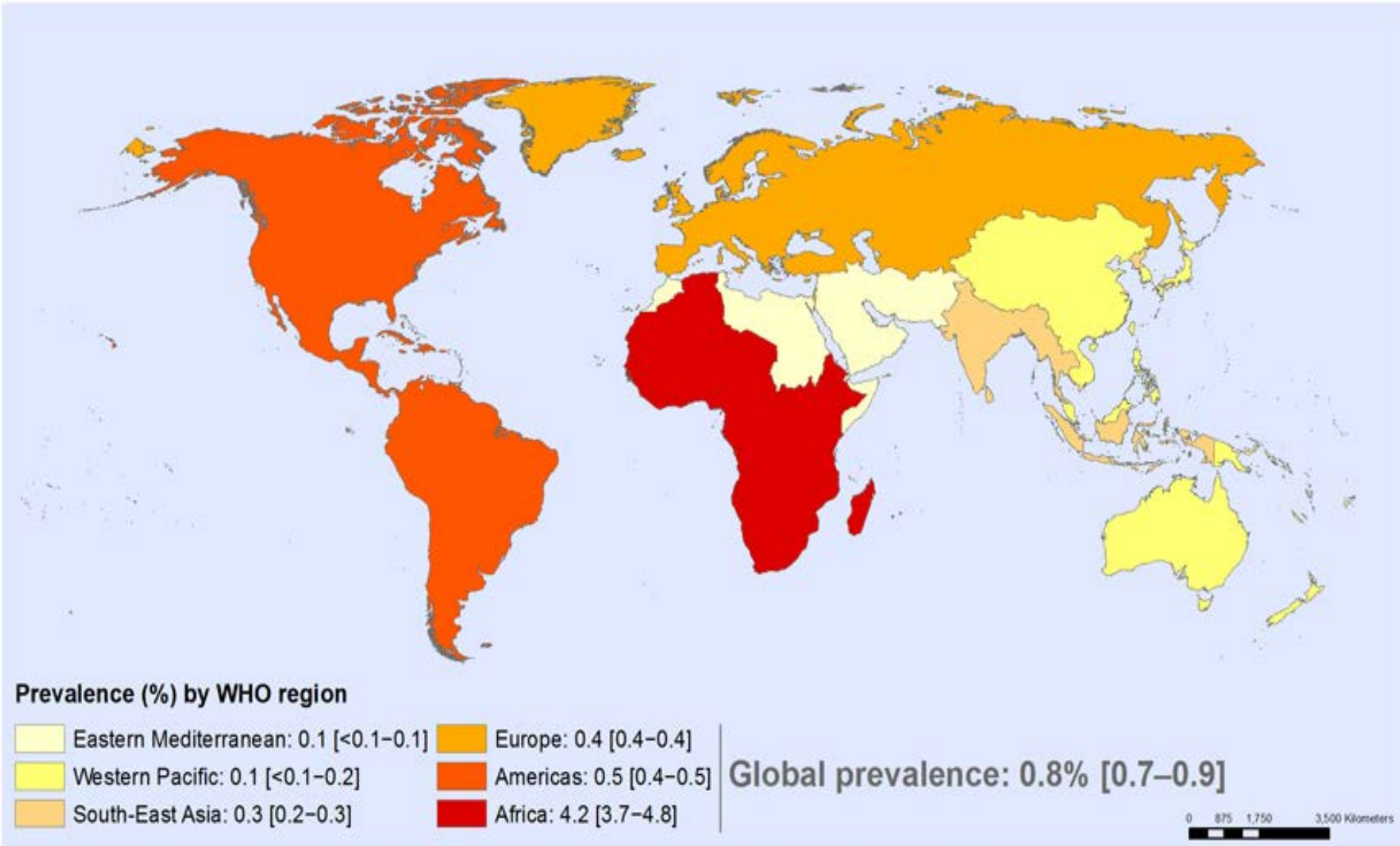
At the end of this session, participants should be able to:

1. Describe characteristics of a complete antiretroviral treatment regimen
2. Explain class-wide side effects and drug interactions of antiretroviral medications
3. Discuss prophylaxis for opportunistic infections and when to initiate

Overview

- Epidemiology of HIV
- Risk factors and diagnosis
- Initial treatment regimens
- Antiretroviral medication class reviews
- Opportunistic infection prophylaxis

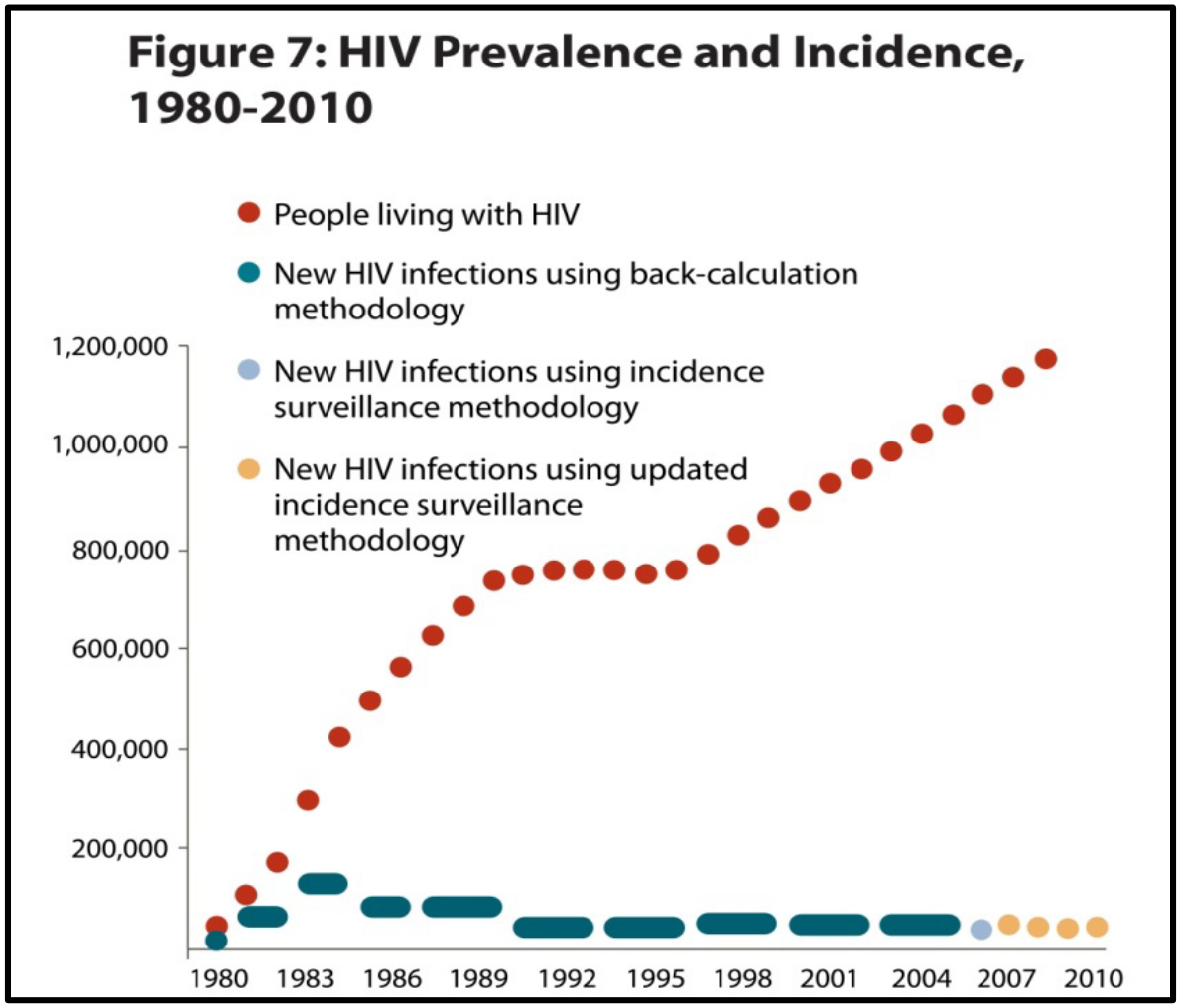
Prevalence of HIV among adults aged 15 to 49, 2016
By WHO region



Source: Image accessed from http://www.who.int/gho/hiv/hiv_013.jpg?ua=1

Human Immunodeficiency Virus (HIV) in the United States

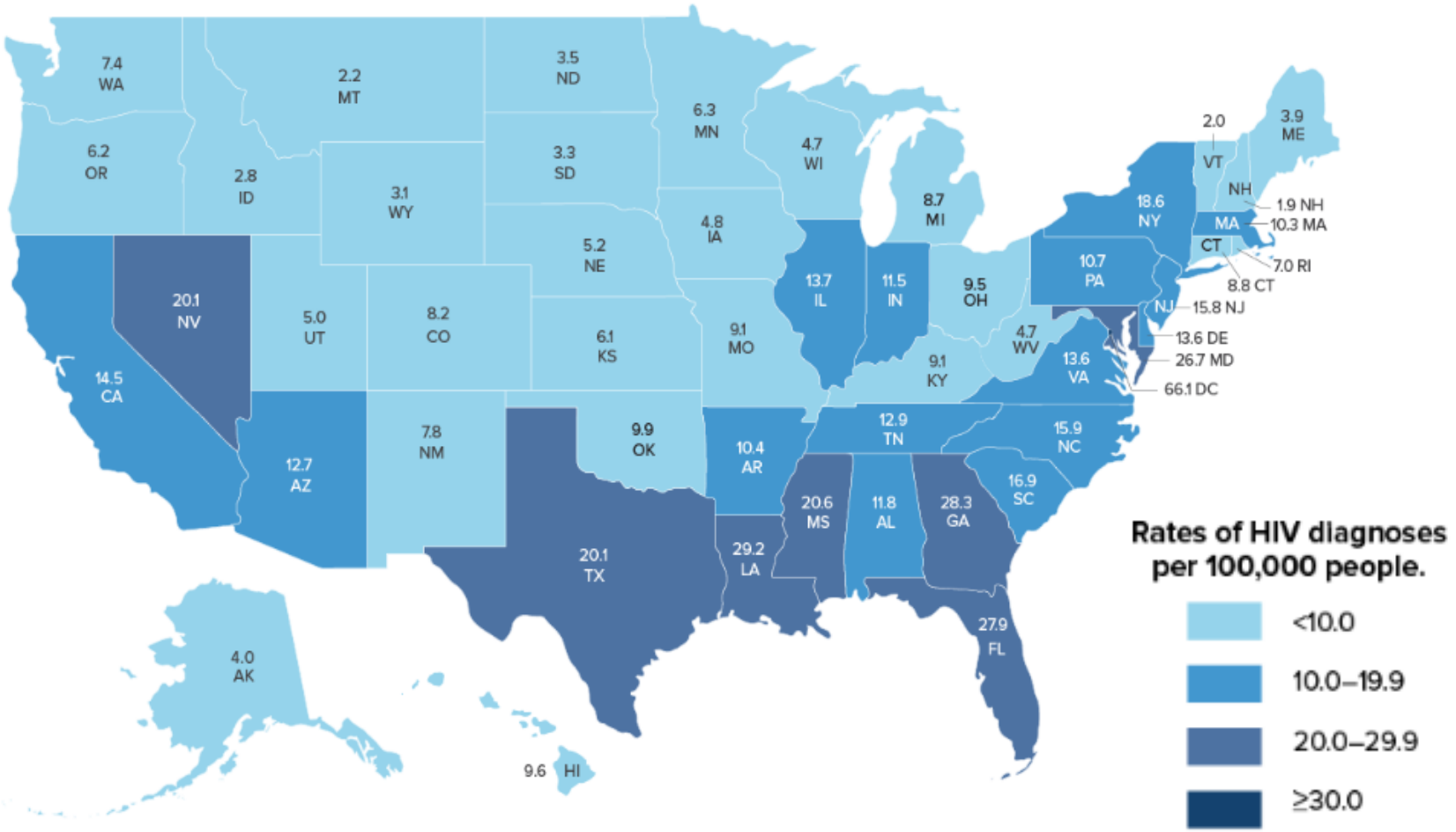
- Overview
  - 1.1 million in U.S. living with HIV
    - 1 in 7 unaware that they have HIV
  - 39,513 new diagnoses of HIV in 2015



Source: HIV in the United States: at a glance. Centers for Disease Control and Prevention website. Updated 6/9/17. Accessed 9/1/17. Image accessed at https://www.cdc.gov/nchhstp/newsroom/images/2012/incidence-fact-sheet-figure7.jpg

HIV in the United States, *continued*

Rates of HIV Diagnoses Among Adults and Adolescents in the US in 2015, by State



Source: CDC. Diagnoses of HIV infection in the United States and dependent areas, 2015. *HIV Surveillance Report* 2016;27.

Human Immunodeficiency Virus (HIV)

- HIV vs. AIDS
  - HIV- infection with human immunodeficiency virus
  - AIDS- diagnosed when a person with HIV has CD4 count < 200 cells/mm^3 or an AIDS-defining illness
- Type of human retrovirus
  - Reverse transcriptase used for viral replication
  - Highly error prone replication
- Transmission
  - Sexual
  - Parenteral
  - Perinatal

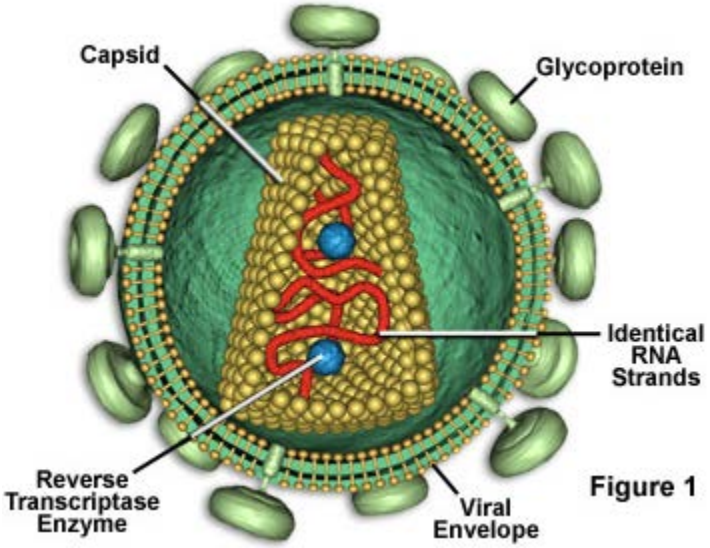
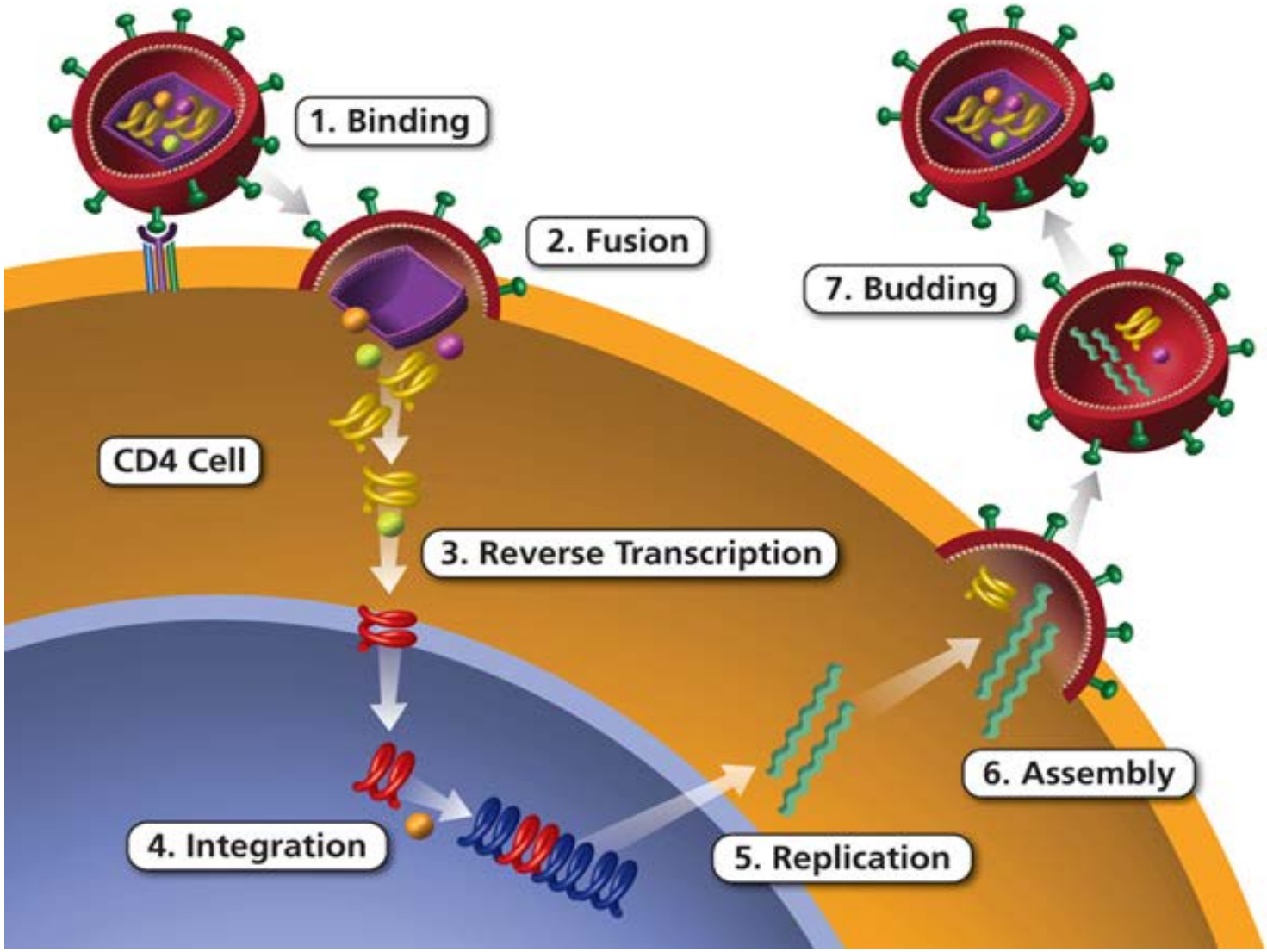


Figure 1

Source: Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. AIDS Info website. Updated 11/16/17. Accessed 11/16/17. Image source: https://micro.magnet.fsu.edu/cells/viruses/images/hivstructurefigure1.jpg

HIV Life Cycle



Source: Image accessed from https://aidsinfo.nih.gov/understanding-hiv-aids/glossary/4597/binding

Risk Factors for HIV

- African American, Latino > Caucasian
- Blood transfusion
  - HIV-1 testing began 1985, HIV-2 in 1992
- Men who have sex with men (MSM)
  - Gay or bisexual men = 67% of **all** HIV diagnoses in United States
- Intravenous drug users
- High-risk sexual behavior
- Percutaneous needle exposure

Source: Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. AIDS Info website. Updated November 16, 2017. Accessed November 16, 2017.

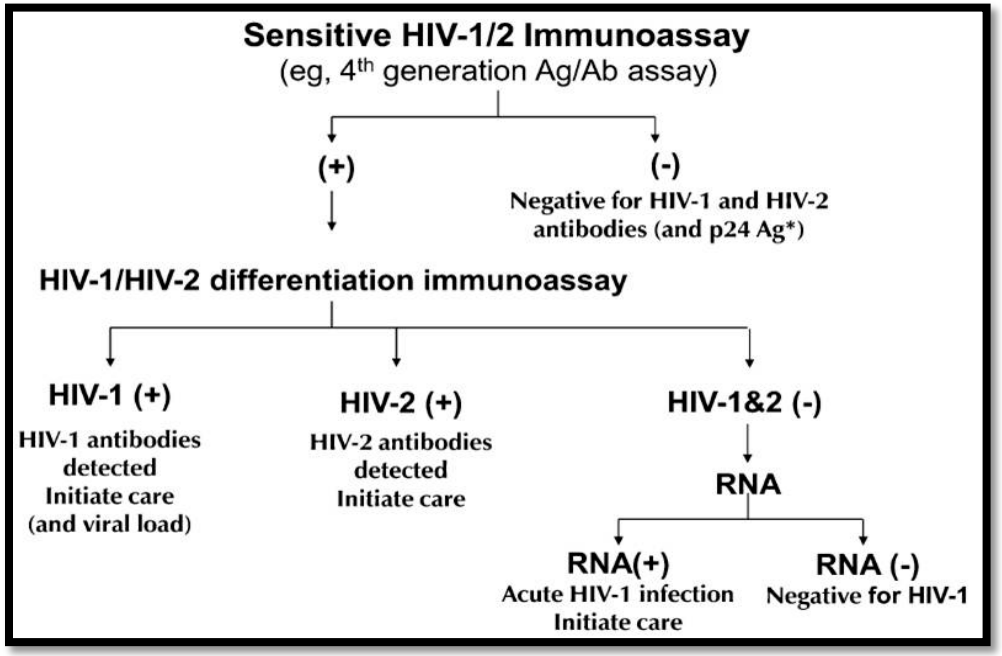
Estimated Per-Act Probability of Acquiring HIV From an Infected Source by Exposure Act*

Type of Exposure	Risk per 10,000 Exposures
Parenteral	
Blood Transfusion	9,250
Needle-Sharing During Injection Drug Use	63
Percutaneous (Needle-Stick)	23
Sexual	
Receptive Anal Intercourse	138
Insertive Anal Intercourse	11
Receptive Penile-Vaginal Intercourse	8
Insertive Penile-Vaginal Intercourse	4
Receptive Oral Intercourse	Low
Insertive Oral Intercourse	Low
Other^	
Biting	Negligible
Spitting	Negligible
Throwing Body Fluids (Including Semen or Saliva)	Negligible
Sharing Sex Toys	Negligible

Source: Imaged accessed at https://www.cdc.gov/hiv/risk/estimates/riskbehaviors.html

Diagnosis of HIV

- Diagnostic tests
  - Immunoassays – antibody detection
    - 1st through 4th generation
    - 4th generation more sensitive and specific
  - HIV RNA viral count
- Signs and symptoms
  - Likely asymptomatic
  - Acute retroviral syndrome



Source: Sax, Paul. Acute and early HIV infection: clinical manifestations and diagnosis. UpToDate website. Accessed November 13, 2017. Image accessed at http://blogs.jwatch.org/hiv-id-observations/wp-content/uploads/sites/2/2012/09/HIV-Testing-Algorithm1.jpg.

Goals of Treatment

- Suppress plasma HIV RNA
- Preserve immune system function
- Reduce morbidity and mortality
- Prevent HIV transmission

Source: Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. AIDS Info website. Updated November 16, 2017. Accessed November 16, 2017.

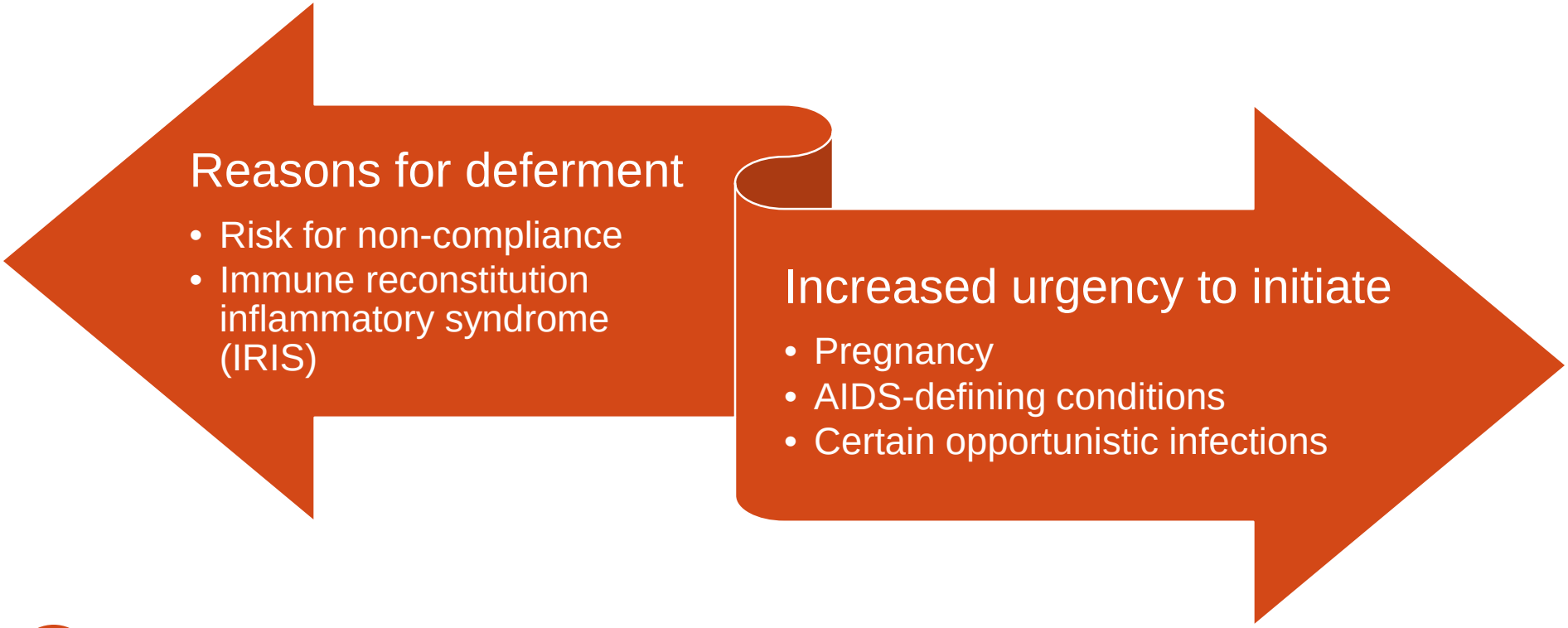
Prior to Starting Therapy…

- HIV antibody testing
- Plasma HIV RNA – "viral load"
- Genotypic resistance testing
- CD4 T cell count and percent
- CBC, CMP, urinalysis
- Hepatitis A, B and C serologies
- Fasting blood sugar
- Lipid panel
- HLA-B*5701
- Pregnancy test

Source: Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. AIDS Info website. Updated November 16, 2017. Accessed November 16, 2017.

When to Start?

- Antiretroviral therapy recommended **REGARDLESS** of CD4 cell count



Source: Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. AIDS Info website. Updated November 16, 2017. Accessed November 16, 2017.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 27, 2015 VOL. 373 NO. 9

Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group*

- Purpose
  - Assess risks and benefits of initiating antiretroviral therapy (ART) in patients with CD4 > 350 cells/mm^3
- Methods
  - Multi-national randomized, controlled trial
  - 4,685 treatment-naïve patients
  - Immediate treatment (CD4 > 500 cells/mm^3) vs. deferred treatment (CD4 < 350 cells/mm^3)

Source: Lundgren, et al. *N Engl J Med*. 2015 Aug 27;373(9):795-807.

START Trial

- Primary outcome
  - Composite of serious AIDS or non-AIDS events
- Results
  - Stopped early due to interim analysis results
  - Study subject baseline stats
    - Median VL = 12,759 copies/mL; CD4 = 651 cells/mm^3
  - Primary outcome (immediate vs. deferred treatment)
    - 1.8% (0.6 events per 100 person years) vs. 4.1% (1.38 events per 100 person years), $p< 0.001$
- Conclusion
  - Immediate initiation of ART in patients with CD4 > 500 cells/mm^3 showed benefit versus deferred treatment

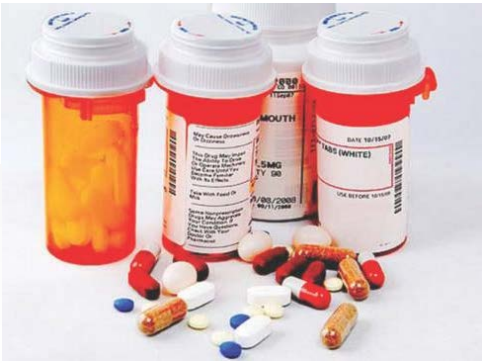
Source: Lundgren, et al. *N Engl J Med*. 2015 Aug 27;373(9):795-807.

What to Start?

- Many factors to consider in selecting regimen

- Underlying resistance
  - Treatment experienced vs. treatment naive

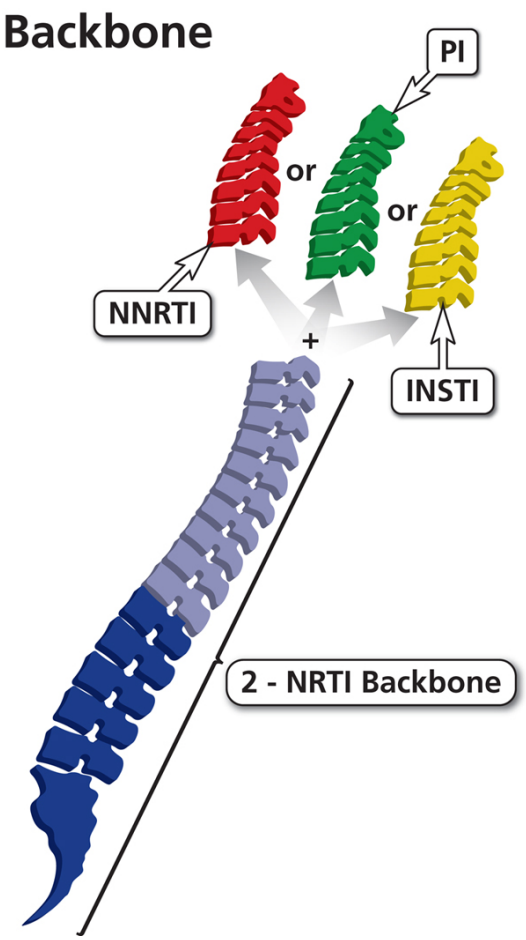
- Patient adherence to regimen
  - Pill burden
  - Side effects
  - Drug interactions
  - Cost



Source: Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. AIDS Info website. Updated November 16, 2017. Accessed November 16, 2017.

What Constitutes a Complete Regimen?

- Monotherapy NEVER appropriate
- Generally, three ACTIVE drugs
  - At least two different drug classes
  - Generally, two NRTIs + one additional agent
  - Can vary with underlying resistance
- Commonly encountered mistakes
  - Prescribing ≤ 2 active medications
  - Failure to properly dose medications



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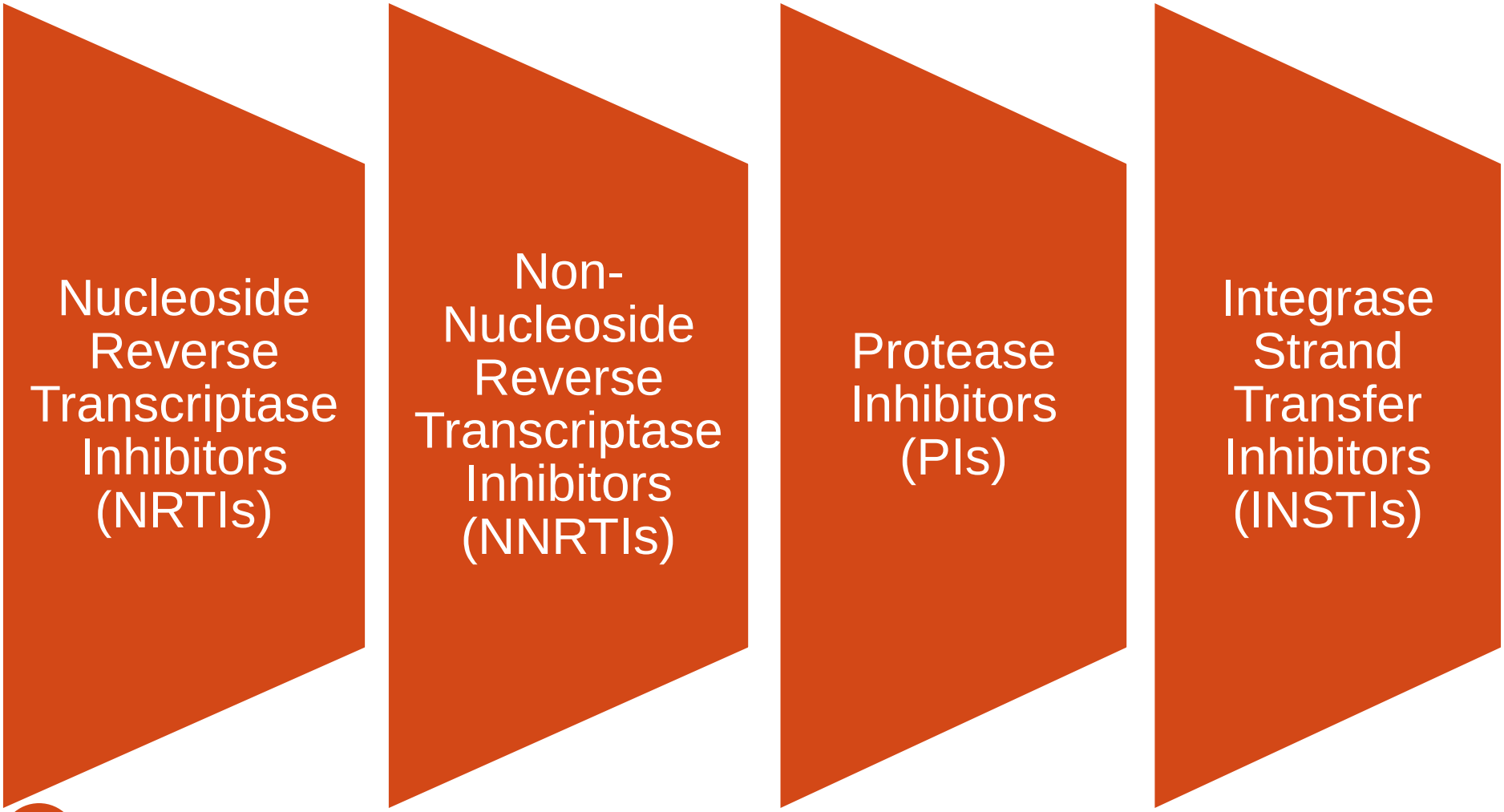
Antiretroviral Medications*



* Not including fusion inhibitors or CCR5 antagonists

Recommended Initial Regimens for Most People with HIV

- Integrase strand transfer inhibitor (INSTI)-based regimens now preferred
  - Durable virologic efficacy
  - Favorable tolerability profiles
  - Ease of use
- 2 NRTIs + INSTI
  - Lamivudine/abacavir/dolutegravir (Triumeq®)*
  - Tenofovir/emtricitabine + dolutegravir (Truvada® or Descovy® + Tivicay®)
  - Tenofovir/emtricitabine + raltegravir (Truvada or Descovy + Isentress)
  - Tenofovir/emtricitabine/elvitegravir/cobicistat (Stribild® or Genvoya®)

* if HLA-B*7501 negative

Souce: Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. AIDS Info website. Updated November 16, 2017. Accessed November 16, 2017.

Recommended Initial Regimens in Certain Clinical Situations

- Protease inhibitor (PI) and non-nucleoside reverse transcriptase (NNRTI) regimens
  - Overall, effective and tolerable
  - Less favorable drug interactions, side effect profile

- 2 NRTIs + "Boosted" Protease inhibitor (PI)
  - Tenofovir/emtricitabine + darunavir + cobicistat or ritonavir
  - Tenofovir/emtricitabine + atazanavir + cobicistat or ritonavir
  - Abacavir/lamivudine + darunavir + cobicistat or ritonavir*
  - Abacavir/lamivudine + atazanavir + cobicistat or ritonavir**

* if HLA-B*5701 negative
* if HLA-B*5701 negative AND HIV RNA < 100,000

Source: Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. AIDS Info website. Updated November 16, 2017. Accessed November 16, 2017.

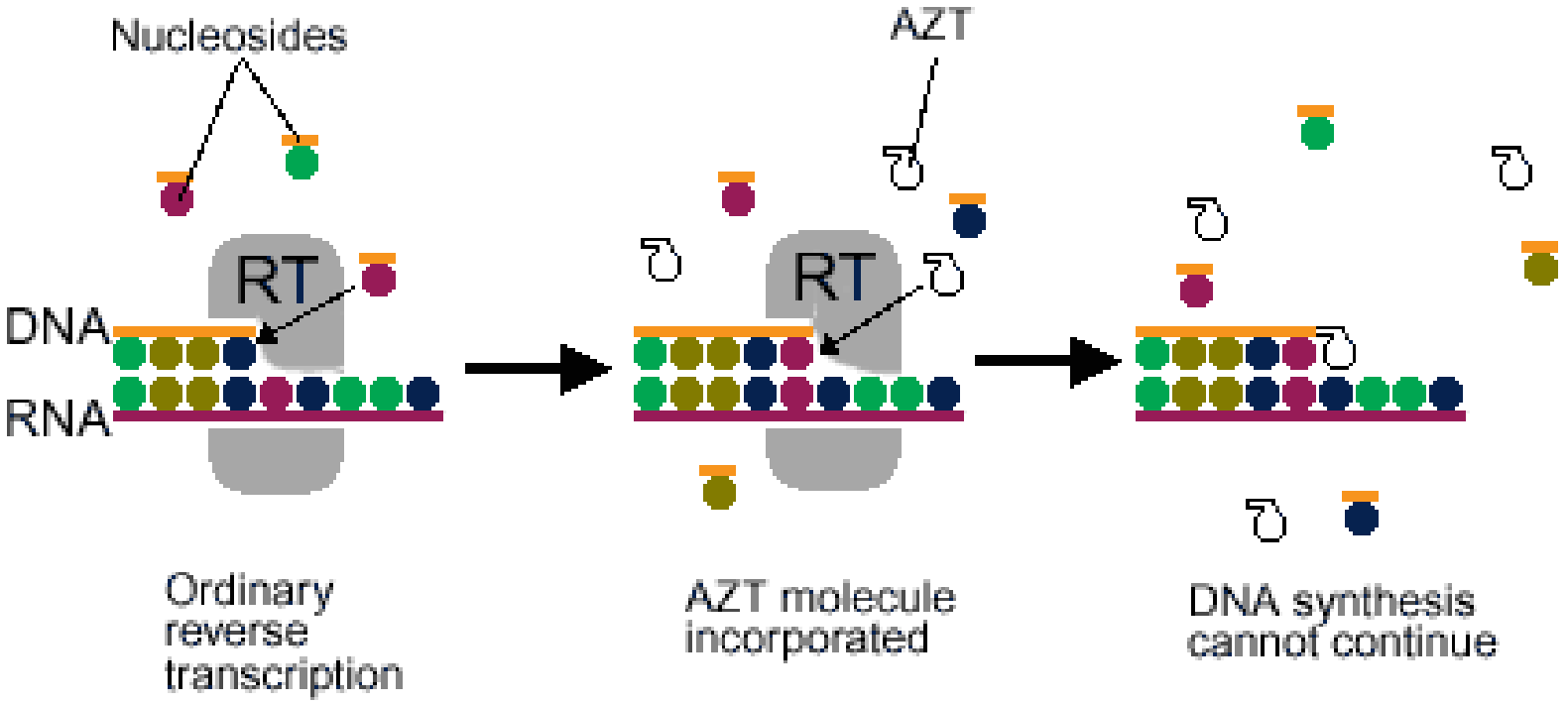
Recommended Initial Regimens in Certain Clinical Situations

- 2 NRTIs + NNRTI
  - Tenofovir/emtricitabine/efavirenz (Atripla®)
  - Tenofovir/emtricitabine/rilpivirine (Complera®)*
- 2 NRTIs + INSTI
  - Abacavir/lamivudine + raltegravir (Epzicom® + Isentress®)**

* HIV RNA < 100,000 and CD4 > 200 cells/mm^3
** HLA-B*5701-negative and HIV RNA < 100,000

Source: Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. AIDS Info website. Updated November 16, 2017. Accessed November 16, 2017.

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)



- Incorporate into viral DNA chain
- Stop viral DNA synthesis

Source: Image accessed at http://www.mcld.co.uk/hiv/images/aztAction.gif

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

- Examples
  - Abacavir (Ziagen®)
  - Lamivudine (Epivir®)
  - Tenofovir disoproxil (Viread®)
  - Emtricitabine (Emtriva®)
  - Tenofovir alafenamide fumarate (Vemlidy®)

- NRTI combination products (“NRTI backbones”)
  - Lamivudine/abacavir (Epzicom®)
  - Emtricitabine/tenofovir disoproxil (Truvada®)
  - Emtricitabine/tenofovir alafenamide fumarate (Descovy®)

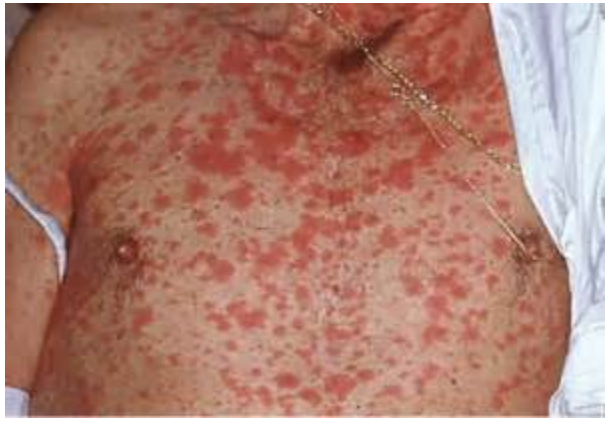
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

- Administration
  - With or without food

- Dose adjustments
  - Typically dosed 1 tablet po q24hr

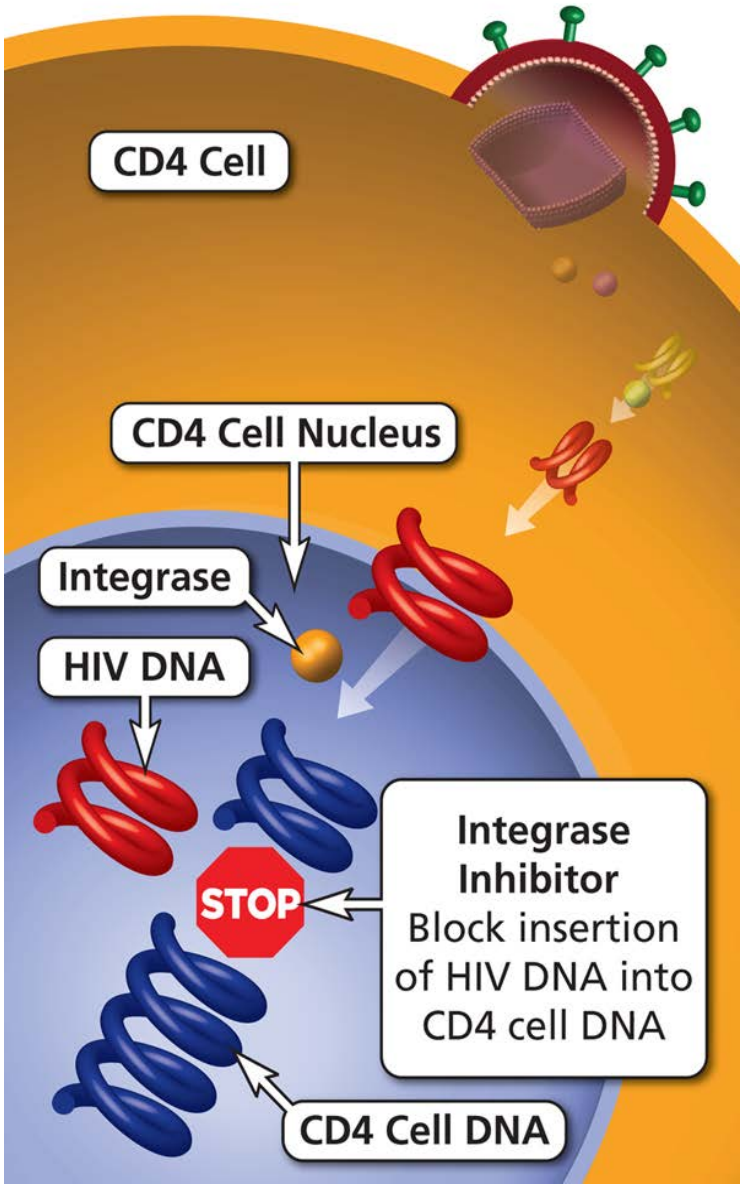
Drug name	CrCl ≥ 50 mL/min	CrCl 30-49 mL/min	CrCl < 30 mL/min
Epzicom® (abacavir/lamivudine)	No dose adjustment	Not recommended	Not recommended
Truvada® (tenofovir disoproxil/emtricitabine)	No dose adjustment	Increase to q48hr interval	Not recommended
Descovy® (tenofovir alafenamide/emtricitabine)	No dose adjustment	No dose adjustment	Not recommended

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)



- Class-wide side effects
  - Headache
  - Nausea
  - Rash
  - Diarrhea
- Agent-specific side effects
  - Abacavir – hypersensitivity reaction, potential cardiovascular risk
  - Tenofovir – decreased bone mineral density, increased SCr, renal failure
- Drug interactions
  - Potential for renal drug interactions

Integrase Strand Transfer Inhibitors (INSTIs)



Source: Image accessed from https://aidsinfo.nih.gov/understanding-hiv-aids/glossary/4597/ binding

Integrase Strand Transfer Inhibitors (INSTIs)

- Examples
  - Dolutegravir (Tivicay®)
  - Elvitegravir (Vitekta®)
  - Raltegravir (Isentress®)
  - Bictegravir (combo product under priority review)

- Combination products
  - Abacavir/lamivudine/dolutegravir (Triumeq®)
  - Tenofovir disoproxil/emtricitabine/elvitegravir/ cobicistat (Stribild®)
  - Tenofovir alafenamide fumarate/emtricitabine/ elvitegravir/cobicistat (Genvoya®)

Integrase Strand Transfer Inhibitors (INSTIs)

- Administration
  - With or without food
  - Exception – Stribild® or Genvoya®

- Dose adjustments

Drug name	Typical Dosing	INSTI-experienced or resistance	CrCl < 30 mL/min	HD
Dolutegravir (Tivicay®, Triumeq®)	1 tablet PO q24hr	1 tablet PO BID	Use with caution	Use with caution
Elvitegravir (Vitekta®, Stribild®, Genvoya®)	1 tablet PO q24hr	1 tablet PO q24hr	No dose adjustment	No dose adjustment
Raltegravir (Isentress®)	1 tablet PO BID	1 tablet PO BID	No dose adjustment	Dose after dialysis

Integrase Strand Transfer Inhibitors (INSTIs)

- Class-wide side effects
  - Generally, well-tolerated
  - Increased blood sugar
  - Increased ALT
  - Headache

- Drug interactions
  - Cation-containing antacids
  - Metformin – max dose of 1000mg/day with dolutegravir

Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial

- Bictegravir = novel, potent INSTI
  - High in-vitro barrier to resistance
  - Low potential for drug-drug interactions
- Purpose of trial
  - Assess efficacy and safety of bictegravir/tenofovir/emtricitabine vs. dolutegravir/abacavir/lamivudine
- Methods
  - Double-blind, multi-center, randomized controlled non-inferiority trial
  - 631 patients randomized to bictegravir (n=316) or dolutegravir (n=315) combination regimens
  - Intention-to-treat analysis

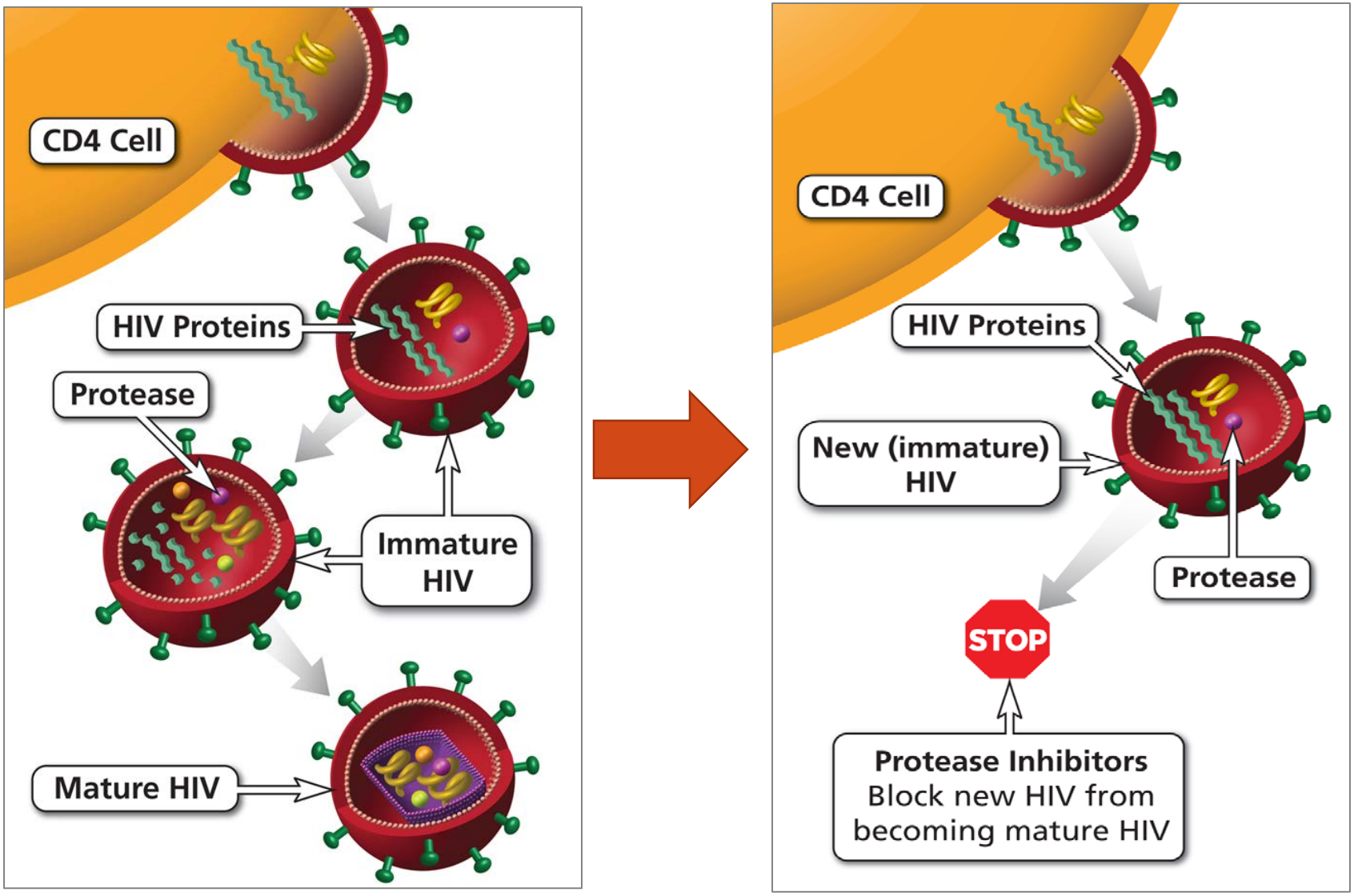
Source: Gallant, et al. *Lancet*. 2017 Nov 4;390(10107):2063-2072.

Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial

- Study subject baseline stats
  - Median HIV-1 RNA (log_{10} copies/mL) 4.42
  - 17% of subjects HIV-1 > 100,000 copies/mL
  - 90% of subjects CD4 cell count ≥ 200 cells/mL
- Results
  - HIV-1 RNA < 50 copies/mL (bictegravir vs. dolutegravir)
    - 92.4% vs. 93% (CI -4.8 to 3.6, p= 0.78)
  - Adverse event profile similar
    - Nausea significantly less in bictegravir (p <0.0001)

Source: Gallant, et al. *Lancet*. 2017 Nov 4;390(10107):2063-2072.

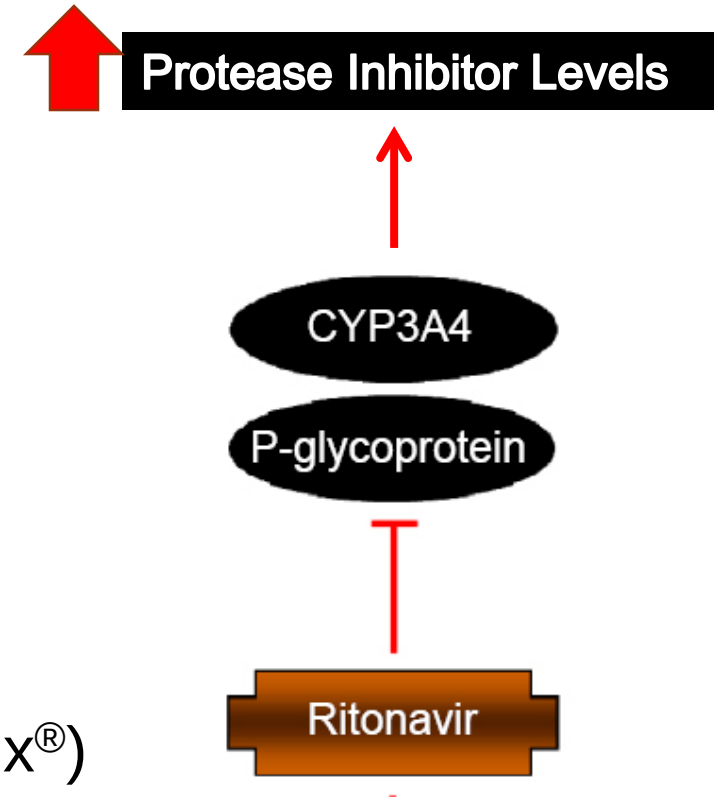
Protease Inhibitors (PIs)



Source: Image accessed at https://aidsinfo.nih.gov/understanding-hiv-aids/glossary/603/protease-inhibitor

Protease Inhibitors (PIs)

- Examples
  - Darunavir (Prezista®)
  - Atazanavir (Reyataz®)
- "Boosters"
  - Cobicistat (Tybost®)
  - Ritonavir (Norvir®)
- Combination products
  - Darunavir/cobicistat (Prezcobix®)
  - Atazanavir/cobicistat (Evotaz®)



Protease Inhibitors (PIs)

- Administration
  - With food
- Dose adjustments
  - Almost always dosed with booster (cobicistat or ritonavir)

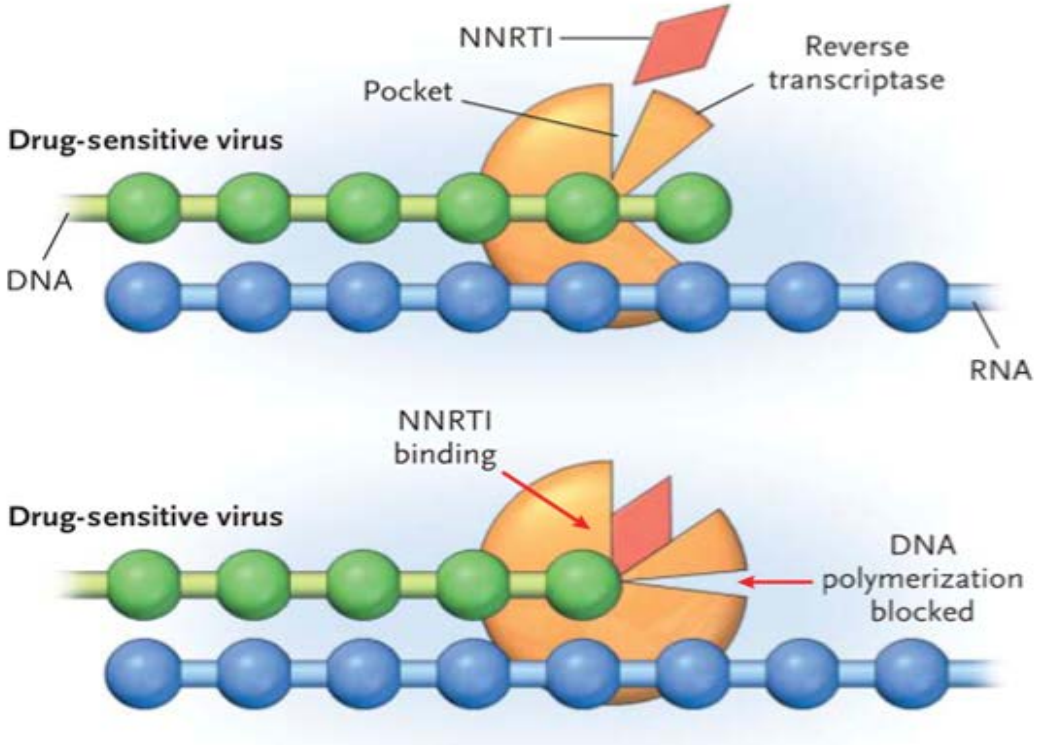
Drug name	Treatment naïve	Treatment experienced	Pregnancy	Hepatic Impairment (Child-Pugh Class C)
Darunavir (Prezista®)	1 tablet PO q24hr	≥ 1 darunavir resistance mutation:1 tablet PO BID	1 tablet PO q24hr	Use not recommended
Atazanavir (Reyataz®)	1 tablet (300mg) PO q24hr	1 tablet PO q24hr	If on tenofovir or H2RA, use 400mg tablet	Use not recommended

Protease Inhibitors (PIs)

Side Effects	
Protease Inhibitors	**“Boosters”**
Fat maldistribution	Diarrhea
Hyperlipidemia	Nausea, vomiting
Hyperglycemia	Hyperlipidemia
Skin rash	Hyperglycemia

- Drug interactions
  - Extensive!
  - CYP3A4 inhibitor
  - CYP3A4 substrate

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)



- Bind to reverse transcriptase enzyme
- Stop viral DNA replication

Source: Image accessed at http://www.hivwebstudy.org/sites/default/files/RT_NNRTI_Resistance.png

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

- Examples
  - Efavirenz (Sustiva®)
  - Rilpivirine (Edurant®)

- Combination products
  - Tenofovir/emtricitabine/efavirenz (Atripla®)
  - Tenofovir/emtricitabine/rilpivirine (Complera®)

- Administration
  - Atripla® – do not take with food
  - Complera® – take with food

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

- Dose adjustments
  - Efavirenz – not recommended in moderate-severe hepatic impairment
  - Rilpivirine – no dose adjustment for renal or hepatic impairment

- Agent-specific side effects
  - Efavirenz – vivid dreams, rash, dizziness, fatigue
  - Rilpivirine – depressive disorder, headache, insomnia

Opportunistic Infection (OI) Prophylaxis

Opportunistic infection (OI)	When to Initiate OI Prophylaxis	Preferred Regimen for OI Prophylaxis	Alternative Regimen for OI Prophylaxis
Pneumocystis pneumonia (PCP)	• CD4 <200 cells/mm^3 • CD4 percent <14%	Bactrim DS PO daily	Dapsone 100mg PO daily
Toxoplasmosis gondii	• Toxoplasma IgG positive • CD4 <100 cells/mm^3	Bactrim DS PO daily	Dapsone 50mg PO daily + (pyrimethamine 50mg and leucovorin 25mg PO weekly)
Mycobacterium avium complex (MAC)	• CD4 <50 cells/mm^3 (after ruling out disseminated disease)	• Azithromycin 1200mg PO weekly • Clarithromycin 500mg PO BID • Azithromycin 600mg PO twice weekly	Rifabutin 300mg PO daily

Source: Guidelines for the prevention and treatment of opportunistic infections in HIV-1 infected adults and adolescents. AIDS Info website. Updated November 16, 2017. Accessed November 16, 2017.

Questions?

References

- Gallant J, Lazzarin A, Mills A, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. *Lancet*. 2017 Nov 4;390(10107):2063-2072.
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