AETC AIDS Education & Training Center Program

Antiretroviral (ART) Selection and Resistance

Elizabeth Sherman, PharmD, AAHIVP
Faculty, South Florida - Southeast AETC
Pharmacist, Memorial Physician Group, Division of Infectious Disease
Associate Professor, Nova Southeastern University
esherman@nova.edu

Disclosure of Financial Relationships

This speaker has no financial relationships with commercial entities to disclose.

This speaker will not discuss any off-label use or investigational product during the program.

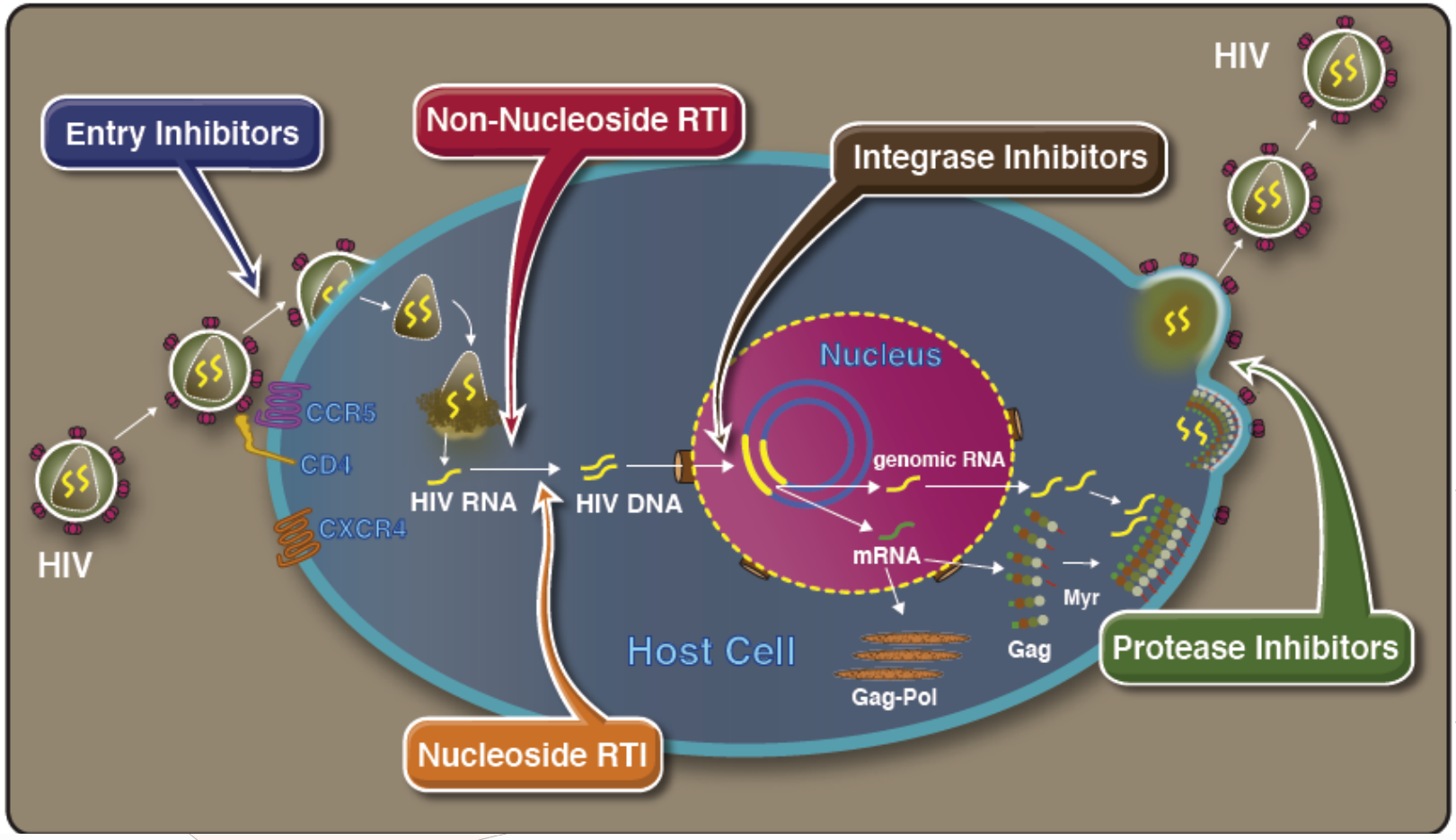
Learning Objectives

- Describe the process for selecting antiretroviral regimens
- Identify common mechanisms for drug interactions with antiretrovirals
- List the available methods and indications for antiretroviral resistance testing

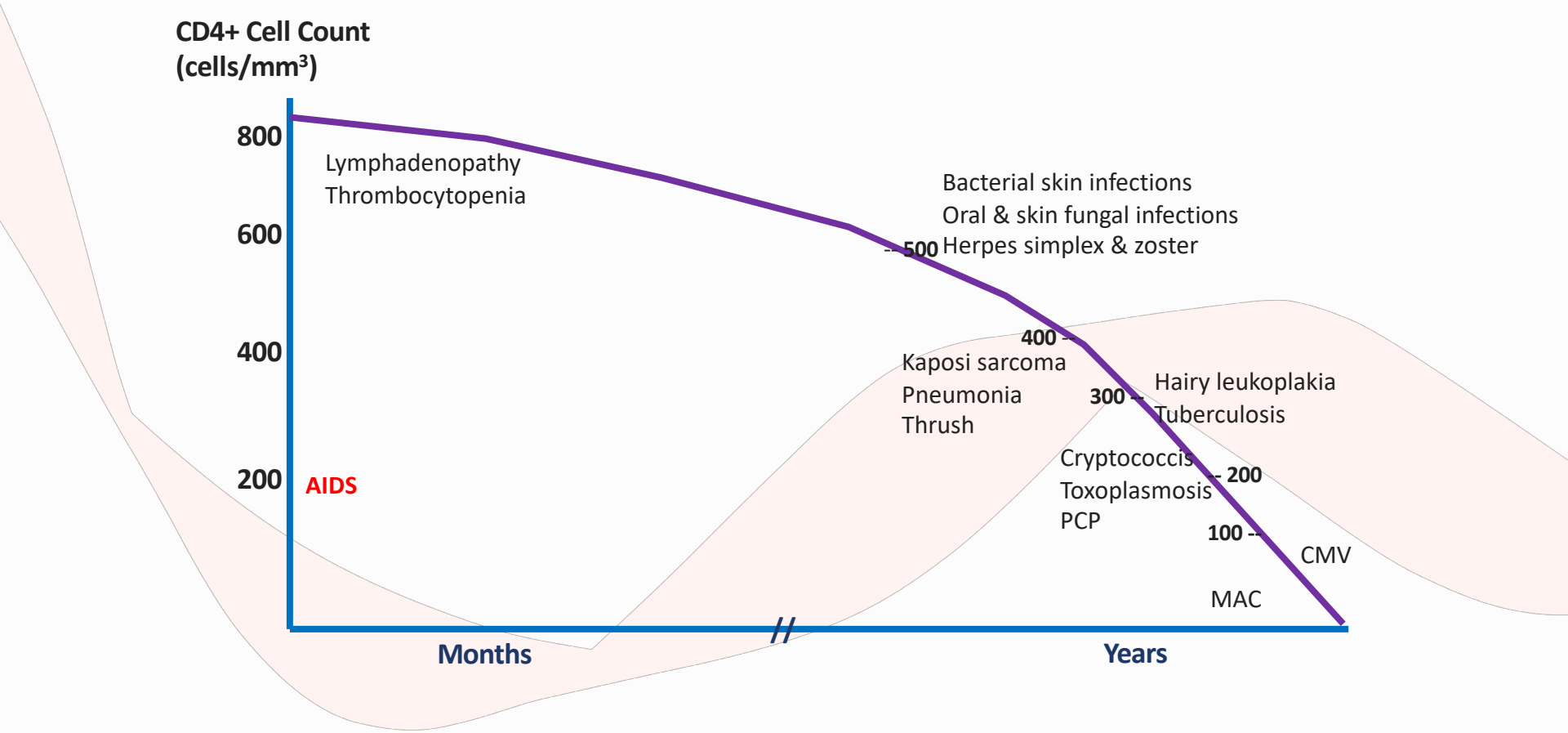
HIV Attacks CD4 T Cells

- HIV attacks immune system CD4 T cells
  - T cells are a type of white blood cell
  - HIV uses T cell machinery to replicate
- Depletion of CD4 T cells by HIV impairs immune defenses (leaving host susceptible to opportunistic infection)
- Antiretroviral therapy (ART) suppresses viral load, allowing improvements in immune system functioning

HIV Life Cycle



Correlation of Opportunistic Infections with CD4 Count



Initiation of Antiretroviral Therapy (ART)

- ART is recommended for all individuals with HIV, regardless of CD4 count, to reduce morbidity and mortality associated with HIV infection and to prevent HIV transmission
- On a case-by-case basis, ART may be deferred because of clinical and/or psychosocial factors, but therapy should be initiated as soon as possible

DHHS panel on antiretroviral guidelines for adults and adolescents. Available at http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

Goals of Antiretroviral Therapy

- Decrease HIV RNA
  - Goal HIV RNA or “viral load” <20-75 copies/mL or “undetectable”
- Increase CD4 count
  - 500-1500 cells/mm^3 is normal CD4 for HIV-uninfected
  - AIDS diagnosis is CD4 < 200 or CD4% < 14% (or AIDS defining illness)
- Improve quality of life and reduce HIV-related morbidity & mortality
- Prevent HIV transmission to others

Tools to Achieve Treatment Goals

1. Selecting individualized ART regimen
2. Maximizing adherence and navigating drug interactions
3. Performing resistance testing

Tools to Achieve Treatment Goals

1. **Selecting individualized ART regimen**
2. Maximizing adherence and navigating drug interactions
3. Performing resistance testing

Process for Selecting an Initial ART Regimen

- Regimen efficacy
  - Standard therapy for HIV typically consists of 3+ drugs from 2+ classes (no monotherapy)
- Comorbidities
  - Potential adverse effects or drug-drug interactions
- Drug resistance
  - Presence of transmitted drug resistance or development of drug resistance on failure
- Adherence potential
  - Pill burden, dosing frequency, food restrictions

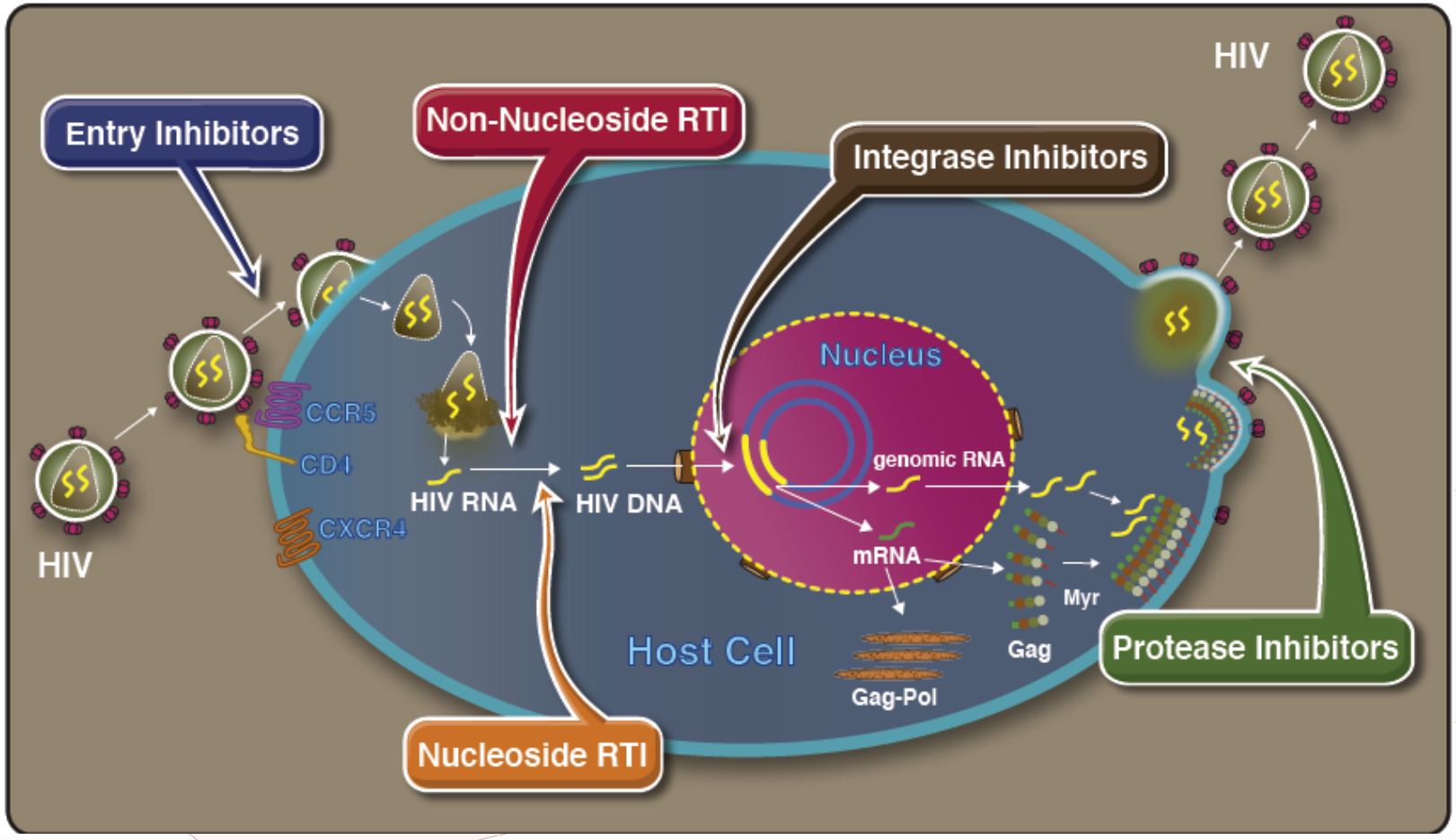
Overview of ART Drug Classes

- Classification based on where in the viral life cycle each drug acts
- 5 Antiretroviral Classes
  - Nucleos(t)ide reverse transcriptase inhibitors (NRTI)
  - Integrase strand transfer inhibitors (INSTI)
  - Protease inhibitors (PI) †
  - Non-nucleoside reverse transcriptase inhibitors (NNRTI) †
  - Entry inhibitors††

†Recommended in certain clinical situations

†† Not recommended for initial therapy

HIV Life Cycle & ART Drug Classes



Antiretroviral Medications

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Abacavir (ABC) (Ziagen®)
Didanosine (ddI) (Videx®)
Emtricitabine (FTC) (Emtriva®)
Lamivudine (3TC) (Epivir®)
~~Stavudine (d4T) (Zerit®)~~ *to be withdrawn by 2020*
Tenofovir (TDF or TAF) (Viread® or Vemlidy®)
~~Zalcitabine (ddC) (Hivid®)~~ *withdrawn 2005*
Zidovudine (ZDV, AZT) (Retrovir®)
3TC/ABC (Epzicom®)
3TC/ABC/ZDV (Trizivir®)
3TC/ZDV (Combivir®)
3TC/TDF (Cimduo®, Temixys®)
FTC/TDF (Truvada®)
FTC/TAF (Descovy®)

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Delavirdine (DLV) (Rescriptor®)
Doravirine (DOR) (Pifeltro®)
Efavirenz (EFV) (Sustiva®)
Etravirine (ETR) (Intelence®)
Nevirapine (NVP) (Viramune®)
Rilpivirine (RPV) (Edurant®)

Integrase Inhibitors (INSTIs)

Bictegravir (BIC)
Dolutegravir (DTG) (Tivicay®)
Elvitegravir (EVG)
Raltegravir (RAL) (Isentress®)

Pharmacokinetic Enhancers "Boosters"

Cobicistat (cobi) (Tybost®)
Ritonavir (r) (Norvir®)

Protease Inhibitors (PIs)

~~Amprenavir (APV) (Agenerase®)~~ *discontinued 2004*
Atazanavir (ATV) (Reyataz®)
Atazanavir/cobicistat (ATV/c) (Evotaz®)
Darunavir (DRV) (Prezista®)
Darunavir/cobicistat (DRV/c) (Prezcobix®)
Fosamprenavir (FPV) (Lexiva®)
Indinavir (IDV) (Crixivan®)
Lopinavir/ritonavir (LPV/r) (Kaletra®)
Nelfinavir (NFV) (Viracept®)
Ritonavir (RTV) (Norvir®)
Saquinavir (SQV) (Invirase®)
Tipranavir (TPV) (Aptivus®)

Entry Inhibitors

Enfuvirtide (ENF, T20) (Fuzeon®)
Ibalizumab (Trogarzo®)
Maraviroc (MVC) (Selzentry®)

Single Tablet Regimens

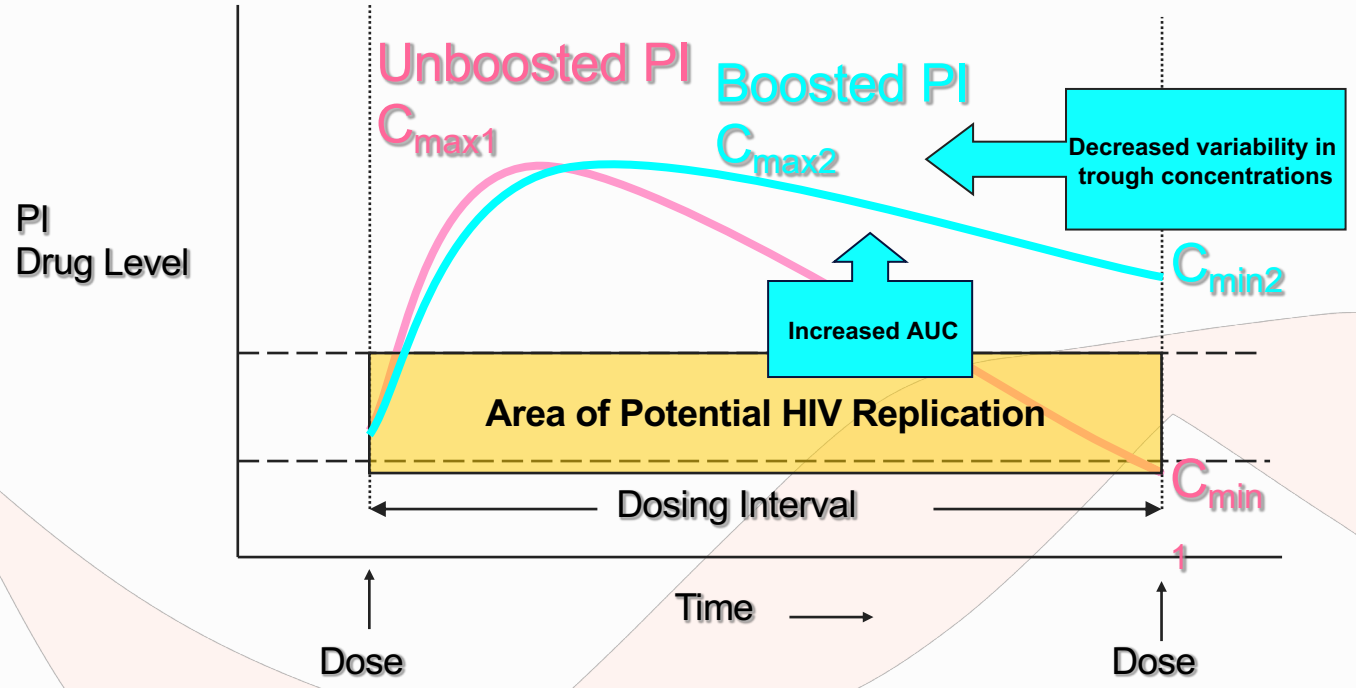
BIC/FTC/TAF (Biktarvy®)
DRV/cobi/FTC/TAF (Symtuza®)
DTG/3TC/ABC (Triumeq®)
DTG/RPV (Juluca®)
DTG/3TC (Dovato®)
DOR/3TC/TDF (Delstrigo®)
EFV/FTC/TDF (Atripla®)
EFV/3TC/TDF (Symfi® or Symfi Lo®)
EVG/cobi/FTC/TAF (Genvoya®)
EVG/cobi/FTC/TDF (Stribild®)
RPV/FTC/TAF (Odefsey®)
RPV/FTC/TDF (Complera®)

HIV Management Principles: Typical 3-Drug Regimen

- Initiate ART with 1 of 2 types of regimens
- Most regimens should include **at least 2 NRTIs plus at least 1 drug from a separate class**:
  - 2 NRTIs + 1 InSTI
  - 2 NRTIs + 1 Boosted PI [reserved for certain clinical situations]
  - 2 NRTIs + 1 NNRTI [reserved for certain clinical situations]
- Advantages and disadvantages to each type of regimen
- Selection based on regimen efficacy, patient comorbidities, drug resistance, drug interactions, and adherence potential

DHHS panel on antiretroviral guidelines for adults and adolescents. Available at http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

Boosting a Protease Inhibitor (PI) With Ritonavir (RTV) or Cobicistat (COBI)



Recommended Initial Regimens for Most People with HIV

2 NRTIs	+	INTEGRASE INHIBITOR
Tenofovir + Emtricitabine **OR** Abacavir + Lamivudine *only w/ Dolutegravir		Raltegravir Bictegravir Dolutegravir*

TAF and TDF are two forms of tenofovir approved by the FDA. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

Recommended Initial Regimens in Certain Clinical Situations

2 NRTIs

Tenofovir + Emtricitabine
OR
Abacavir + Lamivudine

+

PROTEASE INHIBITOR
(boosted with ritonavir or cobicistat)

Darunavir + RTV or Darunavir + COBI
Atazanavir + RTV or Atazanavir + COBI

OR

NNRTI

Doravirine
Efavirenz
Rilpivirine

OR

INTEGRASE INHIBITOR

Elvitegravir/cobicistat
Raltegravir

TAF and TDF are two forms of tenofovir approved by the FDA. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

Recommended Initial Regimens in Certain Clinical Situations

2 NRTIs

Tenofovir + Emtricitabine
OR
Abacavir + Lamivudine

+

PROTEASE INHIBITOR
(boosted with ritonavir or cobicistat)

Darunavir + RTV or Darunavir + COBI
Atazanavir + RTV or Atazanavir + COBI

OR

NNRTI

Doravirine
Efavirenz
Rilpivirine

OR

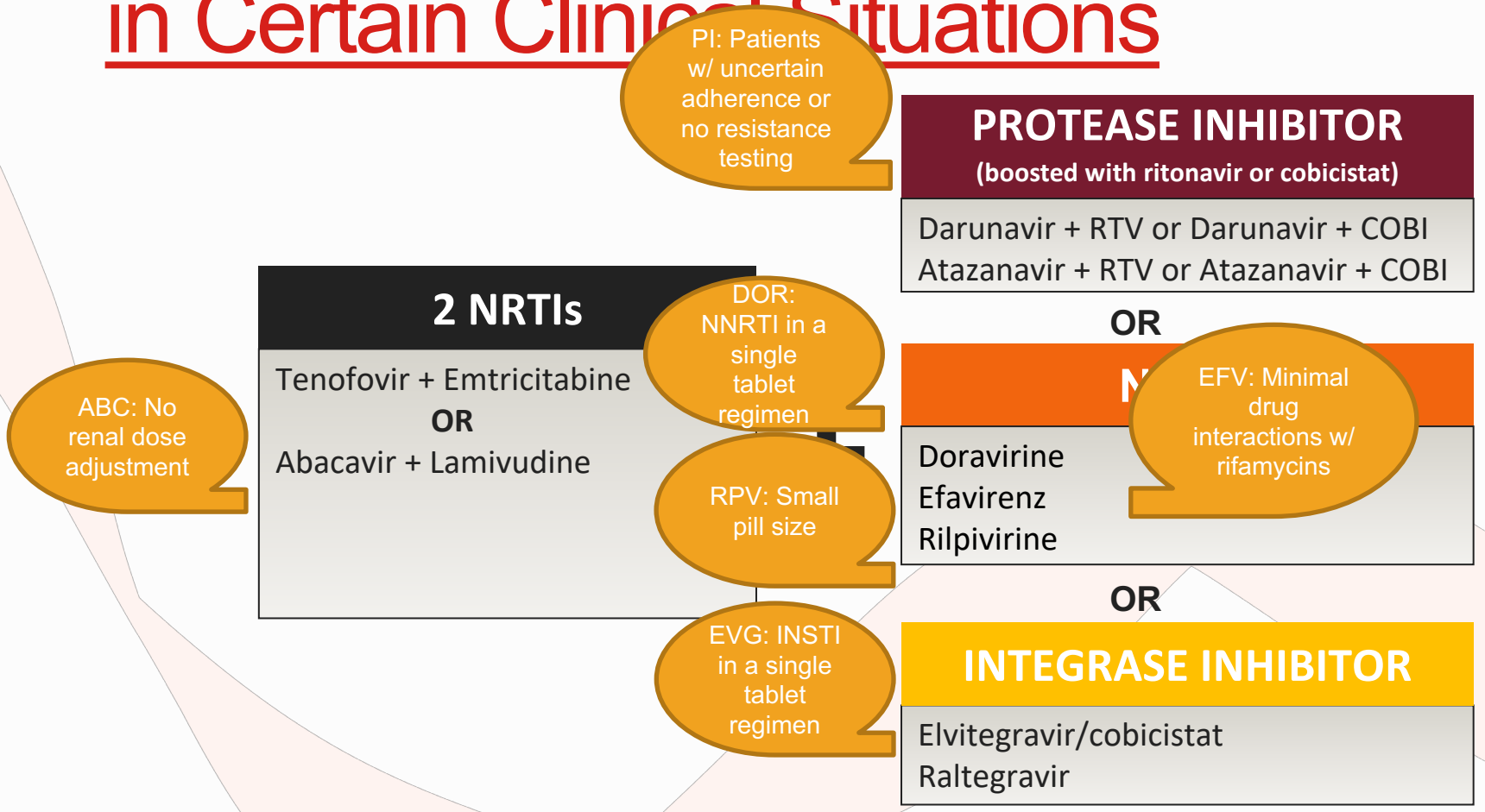
INTEGRASE INHIBITOR

Elvitegravir/cobicistat
Raltegravir

TAF and TDF are two forms of tenofovir approved by the FDA. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

Recommended Initial Regimens in Certain Clinical Situations



TAF and TDF are two forms of tenofovir approved by the FDA. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

AETC AIDS Education & Training Center Program

Selecting an Initial HIV Regimen: The "Chinese Food Rule"

*Tip of the hat to Royce Lin, MD, Associate Clinical Professor of Medicine, UCSF

Recommended Initial Regimens in Certain Clinical Situations

2 NRTIs

Tenofovir + Emtricitabine
OR
Abacavir + Lamivudine

+

PROTEASE INHIBITOR
(boosted with ritonavir or cobicistat)

Darunavir + RTV or Darunavir + COBI
Atazanavir + RTV or Atazanavir + COBI

OR

NNRTI

Doravirine
Efavirenz
Rilpivirine

OR

INTEGRASE INHIBITOR

Elvitegravir/cobicistat
Raltegravir

TAF and TDF are two forms of tenofovir approved by the FDA. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

Recommended Initial Regimens in Certain Clinical Situations

2 NRTIs

Tenofovir + Emtricitabine

OR

Abacavir + Lamivudine

+

PROTEASE INHIBITOR

(boosted with ritonavir or cobicistat)

Darunavir + RTV or Darunavir + COBI

Atazanavir + RTV or Atazanavir + COBI

OR

NNRTI

Doravirine

Efavirenz

Rilpivirine

OR

INTEGRASE INHIBITOR

Elvitegravir/cobicistat

Raltegravir

TAF and TDF are two forms of tenofovir approved by the FDA. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents.
Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

Recommended Initial CHINESE FOOD in Certain Clinical Situations

2 NRTIs

Tenofovir + Emtricitabine

OR

Abacavir + Lamivudine

+

PRO SE INHIBITOR

(booste ritonavir or cobicistat)

Darunavir + RTV or Darunavir + COBI

Atazanavir + RTV or Atazanavir + COBI

OR

NNRTI

Doravirine

Efavirenz

Rilpivirine

OR

INTEGRASE INHIBITOR

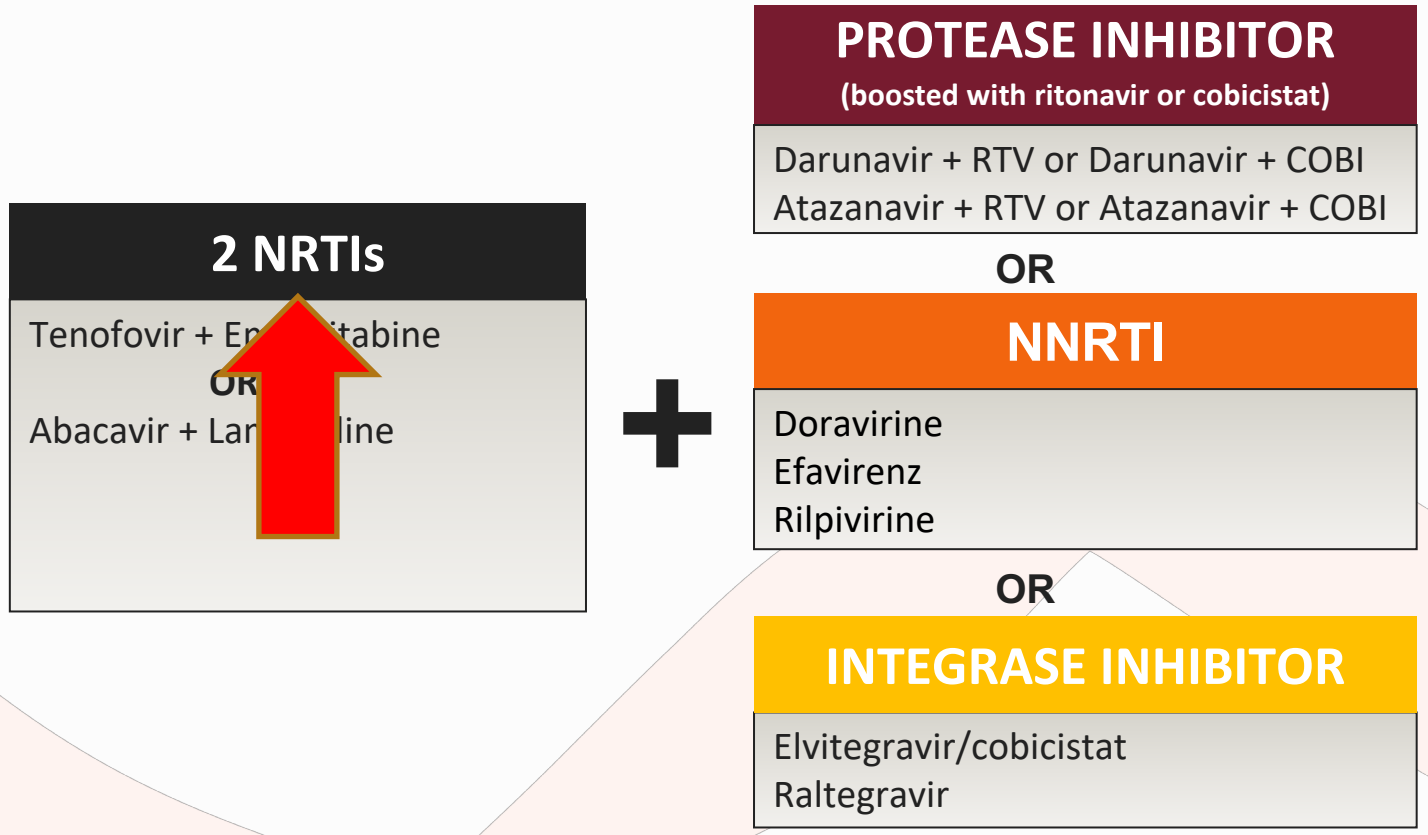
Elvitegravir/cobicistat

Raltegravir

TAF and TDF are two forms of tenofovir approved by the FDA. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

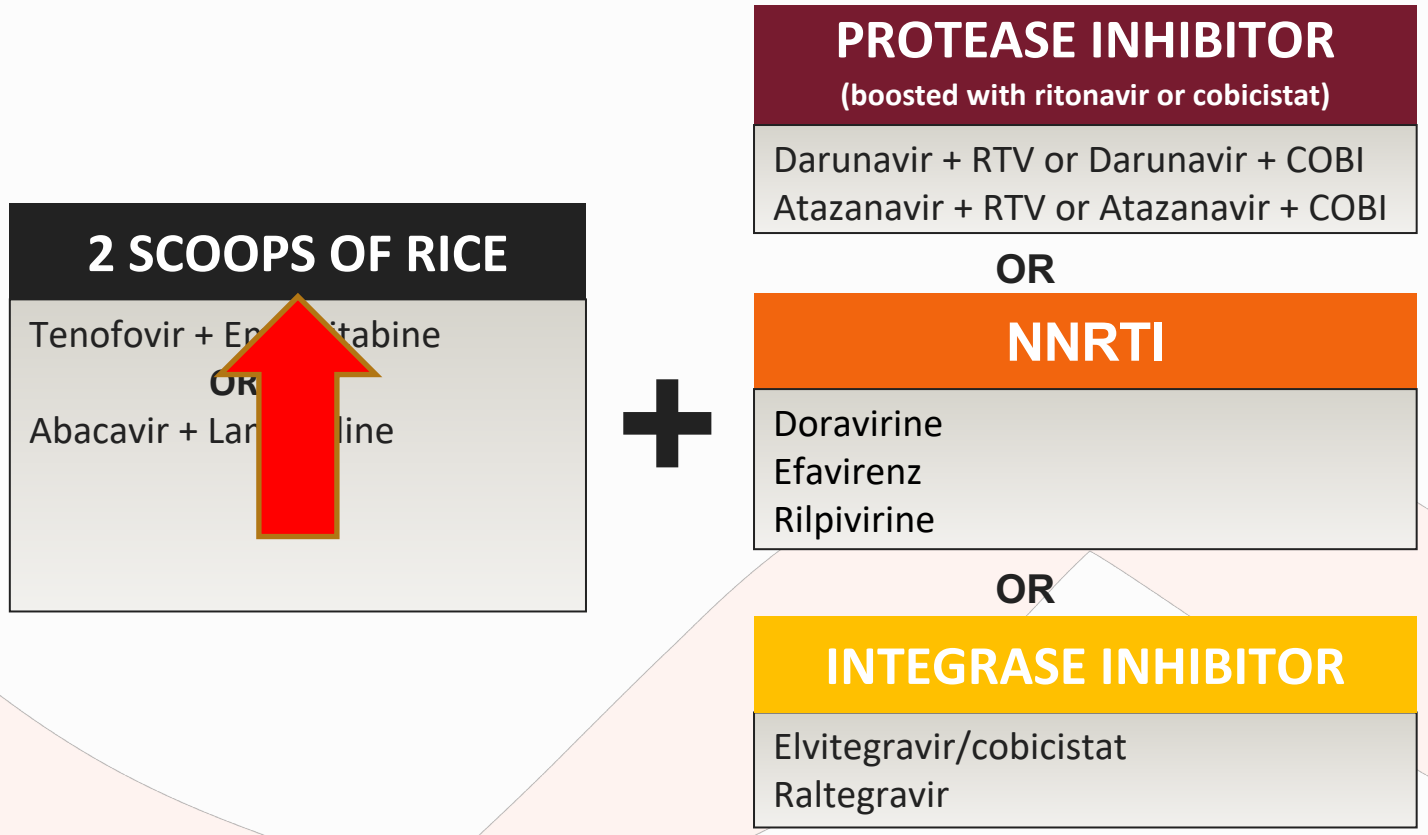
Recommended Initial CHINESE FOOD in Certain Clinical Situations



TAF and TDF are two forms of tenofovir approved by the FDA. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

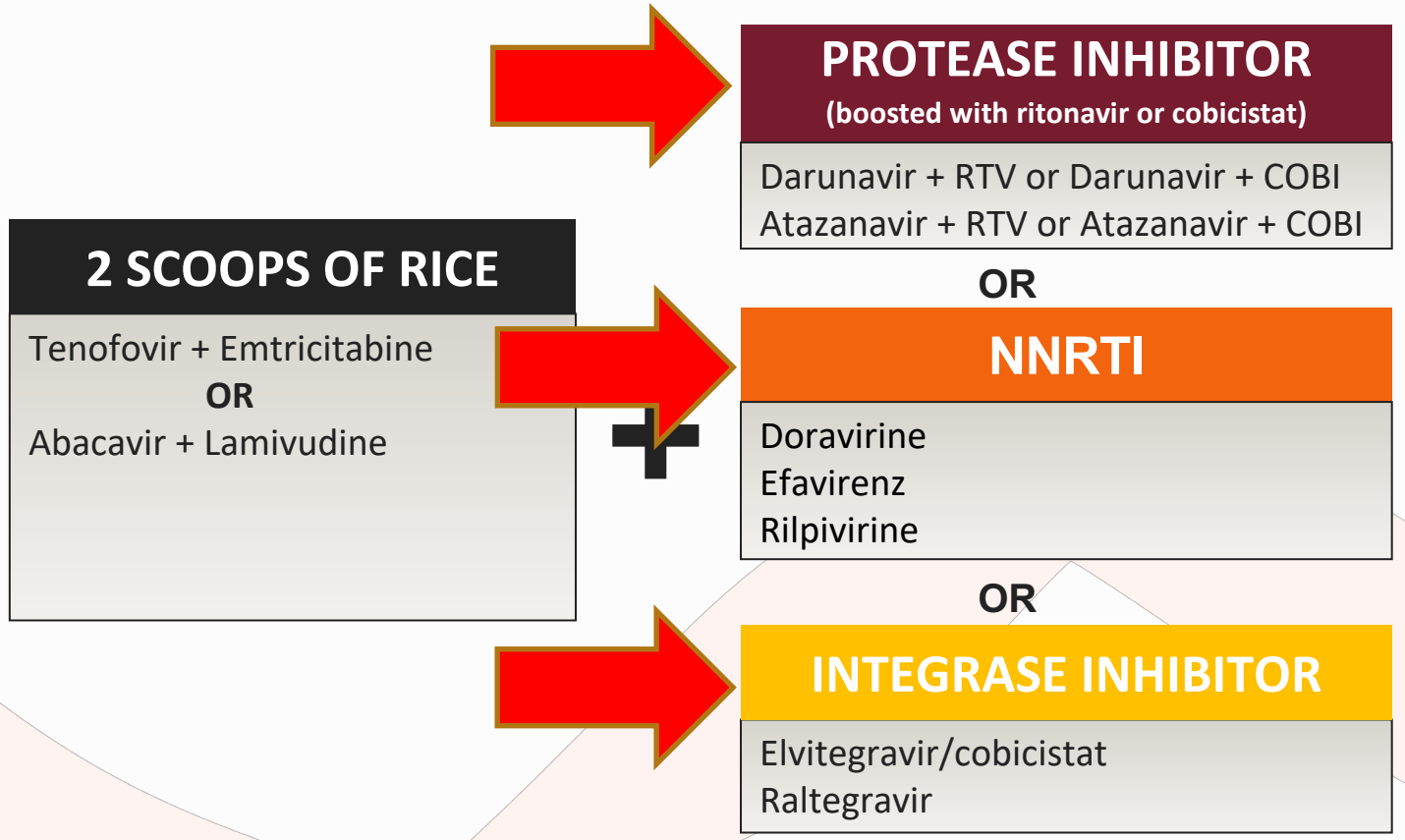
Recommended Initial CHINESE FOOD in Certain Clinical Situations



TAF and TDF are two forms of tenofovir approved by the FDA. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

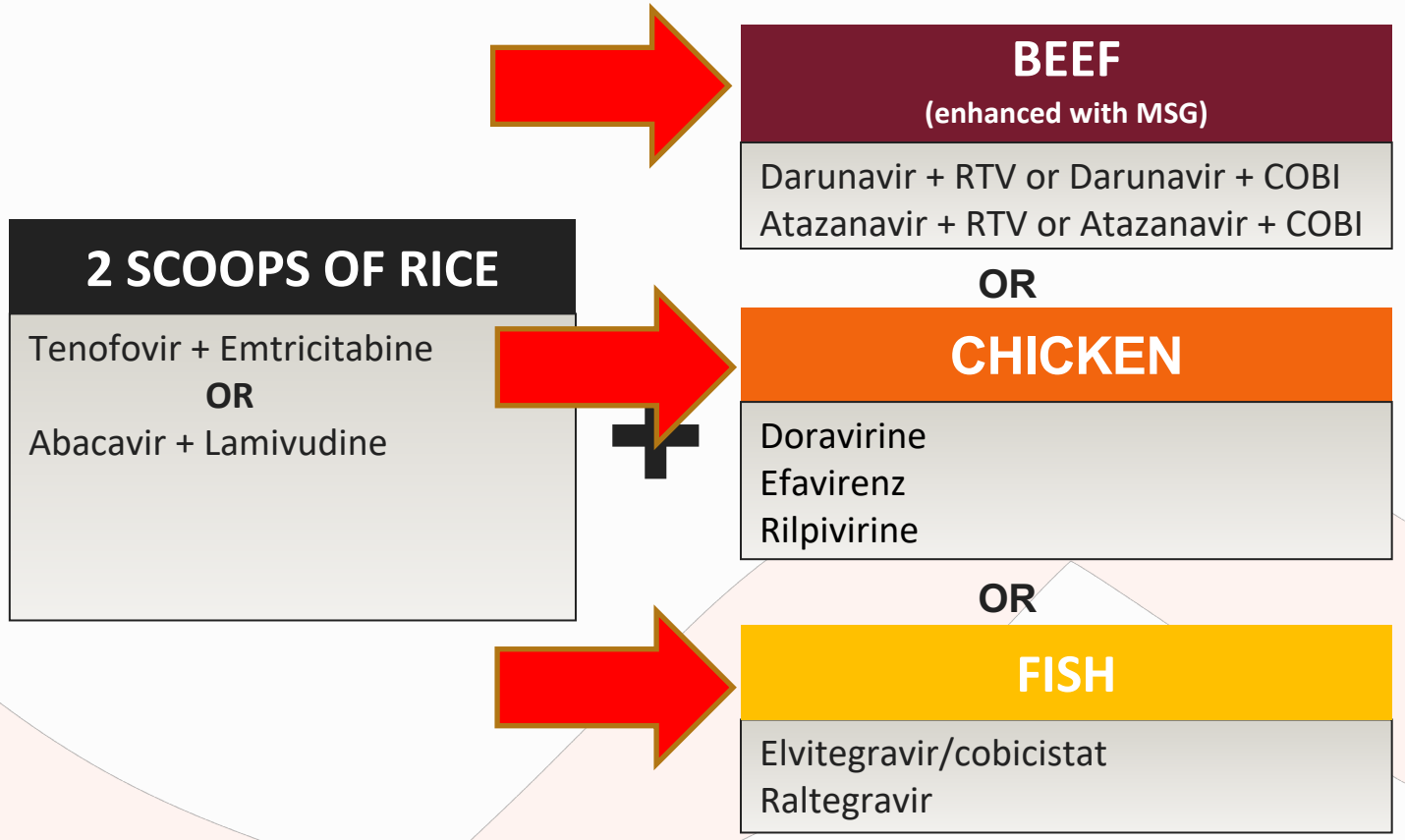
Recommended Initial CHINESE FOOD in Certain Clinical Situations



TAF and TDF are two forms of tenofovir approved by the FDA. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

Recommended Initial CHINESE FOOD in Certain Clinical Situations



TAF and TDF are two forms of tenofovir approved by the FDA. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

HIV Regimen / Chinese Food Selection: A Stepwise Approach

1. Get 2 scoops of rice 
   - Choose 2 NRTIs, Co-formulated when possible
     - Example: Tenofovir + emtricitabine
     - Example: Abacavir + lamivudine

2. Beef, fish, or chicken? 
   - Decide which class to use (PI, INSTI, NNRTI)
   - Choose specific agent based on comorbidities, pill burden, drug interactions, resistance testing, etc.

PI, InSTI, or NNRTI? (Beef, Fish, or Chicken?)

PI + RTV or COBI (Beef + MSG)	INSTI (Fish)	NNRTI (Chicken)
PRO •Very strong, potency well established •Harder to get resistance •Best for pts w/ uncertain adherence or if resistance tests not available	**PRO** •Highly effective for most patients •Very few side effects •Less drug interactions •Low pill burden (Some 1 pill daily) •No resistance seen with dolutegravir or bictegravir (strong, potent)	**PRO** •Low pill burden (1 pill daily) •Efavirenz: minimal drug interactions w/ rifamycins •Rilpivirine is in smallest single tablet regimen  
CON •Many drug interactions (P450 metabolism) •Metabolic effects (↑ cholesterol, glucose) •GI side effects •Boosting required	**CON** •Some delicate, prone to resistance (e.g., raltegravir, elvitegravir) •Dolutegravir: ↑ risk of neural tube defects in infants born to mothers receiving DTG at the time of conception	**CON** •Prone to resistance •Efavirenz has CNS side effects •Rilpivirine has lower efficacy in some patients (use only if CD4>200 and VL<100,000)

Tools to Achieve Treatment Goals

1. Selecting individualized ART regimen
2. **Maximizing adherence and navigating drug interactions**
3. Performing resistance testing

Importance of ART Adherence

- ART works by reducing viral replication to below level of detection
  - Adherence rates near 100% needed for optimal viral suppression
- ART adherence correlated with
  - HIV viral suppression
  - Reduced rates of viral resistance
  - Increase in survival
  - Improved quality of life
  - Reduced HIV transmission to others

DHHS panel on antiretroviral guidelines for adults and adolescents. Available at http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

Adherence Interventions

- Positive interface with clinic
- Encourage regular care
- Patient education
- Social support network
- Counsel and manage side effects
- Medication scheduling reminders
- Simplified regimens

Simplified Regimens

- Use of co-formulated ARV agents and once-daily dosing can reduce pill burden and simplify dosing schedules
- Simplified treatment regimens
  - Effective
  - Favored by patients and providers
  - Associated with better adherence

Advantages and Disadvantages of Single Tablet Regimens (STRs)

Advantages	Disadvantages
▪ Simplicity ▪ Convenience ▪ Fewer copays ▪ Reduces selective non-adherence to components of regimen	▪ Inability to adjust dosages of components if needed due to drug–drug interactions or renal insufficiency ▪ Not available for all ART regimens and combinations

Slide credit: clinicaloptions.com

Single Tablet Regimens (STRs)

Brand Name	Generic Name	Type	Year of FDA Approval
Atripla	Efavirenz/tenofovir DF/emtricitabine	NNRTI + dual NRTI	2006
Complera	Rilpivirine/tenofovir DF/emtricitabine	NNRTI + dual NRTI	2011
Stribild	Elvitegravir/cobicistat/tenofovir DF/emtricitabine	INSTI + booster + dual NRTI	2012
Triumeq	Dolutegravir/abacavir/lamivudine	INSTI + dual NRTI	2014
Genvoya	Elvitegravir/cobicistat/tenofovir AF/emtricitabine	INSTI + booster + dual NRTI	2015
Odefsey	Rilpivirine/tenofovir AF/emtricitabine	NNRTI + dual NRTI	2016
Juluca	Dolutegravir/rilpivirine	INSTI + NNRTI	2017
Biktarvy	Bictegravir/tenofovir AF/emtricitabine	INSTI + dual NRTI	2018
Symtuza	Darunavir/cobicistat/tenofovir AF/emtricitabine	PI + booster + dual NRTI	2018
Delstrigo	Doravirine/tenofovir DF/emtricitabine	NNRTI + dual NRTI	2018
Dovato	Dolutegravir/lamivudine	INSTI + NRTI	2019

Key: DF = disoproxil fumarate; AF = alafenamide; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucelos(t)ide reverse transcriptase inhibitor; INSTI = integrase strand transfer inhibitor

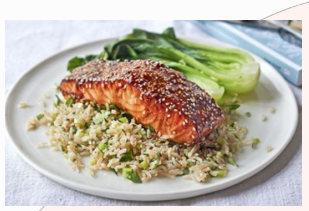
Food Considerations with STRs

Single Tablet Regimen	Food Considerations
Atripla	Empty stomach
Biktarvy	With or without food
Complera	With a full meal (not a protein drink)
Delstrigo	With or without food
Dovato	With or without food
Genvoya	With food
Juluca	With a full meal (not a protein drink)
Odefsey	With a full meal (not a protein drink)
Stribild	With food
Symtuza	With food
Triumeq	With or without food

What exactly does empty stomach, with food, or with a full meal mean?

- Empty stomach: 1 hour before a meal or 2 hours after a meal
- With food: Within 2 hours after eating
- With a full meal: At least 400 calories






Ask About Other Medications: The Importance of Drug Interactions

- Common drug interactions occur between ART and medications used to manage common comorbidities
- Drug interactions range from mild to severe (and even potentially fatal, requiring FDA labeling to prohibit co-administration)
- Ask about all medications: prescription, over-the-counter, herbal, recreational
  - The INSTIs bictegravir, dolutegravir, & raltegravir have the fewest drug interactions
  - Regimens containing cobicistat or ritonavir as boosters have a high potential for drug interactions
- Any changes to the medication list require careful consideration of potential drug interactions

ARV Metabolism and Drug Interaction Potential

ARV Drug Class	Route of Metabolism	Drug Intxn Potential
NRTI	Mostly renal	Medium
NNRTI	Liver metabolism: P450 substrates, some are P450 inducers	High
PI	Liver metabolism: P450 substrates, most are P450 inhibitors	High
Integrase Inhibitors	Liver metabolism •Raltegravir: UGT1A1 enzyme (not P450) •Elvitegravir: P450 substrate (cobicistat: P450 inhibitor) •Dolutegravir: P450 substrate & UGT1A1 •Bictegravir: P450 substrate & UGT1A1	Medium-High
Entry Inhibitor: CCR5	Liver metabolism: P450 substrate	Medium
Entry Inhibitor: Fusion	Peptide undergoes catabolism to amino acids: No known drug interactions	Low
Entry Inhibitor: CD4 post-attachment	Metabolized by CD4 receptor internalization/ catabolism: No known drug interactions	Low

Antiretrovirals Have Drug Interactions With Multiple Medications

- Cholesterol medications
- Anti-acid therapy
- TB and MAC medications
- Hormonal contraceptives
- Asthma medications and corticosteroids
- Seizure medications
- Hepatitis C medications
- Other antiretrovirals
- Antifungals
- Benzodiazepines
- Antiplatelets & anticoagulants
- Erectile dysfunction medications
- Antiarrhythmics, calcium channel blockers
- Antipsychotics and antidepressants
- Herbal and dietary supplements

ARV Interactions with Cholesterol Medications

- Statins (HMG Co-A reductase inhibitors)
  - P450 substrates
    - Degree of 3A4 metabolism varies:
      simva, lova >> rosuva > atorva > pravastatin
  - May be affected by NNRTIs, PIs, & cobicistat
- NNRTIs can ↓ statin levels
  - Monitor statin efficacy, ↑ dose as necessary
- PIs and COBI ↑ statin levels
  - Avoid simvastatin, lovastatin (2000% ↑)

Managing ARV Interactions with Statins

Statin	Interacting Antiretroviral(s)	Prescribing Recommendation
Atorvastatin	•Atazanavir ± ritonavir	Titrate atorvastatin dose carefully and use lowest dose necessary while monitoring for toxicities
	•Darunavir/cobicistat •Darunavir + ritonavir •Elvitegravir/cobicistat •Lopinavir/ritonavir	Do not exceed 20 mg atorvastatin daily
	•Atazanavir/cobicistat •Tipranavir + ritonavir	Do not co-administer
Lovastatin	•HIV protease inhibitors •Elvitegravir/cobicistat	CONTRAINDICATED
Pitavastatin	•HIV protease inhibitors	No dose adjustment necessary
	•Elvitegravir/cobicistat	No data; no dosage recommendation
Pravastatin	•Atazanavir + ritonavir; Atazanavir/cobicistat •Darunavir + ritonavir; Darunavir/cobicistat	Titrate pravastatin dose carefully while monitoring for toxicities
	•Lopinavir + ritonavir	No dose limitations
	•Elvitegravir/cobicistat	No data; no dosage recommendation
Rosuvastatin	•Darunavir + ritonavir •Elvitegravir/cobicistat	Titrate rosuvastatin dose carefully and use lowest necessary dose while monitoring for toxicities
	•Darunavir/cobicistat	Do not exceed 20 mg rosuvastatin daily
	•Atazanavir/cobicistat •Atazanavir + ritonavir •Lopinavir/ritonavir	Do not exceed 10 mg rosuvastatin daily
	•Tipranavir + ritonavir	No dose limitations
Simvastatin	•HIV protease inhibitors •Elvitegravir/cobicistat	CONTRAINDICATED

DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

ARV Interactions with Anti-acid Medications

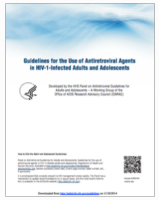
- Indicated for GERD/peptic ulcer disease to decrease gastric acidity
  - Antacids: aluminum, magnesium hydroxide, or calcium carbonate
  - H2 receptor antagonists: cimetidine, famotidine, ranitidine
  - Proton pump inhibitors: lansoprazole, omeprazole, pantoprazole
- Medications decreasing stomach acidity can interfere with ARVs requiring an acidic environment for absorption (e.g., atazanavir, rilpivirine)
- INSTI absorption is decreased by binding with di/trivalent cations

Managing ARV Interactions with Anti-Acid Therapy

Anti-acid	Atazanavir (ATV) Intxns	Rilpivirine (RPV) Intxns	INSTI Intxns
Al, Mg, Ca Antacids	ATV 2 hrs before or 1-2 hour after antacids	Antacids 2 hours before or 4 hours after RPV	•Separate EVG by ≥ 2 hours •RAL/RAL HD not recommended with Al or Mg •RAL no dose adjustment with Ca; RAL HD contraindicated with Ca •Take DTG 2 hours before or 6 hours after (or together w/ food) •Take BIC without food 2 hours before Al, Mg, or Ca
H2 Receptor Antagonists (H2RA)	•Atazanavir with ritonavir or cobicistat: ATV with or 10 hours after H2RA (max famotidine 40mg BID for treatment naïve; 20mg BID for treatment experienced) •Atazanavir alone: ATV 2 hours before or 10 hours after H2RA (max famotidine 20mg dose for treatment naïve; CONTRAINDICATED for treatment experienced)	H2RA 12 hours before or 4 hours after RPV	No dose adjustment
Proton Pump Inhibitors (PPI)	Atazanavir must be boosted with ritonavir or cobicistat: PPI 12 hours prior to ATV (max omeprazole 20mg for treatment naïve; CONTRAINDICATED for treatment experienced)	CONTRAINDICATED	No dose adjustment

Resources: Drug Interactions

- Department of Health and Human Services (DHHS). Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. [**www.aidsinfo.nih.gov**]



  - **Tables 17-20**

- University of Liverpool HIV iChart app for iPhone and Android [**www.hiv-druginteractions.org**]

Tools to Achieve Treatment Goals

1. Selecting individualized ART regimen
2. Maximizing adherence and navigating drug interactions
3. **Performing resistance testing**

How Drug Resistance Occurs

- Untreated HIV produces 10 billion new virions each day
  - Most common form of HIV is wild-type virus
  - Wild-type: Viral strain that has not mutated and is susceptible to all drugs
- High mutation rate, ~1 nucleotide mutation per replication cycle
  - Mutation: Slight change in specific section of genetic material (HIV RNA)
  - Not all mutations cause resistance

Tang MW, Shafer RW. Drugs 2012;72(9):e1-e25.

Drug Resistance Testing Guides Therapy Decisions

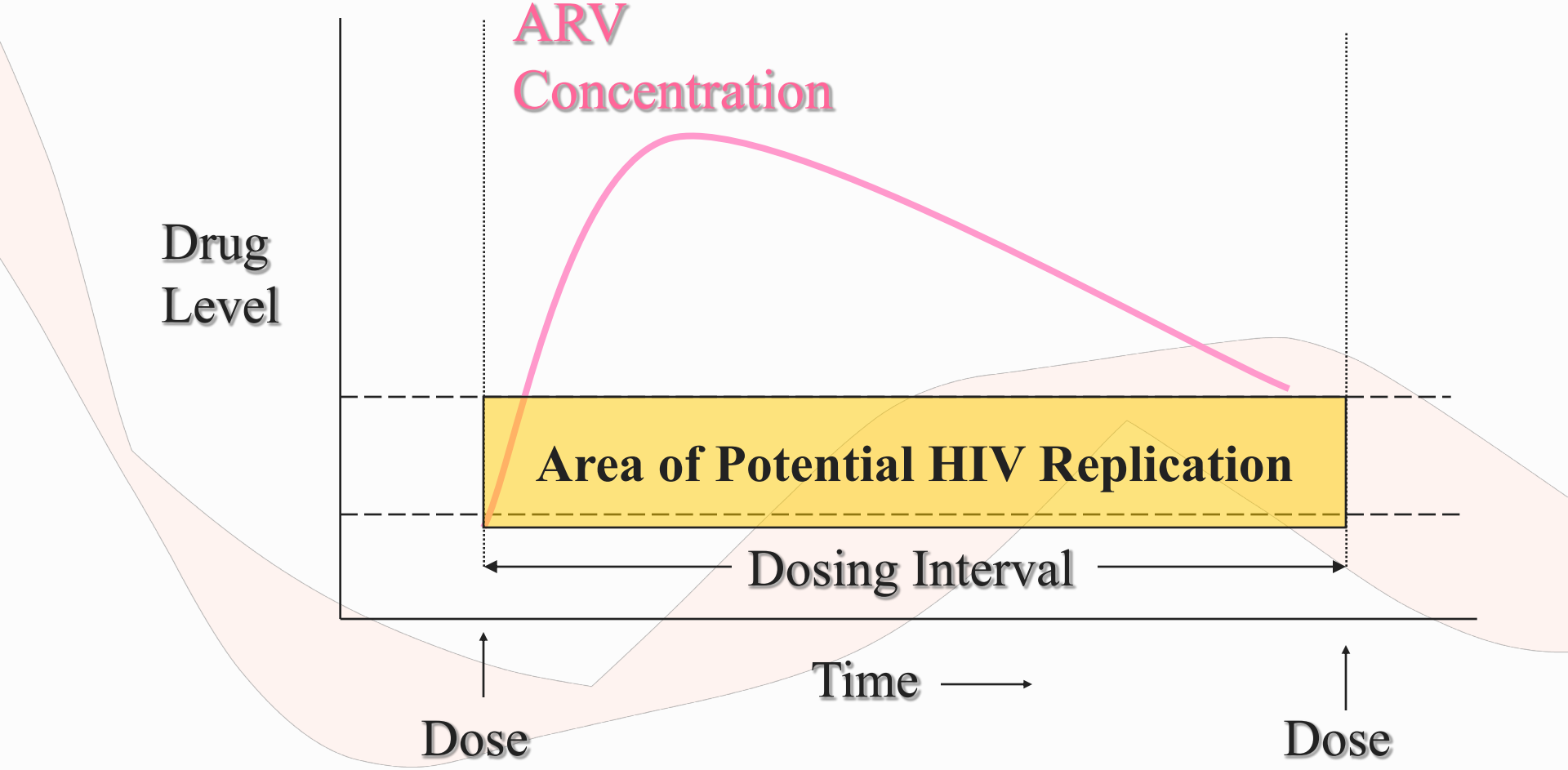
- Drug resistance is the reduction of the sensitivity of the virus to a particular drug
- Resistance results from genetic mutation of viral enzymes & proteins leading to changes in the way drugs interact with them
- Mechanisms for ARV drug resistance
  - Transmitted resistance: Infected with a resistant strain of HIV at baseline
  - Spontaneous resistance: HIV develops mutations easily and becomes resistant
    - HIV usually becomes resistant when not totally controlled by ART
- Once HIV develops resistance to a medication it will stay resistant forever

When to Obtain Resistance Testing

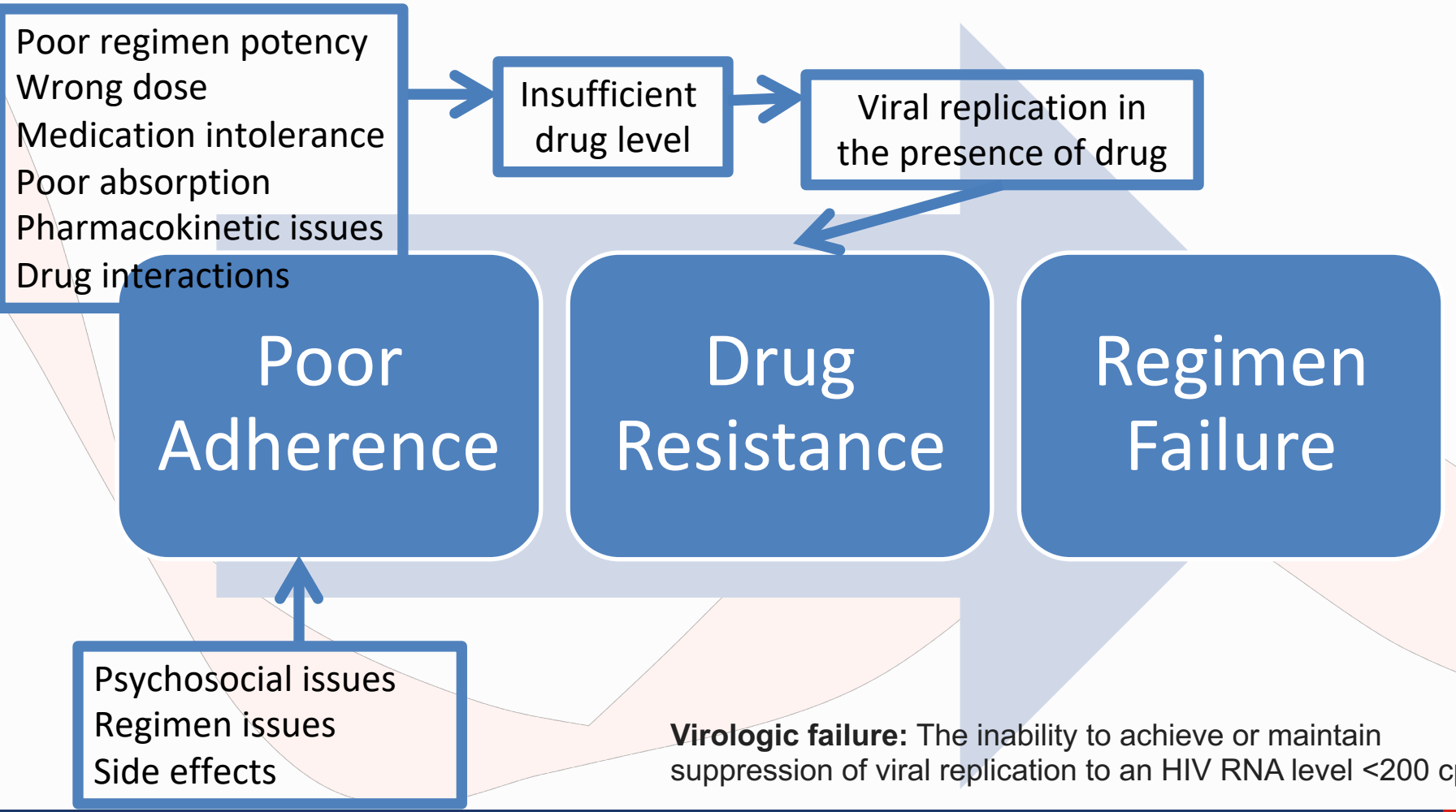
- Obtain genotype prior to initiation of therapy to determine if resistant virus transmitted

- Obtain resistance test if virologic failure during ART or suboptimal suppression of viral load after start of therapy to determine if spontaneous resistance occurred

Poor Adherence May Contribute to Drug Resistance



How Drug Resistance and Regimen Failure Occur



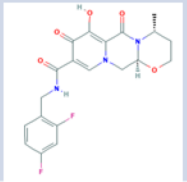
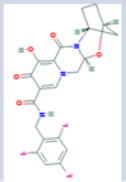
Virologic failure: The inability to achieve or maintain suppression of viral replication to an HIV RNA level <200 cpy/mL

Cross Resistance

- ARV classes work at different stages of viral replication and different mutations confer resistance to each class
- High levels of cross resistance within drug classes
  - Cross resistance: Drug resistance within the same class “crosses over” from one drug to another
- No cross resistance between drug classes

Genetic Barrier to Resistance

- Some ARVs require only one mutation to cause resistance (low genetic barrier) while others require multiple drug resistance mutations (high genetic barrier)
- Genetic barrier: Number of HIV mutations required for development of resistance to each ARV

Low Genetic Barrier	High Genetic Barrier
•Some NRTIs: Single mutation causes lamivudine or emtricitabine resistance •Most NNRTIs: Single mutation causes "cross resistance" to most drug in this class •The INSTIs EVG and RAL	•PIs: Require multiple mutations for resistance •The INSTI DTG (and maybe BIC?)  

Selective Pressure

- If non-effective regimen continued then resistant virus multiplies fastest
  - If ART stopped → no selective pressure → resistant virus will not replicate (archived) → wild-type virus multiplies fastest
- Selective pressure: Pressure exerted by a drug that results in a frequency increase in certain mutations in the next generation
- Resistance testing may not detect small concentrations of archived resistant strains

Archived Mutations

- Archived mutations: Undetected mutations that persist after discontinuation of medication and reappear as a result of selective pressure when medication resumed
- Archived mutations always threaten new regimen efficacy
  - Resistance testing may not identify drug-resistant mutations from past therapies for treatment-experienced patients
  - Resolution: Review patient's ARV history and *all* prior resistance tests
  - A single genotype is a snapshot, but we need the whole photo album!

vs.

Role of Resistance Testing in Treatment Failure

- Resistance tests
  - Indicated if regimen failure due to non-adherence vs. resistance (*i.e.,* no drug resistance mutations detected may signify adherence issue)
  - Use to guide next therapy decisions
- Provisos of resistance testing
  - Requires sufficient amount of virus (viral load >500-1,000 copies/mL; if viral load <500 consider archive genotype)
  - Detects resistance only if present in >10-20% of total virus population
  - Perform while patient is taking the failing regimen

Types of Resistance Tests

Genotype

- Detects drug resistance mutations in HIV genes
- Results in 1-2 weeks
- Cost is approximately 33%-50% of a phenotype
- May need separate test for INSTIs
- Expert interpretation required
- When Indicated: At entry into care and in treatment failure to guide therapy decisions

Phenotype

- Measures ability of virus to grow in different ARV concentrations
- Results in 2-3 weeks
- More familiar reporting results
- When Indicated: Add to a genotype assay in those with known or suspected complex drug resistance patterns

Genotype Resistance Test

- Technique: Genetic code of patient's virus compared to wild-type virus
- Reported as list of mutations identified in the virus sample associated with resistance
  - Mutations in HIV reverse transcriptase, protease, integrase, or envelope genes
- Includes interpretation indicating drug resistance likely correlated with mutations
- Limitation: Complex mutation pattern of multidrug resistant virus difficult to interpret

Phenotype Resistance Test

- Technique: Patient's virus grown in the presence of different concentrations of ARV drugs and compared to wild-type virus
- Reported as susceptibility to each ARV drug
- Combines interaction of all mutations; more useful for complex mutation patterns
- Genotype and phenotype tests have complementary properties and may use both tests together in some circumstances (*e.g.*, highly treatment experienced patients)

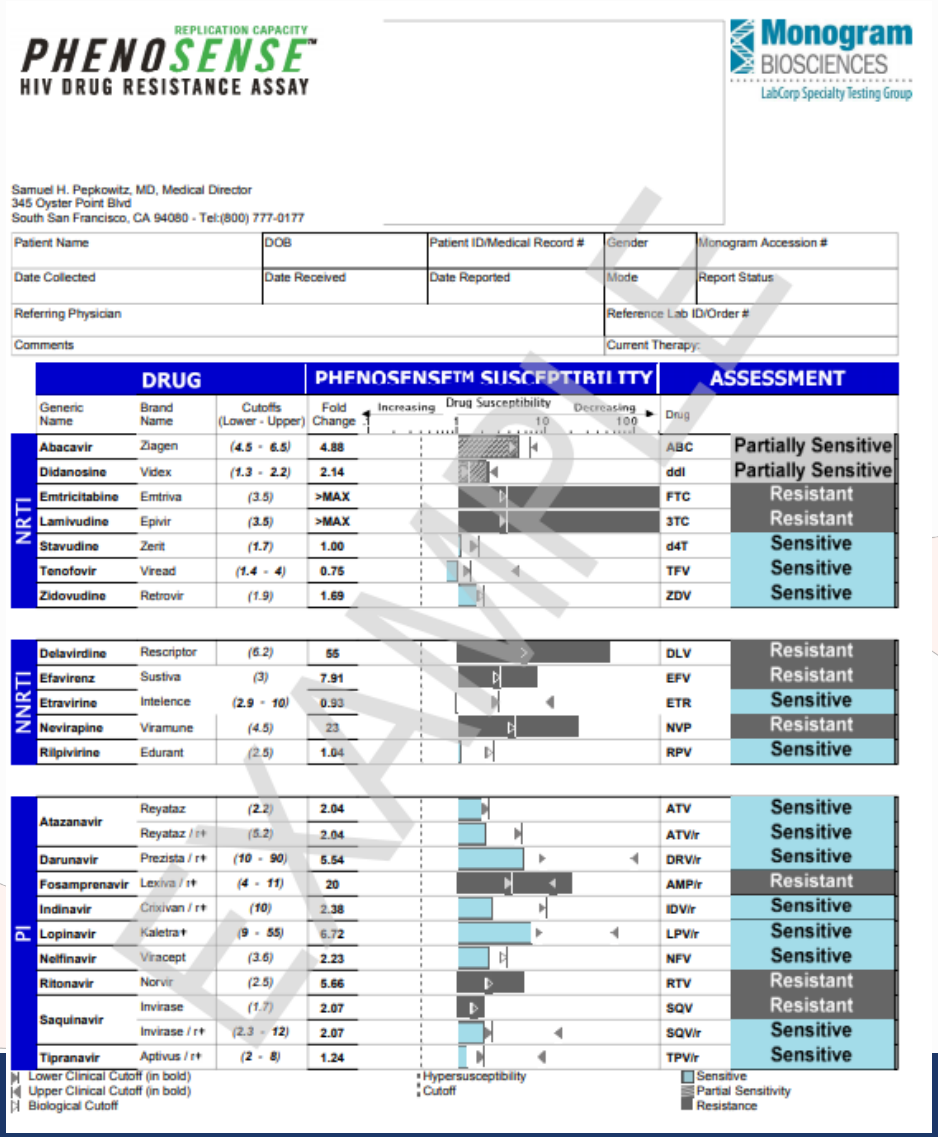
AETC AIDS Education & Training Center Program

How to Interpret a Phenotype

Interpreting HIV Phenotype

- Phenotype refers to virus growth characteristics
- Results expressed as fold-change (FC) in susceptibility compared to wild-type virus
  - Fold change: Ratio of IC_{50} of patient's virus (for specific ARV) compared with reference wild-type strain
- Interpretation of drug activity usually presented in context of clinical cutoffs
  - Clinical cutoffs: Based on patient virologic response in clinical trials
  - If FC is below the lower clinical cutoff, drug is fully active; if FC is above upper clinical cutoff, drug has no activity (if FC between lower and upper clinical cutoffs, the agent likely has partial activity)

Let's Look at a Sample Phenotype



REPLICATION CAPACITY
PHENOSENSE™
HIV DRUG RESISTANCE ASSAY

Monogram BIOSCIENCES
LabCorp Specialty Testing Group

Samuel H. Pepkowitz, MD, Medical Director
345 Oyster Point Blvd
South San Francisco, CA 94080 - Tel:(800) 777-0177

Patient Name	DOB	Patient ID/Medical Record #	Gender	Monogram Accession #
Date Collected	Date Received	Date Reported	Mode	Report Status
Referring Physician			Reference Lab ID/Order #	
Comments			Current Therapy:	

	DRUG			PHENOSENSE™ SUSCEPTIBILITY	ASSESSMENT	
	Generic Name	Brand Name	Cutoffs (Lower - Upper)	Fold Change	Drug	
NRTI	Abacavir	Ziagen	(4.5 - 6.5)	4.88	ABC	Partially Sensitive
	Didanosine	Videx	(1.3 - 2.2)	2.14	ddI	Partially Sensitive
	Emtricitabine	Emtriva	(3.5)	>MAX	FTC	Resistant
	Lamivudine	Epivir	(3.5)	>MAX	3TC	Resistant
	Stavudine	Zerit	(1.7)	1.00	d4T	Sensitive
	Tenofovir	Viread	(1.4 - 4)	0.75	TFV	Sensitive
	Zidovudine	Retrovir	(1.9)	1.69	ZDV	Sensitive
NNRTI	Delavirdine	Rescriptor	(6.2)	55	DLV	Resistant
	Efavirenz	Sustiva	(3)	7.91	EFV	Resistant
	Etravirine	Intelence	(2.9 - 10)	0.93	ETR	Sensitive
	Nevirapine	Viramune	(4.5)	23	NVP	Resistant
	Rilpivirine	Edurant	(2.5)	1.04	RPV	Sensitive
PI	Atazanavir	Reyataz	(2.2)	2.04	ATV	Sensitive
		Reyataz / r†	(5.2)	2.04	ATV/r	Sensitive
	Darunavir	Prezista / r†	(10 - 90)	5.54	DRV/r	Sensitive
	Fosamprenavir	Lexiva / r†	(4 - 11)	20	AMP/r	Resistant
	Indinavir	Crixivan / r†	(10)	2.38	IDV/r	Sensitive
	Lopinavir	Kaletra†	(9 - 55)	6.72	LPV/r	Sensitive
	Nelfinavir	Viracept	(3.5)	2.23	NFV	Sensitive
	Ritonavir	Norvir	(2.5)	5.66	RTV	Resistant
	Saquinavir	Invirase	(1.7)	2.07	SQV	Resistant
		Invirase / r†	(2.3 - 12)	2.07	SQV/r	Sensitive
	Tipranavir	Aptivus / r†	(2 - 8)	1.24	TPV/r	Sensitive

Drug Susceptibility: Increasing ← 1 — 10 — 100 → Decreasing

Lower Clinical Cutoff (in bold)
Upper Clinical Cutoff (in bold)
Biological Cutoff
Hypersusceptibility Cutoff
Sensitive
Partial Sensitivity
Resistance

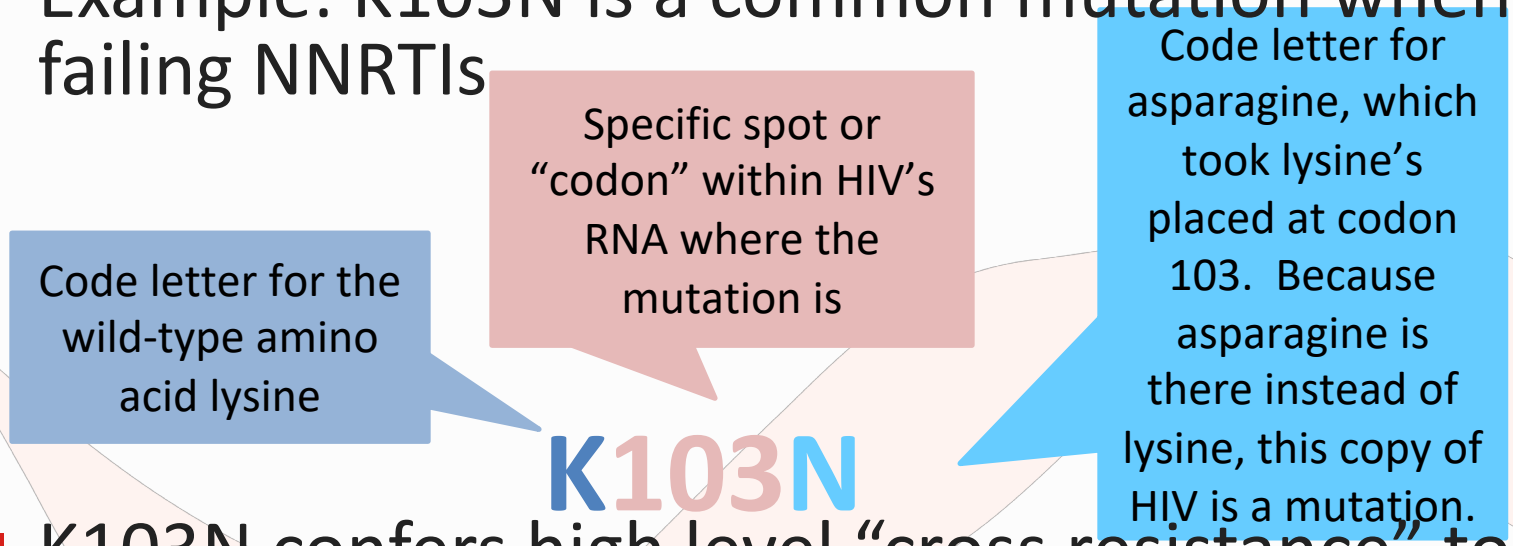
EXAMPLE

AETC AIDS Education & Training Center Program

How to Interpret a Genotype

Shorthand System Used for Naming HIV Genotype Mutations

- Shorthand system used for naming HIV mutations on genotypes
- Example: K103N is a common mutation when failing NNRTIs



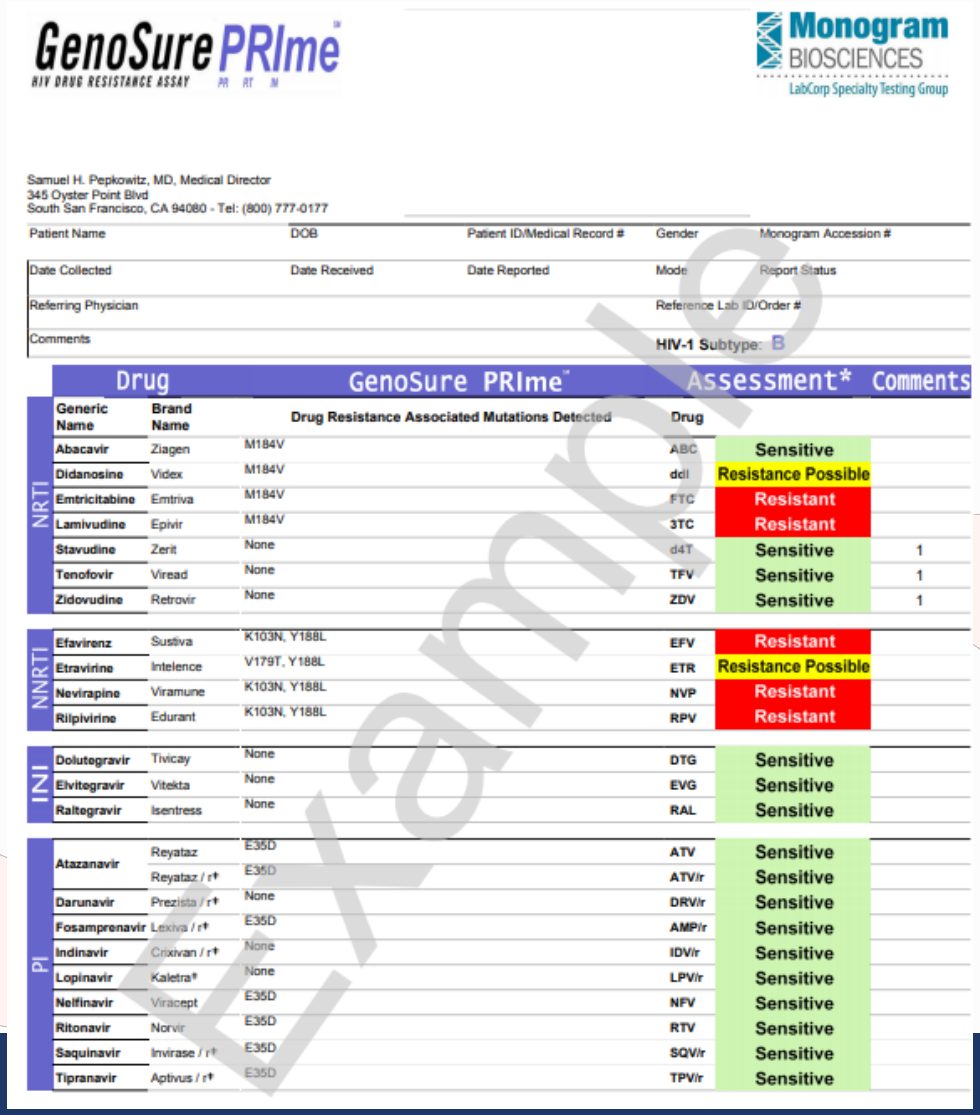
- K103N confers high level "cross resistance" to the NNRTIs efavirenz & nevirapine

Amino acid abbreviations: A alanine, C cysteine, D aspartate, E glutamate, F phenylalanine, G glycine, H histidine, I isoleucine, K lysine, L leucine, M methionine, N asparagine, P proline, Q glutamine, R arginine, S serine, T threonine, V valine, W tryptophan, Y tyrosine

Shorthand System Used for Naming HIV Genotype Mutations

- Mixture: More than one amino acid at a position
  - Components written after the position
  - Often separated by a slash
  - e.g., K103K/N denotes sequence has mixture of wild-type lysine (K) and mutant asparagine (N) at position 103

Let's Look at a Sample Genotype



GenoSure PRIme
HIV DRUG RESISTANCE ASSAY PR RT IN

Monogram BIOSCIENCES
LabCorp Specialty Testing Group

Samuel H. Pepkowitz, MD, Medical Director
345 Oyster Point Blvd
South San Francisco, CA 94080 - Tel: (800) 777-0177

Patient Name	DOB	Patient ID/Medical Record #	Gender	Monogram Accession #
Date Collected	Date Received	Date Reported	Mode	Report Status
Referring Physician			Reference Lab ID/Order #	
Comments			HIV-1 Subtype: B	

	Drug		GenoSure PRIme		Assessment*	Comments
	Generic Name	Brand Name	Drug Resistance Associated Mutations Detected	Drug		
NRTI	Abacavir	Ziagen	M184V	ABC	Sensitive	
	Didanosine	Videx	M184V	ddI	Resistance Possible	
	Emtricitabine	Emtriva	M184V	FTC	Resistant	
	Lamivudine	Epivir	M184V	3TC	Resistant	
	Stavudine	Zerit	None	d4T	Sensitive	1
	Tenofovir	Viread	None	TFV	Sensitive	1
	Zidovudine	Retrovir	None	ZDV	Sensitive	1
NNRTI	Efavirenz	Sustiva	K103N, Y188L	EFV	Resistant	
	Etravirine	Intelence	V179T, Y188L	ETR	Resistance Possible	
	Nevirapine	Viramune	K103N, Y188L	NVP	Resistant	
	Rilpivirine	Edurant	K103N, Y188L	RPV	Resistant	
INI	Dolutegravir	Tivicay	None	DTG	Sensitive	
	Elvitegravir	Vitekta	None	EVG	Sensitive	
	Raltegravir	Isentress	None	RAL	Sensitive	
PI	Atazanavir	Reyataz	E35D	ATV	Sensitive	
		Reyataz / r†	E35D	ATV/r	Sensitive	
	Darunavir	Prezista / r†	None	DRV/r	Sensitive	
	Fosamprenavir	Lexiva / r†	E35D	AMP/r	Sensitive	
	Indinavir	Crixivan / r†	None	IDV/r	Sensitive	
	Lopinavir	Kaletra†	None	LPV/r	Sensitive	
	Nelfinavir	Viracept	E35D	NFV	Sensitive	
	Ritonavir	Norvir	E35D	RTV	Sensitive	
	Saquinavir	Invirase / r†	E35D	SQV/r	Sensitive	
	Tipranavir	Aptivus / r†	E35D	TPV/r	Sensitive	

Example

Notable NRTI Mutations

- M184V
  - Confers high level resistance to lamivudine and emtricitabine
  - Some resistance to didanosine and abacavir
  - Restores some activity to zidovudine, stavudine, and tenofovir
  - Diminishes viral replication capacity
- K65R
  - Broad resistance to all NRTIs except zidovudine
  - Increases susceptibility to zidovudine
- Thymidine analog mutations (TAMs) – 41, 67, 70, 210, 215, 219
  - Decrease susceptibility to all NRTIs
  - Additive resistance with more accumulation
  - If multiple TAMs, assume M184V

Notable NNRTI Mutations

- K103N
  - Most common NNRTI mutation
  - Confers resistance to efavirenz and nevirapine but not etravirine or rilpivirine
- K101P, Y181C
  - Resistance to all NNRTIs

Etravirine: Second Generation NNRTI

- Active against some NNRTI resistant viruses
  - K103N does not effect etravirine
- Resistance predicted using a mutation score
- Total score corresponds to chance of virologic suppression
  - 0-2: Highest response (74%)
  - 2.5-3.5: Intermediate response (52%)
  - ≥ 4: Reduced response (38%)

Tibotec Weighted Mutation Score	**1**	**1.5**	**2.5**	**3**
Mutation in Reverse Transcriptase	90I, 179D, 101E, 101H, 98G, 179T, 190A	138A, 106I, 190S, 179F	101P, 100I, 181C, 230L	181I/V

Vingerhoets J, et al. AIDS 2010;24:503-514.

Estimating Etravirine Susceptibility Using a Genotype

NNRTI	**Efavirenz**	Sustiva	K103N, Y188L	EFV	Resistant
	Etravirine	Intelence	V179T, Y188L	ETR	Resistance Possible
	Nevirapine	Viramune	K103N, Y188L	NVP	Resistant
	Rilpivirine	Edurant	K103N, Y188L	RPV	Resistant

- Genotype shows non-nuke mutations K103N, V179T and Y188L and says “resistance possible” for etravirine
- K103N has a weighted mutation score of 0
- V179T has a weighted mutation score of 1
- Y188L has a weighted mutation score of 0
- Total weighted mutation score 0+1+0 = 1
- Total weighted mutation score range 0-2: Highest response (74% chance of virologic suppression) → Use etravirine!
- Best way to determine etravirine susceptibility: phenotype

Notable PI Mutations

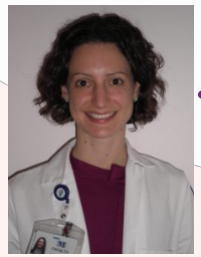
- Signature mutations for non-boosted PIs
  - D30N: nelfinavir; no cross resistance
  - I50L: unboosted ATV
  - I50V: fosamprenavir; some cross resistance to lopinavir
  - G48V: saquinavir; no cross-resistance
  - L90M: often follows unboosted PIs; causes cross resistance
- Boosted PIs (LPV/r, FPV/r, SQV/r, ATV/r, DRV/r) usually do not select for resistance if used as first PI
  - However, if first-line boosted PI failure is not addressed promptly, secondary resistance mutations can accumulate; ideally obtain phenotype to evaluate

Darunavir (DRV) Resistance Affects Dose

- PI for both treatment-naïve & treatment-experienced patients
  - Dose 800mg once daily for treatment-naïve patients
  - Dose 800 mg once daily for treatment-experienced patients if there are zero DRV resistance mutations
  - Dose 600 mg twice daily if there are ≥ 1 DRV mutation(s)
- Darunavir resistance mutations: V11I, V32I, I33F, I47V, I50V, I54L/M, T74P, L76V, I84V, L89V

Notable INSTI Mutations

- Raltegravir and elvitegravir are cross-resistant
  - Q148H/K/R or N155H are major mutations affecting both RAL and EVG causing high level resistance
- Dolutegravir requires several mutations to confer resistance
  - High level resistance seen with Q148H/R/K plus 2 or more additional INSTI mutations



Remember, INSTI resistance is often not evaluated on a standard genotype. You may have to order a separate INSTI resistance test!

Dolutegravir (DTG) Resistance Affects Dose

Adult Population	Recommended Dose
Treatment-naïve or treatment-experienced INSTI naïve	50 mg once daily
INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance	50 mg twice daily
Treatment-naïve or treatment-experienced INSTI naïve when coadministered with certain UGT1A or CYP3A inducers (e.g., carbamazepine, rifampin, efavirenz)	50 mg twice daily

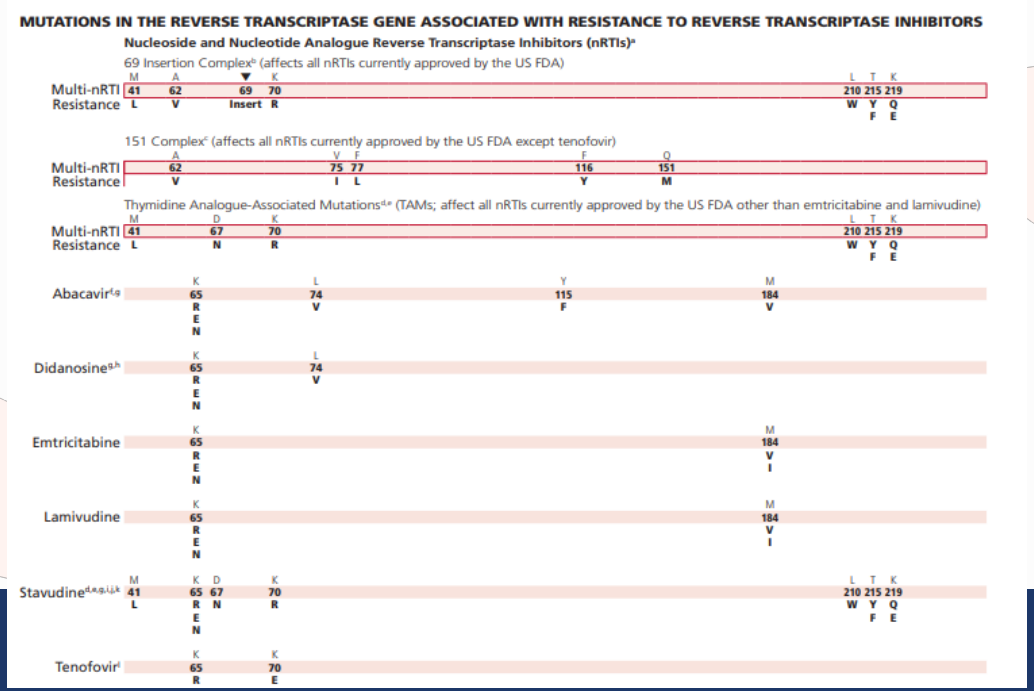
Tivicay package insert. Viiv Healthcare. www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Tivicay/pdf/TIVICAY-PI-PIL.PDF/

Helpful Resources on HIV Resistance

International Antiviral Society-USA

[www.iasusa.org/content/drug-resistance-mutations-in-HIV]

- ARV resistance mutations published yearly



MUTATIONS IN THE REVERSE TRANSCRIPTASE GENE ASSOCIATED WITH RESISTANCE TO REVERSE TRANSCRIPTASE INHIBITORS

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors (nRTIs)[a]

69 Insertion Complex[b] (affects all nRTIs currently approved by the US FDA)

	M	A	▼	K							L	T	K
Multi-nRTI Resistance	41 L	62 V	69 Insert	70 R							210 W	215 Y F	219 Q E

151 Complex[c] (affects all nRTIs currently approved by the US FDA except tenofovir)

	A		V	F			F	Q					
Multi-nRTI Resistance	62 V		75 I	77 L			116 Y	151 M					

Thymidine Analogue-Associated Mutations[d,e] (TAMs; affect all nRTIs currently approved by the US FDA other than emtricitabine and lamivudine)

	M	D	K								L	T	K
Multi-nRTI Resistance	41 L	67 N	70 R								210 W	215 Y F	219 Q E

	K	L	Y	M
Abacavir[f,g]	65 R E N	74 V	115 F	184 V
Didanosine[g,h]	65 R E N	74 V		
Emtricitabine	65 R E N			184 V I
Lamivudine	65 R E N			184 V I

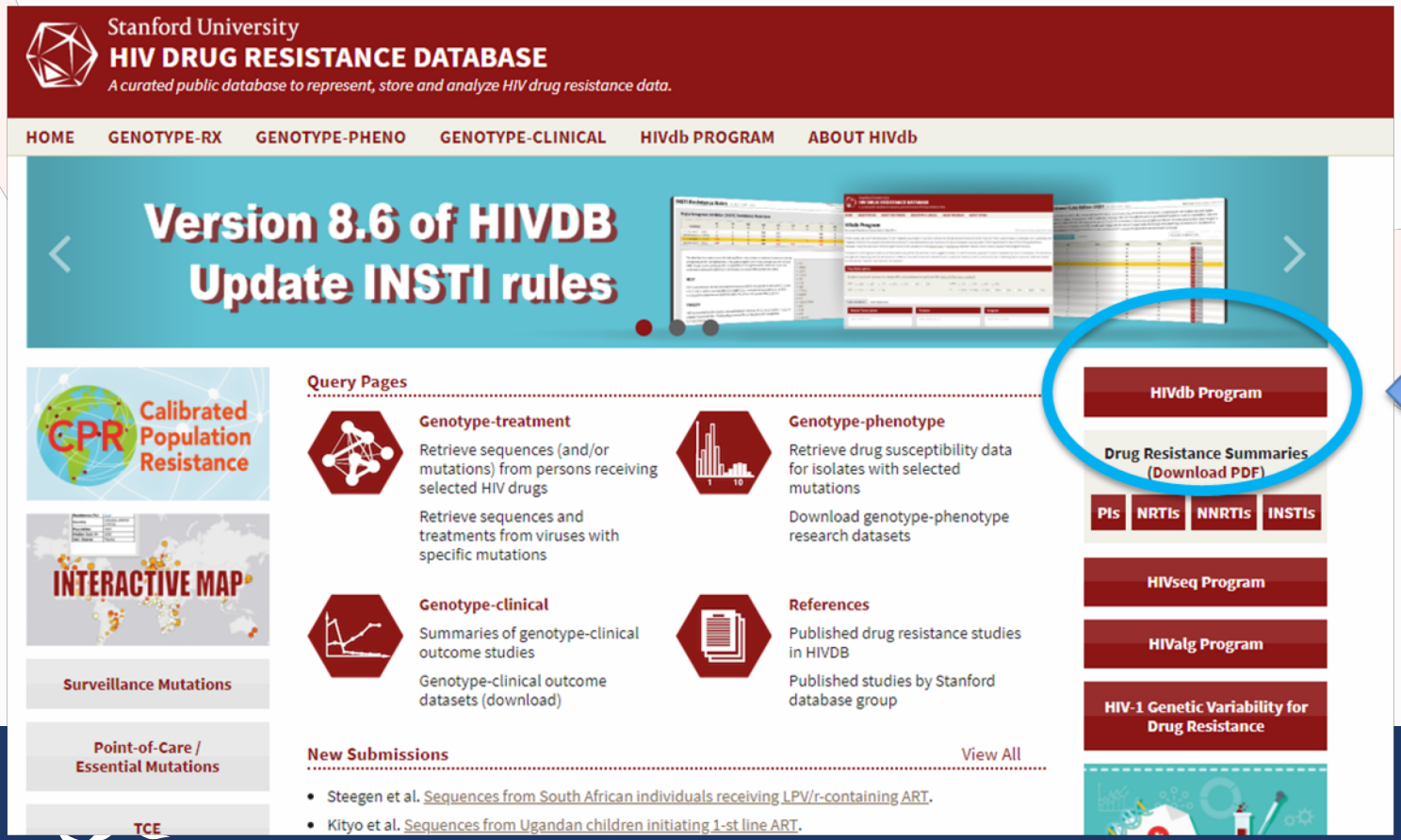
	M	K	D	K							L	T	K
Stavudine[d,e,g,i,j,k]	41 L	65 R E N	67 N	70 R							210 W	215 Y F	219 Q E

	K	K
Tenofovir[l]	65 R	70 E

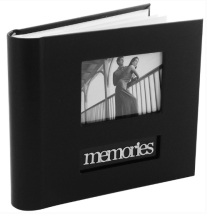
Helpful Resources on HIV Resistance

Stanford University HIV Drug Resistance Database

- [hivdb.stanford.edu] *Click on HIVdb Program



Stanford Database: Create a Master Genotype



Input mutations | Input sequences

Reverse Transcriptase

Input mutation(s)

Select mutations:

40 ---	41 ---	44 ---	62 ---
65 ---	67 ---	68 ---	69 ---
70 ---	74 ---	75 ---	77 ---
90 ---	98 ---	100 ---	101 ---
103 ---	106 ---	108 ---	115 ---
116 ---	118 ---	138 ---	151 ---
179 ---	181 ---	184 ---	
190 ---	210 ---		
221 ---	225 ---	230 ---	
236 ---	238 ---	318 ---	348 ---

184 dropdown: I, V, *

Protease

Input mutation(s)

Select mutations:

10 ---	11 ---	13 ---	20 ---
23 ---	24 ---	30 ---	32 ---
33 ---	35 ---	36 ---	43 ---
46 ---	47 ---	48 ---	50 ---
53 ---	54 ---	58 ---	63 ---
71 ---	73 ---	74 ---	76 ---
77 ---	82 ---	83 ---	84 ---
85 ---	88 ---	89 ---	90 ---
93 ---			

Integrase

Input mutation(s)

Select mutations:

51 ---	66 ---	74 ---	92 ---
95 ---	97 ---	114 ---	118 ---
121 ---	128 ---	138 ---	140 ---
143 ---	145 ---	146 ---	147 ---
148 ---	151 ---	153 ---	155 ---
157 ---	163 ---	230 ---	263 ---

Reset | Analyze

Stanford Database:
Predict Resistance With Master Genotype

Drug Resistance Interpretation: RT

NRTI Resistance Mutations:	**K65R, M184V**
NNRTI Resistance Mutations:	**K103N, Y181C**
Other Mutations:	None

Nucleoside Reverse Transcriptase Inhibitors	
abacavir (ABC)	High-Level Resistance
zidovudine (AZT)	Susceptible
emtricitabine (FTC)	High-Level Resistance
lamivudine (3TC)	High-Level Resistance
tenofovir (TDF)	Intermediate Resistance

Non-nucleoside Reverse Transcriptase Inhibitors	
efavirenz (EFV)	High-Level Resistance
etravirine (ETR)	Intermediate Resistance
nevirapine (NVP)	High-Level Resistance
rilpivirine (RPV)	Intermediate Resistance

RT Comments

NRTI

- **M184V/I** cause high-level in vitro resistance to 3TC and FTC and low-level resistance to ddI and ABC. However, **M184V/I** are not contraindications to continued treatment with 3TC or FTC because they increase susceptibility to AZT, TDF and d4T and are associated with clinically significant reductions in HIV-1 replication.
- **K65R** causes intermediate/high-level resistance to TDF, ddI, ABC and d4T and low/intermediate resistance to 3TC and FTC. **K65R** increases susceptibility to AZT.

NNRTI

- **K103N** is a non-polymorphic mutation that causes high-level resistance to NVP and EFV.
- **Y181C** is a non-polymorphic mutation selected in patients receiving each of the NNRTIs. It causes high-level reduction in NVP susceptibility, intermediate-level reduction in RPV and ETR susceptibility, and low-level reduction in EFV susceptibility. **Y181C** has a high weight in the Tibotec ETR genotypic susceptibility score.

Summary

- Initial ART = 2 NRTIs + INSTI or PI or NNRTI

  (2 scoops of rice + 1 main entrée)
- ART presents high potential for drug interactions due to the way the medications are absorbed and metabolized
- Resistance testing (genotype and phenotype) must be interpreted in context and may require expert advice

AETC AIDS Education & Training Center Program

Antiretroviral (ART) Selection and Resistance

Elizabeth Sherman, PharmD, AAHIVP
Faculty, South Florida - Southeast AETC
Pharmacist, Memorial Physician Group, Division of Infectious Disease
Associate Professor, Nova Southeastern University
esherman@nova.edu

AETC AIDS Education & Training Center Program

Cases

Courtesy of the National HIV Curriculum https://www.hiv.uw.edu/

Elizabeth Sherman, PharmD, AAHIVP

Faculty, South Florida - Southeast AETC

Pharmacist, Memorial Physician Group, Division of Infectious Disease

Associate Professor, Nova Southeastern University

esherman@nova.edu

Case Study 1

A 22-year-old man presents for follow-up after recent diagnosis of HIV. He has an initial CD4 count of 390 cells/mm^3 and HIV RNA level is 46,000 copies/mL; a baseline genotype resistance assay shows no evidence of antiretroviral resistance. He is motivated to start antiretroviral therapy and states that he can take medications without issue.

Case Study 1

According to Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV, which one of the following best describes the recommendations for starting antiretroviral therapy in treatment-naïve persons with HIV infection?

A. Antiretroviral therapy is recommended for all persons with HIV infection
B. Antiretroviral therapy is recommended only for persons with HIV who have a documented decline in CD4 count of at least 100 cells/mm^3
C. Antiretroviral therapy is recommended only for persons with HIV who have a CD4 count less than 200 cells/mm^3
D. Antiretroviral therapy is recommended only for persons with HIV who have an HIV RNA level greater than 30,000 copies/mL

Case Study 2

A 34-year-old woman presents to clinic to discuss starting antiretroviral therapy. She was recently diagnosed with HIV infection and her initial CD4 count was 550 cells/mm^3 and HIV RNA level was 88,000 copies/mL. A repeat CD4 count 4 weeks later is 438 cells/mm^3. Baseline genotype resistance assay shows no mutations that would confer resistance. She is motivated to start therapy and feels she can take medications every day without missing any doses.

Case Study 2

According to the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV, which one of the following is considered a recommended initial antiretroviral regimen for most people with HIV?

A. Rilpivirine-tenofovir AF-emtricitabine
B. Darunavir-cobicistat plus abacavir-lamivudine
C. Bictegravir plus zidovudine-lamivudine
D. Dolutegravir plus tenofovir AF-emtricitabine

Case Study 3

A 45-year-old man with HIV infection has been stable for the last 5 years on an antiretroviral regimen of darunavir boosted with ritonavir and tenofovir DF-emtricitabine. Despite changing to a healthier diet and increasing his exercise, lipid values remain elevated: total cholesterol 268 mg/dL, low density lipoprotein (LDL) 198 mg/dL, high density lipoprotein (HDL) 35 mg/dL, and triglycerides 220 mg/dL. He has a strong family history of cardiovascular disease and his father had a myocardial infarction at age 52. The patient does not want to consider modifying his antiretroviral regimen, but agrees to start lipid-lowering therapy.

Case Study 3

Which one of the following HMG-CoA reductase inhibitors ("statins") is contraindicated for use in this patient?

A. Pravastatin

B. Atorvastatin

C. Simvastatin

D. Rosuvastatin

Case Study 4

A 34-year-old man was recently diagnosed with HIV infection. His baseline laboratory studies showed an HIV RNA level of 45,360 copies/mL, CD4 count 425 cells/mm^3, and HIV genotype with no mutations. An HLA-B*5701 test is performed and is negative. His other medical problems include hypertension, gastroesophageal reflux, and depression. He currently takes lisinopril 10 mg once daily, omeprazole 40 mg once daily, and escitalopram 10 mg once daily.

Case Study 4

Considering potential drug-drug interactions, which one of the following antiretroviral regimens would be most appropriate for this patient?

A. Rilpivirine-tenofovir DF-emtricitabine

B. Rilpivirine and abacavir-lamivudine

C. Atazanavir, ritonavir, and tenofovir DF-emtricitabine

D. Darunavir-cobicistat and tenofovir alafenamide-emtricitabine

Case Study 5

A 35-year-old man who recently tested positive for HIV presents to clinic. Results from baseline laboratory studies include a CD4 count of 190 cells/mm^3, HIV RNA level of 346,000 copies/mL, and an HIV genotype drug-resistance assay that shows a K103N mutation. He has never taken antiretroviral medications.

Case Study 5

What does the notation K103N describe?

A. The strain analyzed (N) has a 103-fold higher relative resistance when compared with wild-type HIV (K)
B. The wild-type amino acid (K) located at amino acid position 103 has been replaced by the mutant amino acid (N)
C. The mutant amino acid (K) has reverted back to the wild-type amino acid (N) at amino acid position 103
D. The mutation threshold number (N) would likely impact antiretroviral therapy at levels of HIV RNA that exceed 103,000 (103K)

Case Study 6

A 53-year-old man with HIV infection returns for follow-up after being out of medical care for several years. In the past, he was treated with a brief course of high-dose zidovudine monotherapy. Subsequently, he received a regimen of indinavir, stavudine, and didanosine, but stopped this regimen because of body shape changes. He next took a triple-nucleoside reverse transcriptase inhibitor regimen consisting of abacavir, lamivudine, and tenofovir DF. On this regimen he never achieved full suppression of HIV and a genotype showed M184V and K65R mutations.

Case Study 6

Which one of the following nucleoside reverse transcriptase inhibitors likely has the greatest activity against the K65R mutation?

A. Zidovudine

B. Stavudine

C. Abacavir

D. Lamivudine

Case Study 7

A 52-year-old man with long-standing chronic HIV infection presents to clinic to establish care after recently moving to the area. He has taken multiple different antiretroviral regimens in the past. He brings records that show an increasing trend in the last three HIV RNA values: undetectable, 1,110 copies/mL, and 3,460 copies/mL. A past genotypic drug resistance assay shows M41L, D67N, K103N, and M184V mutations. His current antiretroviral medications are darunavir, ritonavir, etravirine, and tenofovir alafenamide-emtricitabine. He admits that he has been missing doses of his medications recently. A repeat HIV RNA level and an HIV genotypic resistance test is ordered.

Case Study 7

Which one of the following is TRUE regarding resistance to etravirine?

A. The K103N mutation indicates high-level resistance to etravirine
B. Y181C and G190A confer hypersusceptibility to etravirine
C. Use of etravirine increases the likelihood of developing darunavir mutations
D. An etravirine weighted score above 4, which is based on cumulative mutations, indicates likely resistance to etravirine

Case Study 8

A 45-year-old woman with HIV infection presents to clinic for follow-up. She contracted HIV many years ago and initially received zidovudine monotherapy and later nevirapine plus zidovudine-lamivudine. Subsequently, she had nevirapine changed to nelfinavir, and did well on that regimen for several years before developing virologic breakthrough because of problems with adherence. She is now ready to restart therapy. Her genotypic resistance assay showed the reverse transcriptase mutations M41L, M184V, Y181C, and the protease mutation D30N. You plan to start the patient on a regimen of darunavir, ritonavir, and tenofovir DF-emtricitabine.

Case Study 8

Which one of the following is TRUE regarding use of darunavir and ritonavir in this patient?

A. Because the patient has no darunavir-associated mutations, it is appropriate to use darunavir 800 mg once daily and ritonavir 100 mg once daily
B. Because the patient has a single major protease inhibitor mutation, once daily darunavir dosing is contraindicated
C. Because the patient has taken a protease inhibitor in the past, once daily darunavir dosing is contraindicated
D. Because the patient has thymidine analog mutations, the appropriate dose of darunavir is 600 mg twice daily with ritonavir 100 mg twice daily