AETC AIDS Education & Training Center Program Southeast

Antiretroviral Therapy Basics

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Antiretroviral Therapy Basics (It's not so scary)

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Faculty Disclosure

- I have received a research grant from Gilead Sciences
- I will not discuss any off-label use or investigational product during the program
- This slide set has been peer-reviewed to ensure that there are no conflicts of interest represented in the presentation

Learning Objectives

By the end of this module, the learner will:

- List antiretroviral treatment goals and tools to achieving these goals
- Review the process for selecting antiretroviral regimens
- Identify common mechanisms for drug interactions with antiretrovirals and discuss clinically significant drug interactions for patients with HIV

Antiretroviral Treatment Goals and Tools for Achieving These Goals

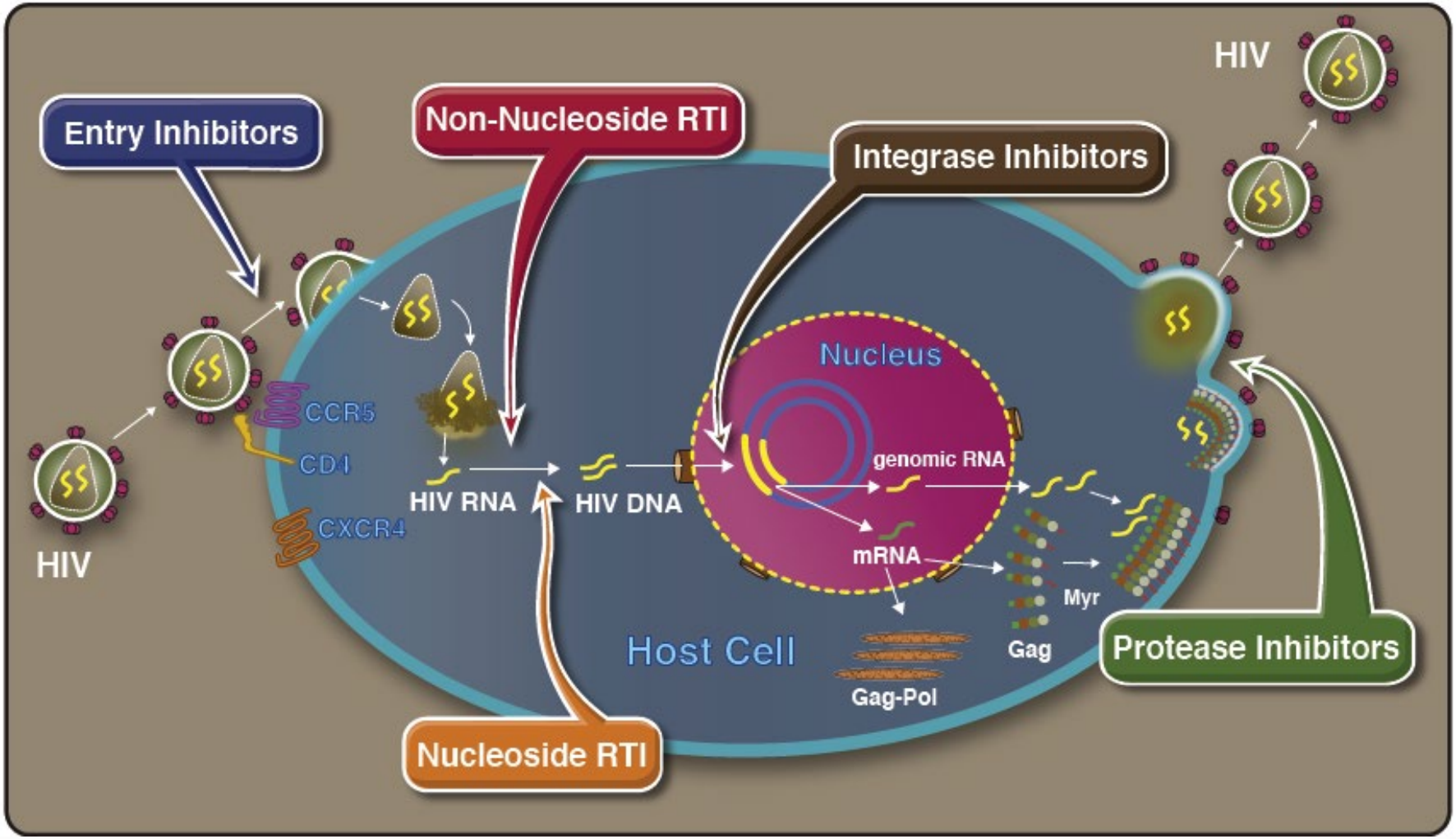
HIV Attacks CD4 T Cells

- 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



Initiation of Antiretroviral Therapy (ART)

- ART recommended for all persons with HIV to reduce morbidity and mortality and to prevent HIV transmission
- Initiate ART immediately (or as soon as possible) after HIV diagnosis
  - Increase ART uptake and linkage to care, decrease time to viral suppression, improve virologic suppression rates
- When initiating ART, educate patients on ART benefits and deploy strategies to optimize care engagement and adherence

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

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

Tools to Achieve Treatment Goals

- Performing pretreatment resistance testing
- Maximizing adherence
- Selecting individualized ART regimen

Tools to Achieve Treatment Goals

- **Performing pretreatment resistance testing**
- Maximizing adherence
- Selecting individualized ART regimen

Use of Drug Resistance Testing to Guide 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
- 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

Tools to Achieve Treatment Goals

- Performing pretreatment resistance testing
- **Maximizing adherence**
- Selecting individualized ART regimen

Importance of ART Adherence

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

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Factors Associated with Poor Adherence

- Neurocognitive impairment
- Depression and other mental illness
- Active substance abuse
- Low health literacy
- Low levels of social support
- Stressful life events
- Homelessness
- Poverty
- Busy or unstructured daily routines
- Nondisclosure of HIV serostatus
- Denial; stigma
- Inconsistent access to medications due to financial and insurance status

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Adherence Interventions

- Provide an accessible, trustworthy, nonjudgmental multidisciplinary health care team
- Find resources to assist with treatment costs to maintain uninterrupted access to both ART and appointments
- Allow flexible appointment scheduling
- Assist with transportation
- Link patients to counseling to overcome stigma, substance use, or depression
- Change ART to simplify dosing or reduce side effects

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Simplified ART 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

Single Tablet Regimens (STRs)

Year of FDA Approval	Brand Name	Generic Name	Antiretroviral Drug Classes
2006	Atripla	Efavirenz/tenofovir DF/emtricitabine	NNRTI + dual NRTI
2011	Complera	Rilpivirine/tenofovir DF/emtricitabine	NNRTI + dual NRTI
2012	Stribild	Elvitegravir/cobicistat/tenofovir DF/emtricitabine	INSTI + booster + dual NRTI
2014	Triumeq	Dolutegravir/abacavir/lamivudine	INSTI + dual NRTI
2015	Genvoya	Elvitegravir/cobicistat/tenofovir AF/emtricitabine	INSTI + booster + dual NRTI
2016	Odefsey	Rilpivirine/tenofovir AF/emtricitabine	NNRTI + dual NRTI
2017	Juluca	Dolutegravir/rilpivirine	INSTI + NNRTI
2018	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
2019	Dovato	Dolutegravir/lamivudine	INSTI + NRTI

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

Full meal of at least 400 calories (good examples and bad examples):





Tools to Achieve Treatment Goals

- Performing pretreatment resistance testing
- Maximizing adherence
- **Selecting individualized ART regimen**

Process for Selecting Antiretroviral Regimens

Process for Selecting an Initial ART Regimen

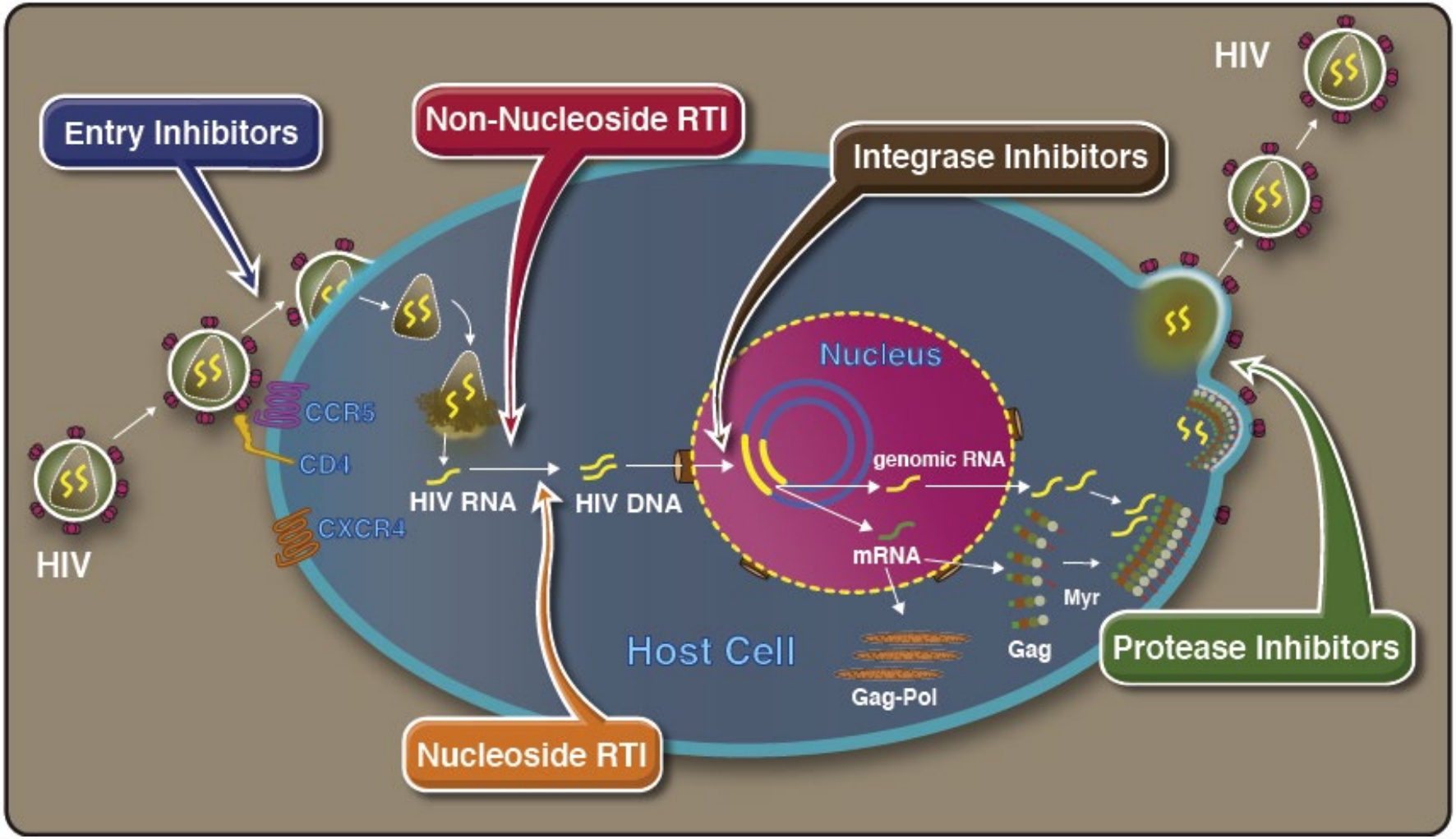
- Regimen efficacy
  - Standard therapy for HIV typically consists of 2-3+ drugs from 2+ classes (no monotherapy)
- Comorbidities
  - Potential adverse effects or drug-drug interactions
- Drug resistance
  - Presence of transmitted drug resistance or development of drug resistance on failure
- Adherence 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 & ARV Drug Classes



Antiretroviral Medications

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

- Abacavir (ABC) (Ziagen®)
- Didanosine (ddI) (Videx®)
- Emtricitabine (FTC) (Emtriva®)
- Lamivudine (3TC) (Epivir®)
- ~~Stavudine (d4T) (Zerit®)~~ *withdrawn 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®)
- Fostemsavir (Rukobia®)

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®)

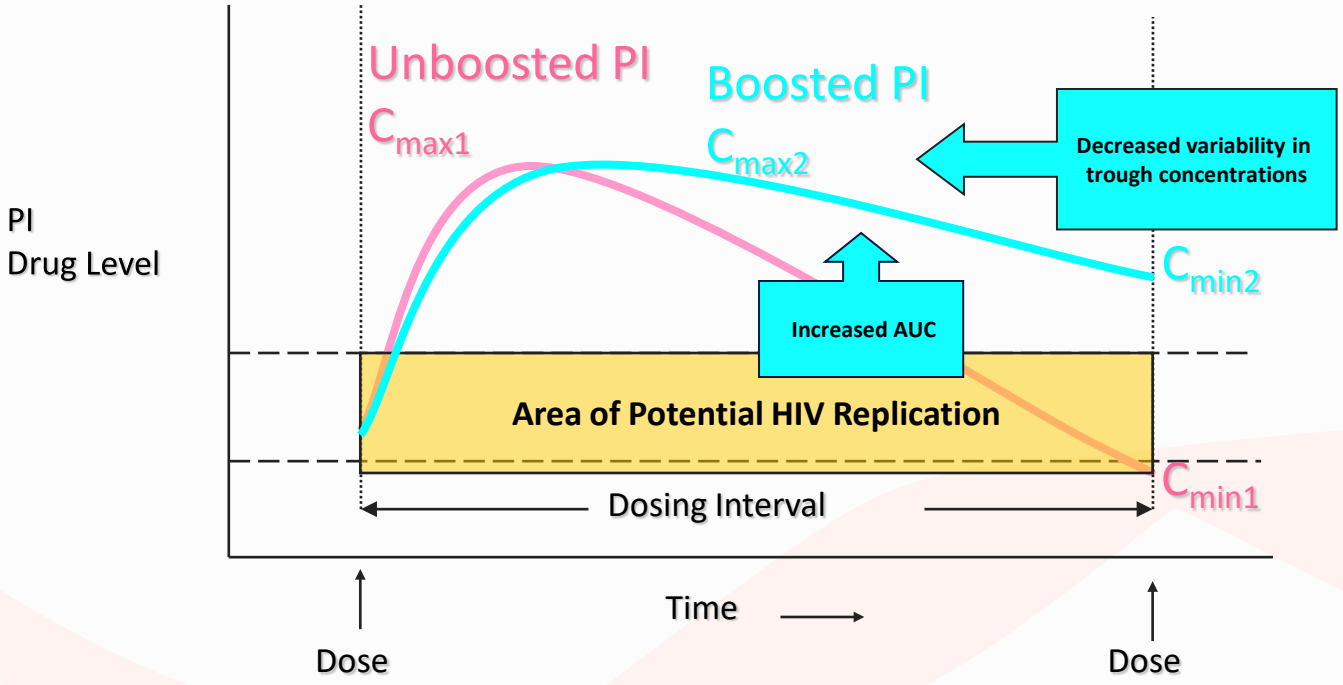
Initial HIV Management Principles

- Initiate ART with 1 of 3 types of regimens
- Most regimens should include **2 NRTIs plus 1 drug from a separate class**:
  - 1-2 NRTIs + 1 INSTI
  - 2 NRTIs + 1 PI (boosted PI) †
  - 2 NRTIs + NNRTI†

†Recommended in certain clinical situations

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

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



Recommended Initial Regimens for Most People with HIV

1-2 NRTIs		INTEGRASE INHIBITOR
Tenofovir + Emtricitabine **OR** Abacavir + Lamivudine *only w/ Dolutegravir **OR** Lamivudine *only w/ Dolutegravir	+	Raltegravir Bictegravir Dolutegravir*

TAF (tenofovir alafenamide) and TDF (tenofovir disoproxil fumarate) 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.

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Recommended Initial Regimens in Certain Clinical Situations

2 NRTIs

Tenofovir + Emtricitabine

OR

Abacavir + Lamivudine *only w/ Darunavir

+

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

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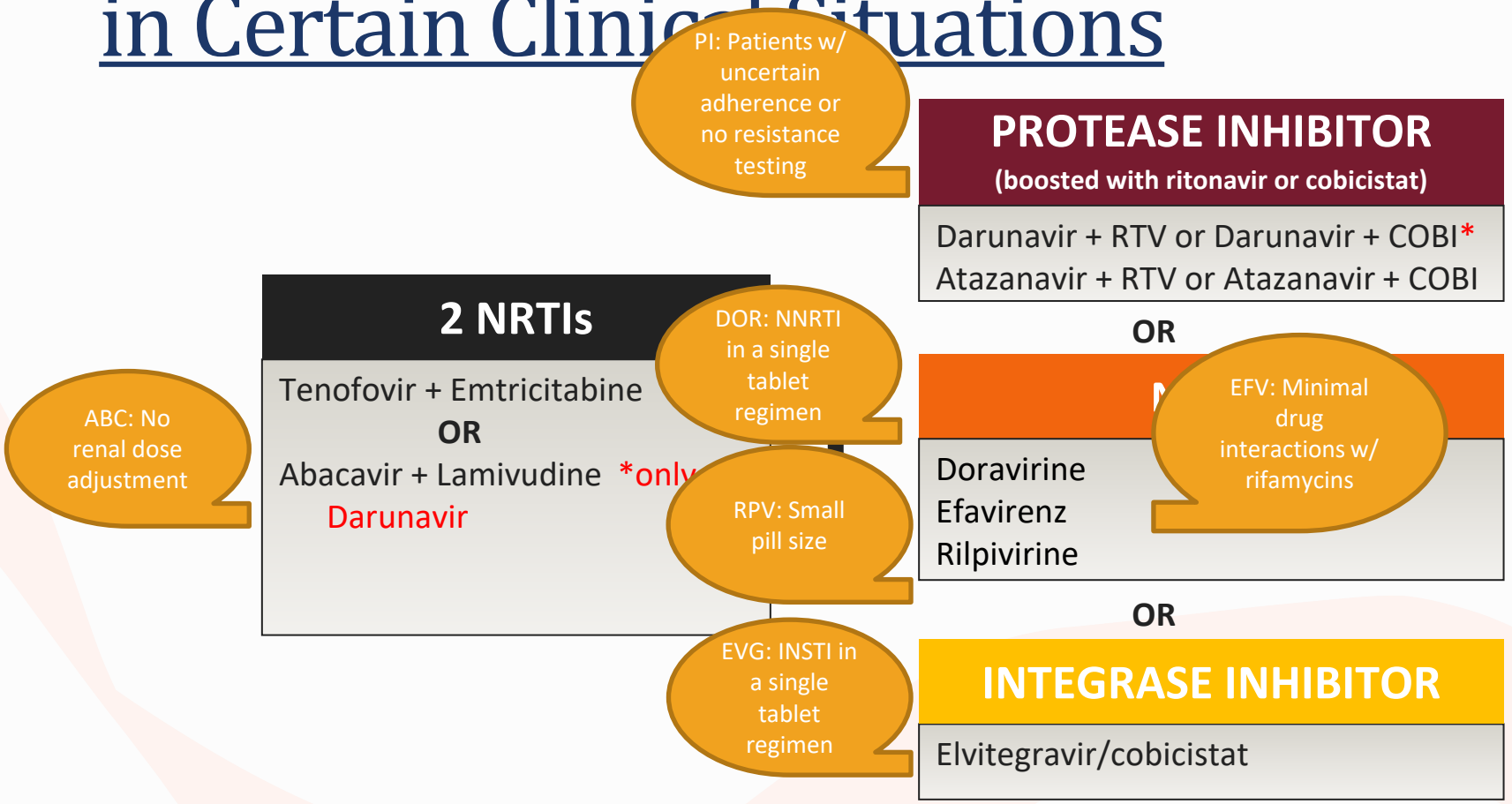

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Selecting an Initial HIV Regimen: The "Chinese Food Rule"

*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 *only w/ Darunavir

+

PRO[illegible]ASE INHIBITOR
(booste[illegible]n ritonavir or cobicistat)

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

OR

NNRTI

Doravirine
Efavirenz
Rilpivirine

OR

INTEGRASE INHIBITOR

Elvitegravir/cobicistat

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Recommended Initial CHINESE FOOD in Certain Clinical Situation

2 NRTIs

Tenofovir + Emtricitabine

OR

Abacavir + Lamivudine *only w/ Darunavir

+

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

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Recommended Initial CHINESE FOOD in Certain Clinical Situations

2 NRTIs

Tenofovir + Em[illegible]tabine

OR

Abacavir + Lam[illegible]line *only w/ Darunavir

+

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

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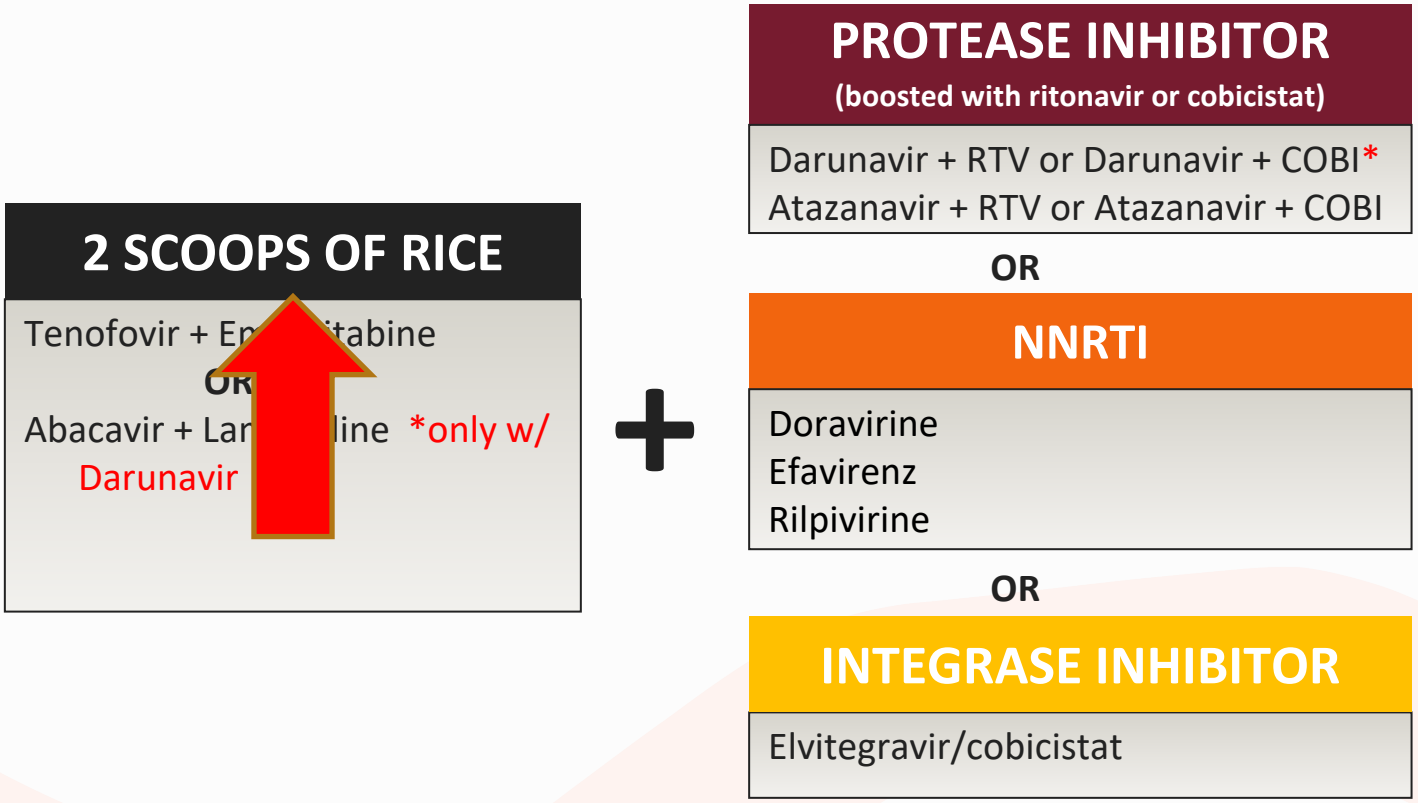

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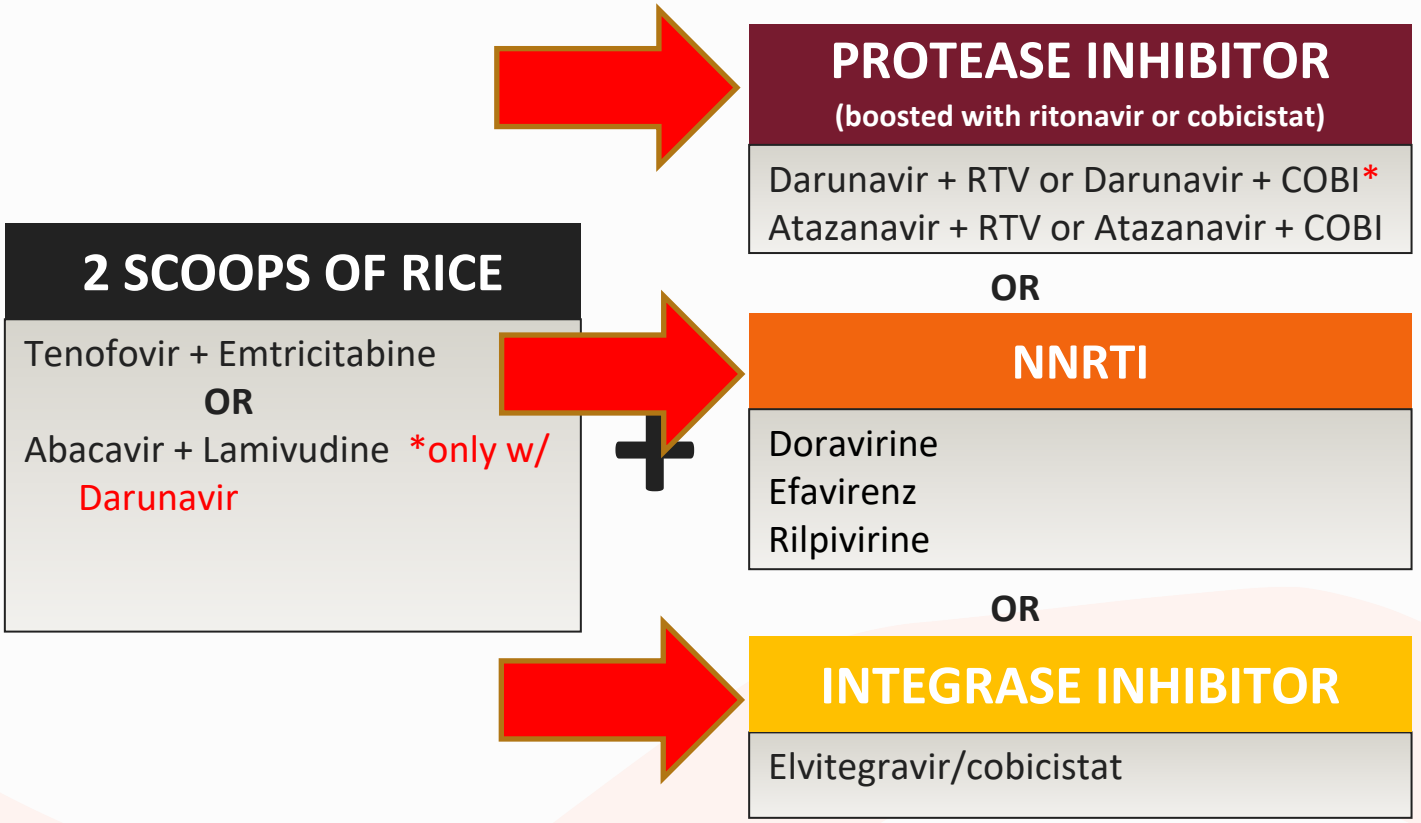

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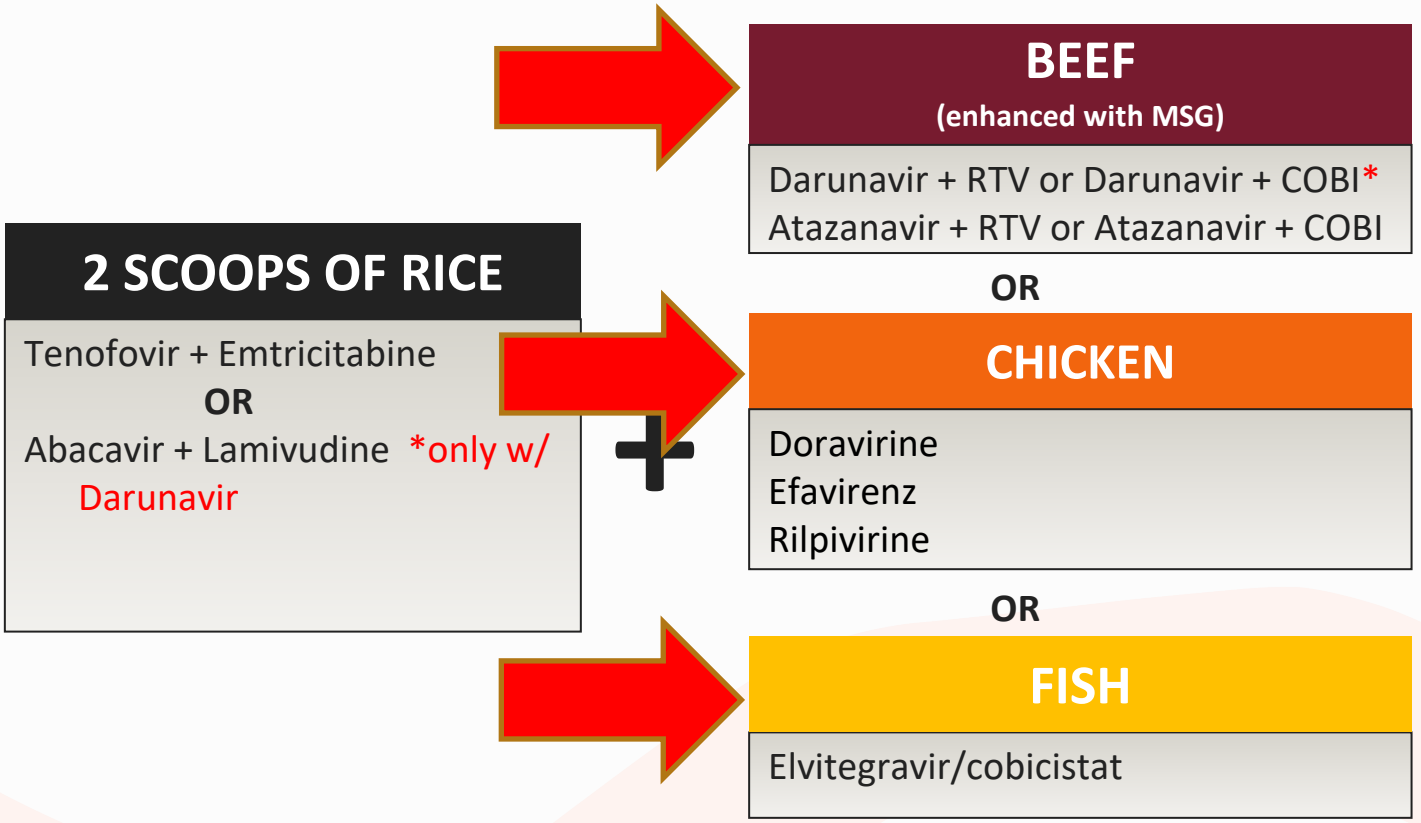

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Recommended Initial Regimens for Most People with HIV

1-2 NRTIs

Tenofovir + Em[illegible]tabine

OR

Abacavir + Lam[illegible]ine *only w/ Dolutegravir

OR

Lamivudine *only w/ Dolutegravir

+

INTEGRASE INHIBITOR

Raltegravir
Bictegravir
Dolutegravir*

TAF (tenofovir alafenamide) and TDF (tenofovir disoproxil fumarate) 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.

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Recommended CHINESE FOOD for Most People with HIV

1-2 SCOOPS OF RICE

Tenofovir + Em[illegible]tabine

OR

Abacavir + Lam[illegible]line *only w/ Dolutegravir

OR

Lamivudine *only w/ Dolutegravir

+

FISH

Raltegravir
Bictegravir
Dolutegravir*

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HIV Regimen / Chinese Food Selection: A Stepwise Approach

1. Get 1-2 scoops of rice

   - Choose 1-2 NRTIs, co-formulated when possible
     - Example: Tenofovir + emtricitabine
     - Example: Abacavir + lamivudine
     - Only one regimen uses 1 NRTI (lamivudine + dolutegravir)

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 •No resistance seen with dolutegravir or bictegravir (strong, potent) •Dolutegravir or bictegravir can be used if resistance tests not available	**PRO** •Efavirenz: minimal drug interactions w/ rifamycins •Doravirine: less drug interactions, can take with or without food •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 •Doravirine comes co-formulated only with TDF/3TC •Rilpivirine has lower efficacy in some patients (use only if CD4>200 and VL<100,000) and requires acidic environment for absorption

Drug Interactions with Antiretroviral Therapy

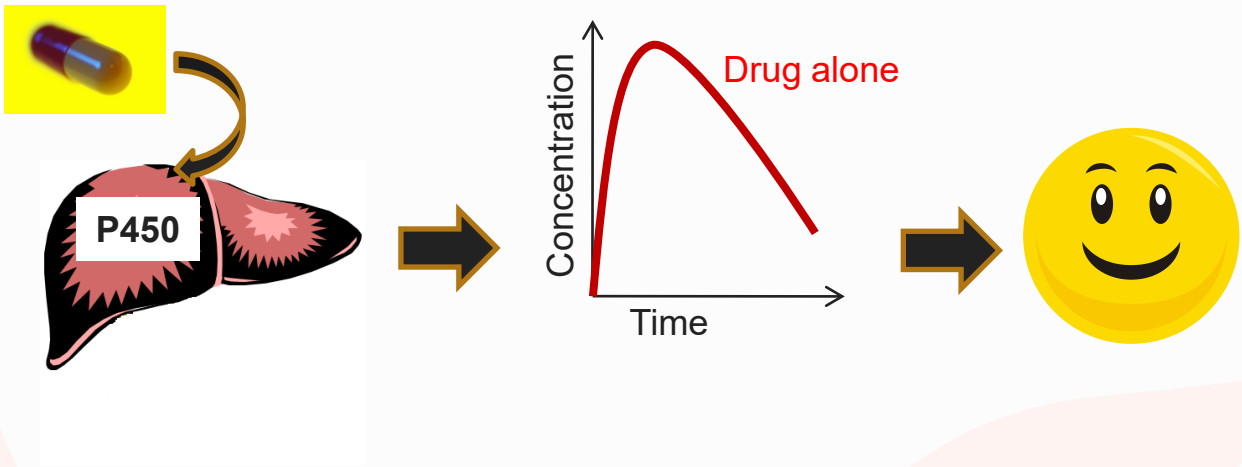
ART Undergoes Pharmacokinetic Transformation

1. Absorption
2. Distribution
3. Metabolism
4. Elimination

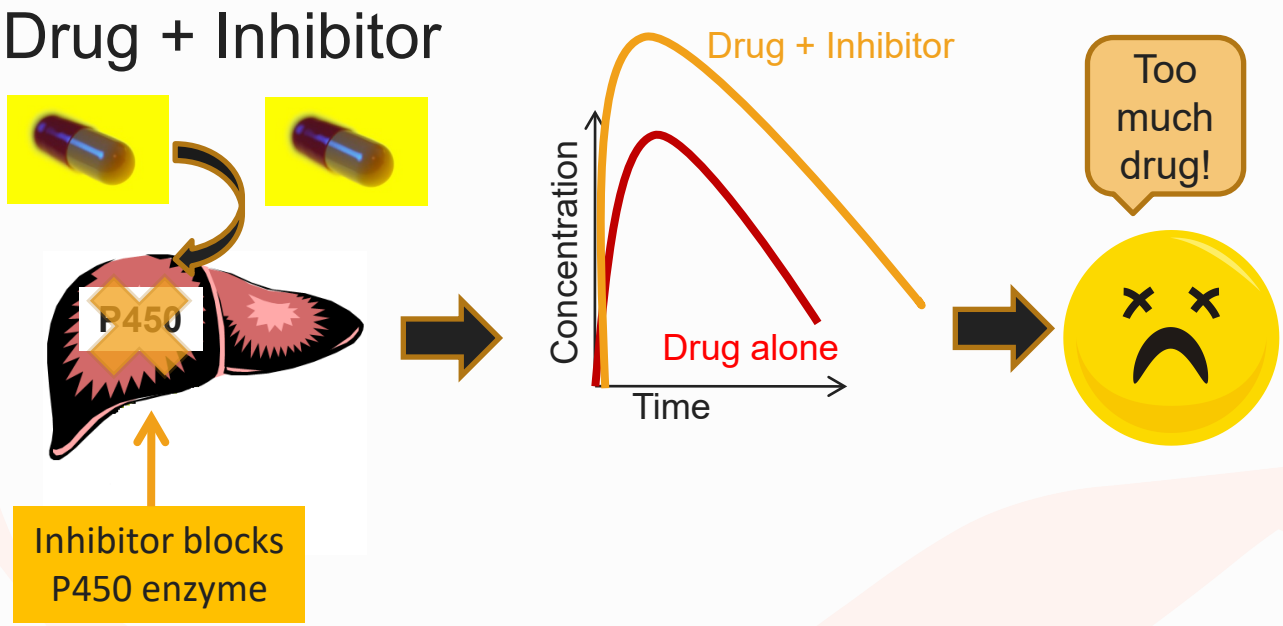
- Setting for most ARV drug interactions
- Cytochrome P450 drug metabolizing enzyme influences/influenced by, many ARVs and many other drugs
- PIs, NNRTIs, maraviroc, INSTIs & cobicistat can be P450 substrates, inducers, or inhibitors

Normal Metabolism of a Drug That is a P450 Substrate

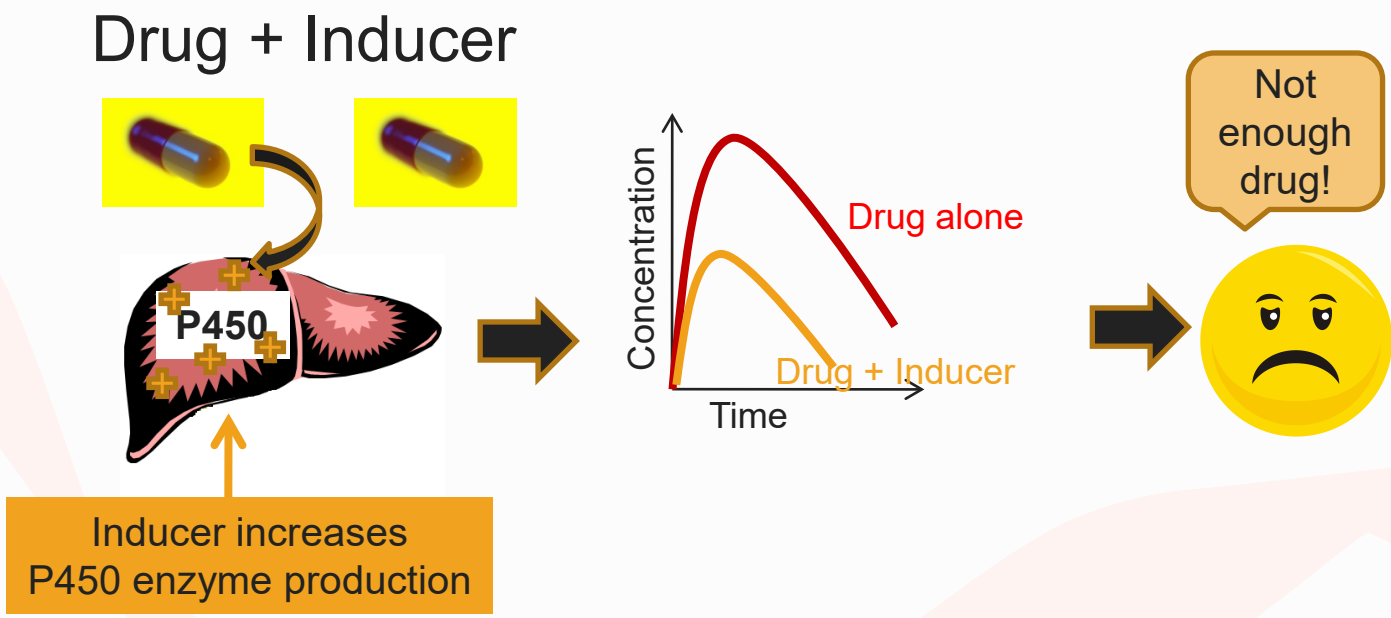
Drug alone



Metabolism of a Drug That Inhibits P450 With a Drug That is a P450 Substrate



Metabolism of a Drug That Induces P450 With a Drug That is a P450 Substrate



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/inhibitors	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 Inhibitors	•CCR5: P450 substrate •Fusion: Peptide undergoes catabolism to amino acids, no known drug interactions •CD4 post attachment: Metabolized by CD4 receptor internalization/catabolism, no known drug interactions •gp120 attachment: P450 substrate	Low-Medium

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 effective dose 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 adjustment needed
	•Elvitegravir/cobicistat	No data; no dosage recommendation
Rosuvastatin	•Darunavir + ritonavir •Elvitegravir/cobicistat	Titrate rosuvastatin dose carefully and use lowest effective 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 adjustment needed
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

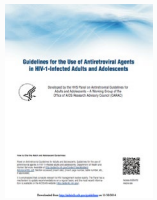
- Indicated for GERD/peptic ulcer disease to decrease gastric acidity
  - Antacids: aluminum, magnesium hydroxide, or calcium carbonate
  - H2 receptor antagonists: cimetidine, famotidine, ranitidine
  - Proton pump inhibitors: lansoprazole, omeprazole, pantoprazole
- Medications decreasing stomach acidity 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) Interactions	Rilpivirine (RPV) Interactions	INSTI Interactions
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 antacids •Take BIC ≥ 2 hours before or 6 hours after Al/Mg antacids
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: ART & 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 20-22**



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

- Southeast AETC Pocket Cards [**www.seaetc.com/provider-resources/reference/**]

Summary

- ART recommended for all HIV+
  - Treatment goals achievable by selecting individualized ART regimen and maximizing adherence

- Initial ART = 1-2 NRTIs + INSTI or PI or NNRTI

  (1-2 scoops of rice + 1 main entrée)

- ART presents high potential for drug interactions due to the way the medications are absorbed and metabolized

AETC AIDS Education & Training Center Program Southeast

Antiretroviral Therapy Basics (It's not so scary)

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