AETC AIDS Education & Training Center Program
Southeast

The ABCs of ART: Designing Initial Antiretroviral Regimens for Beginners

Elizabeth Sherman, PharmD, AAHIVP
Faculty – South Florida, Southeast AETC
Clinical Pharmacist, Memorial Healthcare System
Assistant Professor, Nova Southeastern University
esherman@nova.edu

Disclosures

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- This slide set has been peer-reviewed to ensure that there are no conflicts of interest represented in the presentation

Learning Objectives

- 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
- Discuss clinically significant drug interactions for patients with HIV

GETTING TO KNOW YOU

Which best describes your profession?

A. Physician
B. Midlevel practitioner
C. Nurse
D. Pharmacist
E. Medical assistant
F. Case manager
G. Student
H. Other

How comfortable are you with constructing ARV regimens and recognizing drug interactions?

A. Extremely comfortable: It's a slam dunk every time!
B. Somewhat comfortable: I have some experience and great colleagues to consult if I get stuck
C. Uncomfortable: There are so many new medications, it's hard to keep up!
D. What is Webcast Wednesday and how did I end up here?

Recommended HIV Resources

www.aidsinfo.nih.gov

- DHHS: Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. October 17, 2017.

www.seaetc.com/provider-resources/reference/

Southeast AETC Pocket Cards

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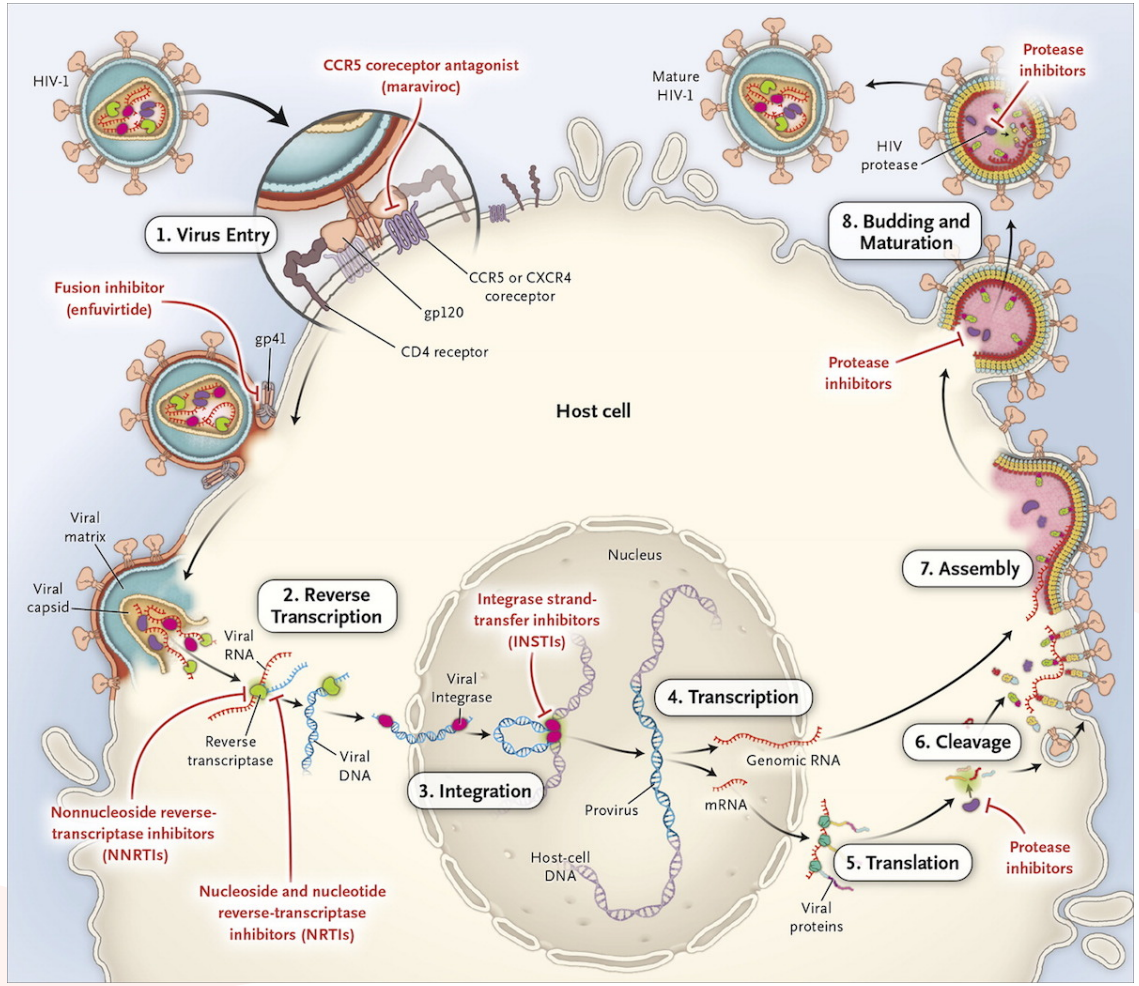
HIV Attacks CD4 T Cells

- 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)

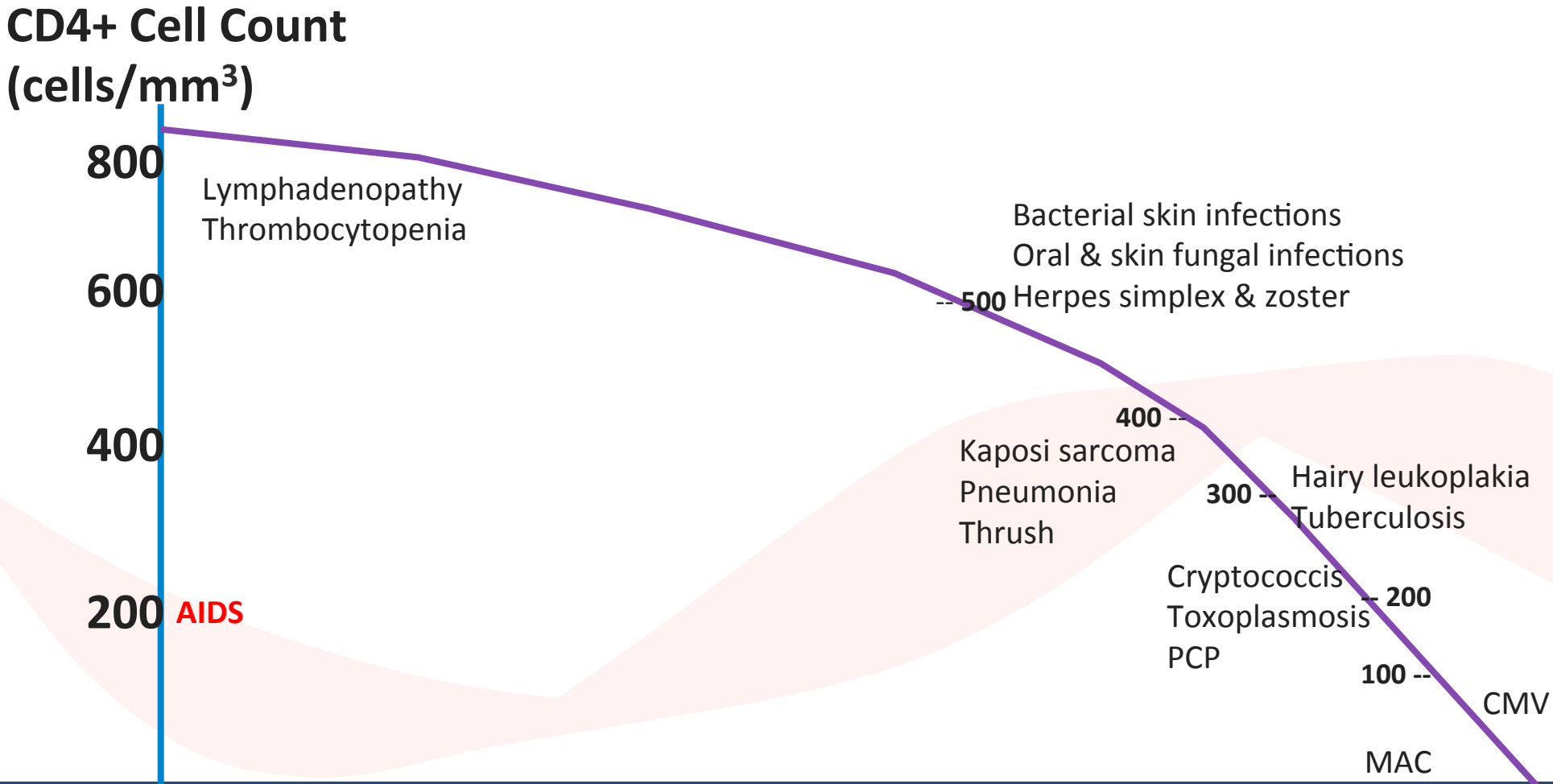
- Antiretroviral therapy (ART) suppresses viral load, allowing improvements in immune system functioning

HIV Life Cycle



Gandhi M, Gandhi RT. Single-pill combination regimens for treatment of HIV-1 infection. N Engl J Med. 2014;371:248-59.

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

- 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
  - HIV viral suppression
  - Reduced rates of viral resistance
  - Increase 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

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

Consequences of Non-adherence

- HIV progression
- Increase AIDS-related morbidity and mortality
- Increased hospitalization rates
- Immunologic failure
- Development of resistant virus

Factors Associated with Poor Adherence

- Neurocognitive impairment
- Untreated major psychiatric disorders
- Active substance abuse
- Unstable housing
- Medication side effects
- Non-adherence to clinic appointments
- Low health literacy
- Low levels of social support
- Stressful life events
- Busy or unstructured daily routines
- Nondisclosure of HIV serostatus
- Denial; stigma
- Cost and insurance coverage issues

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

Single Tablet Regimens (STRs)

Agent	Type	Year of FDA Approval
Efavirenz/tenofovir DF/emtricitabine	NNRTI + dual NRTI	2006
Rilpivirine/tenofovir DF/emtricitabine	NNRTI + dual NRTI	2011
Rilpivirine/tenofovir AF/emtricitabine	NNRTI + dual NRTI	2016
Elvitegravir/cobicistat/tenofovir DF/emtricitabine	INSTI + booster + dual NRTI	2012
Elvitegravir/cobicistat/tenofovir AF/emtricitabine	INSTI + booster + dual NRTI	2015
Dolutegravir/abacavir/lamivudine	INSTI + dual NRTI	2014
Dolutegravir/rilpivirine	INSTI + NNRTI	2017
Bictegravir/tenofovir AF/emtricitabine	INSTI + dual NRTI	2018

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

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

Observational Studies of STRs vs Multicomponent Regimens

Study	Main Finding
LifeLink Database[1] (N = 7073)	STRs associated with higher rate of adherence and lower risk of hospitalization
Commercially insured US HIV pts[2] (N = 6938)	Non STRs associated with 1.5 x risk of incomplete dosing; partial adherence associated with increased rate of hospitalization
Quebec Cohort[3] (N = 4996)	Higher proportion of STR pts adherent to therapy; STRs also associated with lower rate of hospitalization and healthcare utilization
VA Cohort[4] (N = 15,602)	STRs associated with significantly better adherence, lower hospitalization rate

Slide credit: clinicaloptions.com

1. Sax PE, et al. PLoS One. 2012;7:e31591. 2. Cohen C, et al. J Int AIDS Soc. 2012;56(suppl 4):18060. Abstract P1.
3. Lachaine J, et al. ICAAC 2013. Abstract H-663. 4. Rao GA, et al. ICAAC 2013. Abstract H-1464.

Tools to Achieve Treatment Goals

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

Learning Objectives

- List antiretroviral treatment goals and tools to achieving these goals
- **Review the process for selecting antiretroviral regimens**
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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

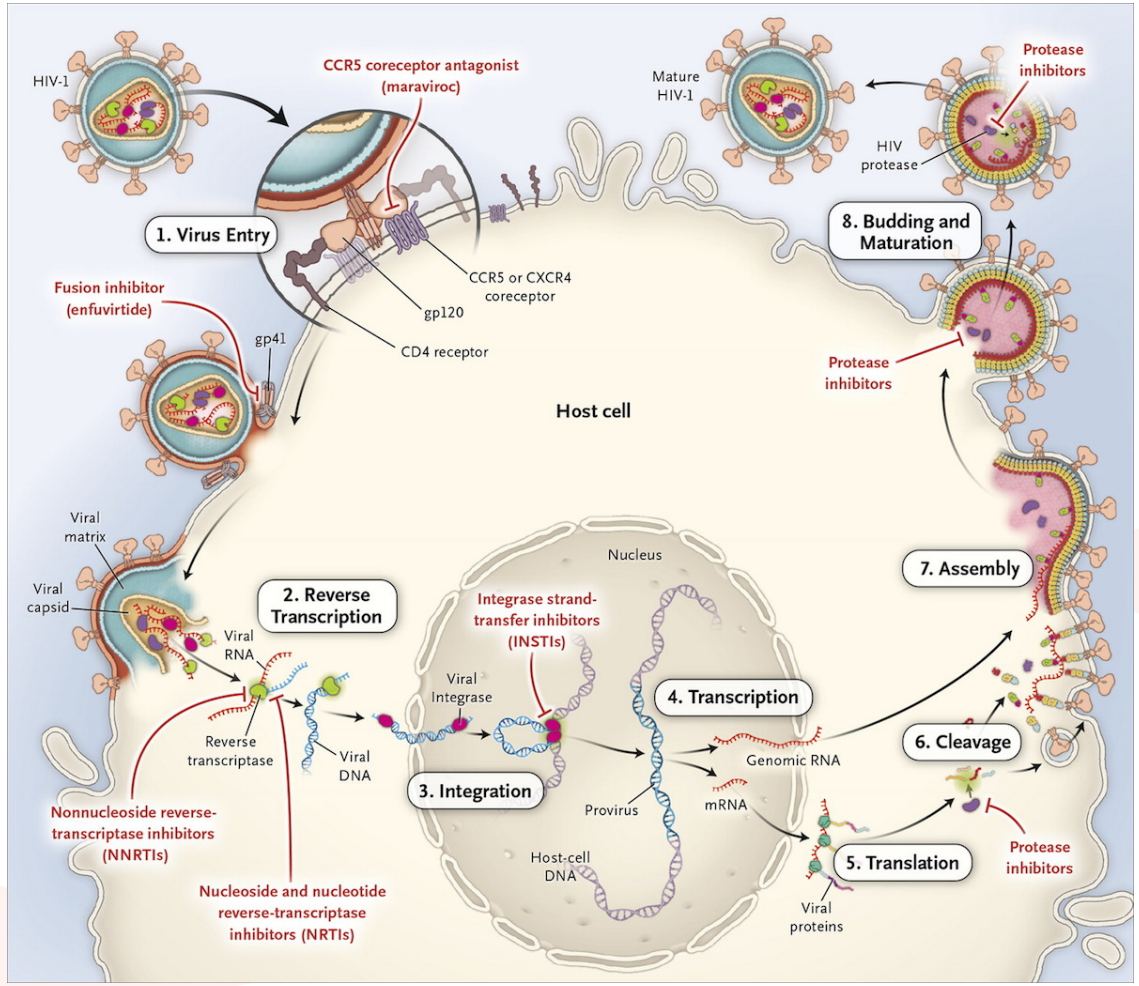
Overview of ART Drug Classes

- 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



Gandhi M, Gandhi RT. Single-pill combination regimens for treatment of HIV-1 infection. N Engl J Med. 2014;371:248-59.

Antiretroviral Medications

Nucleoside Reverse Transcriptase Inhibitors

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

Non-nucleoside Reverse Transcriptase Inhibitors

Delavirdine (DLV) (Rescriptor®)
Efavirenz (EFV) (Sustiva®)
Etravirine (ETR) (Intellence®)
Nevirapine (NVP) (Viramune®)
Rilpivirine (RPV) (Edurant®)

Integrase Inhibitors

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

Pharmacokinetic Enhancers “Boosters”

Cobicistat (COBI) (Tybost®)
Ritonavir (RTV) (Norvir®)

Protease Inhibitors

~~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®)
Maraviroc (MVC) (Selzentry®)

Single Tablet Regimens

EFV/FTC/TDF (Atripla®)
RPV/FTC/TDF (Complera®)
RPV/FTC/TAF (Odefsey®)
EVG/cobi/FTC/TDF (Stribild®)
EVG/cobi/FTC/TAF (Genvoya®)
DTG/3TC/ABC (Triumeq®)
DTG/RPV (Juluca®)
BIC/FTC/TAF (Biktarvy®)

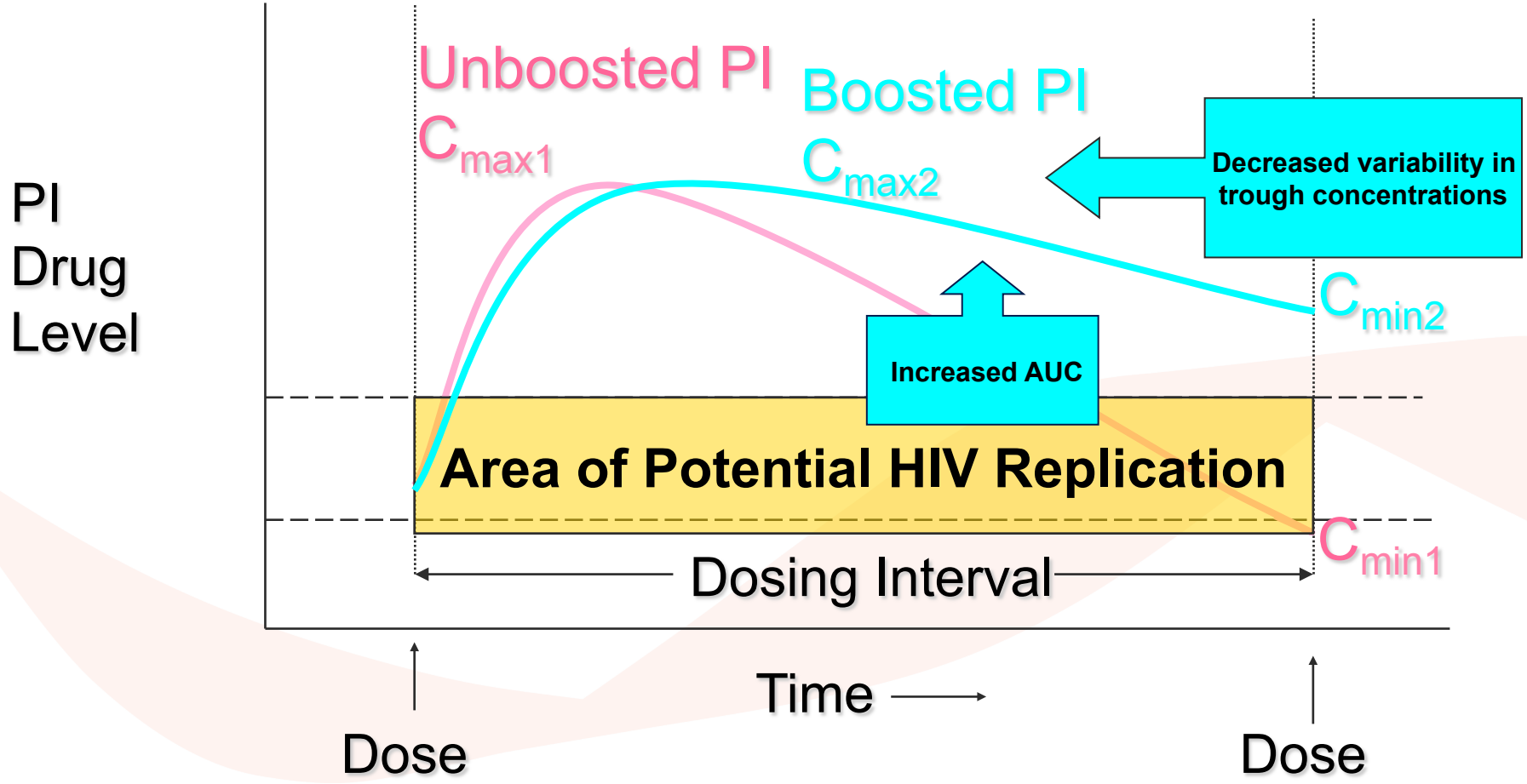
HIV Management Principles

- Initiate ART with 1 of 3 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 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

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

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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

Efavirenz

Rilpivirine

OR

INTEGRASE INHIBITOR

Raltegravir

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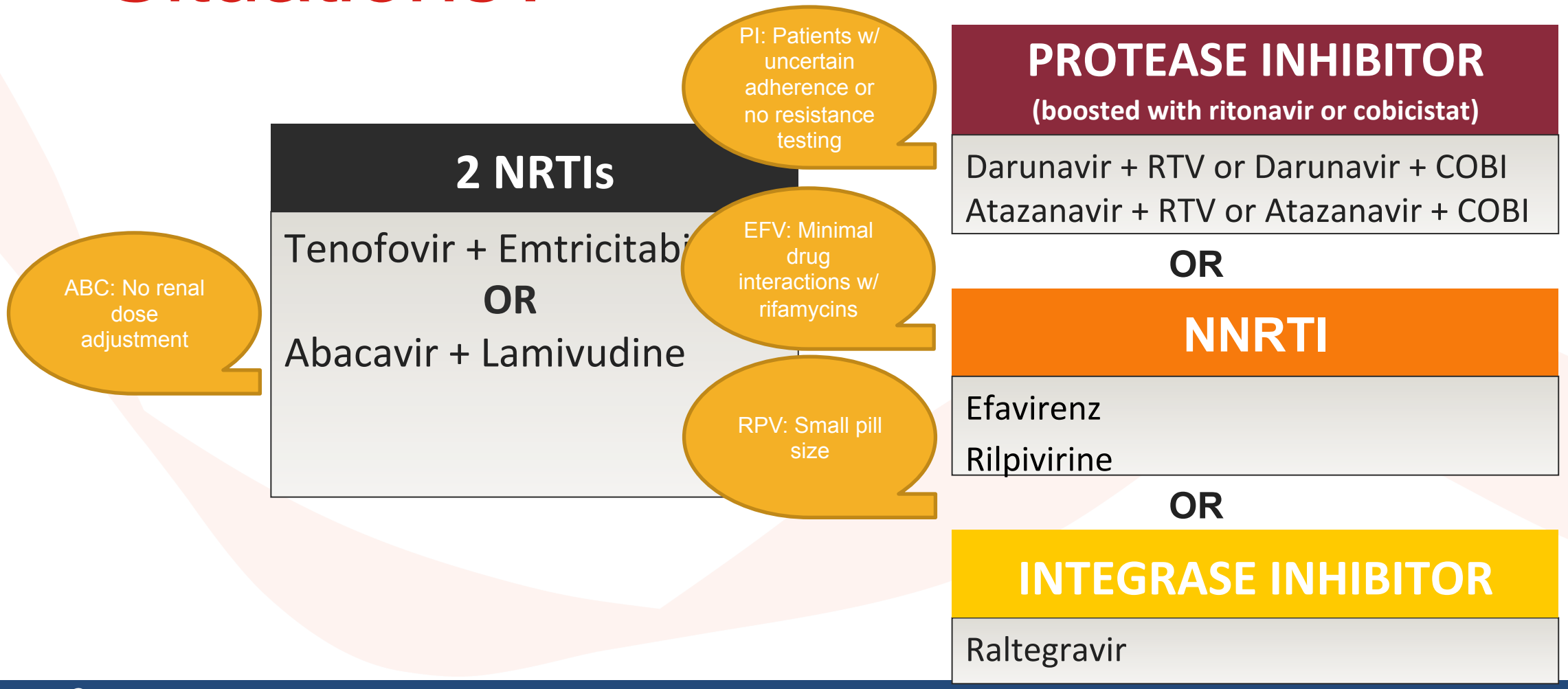
“What Are The Certain Clinical Situations?”



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

Efavirenz

Rilpivirine

OR

INTEGRASE INHIBITOR

Raltegravir

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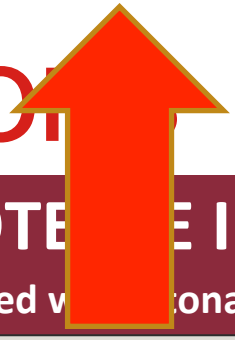
Recommended CHINESE FOOD in Certain Clinical Situation



2 NRTIs

Tenofovir + Emtricitabine

OR

Abacavir + Lamivudine

+

PROTE E INHIBITOR

(boosted w onavir or cobicistat)

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OR

NNRTI

Efavirenz

Rilpivirine

OR

INTEGRASE INHIBITOR

Raltegravir

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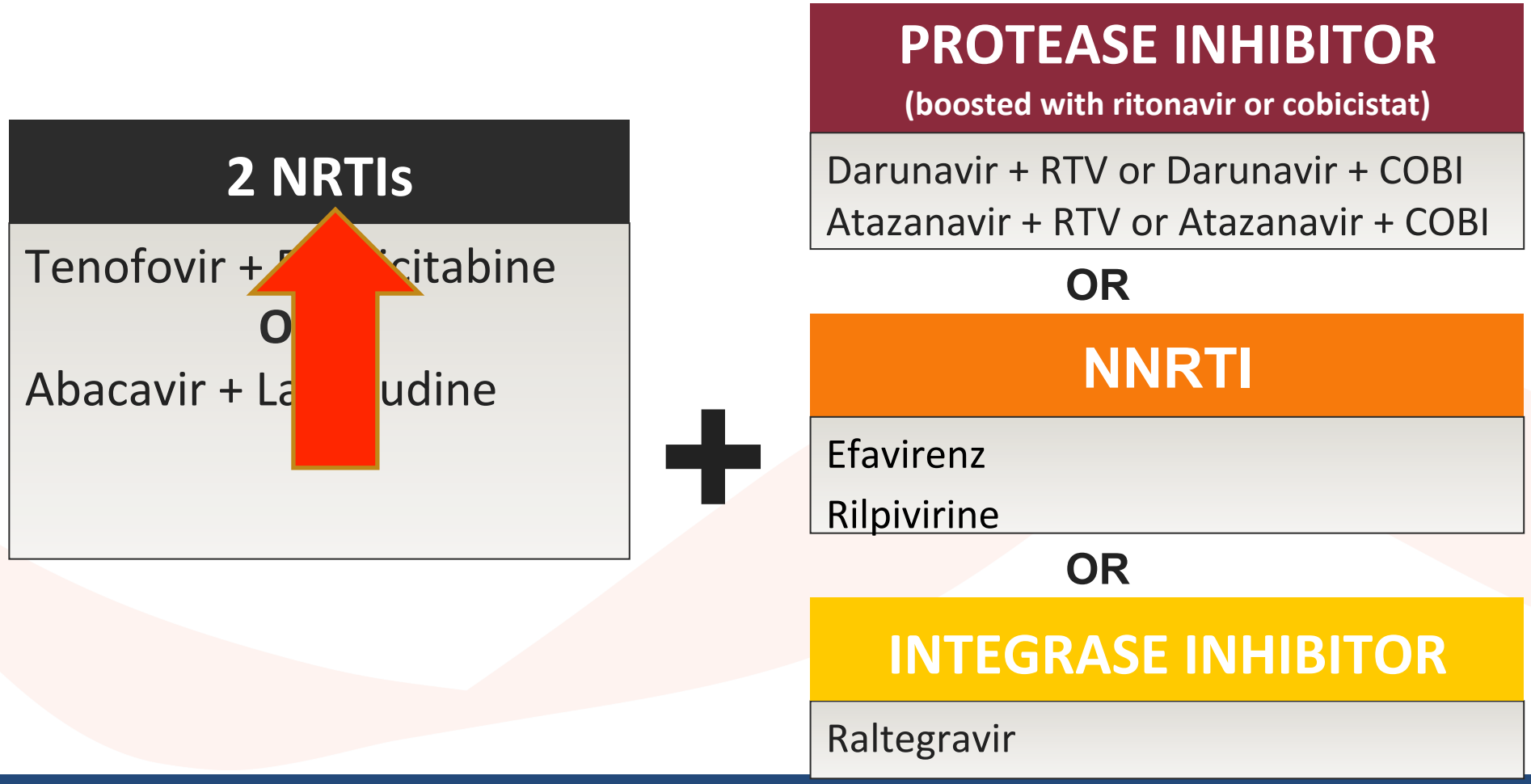

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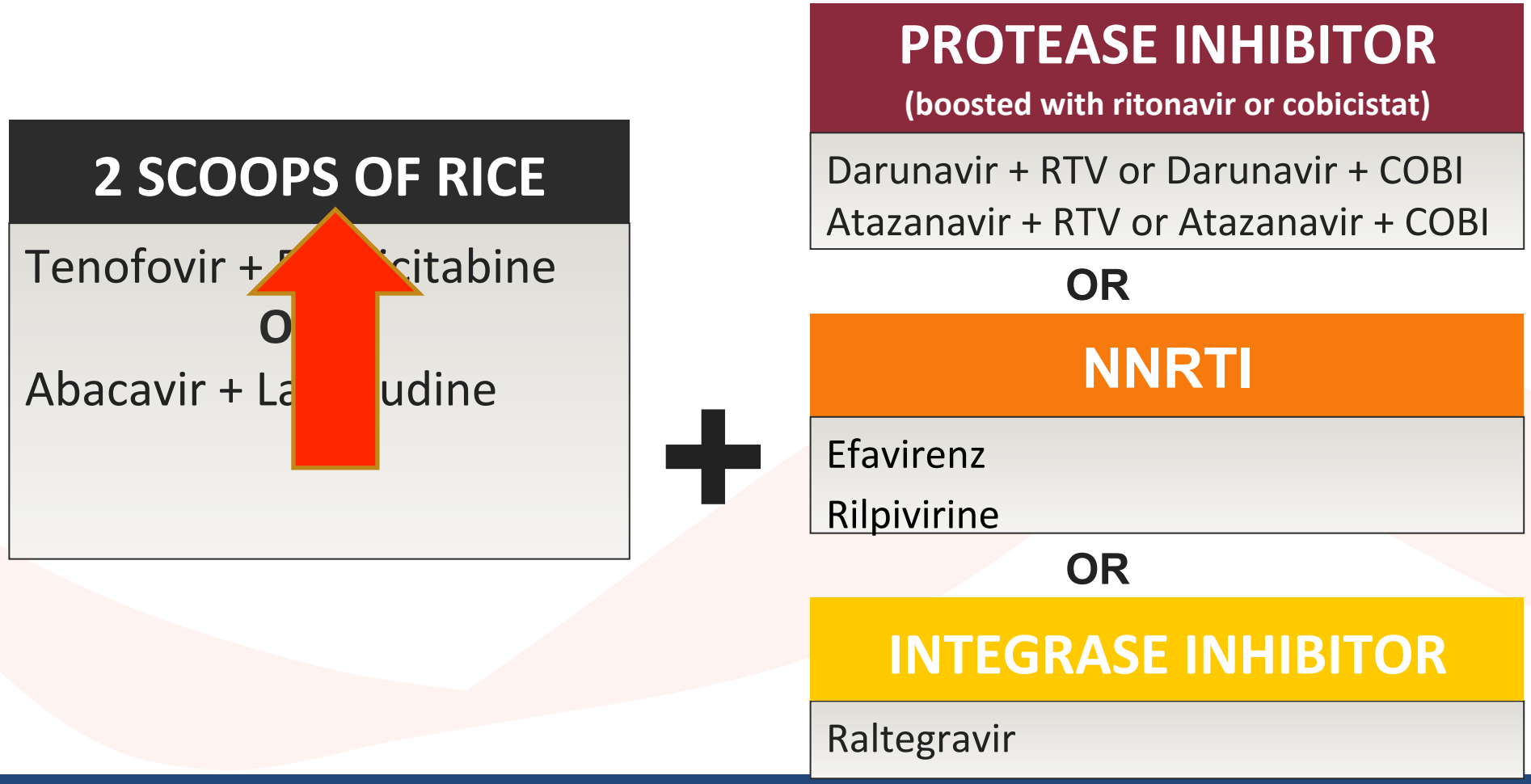

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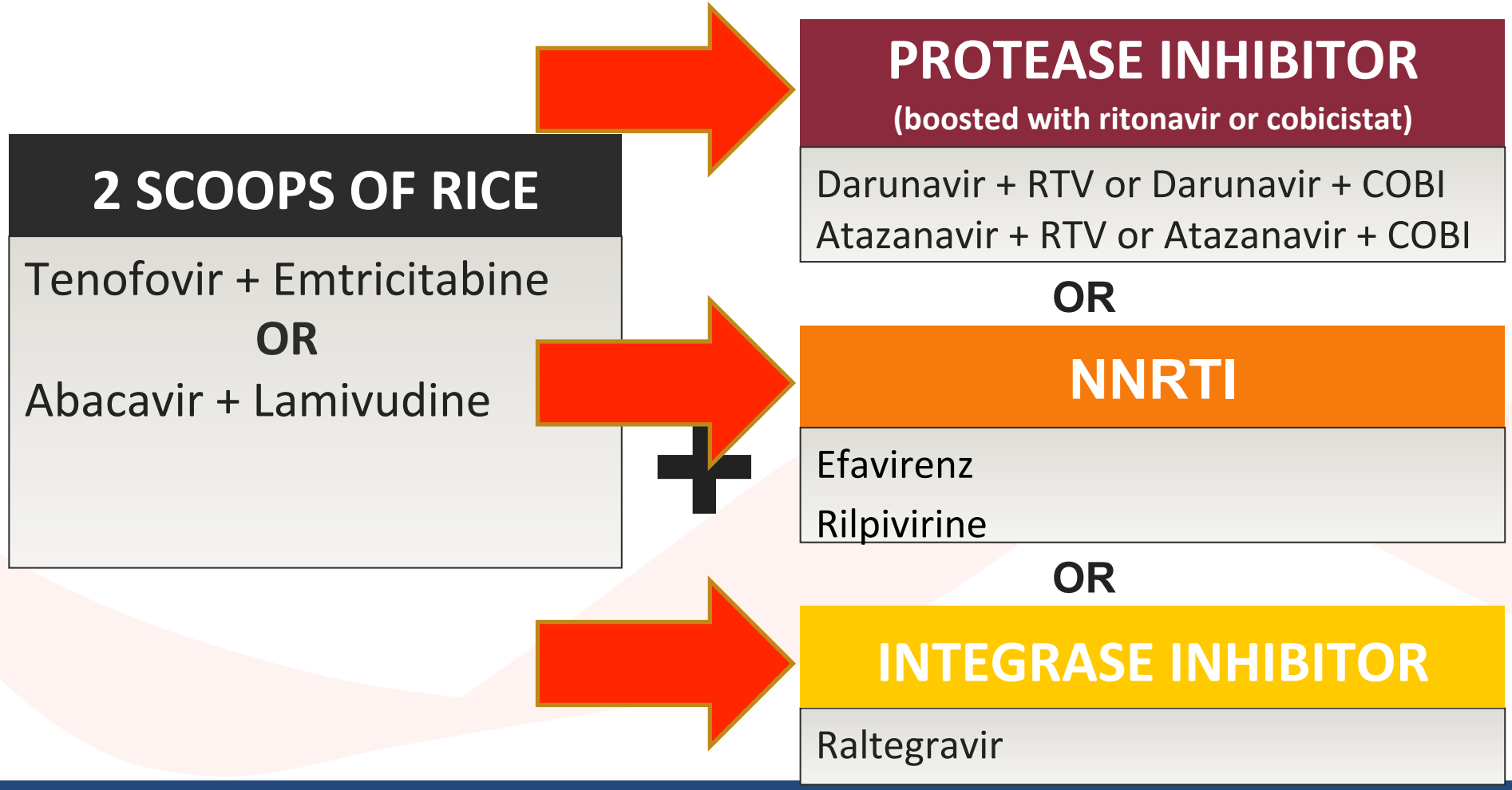

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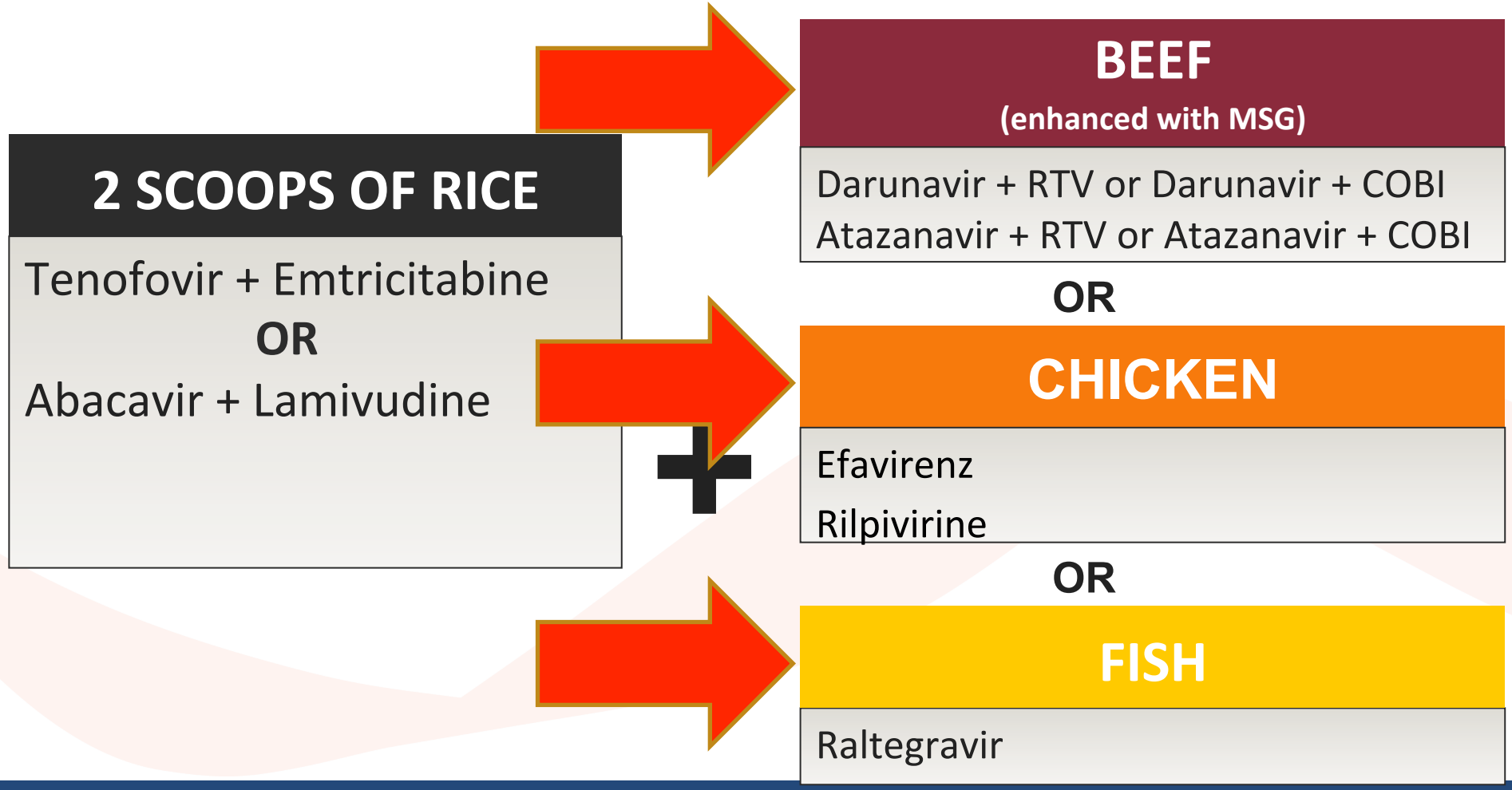

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HIV Regimen / Chinese Food Selection: A Stepwise Approach

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 (strong, potent)	**PRO** •Low pill burden (1 pill daily) •Efavirenz: minimal drug interactions w/ rifamycins •Rilpivirine is in smallest single tablet regimen
CON •No single tablet regimen •Many drug interactions (P450 metabolism) •Metabolic effects (↑ cholesterol, glucose) •GI side effects •Boosting required	**CON** •Some delicate, prone to resistance (except dolutegravir)	**CON** •Prone to resistance •Efavirenz has CNS side effects; cases of neural tube defects after first trimester exposure •Rilpivirine has lower efficacy in some patients

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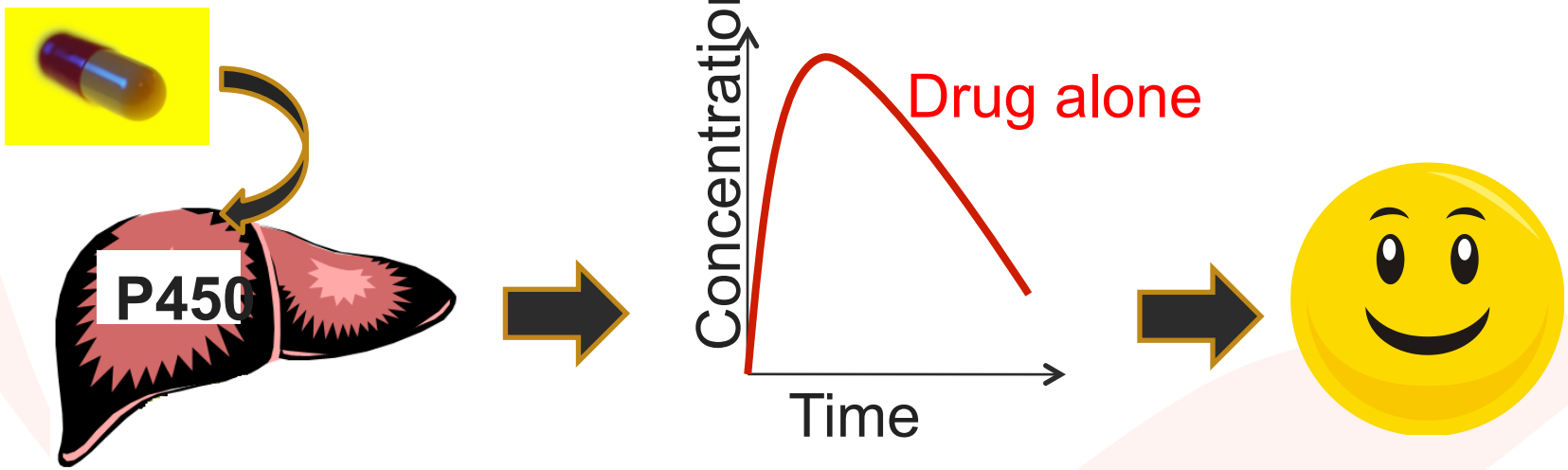
ART Undergoes Pharmacokinetic Transformation

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

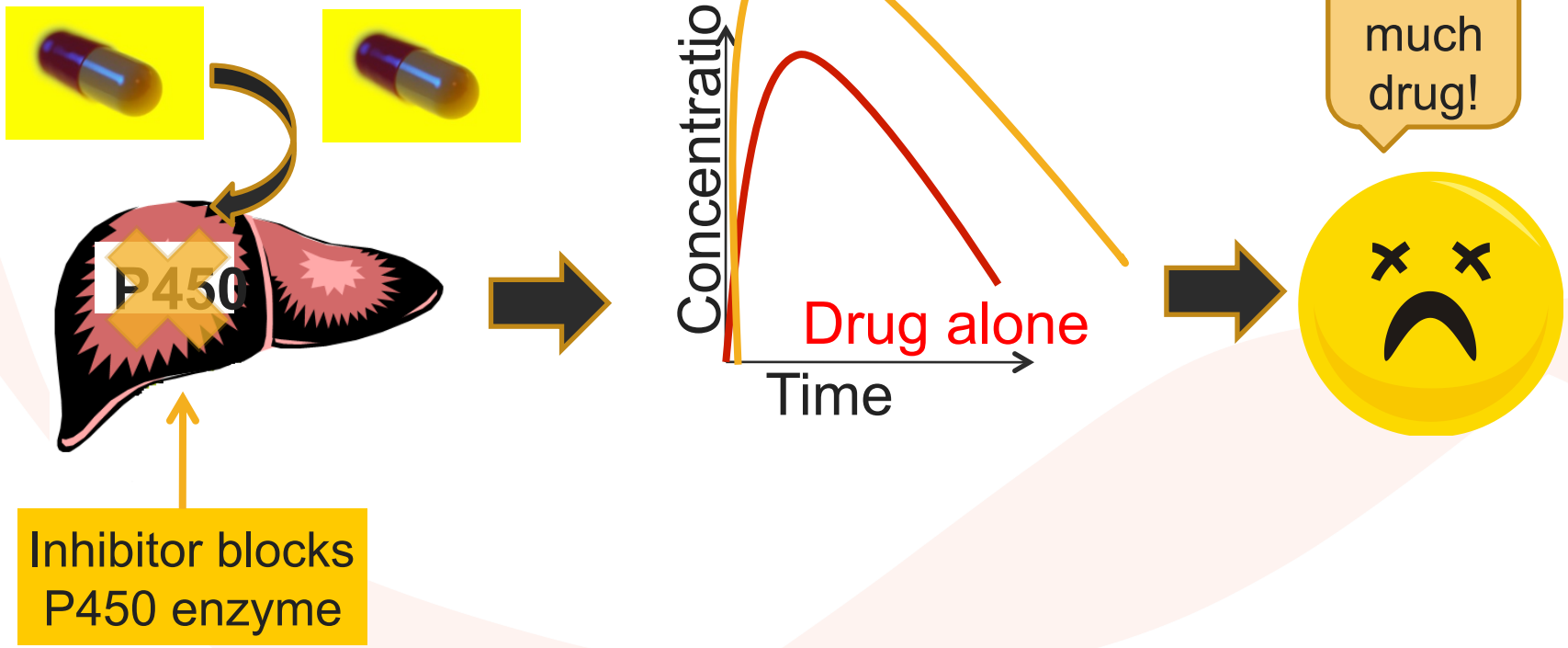
Normal Metabolism of a Drug That is a P450 Substrate

Drug alone



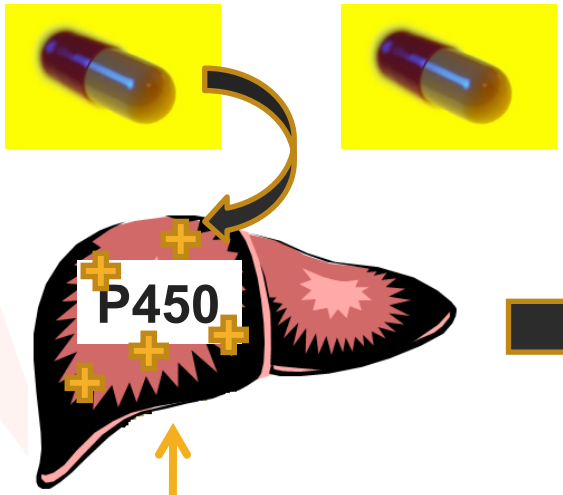
Metabolism of a Drug That Inhibits P450 With a Drug That is a P450 Substrate

Drug + Inhibitor

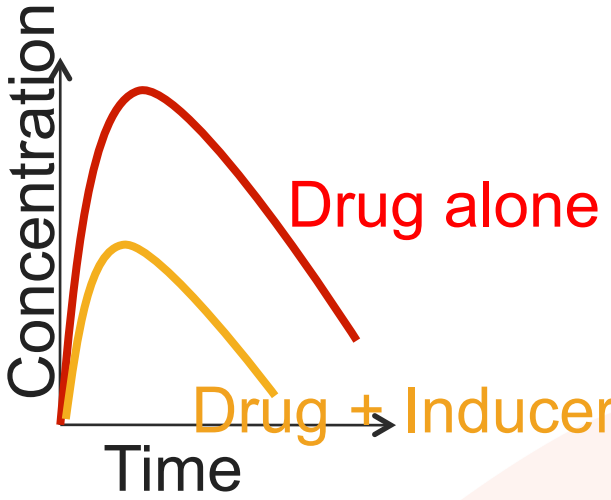


Metabolism of a Drug That Induces P450 With a Drug That is a P450 Substrate

Drug + Inducer



Inducer increases P450 enzyme production



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 (sometimes act as inducers)	High
Integrase Inhibitors	Liver metabolism •Raltegravir: UGT1A1 enzyme (not P450) •Elvitegravir: P450 substrate/inducer (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

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- **Discuss clinically significant drug interactions for patients with HIV**

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
- PIs and COBI ↑ statin levels
  - Avoid simvastatin, lovastatin (2000% ↑)
- NNRTIs can ↓ statin levels
  - Monitor statin efficacy, ↑ dose as necessary

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

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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: esomeprazole, 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 Medications

Anti-acid	Atazanavir (ATV) Intxns	Rilpivirine (RPV) Intxns	INSTI Intxns
Aluminum, Magnesium, Calcium (Al, Mg, Ca) Antacids	ATV 2 hrs before or 1-2 hours after antacids	Antacids 2 hours before or 4 hours after RPV	•Separate EVG by ≥ 2 hours •RAL not recommended with Al or Mg; RAL HD not recommended with Ca; if RAL then no dose adjustment with Ca •DTG 2 hours before or 6 hours after antacid •Take BIC without food 2 hours before antacid
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

Managing ARV Interactions with Anti-acid Medications

Anti-acid	Atazanavir (ATV) Intxns	Rilpivirine (RPV) Intxns	INSTI Intxns
Aluminum, Magnesium, Calcium (Al, Mg, Ca) Antacids	ATV 2 hrs before or 1-2 hours after antacids	Antacids 2 hours before or 4 hours after RPV	•Separate EVG by ≥ 2 hours •RAL not recommended with Al or Mg; RAL HD not recommended with Ca; if RAL then no dose adjustment with Ca •DTG 2 hours before or 6 hours after antacid •Take BIC without food 2 hours before antacid
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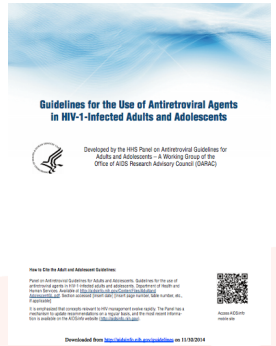
ARV Drug Interaction Resources

- 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]

Summary

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

AETC AIDS Education & Training Center Program
Southeast

The ABCs of ART: Designing Initial Antiretroviral Regimens for Beginners

Elizabeth Sherman, PharmD, AAHIVP
Faculty – South Florida, Southeast AETC
Clinical Pharmacist, Memorial Healthcare System
Assistant Professor, Nova Southeastern University
esherman@nova.edu