ART Part 1:
Introduction to Antiretroviral Therapy

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Disclosures

- This speaker does not have any financial relationships with commercial entities to disclose.
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Learning Objectives

- By the end of this session, each participant will:
  1. List antiretroviral treatment goals and tools for achieving these goals
  2. Describe the process for selecting antiretroviral regimens for treatment-naive people with HIV
  3. Describe the basic adverse effect profile of commonly used antiretroviral medications
  4. Identify common mechanisms for drug interactions and the importance of recognizing clinically significant drug interactions with antiretrovirals

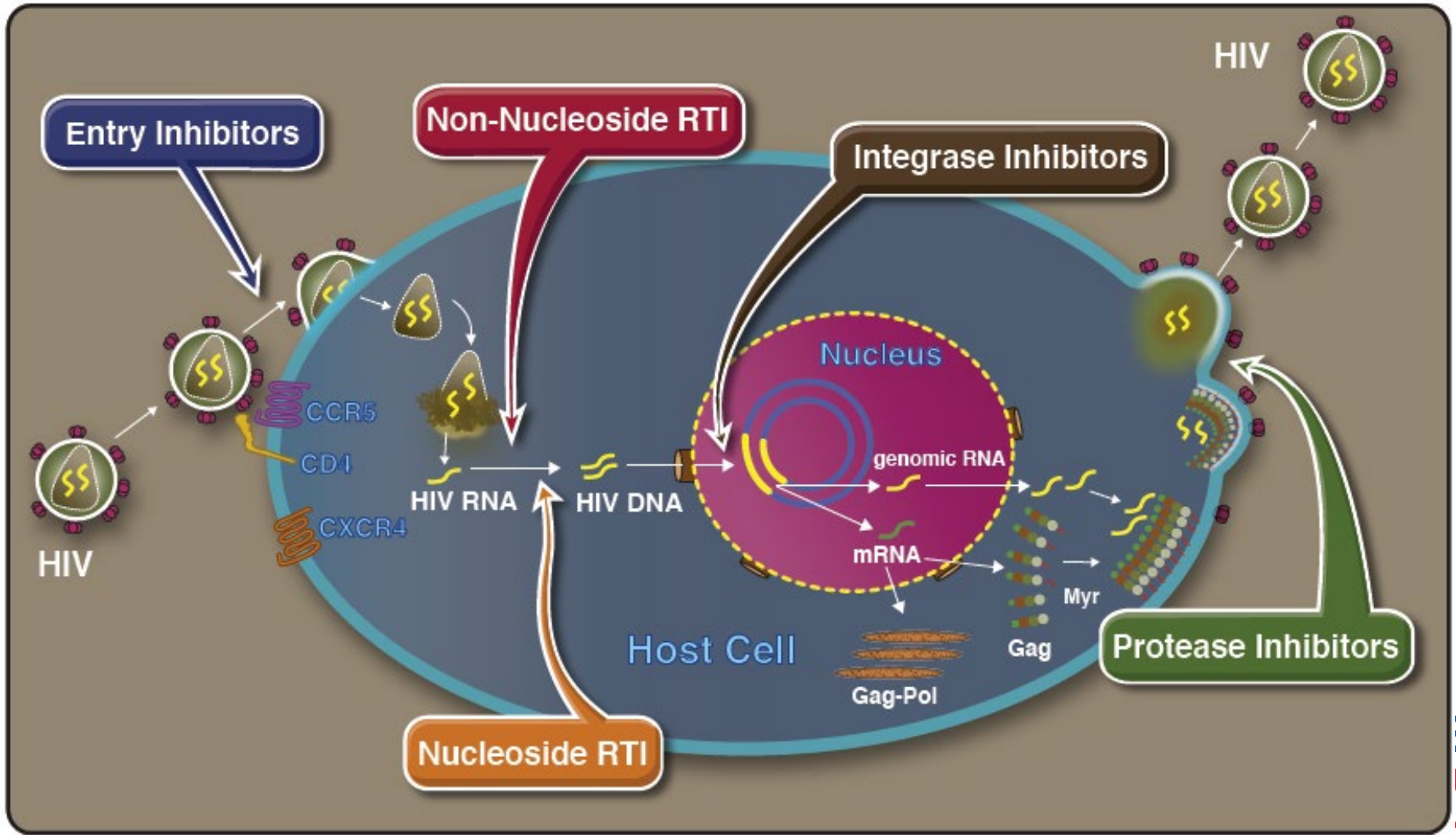
HIV Attacks CD4 T Cells

- 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 infections)

- 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 an HIV diagnosis
  - Purpose: 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

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US HHS. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/

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 range
  - AIDS diagnosis is CD4 < 200 or CD4% < 14% (or AIDS defining illness)
- Improve quality of life and reduce HIV-related morbidity and mortality
- Prevent HIV transmission to others

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

People who take ART daily as prescribed and achieve and maintain an undetectable viral load have effectively no risk of sexually transmitting the virus to an HIV-negative partner.

September, 2017

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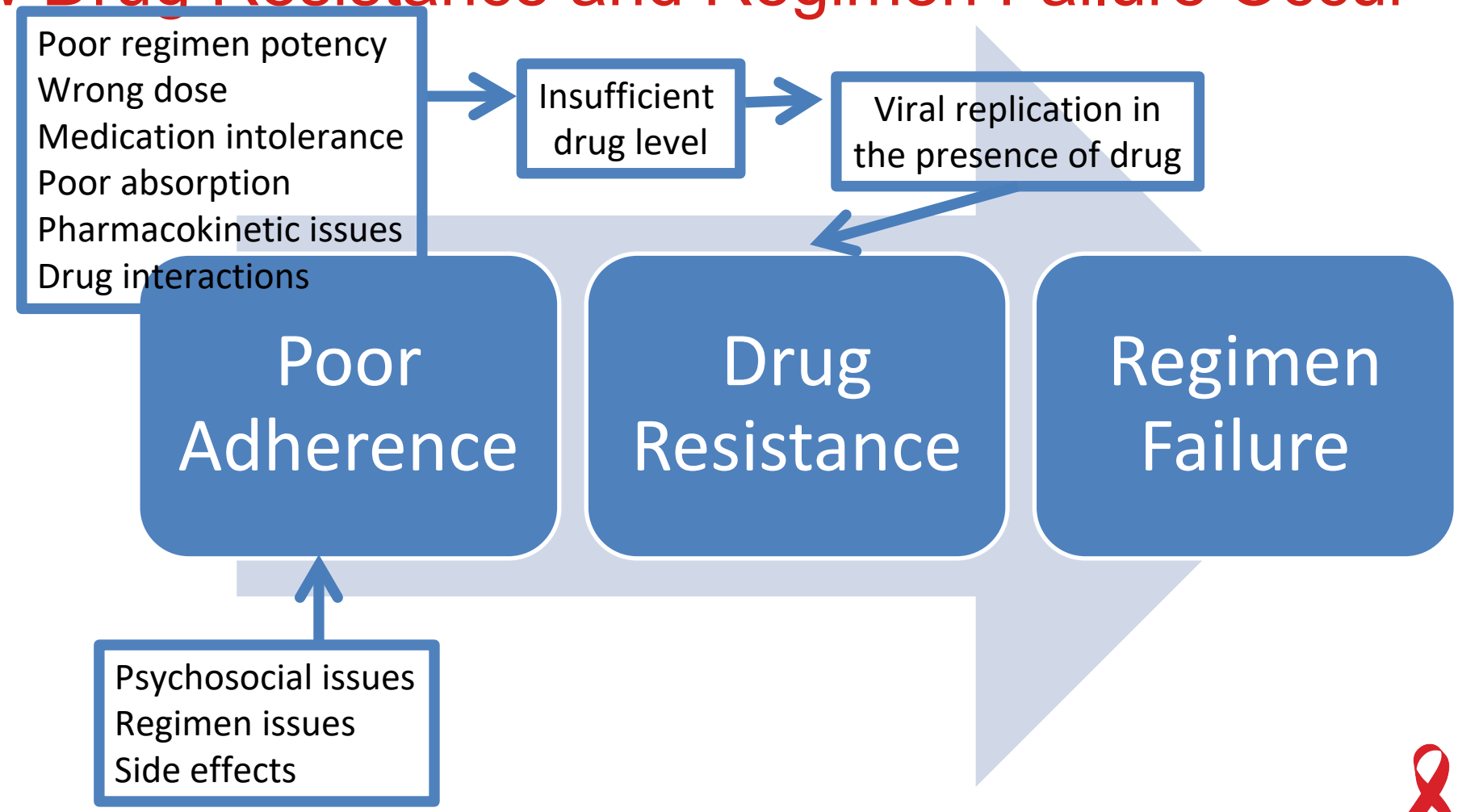
Tools to Achieve Treatment Goals

- Performing pretreatment resistance testing
- Maximizing adherence through use of simplified regimens with reduced pill burden
- Selecting individualized ART regimen

Tools to Achieve Treatment Goals

- **Performing pretreatment resistance testing**
- Maximizing adherence through use of simplified regimens with reduced pill burden
- Selecting individualized ART regimen

How Drug Resistance and Regimen Failure Occur



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 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 acquired**
- Repeat 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 through use of simplified regimens with reduced pill burden**
- Selecting individualized ART regimen

Simplified ART Regimens

- Use of single tablet regimens (STRs)
- Co-formulated antiretroviral 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

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Yang T, Oliyai R, Kent KM. *Antiviral Therapy*. 2022;27(2).

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

STR Brand Name	STR Generic Name	Food Considerations
Atripla	Efavirenz/tenofovir DF/emtricitabine	Empty stomach
Biktarvy	Bictegravir/tenofovir AF/emtricitabine	With or without food
Complera	Rilpivirine/tenofovir DF/emtricitabine	With a full meal (not a protein drink)
Delstrigo	Doravirine/tenofovir DF/emtricitabine	With or without food
Dovato	Dolutegravir/lamivudine	With or without food
Genvoya	Elvitegravir/cobicistat/tenofovir AF/emtricitabine	With food
Juluca	Dolutegravir/rilpivirine	With a full meal (not a protein drink)
Odefsey	Rilpivirine/tenofovir AF/emtricitabine	With a full meal (not a protein drink)
Stribild	Elvitegravir/cobicistat/tenofovir DF/emtricitabine	With food
Symtuza	Darunavir/cobicistat/tenofovir AF/emtricitabine	With food
Triumeq	Dolutegravir/abacavir/lamivudine	With or without food

Key: DF = disoproxil fumarate; AF = alafenamide

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 390 calories

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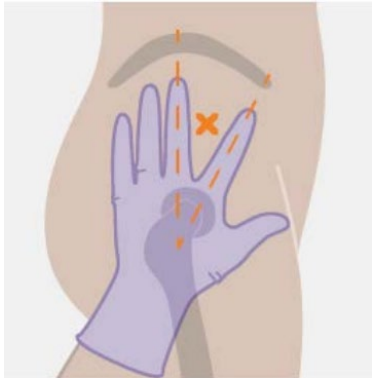
Simplified Regimen: Long-acting cabotegravir/rilpivirine (LA CAB/RPV)

- Intramuscular gluteal injections every 4 weeks or every 8 weeks, administered by a healthcare provider
- HHS guidelines panel recommends LA CAB/RPV as optimization strategy for HIV+ on ART with viral suppression for ≥ 3 months, who –
  - have no baseline resistance to either medication,
  - have no prior virologic failures,
  - do not have active HBV infection (unless also receiving oral HBV treatment),
  - are not pregnant and are not planning on becoming pregnant, and
  - are not receiving medications with significant drug interactions



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Tools to Achieve Treatment Goals

- Performing pretreatment resistance testing
- Maximizing adherence through use of simplified regimens with reduced pill burden
- **Selecting individualized ART regimen**

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

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Overview of ART Drug Classes

- Classification based on where in the viral life cycle each drug acts
- 6 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††
  - Capsid inhibitor††

*Recommended for most people with HIV
†Recommended in certain clinical situations
†† Not recommended for initial therapy

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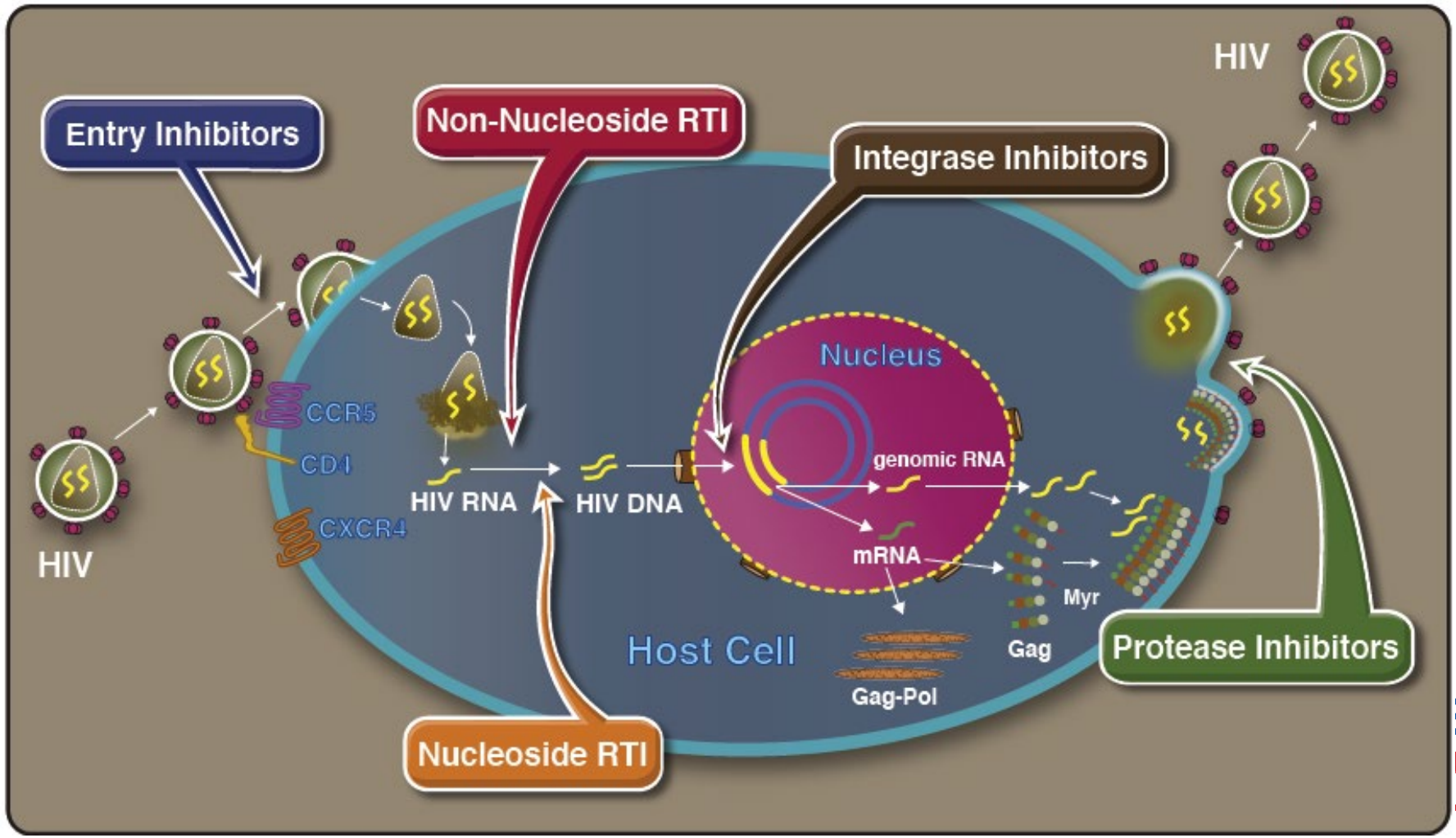
HIV Life Cycle & ARV Drug Classes



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®)~~ *discontinued January 2024*
- 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)
- Cabotegravir (CAB) (Vocabria®)
- 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®)
- Fostemsavir (Rukobia®)
- Ibalizumab (Trogarzo®)
- Maraviroc (MVC) (Selzentry®)

Capsid Inhibitor

- Lenacapavir (LEN) (Sunlenca®)

Single Tablet Regimens

- BIC/FTC/TAF (Biktarvy®)
- DRV/cobi/FTC/TAF (Symtuza®)
- DOR/3TC/TDF (Delstrigo®)
- DTG/3TC/ABC (Triumeq®)
- DTG/RPV (Juluca®)
- DTG/3TC (Dovato®)
- 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®)

Long-Acting Injectable ART

- CAB/RPV (Cabenuva®)

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 + 1 NNRTI†

*Recommended for most patients
†Recommended in certain clinical situations

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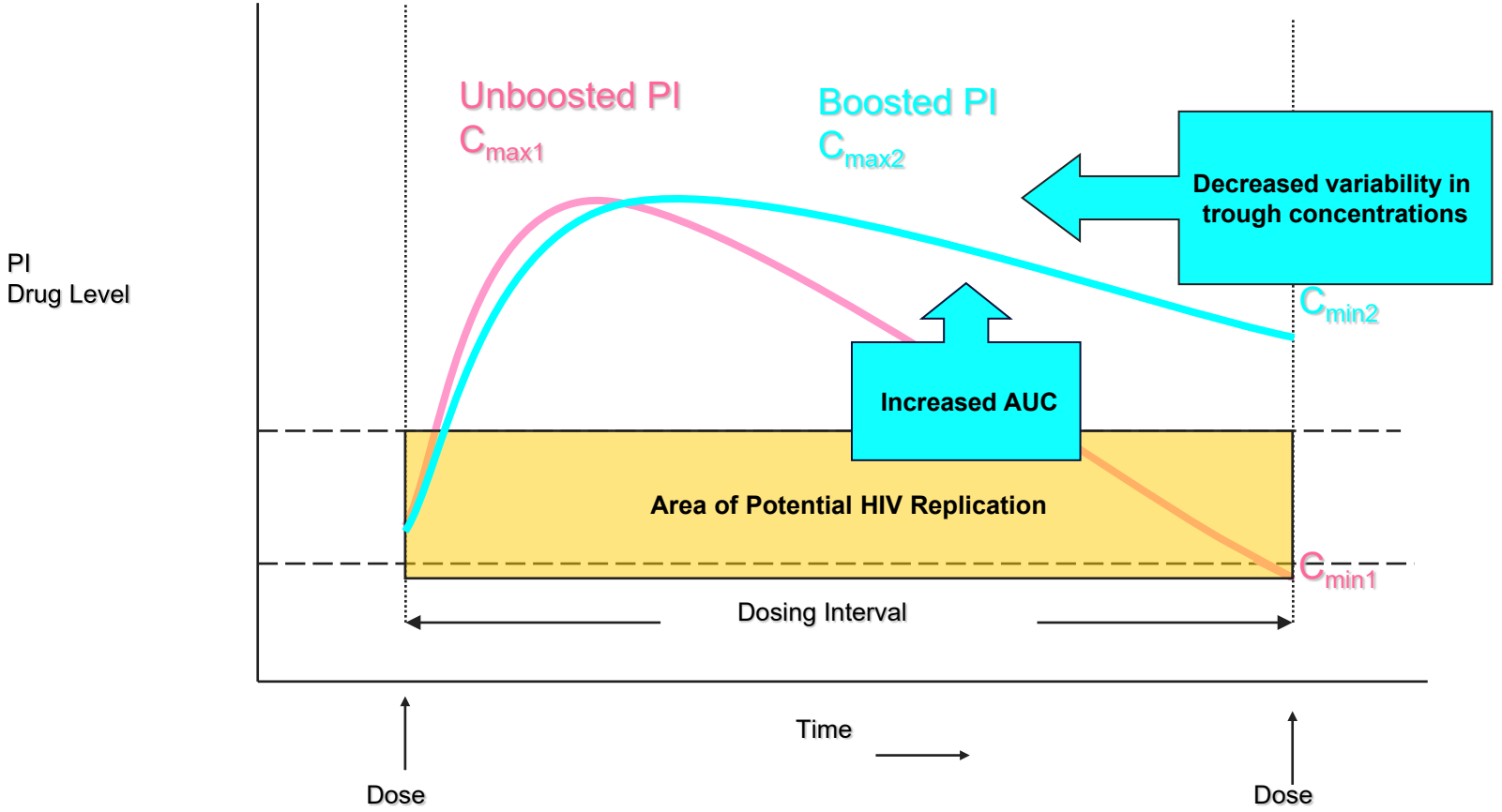
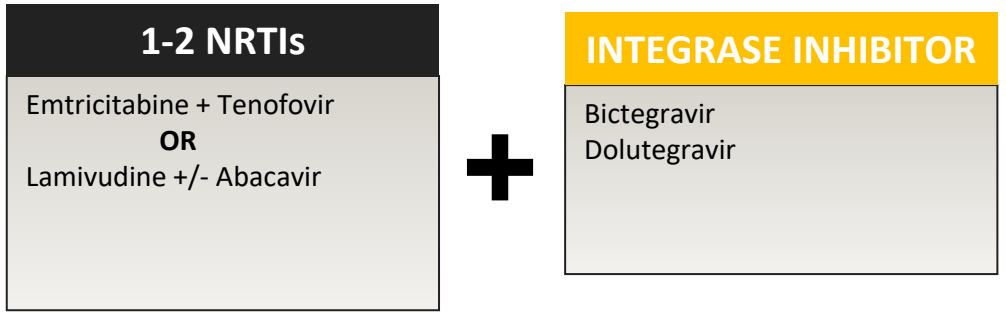
Boosting a Protease Inhibitor (PI) With Ritonavir or Cobicistat



Recommended Initial Regimens for Most People with HIV



Tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (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.

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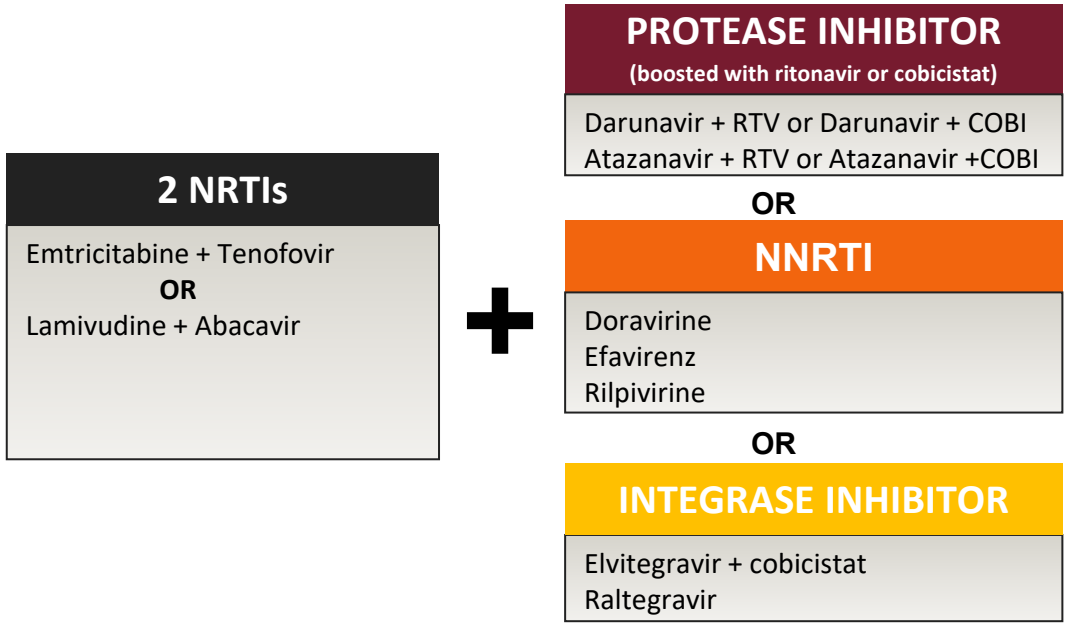
Recommended Initial Regimens in Certain Clinical Situations



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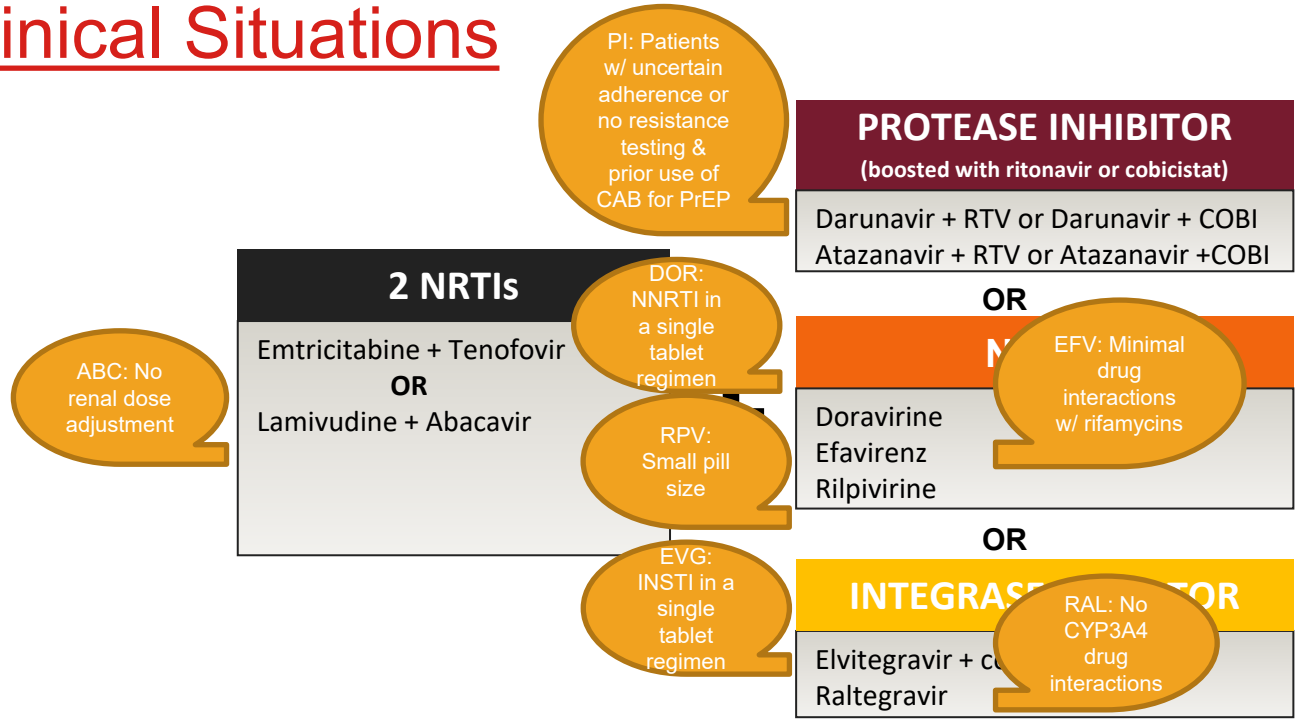

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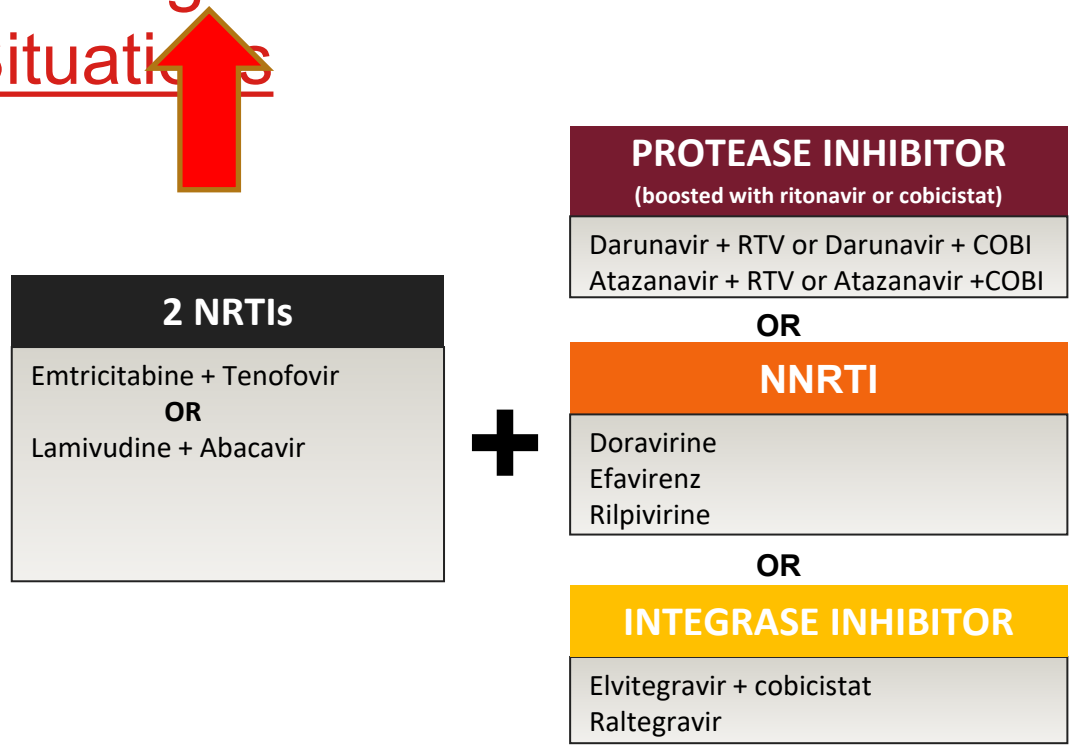
Selecting an Initial HIV Regimen: The “Chinese Food Rule”

Tip of the hat to Royce Lin, MD

Recommended Initial Regimens in Certain Clinical Situations



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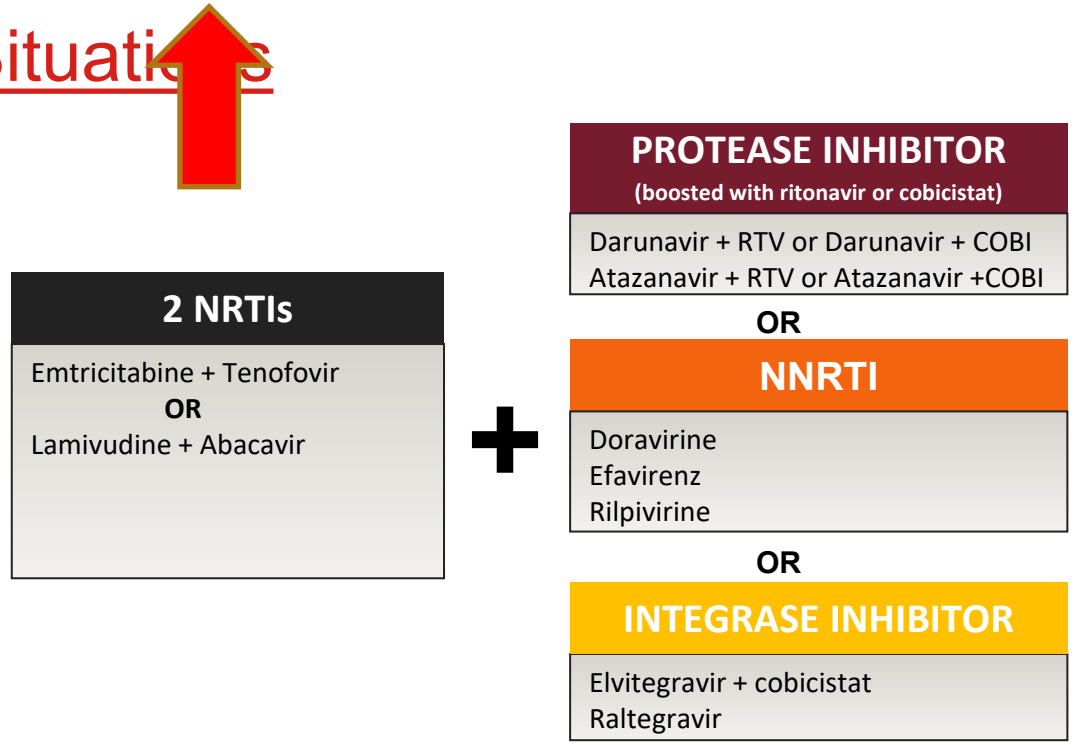

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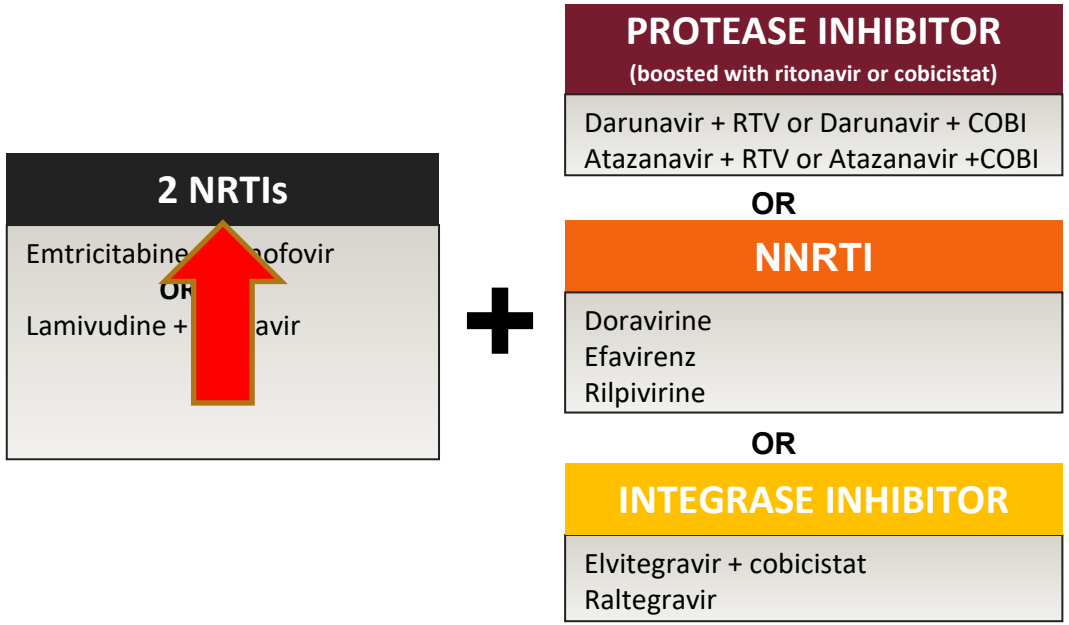

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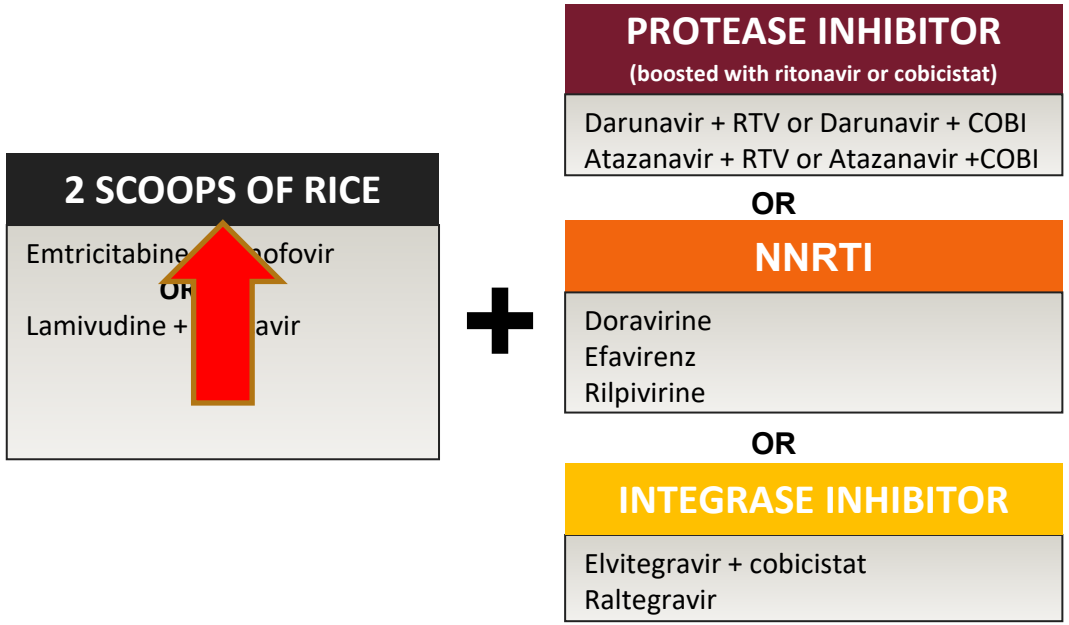

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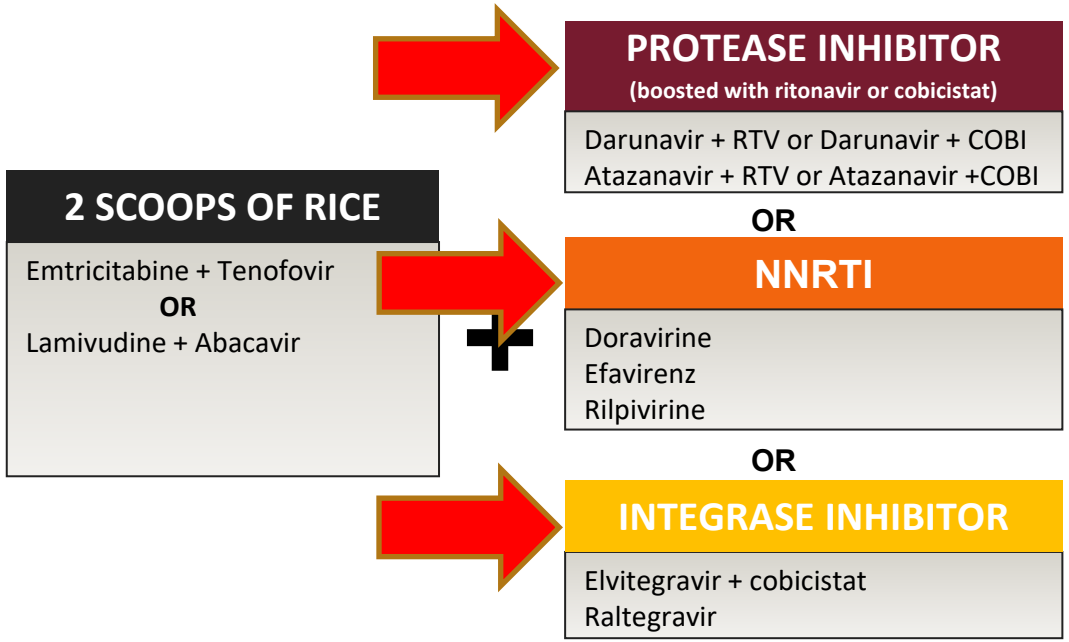

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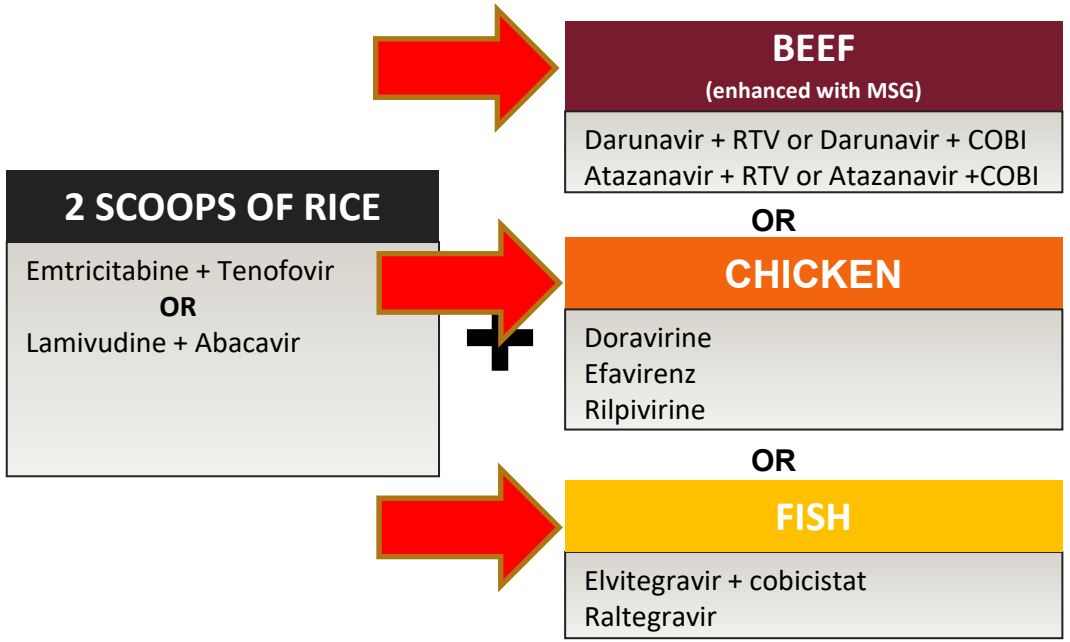

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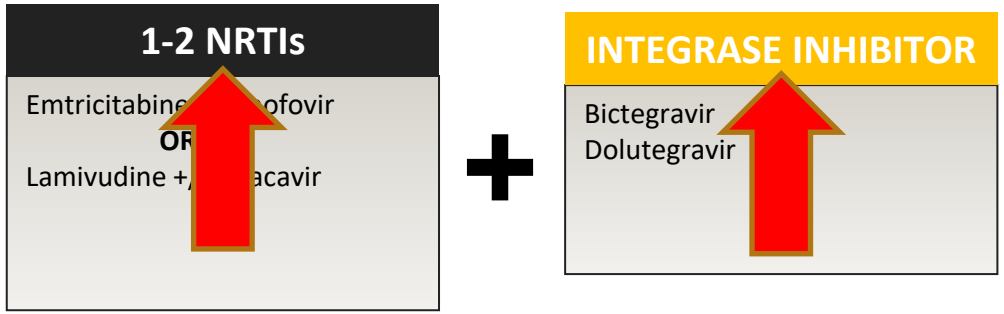

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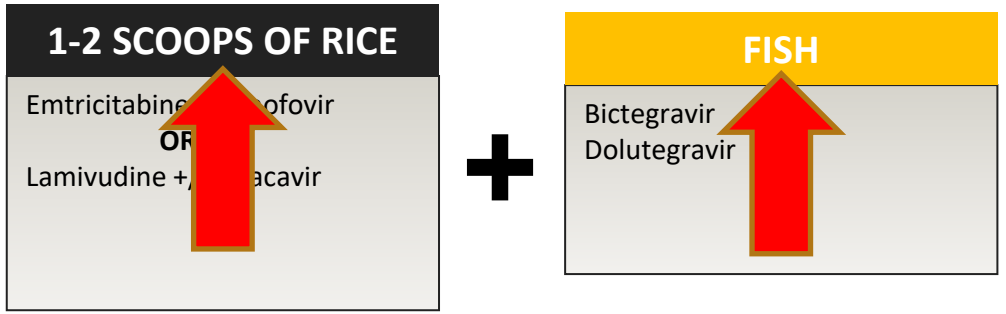

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HIV Regimen / Chinese Food Selection: A Stepwise Approach

1. Get 1-2 scoops of rice 
   - Choose 2 NRTIs, co-formulated when possible
     - Example: tenofovir + emtricitabine
     - Example: abacavir + lamivudine
   - Only 1 regimen uses 1 NRTI (lamivudine + dolutegravir)
     *Only for HIV RNA <500,000, no hepatitis B, no resistance

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

Choosing NRTI Backbone

Abacavir

- Black box warning: Hypersensitivity reaction
- Use only if HLA-B*5701 negative
- Possible ↑ risk of MI
- Less effective if VL>100K (unless its paired with dolutegravir/ lamivudine)

Tenofovir disoproxil fumarate (TDF)

- Loss of bone density (osteopenia and osteoporosis)
- Can cause renal impairment (Fanconi's syndrome, acute renal insufficiency)
- More favorable lipid profile compared to TAF

Tenofovir alafenamide (TAF)

- Less bone mineral density loss or adverse impact on renal function vs. TDF
- Has some P-gp mediated drug interactions that TDF does not have (anticonvulsants, rifampin)

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

PI + RTV or COBI (Beef + MSG)

PRO

- Very strong, potency well established
- Harder to get resistance
- In general, boosted DRV preferred over boosted ATV
- Best for patients with uncertain adherence or if resistance test results not yet available
- Use darunavir-based ART if prior use of long-acting cabotegravir for PrEP and INSTI resistance test result not yet available

CON

- Many drug interactions (P450 metabolism)
- Metabolic effects (↑ cholesterol, glucose)
- GI side effects
- Boosting required

INSTI (Fish)

PRO

- Highly effective for most patients
- Very few side effects
- Less drug interactions
- Less resistance observed with dolutegravir or bictegravir (strong, potent)
- Dolutegravir, bictegravir, and raltegravir have no food requirement

CON

- Some delicate, prone to resistance (e.g., raltegravir, elvitegravir)
- Weight gain (e.g. bictegravir, dolutegravir, especially when used with tenofovir alafenamide)
- DTG and BIC cause benign increase in SCr (mean 0.1 mg/dL)
- Rarely: insomnia, ↑CPK

NNRTI (Chicken)

PRO

- Efavirenz: minimal drug interactions with rifamycins
- Doravirine: less drug interactions, can take with or without food
- Rilpivirine is in smallest single tablet regimen

CON

- Prone to resistance
- Efavirenz has CNS side effects
- Doravirine comes co-formulated only with TDF/3TC
- Oral rilpivirine has lower efficacy in some patients (use only if CD4>200 and VL<100,000) and requires acidic environment for absorption

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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 ritonavir or cobicistat as boosters have a high potential for drug interactions
- Any changes to the medication list require careful consideration of potential 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 Inhibitors	•Maraviroc: Liver metabolism: P450 substrate •Fostemsavir: Liver metabolism: P450 substrate •Enfuvirtide: Peptide undergoes catabolism to amino acids: No known drug interactions •Ibalizumab: Metabolized by CD4 receptor internalization/ catabolism: No known drug interactions	Low-Medium
Capsid inhibitor	•Liver metabolism: P450 substrate & UGT1A1	Medium

Antiretrovirals Have Drug Interactions With Multiple Medications

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

ARV Interactions with Cholesterol Medications

- Statins (HMG Co-A reductase inhibitors) are P450 substrates
  - Degree of P450 metabolism varies:

    simva, lova >> rosuva > atorva > pitava > pravastatin
- May be affected by NNRTIs, PIs, cobicistat
- NNRTIs can ↓ statin levels
  - Monitor statin efficacy, ↑ dose as necessary (statin max dose limit applies)
- PIs and cobicistat ↑ statin levels
  - Avoid simvastatin, lovastatin (2000% ↑)
  - Myopathy including rhabdomyolysis

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

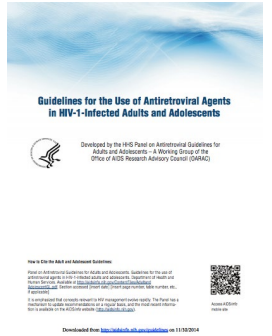
US HHS. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/

Resources: ART and Drug Interactions

- Department of Health and Human Services (HHS). Guidelines for the use of antiretroviral agents in adults and adolescents with HIV.

  [clinicalinfo.hiv.gov/guidelines]

  - **Tables 24-25**



- University of Liverpool HIV iChart app for iPhone and Android

  [www.hiv-druginteractions.org]

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Summary

- ART recommended for all HIV+
- Treatment goals achievable by using viral resistance testing, maximizing adherence, and selecting individualized ART regimen
- Initial ART = 1-2 NRTIs + INSTI or PI or NNRTI

  (1-2 scoops of rice + 1 main entrée)
- Pros and cons (including adverse effects) to each antiretroviral agent
  - ART is not a “one size fits all” approach
- ART presents high potential for drug interactions due to the way the medications are absorbed and metabolized

ART Part 1:
Introduction to Antiretroviral Therapy

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