HIV 1-2-3

A Step-By-Step Approach In Caring For Our HIV-Infected Patients

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Objectives

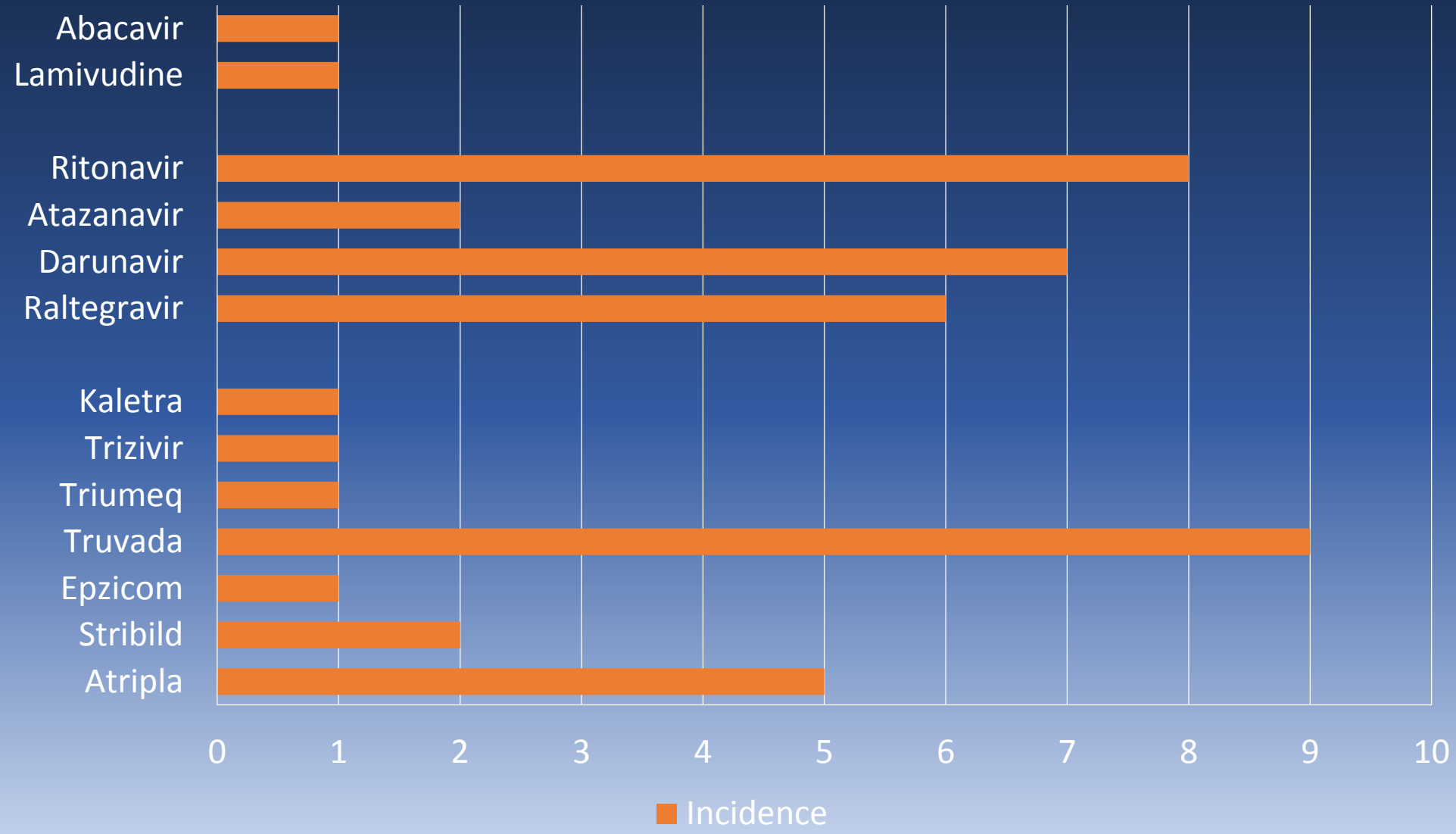
- Recognize appropriate indications for initiation of Highly Active Antiretroviral Therapy (HAART) for inpatients
- Select an appropriate guideline-based medication therapy regimen
- Overcome treatment barriers by recommending alternative dose preparations
- Evaluate the efficacy of a chosen medication regimen

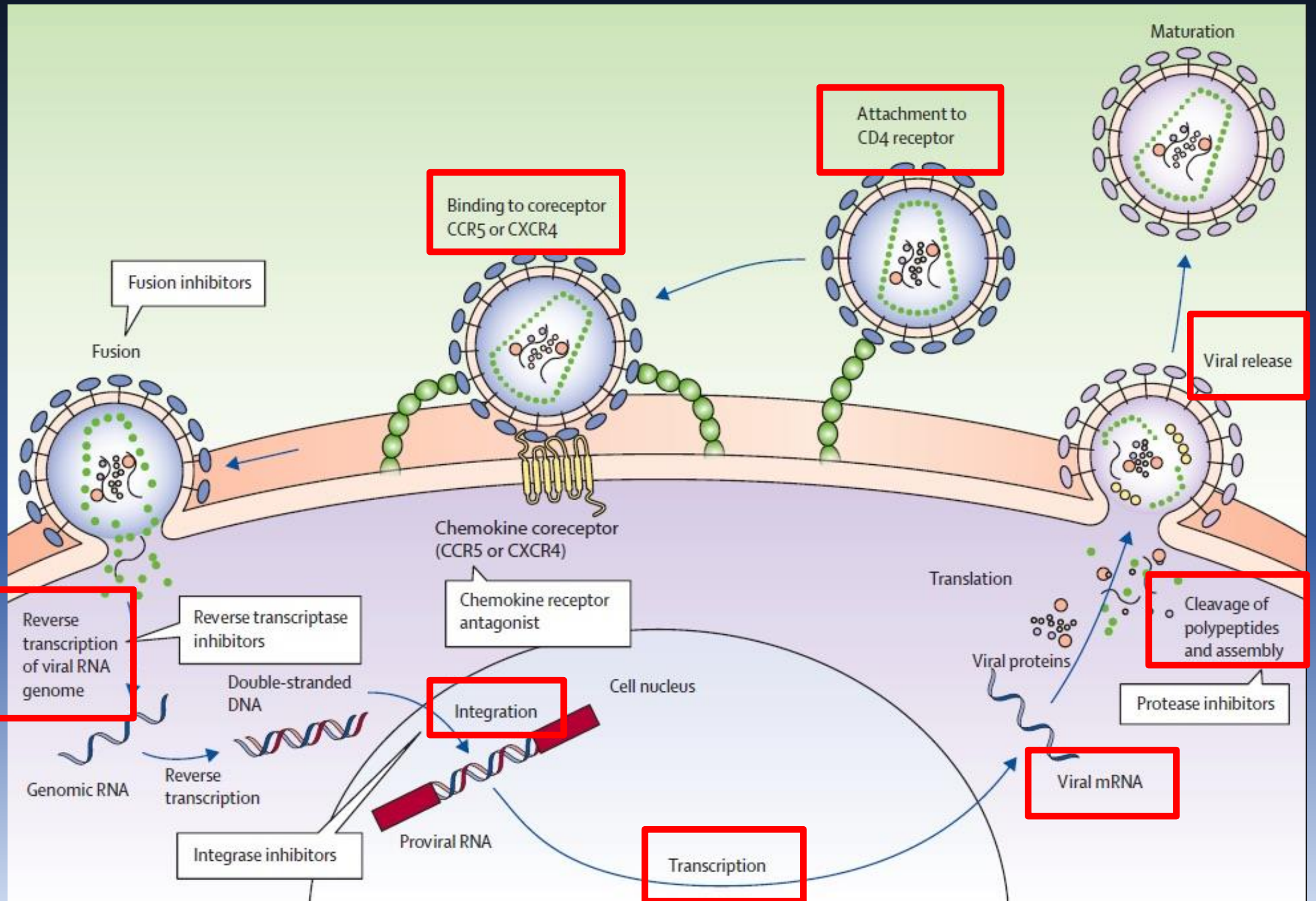
Abbreviations

q ” “ h = every ” “ hours	MATE 1 = Human multidrug and toxin extrusion protein 1
c/mL = copies per milliliter	dL – deciliter
HLD = hyperlipidemia	oz – ounces
ADE = adverse drug events	yr - year
DDI = drug-drug interactions	BCS = Biopharmaceutics Classification System
ART = Antiretroviral therapy	Tsp = teaspoon
/r = ritonavir boosted regimen	PO = by mouth
CrCl = creatinine clearance	HD = hemodialysis
BID = twice daily	mm^3 = cubed millimeters
RNA – Ribonucleic Acid	QD = daily
WHO – World Heath Organization	GIT – Gastrointestinal Tract

Epidemiology

HAART Therapy Options Utilized

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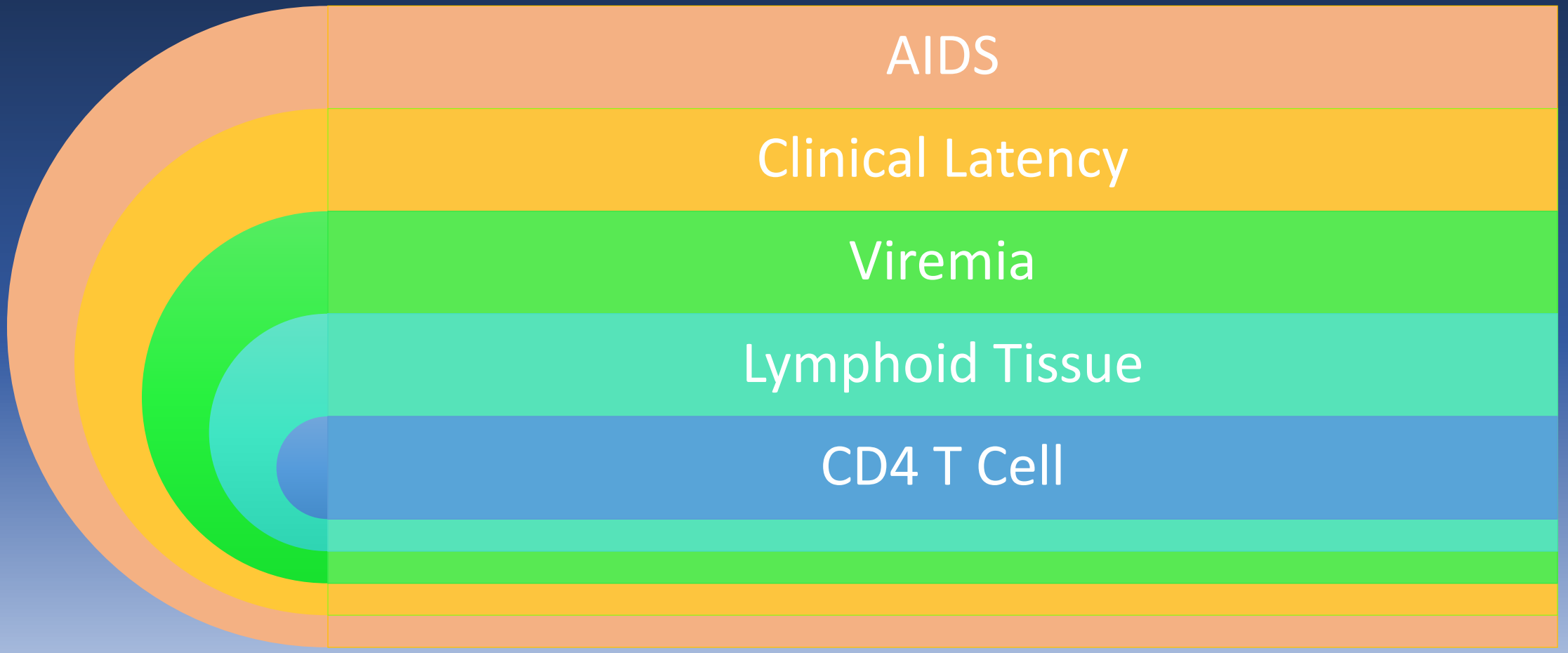
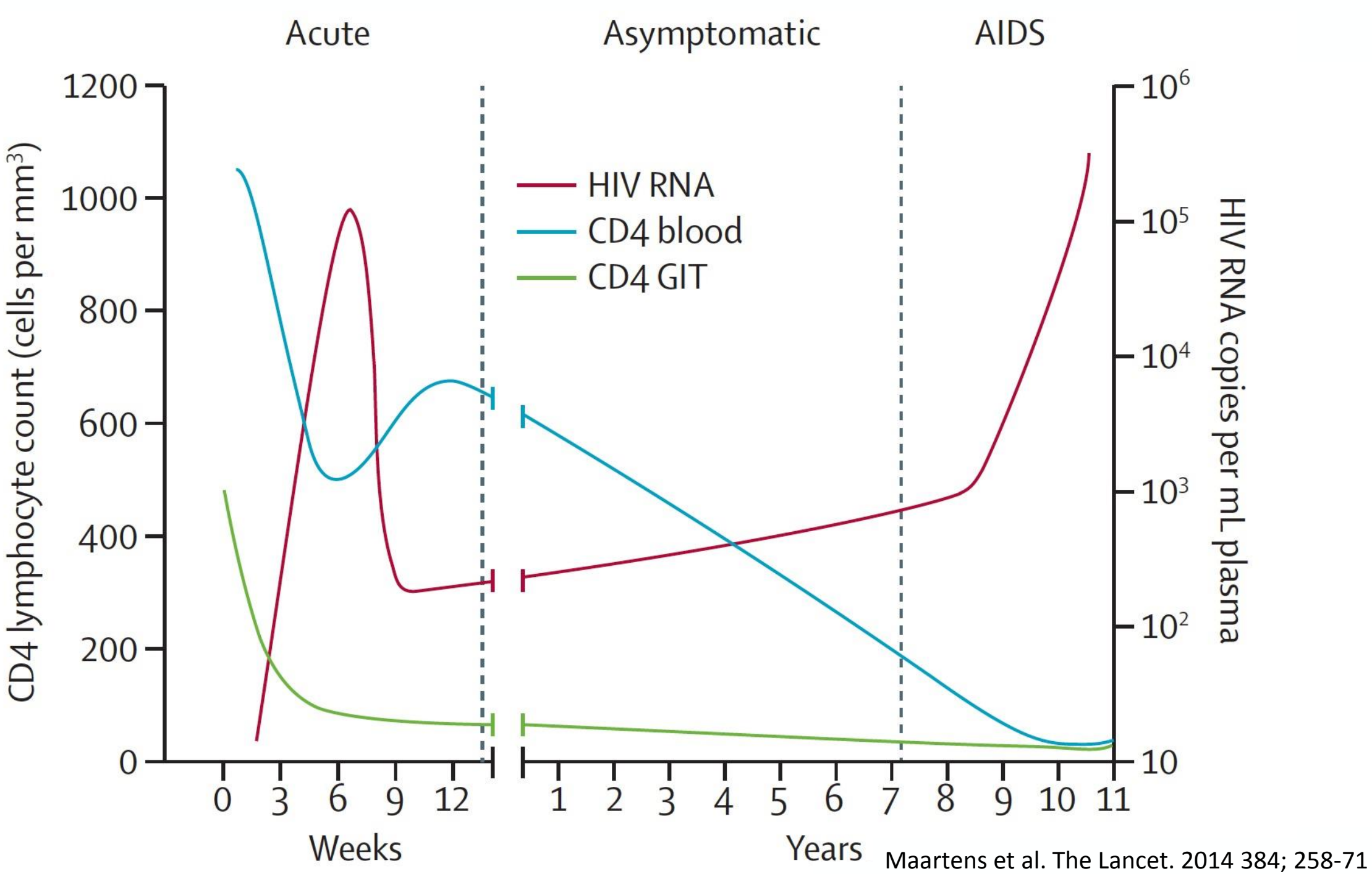
Pathophysiology





Maartens et al. The Lancet. 2014 384; 258-71

Step-By-Step

1. Time For Implementation
2. Regimen For Initiation
3. Monitoring For Suppression

Objective 1

Recognize appropriate indications for initiation of HAART therapy for inpatients

When to Start?

WHO 2010

All adults with CD4 ≦500

Priority:

CD4≦350 WHO stage of 1 or 2

Initiate at any CD4 count for severe/advanced disease (WHO stage 3 or 4)

WHO 2015

ALL adults regardless of WHO clinical stage

At any CD4 count

When To Start ART

ART guideline	Any symptoms Or CD4 <200	CD4 200-350	CD4 350-500	CD4 > 500
International Antiviral Society - USA	Treat	Treat	Treat	Treat
US Department of Health and Human Services	Treat (IA)	Treat (IA)	Treat (IA)	Treat (IA)

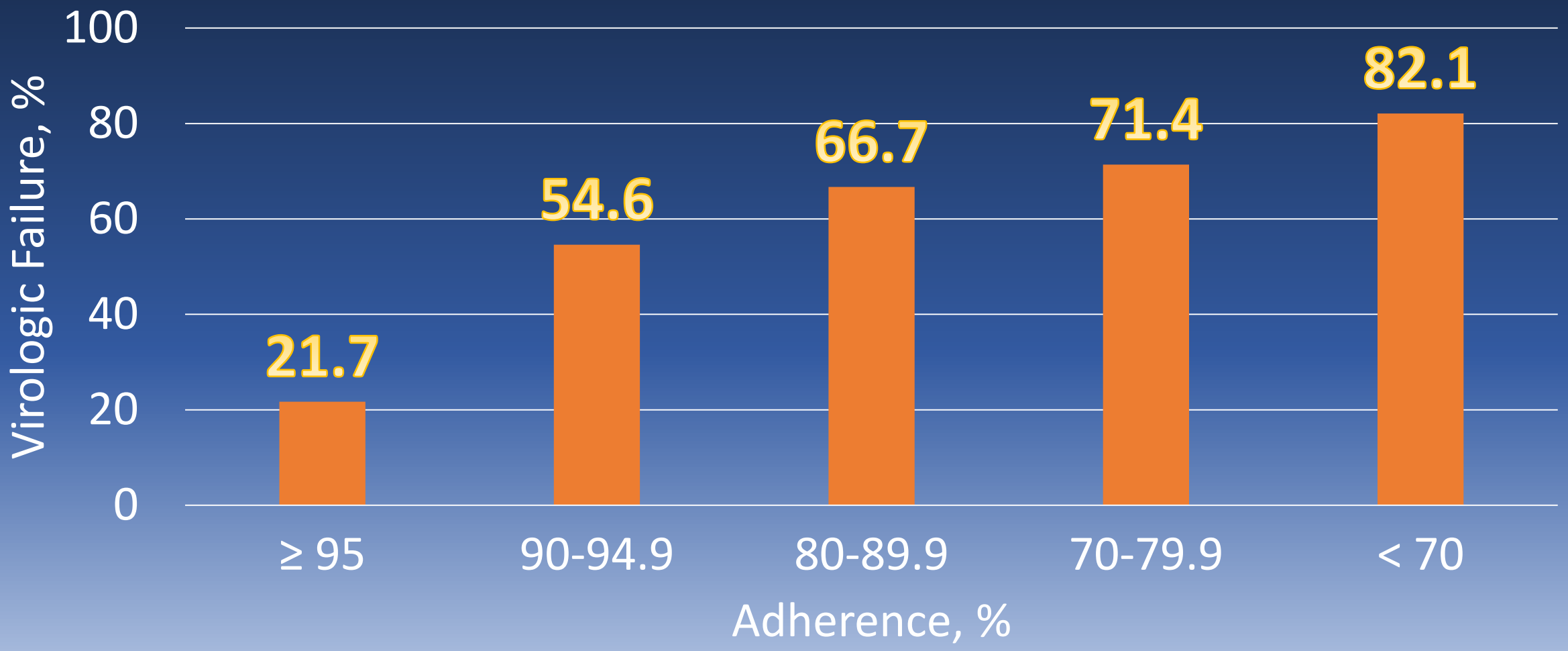
Rating of Recommendations:
A= Strong, B= Moderate, C= Optional
Rating of Evidence:
I= data from randomized controlled trials, II= data from well-designed non-randomized trials or observational cohort studies with long-term clinical outcomes, III= expert opinion

When NOT To Start

Treat regardless of CD4 count

Unwilling to Start

Adherence to Antiretroviral Activity



1. Paterson et al. 2002 136(3): 253.

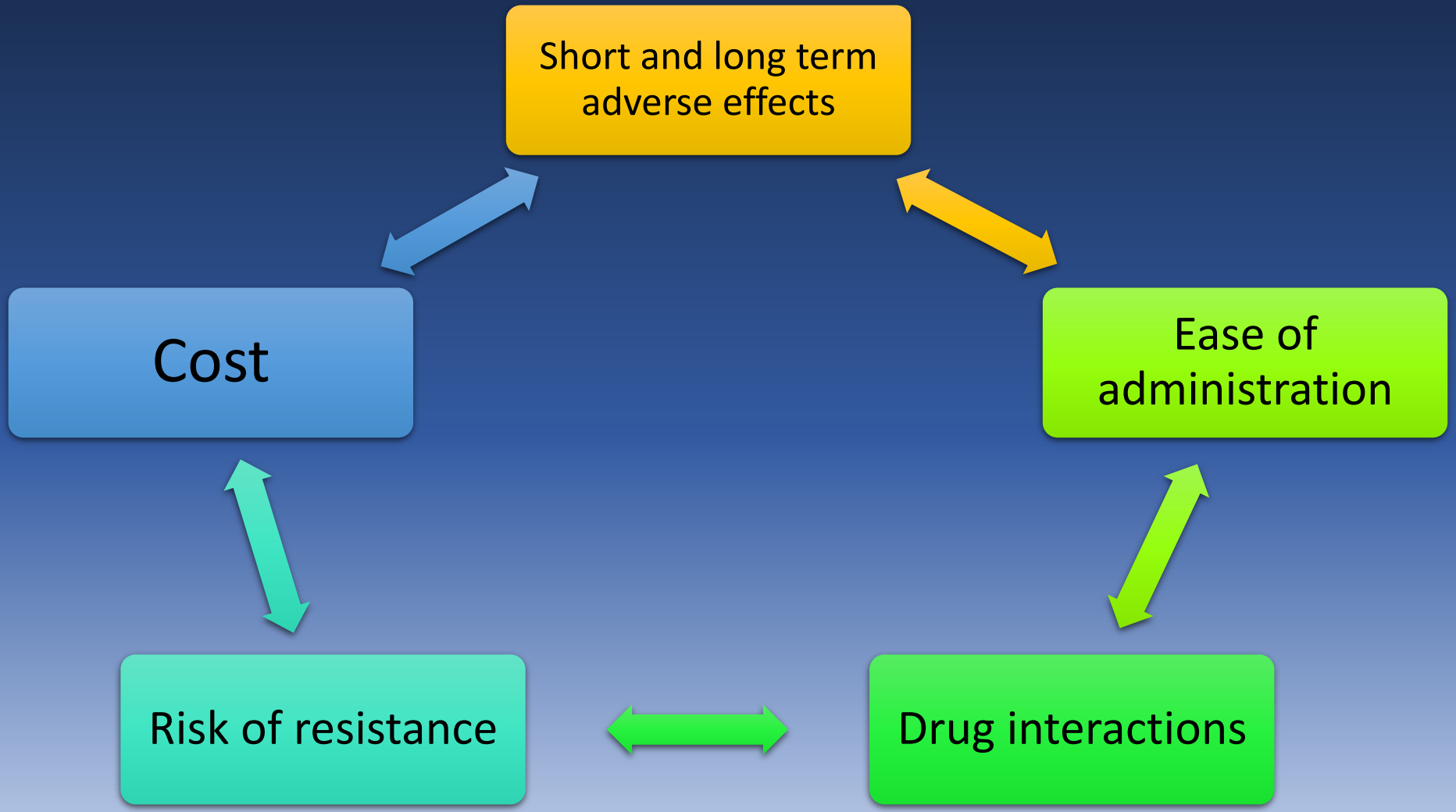
Objective 2

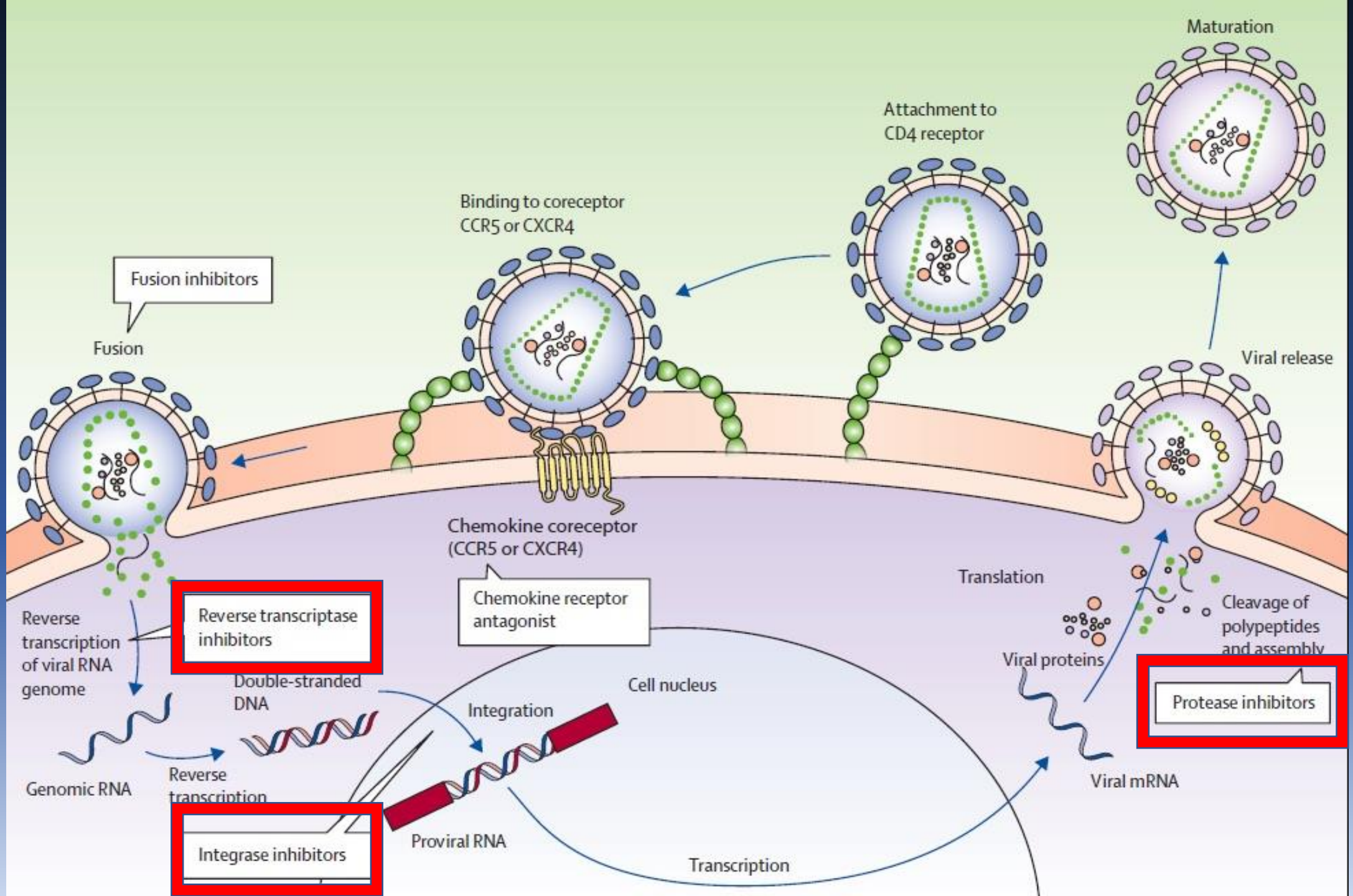
Select an appropriate guideline-based medication therapy regimen

Drug Abbreviations

ABC = Abacavir	**EFV** = Efavirenz	**RTV or /r** = Ritonavir
ddI = Didanosine	**ETR** = Etravirine	**SQV** = Saquinavir
FTC = Emtricitabine	**NVP** = Nevirapine	**TPV** = Tipranavir
3TC = Lamivudine	**RPV** = Rilpivirine	**ENF** = Enfuvirtide
D4T = Stavudine	**ATV** = Atazanavir	**MVC** = Maraviroc
TAF = Tenofovir alafenamide fumarate	**DRV** = Darunavir	**RAL** = Raltegravir
TDF = Tenofovir disproxil fumarate	**FPV** = Fosamprenavir	**EVG** = Elvitegravir
ZDV = Zidovudine	**IDV** = Indinavir	**DTG** = Dolutegravir
DLV = Delavirdine	**NFV** = Nelfinavir	**/c** = Cobicistat

Principles of Therapy

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Nucleoside Reverse Transcriptase Inhibitors (NRTI) – Truvada, Epzicom, Trizivir

Adverse Effects:

- Lactic Acidosis
- Hepatic Steatosis
- Nausea and Vomiting
- ZDV: myopathy, bone marrow suppression

Risk of Resistance:

- ↑ prevalence over PIs, InSTIs

Drug Interactions:

- CYP450: None
- TDF/ZDV: need “boosted” PI

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI) – Efavirenz, Rilpivirine

Adverse Effects:

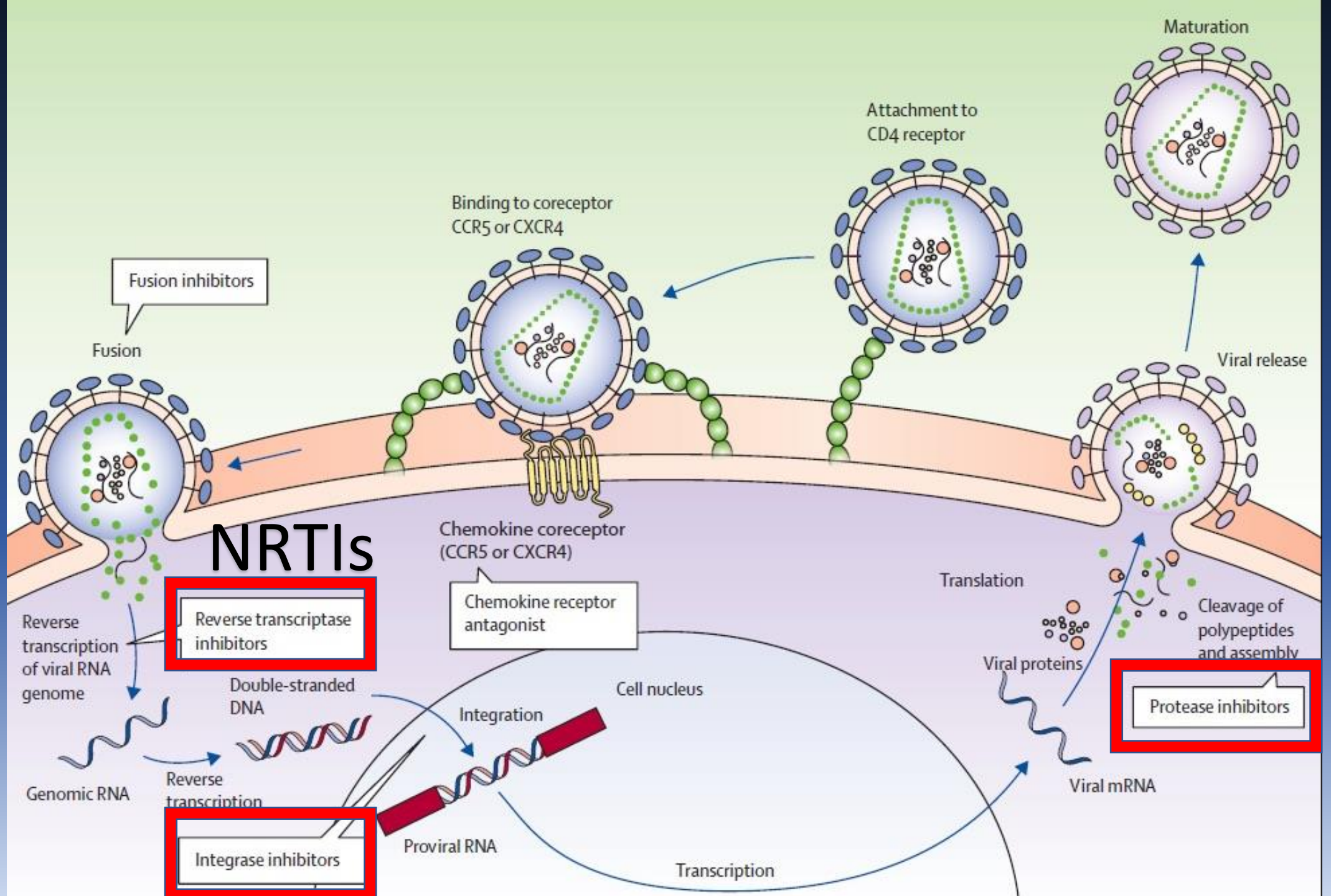
- Suicidal, depression, sleep disturbances
- Rash – all NNRTIs
- RPV: ↑ QT prolongation
- EFV: ↑ LDL, ↑ TG

Risk of Resistance:

- RPV when HIV RNA <100,000 and CD4 >200
- Low genetic barriers

Drug Interactions:

- EFV: Substrate (2B6, 3A4)
  Inhibitor (2C19, 2C9, 3A4)
  Inducer (3A4)
- RPV: Substrate (3A4)
- QT-prolonging agents
- Gastric Suppression: ↓ Drug levels, pH dependent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Protease Inhibitors (PIs) – Atazanavir, Darunavir, Ritonavir

Adverse Effects:

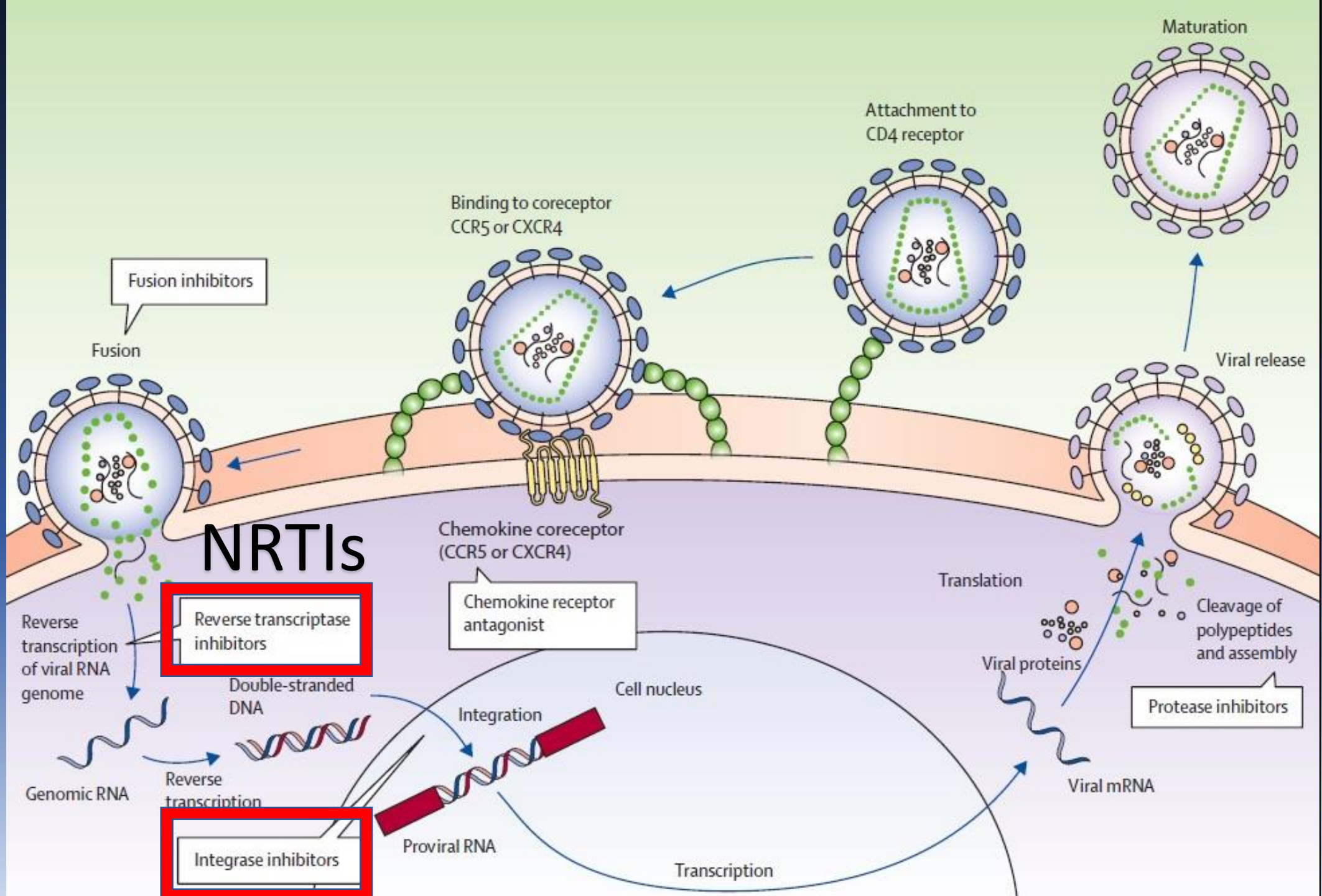
- Bleeding – hemophilia
- Rash
- Drug – induced hepatitis
- Dyslipidemias
- ATV – Cholelithiasis, kidney stones

Risk of Resistance:

- Low transmitted resistance
- DRV/r

Drug Interactions:

- Substrate and inhibitor of CYP3A4
- DRV: Inducer CYP 2C9
- RTV: Inhibitor 2D6
- ATV/r: ↓ concentration with ↑ in pH
- ↑ concentration of immunosuppressants, benzodiazepines
- Consider Rifabutin over Rifampin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Integrase Strand Transfer Inhibitors (INSTI) – Raltegravir, Elvitegravir, Dolutegravir

Adverse Effects: (< 5 %)

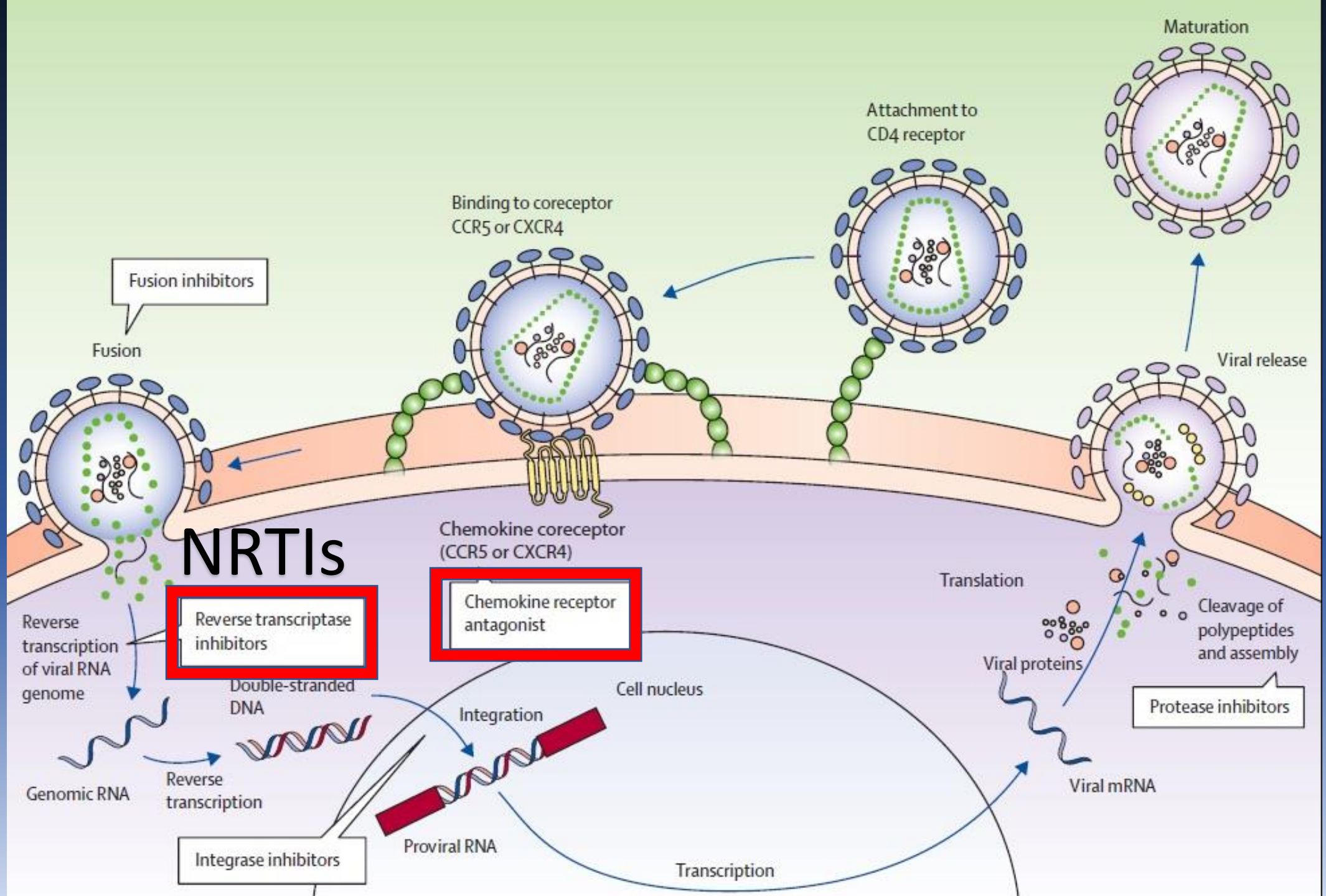
- Nausea/Diarrhea
- Headache
- Insomnia, depression, suicidality
- EVG/c: Dyslipidemias

Risk of Resistance:

- High barrier to resistance
- DTG - resistance uncommon

Drug Interactions:

- EVG/c: Substrate 3A4 Inducer of 2C9
- DTG: Substrate of 3A4 (weak)
- Separate from cations by at least 2 hours; require gastric acid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Chemokine Receptor Antagonist (CCR-5) - Maraviroc

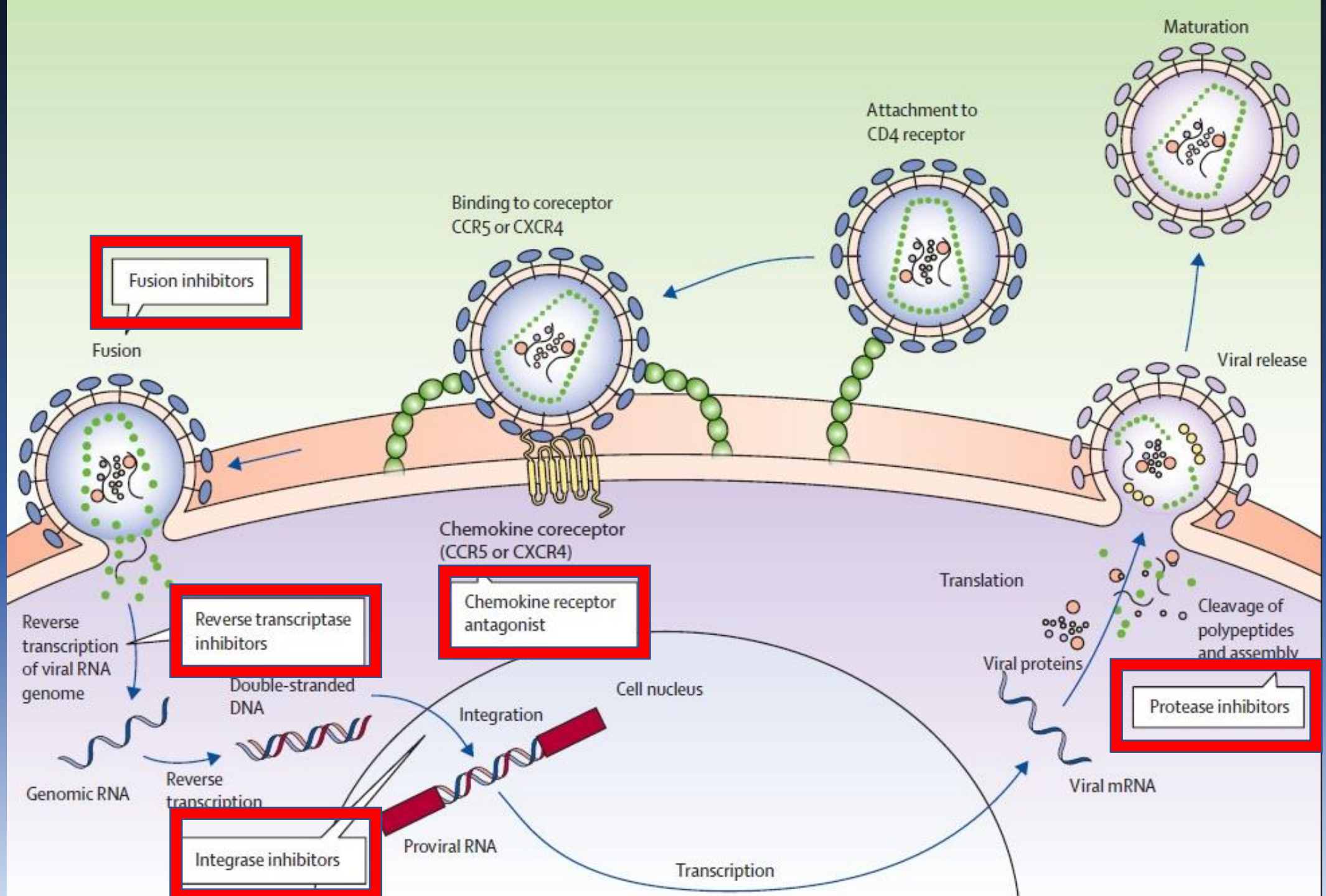
Role: Alternative regimen (with 2 NRTIs) in treatment naïve and treatment experienced patients with multi-drug resistant strains

Adverse Effects:

- Hepatotoxicity
- ↓ Blood Pressure, syncope
- Cough, fever, rash (>10%)

Drug Interactions:

- CYP3A4 substrate
- 3A4 inhibitors, ↓ dose
- 3A4 inducers, ↑ dose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Fusion Inhibitor - Enfuvirtide

Role: Alternative incorporated in a 3-4 drug regimen for treatment experienced patients that is currently active against its viral strain

Adverse Effects:

- Hypersensitivity reaction (fever, rash, chills, ↓BP)
- Diarrhea, nausea, fatigue (> 10%)
- Local injection site reactions

Drug Interactions:

- None clinically significant

Cost:

- Roughly $20,000/year

CYP450 Isoenzyme Inhibitor – Cobicistat

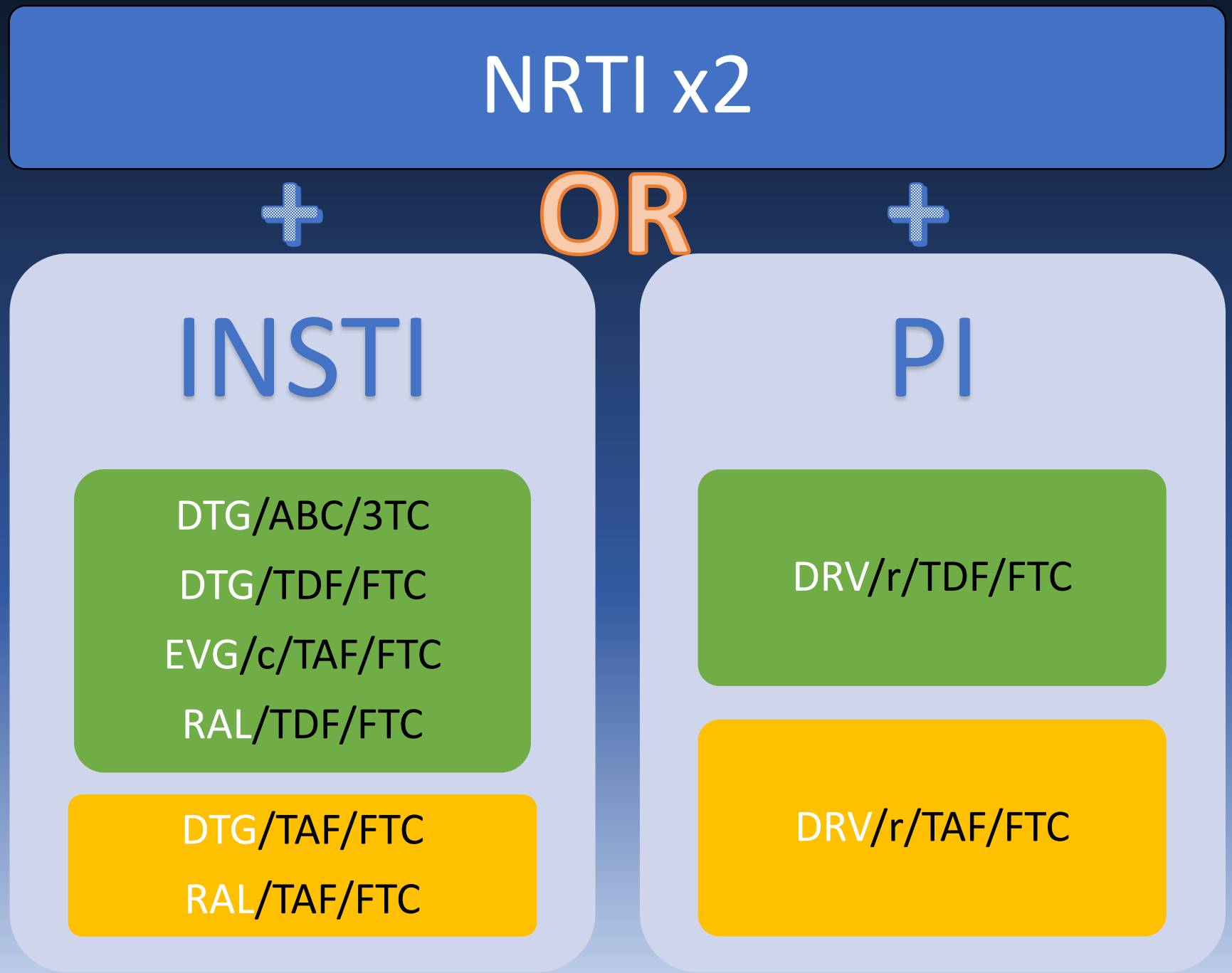
Role: Boost efficacy of Elvitegravir, Emtricitabine, Atazanavir, Darunavir which are susceptible to CYP3A4 metabolism

Adverse Effects:

- Falsely elevate SCr (↑0.4 mg/dL)

Drug Interactions:

- CYP3A4 inhibition primary mechanism


NRTI x2
+
OR
+
INSTI
PI
DTG/ABC/3TC
DTG/TDF/FTC
EVG/c/TAF/FTC
RAL/TDF/FTC
DTG/TAF/FTC
RAL/TAF/FTC
DRV/r/TDF/FTC
DRV/r/TAF/FTC
Class IA
Class IIA

NRTI x2

+ OR +

PI

ATV/c or/r +TDF/FTC

ATV/(c or r) +TAF/FTC
DRV/r/ABC/3TC
DRV/c/TDF/FTC
DRV/c/TAF/FTC

DRV/c/ABC/3TC

NNRTI

EFV/TDF/FTC
RPV/TDF/FTC

EFV/TAF/FTC
RPV/TAF/FTC

Class IB

Class IIB

Class IIIB

Question

- Which HIV medication therapy class is required to be present in every combination regimen according to HIV guidelines?

- A. INSTI (Integrase Strand Transfer Inhibitor)
- B. NNRTI (Non-Nucleoside Reverse Transcriptase Inhibitor)
- C. NRTI (Nucleoside Reverse Transcriptase Inhibitor)
- D. PI (Protease Inhibitor)

Question

- Which HIV medication therapy class is required to be present in every combination regimen according to HIV guidelines?

- A. INSTI (Integrase Strand Transfer Inhibitor)
- B. NNRTI (Non-Nucleoside Reverse Transcriptase Inhibitor)
- **C. NRTI (NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR)**
- D. PI (Protease Inhibitor)

Question

- What HIV medication offers the only subcutaneous injectable option among all classes of therapy?

- A. Enfuvirtide
- B. Zidovudine
- C. Tenofovir
- D. Maraviroc

Question

- What HIV medication offers the only subcutaneous injectable option among all classes of therapy?

- **A. ENFUVIRTIDE**
- B. Zidovudine
- C. Tenofovir
- D. Maraviroc

Objective 3

Overcome treatment barriers by recommending alternative dose preparations

Alternative Administration - NRTIs

Abacavir	Didanosine	Emtricitabine	Lamivudine
Crush/Split ✓	Crush ✗	Open Capsule ✗	Split ✓ 150 mg tab
Food: No preference	Food: No	Food: No preference	Food: No preference
20 mg/mL liquid	Powder Solution: 10 mg/mL	10 mg/mL liquid	10 mg/mL liquid

Manufacturer Notes - NRTIs

Abacavir

*tablets may be crushed and added to semi-solid food or liquid

Didanosine

Mix with liquid antacid to 10 mg/mL concentration (1:1)

Emtricitabine

Solution well tolerated

Cotton candy flavor

Refrigerate

Lavmivudine

Solution well tolerated

Strawberry-Banana flavor

Room Temperature

Alternative Administration - NRTIs

Stavudine

- Open Capsule ✓
- Food: No preference
- Powder Solution 1 mg/mL

Tenofovir Disoproxil Fumarate

- Crush ✓
- Food: No preference
- Oral Powder 40 mg/scoop

Zidovudine

- Crush ✓
- Open Capsule ✓
- Food: No preference
- 10 mg/mL syrup

Manufacturer Notes - NRTIs

Stavudine

[1]dissolve capsule contents in 5-10 mL of tap water

Reconstitute powder with purified water; Refrigerate

TDF

[2]Disintegrate tablets in water, grape juice, or orange juice

Zidovudine

Tablets/opened capsules may be added to small amount of semi-solid food or liquid for immediate consumption

1. Innes S, et al. Antivir Ther 2011; 16(7):1131-4
2. Davis B, In-house study by Gilead Sciences, 2014

Alternative Administration - NNRTIs

Delavirdine

Crush ✓
100 mg tablet

Crush ✕
200 mg tablet

Efavirenz

Crush ✕

Open Capsule ✓

Liquid no longer manufactured

Food: No, with intact dose

Etravirine

Crush ✓

Food: Yes

Nevirapine

Crush ✓
200 mg IR

Crush ✕
400 mg XR

Oral suspension
10 mg/mL

Rilpivirine

Crush ✓

Food: Yes

Manufacturer Notes - NNRTIs

Delavirdine

100 mg tablets dispersed in ≥ 3 oz of water

Efavirenz

[1]Disperse in applesauce, grape jelly, or yogurt (1-2 tsp)

Administer 30 min after mixing; 90 mL additional of water post ingestion

Etravirine

Disperse tablets in 5 mL of water and stir; may add more water, orange juice or milk; drink immediately

Nevirapine

Crushed in small amount of semi-solid food

Rilpivirine

Full dose may be tough to recover due to small tablet size; can be added to small amount of food if ingested immediately

1. Kaul S, et al. Am J Health Syst Pharm 2010;67:217-22

Alternative Administration - PIs

Atazanavir	Darunavir	Fosamprenavir	Indinavir
Open capsules ✓	Crush ✓ IR tablet	Crush ✕	Open Capsules ✕
Food: Yes	Food: Yes		
Powder 50 mg/1.5 gm	Oral suspension 100 mg/mL	Oral suspension 50 mg/mL	Oral suspension 10 mg/mL

Manufacturer Notes - PIs

Atazanavir

Mix powder with food (applesauce or yogurt)

Open capsules mixed with applesauce yielded 91.7% bioavailability comared to intact capsules

Darunavir

Food ↑ bioavailability

[1]Crushed tablets in 15-20 mL water documented adequate drug levels

Fosamprenavir

Suspension taken on empty stomach (1 hr before & 2 hrs after)

Indinavir

Do not open capsules; No pharmacokinetic data available

Bitter taste

[2]10 mg/mL suspension compounded; stability 14 days

1. Kim et al. CJHP 2014;67(1):39-42). ICU case report.
2. Hugen et al. AJHP 2000; 57(14):1332-9.

Alternative Administration - PIs

Nelfinavir

- Crush ✓
- Food: Yes
- Oral Powder 50 mg/g

Ritonavir

- Crush ✗
- Open capsules ✗
- Oral syrup 80 mg/mL

Saquinavir

- Open capsules ✓
- Bitter taste
- Food: Yes
- Also more palatable

Tipranavir

- Open capsules ✗
- Food: Given with Ritonavir ✓
- Oral solution 100 mg/mL

Manufacturer Notes - PIs

Nelfinavir

Dissolve in 5 mL water

Mix with milk, not juice

May crush in pudding

Ritonavir

Mix solution with milk/pudding

Give after popsicle

Give after grape jelly, peanut butter

Give strong flavor after dose; syrup, cheese

Saquinavir

Capsule contents added to 15 mL simple syrup or 3 tsp of jam, stir for 30-60 sec

[1]Open-label study demonstrated 10% higher bioavailability with simple syrup

Tipranavir

Opening capsule not recommended to avoid altering absorption of emulsified suspension

Solution contains 116 IU/mL vitamin E

1. McKay et al. 8th Int Workshop Clin Pharm HIV Ther 2007, abstract 6

Alternative Administration - INSTIs

Dolutegravir

Crush ✓

Food: No preference

Elvitegravir

Crush ✕

Food: Yes

Raltegravir

* Crush ✓

25 & 100 mg chew

Crush ✕

400 mg tablet

* Oral suspension: 20 mg/mL

Manufacturer Notes - INSTIs

Dolutegravir

Crush in small amount of semisolid food or water

Elvitegravir

Insoluable in water; crushing/splitting tablets not recommended

Raltegravir

Chew tabs and suspension not studied in 12 yr or older

Max dose of chew tabs:

300 mg BID

Max dose of suspension:

100 mg BID

Alternative Administration - CCR-5 Antagonist

Maraviroc

Crush ✕

Food: No preference

Oral solution: 20 mg/mL

Alternative Administration - Miscellaneous

Cobisistat

Crush ✕

Food: Yes

Alternative Administration – Dual NRTI

Epzicom 3TC + ABC	Truvada TDF + FTC	Trizivir ABC + 3TC + ZDV	Combivir 3TC + ZDV
[1]Crush/Split ✓	Crush/Split ✓ Grape or orange juice	No data on stability of crushed tablets	Crush ✓
ABC: Liquid 3TC: Liquid	Available as separate liquids	All available as liquid products	Small amount of semisolid food or water

1. European Medicines Agency, 2010

Alternative Administration – NRTI-INSTI

Genvoya

EVG/c + FTC + TAF

Crush/Split ✕

EVG/c insoluble in water

Stribild

EVG/c + FTC +TDF

[1]Crush ✓

No PK/PD data

Food: Yes

Triumeq

ABC + 3TC + DTG

Crush ✓

ABC: Liquid

3TC: Liquid

DTG: Crush ✓

1. Fulco et al. AJHP 2014;71(10);784-6

Alternative Administration - NRTI-NNRTI

Atripla	Odefsey	Complera
FTC + TDF + EFV	FTC + RPV + TAF	FTC + TDF + RPV
Split tabs: Not studied	Crush ✕	Crush ✕
[1]Suspension NOT bioequivalent	Food: Yes	Food: Yes

1. King et al. JAIDS 2011;56(5):e131-2

Alternative Administration – Boosted PI

Prescobix

DRV/c

Crush/Split ✕

DRV: Liquid

RTV: Liquid (sub)

Evotaz

AZT/c

Crush ✓

Split and/or chew

Food: Yes

Kaletra

LPV/r

Crush ✕

[1]Significantly lower AUC with crushed tablets

Liquid 80 mg/20 mg/ 1 mL

1. Best et al. JAIDS 2011;58:385-91

Question

- Which of the following is NOT an appropriate combination for treatment of HIV?

- A. Emtricitabine + Tenofovir + Raltegravir
- B. Lamivudine + Abacavir + Darunavir/Ritonavir
- C. Zidovudine + Atazanavir/Ritonavir + Efavirenz
- D. Emtricitabine + Tenofovir + Efavirenz

Question

- Which of the following is NOT an appropriate combination for treatment of HIV?

- A. Emtricitabine + Tenofovir + Raltegravir
- B. Lamivudine + Abacavir + Darunavir/Ritonavir
- **C. ZIDOVUDINE + ATAZANAVIR/RITONAVIR + EFAVIRENZ**
- D. Emtricitabine + Tenofovir + Efavirenz

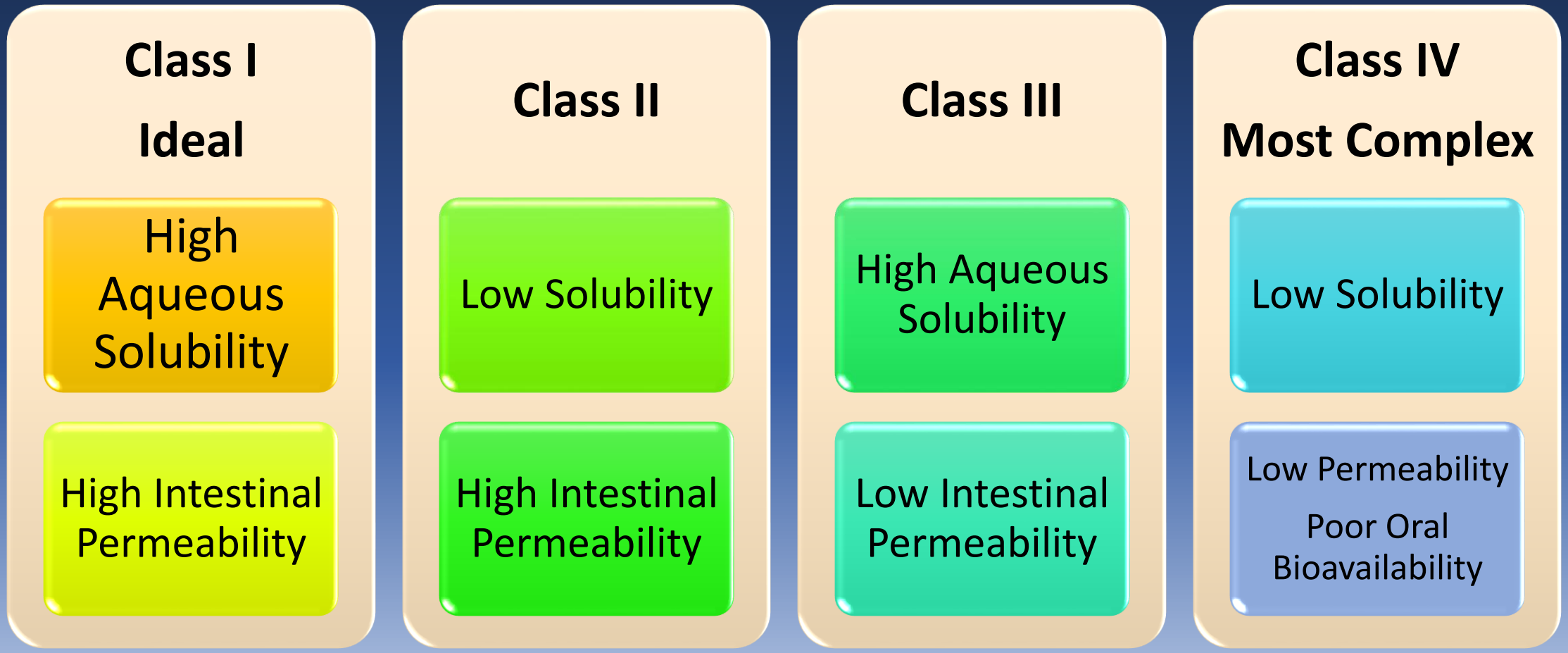
Enteral Tube Considerations

Challenges:	Considerations:
Reduced efficacy	Site of absorption
Drug-enteral formula interactions	Distal location of tube
Tube Occlusions	Effects of food

Barriers to Enteral Administration

- Reduced drug absorption and efficacy
  - Acidic vs. alkaline environment of GI tract
    - pH of stomach – 1 to 2
    - pH of duodenum – 4 to 5
    - pH of distal end of small intestine – 7 to 8
- Inadequate dissolution
  - Require exposure to gastric acid, bile salts, and pancreatic enzymes
  - Bypassed by feeding tubes

Biopharmaceutics Classification System (BCS)



Access this information for each specific antiretroviral at http://www.tsrlinc.net/search.cfm

BCS Classification - NRTIs

Drug Name	BCS	Absorption	Characteristics
Abacavir (ABC)	III	Duodenum	Rapidly and extensively absorbed
Didanosine (ddI)	III	Small Intestine	Acid-labile, enteral tube not recommended
Emtricitabine (FTC)	I		High solubility; high permeability
Lamivudine (3TC)	III	Small intestine	High
Stavudine (D4T)	I	Upper intestine	
Tenofovir disproxil (TDF)	III	Upper intestine	Solubility increases in acidic environment
Zidovudine (ZDV)	I	Small intestine	High solubility; high permeability

BCS Classification - NNRTIs

Drug Name	BCS	Absorption	Characteristics
Delavirdine (DLV)	No Data		
Efavirenz (EFV)	II/IV	Upper intestine	Practically insoluble in water
Etravirine (ETR)	IV	Unknown	Highly Lipophilic, insoluble in water, food
Nevirapine (NVP)	II	Absorbed best in Jejunum	Studied in children age range 5-12
Rilpivirine (RPV)	II	Unknown	Solubility and absorption are pH dependent

BCS Classification - PIs

Drug Name	BCS	Absorption	Characteristics
Atazanavir (ATV)	II	Intestine	Requires pH of <4 for dissolution and absorption
Darunavir (DRV)	II	Small intestine	
Fosamprenavir (FPV)	II	Duodenum	
Indinavir (IDV)	IV	Duodenum	Gastric pH required for absorption
Nelfinavir (NFV)	IV	Unknown	Food ↑ bioavailability
Ritonavir (RTV)	IV	Unknown	Lipophilic drug
Saquinavir (SQV)	IV	Proximal small intestine	
Tipranavir (TPV)	II	Unknown	Antacids may reduce absorption
Lopinavir (LPV)	II	Unknown	

BCS Classification - INSTIs

Drug Name	BCS	Absorption	Characteristics
Raltegravir (RAL)	IV	Primarily Ileum	Chewable tablet: class II Absorption dependent on pH
Elvitegravir (EVG)	II	Unknown	Chelates with polyvalent cations Food ↑ bioavailability
Dolutegravir (DTG)	II		Chelates with polyvalent cations

BCS Classification – Other

Drug Name	BCS	Absorption	Characteristics
Maraviroc (MVC)	III	Small intestine	Cannot crush; feeding tube not recommended

Drug Name	BCS	Absorption	Characteristics
Cobicistat	II	Unknown	Solubility high under acidic conditions; high intestinal permeability

Literature Review

Publication	HIV Regimen	Administration route	Virologic outcome	Sufficient plasma concentration
Kamimura et al.	LPV/RTV, ABC, 3TC	Jejunal tube	Failure	No
Lindholm et al.	RAL, FTC/TDF	Jejunal tube	Supression	Unknown
Kim et al.	DRV, RTV, FTC/TDF	Orogastric tube	Supression	Yes
Kohli-Pamnani et al.	APV, RTV, TDF, 3TC	PEG tube	Failure	Unknown
Leipe et al.	LPV/RTV, ABC, 3TC, TDF	PEG tube	Suppression	Unknown
Sandkovsky et al.	RAL, ETR, TDF/FTC	PEG tube	Suppression	Yes
Scholten et al.	DRV, RTV, RAL, AZT, 3TC	NGD tube	Unknown	Yes

Key Takeaways

- Evidence for feeding tube administration is limited
- Consider the site of drug absorption and gastric acid requirements
- Biopharmaceutics Classification can help determine best drug candidates for enteral tube administration
- Use caution; use as a last resort option if necessary

Objective 4

Evaluate the efficacy of a chosen medication regimen

Therapeutic Drug Monitoring

- Considered when suspected drug-drug interactions present
  - CYP450 inducers/inhibitors
- Considered in pregnancy, concentration-dependent toxicities
- PIs, NNRTIs, and Maraviroc (NOT NRTIs)
- Limitations
  - Few prospective studies showing benefit
  - Incomplete knowledge of therapeutic ranges
  - Considerable inter-individual variation of levels
  - Only a few qualified labs

Response to HAART

- Two markers for antiretroviral treatment
  - HIV RNA (viral load) – assess effectiveness of therapy **AFTER** initiation
  - CD4 lymphocyte cell count – useful **BEFORE** initiation
- Optimal viral suppression – persistently below level of detection
  - HIV RNA <20 to 75 copies/mL
- Virologic failure – persistent viral load > 200 copies/mL

Response to HAART

- CD4 count – most important lab indicator of immune function
- Strongest predictor of disease progression
- Adequate response: ↑ 50 – 150 cells/mm^3 during first year of HAART
  - In general: ↑ 50 - 100 cells/mm^3 per year until steady state level reached
  - The lower the CD4 count and older individual have been associated with less of an increase in their CD4 count despite having virologic suppression

Viral Load Monitoring

After Initiation	• 2-4 weeks (No later than 8 weeks after initiation) (AIII) • 4- to 8- week intervals until viral load falls below detection (BIII)
After Modification	• 4 to 8 weeks after changing therapy (BIII)
Stable Regimen	• Every 3 to 4 months for first 2 years (AIII) • Extended to 6 months if suppressed for >2 years (AIII)
Suboptimal Regimen	• Detectable viremia (> 200 copies/mL) • Every 3 months; Drug resistance testing indicated (AIII)

CD4 Count Monitoring

After Initiation	• 3 months (AIII)
After Modification	• 3 to 6 months (BII)
Stable Regimen	• Monitor at 3 to 6 month intervals for first 2 years (AI) • Rare to modify therapy for poor CD4 response
After 2 Years	• Annually, with consistent virologic suppression (BII) • Every 3 to 6 months with viral load of > 200 copies/mL (AIII)

Drug – Drug Interaction References

HIV iChart

- https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/
- https://www.hiv-druginteractions.org

Step-By-Step

1. Time For Implementation
2. Regimen For Initiation
3. Monitoring For Suppression

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Thank You

Questions?

Supplemental Slides

Discordant responses in CD4 count and viral load

CD4 count	Viral Load	Interpretation
Increases (50-150 cells/mm^3/yr)	**Decreases**	**Effective therapy**
No change or ↓	Decreases	[1]Possible in those with low CD4 count prior to initiation (<350 cells/mm^3)
Increases	Remains high	[2]Inhibited replication of virus due to drug-exposure
Fails to Increase	Increases	Non-adherence suspected Drug resistant HIV

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2. Ghaffari G, et al. Pediatrics. 2004. 114(5): e604-11.

Nucleoside Reverse Transcriptase Inhibitors (NRTI)

Drug Name	Available co-formulations	Renal Adjust	Liver Adjust	Special considerations
Abacavir (ABC)	Epzicom (ABC + 3TC) Trizivir (ABC + 3TC + ZDV)	No	Yes	• With or without food • Avoid combo with Tenofovir (↓ potency) • Requires testing for HLA-B*5701 allele
Didanosine (ddl)	None	Yes	No	• Not recommended first-line therapy
Emtricitabine (FTC)	Truvada (FTC + TDF) Atripla (FTC + TDF + EFV) Complera/Eplivera (FTC + TDF + RPV) Stribild (FTC + TDF + EVG + Cobi) Genvoya (FTC + EVG + Cobi + TAF)	Yes	No	• Do not use with Lamivudine (differs only slightly by 5-fluoro substitution)

Nucleoside Reverse Transcriptase Inhibitors (NRTI)

Drug Name	Available Co-formulations	Renal Adjust	Liver Adjust	Special Considerations
Lamivudine (3TC)	Trizivir (ABC + 3TC + ZDV)	Yes	No	• Used in lower doses for Hep-B – 100 mg PO q24h
Stavudine (d4T)	None	Yes	No	• NOT recommended first line • Highest incidence of lipoatrophy, HLD and lactic acidosis of all NRTIs • Common when used with Didanosine • Contraindicated in pregnancy
Tenofovir alafenamide fumarate (TAF)	Genvoya (EVG + Cobi + FTC + TAF) Descovy (FTC + TAF) Odefsey (FTC + RPV + TAF)	Yes	No	• Prodrug of Tenofovir, ↑ intracellular concentration • Cobi ↑ bioavailability

Nucleoside Reverse Transcriptase Inhibitors (NRTI)

Drug Name	Available Co-formulations	Renal Adjust	Liver Adjust	Special Characteristics
Tenofovir disoproxil fumarate (TDF)	Truvada (FTC + TDF) Atripla (FTC + TDF + EFV) Complera/Eplivera (FTC + TDF + RPV) Stribild (FTC + TDF + EVG + Cobi)	Yes	No	• Avoid combo with Abacavir (↓ antiviral activity) • Check renal function before starting
Zidovudine (ZDV)	Combivir (3TC + ZDV) Trizivir (ABC + 3TC + ZDV)	Yes	No	• Efficacy less with viral load >100,000 c/mL • Trizivir not recommended intitial therapy (Triple NRTI combo) • Preferred in pregnancy

Non-nucleoside Reverse Transcriptase Inhibitors - NNRTIs

Drug Name	Available Co-formulations	Renal Adjust	Liver Adjust	Special Considerations
Delavirdine (DLV)	None	No	No	• Not used much, multiple DDI
Efavirenz (EFV)	Atripla (FTC + TDF + EFV)	No	No	• Take at bedtime, without food (can ↑ serum concentration) • Long T ½ - consider continuing companion agents for several days after discontinuation
Etravirine (ETR)	None	No	No	• Preferred to be combined with Darunavir (PI) – DDI with other PIs
Nevirapine (NVP)	None	No	Yes	• Long T ½ - same recommendation as EFV above • ↓ skin reaction with dosing escalation method

Non-nucleoside Reverse Transcriptase Inhibitors - NNRTIs

Drug Name	Available Co-formulations	Renal Adjust	Liver Adjust	Special Characteristics
Rilpivirine (RPV)	Complera (FTC + TDF + RPV)	No	No	• Take with food • Best if used in patients with viral load <100,000 c/mL • Can ↑ QTc interval • Avoid use with CYP3A inducing agents

Protease Inhibitors (PI)

Drug Name	Available Co-formulations	Renal Adjust	Liver Adjust	Special Characteristics
Atazanavir (ATV)	Evotaz (ATV + Cobi)	Yes HD only	Yes	• "Boosted" regimen recommended for ART-experienced patients or those with concomitant TDF • Boosting not recommended in liver impairment
Darunavir (DRV)	Prescobix (DRV + Cobi)	No	Yes	• Take with food • Contains sulfa moeity • MUST be co-administered with Ritonavir or Cobicistat
Fosamprenavir (FPV)	None	No	Yes	• Ritonavir boosting preferred but not required • Prodrug of Amprenavir • Alternative boosted PI regimen for first-line therapy

Protease Inhibitors (PI)

Drug Name	Available Co-formulations	Renal Adjust	Liver Adjust	Special Considerations
Indinavir (IDV)	None	No	Yes	• Without food or with light meal • Many DDI and ADE exclude as initial regimen
Nelfinavir (NFV)	None	No	Yes	• With food, diarrhea common • Acceptable in pregnant women • Boosting not effective in improving drug levels • Contraindicated with drugs that are extensively metabolized by CYP3A
Ritonavir (RTV)	Kaletra (LPV/r)	No	Refer to PI paired to RTV	• Soft gel caps not equivalent to tablets • Contraindicated with drugs that are extensively metabolized by CYP3A

Protease Inhibitors (PI)

Drug Name	Available Co-formulations	Renal Adjust	Liver Adjust	Special Characteristics
Saquinavir (SQV)	None	No	Yes	• Possible QTc prolongation • Alternative regimen for treatment naive patients • Avoid with Rifampin – ↑ hepatocellular toxicity
Tipranavir (TPV)	None	No	Yes	• Not used in treatment naive patients, for those with multiple PI resistant virus • Not used with Etravirine (↓ 76% of Etravirine levels) • Contraindicated in Child-Pugh class B-C • Contains sulfa moiety • With food

Protease Inhibitors (PI)

Drug Name	Available formulations	Renal Adjust	Liver Adjust	Special Characteristics
Lopinavir – (LPV)	Kaletra (LPV/r): 200 mg/50 mg 100 mg/25 mg	HD Only Avoid QD Dosing In HD	No	• Twice daily regimen when taken with Efavirenz, Nevirapine, or Nelfinavir • Single daily dose used except in treatment-experienced adults or concomitant use of NFV, EFV, NVP • QT prolongation possible

Integrase Strand Transfer Inhibitors (INSTI)

Drug Name	Available Co-formulations	Renal Adjust	Liver Adjust	Special Characteristics
Raltegravir (RAL)	None	No	No	• With or without food • Part of primary regimen with 2 NRTIs for naive patients • CK and rhabdomyolysis reported; relationship unclear • Various formulations are NOT interchangeable
Elvitegravir (EVG)	Stribild (EVG/c + FTC + TDF)	No as Single drug	Yes	• Stribild: • CrCl < 70 mL/min – don't use • Discontinue if CrCl falls below 50 mL/min during therapy
Dolutegravir (DTG)	Triumeq (ABC + DTG + 3TC)	No	Yes	• Co-administered often with (TDF + FTC) and (3TC + ABC) • 50 mg PO BID with EFV, FPV + RTV, TPV + RTV, or Rifampin

Fusion Inhibitors

Drug Name	Available Co-formulations	Renal Adjust	Liver Adjust	Special Characteristics
Enfuvirtide (ENF) (T-20)	None	No	No	• Available as injectable only • Part of 3-4 drug combo in treatment experienced patients • Rotate injection sites, 98% experience local site erythema/induration

Chemokine Receptor Antagonist (CCR-5)

Drug Name	Renal Adjust	Liver Adjust	Special Characteristics
Maraviroc (MVC)	Yes	No	• Treatment-experienced patients with multi-resistant strains

Other Inhibitor

Drug Name	Available Co-formulations	Renal Adjust	Liver Adjust	Special Characteristics
Cobicistat (Cobi) Or (/c)	Stribild (FTC + TDF + EVG/c) Prescobix (DRV/c) Evotaz (ATV/c) Genvoya (EVG/c + FTC +TAF)	No	No	• CYP450 isoenzyme participant • Increases serum levels of Darunavir and Atazanavir (PIs) • Inhibits MATE 1 (proximal tubule enzyme) that secretes creatinine into the urine • Increase in serum creatinine value • Will have artificial reduction in GFR

When to start with active opportunistic infection

- ART should be initiated as soon as possible but within the first 2 weeks after diagnosis
  - Exception: Cryptococcal meningitis – early initiation associated with increased intracranial pressure
  - Mortality higher when started within 1-2 weeks vs. group with delay of 5 weeks
- Active tuberculosis – no survival benefit for early initiation with CD4 count greater than 220 cells/mm^3
  - Exeption: CD4 count of less than 50 – ↑ survival
  - Associated with higher rates of IRIS

SAPiT trial. Naidoo et al. J Acquir Immune Defic Syndr. 2015. 69(5):576-84
CAMELIA trial. Marcy et al. Clin Infect Dis. 2014. 59(3): 435-45

HAART trough concentrations available

Drug Name	Target Trough
Atazanavir	150 ng/mL
Fosamprenavir	400 ng/mL
Indinavir	100 ng/mL
Lopinavir	1000 ng/mL
Nelfinavir	800 ng/mL
Saquinavir	100-250 ng/mL
Tipranavir	20500 ng/mL
Efavirenz	1000 ng/mL
Nevirapine	3000 ng/mL
Maraviroc	>50 ng/mL
*Levels to be drawn at steady-state	

Immune Reconstitution Inflammatory Syndrome, IRIS

- Inflammatory response seen after initiation of ART in those with underlying infections or malignancies
- Manifest as exacerbation of clinical symptoms from the underlying process
- Each opportunistic infection will have amplified symptoms
- Can subside spontaneously and may require NSAIDS or corticosteroid therapy