HIV Treatment 101

MIDWEST AIDS TRAINING + EDUCATION CENTER

WAYNE STATE
School of Medicine

AETC AIDS Education & Training Center Program
Midwest

Disclaimer

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What is HIV?

- Human – Only found in humans
- Immunodeficiency – Weakens immune system by destroying CD4 cells
- Virus – Reproduces by taking over a host cell

HIV Testing

- CDC recommends that everyone between the ages of 13 and 64 get tested for HIV at least once as part of routine health care
  - About 1 in 7 people in the United States who have HIV don’t know they have it
- Michigan requires that providers obtain consent prior to administering an HIV test

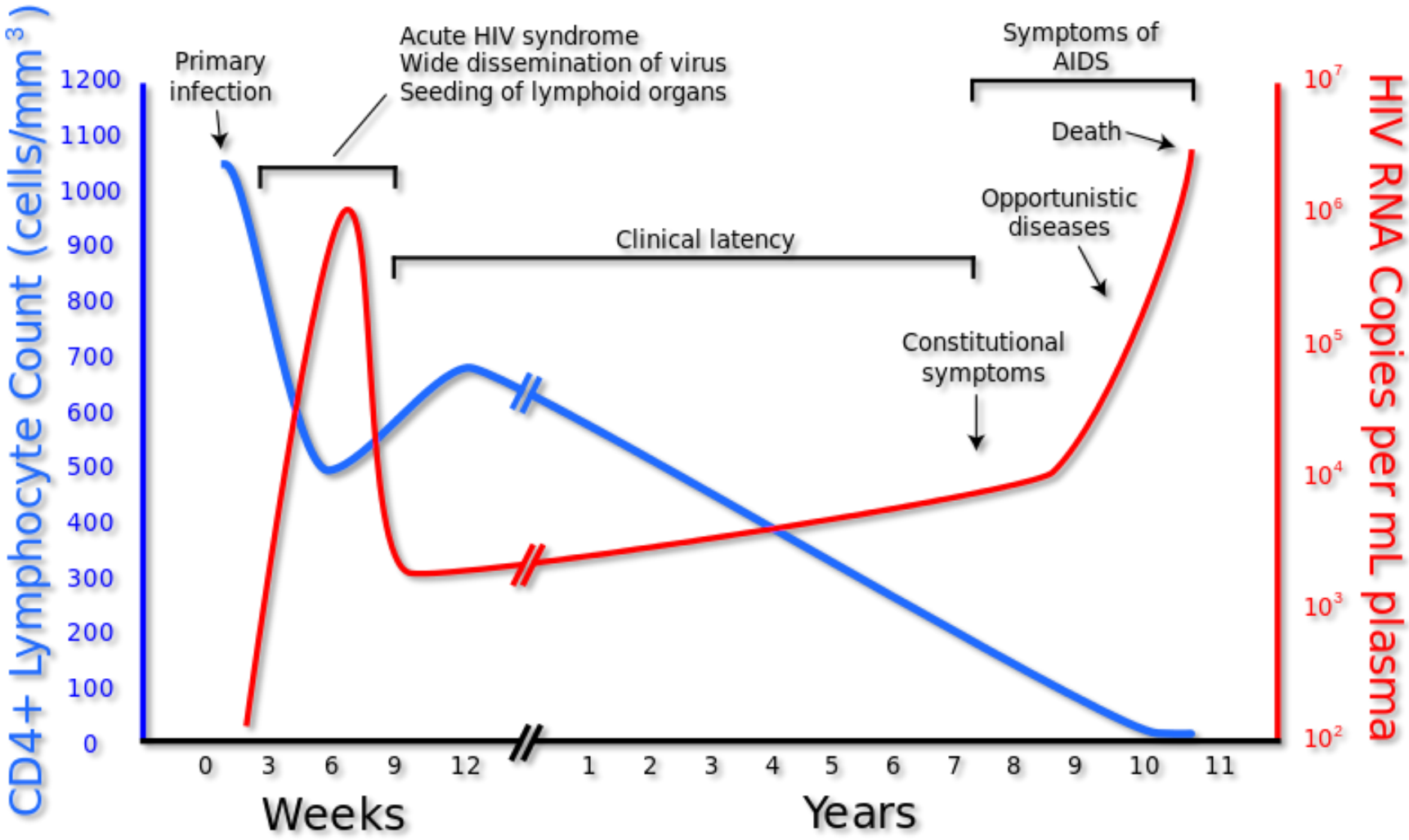
4th Generation HIV Testing

- Simultaneously detects both antigen and antibodies for HIV
- Can be used to diagnosis HIV-1/HIV-2 infection
- Allows detection of acute HIV based on identification of the HIV p24 antigen
- When in doubt: check a viral load

Common HIV Labs

- Viral Load
  - How much HIV is in the blood
  - Lower the better
- CD4 Count
  - How strong the immune system is
  - Higher the better
- Genotype
  - Has HIV found ways to avoid certain medications?
  - Resistance test

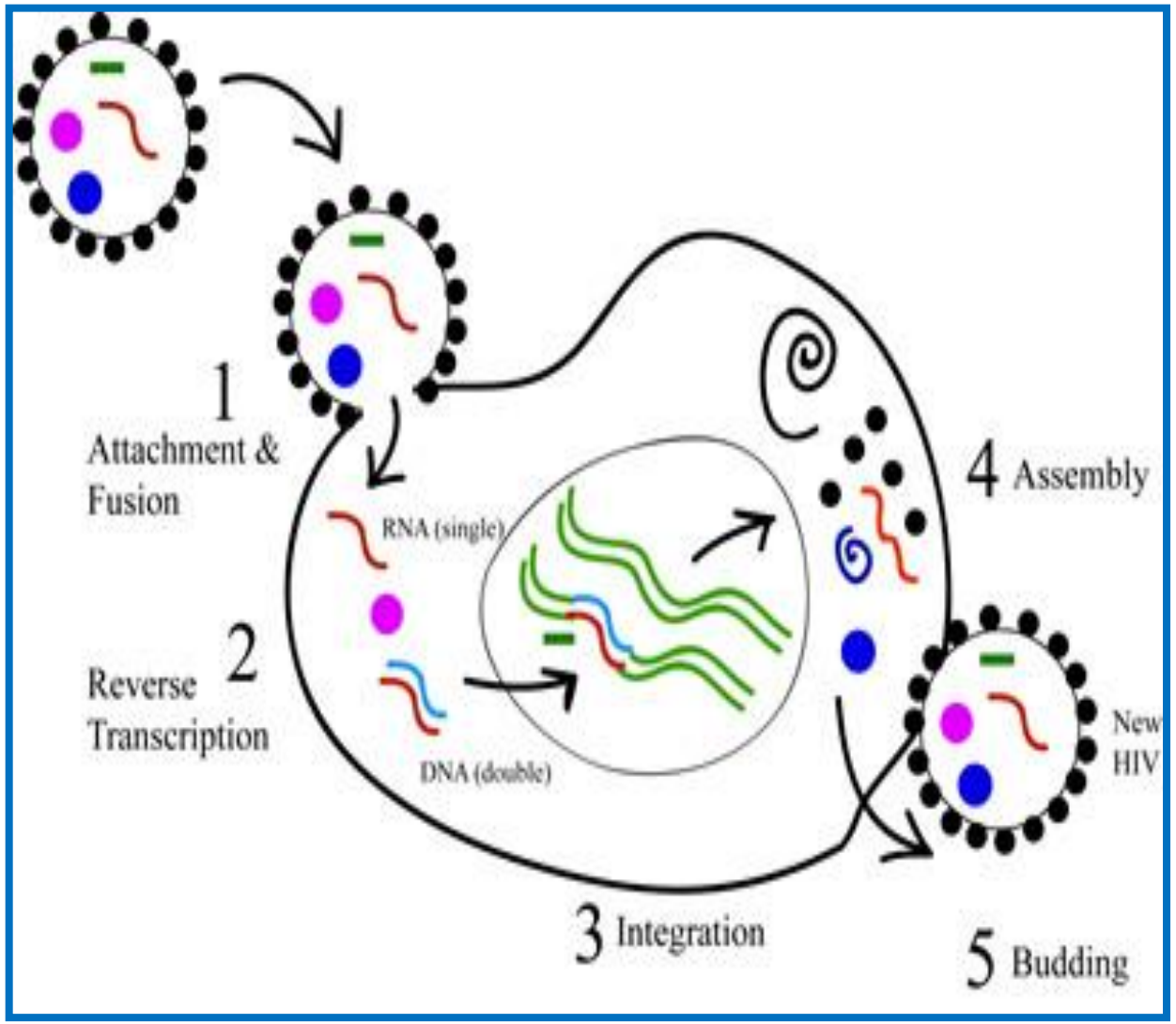
HIV Time Course



Goals of Therapy

- Increase the CD4
  - Above 200, preferably above 500
- Decrease the VL
  - Non-detectable
- Improve quality of life
- Reduce secondary HIV related disease
- Reduce transmission
  - (Undetectable = Untransmittable)

HIV Life Cycle



FDA Approved Antiretrovirals

NRTIs	NNTRIs	PIs	Single Tablet Regimens
Combivir®	Edurant®	Aptivus®	Atripla®
Descovy®	Intelence®	Crixivan®	Biktarvy®
Emtriva®	Pifeltro®	Evotaz®	Complera®
Epivir®	Rescriptor®	Invirase®	Delstrigo®
Epzicom®	Sustiva®	Kaletra®	Dovato®
Retrovir®	Viramune®	Lexiva®	Genvoya®
Trizivir®	**INSTIs**	Norvir®	Juluca®
Truvada®	Isentress®	Prezcobix®	Odefsey®
Videx®	Tivicay®	Prezista®	Stribild®
Viread®	Vitekta®	Reyataz®	Symtuza®
Zerit®	**Entry/Fusion Inhibitors**	Viracept®	Triumeq®
Ziagen®	Fuzeon®		
	Selzentry®		
	Trogarzo®		

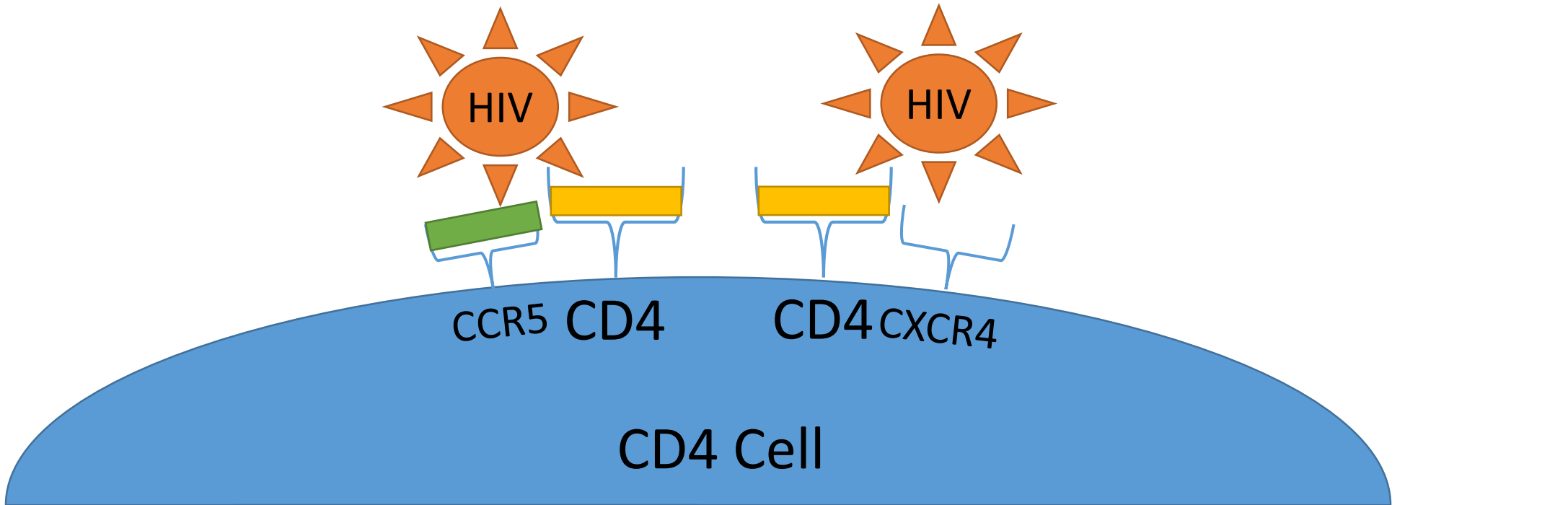
The 1st long acting injectable HIV treatment combining an NNRTI and an INSTI was approved in 2021, the field is constantly evolving

CD4 and CCR5 Inhibitors

- HIV binds to the CD4 receptor to enter the cell
- This binding in not enough to enter the cell
- CD4 also requires binding to a co-receptor
- CD4 inhibitors prevent the HIV from binding to the CD4 receptor
- CCR5 inhibitors prevent HIV from binding to 1 of 2 possible co-receptors

CD4 and CCR5 Inhibitors

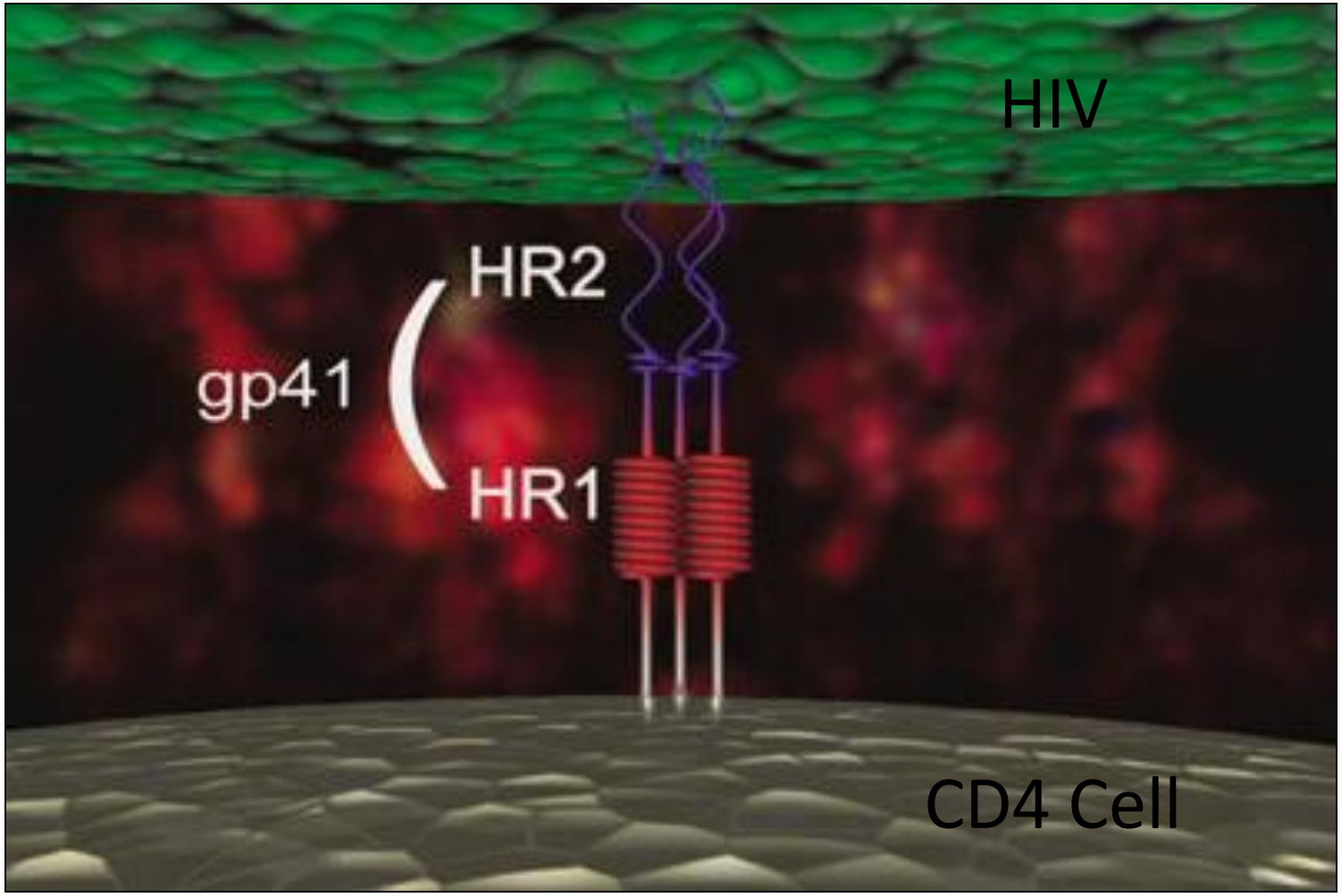
- Trogarzo (ibalizumab)
- Selzentry (maraviroc)



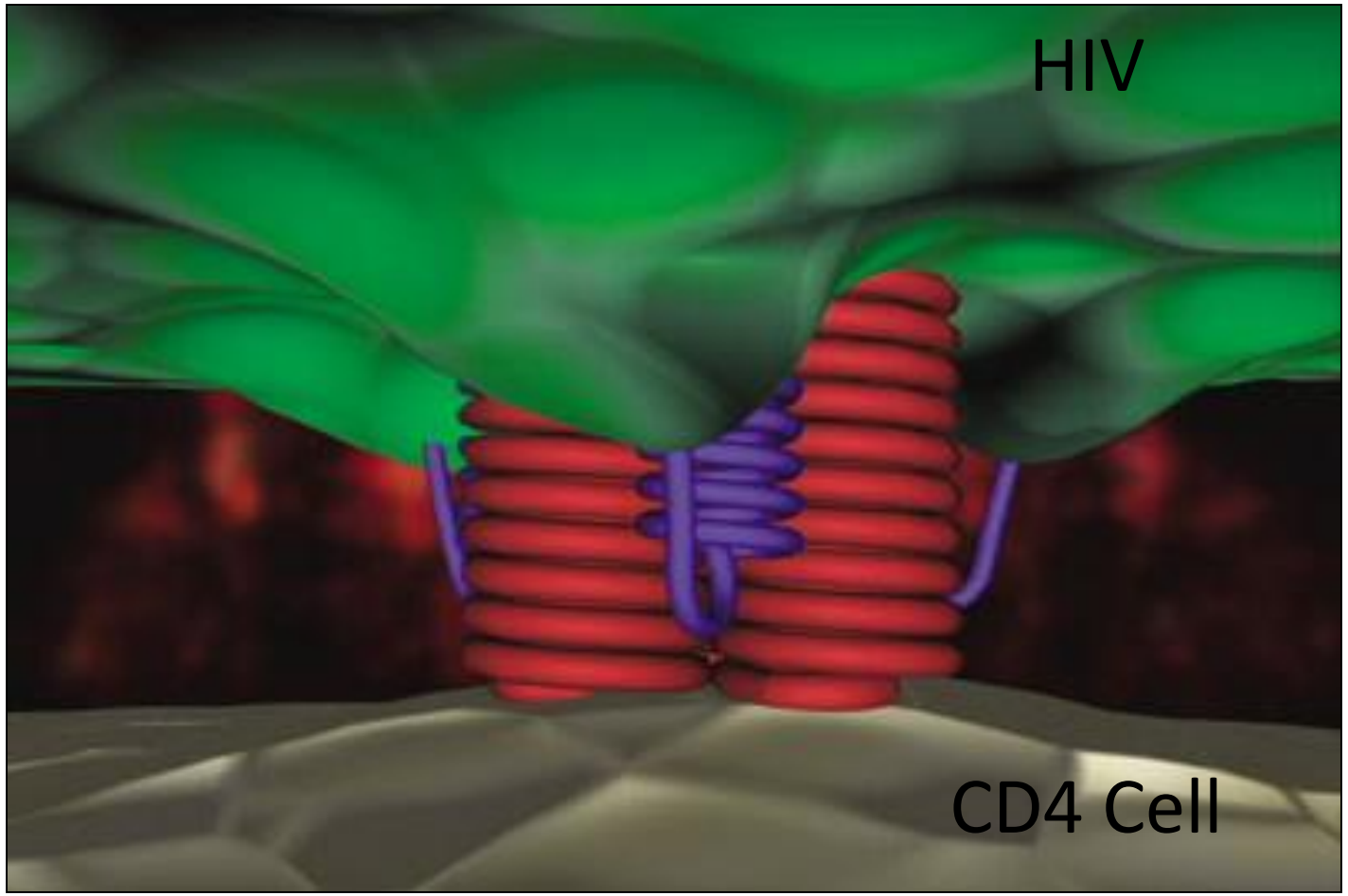
Fusion Inhibitor

- Once bound to the CD4 cell, HIV must fuse with the cell to release its contents into the cell
- Fusion inhibitors block HIV from fusing with the surface of the CD4 cell

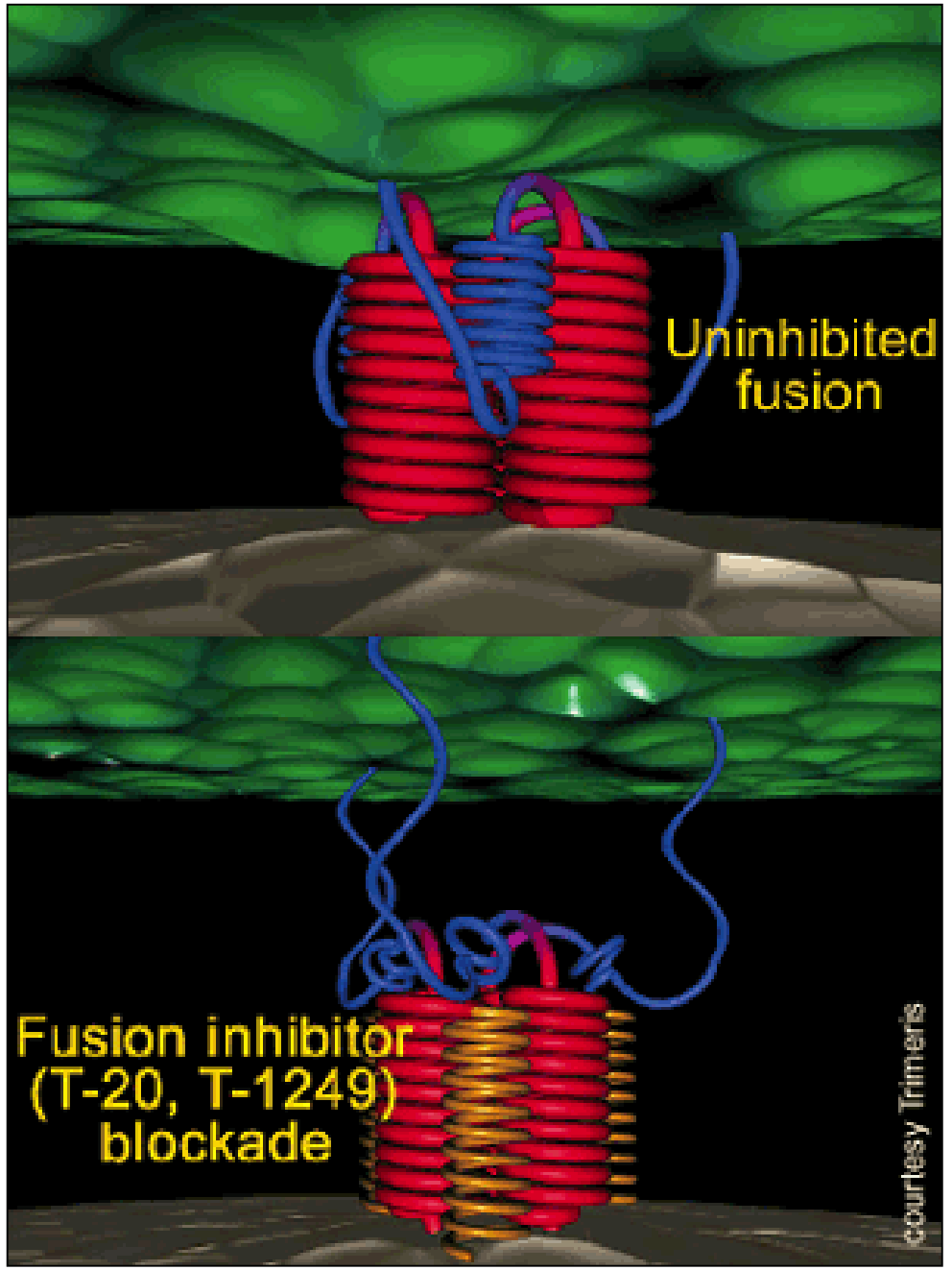
Fusion Inhibitor



Fusion Inhibitor



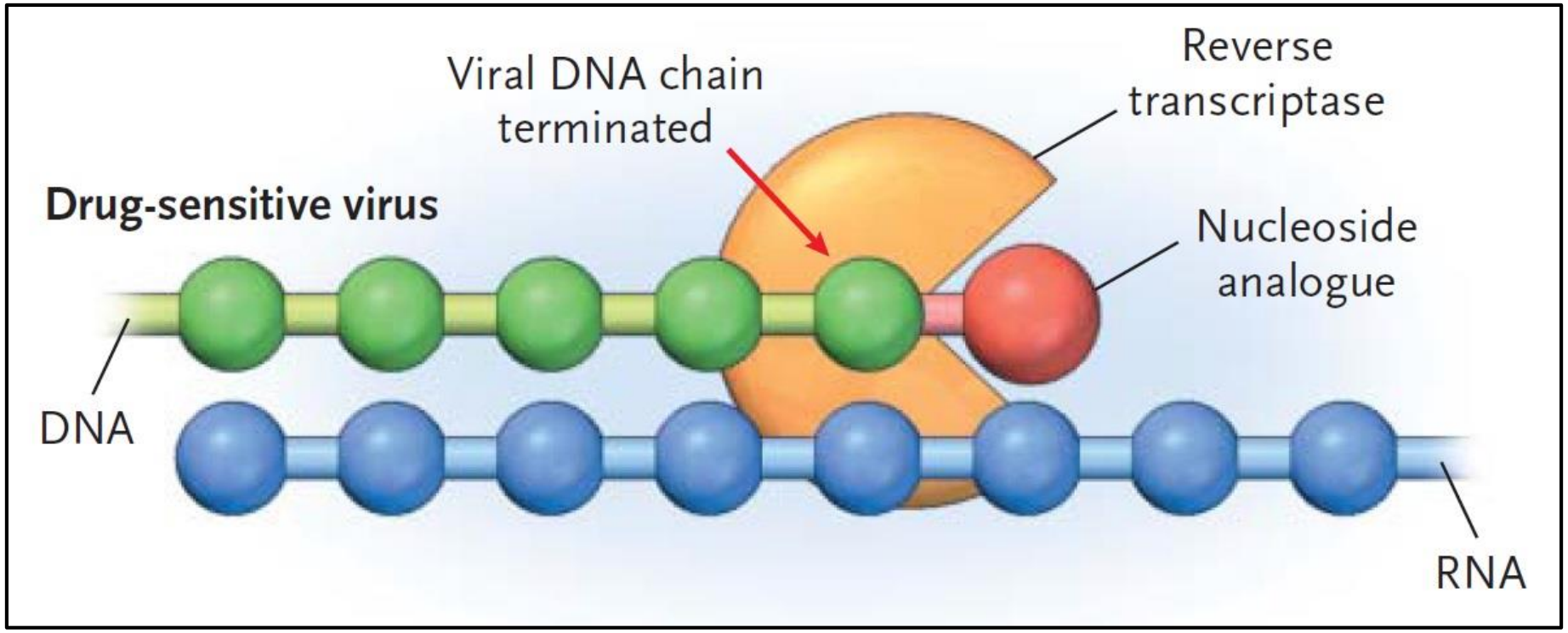
Fusion Inhibitor



Nucleoside Reverse Transcriptase Inhibitors

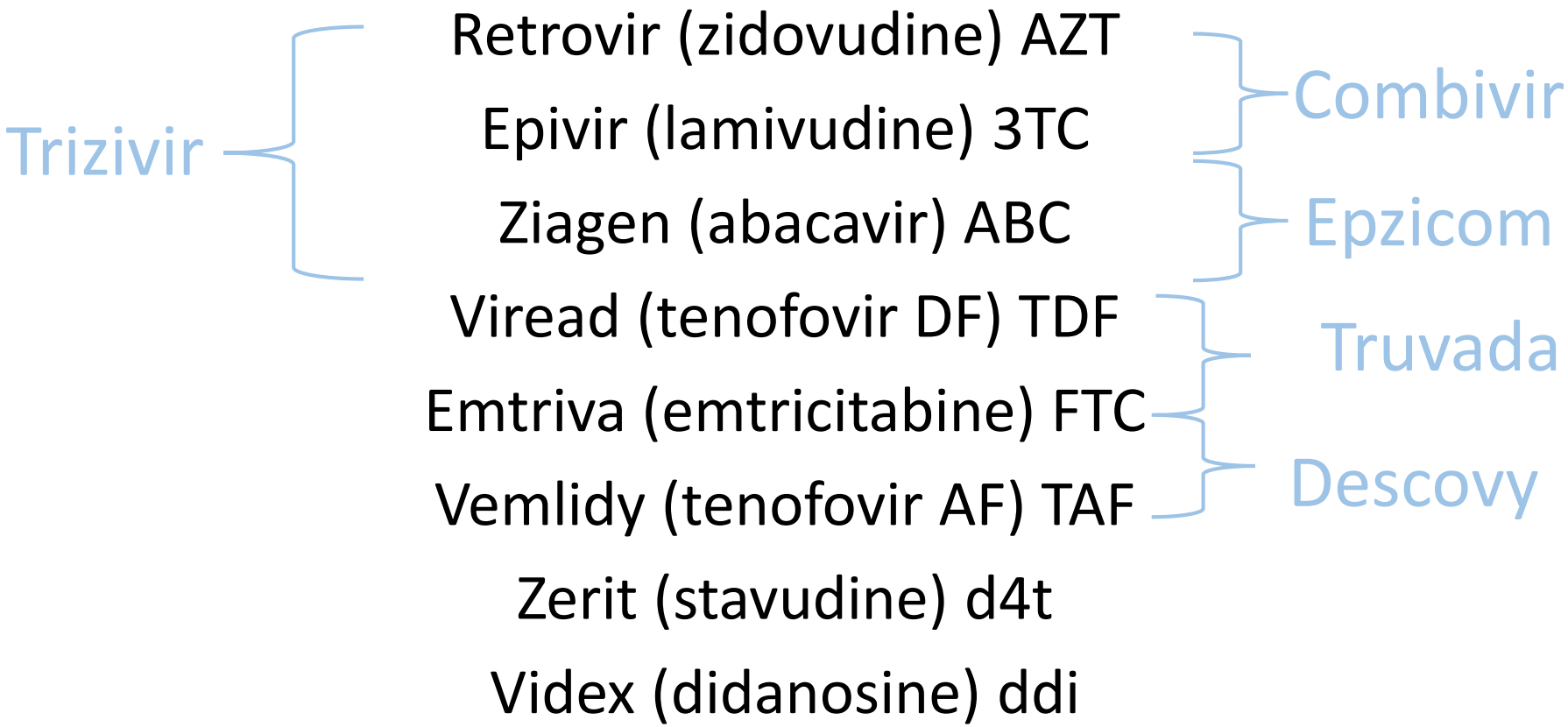
- When HIV copies itself it uses RNA as a template or blueprint to make DNA
- The DNA strand is made up of multiple small building blocks
- NRTIs looks like these building blocks, but are shaped differently
- This difference in shape prevents the reverse transcriptase from attaching the next building block

Nucleoside Reverse Transcriptase Inhibitors



Clavel F et al. N Engl J Med 2004;350:1023-35

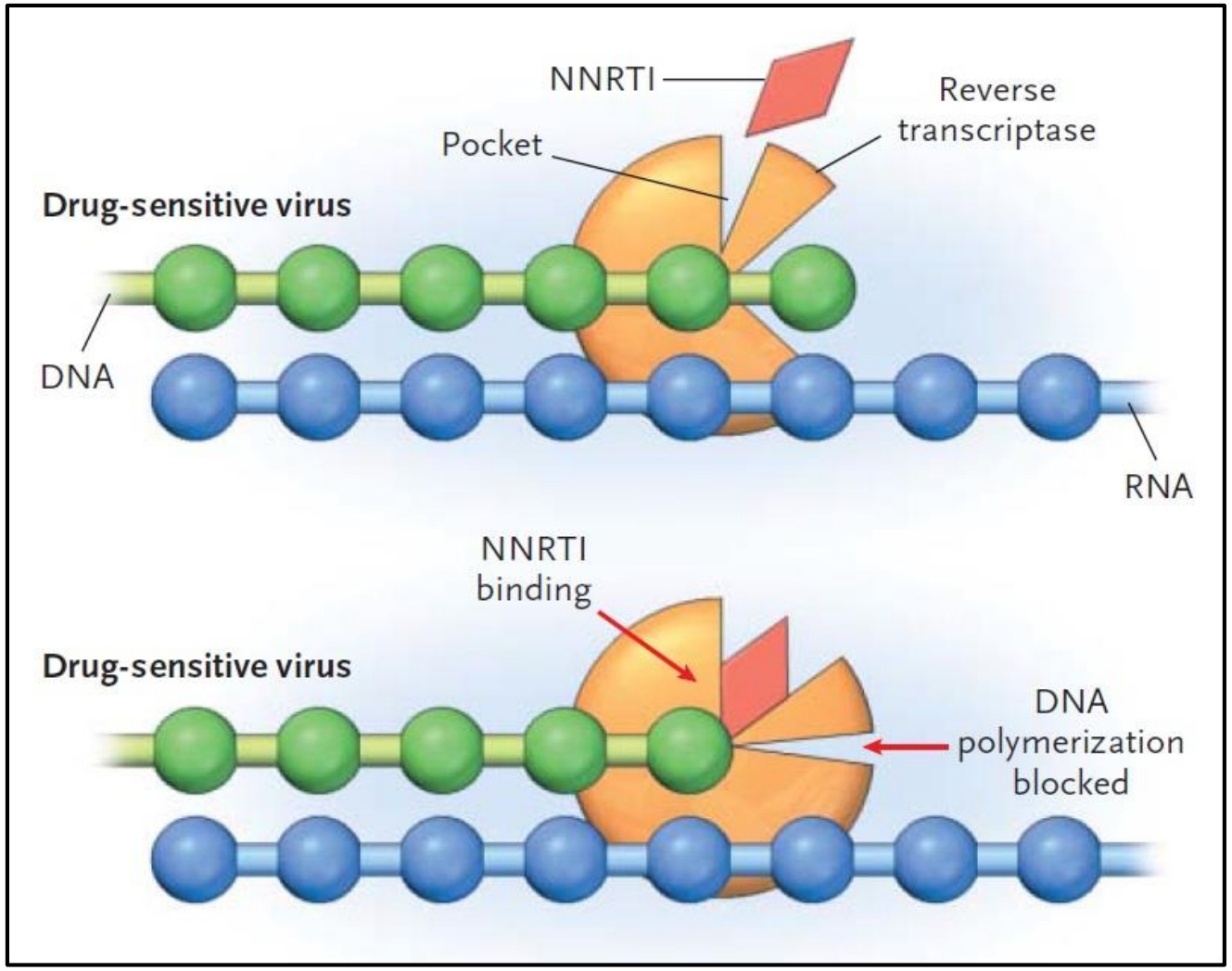
NRTIs: “Nukes”


Trizivir
Retrovir (zidovudine) AZT
Epivir (lamivudine) 3TC
Ziagen (abacavir) ABC
Combivir
Epzicom
Viread (tenofovir DF) TDF
Emtriva (emtricitabine) FTC
Truvada
Vemlidy (tenofovir AF) TAF
Descovy
Zerit (stavudine) d4t
Videx (didanosine) ddi

Non-Nucleoside Reverse Transcriptase Inhibitors

- When HIV copies itself it uses RNA as a template to make DNA
- NNRTIs stick to the enzyme or machinery responsible for making DNA out of RNA preventing it from working

Non-Nucleoside Reverse Transcriptase Inhibitors



Clavel F et al. N Engl J Med 2004;350:1023-35

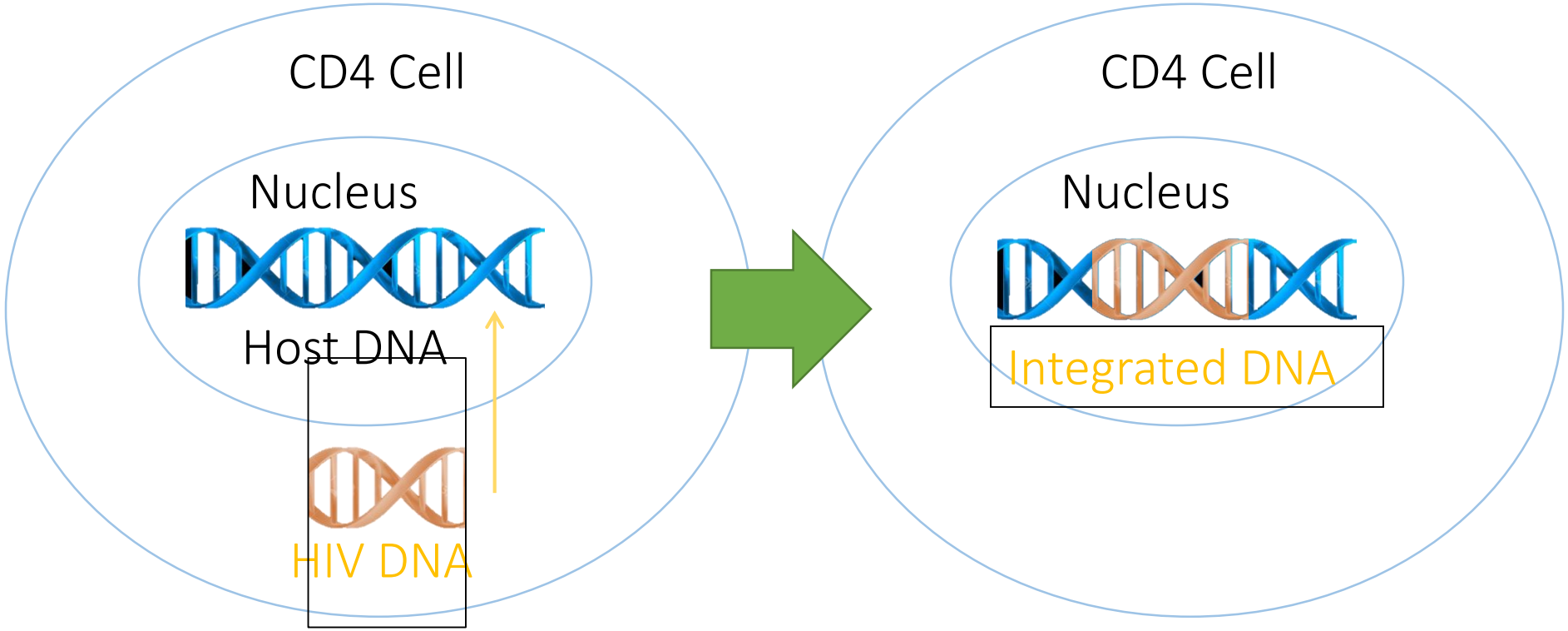
NNRTIs: “Non-Nukes”

- Pifeltro (doravirine) DOR
- Viramune (nevirapine) NVP
- Sustiva (efavirenz) EFV
- Rescriptor (delavirdine) DLV
- Intelence (etravirine) ETV
- Edurant (rilpivirine) RPV

Integrase Inhibitors

- HIV uses human CD4 cells to make copies of itself
- In order to trick CD4 cells into doing this, it first must integrate its DNA into the human DNA (hide its blueprint in the cell's blueprint)
- HIV uses the integrase enzyme to do this
- Integrase inhibitors bind to this enzyme and prevent this process

Integrase Inhibitors



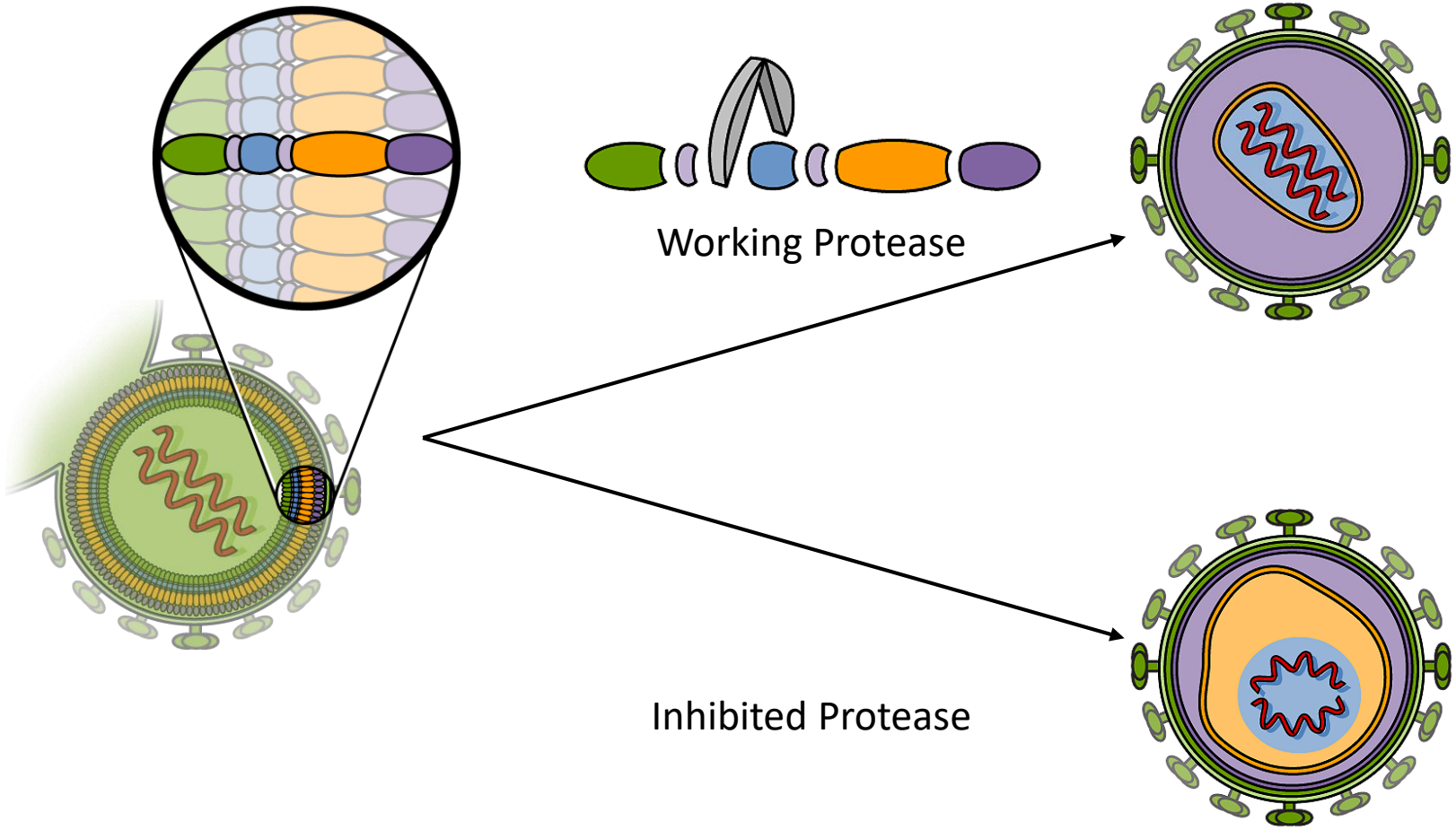
INSTIs

- Isentress (raltegravir) RAL
- Tivicay (dolutegravir) DTG
- Vitekta (elvitegravir) EVG
- Biktarvy (bictegravir) BIC
  - only available in combination with tenofovir alafenamide and emtricitabine

Protease Inhibitors

- When new HIV is made, all the proteins or building pieces are stuck together in long chains
- Protease acts like a pair of scissors cutting these chains into parts so a mature virus can form
- Protease inhibitors bind to these “scissors” and prevent them from working

Protease Inhibitors



PIs

- Norvir (ritonavir) RTV or /r
- Kaletra (lopinavir/ritonavir) LPV/r
- Reyataz (atazanavir) ATV
  - Evotaz (atazanavir/cobicistat)
- Lexiva (fosemprenavir) FPV
- Aptivus* (tipranavir) TPV
- Prezista* (darunavir) DRV
  - Prezcobix (darunavir/cobicistat)
  - Symtuza (darunavir/cobicistat/tenofovir AF/ emtricitabine)
- Invirase* (saquinivir) SQV
- Crixivan (indinavir) IDV
- Viracept (nelfinavir) NFV

*Must be boosted

Building an HIV Regimen for a New Patient

- Three medications from at least 2 different classes (usually…)
  - Never mono therapy
  - NRTIs are the only class we routinely use more than 1 at a time
  - Ritonavir and Cobicistat (boosters) do not count as a class
- Number of medications does not have to match the number of pills

Treatment Initiation Over Time

	1998	2001	2002	2004			2012
CD4 Count	Treat: <500	Treat: <200 Off	Treat			Indiv. >500	(AI) <500 (AII) >500 (BIII)
VL	>20,000			,000			
Other factors					Pregnant HBV HIVAN	Pregnant HBV HIVAN	Pregnant HBV HIVAN High risk of transmitting

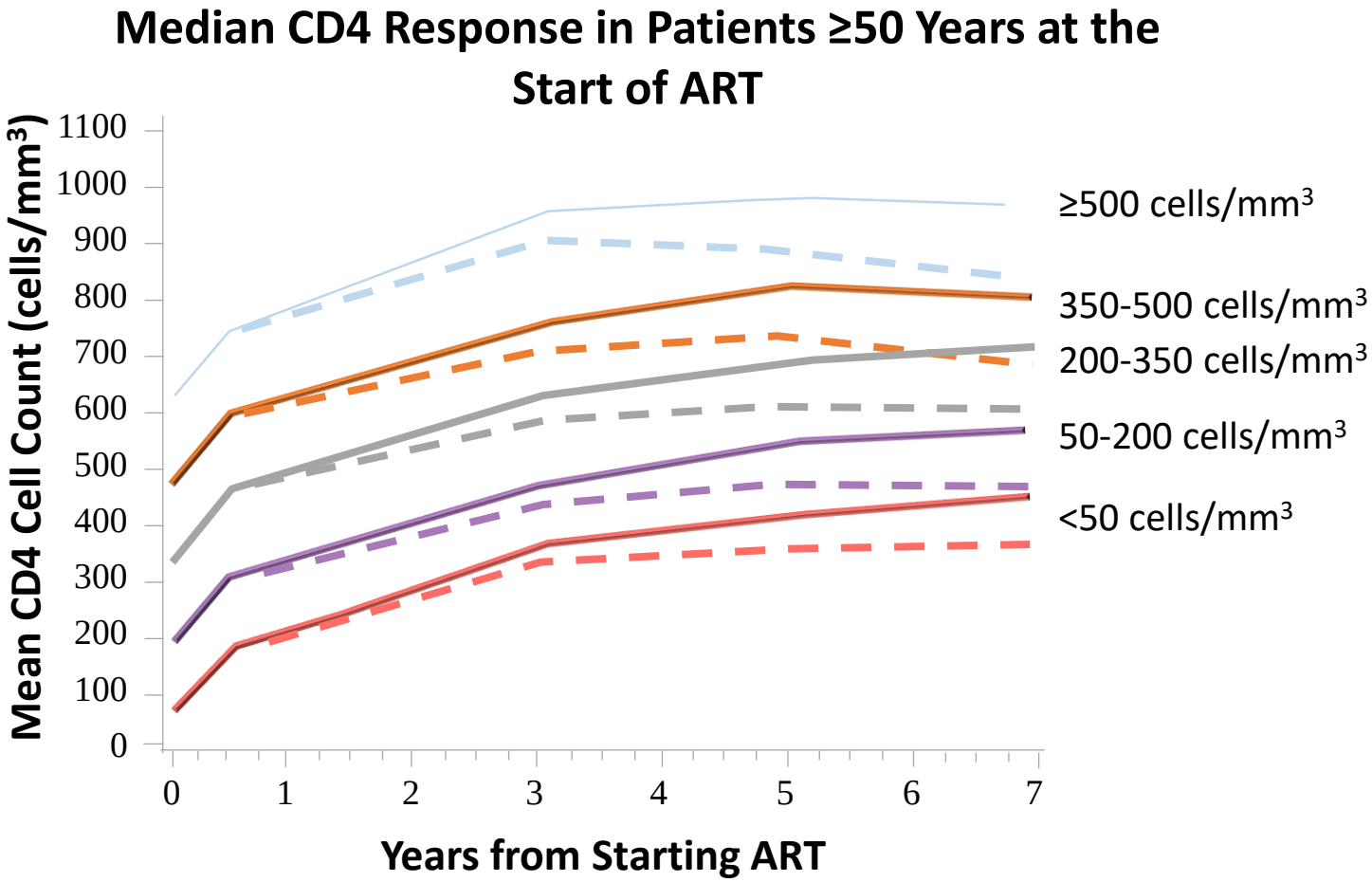
Start Everyone

A1 – Strong Recommendation

Benefits of Early Treatment

- Maintain higher CD4 count to prevent damage to the immune system
- Decrease risk of HIV-associated complications
  - Opportunistic infections
  - Underlying inflammation
- Decrease risk of transmission
  - Undetectable = Untransmittable

Increase in CD4 Count

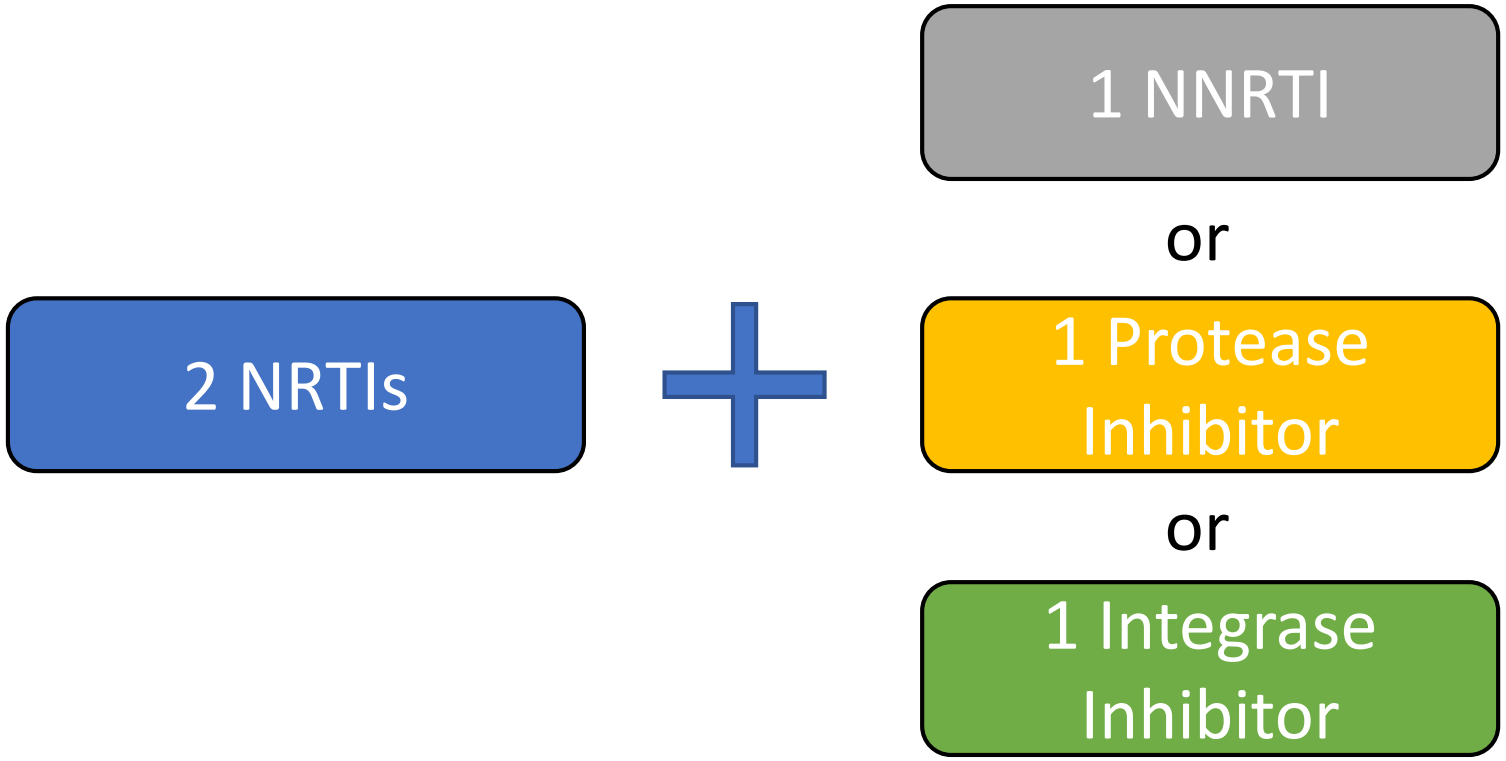


Gras L et al. *J Acquir Immune Defic Syndr*. 2007;45(2):183-192.

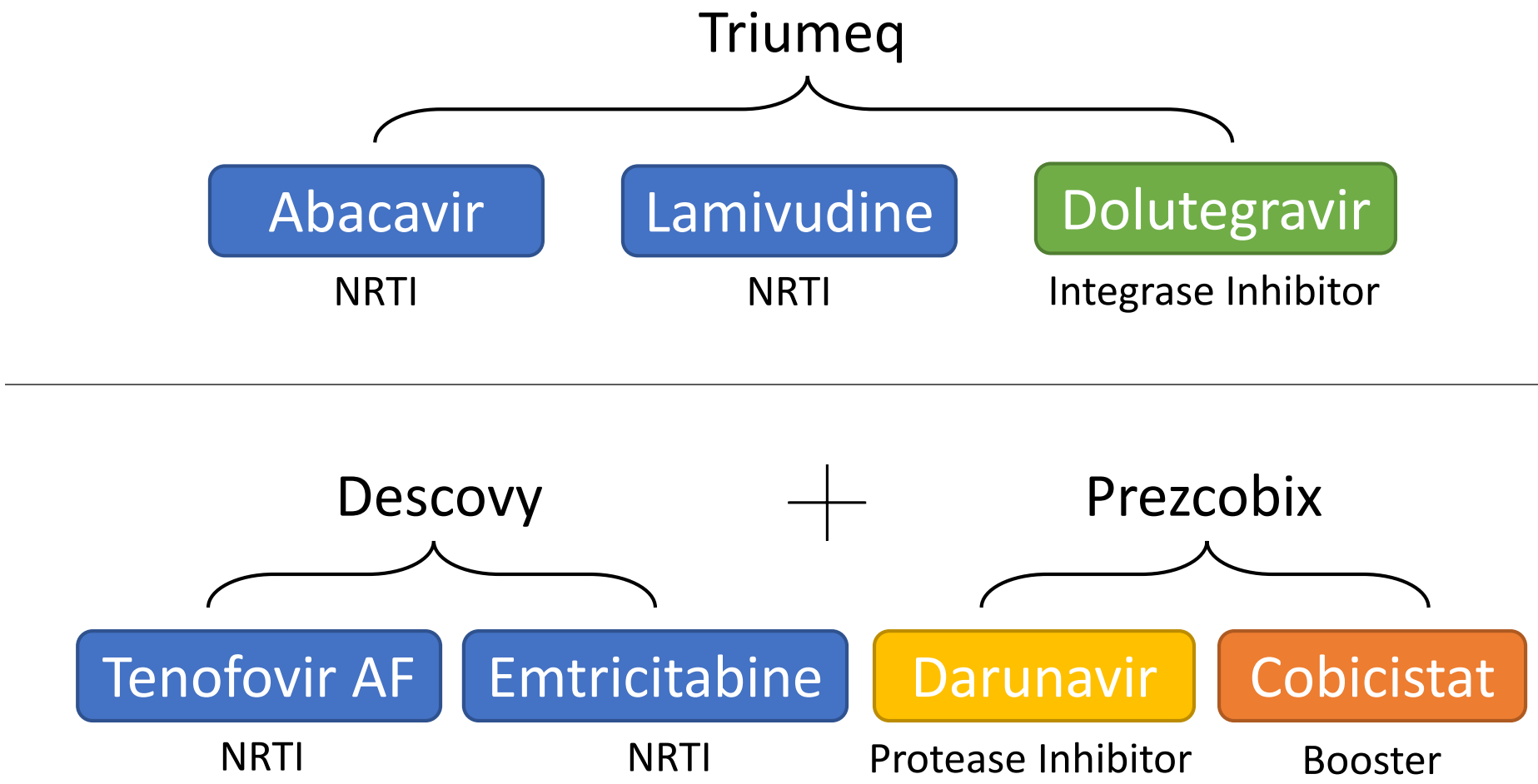
Risk of Early Treatment

- Development of treatment related side effects
- Less time for patient readiness assessment
- Increased total time on medications
  - Greater chance of pill fatigue
  - More long term side effects of medications
- Longer opportunity to develop resistant virus if not adherent to medications

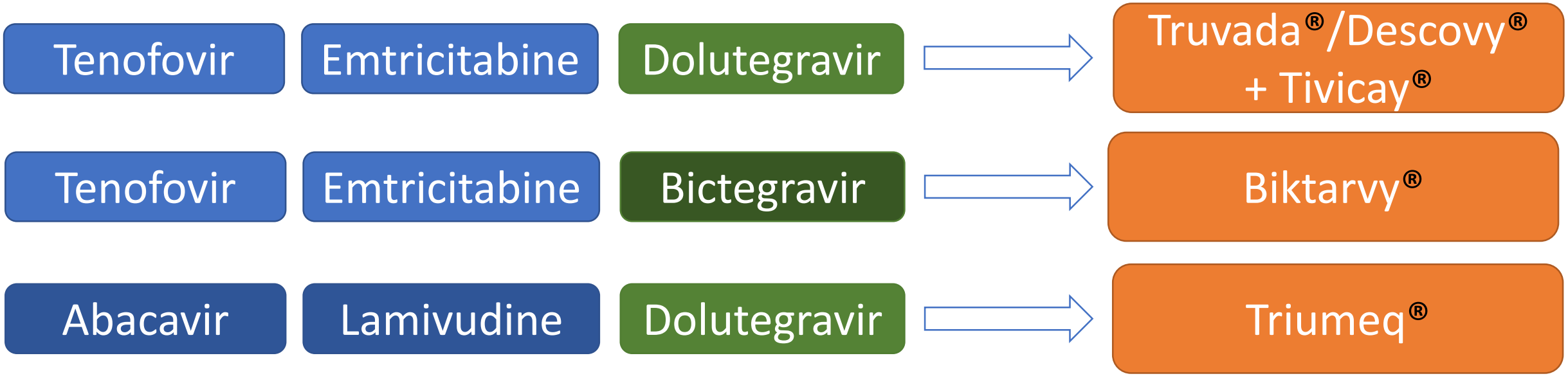
Building An HIV Regimen



Example Regimens



First Line Regimens For Most People



The Rational For Unboosted Integrase Inhibitors

- Fewer drug interactions than NNRTIs, PIs and elvitegravir
- No food requirement
- Good tolerability
- Reduce the HIV viral load very quickly

The differences between recommended regimens is getting more and more subtle… (See extra slides for full details)

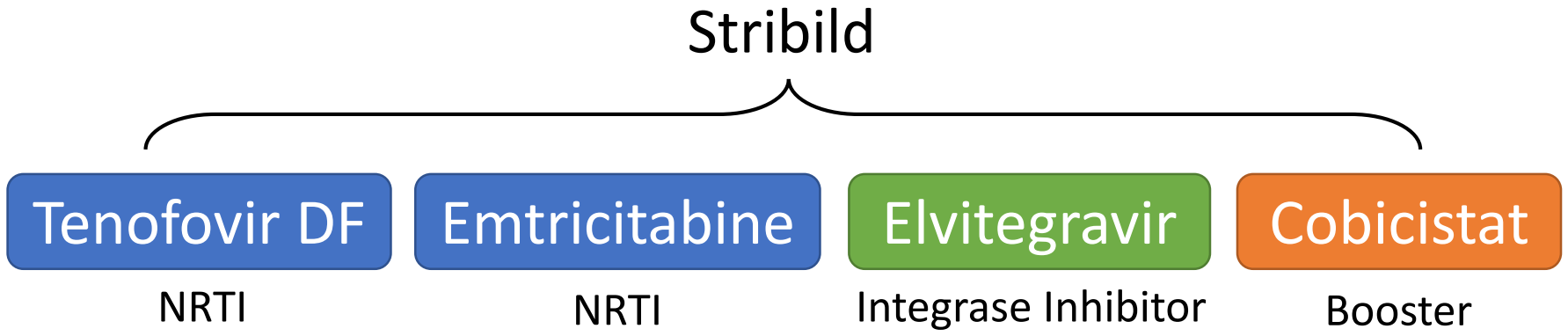
Treatment Naïve – Treatment Selection Factors

- Baseline resistance testing and viral load
- Patient anticipated adherence
- Other health conditions
  - Kidney disease, heart disease
  - Pregnancy/desired pregnancy
  - Hepatitis co-infections
- Side Effects
- Drug interactions
- Patient’s daily schedule and meal times

Treatment Experienced

- Resistance testing
- Antiretroviral medication history
  - Side effect history
  - Allergies
  - Adherence/possible resistance
- All treatment naïve factors

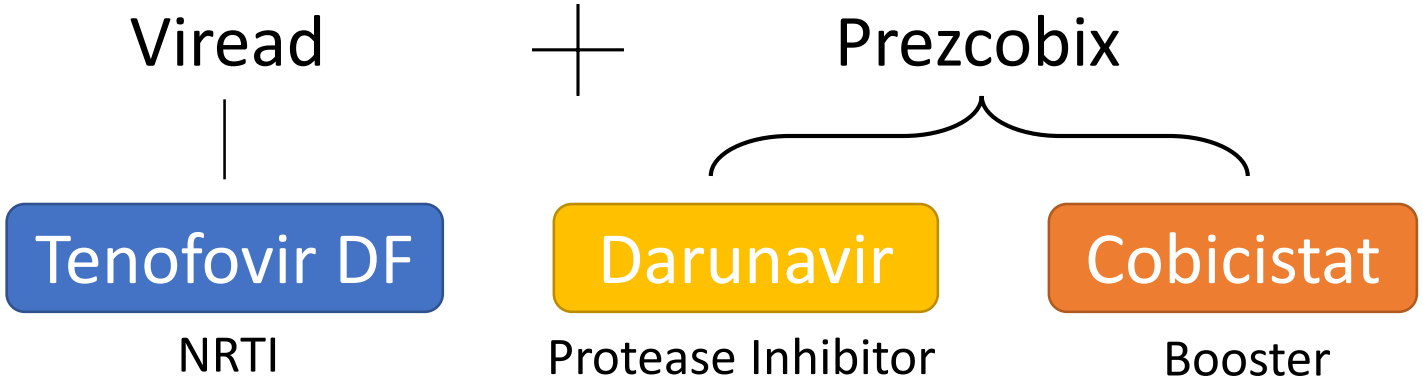
Appropriate or Not?
Question #1



Yes

Probably Not

Appropriate or Not?
Question #2

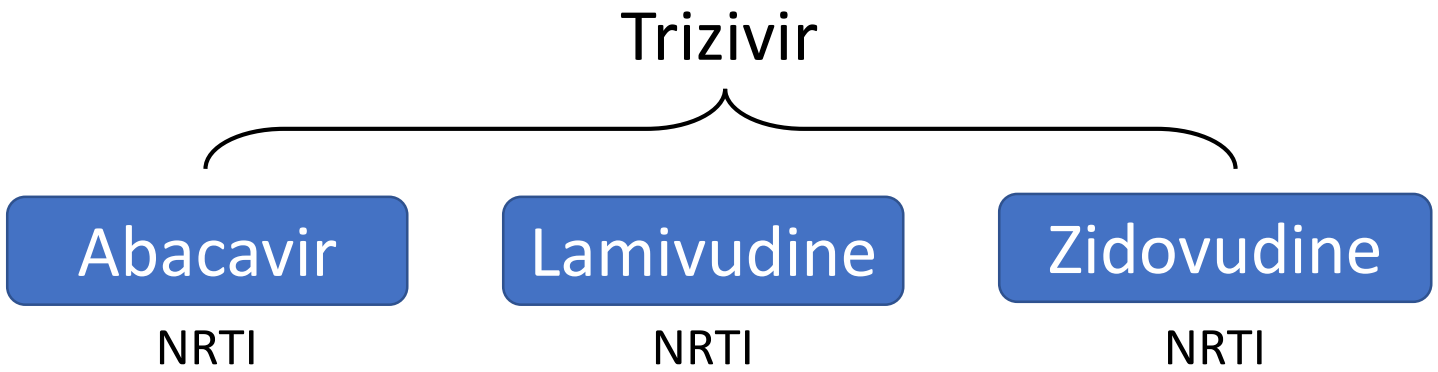


Yes

Probably Not

Only 2 Active Medications

Appropriate or Not?
Question #3



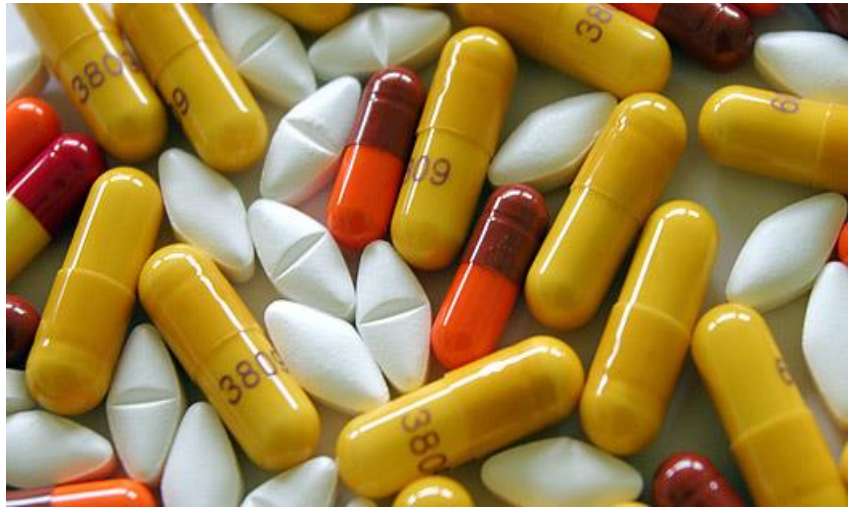
Yes

Probably Not

Only 1 Class

Reason For Therapy Changes

- Viral Failure
- Side Effects
- Drug Interactions
- Comorbidities
- Reduce Pill Burden
- Pregnancy
- Cost/Insurance



Viral Failure

- Possible Causes
  - Suboptimal adherence
  - Pharmacokinetic issues
  - Possible drug resistance
- New regimen selection is based on cause of regimen failure and remaining antiretroviral options

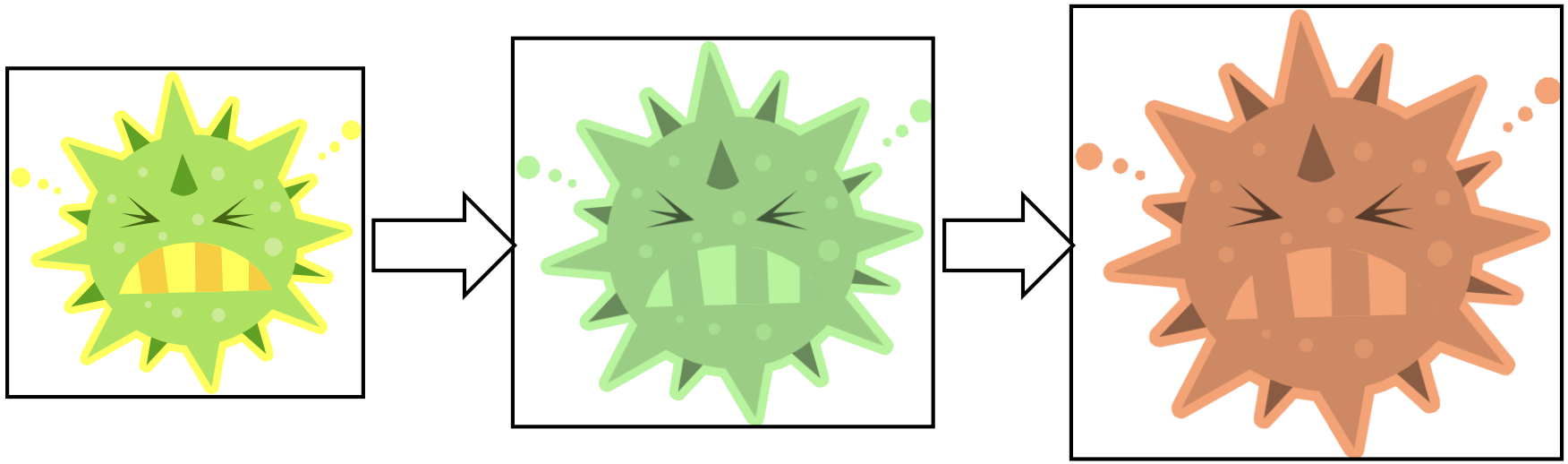
Building A Salvage Regimen

- Three medications, each from a different class
  - Medications selected based on viral resistance
  - Can still use more than 1 NRTI
- Can have more than 3 medications if there are not enough fully active medications left

Medication 1 Partial resistance		Medication 2 Partial resistance		Medication 3 No resistance		Medication 4 No resistance		
½	+	½	+	1	+	1	=	**3 active medications**

What Is Resistance?

- In short:
  - The HIV virus changes and the medications stop working
  - The more mutations present, the fewer medications are left available



How Do Mutations Develop?

High levels of viral production and turnover
10 million to 1 billion copies daily

Reverse transcription of viral RNA into DNA is highly error prone
Average 1 error in every genome

Complex mixture of viral quasi-species each with slightly different mutations

Clavel F et al. N Engl J Med 2004;350:1023-35. Markowitz M et al. J Virol 2003;77:5037-8. Roberts JD et al. Science 1988;242:1171-3.

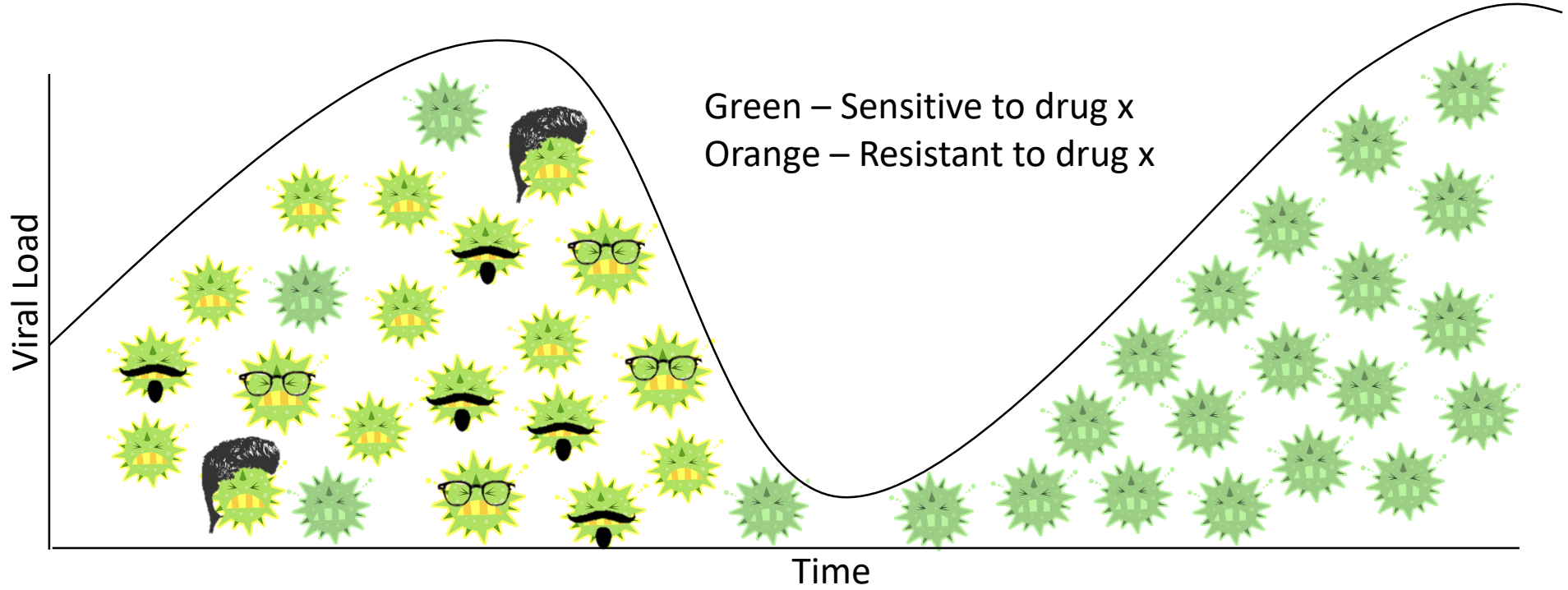
How Does Drug Resistance Occur?

- Option 1 – Develops in a patient taking antiretrovirals
- Option 2 – Transmitted during initial infection or subsequent reinfection

Clavel F et al. N Engl J Med 2004;350:1023-35.

Option 1 – Developed Resistance

- Resistant virus emerge when medication concentrations are
  - Insufficient to suppress viral replication
  - Sufficient to cause a positive selective pressure



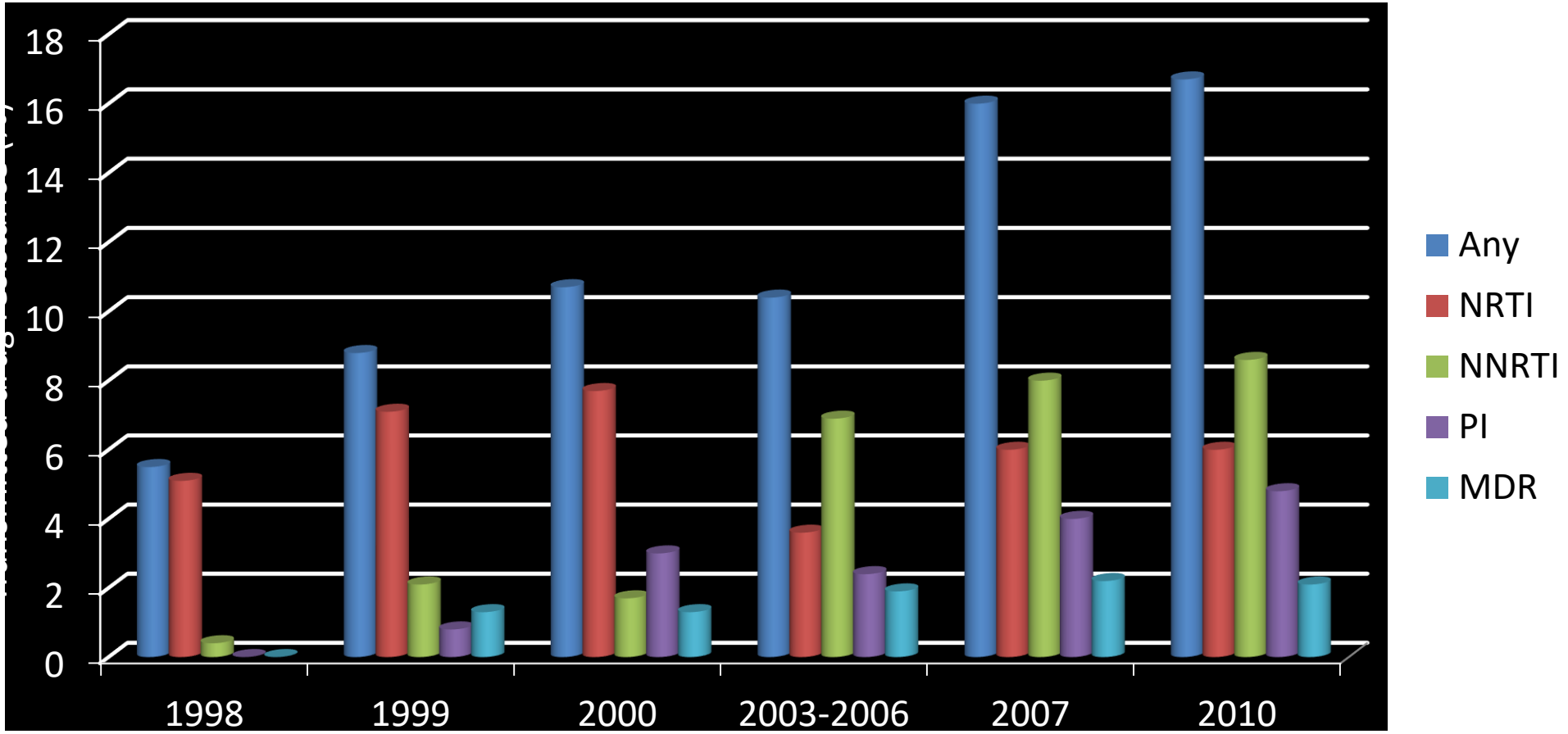
Cause of Developed Resistance

- Low concentrations of antiretrovirals in the body
  - Non-adherence
    - Missed doses
    - Delayed doses
  - Inadequate absorption
  - Drug interactions

Option 2 – Transmitted Resistance

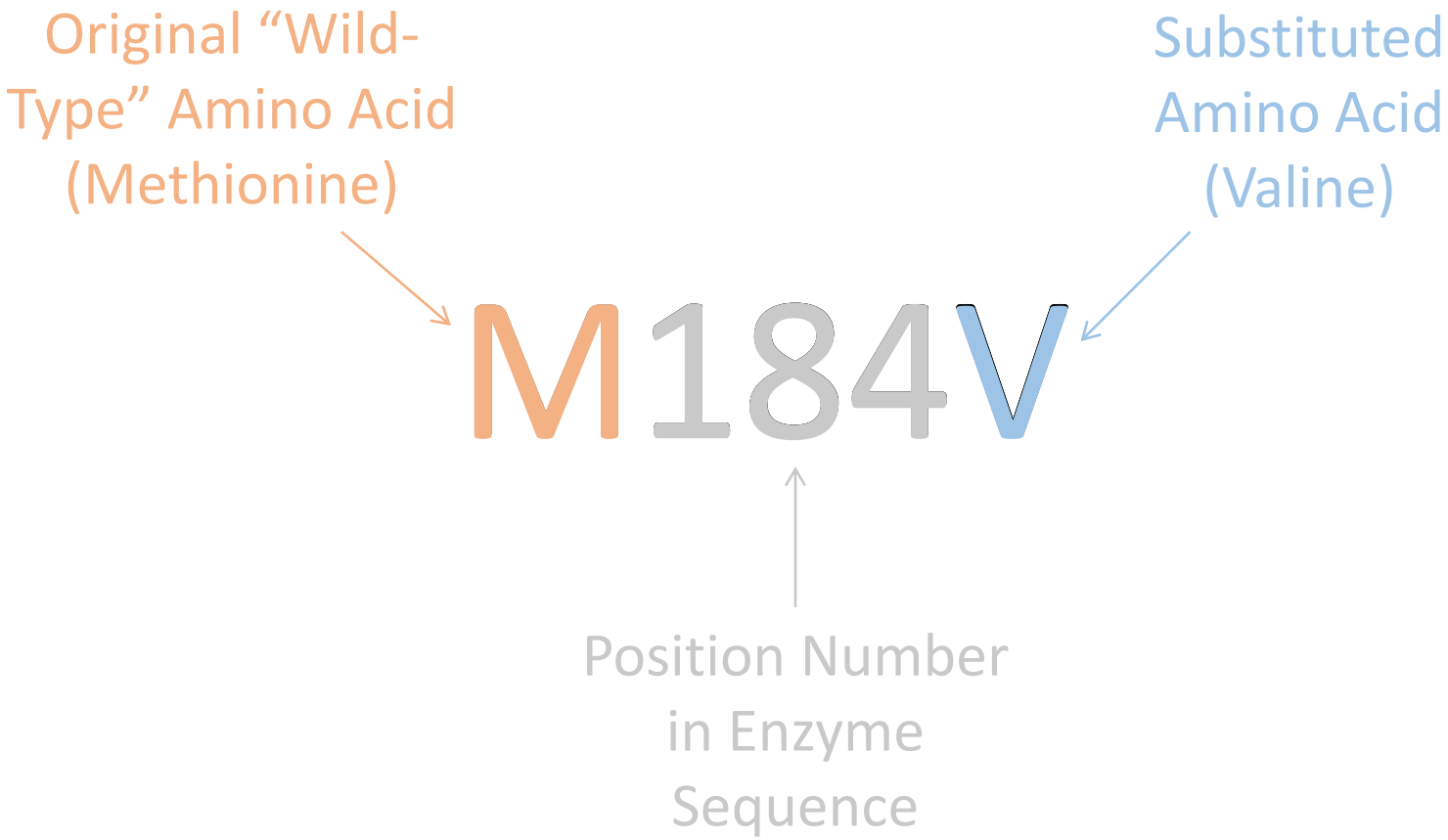
- Viral strains with drug resistance can be transmitted during initial infection or with subsequent re-exposure
- Encourage safe sex practices or clean needle use even after infected
- Patients fully adherence to therapy can develop resistance through exposure from a non-adherent partner

Prevalence of Transmitted Resistance



Bennett D et al. 9th Conference on Retrovirus and Opportunistic Infections, February 24-28, 2002, Seattle, WA. Abstract 372.
Wheeler W et al. 14th Conference on Retrovirus and Opportunistic Infections, February 25-28, 2007, Los Angeles, CA. Abstract 648.
Kim D et al. 17th Conference on Retrovirus and Opportunistic Infections, February 16-19,2010, San Francisco, CA. Abstract 580.
Kim D et al. 20th Conference on Retrovirus and Opportunistic Infections, March 3-6, 2013, Atlanta, GA. Abstract 149.

Mutation Terminology



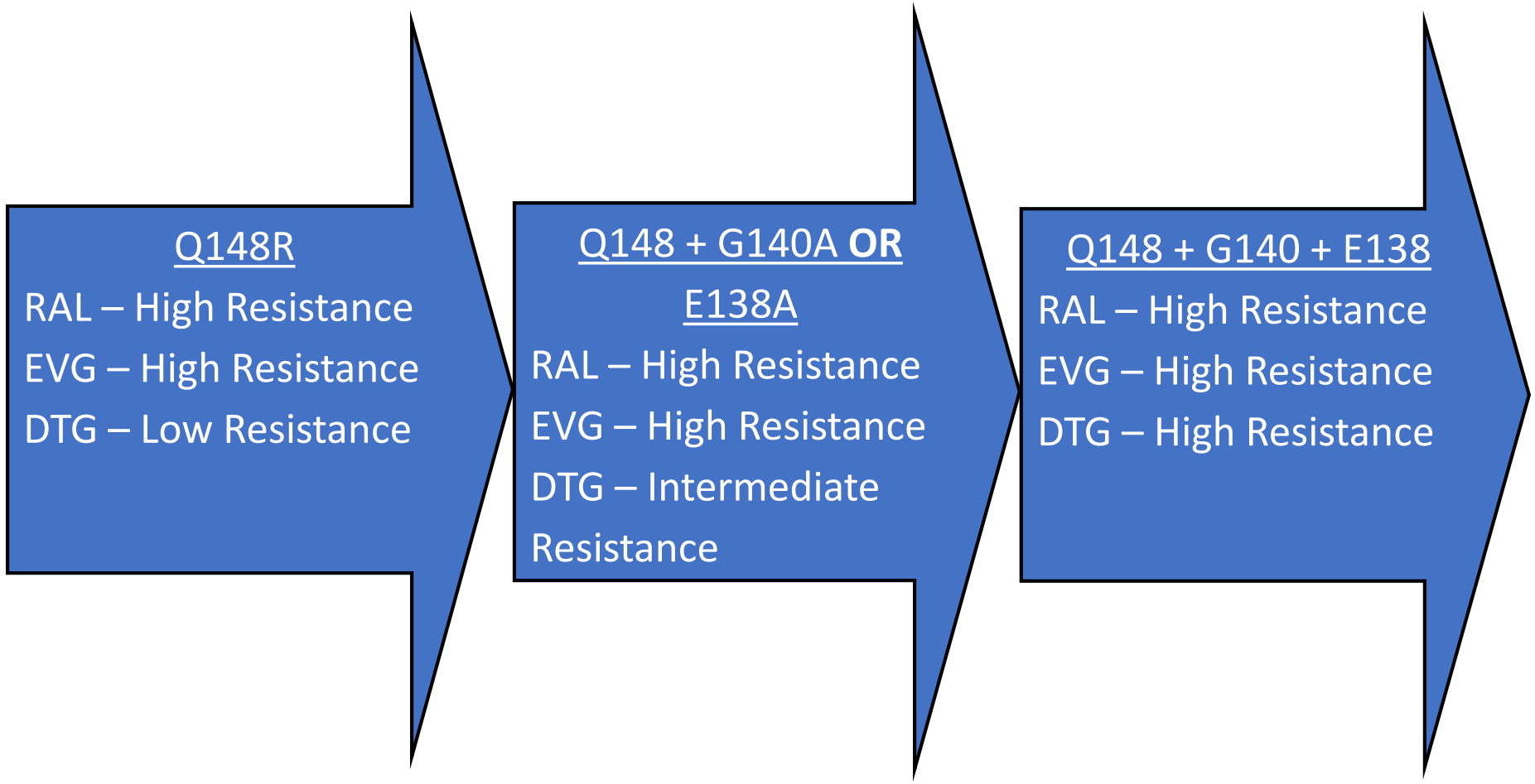
Resistance Accumulation

- Resistance is not usually all-or-nothing
  - “Resistant” vs. “Sensitive”
  - Various shades of gray

- Protease inhibitors resistance often requires multiple mutations
  - 1-2 Primary mutations
  - Various secondary mutations

Clavel F et al. N Engl J Med 2004;350:1023-35.

Integrase Resistance Accumulation



Cross-Resistance

- Resistance developed to one medication also causes resistance to other medication in the same class
  - Patient may never have taken the other medications
  - Limits future treatment options

Clavel F et al. N Engl J Med 2004;350:1023-35.

Cross Resistance Examples

M184V K103N K65R

NRTIs	NNTRIs	PIs	Entry/Fusion Inhibitors
Combivir®	Edurant®	Aptivus®	Fuzeon®
Descovy®	Intelence®	Crixivan®	Selzentry®
Emtriva®	Rescriptor®	Evotaz®	
Epivir®	Sustiva®	Invirase®	**Single Tablet Regimens**
Epzicom®	Viramune®	Kaletra®	Atripla®
Retrovir®		Lexiva®	Biktarvy®
Trizivir®	**INSTIs**	Norvir®	Complera®
Truvada®	Isentress®	Prezcobix®	Genvoya®
Videx®	Tivicay®	Prezista®	Juluca®
Viread®	Vitekta®	Reyataz®	Odefsey®
Zerit®		Viracept®	Stribild®
Ziagen®			Triumeq®

Resistance Testing

Clinical Setting	Rational/Comment
Acute HIV infection	• To determine if resistant virus was transmitted; guide treatment decisions • Consider repeat testing if treatment is deferred
In ART-naive patients with chronic HIV infection	• Transmitted drug-resistant virus is common in some areas; is more likely to be detected earlier in the course of HIV infection • Consider repeat testing at the time of starting ART
In patients with virologic failure	• To assist in selecting active drugs for a new regimen.
In patients with suboptimal suppression of viral load once on ART	• To assist in finding previously unknown mutations and guide future treatment decisions
Pregnancy	• Goal to achieve maximal viral suppression for prevention of perinatal transmission of HIV

DHHS. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.

Last Name	Patient	**First Name**	Unknown
Clinic	UNKNOWN	**Physician**	Unknown
MR Number	123456	**Accession Number**	123456 (49138)
Collection Date	07/17/2010	**Received Date**	07/17/2010
Date Entered	07/17/2010	**File Name**	

Sequence includes PR codons: 1 - 99
Sequence includes RT codons: 1 - 299
There are no insertions or deletions
Subtype: B
No. previous patient sequences: **PR:** 0 **RT:** 0

PI Major Resistance Mutations	V82AV
PI Minor Resistance Mutations	None
Other Mutations	I64V, I72M

Protease Inhibitors

atazanavir/r (ATV/r)	Low-level resistance
darunavir/r (DRV/r)	Susceptible
fosamprenavir/r (FPV/r)	Potential low-level resistance
indinavir/r (IDV/r)	Intermediate resistance
lopinavir/r (LPV/r)	Low-level resistance
nelfinavir (NFV)	Intermediate resistance
saquinavir/r (SQV/r)	Potential low-level resistance
tipranavir/r (TPV/r)	Susceptible

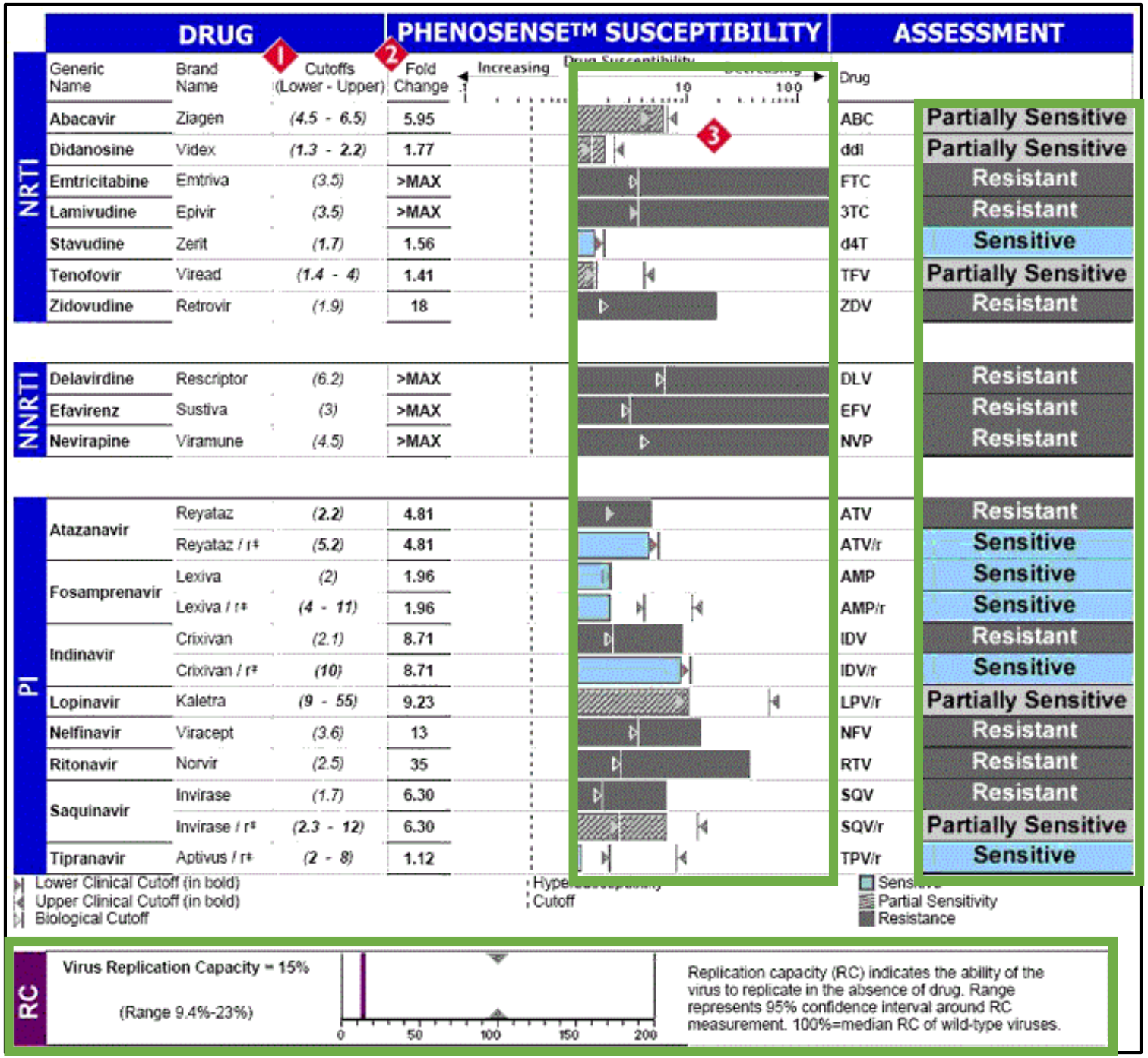
NRTI Resistance Mutations	D67N, K70R, M184IMV, K219Q
NNRTI Resistance Mutations	V90IV, K103N, K238N
Other Mutations	V60I, K102R, D123E, T139KR, S162NS, K166KR, I178M, G196E, D237DN, A272S, T286A, E297K

Nucleoside RTI

lamivudine (3TC)	High-level resistance
abacavir (ABC)	Low-level resistance
zidovudine (AZT)	Intermediate resistance
stavudine (D4T)	Intermediate resistance
didanosine (DDI)	Potential low-level resistance
emtricitabine (FTC)	High-level resistance
tenofovir (TDF)	Potential low-level resistance

Non-Nucleoside RTI

delavirdine (DLV)	High-level resistance
efavirenz (EFV)	High-level resistance
etravirine (ETR)	Potential low-level resistance
nevirapine (NVP)	High-level resistance


DRUG
PHENOSENSE™ SUSCEPTIBILITY
ASSESSMENT
1
2
3
Generic Name
Brand Name
Cutoffs (Lower - Upper)
Fold Change
Increasing
Drug Susceptibility
Decreasing
10
100
Drug
NRTI
Abacavir Ziagen (4.5 - 6.5) 5.95 ABC Partially Sensitive
Didanosine Videx (1.3 - 2.2) 1.77 ddI Partially Sensitive
Emtricitabine Emtriva (3.5) >MAX FTC Resistant
Lamivudine Epivir (3.5) >MAX 3TC Resistant
Stavudine Zerit (1.7) 1.56 d4T Sensitive
Tenofovir Viread (1.4 - 4) 1.41 TFV Partially Sensitive
Zidovudine Retrovir (1.9) 18 ZDV Resistant
NNRTI
Delavirdine Rescriptor (6.2) >MAX DLV Resistant
Efavirenz Sustiva (3) >MAX EFV Resistant
Nevirapine Viramune (4.5) >MAX NVP Resistant
PI
Atazanavir Reyataz (2.2) 4.81 ATV Resistant
Reyataz / r‡ (5.2) 4.81 ATV/r Sensitive
Fosamprenavir Lexiva (2) 1.96 AMP Sensitive
Lexiva / r‡ (4 - 11) 1.96 AMP/r Sensitive
Indinavir Crixivan (2.1) 8.71 IDV Resistant
Crixivan / r‡ (10) 8.71 IDV/r Sensitive
Lopinavir Kaletra (9 - 55) 9.23 LPV/r Partially Sensitive
Nelfinavir Viracept (3.6) 13 NFV Resistant
Ritonavir Norvir (2.5) 35 RTV Resistant
Saquinavir Invirase (1.7) 6.30 SQV Resistant
Invirase / r‡ (2.3 - 12) 6.30 SQV/r Partially Sensitive
Tipranavir Aptivus / r‡ (2 - 8) 1.12 TPV/r Sensitive
Lower Clinical Cutoff (in bold)
Upper Clinical Cutoff (in bold)
Biological Cutoff
Cutoff
Partial Sensitivity
Resistance
RC
Virus Replication Capacity = 15%
(Range 9.4%-23%)
0
50
100
150
200
Replication capacity (RC) indicates the ability of the virus to replicate in the absence of drug. Range represents 95% confidence interval around RC measurement. 100%=median RC of wild-type viruses.

AETC Resources

- **Clinical Consultation Center**
  http://nccc.ucsf.edu
  - HIV Management
  - Perinatal HIV
  - HIV PrEP
  - HIV PEP line
  - HCV Management
  - Substance Abuse Management
- **AETC National Curriculum**
  http://aidsetc.org/nhc
- **AETC National HIV-HCV Curriculum**
  http://aidsetc.org/hivhcv
- **Hepatitis C Online**
  https://www.hepatitisc.uw.edu
- **AETC National Coordinating Resource Center**
  http://aidsetc.org
- **Additional Training for Midwest AIDS Training and Education Center (MATEC)**
  https://matec.info

AETC
Midwest

Questions?

Please contact MATEC at anytime

Phone: 313 962 2000 or

email: matecmichigan@gmail.com

MIDWEST AIDS TRAINING + EDUCATION CENTER

WAYNE STATE School of Medicine

AETC AIDS Education & Training Center Program Midwest