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HIV treatment failure; ART toxicity & complications

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Lawrence Family Medicine Residency

HIV treatment failure; ART toxicity & complications

SESSION 2

HIV/HBV DIDACTIC SERIES

APRIL 17, 2020

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Overall Outline

5 session, 2 hours each

1. HIV & ART overview
   - History, Epidemiology, transmission/risk, staging
   - Med Class Overview, ART initiation
2. Treatment monitoring & Failure
   - 2nd & 3rd line ART, toxicity/complications, monitoring
   - Prevention
3. Opportunistic Infections & Hepatitis B
   - OIs, ART considerations, Prophylaxis
   - HBV dx, tx, surveillance, & HIV-HBV co-infection
4. Special Populations:
   - Pregnancy, antenatal & intrapartum, infant care & pediatric
5. HIV/HBV Case-Based Application
   1. Case Application
   2. Wrap-up/review, miscellaneous items

Source Materials

Liberia Integrated Guidelines for Prevention, Testing, Care, and Treatment of HIV and AIDS
- 5th edition, August 2019

WHO HIV Diagnosis, Treatment, and Opportunistic Infection Guidelines
- 2016, 2018 ART update
- https://www.who.int/publications/guidelines/hiv_aids/en/

WHO Hepatitis B treatment guidelines (2015)
- https://www.who.int/hepatitis/publications/hepatitis-b-guidelines/en/

Reference Materials

Department of Health & Human Services. HIV Guidelines. USA. https://aidsinfo.nih.gov/guidelines

Fundamentals of HIV Medicine. American Academy of HIV Medicine. Oxford University Press. 2017 Edition.

National HIV Curriculum. University of Washington & CDC. USA. https://www.hiv.uw.edu/

Outline

Mechanism of Resistance & defining terms

Resistance Pathways for each ART class

Treatment failure: 2nd & 3rd line ART

ART adverse effects

ART drug-drug interactions

Case

34yo on EFV/TDF/3TC. She has lost 20 pounds in 6 months with diarrhea.

She discloses that she generally takes her meds 3-4 days a week. She misses medications on days when she travels to a nearby village to sell goods and leaves early in the morning.

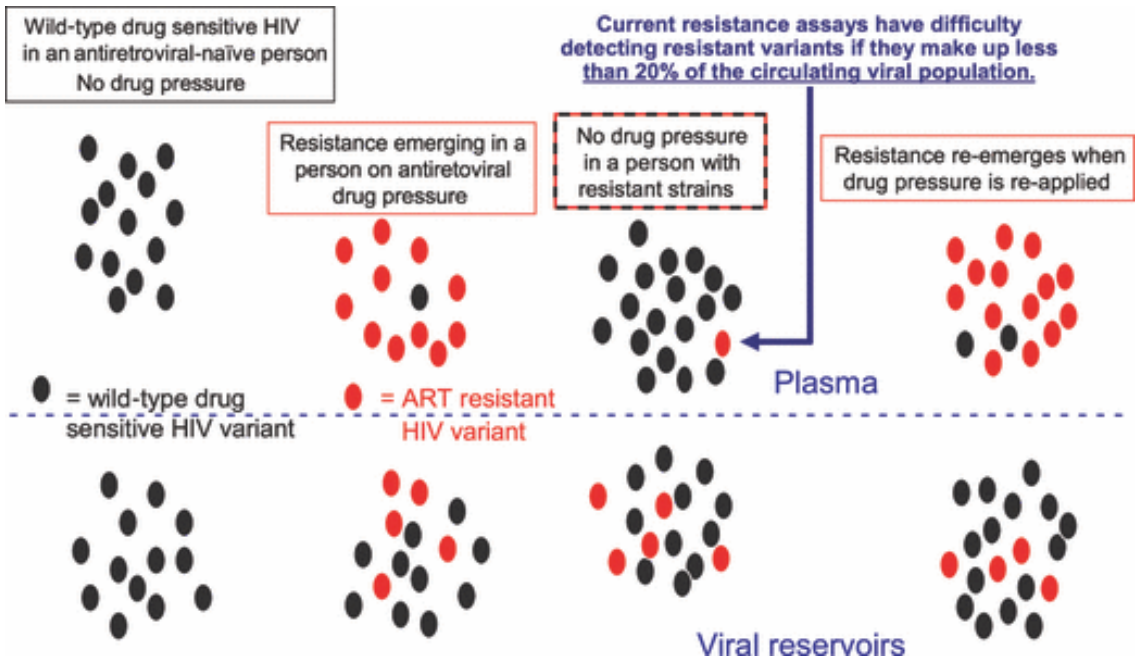
Next step?

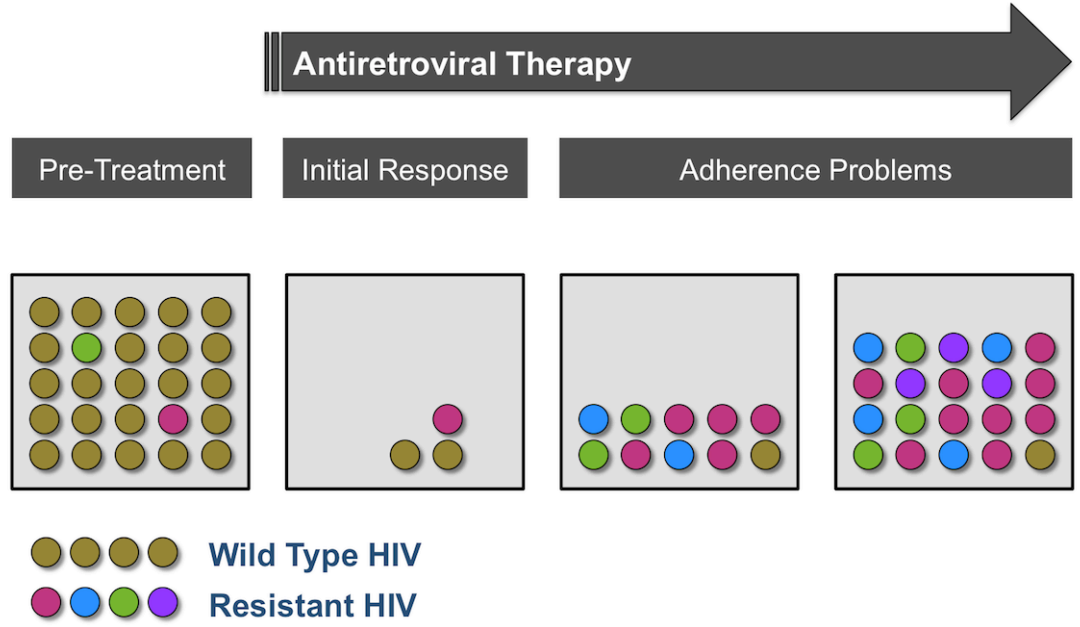
What findings and factors might prompt concern for resistance?

Foundations of Treatment Failure

ART = Selective Pressure
Determines **Viral Fitness**
Viral Population
The most fit virus prevails at any given time point
Once resistance is selected it will **remain** in the population

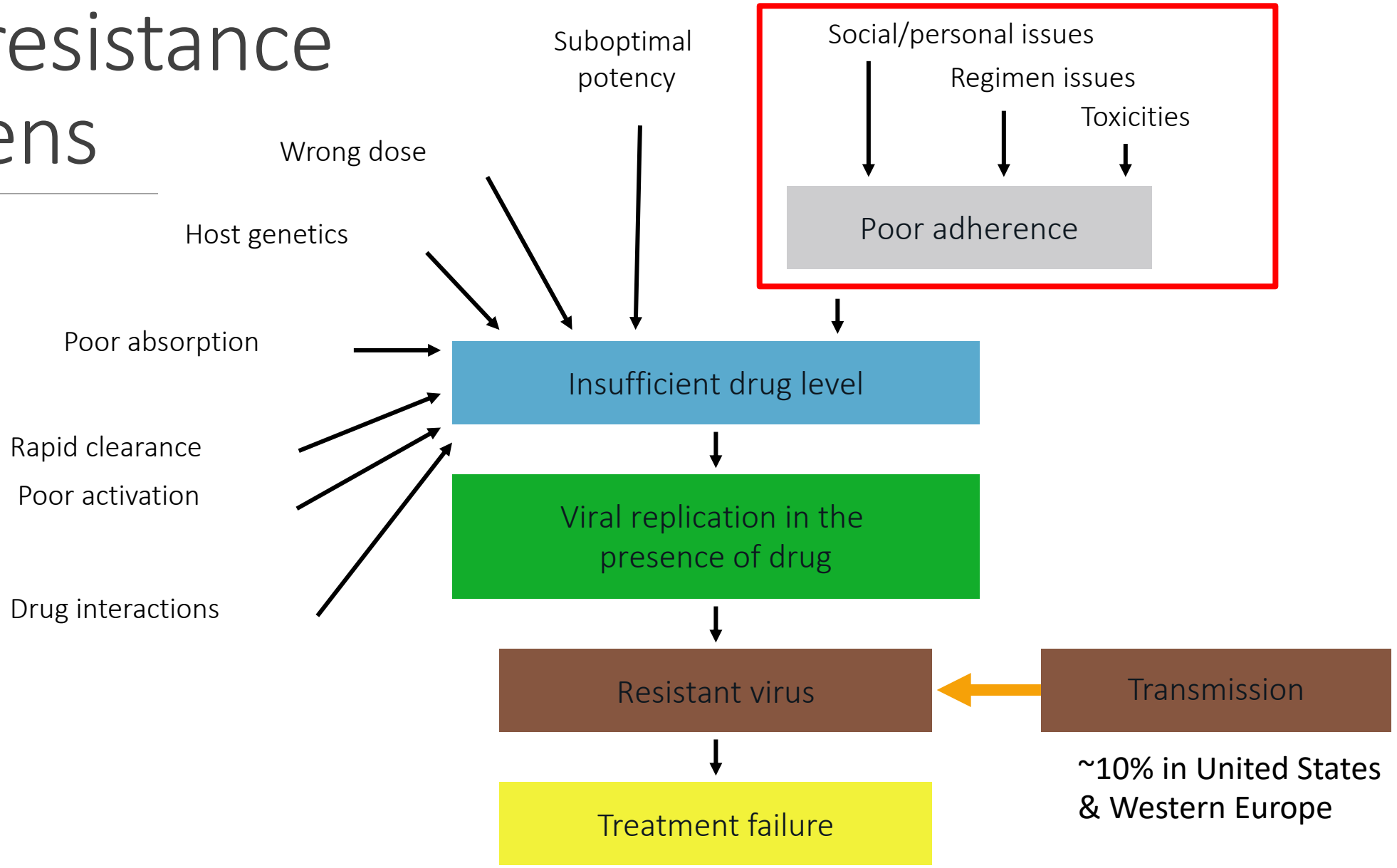
drug + Replicating virus → Resistance



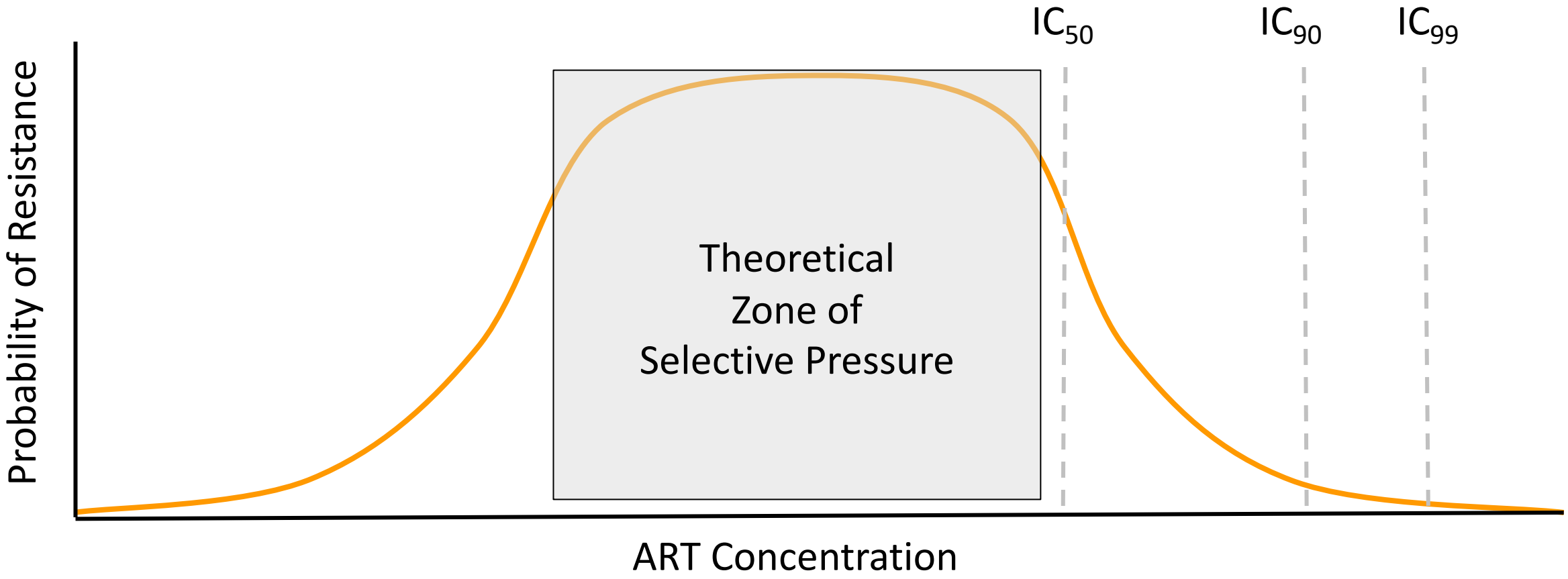


Kozal 2010

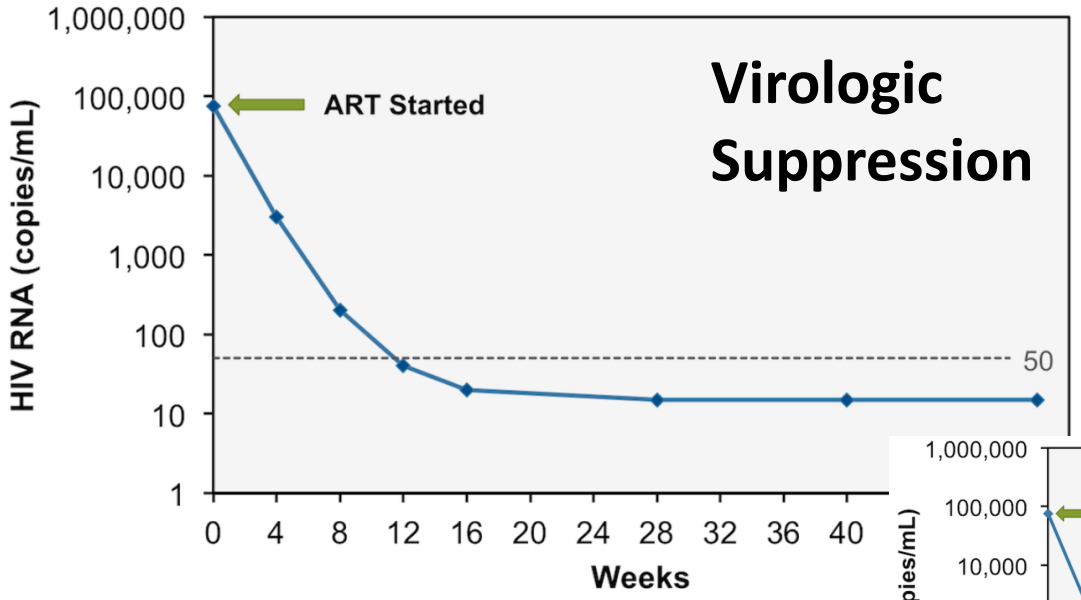
How resistance happens

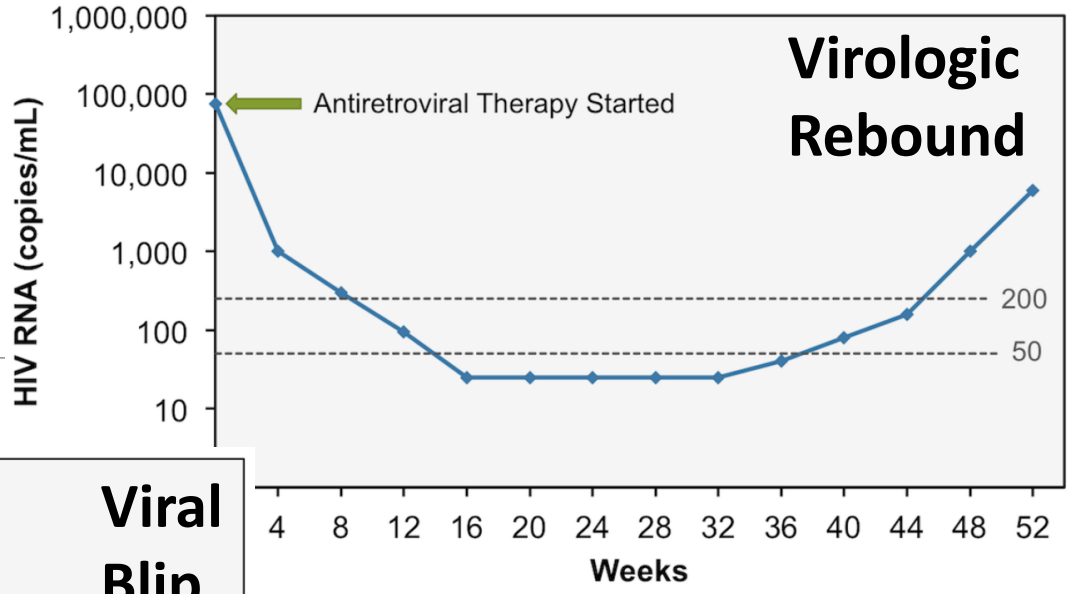


Basic Resistance Model



Slide Adapted from Bositis 2019


Virologic Suppression
ART Started
HIV RNA (copies/mL)
1,000,000
100,000
10,000
1,000
100
10
1
50
0 4 8 12 16 20 24 28 32 36 40
Weeks


Virologic Rebound
Antiretroviral Therapy Started
HIV RNA (copies/mL)
1,000,000
100,000
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200
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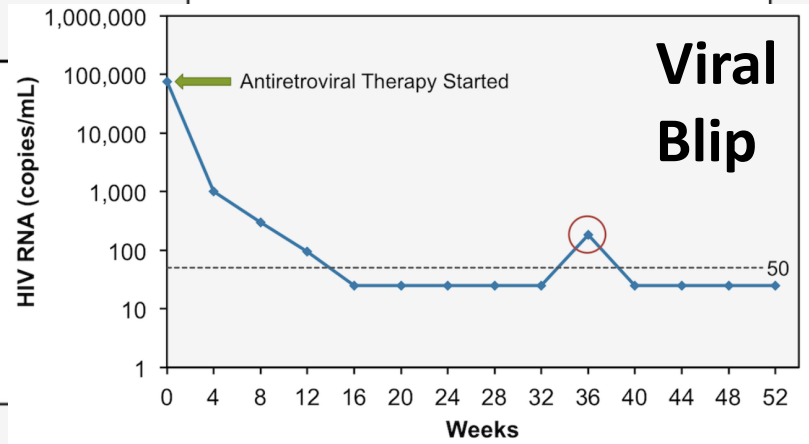
4 8 12 16 20 24 28 32 36 40 44 48 52
Weeks


Viral Blip
Antiretroviral Therapy Started
HIV RNA (copies/mL)
1,000,000
100,000
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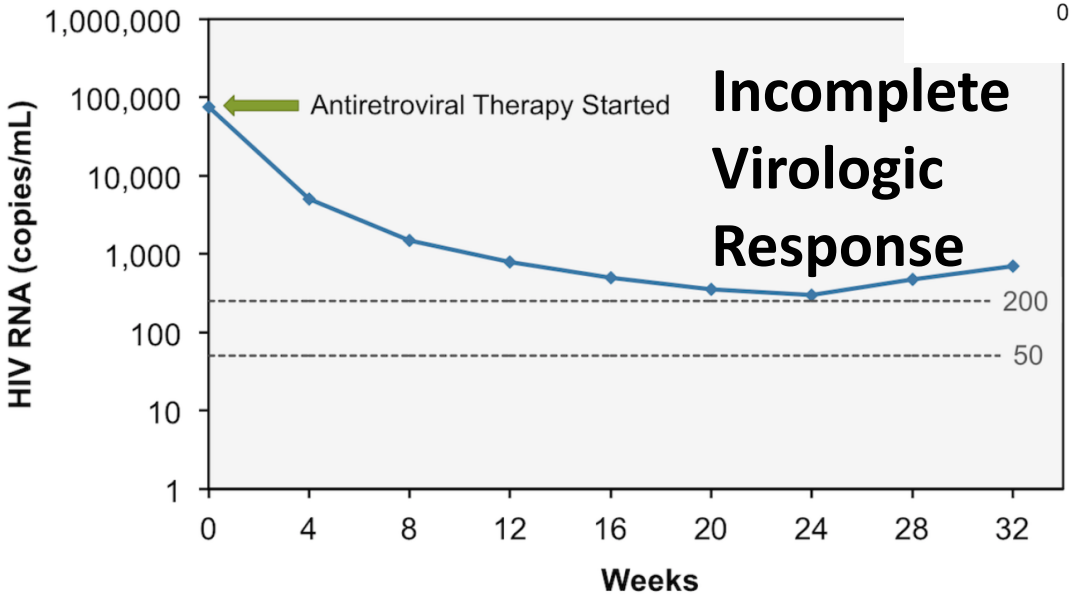
0 4 8 12 16 20 24 28 32 36 40 44 48 52
Weeks


Incomplete Virologic Response
Antiretroviral Therapy Started
HIV RNA (copies/mL)
1,000,000
100,000
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200
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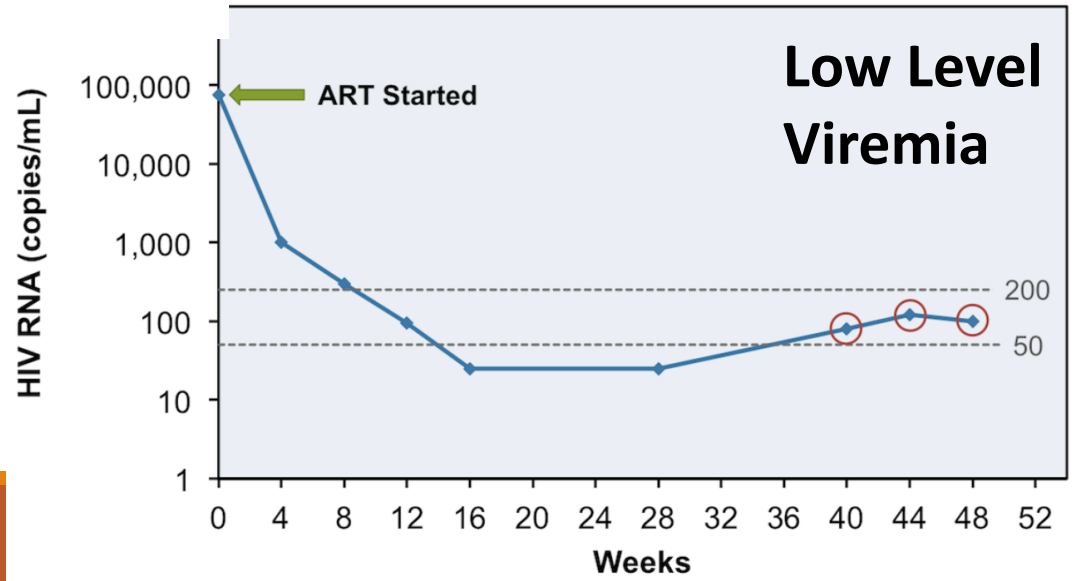
0 4 8 12 16 20 24 28 32
Weeks


Low Level Viremia
ART Started
HIV RNA (copies/mL)
100,000
10,000
1,000
100
10
1
200
50
0 4 8 12 16 20 24 28 32 36 40 44 48 52
Weeks

Terms

Successful ART	VL not detected
Potential Treatment Failure	**Routine** VL detectable (even if < 1,000)
Confirmed Treatment Failure	Targeted or repeat **VL > 1,000** **AND** Patient on **NNRTI-based** regimen* **AND** **Good adherence** for 3 months prior *genotype for INSTI- or PI-based

Genetic Barrier to Resistance

Genetic Barrier
Number of mutations needed to confer resistance

number mutations required to confer resistance

time until resistance

Genetic Barrier to resistance

More “forgiving” regimen

Non-Boosted PI

Small Change per Mutation

BUT

Low Drug Levels

NNRTI

High Drug Levels

BUT

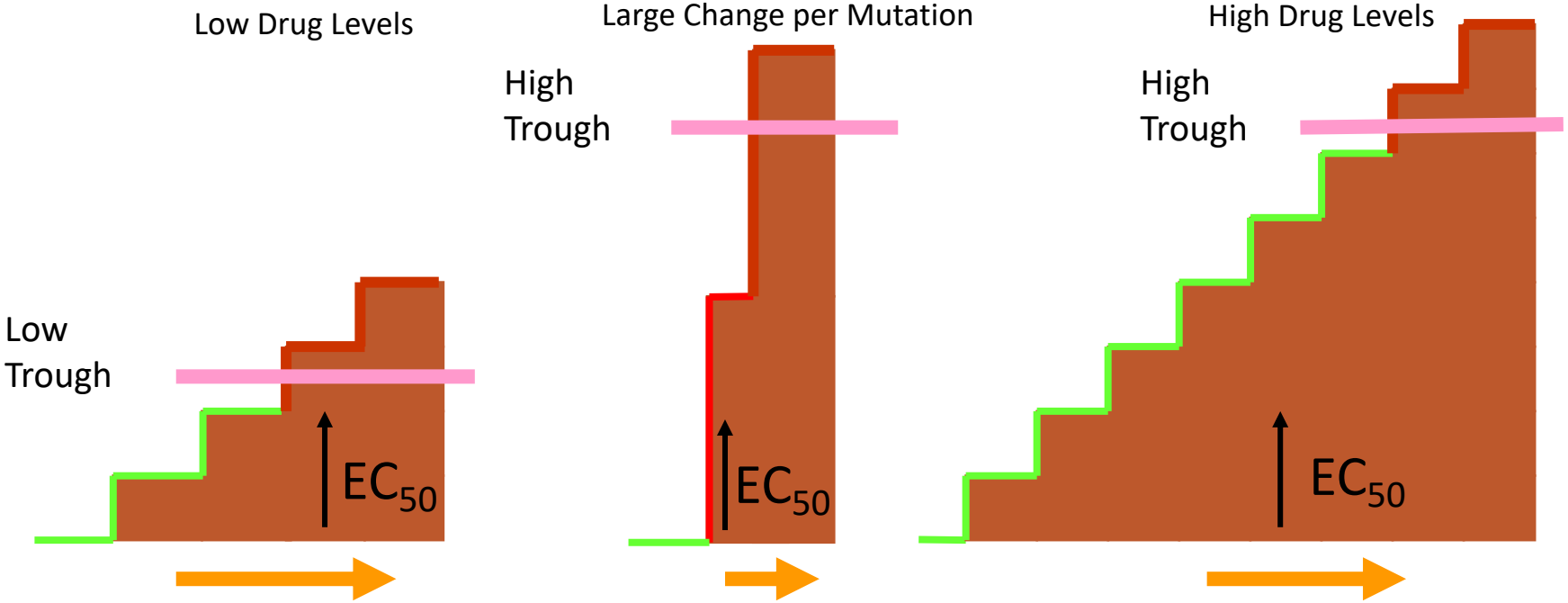
Large Change per Mutation

Boosted PI

Small Change per Mutation

AND

High Drug Levels



Increasing Number of Mutations

Kuritzkes et al 2003; Bositis 2019

Cross-resistance

Resistance to 1 agent in a class → resistance to other agents in the same class

First generation NNRTI & INSTI
- High level of cross-resistance

NRTI
- Varies
- emtricitabine (FTC) & lamivudine (3TC) = *complete* cross-resistance

PI & second-generation NNRTI
- Cumulative progressive resistance mutations expands cross-resistance

Goal: >95% adherence

Adherence

"What challenges have you had taking your ARV?"

"What days / times are you most likely to forget your ARV?"

"Everyone has difficulty taking meds every day. When was the last time you were not able to take your ARV, and how many times in the past week, month were you unable?"

Goal: to help the patient
- No policing
- Encourage transparency

Root cause: there is *always* a reason (or reasons)
- Stigma & disclosure
- Socio-economic barrier
- Transportation & Work
- Psychological
- Misunderstanding
- Side effects

Practical Strategies
- Join with daily routines (meal, cleaning)
- Cell phone alarm
- Take meds with another person
- Keep a med diary

Intensive Adherence Counseling (IAC)

for *any* sign of poor adherence

for any detectable Viral Load (even is <1k)

Patient & Treatment Supporter

Education on ART, adherence, monitoring, failure, & resistance

<u>Indentify Specifics</u>

- Travel, Work, Education
- Stigma, Privacy, Domestic Difficulties
- Substance Use
- Mental Health / Depression

<u>Action Plan</u>

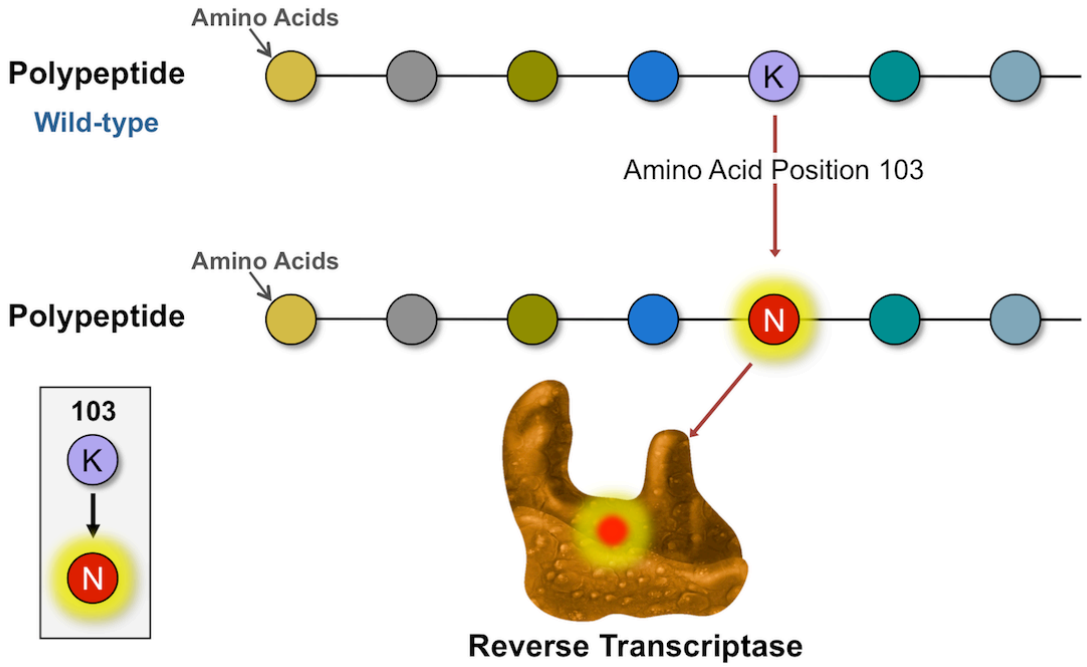
- Specific
- Written on Patient Card
- Monthly appointments
  - Pill Counts
  - Action Plan review
- Viral Load in 3mo

<u>Stopping ART considered if:</u>

- Chronic poor adherence
- IAC counseling completed
- Shared decision making

Mutation Nomenclature

wild-type amino acid — codon position — mutant amino acid



103 = codon (amino acid position)

K103N

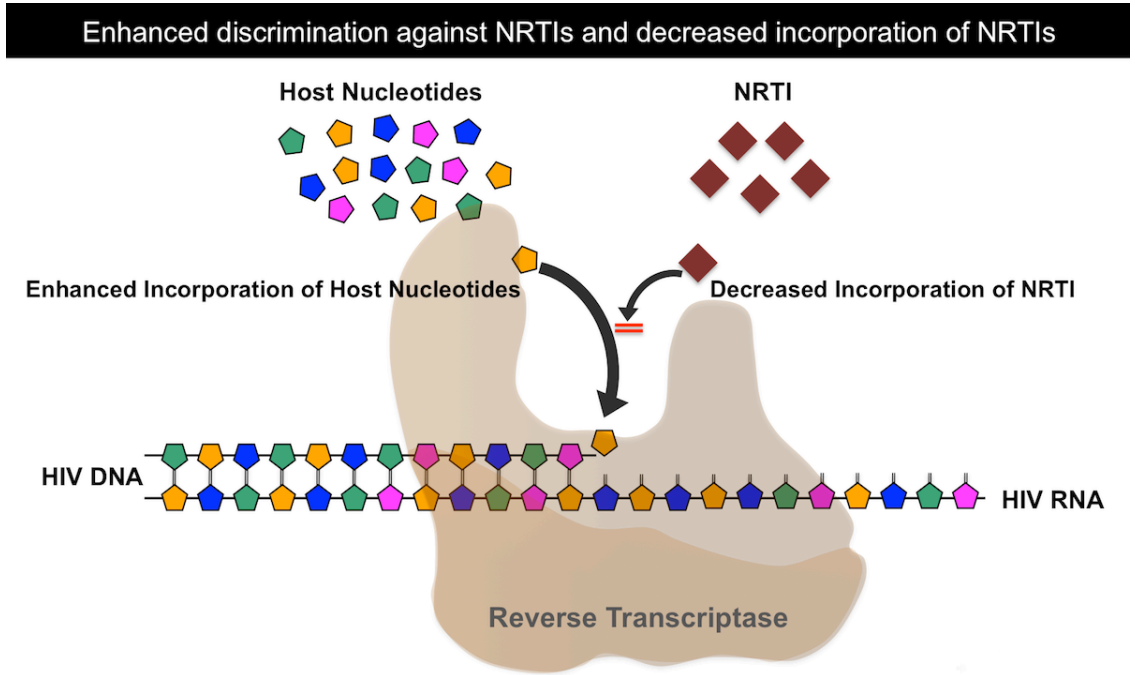
K = Wild-type amino acid

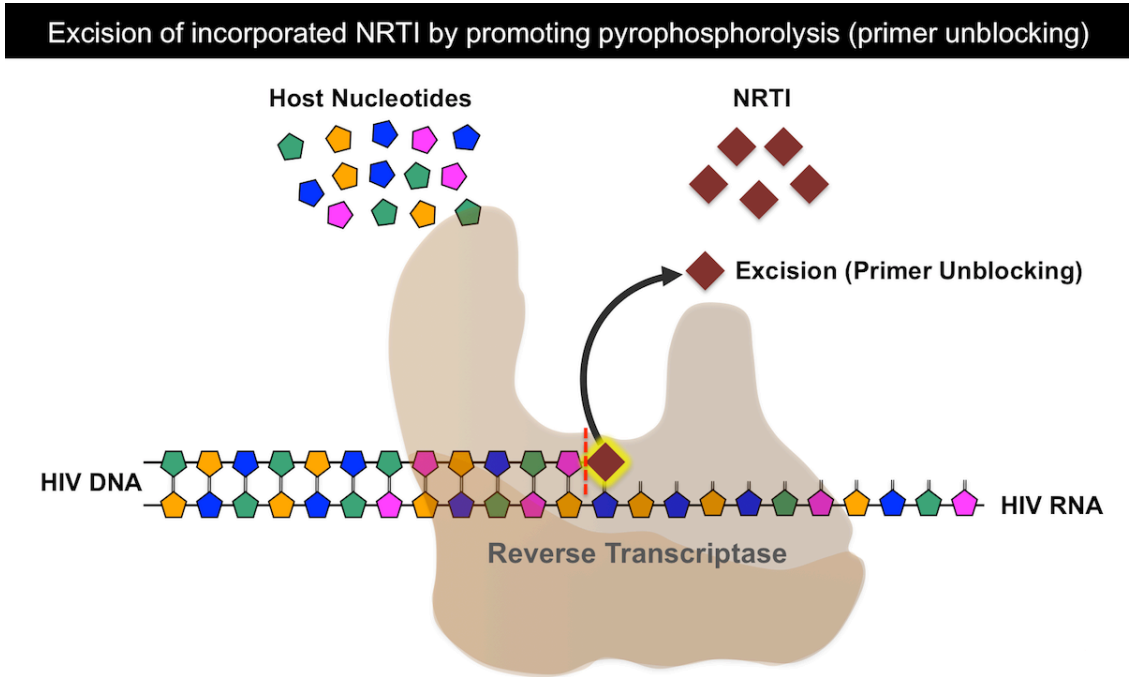
N = Mutant amino acid

NRTI Resistance Mechanisms

Discrimination
[decreased incorporation of NRTI into DNA strand]

Excision
[removal of NRTI from the DNA strand]





NRTI Resistance Pathways

TDF – tenofovir
3TC – lamivudine
ABC – abacavir
AZT – zidovudine

3TC

M184I > **M184V**

Reverses TAM-associated resistance to: *TDF & AZT*

+

Resistance to: **3TC, FTC**
Low level resistance to: **ABC**

Decreases viral fitness

TAM
[thymidine analogue mutations]

AZT or **d4T**

Cumulative Cross-Resistance Class-wide

Co-occurrence worsens ABC + 3TC resistance

K65R

TDF or **ABC**

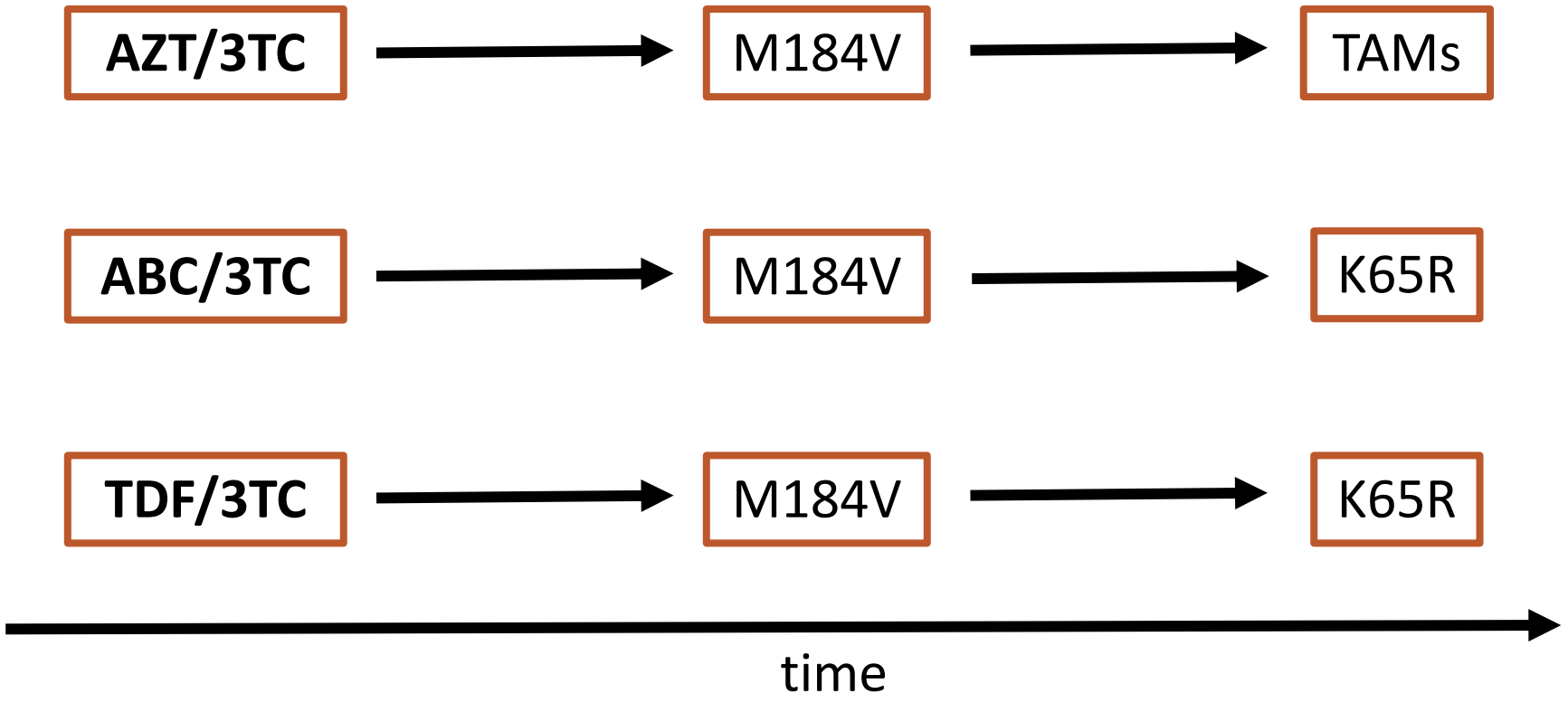
Resistance to: **TDF, 3TC, ABC**

+

^ Susceptibility: **AZT**

*Common in monotherapy

Temporal Sequence of NRTI mutations



Slide Adapted from Bositis 2019

Empiric NRTI Resistance

Monotherapy to TDF or 3TC (or PrEP with TDF/3TC)

- Likely M184V, possible K65R
  - Assume resistance to TDF, 3TC, & ABC
- Unlikely TAM = use AZT

3TC and/or TDF → failure → ***Assume*** M184V / K65R
Resistance: 3TC, TDF, likely ABC

Assume Susceptibility to: AZT
*may give 3TC (AZT/3TC combo) or TDF
(to select for M184V/K65R to ^ AZT susceptibility)

Confirmed virological failure

- Assume resistance to NRTIs in regimen & switch:
  - If on TDF or ABC –> AZT
  - If on AZT –> TDF/3TC

May always continue 3TC after failure

- Inducing M184V decreases viral fitness

AZT → failure → ***Assume Resistance*** Class-Wide due to TAM

May give: TDF/3TC to induce M184V –> ^ TDF susceptibility

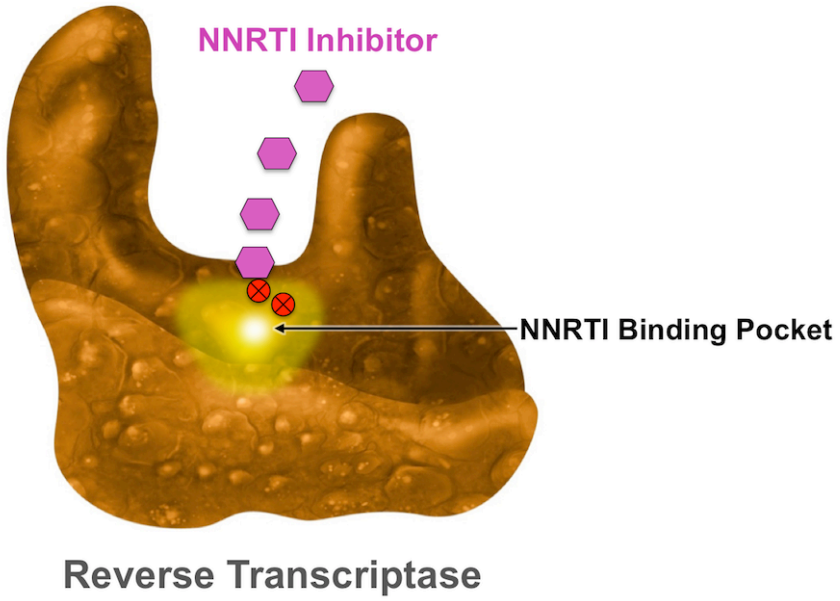
NNRTI Resistance Mechanisms

Low Barrier to resistance

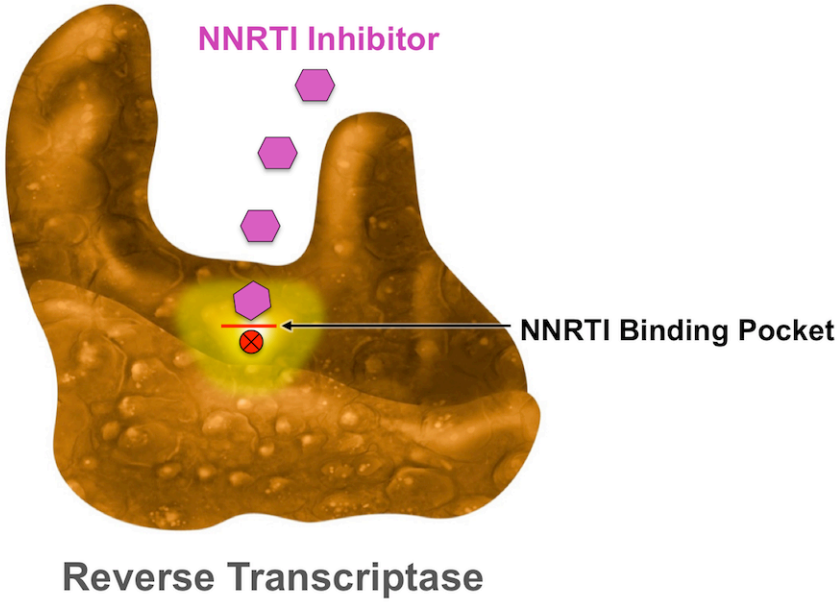
- **Pre-existing** mutations found in all ART-naïve patients are selected **quickly** – within 1 - 4 weeks!
- All NNRTIs bind in a **similar location**

HIV-2 – intrinsically resistant to all NNRTI

Reduced Access
to NNRTI-binding pocket



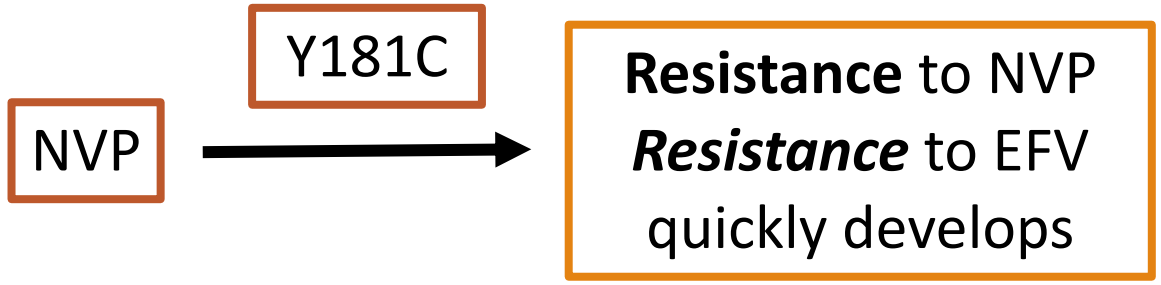
Altered Interaction
with NNRTI-binding pocket



NNRTI Resistance Pathways & Empiric Approach

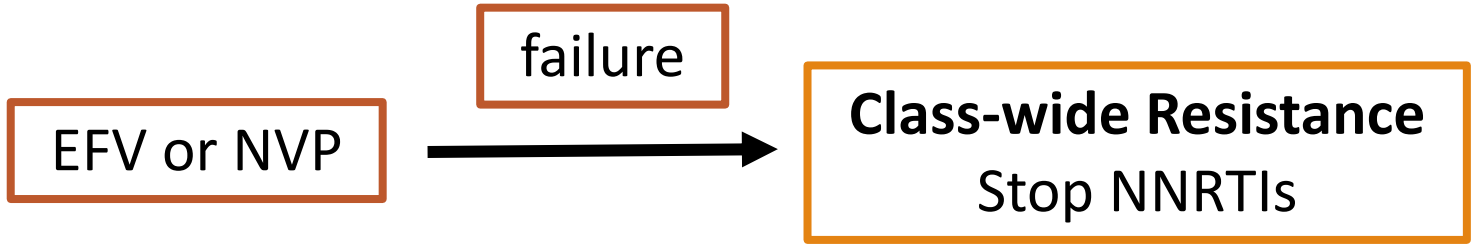
EFV – efavirenz
NVP – nevirapine

Highly fit virus



No impact on viral fitness

Hypersensitive to AZT



PI Resistance Mechanisms

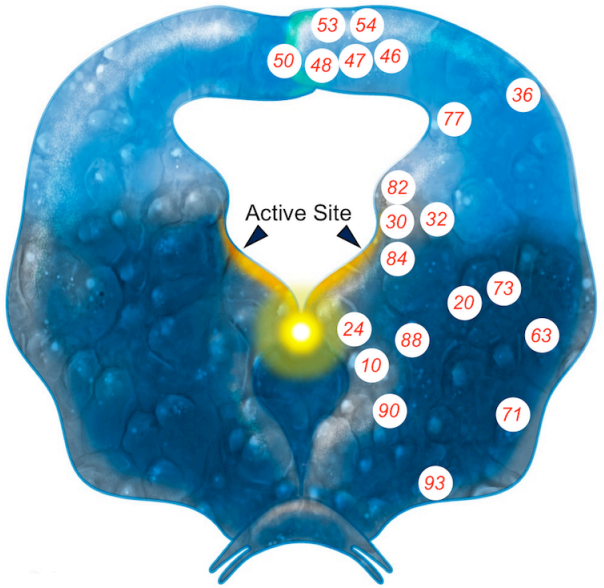
Barrier to resistance is *HIGH*

1. darunavir / ritonavir
2. lopinavir / ritonavir
3. atazanavir / ritonavir

Multiple mutations generally needed for resistance

- Major – cause resistance
  - Many have cross-resistance
  - Often decrease viral fitness
- Minor – do not affect susceptibility but may enhance viral replicative capacity

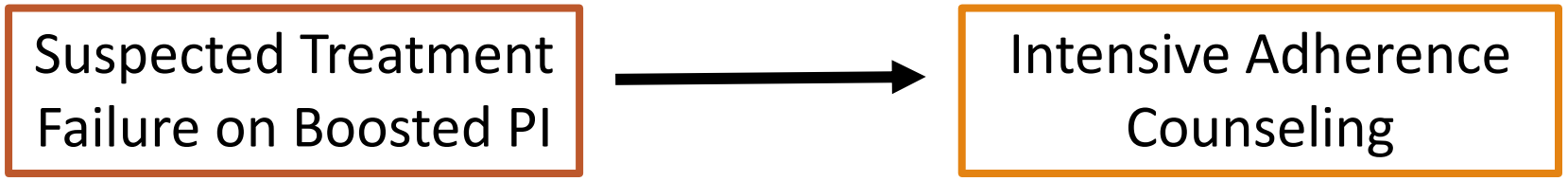
Multiple Mutations
Generally required to alter enzymatic activity



HIV Protease

PI Resistance Principles

Viral Resistance Mutations are **Rare** – Adherence / absorption **predominates**



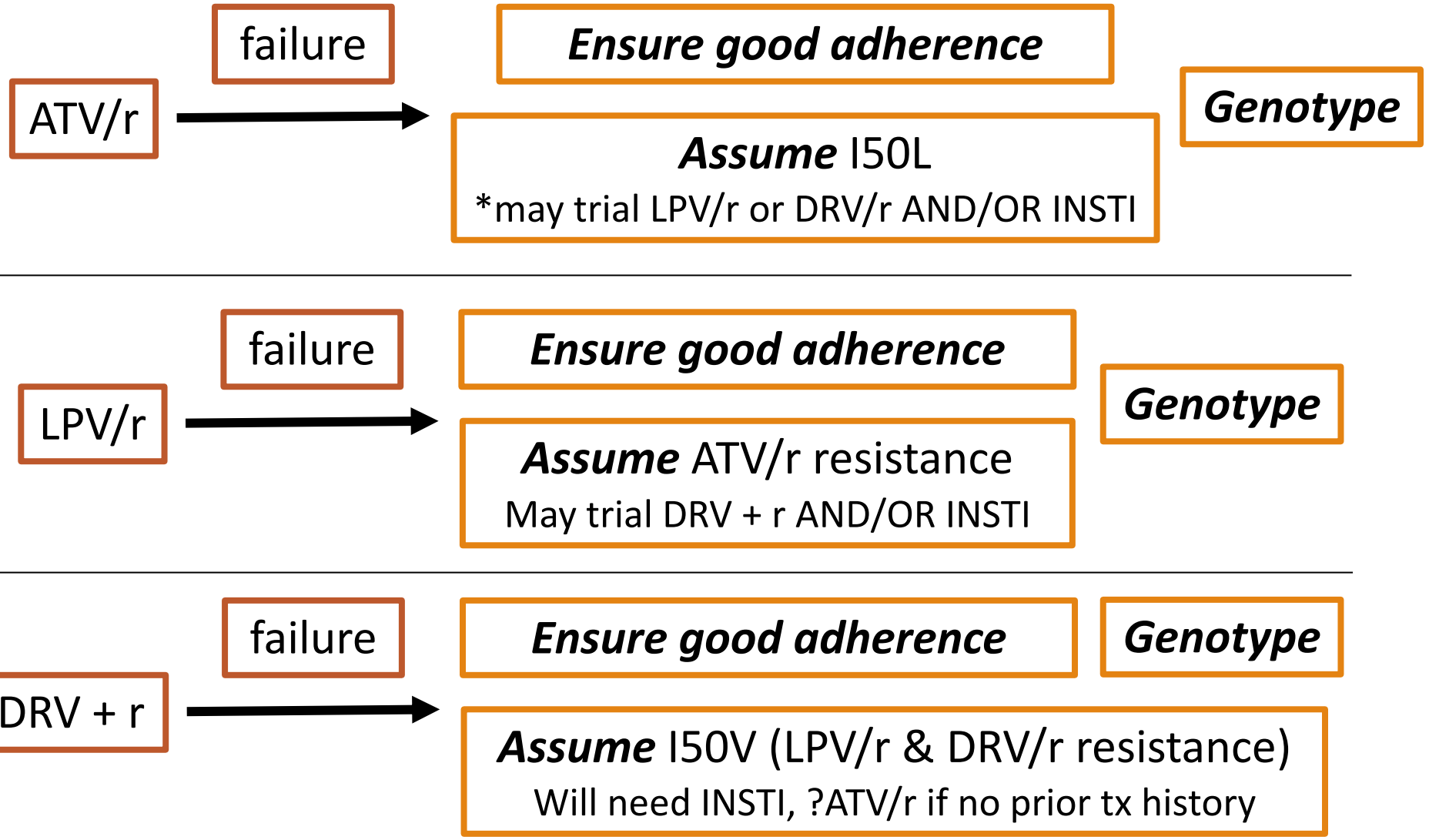
Virologic Failure more likely if prior treatment experience with a different PI

Important to confirmed good adherence prior to viral load!

LPV/r – lopinavir / ritonavir
ATV/r – atazanavir / ritonavir
DRV + r – darunavir + ritonavir

PI Resistance Pathways

Empiric PI Resistance



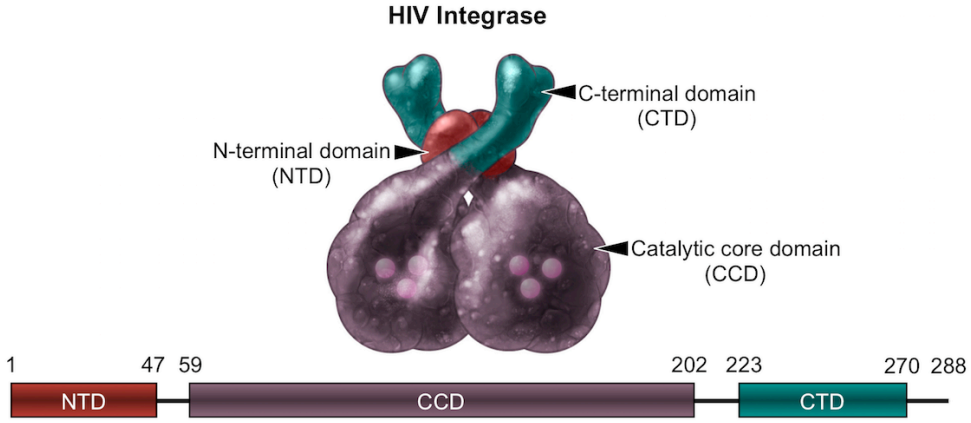
INSTI Resistance Mechanism

High Barrier to Resistance: Viral Resistance Mutations are **Rare** – Adherence / absorption **predominates**

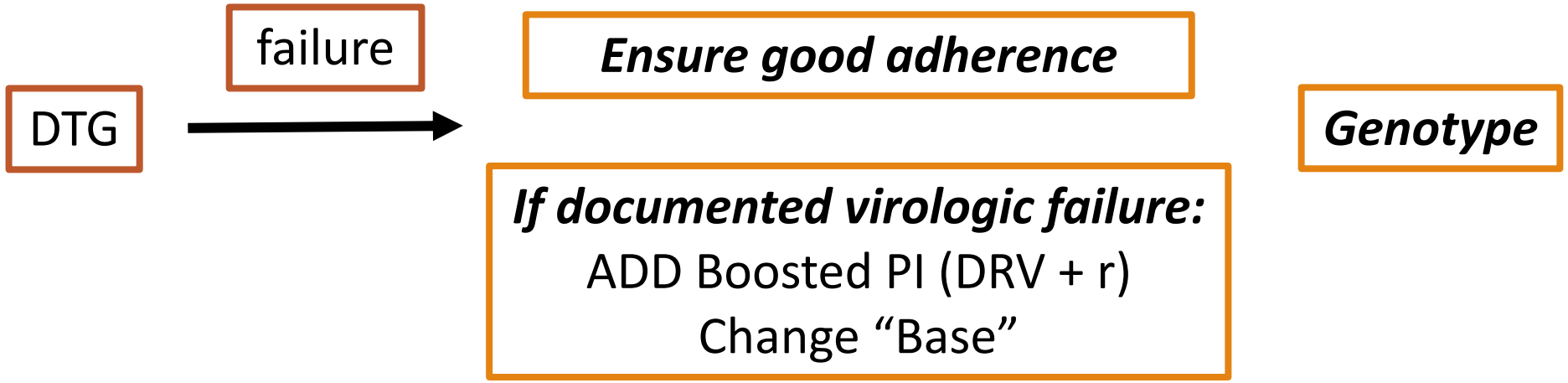
DTG — Highest barrier to resistance

- Little cross-resistance to earlier INSTIs (elvitegravir [EVG] & raltegravir [RAL])
- Very little phenotypic resistance seen even in patients on failing regimens

↑ Time on regimen = ↑ likelihood of resistance



INSTI Resistance Pathways & Empiric Resistance

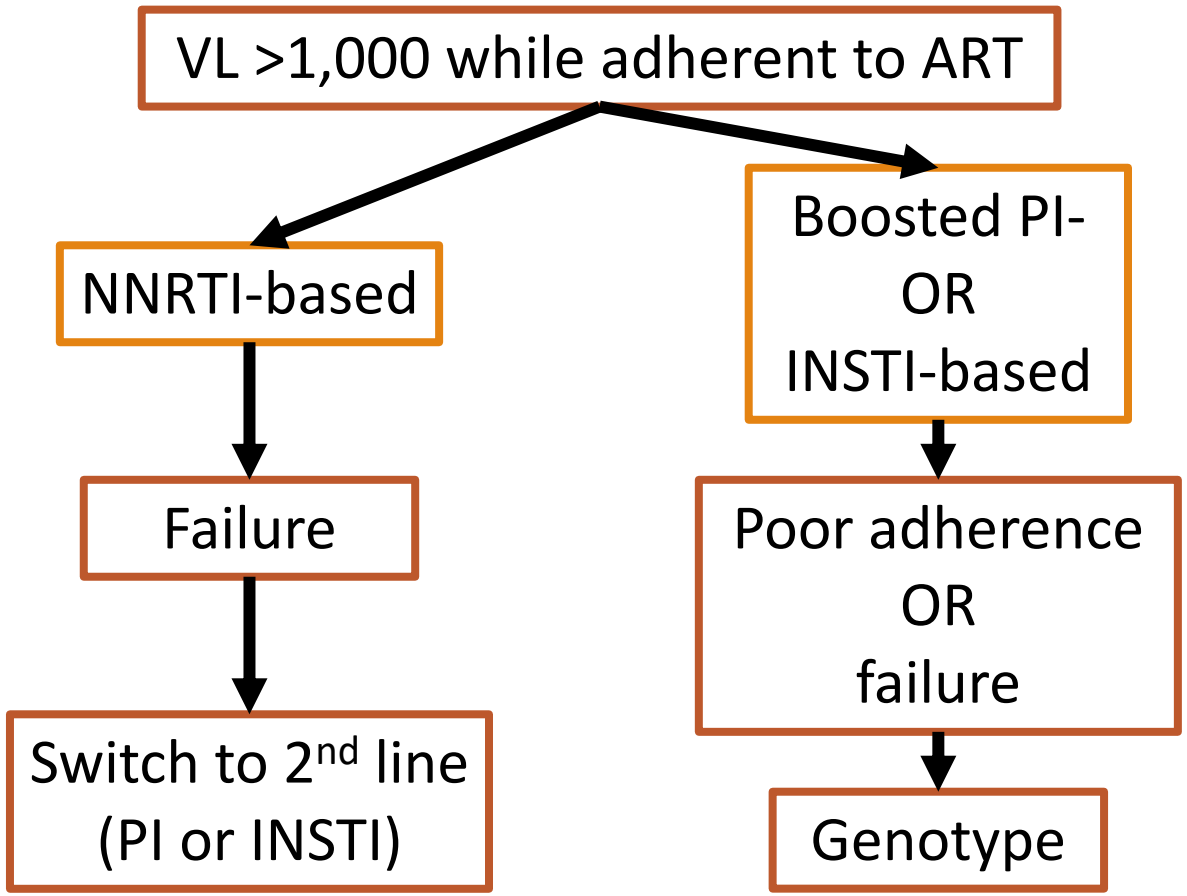


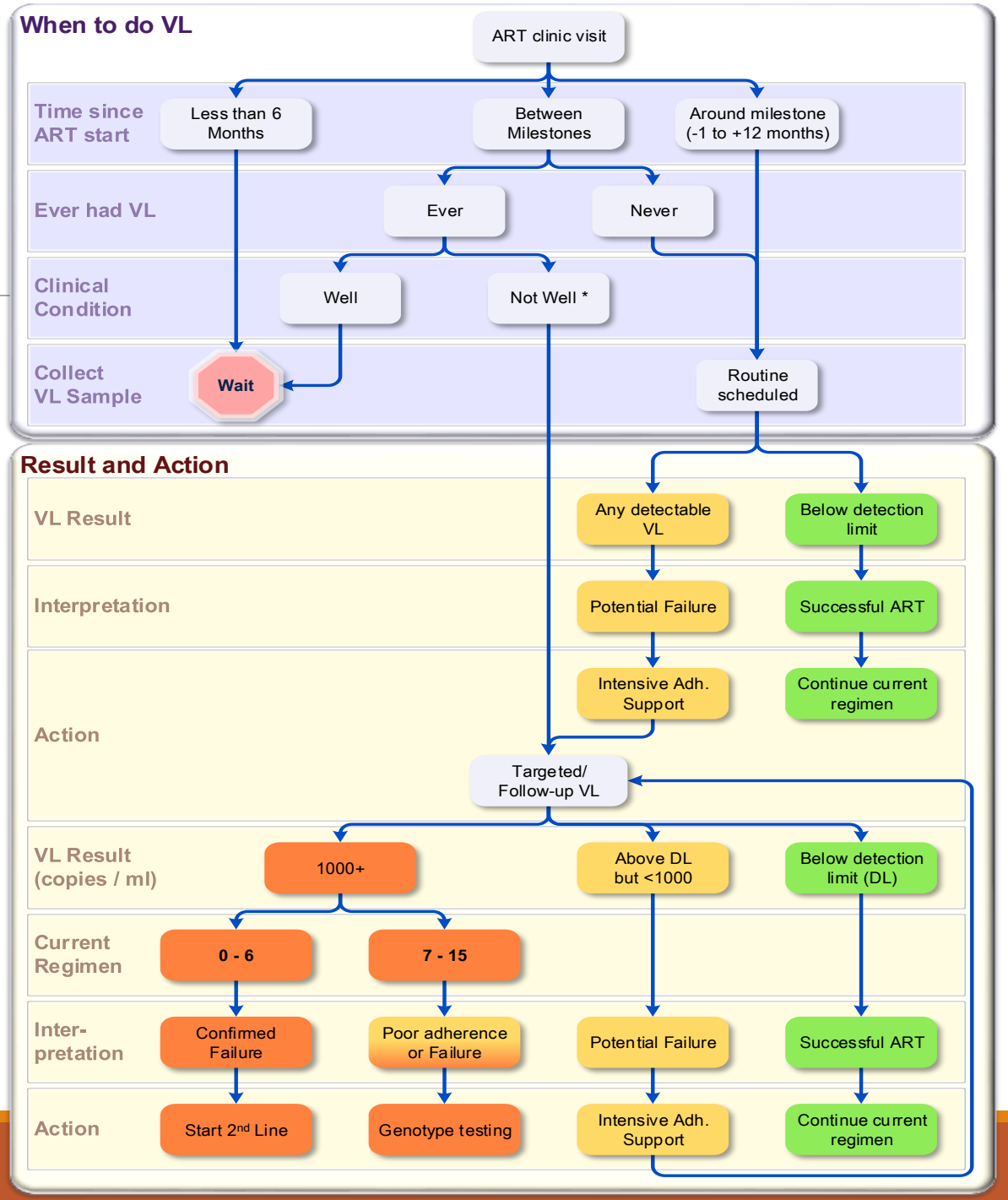
Back to our case…

To refresh: missing about 50% of doses on EFV/TDF/FTC with diarrhea and weight loss over 6mo

- Next step?
- Then?
- Then?

Treatment Monitoring & Follow-up





Definitions (review)

Successful ART

VL not detected

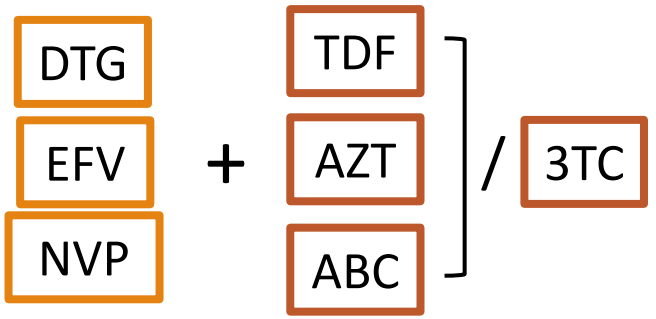
Potential Treatment Failure

Routine VL detectable (even if < 1,000)

Confirmed Treatment Failure

Targeted or repeat **VL > 1,000**
AND
Patient on **NNRTI-based** regimen*
AND
Good adherence for 3 months prior
*genotype for INSTI- or PI-based

First Line ART



START

	Core		Backbone		
Men 30kg Women 45yo +	DTG	/	TDF	/	3TC
Women of childbearing potential "B+"	EFV	/	TDF	/	3TC
Patients < 30kg	NVP	/	AZT	/	3TC

Not for START

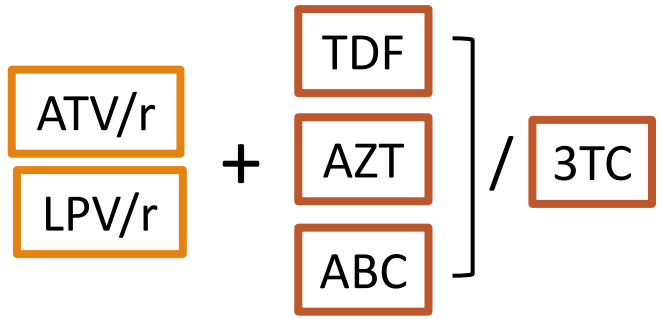
Core		Backbone		
DTG	+	AZT	/	3TC
		ABC	/	3TC
EFV	+	AZT	/	3TC
NVP	+	TDF	/	3TC
		ABC	/	3TC

Case (cont)

We have determined that our patient has a failed EFV/TDF/FTC regimen.

- What is your next step?

2nd line ART



Not for START*

Core Backbone

ATV/r + [TDF / 3TC; AZT / 3TC]

Core Backbone

LPV/r + [TDF / 3TC; ABC / 3TC; AZT / 3TC]

*1st line START for < 3yo IF extra support

Case (cont)

Fast forward 3 years.

- Our patient who was switched to ATV/r/AZT/3TC now presents with a routine VL of 2,350

Next step?

Then?

Then?

3rd line ART

2 Core Agents

DRV + r + DTG*

*DTG is BID if INSTI resistance

Backbone

+ [TDF / 3TC]
[ABC / 3TC]
[AZT / 3TC]

Assumes likely resistance to at least 2 prior agents

- Assumes failure to prior treatment with core of:

ATV/r or LPV/r or DTG

- For likely NRTI resistance, "flip" the backbone (or follow genotype)

If failed on:		Switch to:
ABC or TDF	→	AZT
AZT	→	TDF

Case (cont)

Our patient now on DRV/r/DTG/AZT/3TC presents with asymptomatic viral load of 1,230

- What do you think is going on here?
- What do you do?

Genotype Overview

Obtain for failure evaluation while on PI- or INSTI-based regimens

- *Rationale*: to differentiate resistance virus from poor adherence / low drug levels

*When to **obtain a genotype***: while the patient is **taking failing ART with detectable virus**!

- Genotyping is sensitive to resistance mutations *only* if they are present in a minimum of ~20% of circulating virus at the time of the test
- In the *selective* presence of ART → **mutant virus** is advantaged and present
- In the *absence* of ART → **wild-type virus** is generally most fit and predominates

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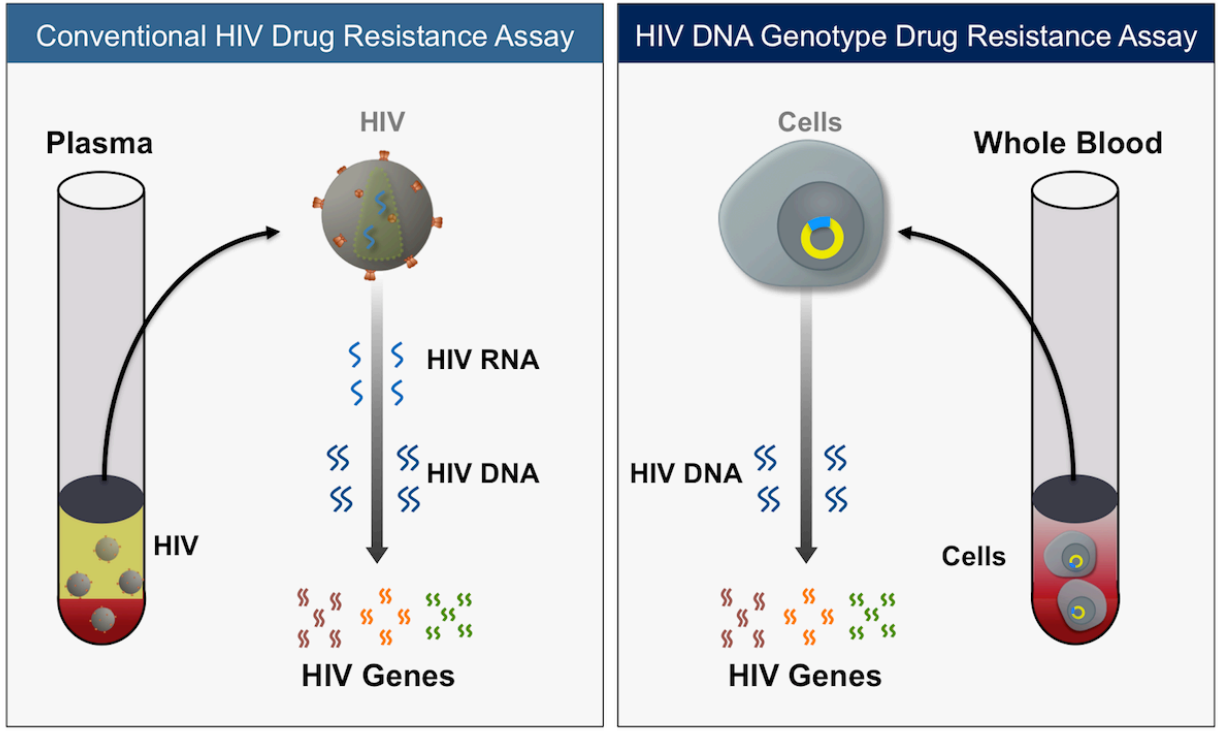
A patient with history concerning for prior virologic failure due to resistance is currently off ART.

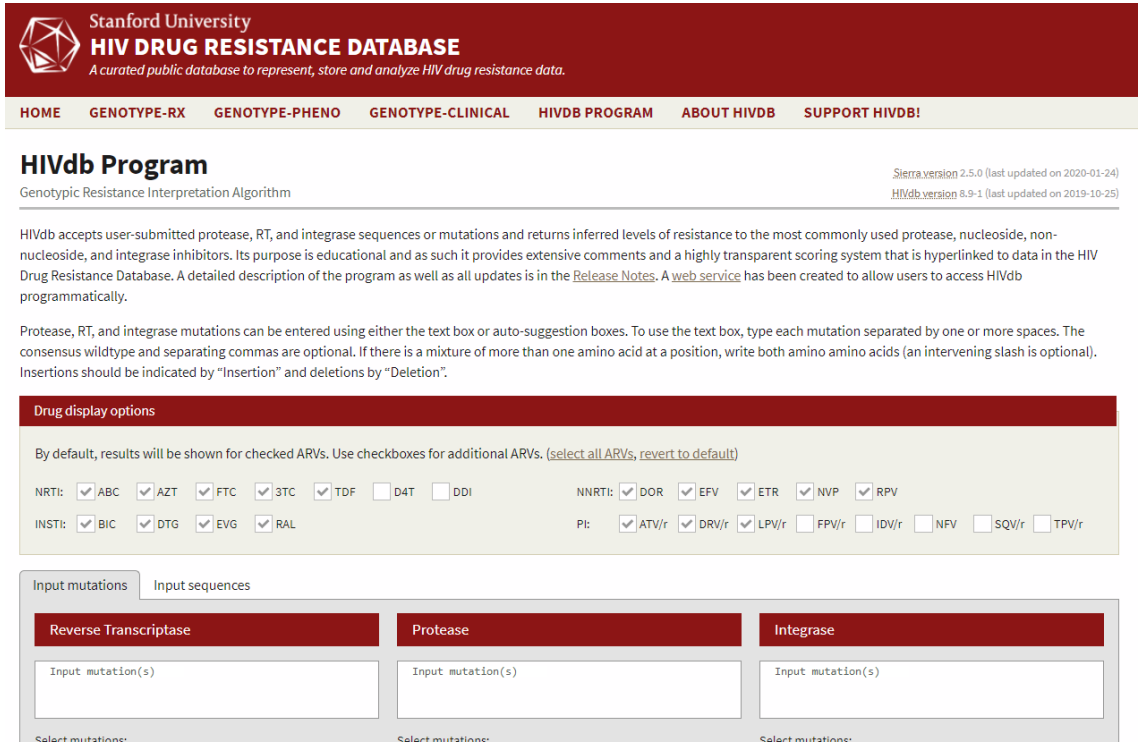
- What are your next steps?

Obtaining & interpreting a Genotype

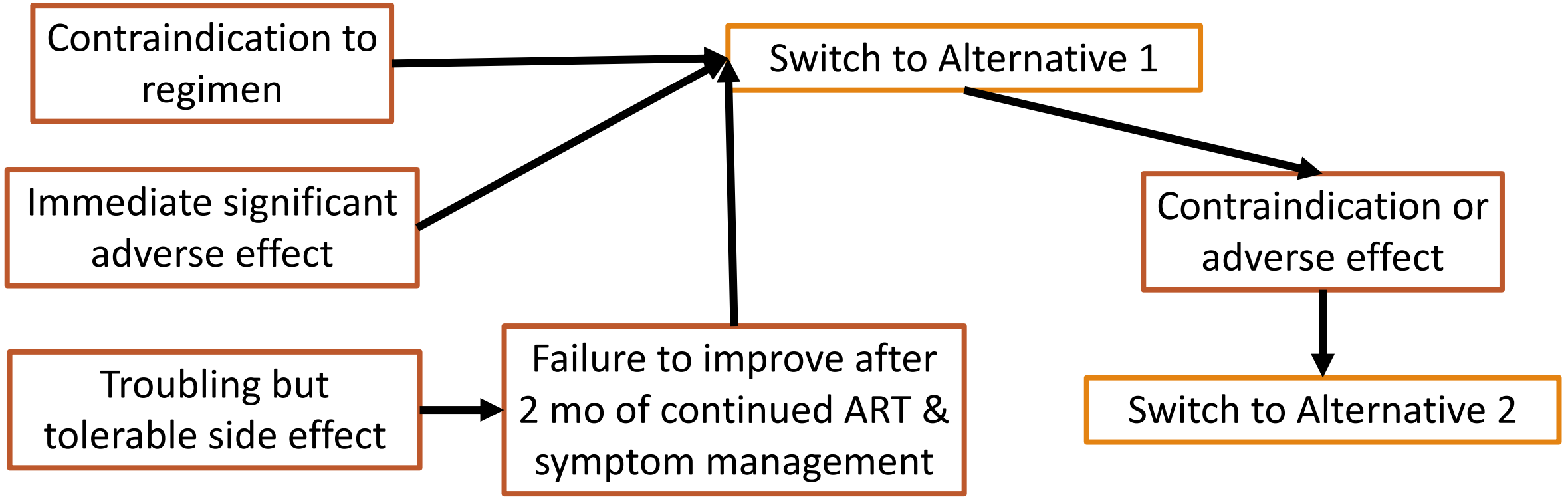
PCR -> averaged genetic sequence -> compared to wild-type



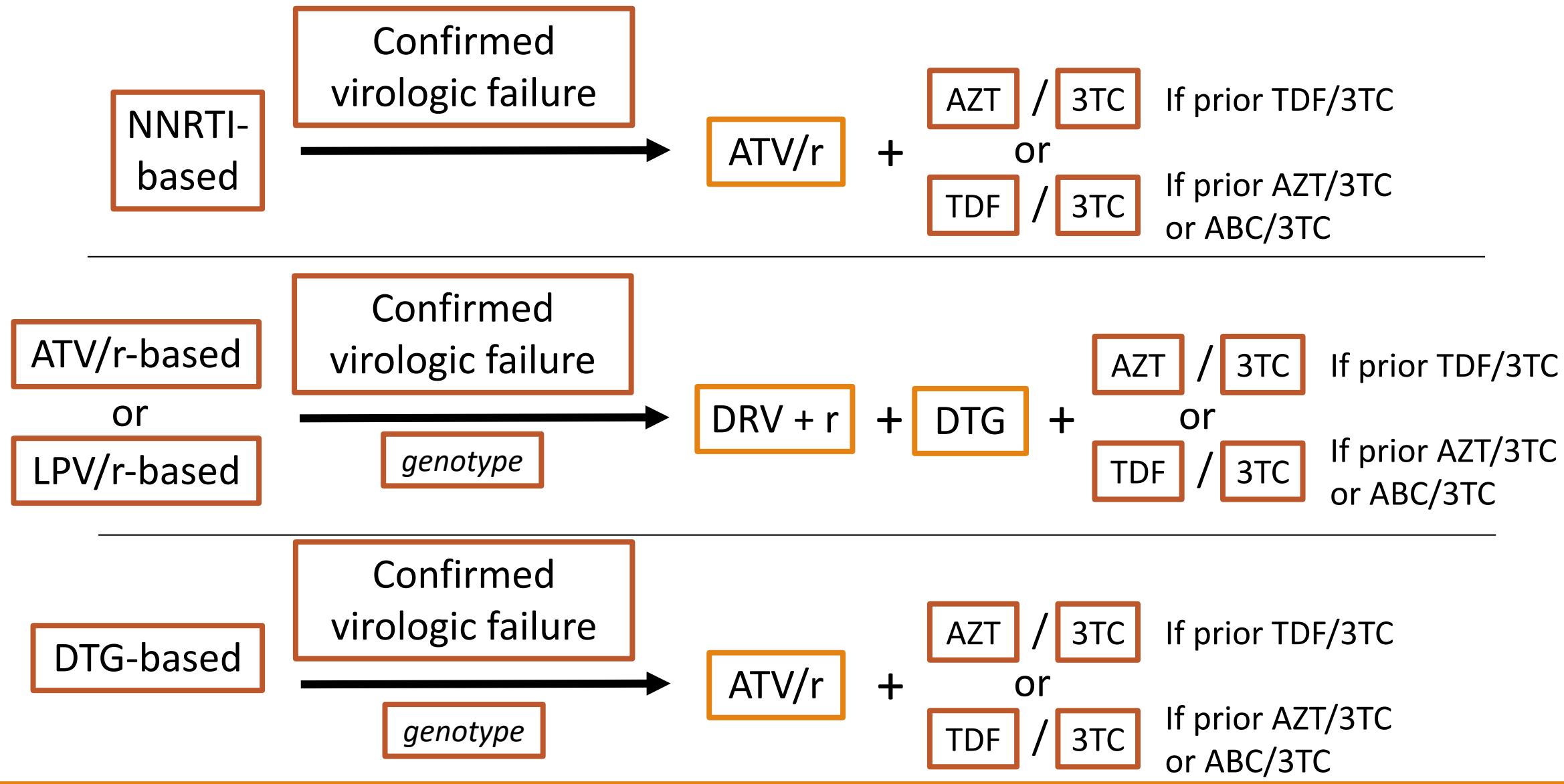
Stanford Resistance Database



Switching regimen (Table 10)



Initial Treatment Failure (go to Alt 1)



2nd line follow-up

Initial 6 months:

- Q 4 weekly visits

If stable, transition to Q 8 weekly visits

EFV or NVP

** Remember the "**tail**" if switching off these! **

EFV & NVP are present in decreasing concentration for 7 days after stopping

When stopping, give at least 7 days of fully active ART regimen to prevent EFV or NVP resistance from developing during the "tail"

ART Adverse Effects, medication interactions

These are **numerous**, and **difficult to remember**

- The *Liberian treatment guideline* has an excellent symptom-based guide to adverse effects and complications

For **medication interactions** – focus on a few high-yield culprits and forget the rest, just use:

https://hiv-druginteractions.org/

Nucleoside Reverse Transcriptase Inhibitor (NRTI) – Adverse Effects & Caution

tenofovir [TDF]

- Fully active against HBV
- Dose adjust if CrCl <50 (q48hr for Crl 30-49, q72 for 10-29)
- Renal Toxicity / Fanconi Syndrome
  - Glucosuria, proteinuria, aciduria, CKD, hyperphos, hypoK
- Osteoporosis
- Tenofovir alafenamide (TAF)

abacavir [ABC]

- Hypersensitivity reaction = absolute contraindication
- Increases cardiovascular disease risk
- No renal dose adjustment in CKD

lamivudine [3TC]

- Well tolerated
- In all 1st & 2nd line regimens
- HBV-active but not preferred for mono-therapy
- Decrease dose for CrCl <50

zidovudine [AZT]

- Q 12 hour dosing
- Bone marrow suppression = anemia & leukopenia
- myopathy
- lipodystrophy
- Lactic acidosis (rare if not co-administered with stavudine)
- Dose adjust for CrCl <15 – take 300mg daily

Nucleoside Reverse Transcriptase Inhibitor (NRTI) – Adverse Effects & Caution (cont)

stavudine [d4t]

- Not included in Liberia 5th edition guideline
- Peripheral neuropathy
- Lactic acidosis (esp in combination with AZT)
- lipodystrophy
- dyslipidemia

Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) – Adverse Effects & Caution

No renal dose adjustment!

nevirapine [NVP]

- Hypersensitivity reaction
  - Rash and/or hepatotoxicity, may be with fever, renal injury, mucous membrane involvememtn
  - Most common in women, those with HBV co-infection & high CD4
    - Caution if CD4 is:
      - >250 in women
      - >400 in men

efavirenz [EFV]

- Neuropsychiatric effects
  - Nightmares, depression, psychosis, ^ suicidality, headache
- Take at bedtime on empty stomach to minimize adverse effects
- ~15% erythematous maculopapular exanthema
- Hepatotoxicity – do not use if cirrhosis CTP Class B or C
- Unfavorable lipid profile effects
- gynecomastia
- QTc prolongation

Protease Inhibitor (PI) – Adverse Effects & Caution

No renal dose adjustment!

lopinavir / ritonavir [LPV/r]

- Diarrhea
- Hyperlipidemia
- Liquid formulation is 40% alcohol by volume

atazanavir / ritonavir [ATV/r]

- Benign hyperbilirubinemia
- nephrolithiasis

darunavir + ritonavir [DRV+r]

- Abdominal pain, diarrhea
- Rash (within 4wks of start, self-resolves)

ritonavir [r]

- Inhibits liver enzyme CYP3A
  - MANY drug-drug-interactions
- Diarrhea, nausea, abdominal pain

Integrase Strand Transfer Inhibitor (INSTI) - Adverse Effects & Caution

dolutegravir [DTG]

No renal dose adjustment!

- Mild side effects: headache, insomnia, nausea – generally self-resolve
- If known liver disease (ie, HBV) -> check LFTs before & after initiation
- BID with rifapentine for MTB treatment
- Neural tube defects if taken at conception
  - Tsepamo Study: NTD in 3/1,000 on DTG vs 1/1,000 on other ART
    - WHO now recommends DTG for use in women of childbearing age. Countries give varying recommendations.
- Increase in serum Creatinine (by ~0.15 on average) without CKD

NNRTI & INSTI Key Drug-Drug Interactions

nevirapine [NVP]

- DO NOT give with: rifampicin or rifapentine

efavirenz [EFV]

- DO NOT give with: simvastatin
- AVOID with: clopidogrel
- May decrease level of: atorvastatin

dolutegravir [DTG]

- metformin should not exceed 1 gram total daily dose
- Separate from divalent cations (ie, iron, calcium, magnesium) – take DTG 2hrs before OR 6hrs after

Worst offenders!!

Boosted PI Key Drug-Drug Interactions

class-wide OR ritonavir

- **Statins**: 20mg atorvastatin max; NO simvastatin
- Variable effects on **warfarin**
- Most **anti-convulsants** lower PI, NNRTI, INSTI levels
- Do NOT give with: **rifampicin, rifapentine**
- Increases concentration of: **Beta-blockers** (except atenolol, labetalol) & **calcium channel blockers**

atazanavir / ritonavir [ATV/r]

- **Antacids**: take ATV 2hrs before OR 1hr after antacid
- **H2 antagonist**: take with ATV/r OR 10hrs before ATV/r
- **PPI**: do not co-administer

darunavir + ritonavir [DRV+r]

- **PPI**: max 40mg omeprazole

lopinavir / ritonavir [LPV/r]

- No significant unique interactions

Any suspected hypersensitivity reaction = STOP the ART & DO NOT re-challenge

NRTI & NNRTI Switches by adverse effects

ABC → (**Hypersensitivity Reaction**: fever, pain, emesis, cough) → AZT

AZT → (Anemia, lipodystrophy, lactic acidosis) → TDF or ABC

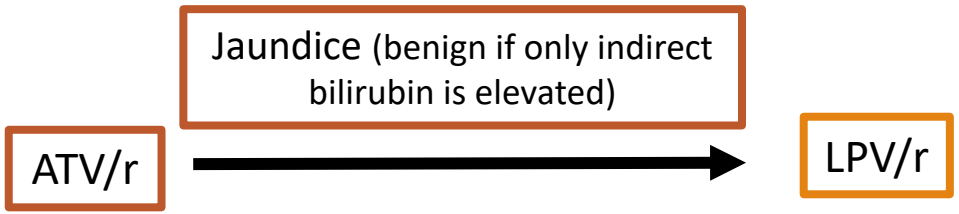
TDF → (Renal failure) → ABC or AZT

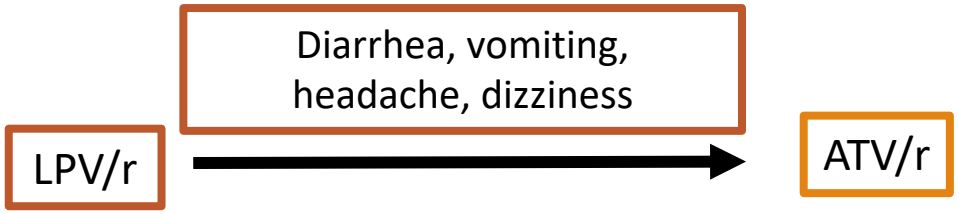
NVP → (**Hypersensitivity Reaction**: fever, rash, hepatitis) → EFV

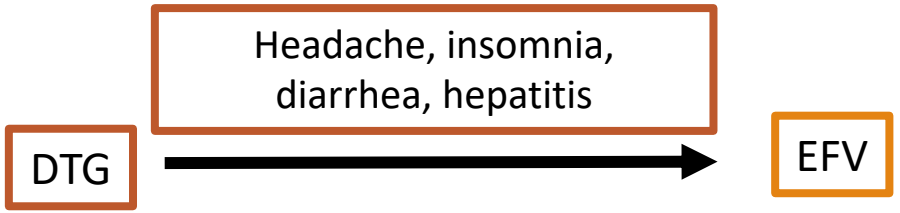
EFV → (Neuropsychiatric, gynecomastia, hepatitis/rash) → NVP

Give dizziness, drowsiness & nightmares 4 weeks to resolve

PI & INSTI Switches by adverse effects







Start by clinical scenario

Condition	Timing of ART start	ART
Anemia (<8g/dl)	NOW	DTG / TDF / 3TC Pedi: DTG + ABC / 3TC
Active MTB	Within 14 days	DTG / TDF / 3TC Pedi <30kg: EFV
Jaundice	Initial evaluation first	EFV / TDF / 3TC DTG only if severe liver dz & HBV/HCV ruled out
Renal Failure	Within 7 days	NVP + ABC/3TC
Psychiatric Illness History	NOW	DTG / 3TC / TDF NVP + TDF / 3TC
Pregnancy	NOW	DTG / TDF / 3TC
New HIV+ in labor	NOW	DTG / TDF / 3TC

Cases

55yoM with CKD recently started on DTG/ABC/3TC develops a cough and vomiting 2 weeks after starting.

- What is going on? Do you switch ART, and if so to what?

23yoF planning pregnancy soon sees you in clinic for new HIV diagnosis & ART start.

- How do you counsel her on ART options?

34yoF presents with suicidal ideation after starting ART recently. She does not know her meds and medical records are missing.

- What ART might she be on, and what do you suggest?

Cases

59yoM with HTN on NVP/TDF/3TC presents with 20lb weight loss and polyuria over 3 months.

- What do you suspect? What studies do you order? What is your recommendation?

63yoF on NVP/AZT/3TC notes an increasingly protuberant abdomen and thinning facial soft tissue.

- What do you suspect? What is your recommendation?

33yoM on NVP/TDF/3TC has VL 2,350 after IAC and 3 months of good adherence.

- What is your recommendation?

43yoF on LPV/r/TDF/3TC with chronic diarrhea without weight loss for 3 months.

- What do you suspect? What is your recommendation?

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