

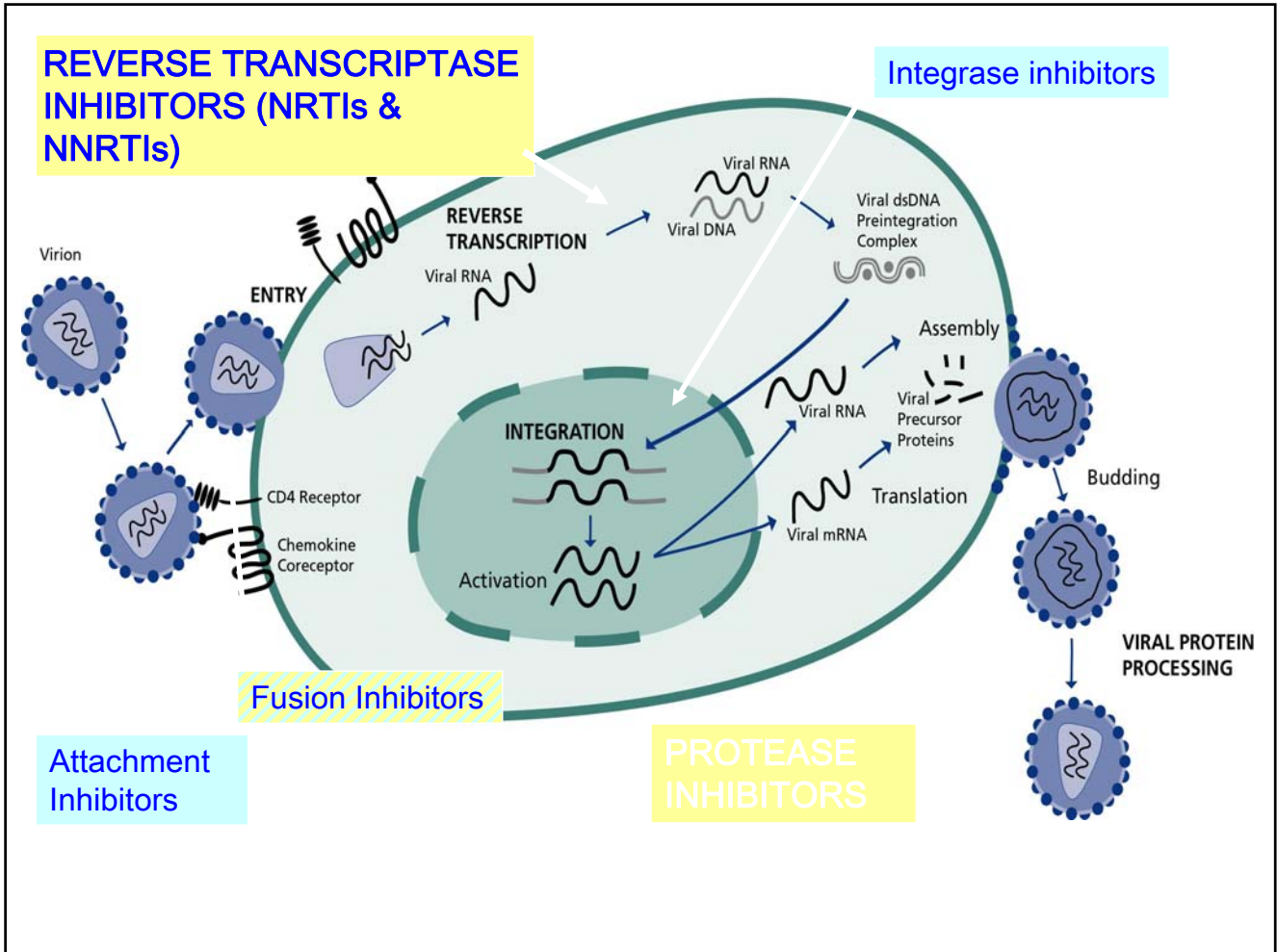
# Paediatric ART 8: Defining and managing treatment failure

Unit 15.1

Paediatric Antiretroviral Therapy Workshop  
Institute for Human Virology-Nigeria ACTION

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## Mechanism of reverse transcriptase inhibitors

NRTI = Nucleoside reverse transcriptase inhibitor

NNRTI = Non-nucleoside reverse transcriptase inhibitor



NRTI (such as d4T) is added onto cDNA chain, blocking further reverse transcription

NNRTI (NVP or EFV) Blocks reverse transcriptase by binding at active site

# Antiretroviral drugs 2005

## Nucleoside analogues

- Zidovudine
- Stavudine
- Lamivudine
- Didanosine
- Abacavir
- Emtricitabine
- Tenofovir

## Non-nucleoside RT inhibitors

- Nevirapine
- Efavirenz
- Delavirdine

## Fusion inhibitor

- Enfuvirtide (T-20)

## Protease inhibitors

- Nelfinavir
- Indinavir
- Saquinavir
- Ritonavir
- Lopinavir/ritonavir
- Atazanavir
- Fosamprenavir
- Tipranavir

## PEPFAR drugs for:

Children- Yellow  
Adults & selected  
children- Blue

# Monitoring the status of HIV infection

## The CD4 count

CD4<sup>+</sup> Tcells/ $\mu$ l

Measures ability to keep ahead of HIV infection

Predicts risk of opportunistic infection

Predicts risk of death

## The viral load

HIV RNA copies/ml

Measures level of infection

Predicts CD4 decline

Predicts risk of opportunistic infection & other complications

Predicts risk of death

## The defining characteristics of HAART

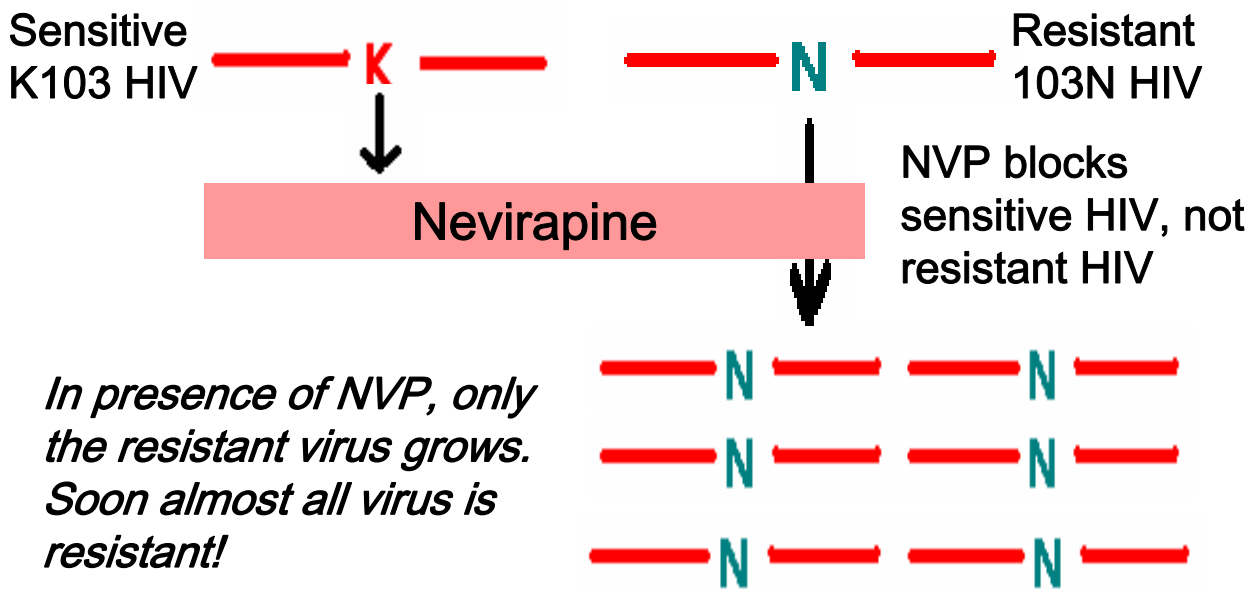
- Potency: The ability to stop HIV from growing
- Durability: The ability to maintain potency indefinitely by presenting a high *genetic barrier* to the evolution of *resistance*

*Potency and durability depend on adherence to therapy*

## How does resistance evolve?

- HIV reverse transcription is error-prone: random changes in HIV reverse transcriptase and protease genes are commonly made
- Most of these changes do not help the virus
- BUT, rarely one of these changes will cause a change in the reverse transcriptase or protease that lets the virus grow even if drug continues to be used.

## The K103N mutation: how it can take over



## Why can't the HIV become resistant to NVP *and* D4T *and* 3TC?

- Because the chances of it *randomly* getting all these mutations *at the same time* is virtually zero
- BUT...it can- and will- get all these mutations *one at a time* if you let it!

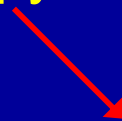
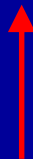
Potency of  
prescribed  
antiretroviral therapy

Nonadherence

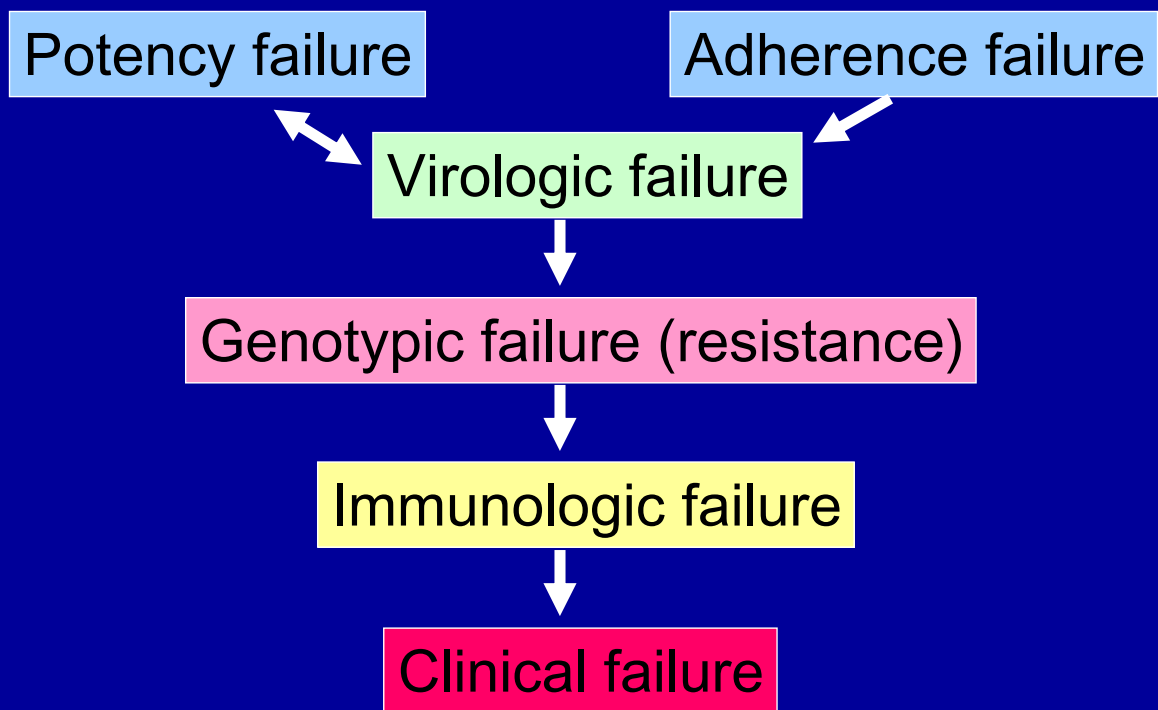
Viral Resistance

Viral replication

Clinical failure



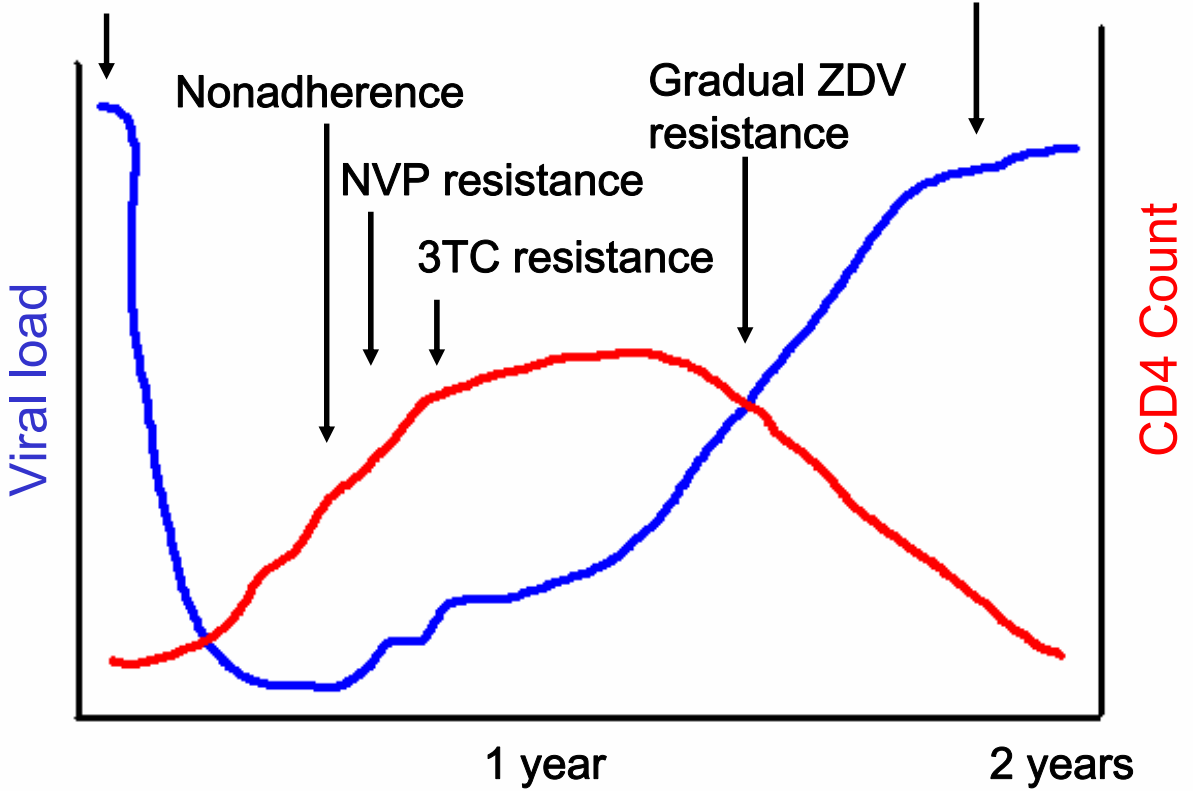
## Treatment failure: progressive steps, different definitions



### Course of treatment failure

Start ZDV/3TC/NVP

Clinical deterioration



## Which definition matters?

- If viral load is nondetectable or following path towards nondetectable, cannot blame slow CD4 rise or clinical events on “treatment failure”
- If viral load is not available, assessment should focus on estimating viral load response
- *Adherence history* may be best guide: if there are adherence problems, especially if NNRTI being used, then virologic failure and resistance are likely (regardless of clinical status)
- Immunologic or true clinical failure indicate late or very late virologic failure

## Recognizing treatment failure: Immunologic

- If CD4 or other factors suggest failure may be present, repeat CD4 at closer interval
- WHO: If CD4 at or below age-specific threshold for severe immunodeficiency
- WHO: “Consideration of previous CD4 is most useful”
- I.e. if CD4 not rising or is falling, failure is likely

## Recognizing treatment failure: clinical

- Some clinical events may not indicate treatment failure
  - Immune reconstitution syndrome
  - Infections that are common with mild or no immunodeficiency, such as TB, zoster, single episode of bacterial infection
  - May be unrelated to HIV, e.g. malnutrition
- WHO: Stage 3 or 4 events- but not necessarily if CD4 is good

## Recognizing treatment failure: Adherence history

- History of sustained poor adherence-frequent missed doses
- Stopping all drugs simultaneously usually does NOT cause resistance
- Taking less than 3 drugs- resistance to drug(s) that is/are being taken will develop

## Recognizing treatment failure: Virologic

- Repeat suspicious viral loads if possible
- Failure of viral load to decrease as expected
- Detectable virus after becoming undetectable
- Low level detectable viral load may not be significant
- Early detected low-moderate viral load may indicate only partial resistance
- Sudden large increase in viral load suggests nonadherence

## Resistance consequences of treatment failure

- Drugs have characteristic patterns of resistance
- Some drugs resistance almost always occurs with one mutation or set of mutations; others may take one of two or more pathways
- Resistance selected by a drug may or may not cause resistance to other drugs
- Understanding these patterns allows one to predict what alternatives therapies may be effective

## ARV resistance: the strange case of 3TC

- 3TC almost always selects for M184V mutation
- Readily selected (within few months of treatment failure)
- Confers very high level resistance to 3TC
- May be first step to ABC or DDI resistance

## The “good” side of 3TC resistance

- Hypersensitivity to
  - ZDV ~2-5 fold
  - D4T ~2-fold
  - TDF 4-8 fold
- Can reverse resistance to these drugs
- Makes virus less “fit”- grows slower
- *Benefit of continuing 3TC despite resistance:*
  - Wild-type virus is always present- 3TC remains effective against wild-type
  - 3TC-resistant virus grows slower, more sensitive to ZDV, D4T, TDF- only 2 effective drugs may be sufficient. I.e. ZDV, D4T, or TDF + 3TC + 3<sup>rd</sup> drug

## Patterns of cross-resistance: “thymidine analogue mutations”

- ZDV, D4T, TDF:
  - Resistance with 2-3 TAMs
  - Partially reversed with 3TC resistance
  - *Pair 3TC with these drugs: ZDV/3TC, D4T/3TC, TDF/3TC*
- ABC resistance
  - TAMs + M184V (3TC resistance)
- DDI partial resistance

## Patterns of ARV resistance: K65R

- Resistance to:  
ABC, DDI, TDF > 3TC
- Hypersensitivity to ZDV
  - *ZDV/3TC works well after ABC/3TC failure*
  - Avoid using combination of any 2: ABC, DDI, TDF unless ZDV also used

## Patterns of resistance: NNRTIs

- Most of the time NNRTI resistance caused by K103N which produces resistance to all NNRTIs
- Trial of NVP *or* EFV *or* NVP + EFV with 2 NRTIs: no benefit of using NVP/EFV

## Patterns of resistance: LPV/r

- Resistance to LPV requires 5-10 mutations
- LPV very powerful- even with partial resistance is still effective
- No resistance when used as 1<sup>st</sup> PI, even if detectable virus
- Resistance can occur if patient has previously failed other PIs

## Patterns of resistance: NFV

- Single mutation
- LPV/r still very effective

## When to switch

- Early?
  - Prevents clinical failure
  - Less cross-resistance to new regimen
  - “Burns up” drugs
- Late?
  - Clinical failure may not occur for a long time
  - Holds other *classes* of drugs in reserve
- Depends on ability to monitor and available options for treatment

## What to switch to

- First address adherence issues (consider stopping treatment *but not follow up* while doing this)
- Knowledge of resistance patterns allows an educated guess
- In general, err on the side of more potent treatment- you do not want to have to consider 3<sup>rd</sup> line therapy!

## Considerations for failure of ZDV or D4T/3TC/NVP or EFV

Timing of failure	Likely resistance	Consider*
Early (< 6-12 months)	NVP +/- 3TC	Continue ZDV or D4T/3TC Substitute LPV/r (d/c NVP) i.e. ZDV or D4T/3TC/LPV/r
Late (>12 months)	NVP, 3TC; partial ZDV, D4T, ABC, and DDI	Stronger NRTI: ZDV/ABC/3TC + LPVr <i>or</i> DDI/ABC/+/-ZDV + LPV/r Stronger PI: 2 NRTI + LPV/r/SQV Include TDF: ZDV/TDF/3TC + LPV/r

\*WHO recommendation is DDI/ABC + PI  
Consider referral to higher level center

## Considerations for failure of ABC/3TC/NVP or EFV

Timing of failure	Likely resistance	Consider*
Early (< 6-12 months)	NVP +/- 3TC	ZDV or D4T/3TC/LPV/r*
Late (>12 months)	NVP, 3TC, TDF, ABC, DDI Virus will be hypersensitive to ZDV	ZDV/3TC + LPV/r*

\*NFV may be considered, but less potent

## 2<sup>nd</sup> line treatment failure

- This gets really difficult without resistance testing!
- Use of 4 or more drugs
  - Multiple NRTI
  - 2 PIs

#1 rule of salvage therapy

*Your first chance is your  
best chance!*