

Pediatric HAART 2: What is highly active antiretroviral therapy (HAART)?

Unit 8.1

Paediatric Antiretroviral Therapy Workshop
Institute for Human Virology-Nigeria ACTION
Abuja
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Goals



- Understand how potency and durability define HAART
- Understand why adherence is necessary for HAART success

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

The definition of HAART



Highly active antiretroviral therapy (HAART) is any treatment that, when adhered to, is potent enough to suppress HIV replication to an undetectable level and has a genetic barrier to the evolution of resistance high enough to indefinitely maintain viral suppression, thereby preventing disease progression and maximizing the opportunity for recovery.

The ideal HAART regimen



- ***Potent*** enough to stop viral replication
- ***Durable***: high genetic barrier to resistance (multiple mutations required for resistance)
- ***Convenient***: Family can adhere, low pill count.
- ***Non-toxic***
- ***Tolerable***: Side-effects are transient or tolerable; reasonable palatability
- ***Sustainable***: Cost supportable, supply assured

Why does the viral load need to be undetectable?



- If the viral load is undetectable, HIV will not cause any harm
- Most importantly, the viral load is undetectable, resistance to the drugs will not develop
- Once resistance develops, the viral load increases AND more resistance develops

What is resistance?



- Resistance is when *mutations* in HIV genes allow it to grow in the presence of a drug
- Resistance may be partial or high-level
- For some drugs, only one mutation will cause high-level resistance (e.g. NVP, EFV)
- For other drugs, many mutations are needed (e.g. ZDV, LPV)
- Resistance may be to one drug, or to several related drugs

How does resistance evolve?

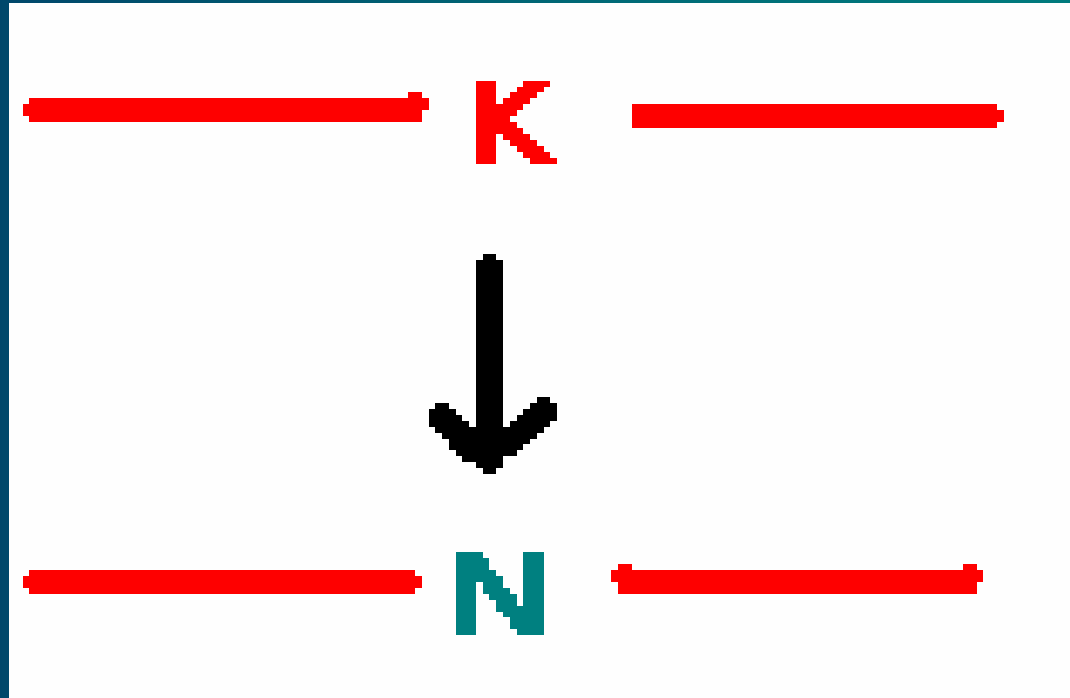


- HIV reverse transcription is error-prone: random changes in HIV reverse transcriptase and protease genes are commonly made
- Most of these changes do not help the virus
- BUT, rarely one of these changes will cause a change in the reverse transcriptase or protease that lets the virus grow even if drug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

Example of resistance: the K103N reverse transcriptase mutation



Wild-type RT:
Sensitive to
NVP



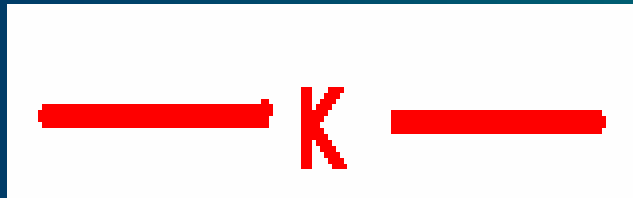
Mutant RT:
Resistant to
NVP *and* EFV

This mutation happens thousands of times every day IF virus is growing

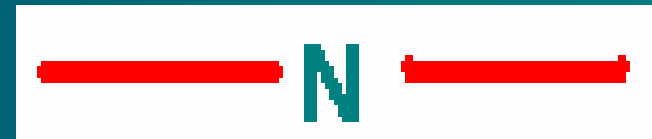
The K103N mutation: how it can take over



Sensitive
K103 HIV



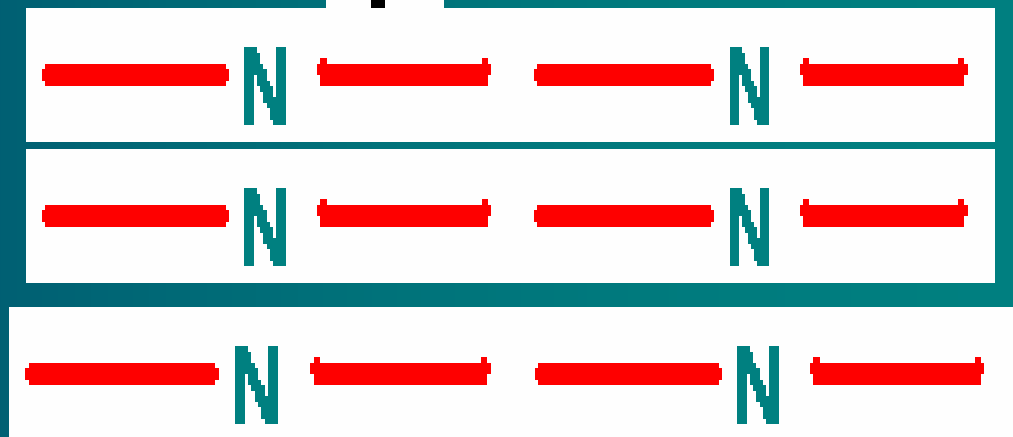
Nevirapine



Resistant
103N HIV

NVP blocks
sensitive HIV,
not resistant HIV

*In presence of NVP, only
the resistant virus
grows. Soon almost all
virus is resistant!*



So, how do we keep resistant virus from taking over?



- By *only* giving NVP with other drugs that are not affected by the K103N mutation
- Such as...D4T: requires several mutations (215, 41, etc.) to be resistant
- Such as...3TC: requires M184V for resistance

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



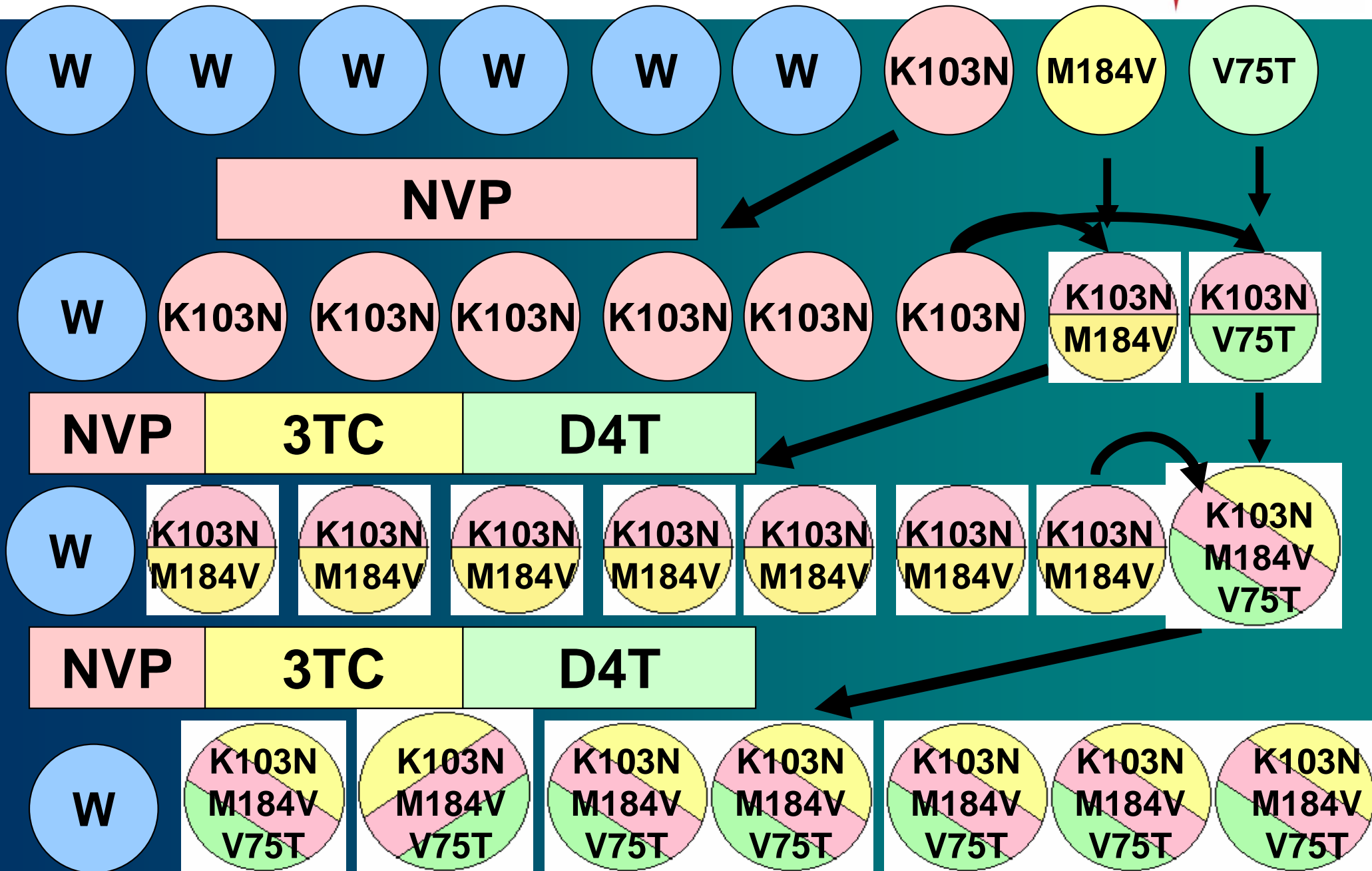
- Because the chances of it *randomly* getting all these mutations *at the same time* is virtually zero
- BUT...it can- and will- get all these mutations *one at a time* if you let it!

So, HAART means:

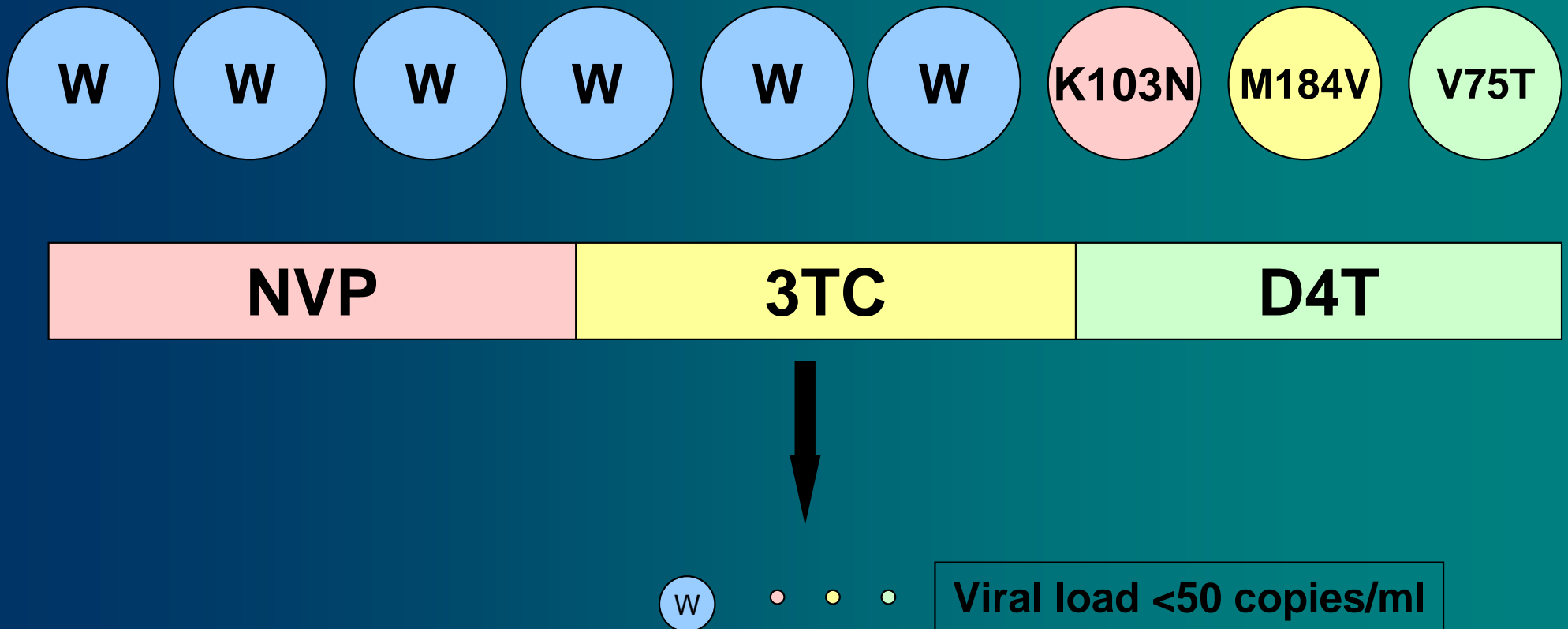


- A combination of drugs that is *POTENT* enough to stop HIV from growing AND...
- Requires many different mutations to fail- i.e. has *HIGH GENETIC BARRIER TO RESISTANCE* AND...
- That the patient takes every day, *ALL DOSES*.

Evolution of multiresistant HIV



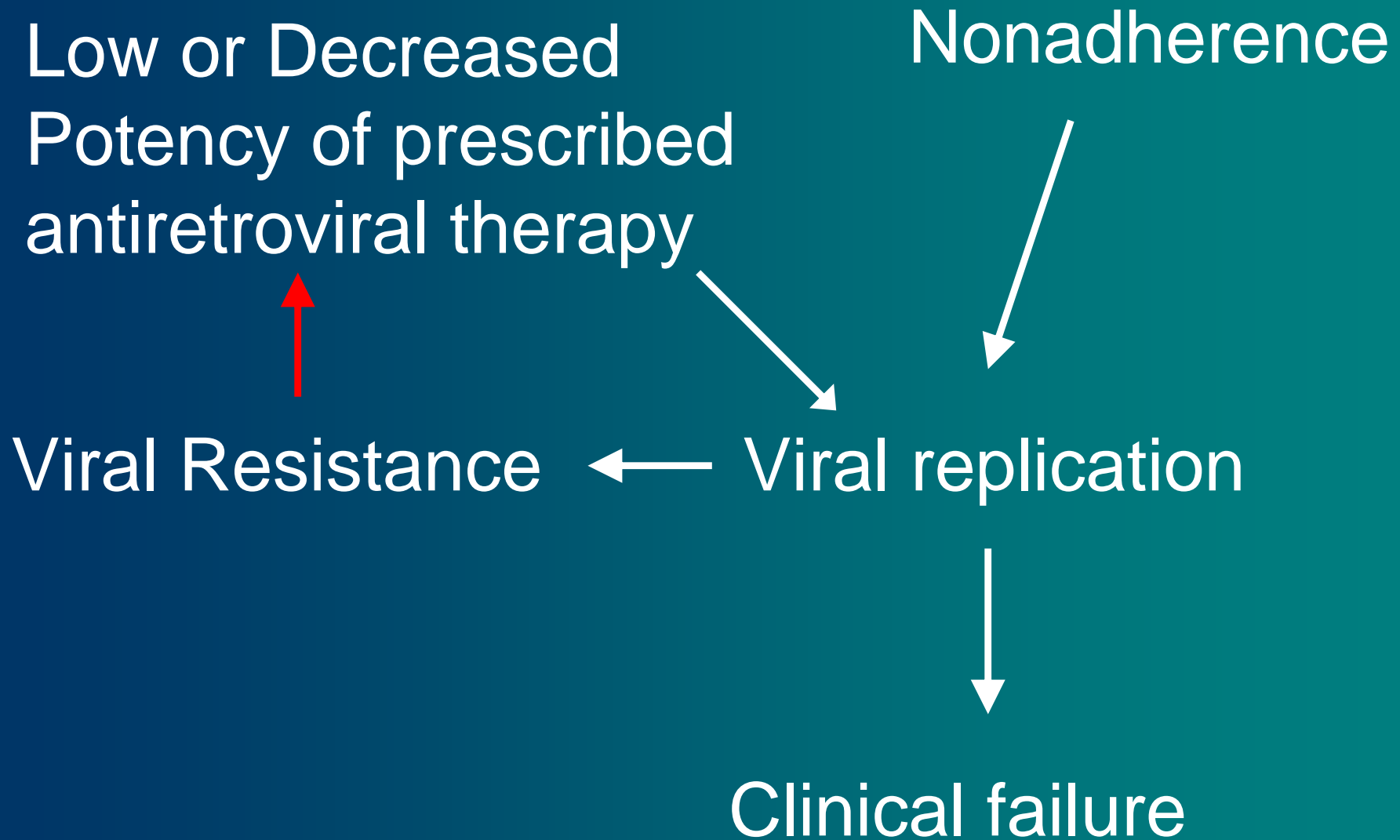
Prevention of resistance and control of HIV with highly active antiretroviral combination therapy



Viral resistance- a numbers game



- Viral genome: 9.7×10^3 bp
- Viral RT error rate: $\sim 1 \times 10^{-4}$ /base
- Virions/day: $\sim 10^9$ /day
- Total viral burden: $\sim 10^{10}$ virions
- *Thousands of virions with any single point mutation are in the host at any one time and thousands more are produced every day*

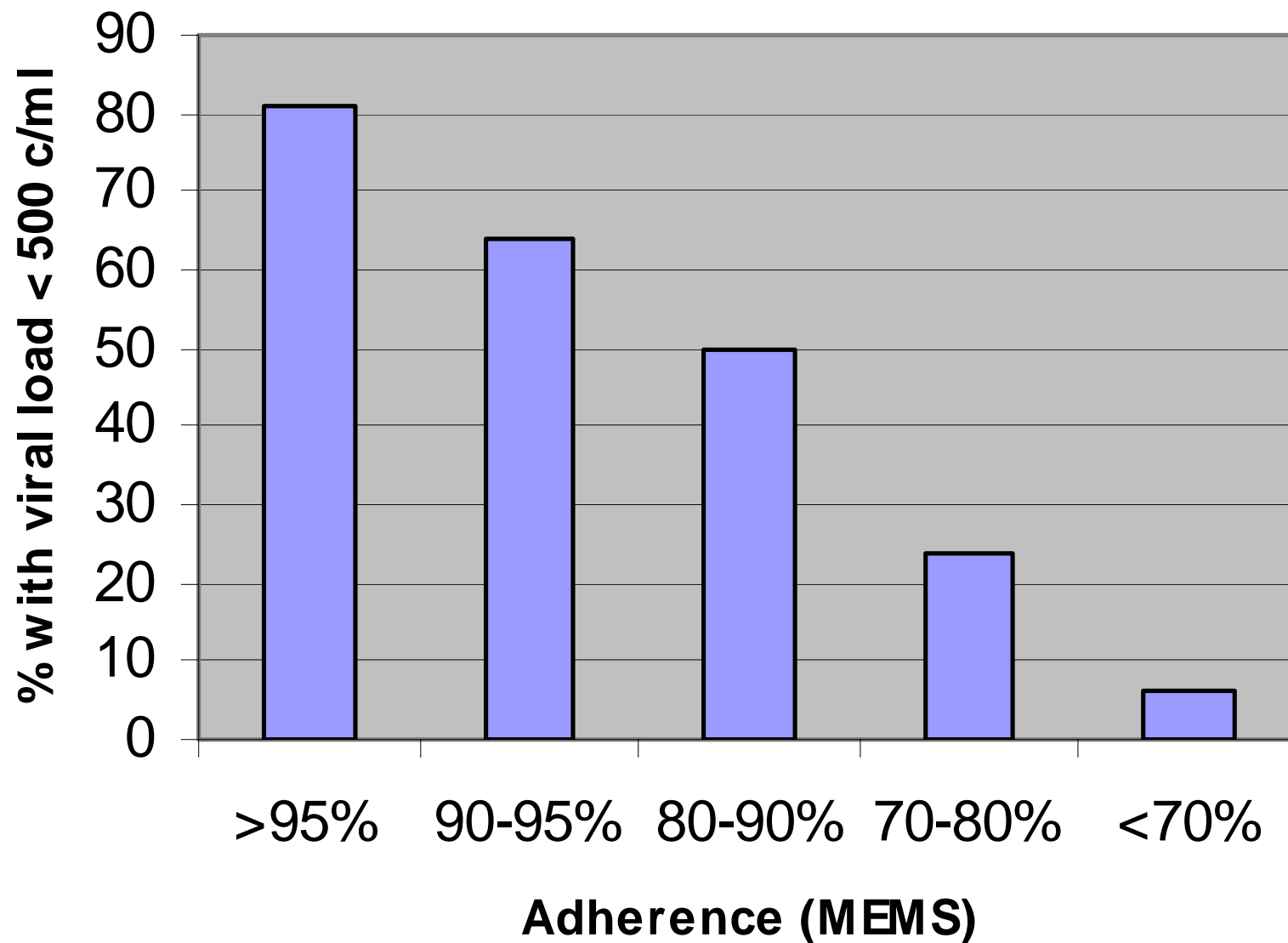


How good must adherence be?

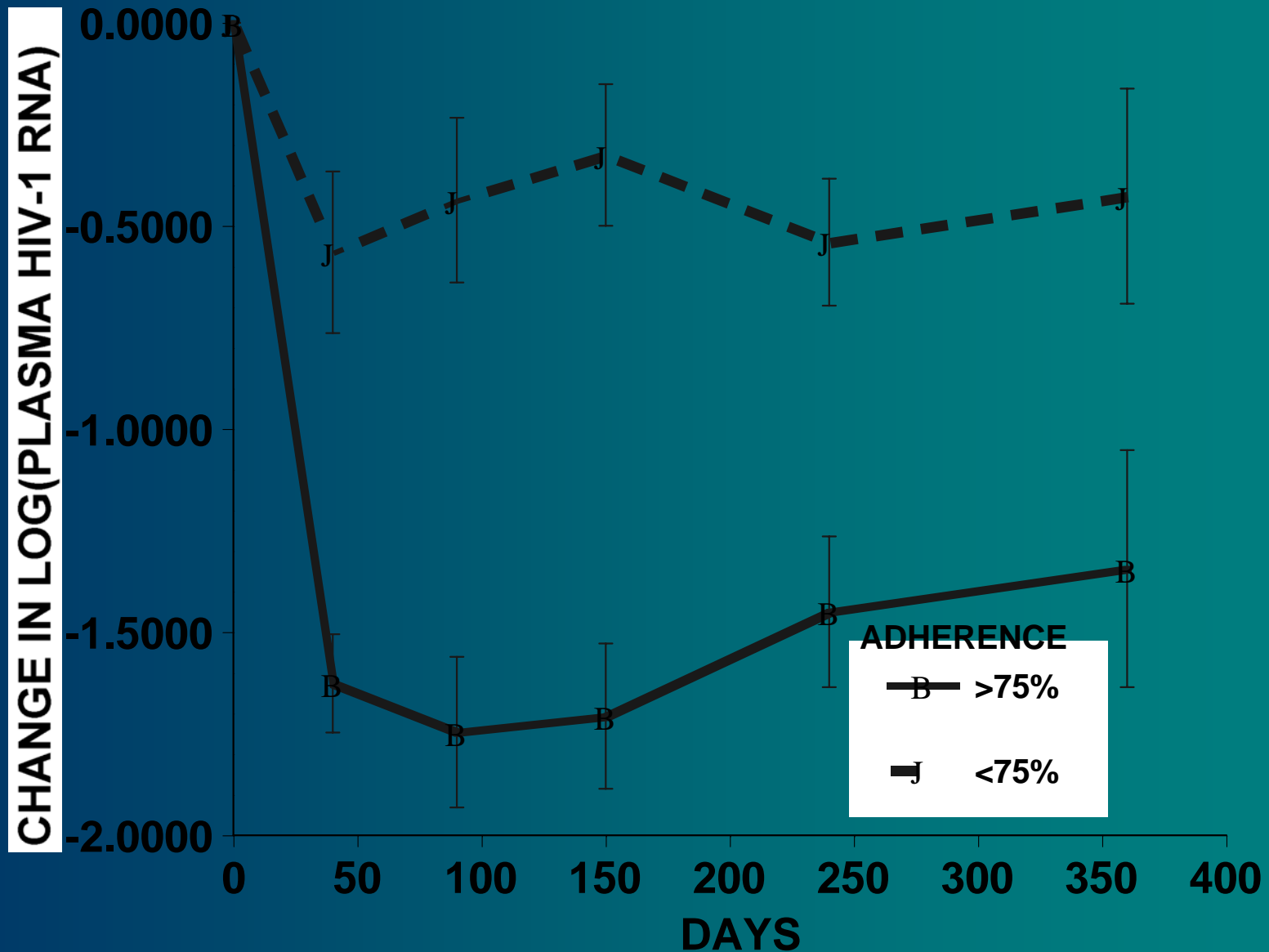


- Generally > 95% of doses
- Some treatment regimens are more “forgiving” than others: D4T/3TC/NVP is a less “forgiving” regimen- *but can work excellently for years if adherence is maintained.*
- Missing 1 dose per week is 93% adherence
- Adherence < 80% almost always fails
- “Good” adherence taking “most” doses will lead to failure
- *Rare* missed dose is tolerated

Adherence and virologic response at 6 months (Paterson, et al. Chicago 1999)



Adherence to HAART and virologic response in children (Watson 1999)



But what happens when patient *can't* take all ARVs?



- If circumstances make >95% adherence impossible, patient can safely (and should) STOP ALL ARVs
- Stop NVP 1 week before D4T and 3TC if possible
- Stay off all ARVs until adherence problem resolved
- Restart all ARVs simultaneously when ready

Pediatric antiretroviral therapy: Choosing a regimen

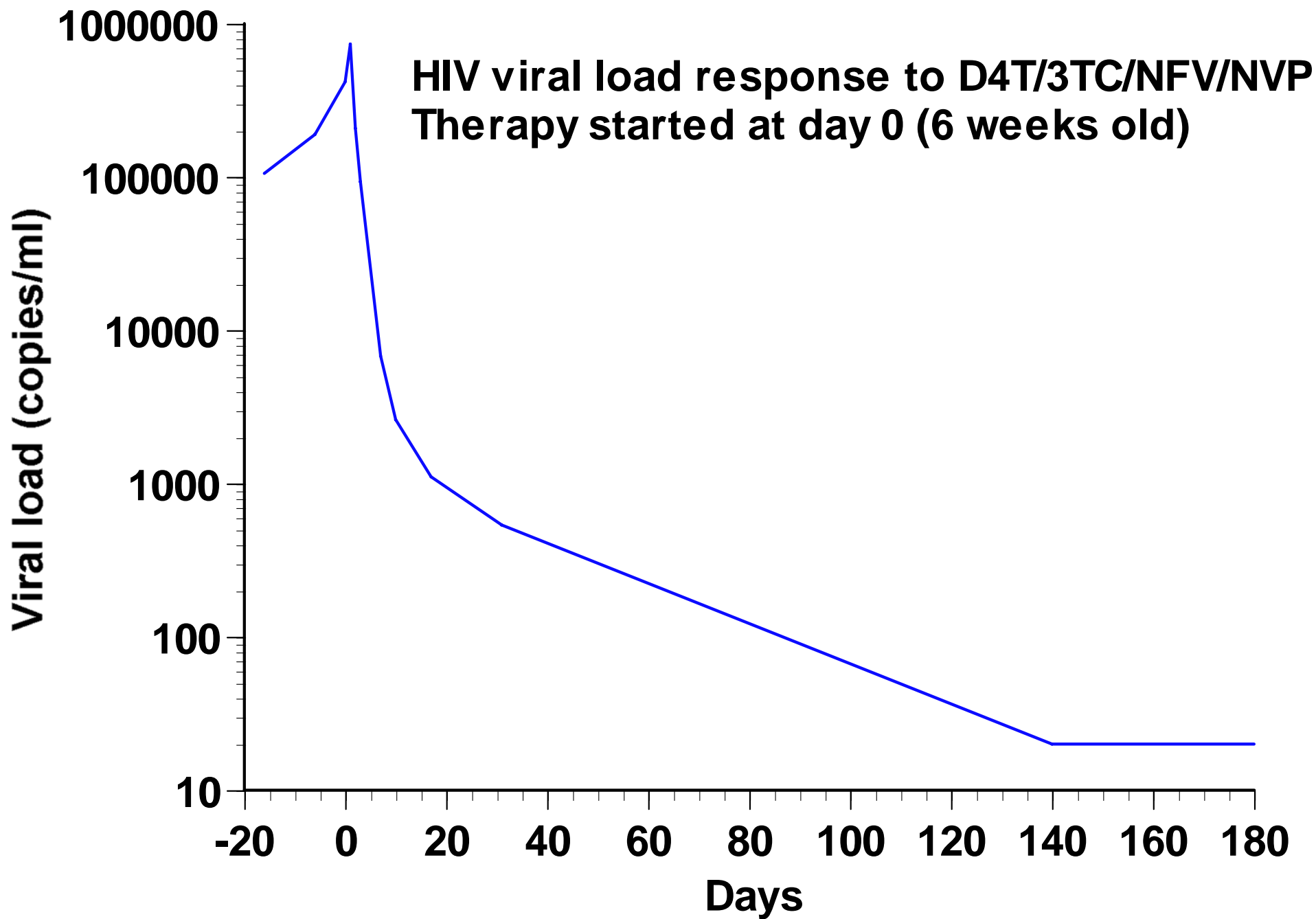


- **Optimizing potency**
 - Activity of drugs and combinations
 - Ease of developing resistance
 - Assess resistance status
 - * History
 - * Resistance testing
- **Optimizing adherence**
 - Palatability
 - Side effects
 - Schedule

Response to HAART in children



- **Viral load drops very rapidly- About 100-fold in 2-3 weeks**
- **CD4 response**
 - Return to normal in about a year
 - Can stop TMP/SMX (Bactrim) when CD4 above prophylaxis guidelines
- **Rapid clinical response**
 - May feel better in 1-2 weeks
 - Risk of opportunistic infection rapidly decreases
 - Rapid weight gain



Expected fall in viral load

Time	Log fold drop in viral load	Fold-drop in viral load	Viral load (example)	Viral load (example)
0	--	--	600,000	100,000
1 month	2	100	6,000	1,000
3 months	3	1,000	600	100
6 months	4	10,000	60	<50

If viral load at these follow up times is 3-fold or more than these examples, full suppression not likely

Examples of full virologic suppression rates in adult clinical trials

(All subjects ITT analysis)



AZT/3TC/NVP 67% VL < 20 at 36 weeks

AZT/3TC/NFV 44%

D4T/3TC/NFV 52% VL < 50 at 48 weeks

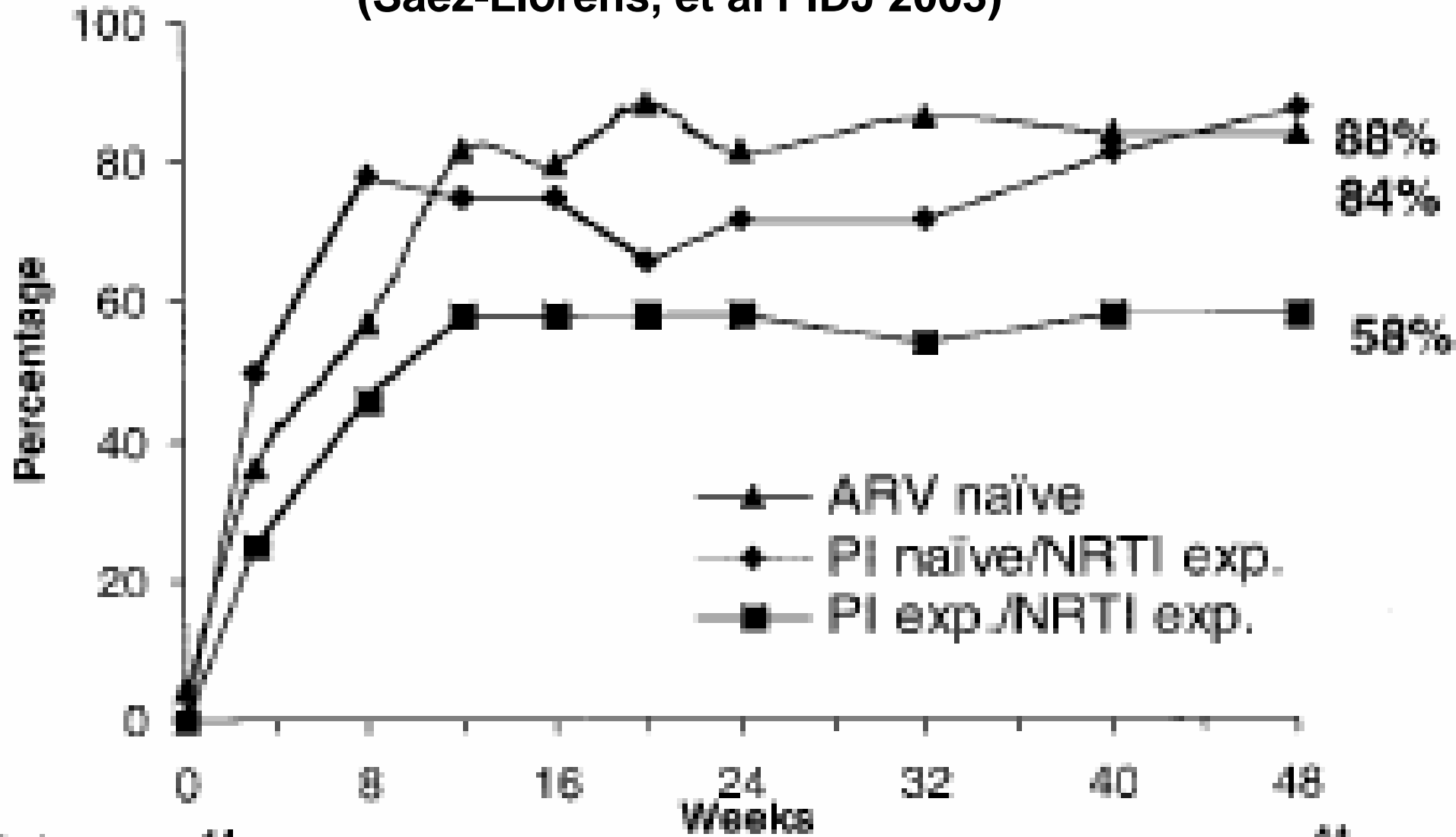
D4T/3TC/LPV/r 67%

D4T/3TC/NVP 56% VL < 50 at 24 weeks

D4T/3TC/EFV 62%

Percentage of children with viral load <400 copies/ml in response to D4T/3TC + LPV/r (ART-naïve) or 1-2 NRTI + LPV/r + NVP (ART-experienced)

(Saez-Llorens, et al PIDJ 2003)



ART naïve:	44
PI naïve/NRTI exp.:	32
PI exp./NRTI exp.:	24

44
32
24

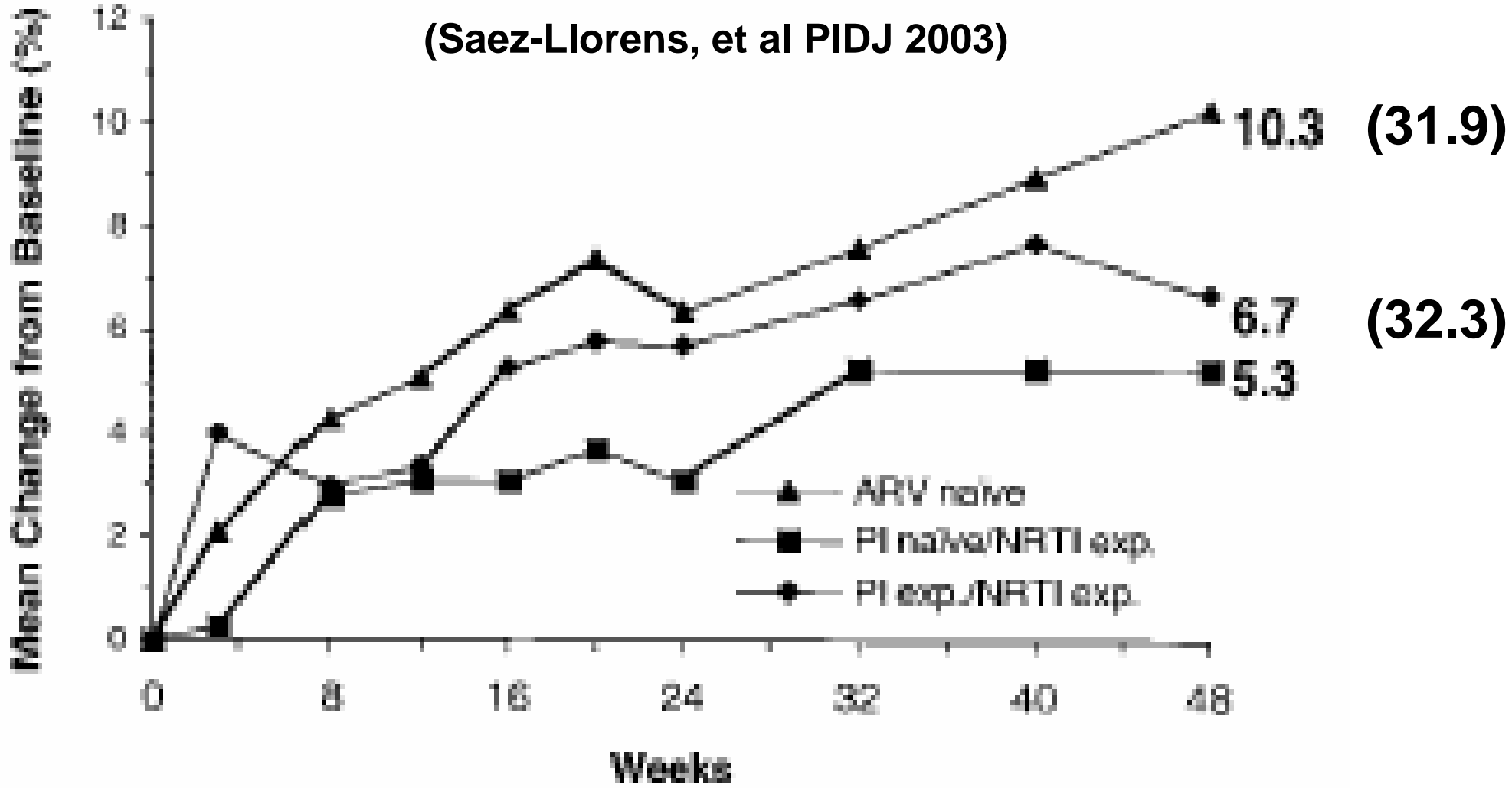
How fast should the CD4% increase with successful HAART?



- About 5% (e.g. from 10% to 15%) in first 2-3 months
- About 10% in first year
- Increase will be less in child with milder immune suppression
- Rise fastest in infants (and very slow in older adults)
- Adults: 50-100 CD4 cells/ μ l per year

Increase in CD4% in response to D4T/3TC + LPV/r (ART-naïve) or 1-2 NRTI + LPV/r + NVP (ART-experienced). Mean final CD4% in parentheses.

(Saez-Llorens, et al PIDJ 2003)



ART naïve: 44
 PI naïve/NRTI exp.: 32
 PI exp./NRTI exp.: 24

43
 32
 23