Current issues in pediatric HIV care

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HIV and the brain of children

- *Encephalopathy and subclinical cognitive impairment- major effect in first few months of life- prevented by* early *ART*
- Bacterial meningitis: pneumococcal, *H. influenzae, N. meningitis*, others
- TB meningitis
- Cryptococcal meningitis
- Stroke
- Malaria is common in all children

Difficult questions

- Initial therapy
  - When to start?
  - What NRTIs to use?
  - What "3rd drug to use?
- HIV/TB co-treatment
  - In small children?
  - In children who have failed NNRTI?
- Laboratory monitoring
- Treatment failure
  - How to diagnose?
  - How to manage?

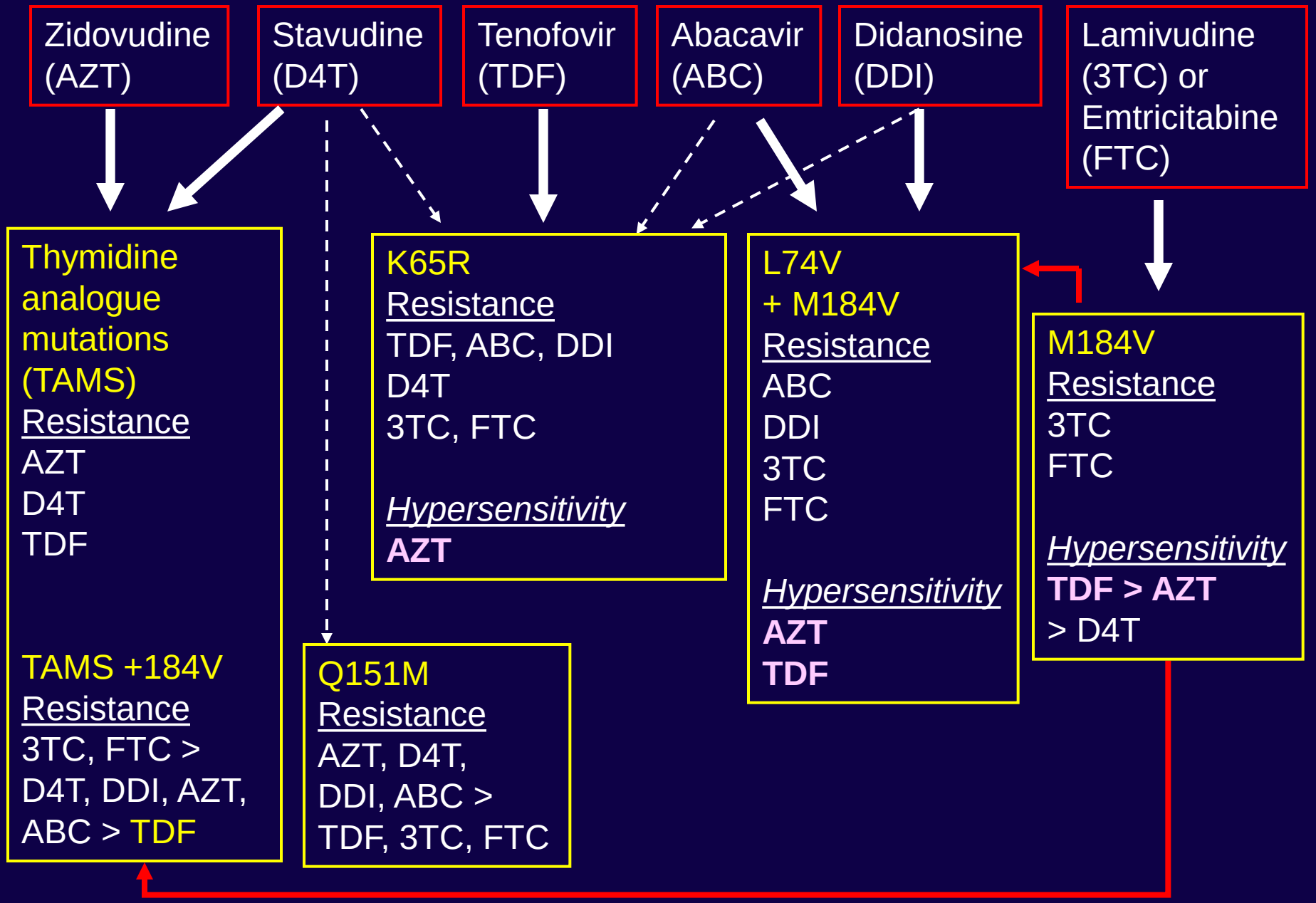
WHO 2010 Recommendations for Pediatric ART According to CD4% and CD4 count			
Criterion	**Age**		
	< 24 months	**24-60 months**	**>5 years**
CD4%	**Treat all**	**< 25%**	**< 20%**
CD4/µl	**Treat all**	**< 750**	**< 350**

All children with WHO stage 3 or 4 disease should initiate ART

What NRTI to use?

- ABC versus TDF
- ABC/3TC
  - Safe: no clear long-term toxicity
  - Resistance
    - *Selects for* L74V > K65R + M184V : Both cause hypersensitivity to AZT
    - Resistance with TAMs + M184V
  - Potency < TDF in RCT in adults, > AZT in children
- TDF/3TC
  - *Potential* for renal or bone toxicity
  - Resistance
    - K65R: hypersensitivity to AZT
    - Resistance with TAMs reversed with M184V: good 2nd-line after AZT/3TC failure

Nucleoside reverse transcriptase inhibitor resistance and cross-resistance



Which "3rd drug" in young children?

- NVP has higher failure rate in young children *even without prior NVP exposure*
- EFV?
  - Several studies suggest more potent than NVP
  - Dosage problem:
    - Approved dosage has been found to be too low for young children
    - < 3 years of age requires relatively high dosages
  - Potential CNS side effects
- LPV/r?
  - Expensive
  - Sometimes not well tolerated
  - Lipid and fat distribution effects
  - Drug interactions

TB/HIV co-treatment in child

- EFV?
- Higher-dosage NVP?
  - But NVP less active….
- LPV/r?
  - Lowered drug levels with RIF/LPV/r
  - Even doubling LPV/r dosage does not achieve adequate levels- ~ 40% failure rate
  - Adding RTV achieves good levels of LPV

Laboratory monitoring

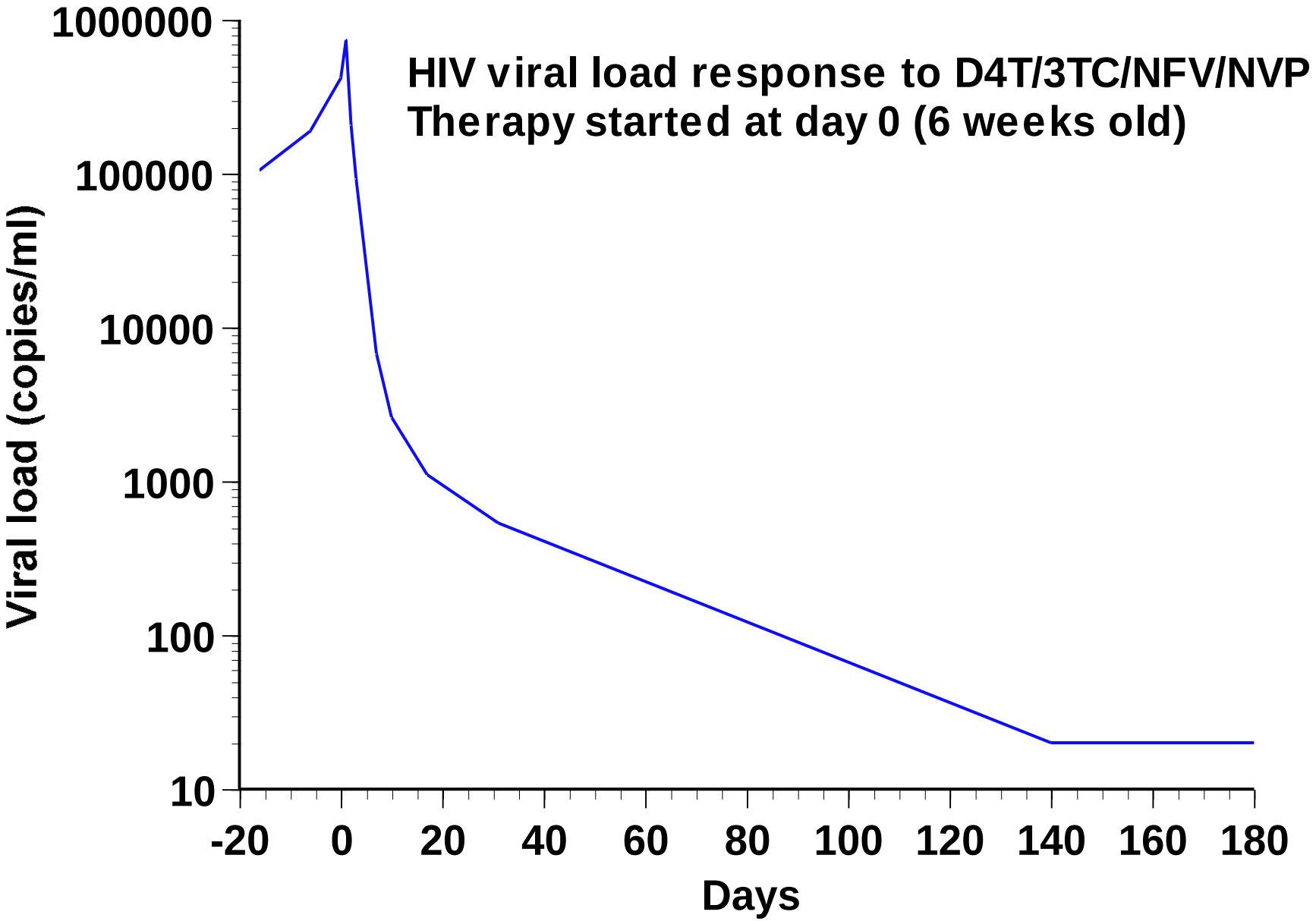
- When to do viral load?
  - Routine?
  - If NVP used in young child?
  - Any regimen of questionable potency
    - 2nd line after AZT or D4T failure
    - RIF co-treatment in some cases
- Should we do CD4 in children on ART?
- Are any labs other than VL really necessary after starting ART?

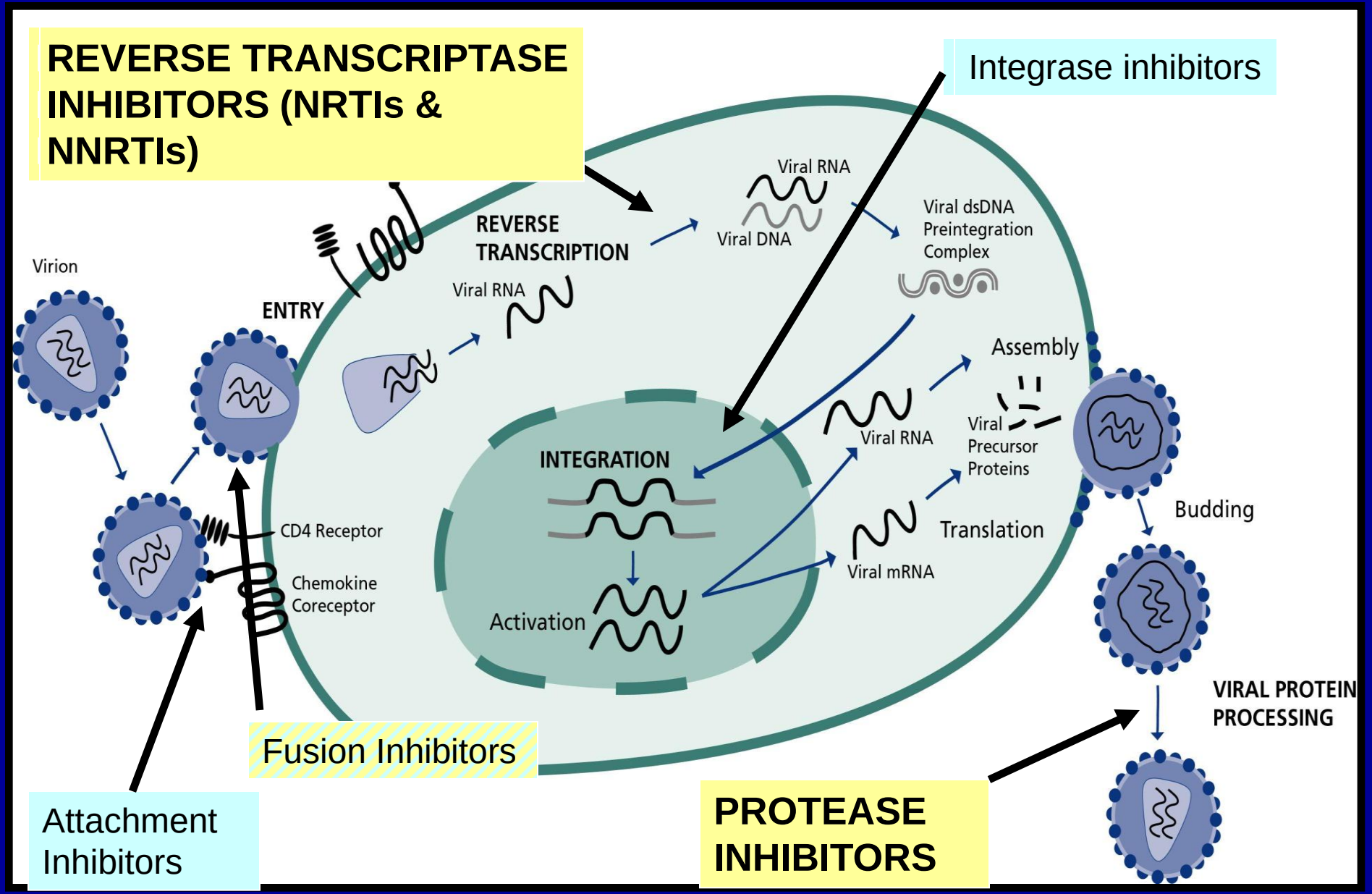
Treatment failure in children

- Difference between *definition* and *diagnosis*
  - May be *defined* as failure of VL to decay as it should
  - In absence of VL may attempt to diagnose, but CD4 and clinical criteria are unreliable (poor sensitivity and poor specificity)
  - *History* important in making diagnosis
- What to do after AZT or D4T failure
  - Paucity of empiric evidence
  - TDF/3TC/LPV/r probably best
  - AZT/ABC/3TC/LPV/r alternative
- What to do about LPV/r failure?
  - Does patient really have resistance?
  - Use of darunavir/ritonavir and raltegravir

What is treatment failure?

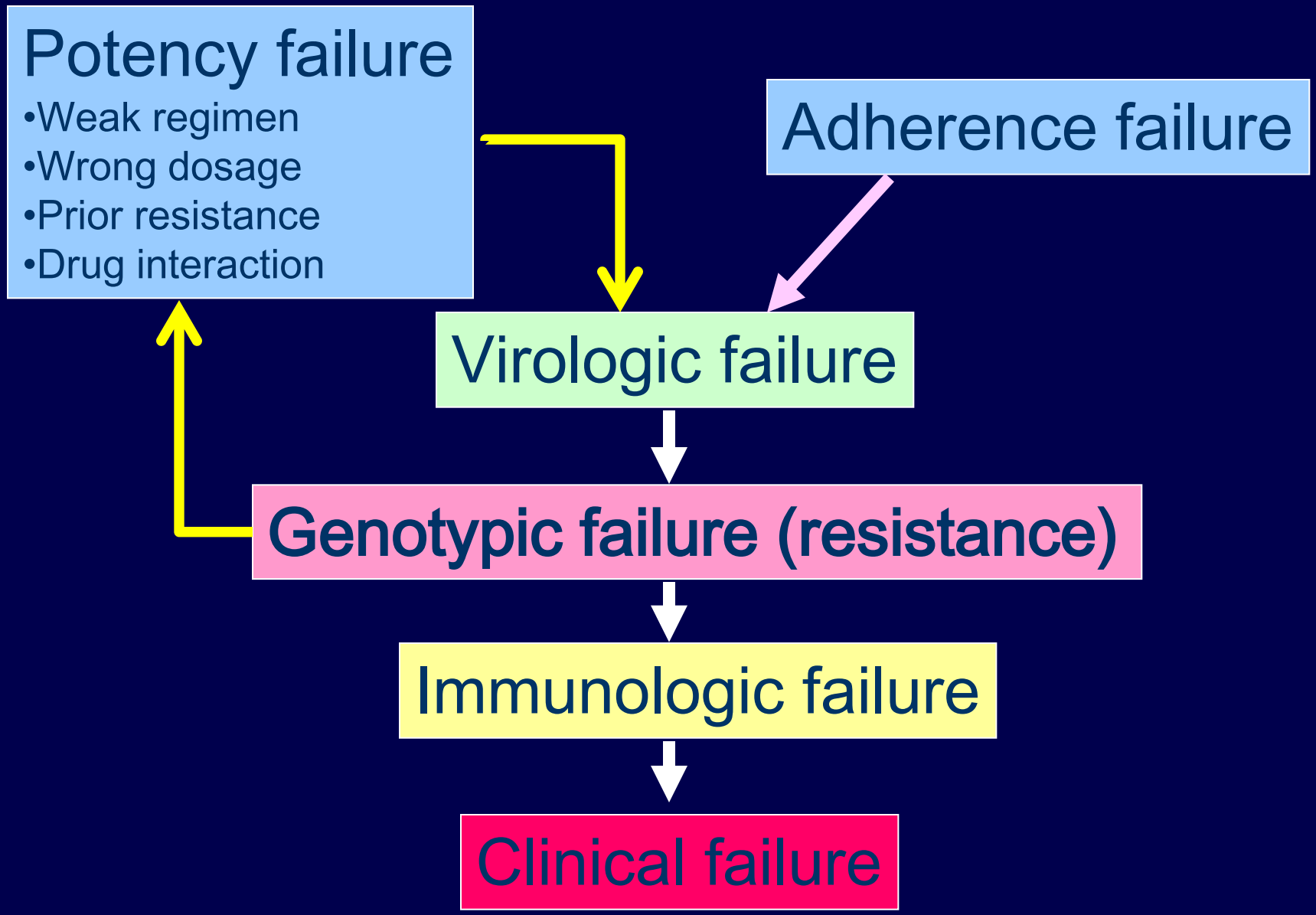
- Failure of viral load to follow expected decay after ART initiation
  - ~100-1,000-fold in 1 month
  - ~10,000-fold in 3 months
  - ~100,000-fold in 6 months
- Difference between *definition* of failure and *diagnosis* of failure in absence of VL
- 2 critical questions:
  - What was cause of failure?
  - What resistance has evolved?


HIV viral load response to D4T/3TC/NFV/NVP
Therapy started at day 0 (6 weeks old)
Viral load (copies/ml)
1000000
100000
10000
1000
100
10
-20
0
20
40
60
80
100
120
140
160
180
Days



HIV DRUG TARGETS: CURRENT AND FUTURE

Treatment failure: progressive steps, different definitions



Diagnosis and misdiagnosis of failure

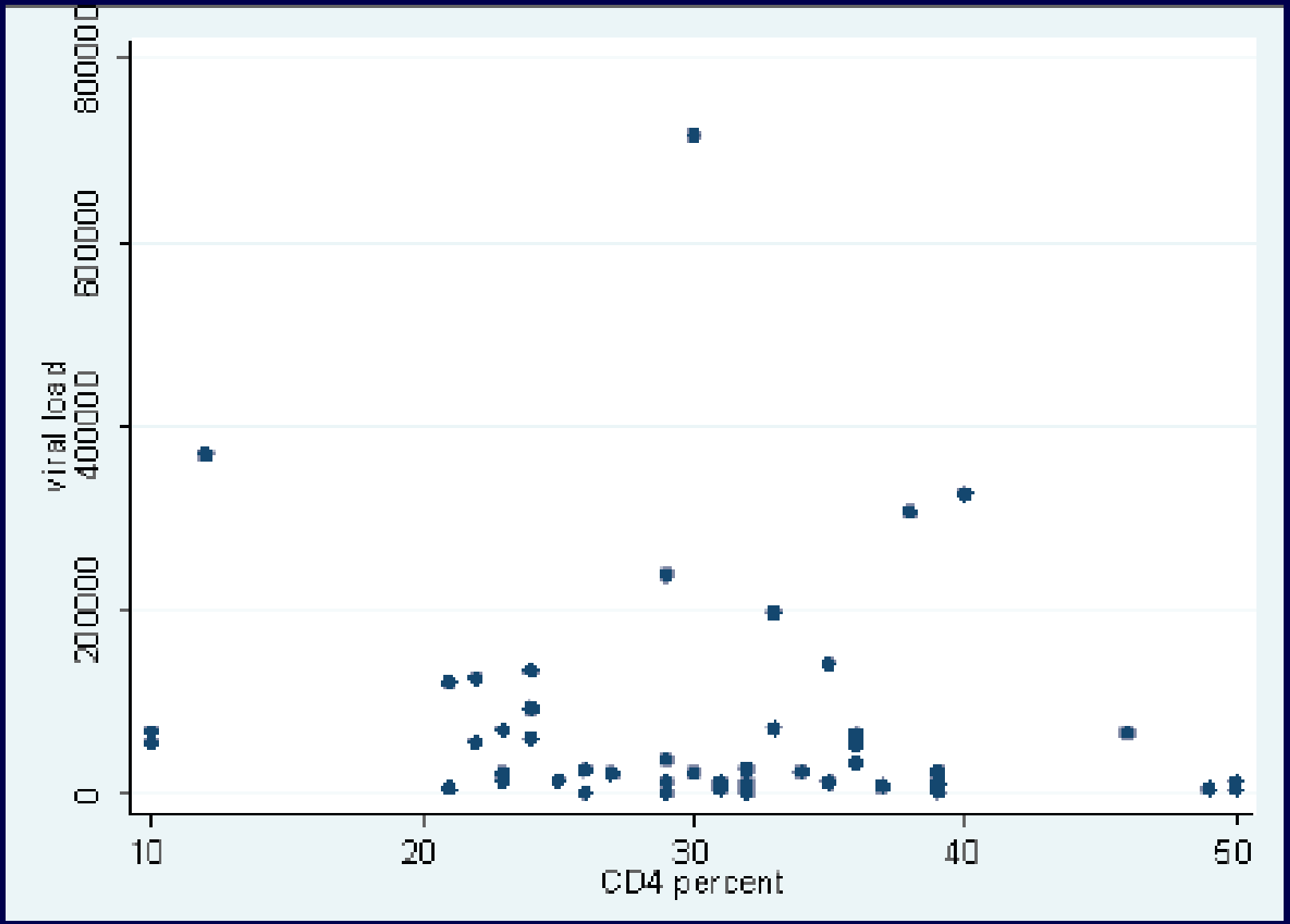
or

Kenya is too poor *not* to do viral loads

CD4 response in Thai children treated with D4T/3TC/NVP or EFV

Data are median (interquartile range). Puthanakit T, CID 2005; 41:100–7

Parameter, time point	All patients[a] (n = 107)	HIV RNA level at week 72		
		<50 copies/mL[b] (n = 85)	≥50 copies/mL (n = 22)	P[c]
CD4 cell percentage				
Week 0	3 (1–9)	4 (1–10)	3 (2–6)	.48
Week 8	9 (5–15)	9 (6–16)	7 (3–12)	.13
Week 24	12 (8–18)	12 (8–18)	11 (7–19)	.62
Week 48	17 (11–20)	18 (13–20)	11 (9–19)	.03
Week 72	21 (15–26)	21 (18–27)	14 (11–20)	.002
Increase in CD4 cell count from baseline				
Week 8	126 (73–275)	143 (80–283)	95 (17–214)	.12
Week 24	226 (127–330)	218 (127–318)	240 (89–414)	.68
Week 48	332 (187–457)	353 (243–483)	209 (131–390)	.07
Week 72	532 (287–709)	565 (330–729)	274 (156–631)	.006



Poor correlation between CD4 and VL in Ugandan children receiving ART for > 12 months

(Barlow-Mosha L, CROI 2011)

Performance of WHO criteria for treatment failure: Too poor not to do viral loads

- 500 adults in Kampala on NNRTI (Meya D, CROI 2007)
  - 76% (37/49) patients with virologic failure would be left on 1st line ART
  - 60/346 patients would be switched to 2nd line unnecessarily
  - Of 72 patients meeting WHO definition, 60 (83%) did not have failure
- Proportion of children with virologic failure who met clinical & immunologic criteria for failure:
  - Cambodia: 2/22
  - Tanzania: 2/57

Causes of treatment failure

- Prior exposure of virus to ARVs
  - SD NVP without tail coverage in infant
  - Mother or child previously failed ART
  - Exposure to maternal ARVs in breast milk
    - Maternal AZT/3TC/NVP → infant M184V ± K65R + Y181C or K103N
    - Less resistance with maternal PI
  - Infection with resistant virus (e.g. 2.4% of children < 3 years of age in southern Africa with no sdNVP exposure had NNRTI resistance)
- Evolution of resistance on therapy
  - **Non-adherence**
  - Wrong dosage
  - Inadequate potency- including AZT/3TC/NVP in small children

P1060: Randomized trial of ZDV/3TC + **NVP** versus **LPV/r** in Africa & India

Palumbo P, NEJM 2010, CROI 2011, CROI 2012

- Cohort 1
  - 6-36 months of age
  - Perinatal NVP exposure
  - Median age = 0.7 yr (~75% < 12 m.o.)
  - Median VL > 750,000 copies/ml
- Cohort 2
  - 2-36 months of age
  - Median age 1.7 yr
  - No NVP exposure
  - Median VL = 526,000

P1060: Comparison of Cohort 1 (NVP-Exposed) and Cohort 2 (Not NVP-Exposed) Results

Cohort 1: Palumbo P et al.NEJM 2010;363:1510-20

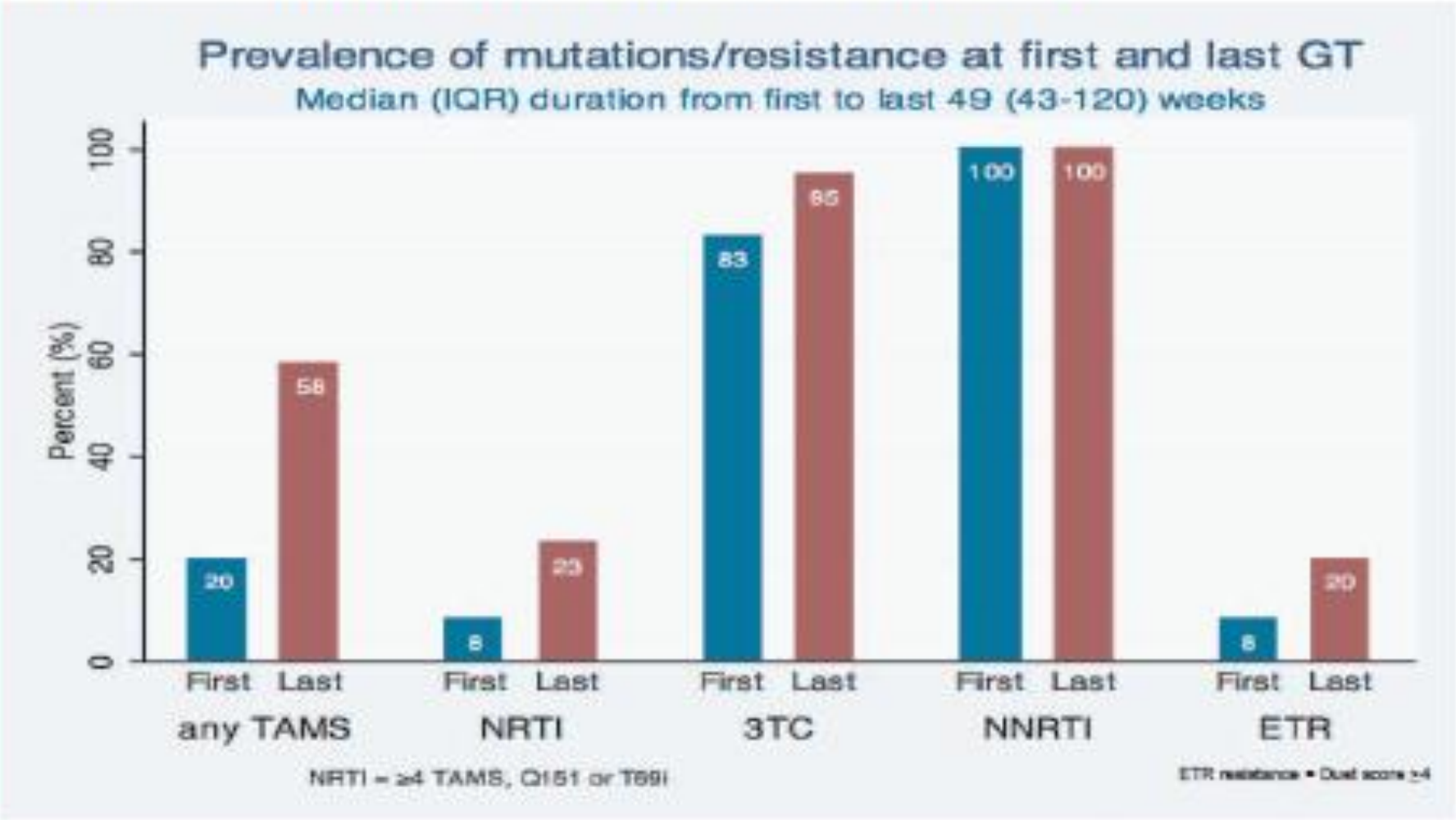
Cohort 2: Palumbo P et al. 18th CROI, Boston, 2011 Abs 129LB

Result (at 24 wks)	Cohort 1 NVP	Cohort 2 NVP	Cohort 1 LPV/r	Cohort 2 LPV/r
Number	82	147	82	140
Primary endpoint	40%	40%	22%	19%
Viral failure/death	27%	29%	10%	12%
Viral failure	24%	20%	7%	4%
Protocol-Defined Toxicity	(N=2) 2%	(N=15) 10%	(N=1) 1%	(N=5) 4%
Death	N=4	N=10	N=3	N=3

LPV/r Superior to NVP ART Regardless of Prior sdNVP Exposure

In cohort 1, less difference between NVP and LPV/r if > 12 months of age

Figure 1. Prevalence of resistance mutations at first and last GT



Accumulation of resistance mutations in Thai children from first detectable viral load to most recent sample (median 72 weeks after first detectable VL). Children were treated with D4T or AZT/3TC/NVP or EFV and were median 7 years of age (IQR 4-9) at initiation of ART with median VL = 214,000 c/ml, CD4% = 5 (IQR = 1-13). Puthanakit T, CROI 2011.

Failing and unfailing

- NNRTI regimen: rapid evolution of NNRTI resistance → re-establishment of adherence will only select for NRTI resistance
- PI/r regimen: more durable → re-establishment of adherence regains virologic control: can “unfail” PI/r *if child has not been failing too long*

Resistance consequences of early or late switch in children started on PI or NNRTI

	Total	PI-low	PI-higher	NNRTI-low	NNRTI-higher
Children expected to have tests (virologic failure)	165	33	23	27	25
Children with tests	91	28	18	23	22
1-2 thymidine analogue mutations	15	3	4	3	5
≥ 3 thymidine analogue mutations	4	0	0	0	4

Number of children with emergence of thymidine-analogue mutations according to assigned treatment group: PI versus NNRTI and low (> 1,000 c/ml) versus high (>30,000 c/ml) viral load threshold for switch to 2nd-line. PENPACT1, Lancet 2011.

Do we have to take Kaletra forever?
or
Can children **with sd NVP exposure history** and virologic suppression on LPV/r switch to NVP?

Coovadia JAMA 2010

- Johannesburg, SA
- All children started on D4T/3TC/PI (RTV or LPV/r) and maintained on D4T/3TC/LPV/r
- Eligible for randomization if VL < 400 c/ml for at least 3 months
- Randomized to continue LPV/r or switch to NVP

Results of LPV/r to NVP switch study

	Continue LPV/r group (n = 99)	Switch to NVP group (n = 96)	p
Baseline			
Median age at ART start (mo)	11	9	NS
VL > 750,00 at ART start (%)	57	54	NS
Median age at randomization (mo)	20	19	NS
Outcomes at 52 weeks			
VL > 50 c/ml (%) (primary endpoint)	58	43	0.02
Confirmed VL > 1,000 c/ml (%)	2	18	< 0.001
NNRTI resistance among failures	0/2	13/15	
3TC resistance among failures	0/2	12/15	

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Preventing and preparing for failure

- Get history to assess potential resistance
- Start with a potent initial regimen
  - Should we use NVP in young children?
    - Alternatives: EFV, LPV/r, or ??
    - Omit 2-week lead in?
  - Nucleoside choice?
    - ABC or TDF
- Start with regimen with predictable and manageable resistance pattern
  - ABC or TDF failure leave AZT fully active

Importance of systematic adherence program cannot be overemphasized!

Making the best of a bad situation: Options after 1st-line failure

- ABC (or TDF)/3TC/NNRTI failure: AZT/3TC/LPV/r fully active
- AZT/3TC/NNRTI failure
  - TDF/3TC/LPV/r best option
  - ABC/AZT/3TC/LPV/r alternative
  - Consider repeat VL after 3-6 months on 2nd line
- ABC/3TC/LPV/r
  - Is failure due to high-level LPV resistance?
  - Not clear how effective AZT/3TC/EFV is with M184V
  - AZT/TDF/±3TC/EFV: 3 active drugs unless K65R present
- D4T/3TC/NNRTI
  - TDF/3TC/LPV/r good unless K65R
  - Repeat VL & consider genotype or empirically adding AZT

When all else fails: 3rd line treatment

- How confident are you about the 2nd-line ART? Confirm failure with VL
- Are you sure child adherent?
- Genotype
  - Cheaper than 3rd-line drugs and often wild-type
  - Often an expensive adherence test
  - Botswana: Only 7/28 children failing LPV/r had PI mutation and only 1 high-level resistance
  - Interpretation can be difficult: seek consultation

3rd line options for NRTI/NNRTI/LPV resistance

- Yes, you can give these drugs to children (in the right dosage)
- Darunavir/ritonavir
  - Extremely potent
  - Active against most LPV-resistant virus
- Raltegravir
- 1-2 NRTI, e.g 3TC ± TDF
- Etravirine
  - May or may not be active depending on NNRTI mutations
  - May not be necessary
- CCR5-binding attachment inhibitors (maraviroc)
  - Not active: Most children have CXCR4-tropic virus at this point

How to avoid spending a lot of money on treatment failure

- Get a history
- Systematic adherence program
  - Community-based support
  - Tracking of patient
- Start with a potent regimen that leaves good empiric 2nd-line options
  - If using NVP, consider early VL (by 3 months)
- Strategic use of VL
  - Need for low-cost semiquantitative technololgy
  - VL the only important lab test on therapy (except maybe semiannual creatinine on TDF)