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Our Issues, Our Drugs, Our Patients

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Holding strategies should be included in paediatric ARV treatment guidelines

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National consolidated guidelines, SA NDOH, April 2015

6.4.5 Viral load monitoring and first-line ARV treatment failure for infants and children (page 63)

- Changing a child from first to second-line ARV is a decision that should only be undertaken after careful consideration and discussion (even telephonically) with an expert.
- Second-line treatment is generally used following treatment failure, as reflected by a VL greater than 1000 copies/ mL despite good adherence
- Always attempt to improve adherence before switching regimens, as poor adherence to treatment is the most common cause of virological failure
- If it is not possible to improve adherence:
  - Holding strategies or Directly Observed Therapy (DOT) may be attempted

The context of paediatric antiretroviral therapy: worlds apart

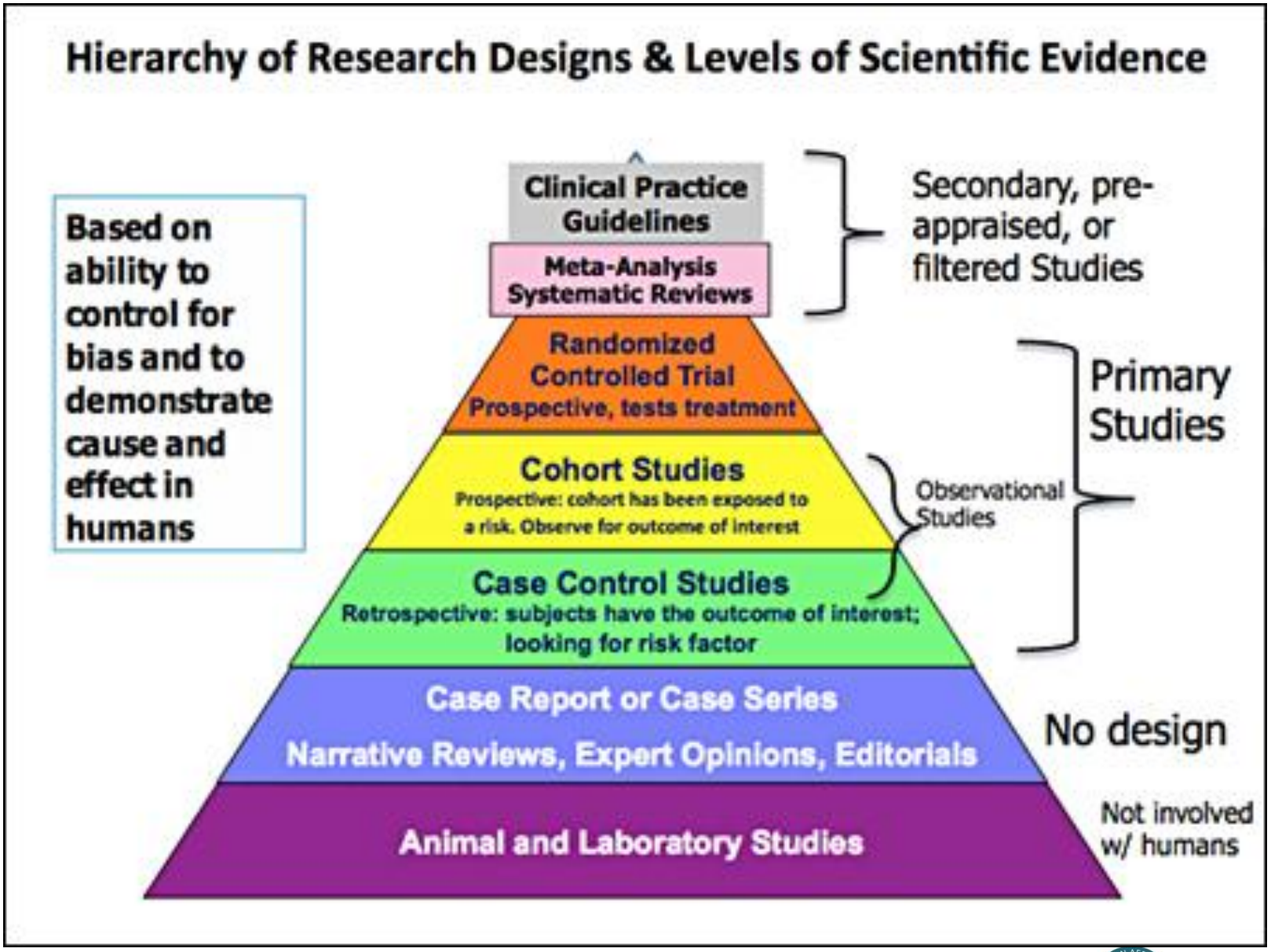
The 'ideal'

- Diagnosed early & starts ART early
- No perinatal NNRTI exposure
- Parents are reliable caregivers
- Tolerates ART well
- Good adherence
- Remains on 1st line ART with viral suppression
- Early disclosure
- Copes well with adolescence
- Able to tolerate & adhere to 2nd line when required (pill burden & side-effects)
- Genotyping available
- 3rd line regimen available & tolerable if required

'Reality' (sometimes)

- Delayed diagnosis & ART initiation
- Perinatal NNRTI exposure
- Low nadir CD4 count
- TB diagnosis at ART initiation
- Unavailability of super-boosting LPV/r
- High medication burden (TB & ART)
- Poor tolerance of meds
- Erratic adherence
- 'Social issues' / 'caregiver challenges'
- Viral non-suppression on 1st line PI regimen <3 yrs of age
- PI resistance on genotyping
- CD4 count <350
- Repeat diagnosis of TB
- Changing caregivers
- Non-disclosure
- ….

Hierarchy of Research Designs & Levels of Scientific Evidence



Case 1

- 5 yr old boy, born 17/01/2011
- Mother diagnosed HIV+ 5 yrs earlier, not on ART, substance abuser, unbooked pregnancy, received NVP at birth
- HIV PCR + at 6 weeks of age at local clinic
- Hospitalised with severe pneumonia at 3 mths
- Started ABC/3TC/LPV/r at 3 ½ mths
- Admitted into convalescent care facility & remained there until 2 yrs of age
- Viral non-suppression

Time on ARV regimen	Age (mths)	ARV regimen	Viral load abs	Viral load log	CD4 abs	CD4%	Weight (kg)
Baseline	3	Started ABC/3TC/LPV/r	10 000 000	>6.7	1141	23	5.36
5 mths	8	cont.	19 335	4.29	1050	21	7.62
8 mths	11	cont.	1500	3.18	1676	24	9.88
11 mths	15	cont.	4085	3.61	1208	27	10.9
Lopinavir trough levels: >1 mg/L (11.8 & 5.5)							

Genotyping: V82A, L10F (intermediate res to LPV, MS 30, susceptible to DRV), L74V, M184I, T215A/T (high res to ABC & 3TC), Y181C, H221Y (high res to NVP, intermediate res to EFV & ETR)

Time on ARV regimen	Age (mths)	ARV regimen	Viral load abs	Viral load log	CD4 abs	CD%	Weight
		Starts 3TCm					
3 mths	20	cont.			1159	22	12.3
6 mths	22	cont.			1066	20	12.8
9 mths	26	cont.			650	19	12.5
12 mths	28	cont.			1009	14	14.2
No 3TC for 1 month							
19 mths	36	cont.			596	24	14.9
Mother demises, caregiver is father then grandmother							
23 mths	39	cont.			734	18	15.8
26 mths	42	cont.			648	15	16.4
30 mths	46	cont.			995	20	15.9
32 mths	49	cont.			812	25	17
35 mths	52	cont.			819	25	16.9
39 mths	56	cont.			660	29	16.5
Diagnosed with PTB, RHZE started							
44 mths	60	cont.			760	23	17.3

- 3rd line regimen will be:
  - Darunavir: 375 mg bd (2x150 mg tabs + 1x75 mg tab bd)
  - Ritonavir: 0.6 ml solution bd or 100 mg tablet bd
  - Raltegravir: 100 mg bd (1x100 mg chewable tab bd)
  - Zidovudine: 200 mg am (2x100mg tabs), 100 mg pm (1x100 mg tab)
  - Lamivudine: 150 mg (1 tab) once daily

- 3rd line ART pill burden at current weight (18 kg):
  - 6-8 tabs twice a day (14 tabs a day)

Case 2

- 10 yr old boy, born 15/03/2006
- Ex-prem, birthweight 900g
- Started d4T/3TC/LPV/r in 2007
- Concurrent Rifampicin-based TB Rx (disseminated BCG & TB meningitis) apparently without Ritonavir superboosting
- Prolonged virological failure
- 2013: genotyping done: high level LPV res, susceptible to DRV, M184V, D67N
- CD4 count at time: 2341 / 31%
- Started 3TC monotherapy in 2013 (age 7 yrs) at primary clinic
- Diagnosed with TB and severe anaemia 16 months later (CD4 712 at time)
- TB Rx started but required recurrent blood transfusions (3TC-associated red cell aplasia suspected)
- CD4 count remained >900 & >25% throughout
- Motivation for 3rd line ART to be started after completing rifampicin-based TB Rx
- Started Darunavir/ritonavir/Raltegravir/Abacavir May 2015
- Virally suppressed with CD4 1616/37% 7 months later

Recognising and managing ARV treatment failure

- The causes of virologic treatment failure (poor adherence, dug resistance, poor absorption of medications, inadequate dosing, drug-drug interactions) should be assessed and addressed

- New ARV regimens should be chosen based on treatment history and ideally, drug-resistance testing

- The goal of therapy following treatment failure is to achieve and maintain virologic suppression

- **When complete virologic suppression cannot be achieved, the goals of therapy are to preserve or restore immunologic function (as measured by CD4 count), prevent clinical disease progression, and prevent development of additional drug resistance that could further limit future ARV options**

US guidelines, 2016
http://aidsinfo.nih.gov/guidelines

1. When is it that complete viral suppression 'cannot' be achieved…?

- Actually not achieved (e.g. already on 2nd line)
  - No resistance on drug-resistance testing
    - Assumed poor adherence ± intolerance/side-effects
    - Some will eventually suppress
  - LPV or ATV resistance on drug-resistance testing
    - Some may still suppress on failing regimen but risk of accumulating further PI mutations including to 3rd line drugs (Darunavir)

- Anticipated that won't be achieved (e.g. failing 1st or 2nd line)
  - Previous significant adherence problems
  - Very poor tolerance of ARVs (e.g Kaletra or Ritonavir) & unable to swallow tablets
  - Large pill burden & lack of a reliable caregiver in young children
  - Known drug-drug interactions likely to lead to subtherapeutic plasma drug concentrations (e.g. LPV/r or DRV/r & rifampicin)
  - Health system / drug supply issues

- Lack of dosing/safety data in age group/unable to formulate optimal cART regimen
  - E.g. LPV/r & RAL in neonates, DRV/r in infants <3yrs, DTG <12 yrs

What to do while actively addressing these issues or in some cases waiting for these issues to be resolved?

Dosing of 3rd line ARV drugs:
E.g. Darunavir/ritonavir

Weight band (kg)	Dose of darunavir and ritonavir: administer doses in table below twice daily with food
10 - <11	DRV 200mg (2.0 ml) + RTV 32 mg (0.4 ml)
11 - <12	DRV 220mg (2.2 ml) + RTV 32 mg (0.4 ml)
12 - <13	DRV 240 mg (2.4 ml) + RTV 40 mg (0.5 ml)
13 - <14	DRV 260 mg (2.6 ml) + RTV 40 mg (0.5 ml)
14 - <15	DRV 280 mg (2.8 ml) + RTV 48 mg (0.6 ml)
15 - <30	DRV 375 mg (2 x 150 mg + 1 x 75 mg tablets or 3.8 ml) + RTV 48 mg (0.6 ml) or 100 mg capsule if able to swallow
30 - <40	DRV 450 mg (3 x 150 mg + or 4.6 ml) + RTV 100 mg capsule (or 1.25 ml)
≥40	DRV 600 mg (1 x 600 mg or 4 x 150 mg tablets or 6 ml) + RTV 100 mg capsule (or 1.25 ml)

2. What is the best way of preserving CD4 count & preventing clinical disease progression and at same time preventing development of additional drug resistance that could further limit future ARV options?

	Preserve CD4 / prevent disease progression	Prevent further resistance / limit future ARV options
Complete interruption of cART	X X	✓ ✓
Remain on failing regimen	✓	X
Switch to suboptimal $2^{nd}/3^{rd}$ line cART	✓	X
Holding regimen	?	✓

Recommendations on 2nd & 3rd line ART regimens for children

1st line regimen	2nd line regimen		3rd line regimen	
	SA 2015	WHO 2015	SA 2015	WHO 2015
2 NRTIs + LPV/r	Expert opinion (genotype result & expert committee consensus)	If <3 yrs of age: 2 NRTIs + RAL If >3 yrs: 2 NRTIs + EFV	Based on genotype result & expert committee consensus	DTG + 2 NRTIs Or DRV/r + 2 NRTIs Or DRV/r + DTG + 2 NRTIs
2 NRTIs + EFV	2 NRTIs + LPV/r	2 NRTIs + LPV/r		

- 2nd line: If RAL is not available, no change is recommended unless in the presence of advanced clinical disease progression or lack of adherence specifically because of poor palatability of LPV/r. In this case, switching to a second-line NVP-based regimen should be considered.
- DRV/r should not be used in children younger than three years of age.
- RAL can be used in children failing PI-based second-line treatment when DTG is not available and when RAL has not been used in a previous regimen. DTG is currently only approved for children 12 years and older, however studies are ongoing to determine dosing in younger children and approval to lower age groups is expected in the near future.

Paediatric/adolescent data on the use of the 'holding strategy'

- Observational studies
  - Lazarus 2013
  - Linder 2014 / 2016
  - Patten 2016 (IeDEA group) (unpublished)

- Randomised controlled trial
  - Agwu 2014 (IMPAACT P1094) (unpublished)

AIDS & Clinical Research

Lazarus et al., J AIDS Clin Res 2013, 4:10
http://dx.doi.org/10.4172/2155-6113.1000246

Research Article Open Access

Lamivudine Monotherapy as a Holding Strategy in HIV-Infected Children in South Africa

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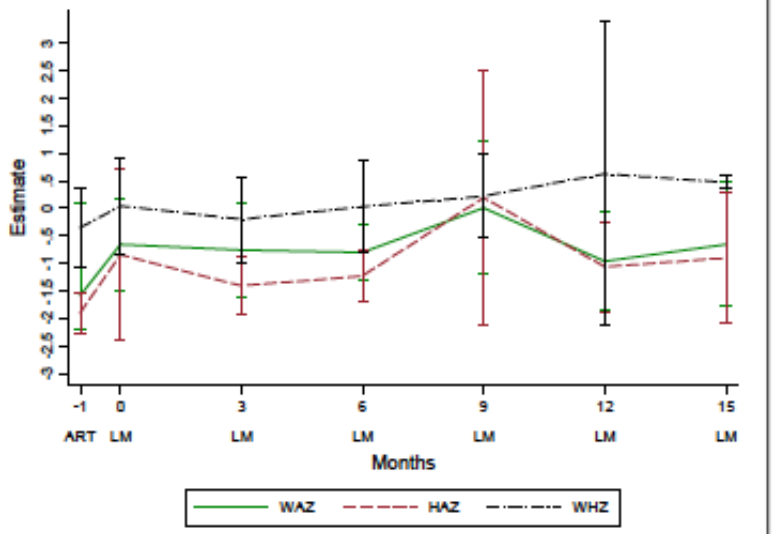
- Retrospective review of 23 patients ≤16 years of age who received lamivudine monotherapy (LM) as a holding strategy for at least 3 months at 4 ARV sites in Johannesburg.
- Indications for LM were intractable adherence issues (87%) & multi-drug resistance precluding an active new ART regimen (13%).
- Median (IQR) duration of LM was 6.13 months (3.93-9.31).
- After 6 months of LM, absolute CD4 decreased by 23%. Neither nadir CD4 (p=0.35) nor pre-LM ART regimen (p=0.50) predicted CD4 count decline.
- LM was stopped in 9 children, 7 of whom restarted cART due to CD4 decline (3), disease progression (1) and adherence issues resolved (3).
- The other 14 (60.9%) children were continuing LM at time of data collection.
- No deaths occurred during follow-up.

Variable	ART Initiation	LM Initiation
Median age in years (IQR)	6.20 (1.10–7.52)	8.02 (4.07–11.80)
Median CD4+ cells/mm^3 (IQR)	560 (214-1052)	671 (520-1239)
Median CD4+ % (IQR)	12.6 (7.0-15.0)	25.4 (18.0-32.1)
Weight-for-age z-score (IQR)	-0.92 (-1.9,0.16)	3.3 (-0.3,5.2)
Height-for-age z-score (IQR)	-1.5 (-2.2,-1.2)	-1.4 (-1.7,-0.8)
Weight-for-height z-score (IQR)	-0.3 (-1.3,0.7)	4.9 (0.9,8.5)

Table 1: Characteristics at ART and LM initiation respectively.



WAZ: Weight-for-age z-score
HAZ: Height-for-age z-score
WHZ: Weight-for-height z-score

Figure 1: Growth parameters at antiretroviral therapy (ART) initiation and during lamivudine monotherapy (LM): medians with 95% confidence interval.

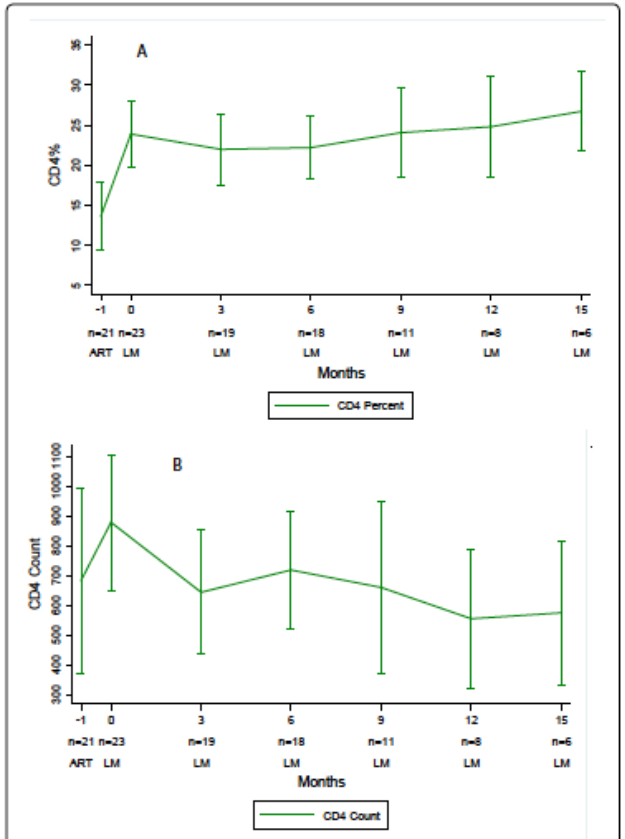


Figure 2: CD4 percentage (Figure 2A) and CD4 cells/mm^3 count (Figure 2B) from antiretroviral therapy (ART) initiation and during lamivudine monotherapy (LM): medians with 95% confidence intervals.

Pediatr Infect Dis J. 2016 Mar 30. [Epub ahead of print]

Lamivudine Monotherapy: Experience of Medium Term Outcomes in HIV Infected Children Unable to Adhere to Triple Therapy.

Linder V, Goldswain C, Adler H, Carty C, Harper K, Jackson V, Lambert JS, Boon G.

- Retrospective review of 71 children with 1st line ART failure managed with lamivudine monotherapy (LM) for ≥3 months at 2 health facilities in Eastern Cape Province, SA
- Median (IQR) age at LM initiation: 9.6 years (6.7-12.5)
- Analysed by absolute CD4 count at LM initiation (Group 1>200; Group 2 ≤200)
- **Study end-point: decline in absolute CD4 by ≥25% or to ≤200 or WHO stage 3 or 4 event or re-initiation of 2nd or 3rd line ART**
- Mean duration of LM: 24.35 months
- 71.8% of children had CD4 count drop ≥25%; 15.6% with CD4 >200 at start of LM dropped to ≤200; 6 children (8.1%) had stage 3 or 4 event (all TB) but there was no difference between the groups
- There were no deaths
- ART was re-initiated earlier in the children with CD4 ≤200 at start of LM (Group 2), 11.38 vs 26.1 months

Conclusion: LM is a potential alternative for young patients pending availability/willingness to adhere to 2nd or 3rd line ART but is associated with rapid CD4 count decline, and should be avoided if CD4<200

Outcomes in HIV-positive children on lamivudine monotherapy as a holding regimen in the IeDEA Southern African cohorts

Patten G, Bernheimer J, Cox V, Fairlie L, Rabie H, Sawry S, Technau K, Eley B, Davies M-A

Aim: to investigate characteristics of children placed on LM and their outcomes

Methods: children <16 years at ART start from 5 IeDEA-SA cohorts who received LM

Kaplan-Meier estimates were obtained for probability of **immunological decline (ID)**, defined as: **a drop in CD4 below 500, or in those who initiated LM with CD4<500, a drop in CD4 of more than 10%**
In patients who received LM for more than 90 days, we determined predictors of ID using Cox-proportional hazards models. Average CD4 trajectory over time was modelled using linear mixed-effects models.

Results

- Of those who were on LM for >90 days, 44% (72/163) experienced a drop in CD4 meeting the definition of ID; 21% (34/163) experienced a gain in CD4 of more than 10%.
- Among 126 patients on LM for more than 6 months, the 6 month risk of ID was 23% (95% CI 17.7%-30.4%).
- Predictors of ID include older age at ART start, treatment interruption prior to LM start and CD4 count prior to LM start. Ever having been on a PI regimen was not associated with ID.

Characteristics and outcomes of patients started on Lamivudine Monotherapy (n=232)

Characteristics at ART start		
Male (%)	135	58%
Median Age in years (IQR)	7.4	(3.3-10.0)
Median CD4 count (IQR) (n=166)	346.5	(185-604)
Median CD4% (IQR) (n=161)	12.6	(7.3-18.0)
Characteristics at LM start		
Median Age in years (IQR)	12	(7.2-14.6)
Median time on ART (IQR)	3.5	(1.9-5.7)
Median CD4 count (IQR) (n=221)	601	(425-869)
Median CD4% (IQR) (n=220)	21.7	(16.4-28.0)
CD4 < 500 cells/uL (%) (n=221)	75	34%
Median log VL (IQR) (n=220)	4.2	(3.7-4.7)
On efavirenz-based regimen (%)	122	53%
Outcomes on LM		
Median time in days on LM	309	(88.5-664)
Resumed ART (%)	173	75%
Remained in care on LM (%)	43	19%
Died on LM (%)	4	2%
Transferred out on LM (%)	9	4%
Lost to follow-up (%)	3	1%

Multivariable associations with immunologic decline, stratified by site (n=163)

		Adjusted HR (95% CI)	p
Age in years at ART start	<2	1	-
	2-6	2.2 (1.1-4.4)	0.0004*
	6-9	2.4 (1.2-4.7)	
	>9	4.4 (2.1-9.1)	
Prior Treatment Interruption		1.9 (1.1-3.5)	0.03
CD4 at LM start	<500	1	-
	500-750	1.0 (0.7-1.6)	0.0153*
	750-1000	0.9 (0.5-1.5)	
	>=1000	0.4 (0.2-0.7)	
Ever on a PI-based regimen		1.3 (0.9-1.9)	0.121

*Derived from Wald's test

3TC/FTC Monotherapy vs. Continuing Failing cART as a Bridging ART Strategy in Persistently Non-adherent HIV-infected Youth with M184V Resistance: IMPAACT P1094

Allison Agwu, Meredith Warshaw, George Siberry, Ann Melvin, Elizabeth McFarland, Andrew Wiznia, Lee Fairlie, Sandra Boyd, Hans Spiegel, Elaine Abrams, and Vincent Carey for the P1094 Study Team

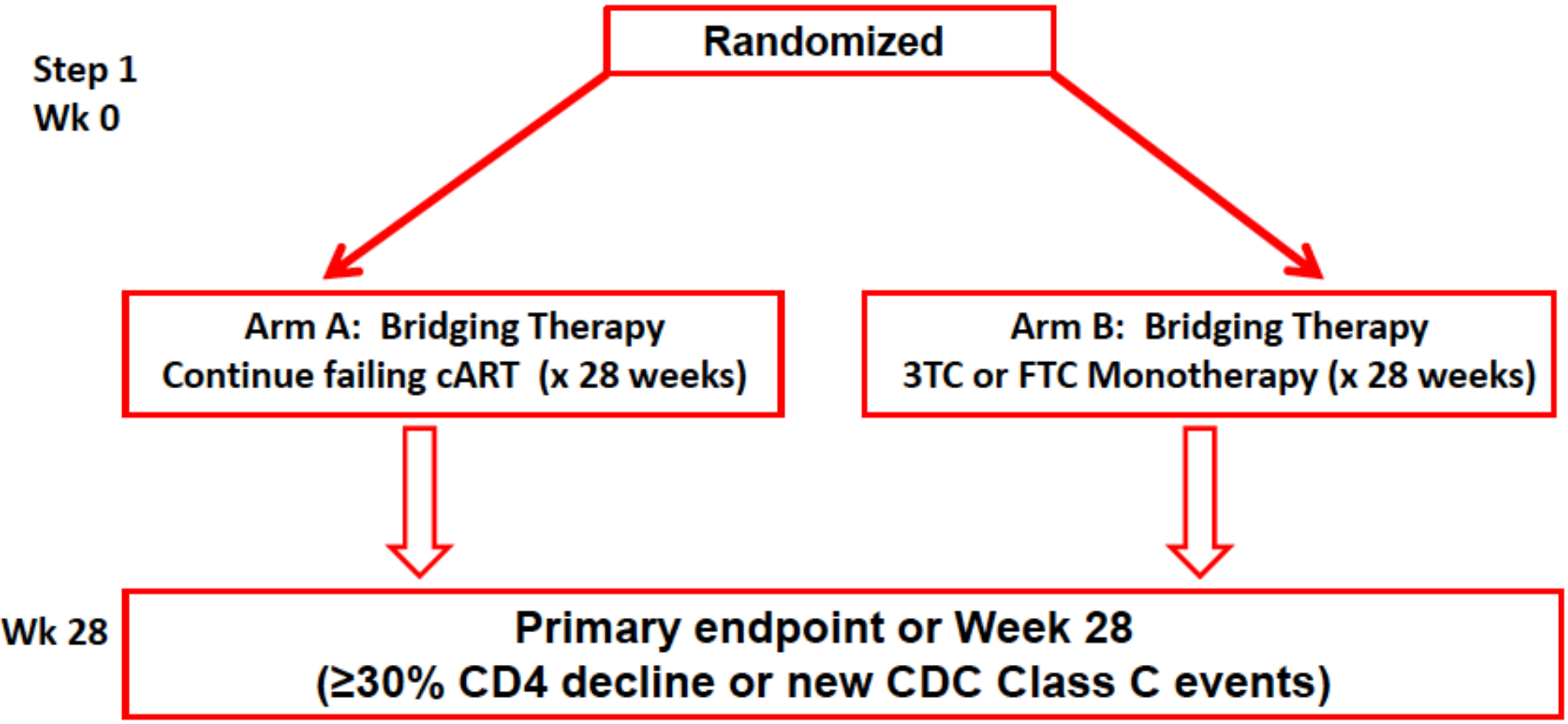
Presented at 6th International Workshop on HIV Pediatrics, Melbourne, Australia, July 18, 2014

Primary Objective of IMPAACT P1094

To compare immunologic deterioration during a 28 week "bridging" ART strategy of 3TC or FTC monotherapy vs. continuing failing cART in HIV-infected children, adolescents, and young adults with virologic failure and documented M184V resistance who are likely to be non-adherent to an optimized cART regimen due to problems related to adherence, tolerability, or toxicity

Primary endpoint: ≥30% decline in absolute CD4

HIV-infected School-Aged Children and Adolescents Failing cART with the M184V Mutation and Unlikely to Adhere to Optimal cART



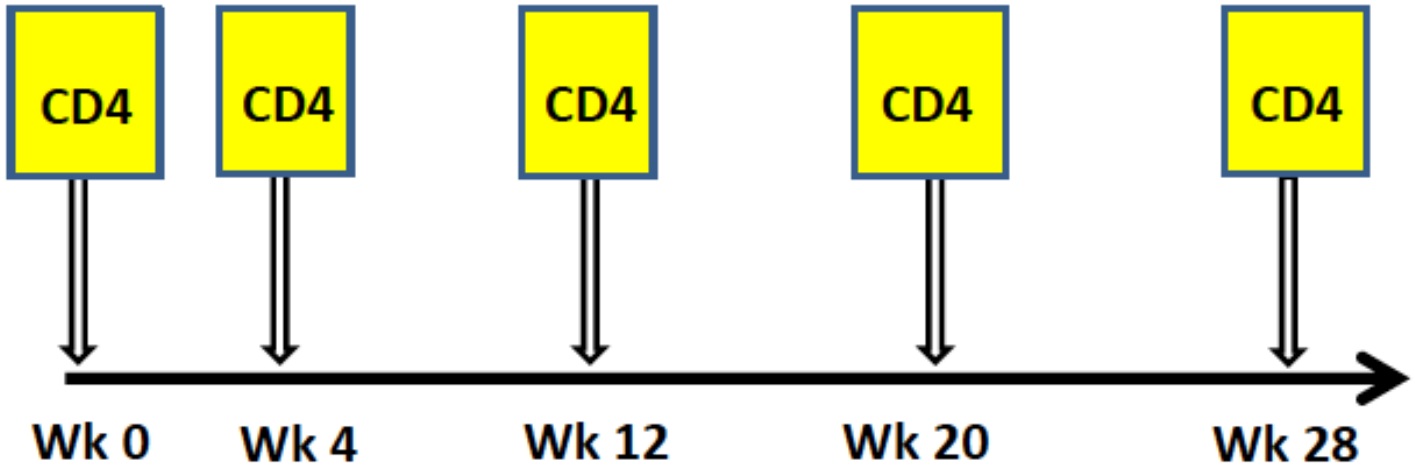
Step 1 [Wk 0-28]: Patients with virologic failure are randomized to 3TC/FTC Bridging vs. Continuing failing cART for at least 6 months and only switch if they reach endpoints as defined in the protocol.

Agwu A, et al. 6th Intl Workshop on Peds HIV. 2014. Abstract O_011

Study design

- Randomized controlled trial
- Sites: domestic & international
- Inclusion criteria:
  - Ages 8-24 years
  - cART for a minimum of 6 months
  - Documented non-adherence
  - Persistent VF (HIV-1 plasma RNA ≥400 copies/mL)
  - M184V resistance mutation at or prior to screening
  - CD4≥100 cells/mm^3
  - Attempts to improve adherence unsuccessful

Frequency of CD4 Monitoring during Step 1



Primary endpoint: ≥30% decline in absolute CD4

Additional measurements: adherence, viral load, HIV-genotype and phenotype, immune activation markers

Study Enrollment

- 33 perinatally HIV-infected participants enrolled
  - 16 randomized to continuing failing cART
  - 17 randomized to 3TC/FTC monotherapy
  - US, Brazil, Thailand, Argentina
- Early study closure in February 2013 due to slow accrual at US sites and long regulatory processing times delaying opening at international sites.

Baseline Demographic and Clinical Characteristics

		Treatment Arm		
		cART (N=16)	3TC/FTC (N=17)	Total (N=33)
Age at Entry (Years)	Median (Q1, Q3) Min, Max	16.5 (14.0,19.5) 11,24	15(13,20) 10,21	15 (14,20) 10,24
Gender	Male	4 (25%)	7 (41%)	11 (33%)
Race	Black White Asian	9(56%) 4(25%) 3(19%)	8 (47%) 6 (35%) 3(18%)	17 (52%) 10(30%) 6 (18%)
Hispanic ethnicity		6 (38%)	8 (47%)	14(42%)
Screening CD4	Median (Q1,Q3) Min, Max CD4<400 CD4≥400	490 (377,615) 262,897 5(31%) 11 (69%)	461 (384,683) 156,1078 5(29%) 12(71%)	472(384,651) 156,1078 10(30%) 23 (70%)
HIV RNA $\log_{10}$ copies/ml	Median (Q1,Q3) Min, Max	4.1(3.3,4.6) 2.2, 5.6	4.0 (3.2,4.1) 2.2,4.9	4.0 (3.2,4.5) 2.2,5.6

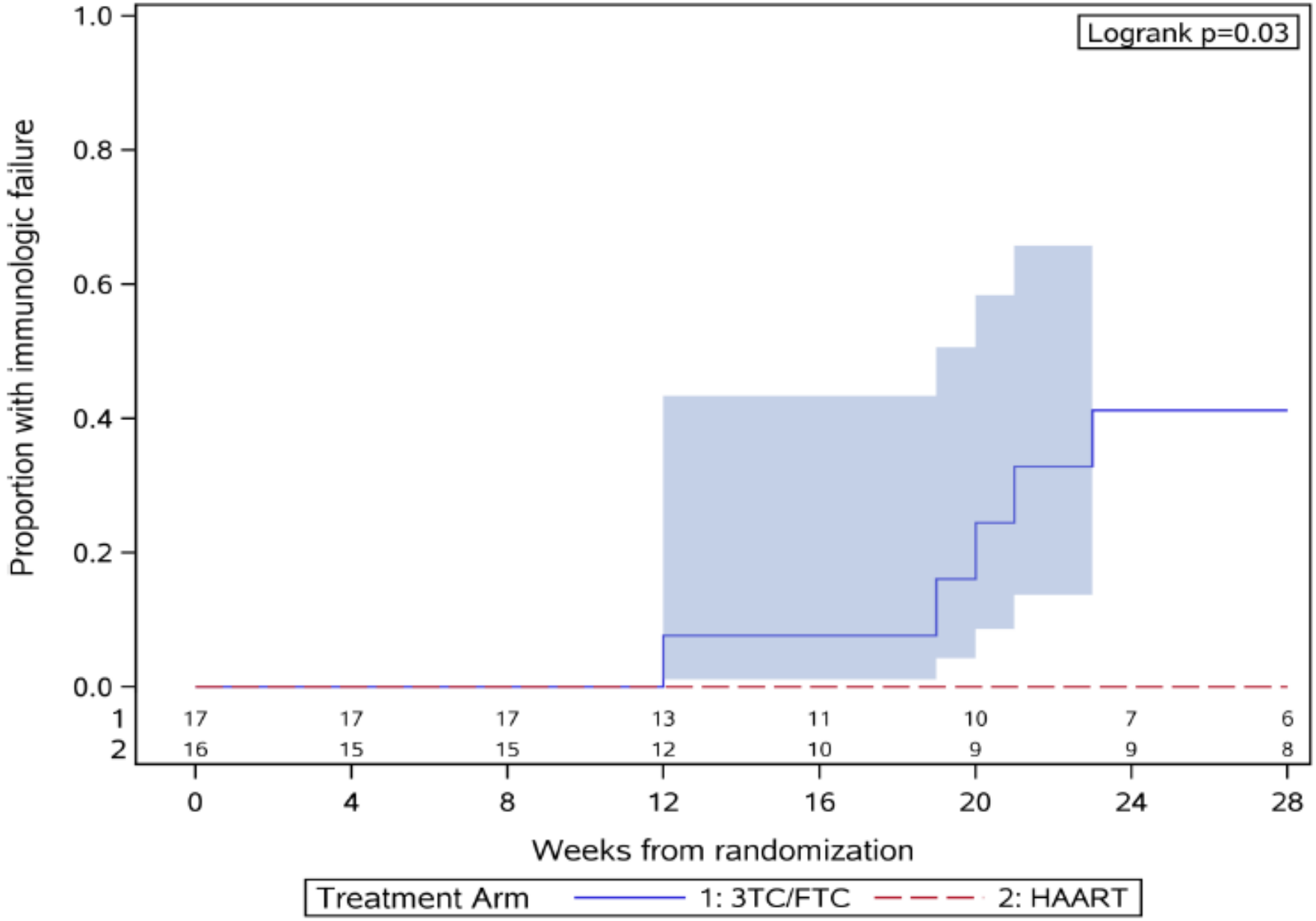
Measures used to Determine Chronic Non-adherence*

		Treatment Arm		
		cART N=16	3TC/FTC N=17	Total N=33
# mechanisms used to determine non-adherence	Median (Q1,Q3) Min, Max	3 (2-3.5) 1,6	2 (2,3) 1,5	3 (2,3) 1,6
Patient admission of non-adherence		13 (81%)	13 (76%)	26 (79%)
Persistent viremia		12 (75%)	11 (65%)	23 (70%)
Pill counts		3 (19%)	4 (24%)	7 (21%))
Pharmacy refill history		8 (50%)	4 (24%)	12 (36%)
Agreement of 2 providers		9 (56%)	11 (65%	20 (61%)
Other		2 (13%)	1 (6%)	3 (9%)

Interventions attempted*: counseling (94%), frequent clinic visits (75%), reminders (56%), DOT (6%), G-tube (6%) , home visits (19%), therapy (56%), peer support (31%), regimen modification/simplification (25%), rewards (31%), ADL triggers (44%)

***not mutually exclusive**

Probability of ≥30% Decline in Absolute CD4 Count



One Grade 3+ adverse event (Grade 4 hyperbilibirubinemia in continuing cART arm).

Some observations from the available paediatric studies

- Small sample sizes (observational studies: 23, 71, RCT: 33 (17))
- Variable follow-up period on LM (only 28 weeks in RCT)
- Consistent CD4 decline observed
  - Expected
  - Quantified: up to 70% of children experienced a 25% decline in absolute CD4 after 24 months on LM
  - Fluctuations
  - 21% of children experienced a 10% gain in CD4 count
- Few adverse clinical outcomes (notably TB)
- Unknown adherence to holding regimen
- Data on multi-NRTI holding regimens lacking
- Older paediatric cohorts
- Variable access to genotyping and 2nd/3rd line regimens

- What is a clinically relevant definition of immunological failure in context of LM?
  - Percentage decline (10/25/30%) in CD4 absolute count or percentage?
  - Absolute CD4 count level e.g. >5 yrs: 200 / 350 / 500; <5 yrs: 25%?

MIDTOWN THROWDOWN

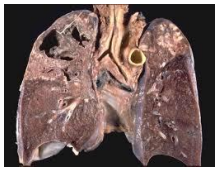
- In times of uncertainty
- Limited data
- “limited” resources

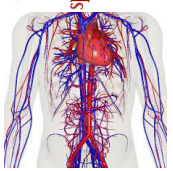
What we agree on

- The **long term survival** of tomorrows adults **depends on what we do with todays infants and children**
- "Mindless" switching between regimens **WILL NOT** solve the issues of social concern and poor adherence to care
- Resolving issues around adherence and tolerability is **MORE IMPORTANT** than access to new regimens for many patients
- We are **unlikely** to have a **randomized** study to answer this question – ever: **ALL current data is flawed**
- **PREVENTION IS BETTER THAN CURE**

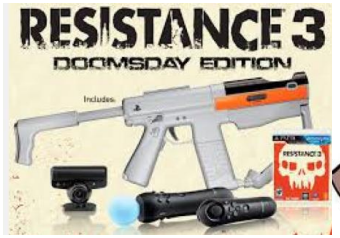
What is the main concern

Absence of ART will lead to an increase in the risk of opportunistic infections
I am very worried about…..



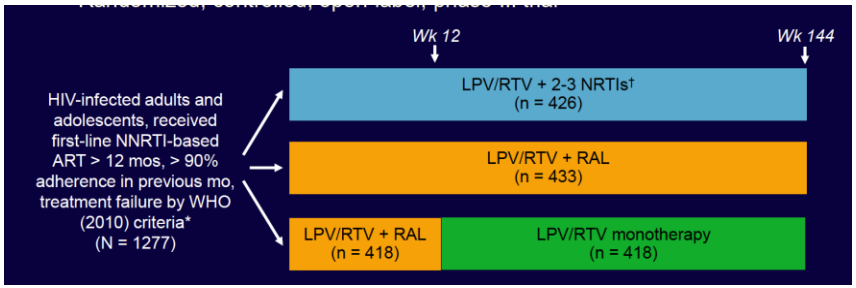


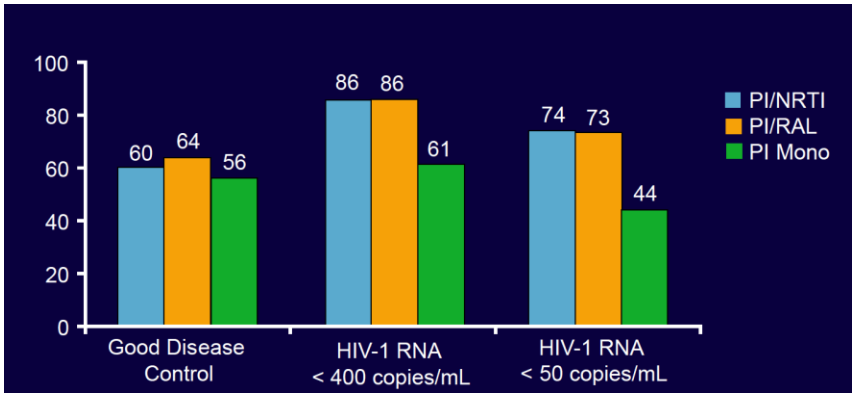
And about….



And also ….

Bridging regimens cause resistance
Resistance harms future therapy





Penpact1 – Switching early vs delayed

Risk factors for PI resistance

- Children 50% of children tested at 56 months of age had major PI mutations (starting at 16 months)
- Unsuppressed VL at month 12 of therapy
- Time on failing regimen is significant (duration 38 months)
- Does TB play a role?

Can we agree that?

- Failing multiclass therapy, not NRTI bridging regimens is the most important driver of resistance
  - Bridging regimens for children on an NNRTI will not compromise second line therapy with a PI
  - NRTI bridging regimens will not compromise 3dr line therapy
  - "Blindly" **continuing PI** in patients who are failing **DOES** place 3dr line at risk

Not being on ART is always catastrophic

CHER Children <12 weeks

- All infants should start ART
- Disease progression and Death
- Even children on early ART

	<25%	<1000	<25%	<1000
	AIDS		Death	
1	16	23	4.5	6.6
2	8.8	9.4	2	1.7
3	6	5.1	1.2	0.6

PREDICT - Children 3-10 years

- No difference in AIDS free survival
- No difference in CNS outcomes
- Growth and CD4 recovery may be better in early ART

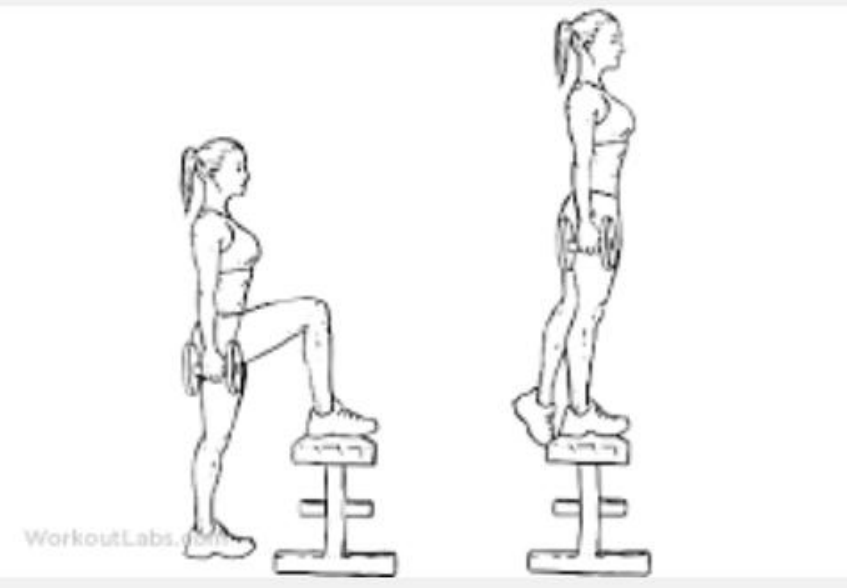
START

Cause	Imm. ART	Def. ART
Accident/violence/suicide	4	6
AIDS, active disease	1	4
Cardiovascular disease	3	1
Non-AIDS cancer -HBV/HCV	1	1
Substance abuse	0	2
Other*	0	4
Unknown	3	3
Total	12	21

155 people to treat for a year to prevent 1 event

Providing ART with step up adherence is the answer

- Providing ART DOES NOT ensure retention in care
- Good evidence from the pMTCT program
- Good cohort data out dide of research setting
- We are providing care



- "Retention of Option Bplus women lower than retention of other adults starting ART in Zimbabwe, it was similar in Malawi. poorer retention in younger women in both countries" Di Gibb

What is the real question

- What do we do with babies
- Should we be using 3TC or ABC/3TC/AZT
- Should we use IPT while on holding regimen
- What measures must we put in place to ensure success of future therapy
- When should we restart potentially suppressive therapy
  - CD4
  - VL
  - Can we develop robust supportive strategies to ensure success of 3dr line patients
- When should we get the resistance test
- How do we communicate
- Should viral load be part of the follow-up monitoring

Thank you