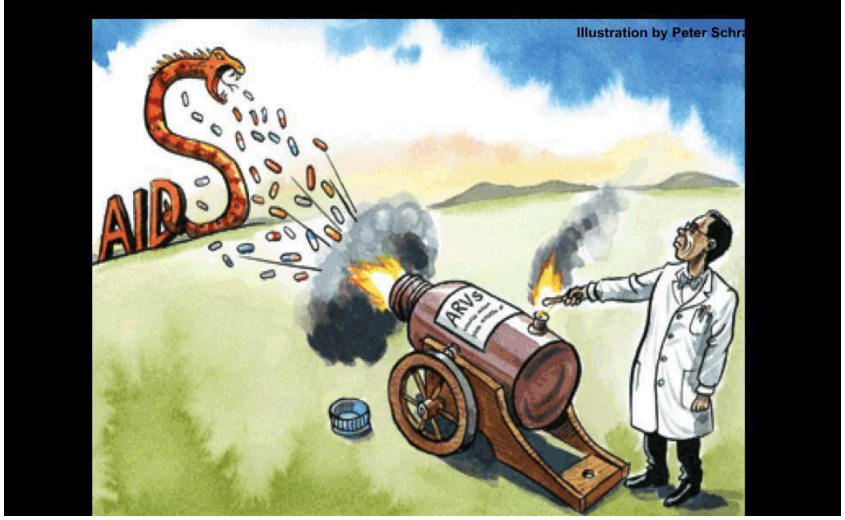


Is current first line ART good enough?

Francois Venter

Wits Reproductive Health & HIV Research Institute

Results: by April 2011

Budget: $3.5 billion

50% ARV price reduction

MTCT reduced to <5%

80% of 3,686 health facilities providing ARVs

10,542 nurses trained

Initiated on ARVs:
400,000
57,000 pregnant women
Total: 1,7 million on ART

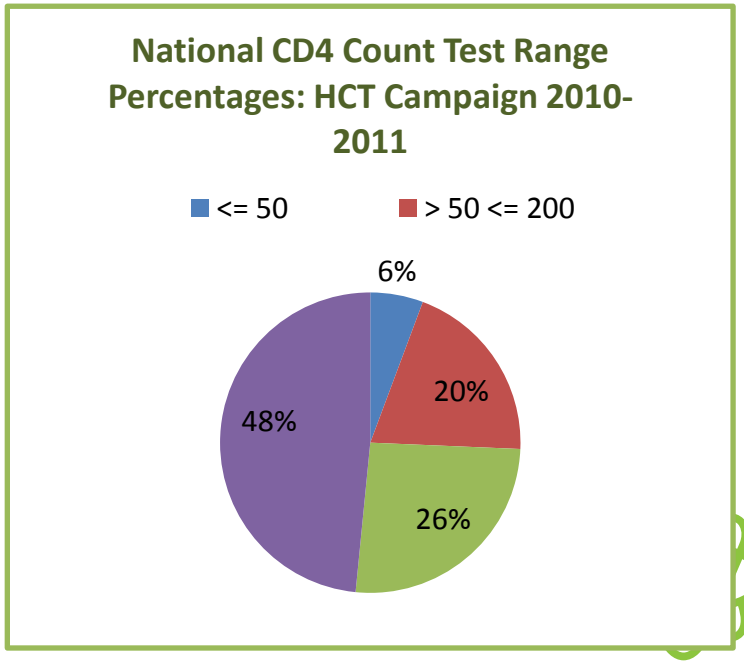
CD4 tests:
48% had counts over 350

HIV positive:
2,155,312
(16%)

Tested:
13,269,746
people

Counselled:
15,018,720
people

Wellness Screening	Condoms	Circumcision (MMC)
• TB- 8 million • HB • Cholesterol • BP	• 524,000 Female condoms • 185 million male condoms	• 237,000 males circumcised



Results: by April 2011

Now 2.5 million!

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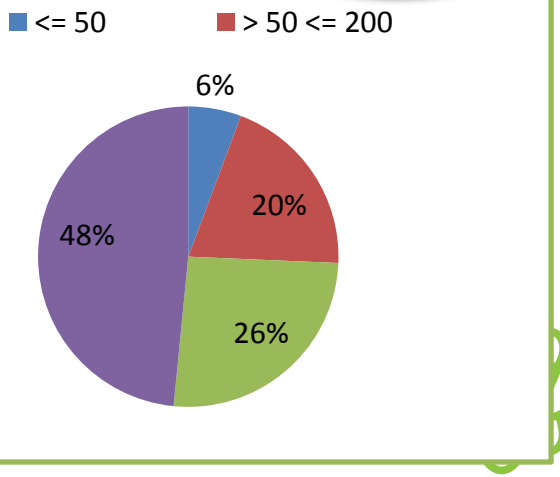
National CD4 Count Test Range Percentages: HCT Campaign 2010-2011



New WHO guidelines

- PMTCT/ paeds/ new drug options/ monitoring/ discordants/ diseases – NOT controversial
- CD4<500 – controversy – for individual benefit, and for public health

Evolution of WHO ART Guidelines in Adults

Topic	2002	2003	2006	2010	2013
When to start	CD4 ≤200	CD4 ≤ 200	CD4 ≤ 200 - Consider 350 - CD4 ≤ 350 for TB	CD4 ≤ 350 -Irrespective CD4 for TB and HBV	**CD4 ≤ 500** -Irrespective CD4 for TB, HBV, PW and SDC CD4 ≤ 350 as priority
1st Line	8 options - AZT preferred	4 options - AZT preferred	8 options - AZT or TDFpreferred - d4T dose reduction	6 options &FDCs - AZT or TDF preferred - d4T phase out	2 options & FDCs - TDF and EFV preferred across all populations
2nd Line	Boosted and non-boosted PIs	Boosted PIs -IDV/r LPV/r, SQV/r	Boosted PI - ATV/r, DRV/r, FPV/r LPV/r, SQV/r	Boosted PI - Heat stable FDC: ATV/r, LPV/r	Boosted PI Heat stable FDC: ATV/r, LPV/r
3rd Line	None	None	None	DRV/r, RAL, ETV	DRV/r, RAL, ETV
Viral Load Testing	No	No (Desirable)	Yes (Tertiary centers)	Yes (Phase in approach)	Yes (preferred for monitoring, use of PoC, DBS)

Earlier initiation

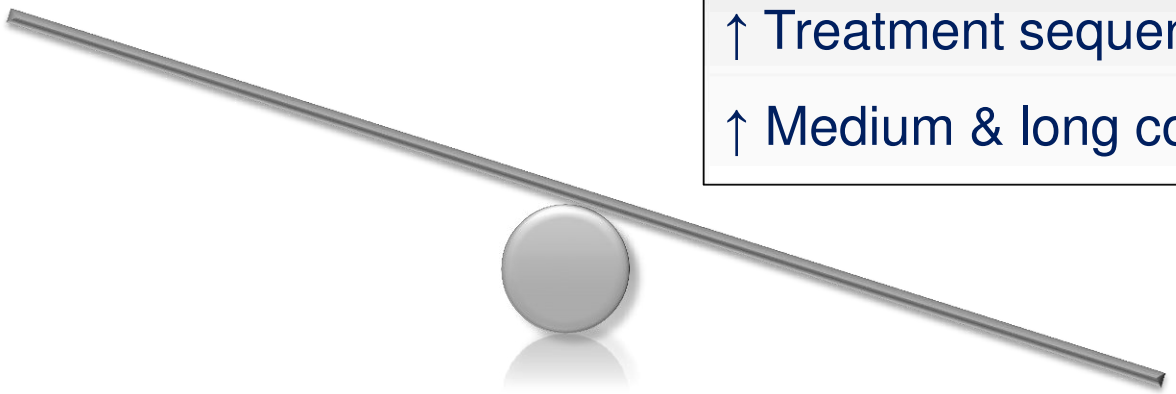
Simpler treatment

Less toxic, more robust regimens

Better monitoring

Balance of Evidence, Feasibility and Cost-Benefit Analysis Favors Earlier Initiation of ART

Delayed ART	Earlier ART
↓ Drug toxicity	↑ Clinical benefits (HIV- and non-HIV related)
↓ Resistance	↓ HIV and TB transmission
↓ Upfront costs	↑ Potency, durability, tolerability
Preservation of Tx options	↑ Treatment sequencing options
	↑ Medium & long cost savings



So what we got?

- Fixed dose combination

Tenofovir

XTC

Efavirenz

Benefits (1)

- A number of FDCs available – makes dispensing easier
- ?1st data that single tablet/day helps adherence

difference. Multivariate analyses found that STR led to a 23% reduction in hospitalisations and a 17% reduction in overall healthcare costs. ART adherence appears to be a key mechanism mediating hospitalisation risk, as patients with ≥95% adherence (regardless of regimen type) had a lower hospitalisation rate compared with <95% adherence.

Open Access Research

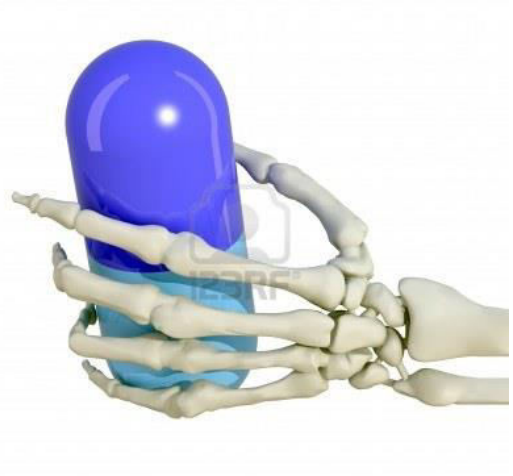
BMJ open

Association between daily antiretroviral pill burden and treatment adherence, hospitalisation risk, and other healthcare utilisation and costs in a US medicaid population with HIV

Cohen CJ, Meyers JL, Davis KL. *BMJ Open* 2013;**3**:e003028. doi:10.1136/bmjopen-2013-003028

Benefits (2)

- >10 years experience, millions of patients, millions of patient ‘years’, very well tolerated
- EFV side effects predictable, treatable, substitutions easy
- Do we chance on new drugs?



Benefits (3)

- Anti-tuberculous, other OI drug ‘friendly’
- And treats hepatitis B for free
- A5221 STRIDE study – EFV levels high on TB Rx!

Benefits (4)

- Everyone pretty happy re teratogenicity

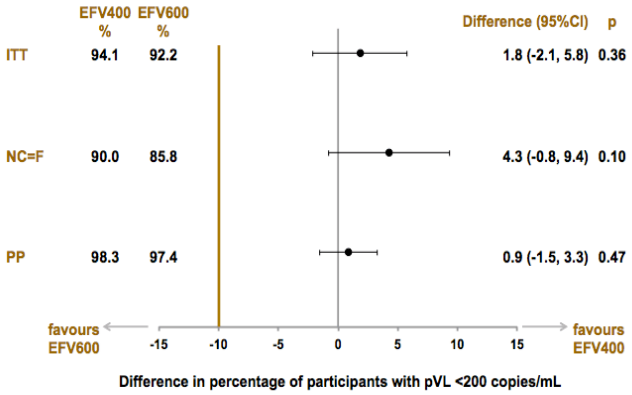
And it may get better!

- ENCORE – compared efavirenz 400mg to 600mg, equal efficacy, less side effects
- Slight cost drop, big reduction in side effects
- Will it work with TB?
- EFV and RIF–based tuberculosis therapy coadministration was associated with a trend toward higher, not lower, EFV Cmin compared to EFV alone (Luetkemeyer AF, CID, 2013)

Baseline characteristics

Characteristic	EFV 400mg N=321	EFV 600mg N=309	Total N=630
Male, n (%)	221 (68.8)	206 (66.5)	427 (67.7)
Mean age in years (SD)	36.1 (10.0)	35.8 (10.0)	36.0 (10.0)
Ethnicity, n (%)			
African	118 (36.8)	116 (37.4)	234 (37.1)
Asian	106 (33.0)	103 (33.2)	209 (33.1)
Caucasian	97 (30.2)	90 (29.0)	187 (29.6)
Aboriginal Australian	0 (0.0)	1 (0.3)	1 (0.2)
CDC category A, n (%)	264 (82.2)	265 (85.8)	529 (84.0)
Median pVL in log_{10} copies/mL (IQR)	4.76 (0.84)	4.73 (0.90)	4.75 (0.88)
pVL copies/mL, n (%)			
<100,000	214 (66.7)	202 (64.4)	416 (66.0)
≥100,000	107 (33.3)	107 (34.6)	214 (34.0)
Mean CD4+ T cells/µL (SD)	273 (97)	272 (101)	273 (99)
100 < CD4+ T cells/µL ≤ 350, n (%)	244 (76)	224 (72)	468 (74)

Primary endpoint: non inferiority at week 48



Newer drugs add little

- Etravirine – doesn't address CNS side effects
- Rilpivarine?

A randomized crossover study to compare efavirenz and etravirine treatment

Alain Nguyen[a], Alexandra Calmy[a], Cécile Delhumeau[a], Isabelle K. Mercier[a], Matthias Cavassini[b], Aurélie Fayet-Mello[b], Luigia Elzi[c], Daniel Genné[d], Andri Rauch[e], Enos Bernasconi[f], Bernard Hirschel[a] and the Swiss HIV Cohort Study*

AIDS 2010, Vol 24

Newer drugs add little: Integrase inhibitors, CCR-5 blockers

- Raltegravir – not co-formulated, BD dosing, TB data less robust (although data on all these forthcoming and promising)
- Elvitigravir – needs boosting
- SAILING/SPRING study – dolutegravir may be better
- Maraviroc? – don't bet on it…

IAS 2013
KUALA LUMPUR
MALAYSIA
30 June – 3 July

RHI

What about TAF?

- Tenofovir ‘prodrug’
- Exciting – less bone/renal effects
- But what is Gilead up to? Co-formulating with its internal products – will we get TAF?

Other alternative to TDF?

- Abacavir – expensive, also low side effect
- Low dose d4T? Results only here in 2016, benefit is likely to be cost
- Low dose AZT? Only being talked about

What's not to like????

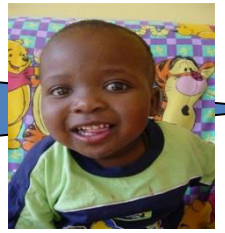
- Resistance barrier – only alternative is a (toxic) PI, or etravirine; anyway, >90% suppress
- ??dolutegravir

Vision… chronic care for HIV with any CD4 count!

Minimal hospitalisation

Diagnosis and staging, good primary care that suits patients

Good ARV access



CD4

prevention

8 to 10 years

40 years

Conclusion

- What are we trying to ‘fix’? Current FDCTDF/XTC/EFV is very safe, very robust, lower dose EFV may make better
- Maybe a little more of a resistance barrier? A tiny reduction in side effects?
- New drugs are a while away… especially in FDC form, and will add little