Is current first line ART good enough?

Francois Venter
Wits Reproductive Health & HIV Research Institute
Results: by April 2011

Budget: $3.5 billion

Counselled: 15,018,720 people

Tested: 13,269,746 people

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

CD4 tests: 48% had counts over 350

Initiated on ARVs: 400,000
57,000 pregnant women
Total: 1.7 million on ART

Wellness Screening
- TB: 8 million
- HB
- Cholesterol
- BP

Condoms
- 524,000 Female condoms
- 185 million male condoms

Circumcision (MMC)
- 237,000 males circumcised

80% of 3,686 health facilities providing ARVs

10,542 nurses trained

MTCT reduced to <5%

50% ARV price reduction

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

- <= 50: 6%
- > 50 <= 200: 48%
- > 200: 26%
- > 200: 20%
Results: by April 2011

Counselled: 15,018,720 people

Tested: 13,269,746 people

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

CD4 tests: 48% had counts over 350

Initiated on ARVs: 400,000

57,000 pregnant women

Total: 1.7 million on ART

Budget: $3.5 billion

50% ARV price reduction

MTCT reduced to <5%

10,542 nurses trained

80% of 3,686 health facilities providing ARVs

Condoms
- 524,000 Female condoms
- 185 million male condoms

Wellness Screening
- TB - 8 million
- HB
- Cholesterol
- BP

Circumcision (MMC)
- 237,000 males circumcised

MTCT reduced to <5%

Now 2.5 million!
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

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>When to start</td>
<td>CD4 ≤ 200</td>
<td>CD4 ≤ 200</td>
<td>CD4 ≤ 200 - Consider 350</td>
<td>CD4 ≤ 350 - Irrespective CD4 for TB</td>
<td>CD4 ≤ 500 - Irrespective CD4 for TB, HPV, PW and SDC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CD4 ≤ 350 for TB</td>
<td>CD4 ≤ 350 - Irrespective CD4 for TB and HBV</td>
<td></td>
</tr>
<tr>
<td>1st Line</td>
<td>8 options</td>
<td>4 options</td>
<td>8 options</td>
<td>6 options &amp; FDCs</td>
<td>2 options &amp; FDCs</td>
</tr>
<tr>
<td></td>
<td>- AZT preferred</td>
<td>- AZT preferred</td>
<td>- AZT or TDF preferred</td>
<td>- AZT or TDF preferred</td>
<td>- TDF and EFV preferred</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- d4T dose reduction</td>
<td>- d4T phase out</td>
<td>preferred across all populations</td>
</tr>
<tr>
<td>2nd Line</td>
<td>Boosted and non-boosted PIs</td>
<td>Boosted PIs</td>
<td>Boosted PI</td>
<td>Boosted PI</td>
<td>Boosted PI</td>
</tr>
<tr>
<td>3rd Line</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>DRV/r, RAL, ETV</td>
<td>DRV/r, RAL, ETV</td>
</tr>
<tr>
<td>Viral Load Testing</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>(Desirable)</td>
<td>(Desirable)</td>
<td>(Tertiary centers)</td>
<td>(Phase in approach)</td>
<td>(Preferred for monitoring, use of PoC, DBS)</td>
</tr>
</tbody>
</table>

- 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

- ↓ Drug toxicity
- ↓ Resistance
- ↓ Upfront costs
- Preservation of Tx options

Earlier ART

- ↑ Clinical benefits (HIV- and non-HIV related)
- ↓ HIV and TB transmission
- ↑ Potency, durability, tolerability
- ↑ Treatment sequencing options
- ↑ Medium & long cost savings

2013 WHO consolidated Guidelines
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

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 $\geq 95\%$ adherence (regardless of regimen type) had a lower hospitalisation rate compared with $< 95\%$ adherence.
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)
Newer drugs add little

- Etravirine – doesn’t address CNS side effects
- Rilpivirine?

A randomized crossover study to compare efavirenz and etravirine treatment

Alain Nguyen⁹, Alexandra Calmy⁹, Cécile Delhumeau⁹, Isabelle K. Mercier⁹, Matthias Cavassini⁹, Aurélie Fayet-Mello⁹, Luigia Elzi⁹, Daniel Genné⁹, Andri Rauch⁹, Enos Bernasconi⁹, Bernard Hirschel⁹ and the Swiss HIV Cohort Study*
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...
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!

Diagnosis and staging, good primary care that suits patients

Good ARV access

Minimal hospitalisation

CD4

8 to 10 years

40 years

prevention
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