SHOULD A TRIAL EVALUATING THE USE OF LOW DOSE STAVUDINE BE CONDUCTED?

ETHICAL, CLINICAL AND COMMUNITY CONSIDERATIONS

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MSF South Africa
We loved each other so much

- No monitoring required in first 6 month: a dream pill <> AZT
  ...until after 9 months on Rx
ARV with potential for dose optimization: equivalent efficacy with improved safety profile and lower costs

<table>
<thead>
<tr>
<th>ARV</th>
<th>Current dose</th>
<th>Potential optimised dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT</td>
<td>300mg BID</td>
<td>200 mg BID</td>
</tr>
<tr>
<td>3TC</td>
<td>300 mg OD</td>
<td>150 mg OD</td>
</tr>
<tr>
<td>d4T</td>
<td>30 mg BID</td>
<td>20 mg BID</td>
</tr>
<tr>
<td>EFV</td>
<td>600 mg OD</td>
<td>400 mg OD</td>
</tr>
<tr>
<td>LPV/r</td>
<td>400/100 mg BID</td>
<td>200/100 or 200/150 mg BID</td>
</tr>
<tr>
<td>ATV/r</td>
<td>300/100 mg OD</td>
<td>300/50 or 200/50 mg OD</td>
</tr>
<tr>
<td>DRV/r</td>
<td>600/100 BID</td>
<td>400/50 mg OD</td>
</tr>
<tr>
<td>RTV</td>
<td>100 mg (booster)</td>
<td>50 mg (booster)</td>
</tr>
<tr>
<td>RAL</td>
<td>400 mg BID</td>
<td>100-200 mg BID</td>
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</tbody>
</table>

Adapted from Andrew Hill, 2009
Reduced referral and case fatality rates for severe hyperlactataemia following preventive interventions in South African public sector antiretroviral programme. Charlotte Schutz, Dave Stead, Kevin Rebe, Meg Osler, Andrew Boulle, Graeme Meintjes

Initial outcomes for D4T 30 mg dose reduction

Toxicity Associated with Stavudine Dose Reduction from 40 to 30 mg in First-Line Antiretroviral Therapy

Mar Pujades-Rodríguez, Emmanuelle Dantony, Loretxu Pinoges, René Ecochard, Jean-François Etard, Esther Carrillo-Casas, Elisabeth Szumilin, for the AIDS Working Group of Médecins Sans Frontières
Non inferiority limited to virological endpoint? Side effects and co-infections

- **Risk of death**: patients receiving d4T were 60% more likely to die than those on TDF over the first year on treatment (SA study, 2005-2011)*

- **Toxicity-driven regimen switch**: risk of a for D4T30 mg was almost six times higher than TDF, MSF, Lesotho cohort **

- **HBV**: ~ 5% of HIV-positive HBV co-infected with HBV (SA)
  - De facto 3TC sole active agent: resistance up to 90% at five years***

- **HIV-TB**: A South African study* found that people on TB treatment had a much increased risk of toxicity that led to them having to switch from D4T to another drug, irrespective of whether 30mg or 40mg doses were used****

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Regimen sequencing: advantages to initiate with TDF compared with D4T initiation

Expected NRTIs sensitivity spectrum after 2 years of treatment if virological failure HIV-1

<table>
<thead>
<tr>
<th>Cross Resistance</th>
<th>AZT (Zidovudine)</th>
<th>d4T (Stavudine)</th>
<th>TDF (Tenofovir)</th>
<th>ABC (Abacavir)</th>
<th>ddl (Didanosine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td>d4T</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td>TDF</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td>ABC</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td>ddl</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
</tbody>
</table>
Any chance for stavudine 20mg to be hardly toxic?

- **BMS study**: D4T 30 and 40mg vs. D4T 20 and 15mg (early 1990s): peripheral neuropathy: 21% <> 15%

- **Mitochondrial DNA quantification study**:
  - TDF <> 20-30 mg D4T:
  - 29% and 32% decrease mtDNA copies/cell standard-dose (30–40 mg) ($P < 0.05$) and low-dose stavudine (20–30 mg) ($P < 0.005$) arms, respectively, when compared with TDF at 4 weeks.

D4T in Children

- Stavudine -> Abacavir in 12.6% of children at 3 years (N=2222)

*Palmer, Megan; Chersich, Matthew; Moultrie, Harry, et al. Frequency of stavudine substitution due to toxicity in children receiving antiretroviral treatment in Soweto, South Africa. J AIDS. 2012. doi: 10.1097/QAD.0b013e32835c54b8
Ethics: opening a double standard door?

- Removed as recommended first-line antiretroviral drug by the US DHHS (2004) and WHO (2009)

- **2011: European Medicines Agency (EMA)** “use of the medicine should be severely restricted in both adults and children... should only use the medicine when other appropriate treatments are not available”

- SA: 40% of people on ART are still on D4T (NDOH)

2010

c.9,000 patients treated with d4T across Europe

2011

>1.2 million people on d4T in LMIC
## Programmatic: Stavudine (d4T) phasing out agenda

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<tbody>
<tr>
<td>South Africa</td>
<td>TDF</td>
<td>82%</td>
<td>66%</td>
<td>↓ 20%</td>
<td>Feb 2010</td>
<td>NA</td>
</tr>
<tr>
<td>Mozambique</td>
<td>AZT</td>
<td>78%</td>
<td>7%</td>
<td>↓ 91%</td>
<td>March 2010</td>
<td>2011</td>
</tr>
<tr>
<td>Tanzania</td>
<td>TDF</td>
<td>72%</td>
<td>63%</td>
<td>↓ 12%</td>
<td>Jan 2011</td>
<td>2015</td>
</tr>
<tr>
<td>Uganda</td>
<td>TDF</td>
<td>18%</td>
<td>3%</td>
<td>↓ 83%</td>
<td>2009</td>
<td>2010</td>
</tr>
<tr>
<td>Kenya</td>
<td>TDF</td>
<td>68%</td>
<td>54%</td>
<td>↓ 21%</td>
<td>Feb 2010</td>
<td>2013-2015</td>
</tr>
<tr>
<td>Cameroon</td>
<td>AZT or TDF</td>
<td>63%</td>
<td>57%</td>
<td>↓ 10%</td>
<td>Jun 2010</td>
<td>2015</td>
</tr>
</tbody>
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WHO, 2011 (preliminary data)
Zimbabwe: phasing out D4T
Summary % Regimen Breakdown for 1st line existing patients

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</thead>
<tbody>
<tr>
<td>Adult TDF</td>
<td></td>
<td>32%</td>
<td>45%</td>
<td>54%</td>
<td>60%</td>
<td>64%</td>
<td>64%</td>
</tr>
<tr>
<td>Adult D4T</td>
<td></td>
<td>60%</td>
<td>50%</td>
<td>42%</td>
<td>36%</td>
<td>33%</td>
<td>33%</td>
</tr>
<tr>
<td>Adult AZT</td>
<td></td>
<td>8%</td>
<td>5%</td>
<td>4%</td>
<td>4%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Paeds AZT</td>
<td></td>
<td>93%</td>
<td>93%</td>
<td>92%</td>
<td>92%</td>
<td>92%</td>
<td>92%</td>
</tr>
<tr>
<td>Paeds D4T</td>
<td></td>
<td>7%</td>
<td>7%</td>
<td>8%</td>
<td>8%</td>
<td>8%</td>
<td>8%</td>
</tr>
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Programmatic issues

- Greater frequency of regimen switches

- Suboptimal adherence & resistance: study in Nigeria showed that 70% of the patients on TDF based regimens had less resistance compared to D4T regimens*

- FDC, one pill once a day) -> long term community based approached

Financial savings: shortsighted?

- TDF decreased in price—now cheaper than AZT $76
- EFV: US$97 ppy (2009) -> to $52 today)
- **GS 7340** (TDF pro-drug): API volume of active pharmaceutical ingredient for tenofovir down by 5/6 might allow a lowest global price of $20 or less — lower than the putative 20 mg stavudine price of $25.
- FDC of TDF-3TC-EFV decreased by 53% to US$173 per person per year over same period.
Patient VS budget centred cost-effectiveness

Will we end up cutting pills in two?

Facility costs in Malawi are lower than average in all three major cost categories: ARVs and personnel drive ~70% of total cost. Despite low costs, retention rates at 12 months are high.

ARV costs in Malawi will increase as the phased uptake of TDF continues. Likewise, lab costs will increase as VI scales up.

* ARV prices in SSA have decreased by 53% since 2004, from $7000 to $3064 papy.

Courtesy Clinton Health Foundation
Conclusions

1. 96 weeks endpoint non inferiority study will not tell us more than what we learned from years of 30 mg dose reduction
2. …while might create false expectations
3. D4T 20 mg would not make any substantial saving, potentially cost more than TDF pro-drug regimen
4. Study design is ill adapted

- Time frame: 96 weeks is too short
- Limited endpoints: efficacy <> effectiveness
- Potential space for re-designing with D4T experienced patients? Would potentially SAVE d4T from the dustbin of ART history!
Acknowledgements

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