The Future in HIV treatment in South Africa

Dr Francesca Conradie
President of the Southern African HIV Clinicians Society
• The big picture
  – Test and Treat

• The patient level
  – New compounds
  – New Formulations
“Test & Treat / offer” vs other biological prevention

90% of all living with HIV will know their HIV status

90% of all living with HIV will receive sustained antiretroviral therapy

90% of all receiving antiretroviral therapy will have durable viral suppression
ART coverage significantly decreased individual risk, KwaZulu Natal, South Africa (2004-11)

- Africa Centre longitudinal surveillance cohort with community and individual data
- Between 2004 and 2011, 1395 HIV seroconversions and over 53,042 person-years of observation (crude HIV incidence rate of 2.63 (95% C.I. 2.50 to 2.77) per 100 person-years

Every % point increase in ART coverage among all HIV+ adults in a community, was associated with a 1.7% decline in the hazard of HIV acquisition ($p < 0.001$)
Changing disease severity over time

Adjusted proportion of patients started ART by CD4 category

Source: Consolidated National report covering monthly and quarterly ART data to end March 2014

Thanks: Andrew Boulle
Test and Treat/ offer

Guideline on When to Start Antiretroviral Therapy and on Pre-exposure Prophylaxis for HIV

September 2015
### Recommendation 1: When to start ART among people living with HIV

<table>
<thead>
<tr>
<th>Target population</th>
<th>Specific recommendation</th>
<th>Strength of the recommendation</th>
<th>Quality of the evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults* (&gt;19 years)</td>
<td>ART should be initiated in all adults living with HIV at any CD4 cell count</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>As a priority, ART should be initiated in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤350 cells/mm³</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>Pregnant and breastfeeding women</td>
<td>ART should be initiated in all pregnant and breastfeeding women living with HIV at any CD4 cell count and continued lifelong</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>Adolescents (10–19 years old)</td>
<td>ART should be initiated in all adolescents living with HIV at any CD4 cell count</td>
<td>Conditional</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>As a priority, ART should be initiated in all adolescents with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤350 cells/mm³</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>Children (1 to &lt;10 years old)</td>
<td>ART should be initiated in all children 1 to &lt;10 years old living with HIV at any CD4 cell count</td>
<td>Conditional</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>As a priority, ART should be initiated among all children &lt;2 years old and those with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4% &lt;25% (if &lt;5 years old) or CD4 count ≤350 cells/mm³ (if ≥5 years old)</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>Children (&lt;1 year old)</td>
<td>ART should be initiated in all children living with HIV younger than 1 year old at any CD4 cell count</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
Fig. 1. Uptake of WHO policy on the threshold for initiating ART among adults and adolescents living with HIV in low- and middle-income countries, 2014
Overview of when to start ART studies

1995-2005

Several ACTG and CPCRA studies (early Post HAART Era): ART initiation CD4 < 200 cells/mm³ - Impact on AIDS mortality and major OIs incidence

2005-2010

Recent observational studies (ART initiation at CD4 > 350 cells/mm³) impact on mortality, disease progression and incidence of non-AIDS events (chronic inflammation)

2010-2013

Early ART trials (START and TEMPRANO): initiation of cART at CD4 count >500 vs. <350 cells/mm³

2015-2016

HPTN 052: reduction of HIV transmission among HIV serodiscordant couples and risk of TB in adults. (impact on HIV incidence)

CIPRA and SMART studies (ART initiation at CD4 ≤ 350) Impact on HIV mortality, disease progression, and co-morbidities (tuberculosis)
New data from Temprano

<table>
<thead>
<tr>
<th>Severe morbidity</th>
<th>N</th>
<th>TAR (PY)</th>
<th>Rate (/100PY)</th>
<th>AHR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHOART</td>
<td>111</td>
<td>2,247</td>
<td>4.94</td>
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</tr>
<tr>
<td>EarlyART</td>
<td>64</td>
<td>2,310</td>
<td>2.77</td>
<td>0.56</td>
<td>(0.41 - 0.76)</td>
</tr>
<tr>
<td>No IPT</td>
<td>104</td>
<td>2,225</td>
<td>4.67</td>
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<tr>
<td>IPT</td>
<td>71</td>
<td>2,332</td>
<td>3.04</td>
<td>0.65</td>
<td>(0.48 - 0.88)</td>
</tr>
<tr>
<td>Baseline CD4 &gt;500/ul</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHOART</td>
<td>38</td>
<td>918</td>
<td>4.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EarlyART</td>
<td>23</td>
<td>964</td>
<td>2.39</td>
<td>0.56</td>
<td>(0.33 - 0.93)</td>
</tr>
<tr>
<td>No IPT</td>
<td>37</td>
<td>918</td>
<td>4.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPT</td>
<td>24</td>
<td>965</td>
<td>2.49</td>
<td>0.61</td>
<td>(0.37 - 1.02)</td>
</tr>
</tbody>
</table>

N: number of events. PY: person-years; TAR: time at risk; AHR: adjusted hazard ratio; CI: confidence interval
START: Immediate vs Deferred ART

- International, randomized phase IV study
  - 215 sites in 35 countries
  - Randomized 1:1
    - ART-naive adults with CD4+ cell count > 500 cells/mm³ (N = 4685)
    - Immediate ART*
      - 41
    - Delayed ART* (until CD4+ cell count ≤ 350 cells/mm³)
      - 86
  - Interim results: serious AIDS and non-AIDS events, n

*Any licensed ART allowed, according to national guidelines.

- Study stopped by data and safety monitoring board following results of interim analysis
  - Risk of serious illness or death reduced by 53% with immediate ART
  - Rates of serious AIDS-related and non–AIDS-related events lower in immediate ART arm

When to Start Therapy: Balance Now Favors Early ART

- Drug toxicity
- Preservation of limited Rx options
- Risk of resistance (and transmission of resistant virus)

- ↑ potency, durability, simplicity, safety of current regimens
- ↓ emergence of resistance
- ↓ toxicity with earlier therapy
- ↑ subsequent treatment options
- Risk of uncontrolled viremia at all CD4 levels
- ↓ transmission

Delayed ART

Early ART
Key to successful antiretroviral therapy?

• Adherence
• Adherence
• Adherence
• Adherence
• Adherence
• Adherence
• Detection of toxicity
Definition of Adherence

The extent to which a person’s behavior ... coincides with medical or health advice.

-- Haynes, 1979

Definition of Non-Adherence

Non-Adherence is present when the actual treatment a subject receives is different from the nominal (intended) assignment
Medication Adherence

The process, over time, by which patients take their medications as prescribed

1. Initiate
   - Patient does not initiate treatment
     - Binary (Yes/No)

2. Implement
   - Patient delays, omits, or takes extra doses
     - Dosing History

3. Persist
   - Patient discontinues treatment
     - Time to event

Time
Predictors of Medication Adherence

1. Initiate
   - Patient’s lack of insight into the illness
   - Patient’s lack of belief in benefit of treatment
   - Patient’s concerns about medication
   - Poor provider-patient relationship
   - Presence of psychological problems (depression)
   - Inadequate follow-up or discharge planning
   - Cost of medication

2. Implement
   - Presence of cognitive impairment
   - Complexity of treatment
   - Alcohol abuse
   - Family disorganisation
   - Unability to build Medication Taking Habits

3. Persist
   - Missed appointments
   - Previous behavior & experiences
   - Patient’s lack of insight into the illness
   - Patient’s lack of belief in benefit of treatment
   - Patient’s concerns about medication
   - Poor provider-patient relationship
   - Presence of psychological problems (depression)
   - Inadequate follow-up or discharge planning
   - Cost of medication

Changes over time

Clinical outcomes & side effects

Osterberg & Blaschke, 2005, NEJM
Key to successful antiretroviral therapy?

• Perfect patient

And

• Perfect health care system
Data on patient adherence in South Africa

Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007–2009: systematic review

Matthew P. Fox1,2,3 and Sydney Rosen1,2,3

1 Center for Global Health and Development, Boston University, Boston MA, USA
2 Health Economics and Epidemiology Research Office, Wits Health Consortium, Johannesburg, South Africa
3 Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
Strategies to improve patient retention on antiretroviral therapy in sub-Saharan Africa

Anthony D Harries,1,2 Rony Zachariah,3 Stephen D Lawn,2,4 and Sydney Rosen5,6

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• the need for simple and standardized monitoring systems to track what is happening,
• reliable ascertainment of true outcomes of patients lost to follow-up,
• implementation of measures to reduce early mortality in patients both before and during ART,
• **ensuring uninterrupted drug supplies**, 
• consideration of simple, non-toxic ART regimens,
• decentralization of ART care to health centres and the community,
• a reduction in indirect costs for patients particularly in relation to transport to and from clinics,
• strengthening links within and between health services and the community,
• the use of ART clinics to deliver other beneficial patient or family-orientated packages of care such as insecticide-treated bed nets, and
• innovative (thinking ‘out of the box’) interventions. High levels of retention on ART are vital for individual patients, for credibility of programmes and for on-going resource and financial support.
Structural barriers to antiretroviral treatment

• Poverty-related,
  – competing demands in the context of resource-constrained settings,
  – the lack of transport infrastructure,
  – food insecurity,
  – the role of disability grants and poor social support

• Institutional
  – overburdened health care facilities,
  – limited access to mental health services
  – difficulties in ensuring adequate counselling.

  – Political and cultural barriers
    controversies in the provision of treatment for AIDS,
    migration, traditional beliefs about HIV and AIDS,
    poor health literacy gender inequalities.
Need for novel approaches to support adherence

• Never run out of meds
• Drop CD4+ beyond diagnosis
• Alternate delivery methods
  – MSF adherence clubs
  – Pharmacy dispensing unit
  – Private pharmacy
  – Home Delivery
Costs of test and treat?

• Can we afford it?
The patient level

<table>
<thead>
<tr>
<th></th>
<th>INSTIs</th>
<th>NRTIs</th>
<th>PI(s)</th>
<th>NNRTIs</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved</td>
<td>Dolutegravir</td>
<td>TAF</td>
<td>DRVc</td>
<td>Doravirine (MK1349) RPV-LA</td>
<td>TAF/FTC/EVGc Cenicriviroc BMS663068</td>
</tr>
<tr>
<td>Phase 3</td>
<td>GSK126744</td>
<td>Racivir</td>
<td>Amodoxovir Elvucitabine</td>
<td>ABC/3TC/DTG TAF/FTC/DRVc</td>
<td></td>
</tr>
<tr>
<td>Phase 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
New Drugs

New fixed dose combinations (FDCs)

• dolutegravir/abacavir/lamivudine (DTG/ABC/3TC)
• elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate (EVG/COBI/FTC/TAF)
• darunavir (DRV)/cobicistat/ FTC/TAF
• TAF/3TC, cenicriviroc/3TC
• dolutegravir/rilpivirine
• Once daily regimen of raltegravir (RAL)
Five compounds are in phase II including

- Doravirine (NNRTI)
- BMS-663068,
- the long-acting injectables
  - S/GSK1265744LAP
  - rilpivirine-LA
  - PRO 140
• Head to head with EFV
**A** Proportion of Participants with HIV-1 RNA Level <50 Copies/ml

- DTG-ABC-3TC, 88%
- EFV-TDF-FTC, 81%

Difference in response at wk 48, 7 percentage points (95% CI, 2.1-12.5)  
P=0.003

**B** Change in CD4+ T-Cell Count

- DTG-ABC-3TC, 267 cells/mm³
- EFV-TDF-FTC, 208 cells/mm³

Difference in response at wk 48, 59 cells/mm³ (95% CI, 33-114)  
P<0.001
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>DTG-ABC-3TC</th>
<th>EFV-TDF-FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-Treat Population</td>
<td>364/414</td>
<td>338/419</td>
</tr>
<tr>
<td>Per-Protocol Population</td>
<td>362/403</td>
<td>335/412</td>
</tr>
<tr>
<td>Baseline HIV-1 RNA ≤100,000 Copies/ml</td>
<td>253/280</td>
<td>238/288</td>
</tr>
<tr>
<td>Baseline HIV-1 RNA &gt;100,000 Copies/ml</td>
<td>111/134</td>
<td>100/131</td>
</tr>
<tr>
<td>Baseline CD4+ T-cell count &gt;200 Cells/mm³</td>
<td>31.9/357</td>
<td>290/357</td>
</tr>
<tr>
<td>Baseline CD4+ T-cell count ≤200 Cells/mm³</td>
<td>45/57</td>
<td>48/62</td>
</tr>
<tr>
<td>Women</td>
<td>57/67</td>
<td>47/63</td>
</tr>
<tr>
<td>Men</td>
<td>307/347</td>
<td>291/356</td>
</tr>
<tr>
<td>Age &lt;50 Yr</td>
<td>31.9/361</td>
<td>302/375</td>
</tr>
<tr>
<td>Age ≥50 Yr</td>
<td>45/53</td>
<td>36/44</td>
</tr>
<tr>
<td>White</td>
<td>255/284</td>
<td>238/285</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>109/130</td>
<td>99/133</td>
</tr>
</tbody>
</table>

Percent Difference between Groups (95% CI)

- EPV-TDF-FTC Better
- DTG-ABC-3TC Better
Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naive adults with HIV-1 infection (FLAMINGO): 96 week results from a randomised, open-label, phase 3b study

Jean-Michel Molina, Bonaventura Clotet, Jan van Lunen, Adriano Lazzarin, Maellies Cavassini, Keith Henry, Vitali Kulig, Naomi Giffens, Carlos Fernando de Oliveira, Clare Brennan, on behalf of the FLAMINGO study team

Figure 2: Proportion of patients with HIV-1 RNA less than 50 copies per mL by visit.
Analysed with Food and Drug Administration snapshot algorithm. Error bars are 95% CIs.
Challenges with Dolutegravir in South Africa

- Not yet registered
- Interactions with TB treatment
Conclusions

• While there are new ART regimens available and soon to be available, we need to see the big picture.

• Find, and treat all HIV infected persons
Acknowledgments

• RHI: Michelle Moorhouse, Francois Venters, Vivian Black
• DoH: Yogan Pillay, Aaron Motsoaledi, Precious Matsotso, Zuki Panini