EDCTP Stake Holders Meeting

Treatment and care III
Implementation research.

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IDM and Medicine
University of Cape Town.
The pandemic historically:

- 3000 people died in the 9/11 World Trade Center disaster and on that same day in Africa, 6500 people died of AIDS - just like the day before, and the day after, and the day after that....
The pandemic historically:

- 3000 people died in the 9/11 World Trade Center disaster and on that same day in Africa, 6500 people died of AIDS—just like the day before, and the day after, and the day after that....
Cumulative survival curve for HIV-infected persons (without hepatitis C coinfection) and persons from the general population. Persons with HIV infection are divided into 3 calendar periods of observation. Dashed lines indicate 95% CIs. HIV = human immunodeficiency virus; HAART = highly active antiretroviral therapy.
Figure 3:

**Virological suppression by duration on treatment**

- **HIV RNA level under 400 copies/ml (%)**
  - 0: 94.8
  - 4: 93.6
  - 8: 94.3
  - 12: 93.0
  - 16: 93.2
  - 20: 95.7
  - 24: 93.1
  - 28: 97.5
  - 32: 97.5

- **HIV RNA level under 50 copies/ml (%)**
  - 0: 80.2
  - 4: 81.7
  - 8: 82.8
  - 12: 76.7
  - 16: 82.4
  - 20: 83.8
  - 24: 87.5
  - 28: 87.5
  - 32: 87.5

**Improvement in absolute CD4 cell count by duration on treatment**

- **Mean CD4 cell count (cells/mm³)**
  - 0: 84.4
  - 4: 88.0
  - 8: 89.0
  - 12: 97.5
  - 16: 97.5
  - 20: 97.5
  - 24: 97.5
  - 28: 97.5
  - 32: 97.5

- **CD4 cell count > 200 cells/ml (%)**
  - 0: 6.1
  - 4: 49.9
  - 8: 58.5
  - 12: 72.0
  - 16: 77.5
  - 20: 84.4
  - 24: 88.0
  - 28: 89.0
  - 32: 97.5
WHO/UNAIDS initiatives

- **3 by 5 in 2003**
  - 3 million on ART by 2005
  - Achieved this in 2007......
  - 400,000 people in December 2003 to 1.3 million in December 2005. This included an eight-fold increase in sub-Saharan Africa.

- **Eligibility:** <200,

- **2010:** <350 and stage 3 and 4.
Universal access and MDG 6 by 2015

• reduce new infections by 50 percent among young people (15-24 years),
• reduce TB-related mortality by 50 percent,
• eliminate new infections in children,
• and reduce HIV-related mortality.
A: TB Incidence by CD4 without HAART
B: TB Incidence by CD4 with HAART

A: Cape Town AIDS Cohort
B: Cape Town ART Cohort

R² = 0.9702

R² = 0.9643

B: Lawn, Myers, Edwards Bekker, Wood. AIDS 2009
CD4 Count Recovery of ART Cohort

Percentage of patients with CD4 below contour vs. Duration of ART (months)

- **1000 cells/ul**
- **500 cells/ul**
- **200 cells/ul**

**TB rates**:
- **TB rate 9.3-16.8**
- **TB rate >4.2-5.5**
- **TB rate = 1.5**
Antiretroviral therapy and TB incidence in Botswana


Source: Ministry of Health, Botswana.
Treatment expansion

• Treatment access expanded extensively, increasing by 63 percent between 2009 and 2011.

• Treatment reached 8 million people in 2011, the first time the number of people being treated for HIV exceeded the number of those who were eligible but going without.
Treatment coverage in low- and middle-income countries

Treatment vs need in South Africa

- Estimated number on treatment
- Estimated number in need of treatment
Causes of death in South Africa

- AIDS-related deaths
- Registered deaths (all causes)

Deaths (in thousands):

<table>
<thead>
<tr>
<th>Year</th>
<th>AIDS-related deaths</th>
<th>Registered deaths (all causes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>200,000</td>
<td>600,000</td>
</tr>
<tr>
<td>2002</td>
<td>250,000</td>
<td>650,000</td>
</tr>
<tr>
<td>2003</td>
<td>300,000</td>
<td>700,000</td>
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<tr>
<td>2004</td>
<td>350,000</td>
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<tr>
<td>2005</td>
<td>400,000</td>
<td>800,000</td>
</tr>
<tr>
<td>2006</td>
<td>450,000</td>
<td>850,000</td>
</tr>
<tr>
<td>2007</td>
<td>500,000</td>
<td>900,000</td>
</tr>
<tr>
<td>2008</td>
<td>550,000</td>
<td>950,000</td>
</tr>
<tr>
<td>2009</td>
<td>600,000</td>
<td>1,000,000</td>
</tr>
</tbody>
</table>
Antiretroviral therapy and mortality, Northwest Province, South Africa

Number of people ever receiving antiretroviral therapy and annual number of deaths by age group, Northwest Province, South Africa, 1997–2007.

Source: Ministry of Health, South Africa.
ART beyond the individual

Community
- Community infectiousness
- Community well being

Partner
- Safer conception
- status

Individual
- Wellbeing
- infectiousness
Eligibility: <500 CD4 Tcells with immediate ART for TB, pregnant women and discordant couples.

An estimated **17 million** people are eligible to take antiretroviral drugs, but under the new recommendations this number will increase to **26 million**.
LGB’s ingredients of scale up

• widespread awareness of the value of testing and subsequent treatment even in the face of few symptoms.
• life-long commitment to antiretroviral drugs (ARVs) and supporting patients to adhere to a daily regimen
• adequate health infrastructure including health staff resourcing
• sustainable and reliable supply chains of effective drugs
IOMs ingredients.....

- Immediately introduce and scale up ART programs in resource-poor settings.
- Devise strategies to ensure high levels of patient adherence to complicated treatment regimens.
- Rapidly address human-resource shortages to avoid the failure of program implementation.
- Continuously monitor and evaluate the programs to form the most effective guidelines and treatment regimens for each population.
- Prepare to sustain ART for decades.
Tension

- Consolidate gains
- Ensure quality
- Optimise at current level

- SCALE UP, SCALE UP, SCALE UP!!!
  - With promise of less morbidity and mortality
  - Reduced force of infection and decreased transmission
Note...earlier start (WHO)

- Not all observational studies have consistently demonstrated the beneficial impact of initiating ART earlier on mortality and the incidence of non-AIDS events associated with chronic inflammation and ongoing viral replication,
- longer follow-up is needed to evaluate potential harms and benefits.
- The long-term safety profile of ART and the implications of earlier initiation on drug resistance and toxicity will also need to be closely monitored.
- START and TEMPRANO are in the field.
Where are we??

• End of 2011 on 2010 guideline eligibility:
  • 54% coverage (8 million)
  • Range per region 15-68%
  • 9 LMIC with coverage >80%
  • 68 countries < 50% coverage
  • Median CD4 <350 in most settings incl high income
The Treatment Cascade

Unawares, tested but unlinked, Tested but now infected

Identify populations

TEST COUNSEL Support

Link

CD4

Pre-ART Retention Preparation

Link

ART Adherence Retention Return to care

Transfer out Recycle in care Default Fail 1st, 2nd line

Key populations: access to care, stigma, legal barriers,

CDU Adherence club

Community based care and support

CDU= chronic Dispensing Unit
Objective

Aware HIV+ 79%

Linked to care 60%

Viral Load suppressed 55%

100 HIV+ persons

Achieved

Not Achieved

Not Virally Suppressed

Overall: ~26% of HIV+ persons were in care and estimated to have a viral load <500 copies/ml
Adherence to any medication-consequences of ART non-adherence

Initiation
- Untreated positives
- Return to care when sick
- Increased morbidity/mortality infectious

Persistence
- Loss to follow up
- Cycling in care
- Risk of resistance
- Increased morbidity/mortality infectious

Performance
- Failure of 1st line
- Increased cost
- Increased toxicity/morbidity
- Increased resistance infectiousness
Situated IMBs model applied to ART

Adherence information
I know what taking HAART involves

Adherence motivation
Taking HAART will be good for me and it will ensure I stay healthy.

Adherence behavioural skills
I know how to take my medication correctly

Adherence Behaviour
- Proper dosing
- Optimal adherence
- Adherence levels over time

Moderating factors affecting adherence
- Psychological health
- Living situation
- Access to medical care services and insurance coverage
- Substance use or addiction

Health outcomes
- Viral load
- Drug resistance
- CD4 counts
- Objective health status
- Subjective health

Adapted from Fisher et al, 2006
Opportunities for translational research

- HCT
- Linkage
- Enroll in care
- Retention
  - HIV care
  - Managing co-morbidities
  - Positive prevention
  - Prep for ART
- Primary resistance
- 1st line
  - Start ART
    - Adherence
    - Monitoring response
    - Monitoring toxicities
- Retention
- 2nd and 3rd line ART
  - Secondary resistance
<table>
<thead>
<tr>
<th>Activity</th>
<th>recommendation</th>
<th>evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community based in GE</td>
<td>strong</td>
<td>Low</td>
</tr>
<tr>
<td>Community based KP</td>
<td>strong</td>
<td>low</td>
</tr>
<tr>
<td>Adolescents in GE</td>
<td>strong</td>
<td>low</td>
</tr>
<tr>
<td>Adolescents KP</td>
<td>strong</td>
<td>Very low</td>
</tr>
<tr>
<td>Adolescents in low and conc E</td>
<td>conditional</td>
<td>Very low</td>
</tr>
</tbody>
</table>
# When to start

<table>
<thead>
<tr>
<th>Activity</th>
<th>recommendation</th>
<th>evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;350 stage 3/4</td>
<td>strong</td>
<td>moderate</td>
</tr>
<tr>
<td>&gt;350 &lt;500</td>
<td>strong</td>
<td>moderate</td>
</tr>
<tr>
<td>Any in TB</td>
<td>strong</td>
<td>low</td>
</tr>
<tr>
<td>Any in HepB</td>
<td>strong</td>
<td>low</td>
</tr>
<tr>
<td>Any if discordant</td>
<td>strong</td>
<td>high</td>
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</table>
### What to start

<table>
<thead>
<tr>
<th>Activity</th>
<th>recommendation</th>
<th>evidence</th>
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</thead>
<tbody>
<tr>
<td>TNF, 3TC, EFV</td>
<td>strong</td>
<td>moderate</td>
</tr>
<tr>
<td>AZT for TNF</td>
<td>strong</td>
<td>moderate</td>
</tr>
<tr>
<td>NVP for EFV</td>
<td>strong</td>
<td>moderate</td>
</tr>
<tr>
<td>Discontinue Stavudine</td>
<td>strong</td>
<td>moderate</td>
</tr>
<tr>
<td>Adolescents go to ABC</td>
<td>strong</td>
<td>Very low</td>
</tr>
</tbody>
</table>

2\(^{nd}\) line consists of heat stable LPV/r or ATV/r – Strong with moderate evidence
DRV is not heat stable.
3\(^{rd}\) line: conditional recommendation- new agents.
## Monitoring response and toxicities

<table>
<thead>
<tr>
<th>activity</th>
<th>recommendation</th>
<th>evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral load</td>
<td>strong</td>
<td>low</td>
</tr>
<tr>
<td>If no VL, CD4/clinical</td>
<td>strong</td>
<td>moderate</td>
</tr>
<tr>
<td>toxicities</td>
<td>strong</td>
<td>low</td>
</tr>
</tbody>
</table>
Integration of care

• Where possible ART should be commenced in setting of initial care, eg.
  – ANC setting, TB clinic, methadone clinics.
  – Strong recommendation, very low evidence!
Methods to improve adherence

• Mobile phone technology
  – Strong recommendation, moderate quality

• Ways to measure adherence
Decentralisation of services

• Move from hospitals to peripheral clinics
• Initiate and maintain from peripheral clinics
  – Strong recommendation and low quality evidence
• Initiate in peripheral clinics and maintain at community level
  – Strong recommendation and moderate evidence
Task shifting

• Trained Non-physician clinicians, nurses, midwives can initiate and maintain ART and trained and supervised community health workers can dispense ART between clinic visits
  – Strong recommendation and moderate quality evidence
Key populations

- Drug users
- Incarcerated populations
- MSM
- TB co-infected
- Sex workers
- Adolescents
Adolescents (10 – 19) Living with HIV

2.1 million [1.6 million – 2.6 million] of whom 60% are girls (2011)

Note: The map is stylized and not to scale. It does not reflect a position on the part of UNICEF on the legal status of any country or territory or the delimitation of any frontiers.

Source:
- Country data: UNAIDS 2009 estimates
Two populations-

Perinatally infected youth, pHIVa
- F=M
- Younger
- Developmental stunting
- >treatment experienced
- Unaware of status
- Transitioned ex Paediatric Care
- Transition into Adult Care

Sexual and IDU Transmission, bHIVa
- F > M in Africa
- M>F elsewhere
- Older
- Treatment naïve
- Aware of status
- Transition into adult care
Adolescents (10-19yo) living with HIV: South Africa.

Leigh Johnson 2013
A history of perinatal HIV

50% @ 2 years

Paediatric Mortality

MTCT 30%

Mono/Dual ART

cART

Universal access

36% are slow-progressors with median survival = 16.0 years.

Long term survivors

MTCT <2%

pHIV

76% Reduction in mortality

88 90 92 94 96 98 00 02 04 06 08 10 12 14

Year

The paediatric HIV legacy

- In resource rich settings:
  - ART experienced (mean > 10 years)
  - Suboptimal regimens before (mono-dual-)
  - PHACS cohort:
    - 10-20% cART as first regimen
    - Mean exposure: 7 antiviral agents

- In resource-limited settings:
  - Present later
  - More cART at initiation (delay in access)
  - But this is changing with new guidelines and universal access.
Burden of HIV infection: children <15 yrs

N America: 4500
49% >15 yrs
Mortality<1%

Latin America/Caribbean: 60 000 >15 yrs

W/C Europe: 1600
50%>15 years
Mortality<1%

Asia-Pacific: 180 000
39% ART coverage

SSA: 3 M
S/E Africa: 2.2 M
W Africa: 990 000
21% ART coverage
The Paediatric legacy for Adult services:

Collaborative HIV Paediatric Study cohort (CHIPS)(UK and Ireland- 1996-2007)

654 perinatally infected (76% Black African)

- 64% on ART (mean 10 years)
- CD4 < 200 : 27.2%
- 518 on ART:
  - 47% triple class experienced
  - 78% virally suppressed

Foster C, et al AIDS Patient Care and STDs 2009
Adolescents in care in IeDEA Southern Africa – December 2011

Characteristics at last visit

- **Median BMI-for-age z-score (IQR)**: -0.72 (-1.61 to 0.08)
- **Median CD4 (IQR)**: 513 (320 - 711)
- **CD4 <200 (%)**: 11%
- **Viral load >400 at last visit (%)**: 39%

Davies M; Cornell M, Boulle A. Personal Communication 2013
The Young and the Resistant

Canada: 45 youth transferred to adult services
- 38/45 resistance testing:
  - 73% resistance to single drug
  - 31.6% resistant to 3 classes


CHIPS Cohort: 166 resistance assays
- 52% Dual class resistance
- 12% Triple class resistance

Foster C, et al AIDS Patient Care and STDs 2009

Hanan-Crusaid Clinic, CT: 78 children on 2nd line,
- 20% failed -TAMS: 62%; PR: 50% in those on full dose Rtvr

Orrell C, et al Ped IDJ 2013
There is a need for HEALTH CARE TRANSITION from child to adult services.... That is safe and effective

Multiple position papers...

All agree:
Continuous, coordinated, culturally appropriate, compassionate, collaborative, family centred.....

Evidence based.....

Little data on best practices and even fewer on outcomes.
Opportunities for translational research

1. HCT
   - Linkage
   - Enroll in care
   - Retention
   - HIV care
   - Managing co-morbidities
   - Positive prevention
   - Prep for ART

2. Initiate ART
   - 1st line
   - Retention
   - Adherence
   - Monitoring response
   - Monitoring toxicities
   - 2nd and 3rd line
   - ART

3. Primary resistance
4. Secondary resistance
Research gaps: Testing and LTC

- Reaching “unawares” for testing - risk perception and regular HIV testing
- Recognition of the need/desire for treatment even when asymptomatic.
- Linkage to care beyond HIV testing
  - point of care diagnostics and strategies
  - Cell phone, cash incentives, navigators, etc
- to identify and “follow” newly diagnosed individuals into care (identification systems).
HIV Counselling and Testing

Prevention package

Treatment Cascade

Prevention Cascade

Treatment package
Research gaps : HIV care

• Retention in HIV care
  – identifiers
• Quality of HIV Care
• Positive prevention
• Safer conception
• Fertility intent and safer contraception
• Management of co-morbidities
• Discordant couples ? Identification and management
• Special needs of key populations
  – Health care sensitization, incarcerated LTC.
Research gaps:

- ART optimisation
- Reduction of time at low CD4
- Reduction of uncontrolled viraemia
- Monitoring ART performance
  - Frequency, platform
- Monitoring ART toxicity
  - Frequency, key population (TDF in adolescents)
- Task shifting
- Resistance surveillance
- Community well being and viral load
Community CD4 and VL survey

<table>
<thead>
<tr>
<th>CD4 count</th>
<th>Total (N=219)</th>
<th></th>
<th></th>
<th>On ART (N=79)</th>
<th></th>
<th></th>
<th>Not yet on ART (N=140)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>95% CI</td>
<td>N</td>
<td>%</td>
<td>95% CI</td>
<td>N</td>
<td>%</td>
<td>95% CI</td>
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<tr>
<td>≤200 cells/µl</td>
<td>33</td>
<td>13.0</td>
<td>0.09; 0.18</td>
<td>10</td>
<td>11.5</td>
<td>0.06; 0.20</td>
<td>22</td>
<td>13.6</td>
<td>0.09; 19.8</td>
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<tr>
<td>201-350 cells/µl</td>
<td>72</td>
<td>28.5</td>
<td>0.23; 0.34</td>
<td>26</td>
<td>29.9</td>
<td>0.21; 0.41</td>
<td>44</td>
<td>27.2</td>
<td>0.20; 0.35</td>
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<tr>
<td>351-500 cells/µl</td>
<td>60</td>
<td>23.7</td>
<td>0.19; 0.29</td>
<td>19</td>
<td>21.8</td>
<td>0.14; 0.32</td>
<td>41</td>
<td>25.3</td>
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<tr>
<td>&gt;500 cells/µl</td>
<td>88</td>
<td>34.8</td>
<td>0.29; 0.41</td>
<td>32</td>
<td>36.8</td>
<td>0.27; 0.48</td>
<td>55</td>
<td>34.0</td>
<td>0.27; 0.42</td>
</tr>
</tbody>
</table>
Viral loads of individuals receiving ART are displayed in grey, viral loads of individuals not yet receiving ART are displayed in black.
Research gaps: on ART programs

- Retention in care
  - Logistics, motivations.
  - Personal identifiers
- Adherence to drug
  - Monitoring performance
  - Strategies/interventions
  - Early identification
- Recognition and Management of failure
  - Viral load test frequency, platform, resistance testing
- Task shifting
- Decentralisation of care
- Integration into TB, ANC, PHC, oncology services
- ART program performance
- Resistance surveillance
Research gaps: long term follow up and after first line....

- **Management of failure:** 1\textsuperscript{st} and 2\textsuperscript{nd} line
- **Retention in care**
  - Cycling, defaulters, return to care, migration
- **Long term toxicities**
- **Ongoing morbidities**
  - Cancer, metabolic, age related.
- **Aging on ART**
- **Adherence fatigue**
- **Facility decongestion, task shifting**
- **Community based drug distribution**
- **Community well being and viral load**
Novel research gaps

• Integrating the double helix of the prevention and Treatment cascades
Novel research gaps

• Integrating the double helix of the prevention and Treatment cascades
• Reducing viral reservoirs
• Working towards viral cure.....

– Visconti, Berlin, Mississippi- patients
  – Kampala, Dakar, Chang Mai patients??
Thanks

• My Gurus : Graeme Meintjies, Marc Mendelsohn, Francois Venter, Richard Kaplan, Catherine Orrell, Robin Wood
• WHO 2013 ART Guidelines
• Carlie Williams, IDEAA, others whose slides were borrowed
• Add my thanks to Europe and EDCTP- in this time of Economic downturn when There us still SO much to do!!