HAART as Prevention

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World Health Organization

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Cape Town, South Africa
21 July 2009
Smallpox eradication 1796 to 1977: Edward Jenner to Merca Town, Somalia
Outline:

• Background

• Treatment of persons already living with HIV

• Universal voluntary HIV testing and immediate ART model

• Conclusions
2005 G8 Summit at Gleneagles, Final Communiqué:
“...working with WHO, UNAIDS and other international bodies to develop and implement a package of HIV prevention, treatment and care, with the aim of as close as possible to universal access to treatment for all those who need it by 2010.”

2009 G8 Summit at L'Aquila, Final Communiqué:
We have made progress towards universal access...in the current global crisis we reaffirm our commitment to address the most vulnerable.
Unprecedented investment faces most serious economic crisis since 1930's
Towards universal treatment access
Malawi: scale-up against formidable odds

<table>
<thead>
<tr>
<th>Year</th>
<th>New patients on ART each year</th>
<th>Cumulative patients ever started on ART</th>
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</thead>
<tbody>
<tr>
<td>2005</td>
<td>25,000</td>
<td>37,840</td>
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<tr>
<td>2006</td>
<td>35,000</td>
<td>70,000</td>
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<tr>
<td>2007</td>
<td>40,000</td>
<td>110,000</td>
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<tr>
<td>2008</td>
<td>45,000</td>
<td>155,000</td>
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<tr>
<td>2009</td>
<td>45,000</td>
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Mind the prevention gap.....

End 2007:
• 3 million were receiving ART
  --about 1 million people added
• 6.7 million in need
• 2.7 million new infections
Estimated treatment gap in low- and middle-income countries 2002-2007

- Estimated gap: <200 CD4 but not on ART
- On ART

- 2003: 1,000,000 people
- 2004: 1,500,000 people
- 2005: 2,000,000 people
- 2006: 2,500,000 people
- 2007: 3,000,000 people

- 95% of the estimated gap were on ART
- 69% of the estimated gap were on ART
Antiretroviral therapy - an entitlement program?

"As a result, taxpayers are accumulating an indefinite—and indefinitely growing—responsibility for keeping people alive. Somehow, somebody has to work out how to stop the disease spreading".

The Economist, 9 August, 2008
Combination prevention
Multiple disciplines and approaches

HIV prevention

- Biomedical Interventions
- Structural Interventions
- Community Interventions
- HIV testing and linkage to care
- Individual and small group behavioral interventions

Adapted from Coates T
Efficacy trials of biomedical interventions for HIV sexual transmission, 2009

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Completed</th>
<th>Efficacious</th>
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</thead>
<tbody>
<tr>
<td>Male circumcision</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>STI treatment</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>HSV-2 suppression</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Cervical barriers</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Microbicides</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>HIV vaccines</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>24</strong></td>
<td><strong>4</strong></td>
</tr>
</tbody>
</table>

Adapted from Cohen J, Science 2008
Evidence supports ART for prevention of HIV transmission

- Transmission only occurs from persons with HIV
- Viral load is the single greatest risk factor for HIV transmission
- ART can lower viral load to undetectable levels
- PMTCT proof of concept of ART reducing transmission
- Observational evidence in heterosexual couples
- Previous modelling work suggests considerable potential
- Knowing one's HIV status is key to ART for prevention
- When to start ART is not known with certainty
HIV treatment reduces viral load and heterosexual transmission

HIV sexual transmissibility meta-analysis: No transmission on ART below 400 copies/ml

Estimated Numbers of Perinatally Acquired AIDS Cases by Year of Diagnosis, 1985–2007—United States and Dependent Areas

PACTG 076 & USPHS ZDV Recs

CDC HIV Testing Recs

Note: Data have been adjusted for reporting delays and missing risk-factor information.
Community studies suggest population-level impact of ART

British Columbia, Canada

Taiwan

Wood et al. BMJ 2009;338b:1649
Fang et al. JAIDS 2004;190:879-85
Late initiation of ART and mortality

Source: Egger M, CROI 2007
When to start ART….or how late is too late?

- 17,517 patients from US and Canada (1996-2005)
- 69% increase in mortality for those who started treatment below CD4+ <350/cu mm
- 94% increase in mortality for those who started treatment below CD4+ <500/cu mm
When to Start Consortium: analysis of 18 cohorts suggests that earlier start improves outcome

When to start consortium. Lancet 2009 Apr 18;373(9672):1352-63
Randomized controlled trial of earlier versus deferred ART in Haiti
CIPRA HT 001

Start ART at CD4+ <350/cu mm, compared to AIDS or CD4+ <200/cu mm
• 816 patients
• First line regimen: AZT, 3TC, EFV
• 23 deaths in deferred group, 6 in early treatment group (p<.001)
• 36 vs. 18 cases of TB in deferred vs early treatment group (p<.013)
• DSMB recommended immediate end of trial

Pape J, Fitzgerald D et al, 2009
• HIV may be associated with serious non-AIDS defining events
  • Cardiovascular
  • Renal
  • Liver
  • Non-AIDS malignancies

• At higher CD4 counts non-AIDS events are much more common than AIDS events

• Does ART use reduce risk of some serious non-AIDS events?

Slide courtesy of A Phillips
CD4 level is associated with TB incidence: earlier start may decrease TB risk

Figure. Schematic of Risk of TB and Change in CD4 Cell Count From Onset of HIV Seroconversion

- HIV seroconversion
- Start ART
- "TB death zone"

Havlir, Getahun et al. 2008 JAMA 300(4):423-430

Slide adapted by Dr. Abhishek Sharma
CD4 cell count over the course of untreated HIV-1 infection in adults

When to start ART?
A matter of perspective

2-4 years earlier significant period

2-4 years earlier now appears like a short period

Slide adapted from Julio Montaner
### Key characteristics of current US, European and WHO ART guidelines

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>When to Start in asymptomatic patients (preferred approach)</th>
<th>Preferred initial ARV therapy</th>
<th>Preferred subsequent ARV therapy</th>
<th>Preferred treatment failure/switching criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHHS (2008)</td>
<td>CD4 $&lt;$350 (stronger if $&lt;$ 200)</td>
<td>2NRTI (TDF/FTC) + NNRTI (EFV) or bPI (ATV/r or DRV/r or FPV/r or LPV/r)</td>
<td>Guided by resistance testing/tropism testing</td>
<td>VL + CD4 (no consensus on thresholds)</td>
</tr>
<tr>
<td>IAS (2008)</td>
<td>CD4 $&lt;$ 350 (consider if $&gt;$ 350 in some situations)</td>
<td>2NRTI (ABC/3TC or TDF/FTC) + NNRTI (EFV) or bPI (ATV/r or DRV/r or FPV/r or LPV/r or SQV/r)</td>
<td>Guided by resistance/tropism testing</td>
<td>VL&gt; 500-1000</td>
</tr>
<tr>
<td>EACS (2008)</td>
<td>CD4 $&lt;$ 350 (consider if $&gt;$ 350 in some situations)</td>
<td>2NRTI (ABC/3TC or TDF/FTC) + NNRTI (NVP or EFV) or bPI (FPV/r or LPV/r or SQV/r)</td>
<td>Guided by resistance testing</td>
<td>VL &gt; 500-1000</td>
</tr>
<tr>
<td>BHIVA (2008)</td>
<td>CD4 $&lt;$ 350 (consider if $&gt;$ 350 in some situations)</td>
<td>2NRTI (TDF/FTC) + NNRTI (EFV)</td>
<td>Guided by resistance testing</td>
<td>VL &gt; 400</td>
</tr>
<tr>
<td>WHO EURO (2007/2008)</td>
<td>CD4 between 200-350</td>
<td>2NRTI (ABC/3TC or AZT/3TC or TDF/XTC) + NNRTI (EFV)</td>
<td>2 NRTI (ABC/ddI or TDF/XTC or AZT/3TC or TDF/ABC or AZT/ddI) + bPI (LPV/r)</td>
<td>VL &gt; 400 (early failure) VL &gt; 1000-10,000 or 25% reduction in CD4 (late failure)</td>
</tr>
<tr>
<td>WHO Global (2006)</td>
<td>CD4 $&lt;$ 200 (consider between 200-350 but start before reach 200)</td>
<td>2NRTI (AZT/3TC or TDF/XTC) + NNRTI (NVP or EFV)</td>
<td>2 NRTI (ABC/ddI or TDF/XTC or AZT/3TC) + bPI (ATV/r or LPV/r)</td>
<td>Clinical + CD4 (if available VL &gt; 10,000)</td>
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</table>
Coverage of ART among eligible people living with HIV, Kenya (2007 KAIS)

- 57% Unaware of status, not on ART
- 39% know status, on ART
- 4% know status, not on ART

Among those who knew status and were eligible 92% were on ART.
Counseling and testing is feasible and works in a wide variety of settings.
"Essentially, all models are wrong, but some are useful."

– George E. P. Box
Approach to estimating $R_0$

• Southern-African type epidemic  
  • Data from SA, Uganda, Malawi and elsewhere

• Initial doubling time in South Africa $\approx 1.25$ years  
  • Each person infects one other person every 1.25 years.

• Life expectancy after infection $\approx 10$ years

• Each HIV positive person infects $10/1.5 \approx 7$ people

• Cutting transmission by a factor of more than 8 would eliminate HIV infection ($R_0<1$)
Infectivity varies through the course of infection

Relationship between HIV testing frequency, CD4 count, and $R_0$
Program implementation
HIV and ART incidence, prevalence and mortality, 1980-2040

Proportion of adolescents and adults 15 years or older

Strategy
- No ART
- <350
- Universal

Graphs showing the trend of HIV and ART incidence, prevalence, and mortality.
## Estimated number of AIDS-related deaths for 2008 to 2050

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Deaths</th>
<th>Deaths averted</th>
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</thead>
<tbody>
<tr>
<td>Neither strategy</td>
<td>11,078,000</td>
<td>--</td>
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<tr>
<td>ART started &lt;350</td>
<td>8,658,000</td>
<td>2,419,000</td>
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<tr>
<td>ART started &lt;350 + universal voluntary HIV testing/immediate ART</td>
<td>3,879,000</td>
<td>7,199,000</td>
</tr>
<tr>
<td>ART started &lt;350 + universal voluntary HIV testing/immediate ART + other prevention strategies</td>
<td>3,727,000</td>
<td>7,350,000</td>
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Estimated and projected funding and costs: We appear to be in the right ball park….

Blue: 17% global funding (UNAIDS)
Brown: 17% projected funding (UNAIDS)
Green: Universal testing + immediate ART
Red: <350 with universal voluntary testing

Annual cost savings

Conclusions from modeling exercise

• Universal voluntary HIV testing and immediate ART combined with other prevention interventions:
  • 95% reduction in new HIV cases in 10 years
  • Incidence reduced from 15-20,000 to 1000 per million
  • Prevalence or the number of people living with HIV becomes less than 1% by 2050
  • Initial resources would be higher but over time, given the reduction in HIV incidence, this approach may provide cost savings
  • Estimated costs are within UNAIDS estimates for Universal Access for a population this size.

• Theoretical model
WHO next steps

Consultation on ART as prevention (Nov 2009)

• Researchers (clinical, socio-behavioural, prevention & modellers)
• NGOs, civil society & people living with HIV
• Ethicists & human rights experts
• Health economists, donors, research funding agencies
• Affected country representatives
• UNAIDS Co-sponsors and WHO HQ and Regional staff

Focus

• Explore human rights and ethical implications
• Clarify research priorities
• Explore feasibility and acceptability
Public health is purchasable. Within a few natural and important limitations any community can determine its own health.

--Hermann M. Biggs
(29 Sep 1859 - 28 Jun 1923)
New York City's Public Health Officer and public health pioneer
<table>
<thead>
<tr>
<th>Brian Williams (Senior author)</th>
<th>Jonathan Mermin</th>
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<tbody>
<tr>
<td>Charles Gilks</td>
<td>Julio Montaner</td>
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<td>Christopher Dye</td>
<td>Jung-Der Wang</td>
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<td>Kevin De Cock</td>
<td>Navneet Garg</td>
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<td>A.D. Harries</td>
<td>Marco Vitoria</td>
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<td>Alexandra Calmy</td>
<td>Miriam Sabin</td>
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<td>Andrew Ball</td>
<td>Mona Sfeir</td>
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<td>Andrew Phillips</td>
<td>Nicole Schiegg</td>
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<td>Brad Hersh</td>
<td>Paula Akugizibwe</td>
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<td>Caroline Ryan</td>
<td>Pedro Kahn</td>
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<td>Celicia Serenata</td>
<td>Rebecca Bunnell</td>
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<td>Charles Holmes</td>
<td>Richard Skolnik</td>
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<td>Chi-Tai Fang</td>
<td>Robin Wood</td>
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<td>Rod Bennett</td>
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<td>Steve Lawn</td>
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<td>Diane Havlir</td>
<td>Susan Allen</td>
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<td>Haileyesus Getahun</td>
<td>Yves Souteyrand</td>
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<tr>
<td>Jim Kahn</td>
<td>International AIDS Society</td>
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<tr>
<td>John Stover</td>
<td>WHO staff</td>
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<td>PEPFAR staff</td>
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