Early Diagnosis and Treatment of HIV Infection Benefits Individuals and Society

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Rotterdam, the Netherlands
International HIV management guidelines based on scientific evidence

- Better health outcomes are achieved when HIV-infected individuals are:
  - identified soon after infection (higher CD4 counts);
  - immediately connected to long-term healthcare;
  and
  - cART is initiated as soon as possible
Why treating earlier: benefits patients

- Biological plausibility
- Increased healthfull survival
- Avoid immune reconstitution syndrome
  - Important cause of treatment-related morbidity and mortality if treatment is started late (lower CD4 count)
Increased healthful survival

Life expectancy is similar to that of the non-HIV-infected people if cART is started early enough to increase and maintain CD4+ cell count above 500 cells/mm³

cART: virologic and immunologic response

Percentage <quantification limit HIV-RNA assay and CD4 cell count change after start cART
Risk of death and certain complications “not thought to be HIV-associated”: D.A.D.

Cause-specific mortality associated with most recent CD4 count

<table>
<thead>
<tr>
<th>CD4+ (cells/mm³)</th>
<th>Overall</th>
<th>HIV</th>
<th>Cancer</th>
<th>Cardiac</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>100</td>
<td>10</td>
<td>1.0</td>
<td>10.0</td>
<td>100</td>
</tr>
<tr>
<td>50–99</td>
<td>100</td>
<td>10</td>
<td>1.0</td>
<td>10.0</td>
<td>100</td>
</tr>
<tr>
<td>100–199</td>
<td>100</td>
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<tr>
<td>200–349</td>
<td>100</td>
<td>10</td>
<td>1.0</td>
<td>10.0</td>
<td>100</td>
</tr>
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<td>350–499</td>
<td>100</td>
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<td>10.0</td>
<td>100</td>
</tr>
<tr>
<td>&gt;500</td>
<td>100</td>
<td>10</td>
<td>1.0</td>
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<td>100</td>
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Why start early?:

Population health benefits

- Curves the epidemic
- Societal benefits
The case for expanding access to highly active antiretroviral therapy to curb the growth of the HIV epidemic

Julio S G Montaner, Robert Hogg, Evan Wood, Thomas Kerr, Mark Tyndall, Adrian R Levy, P Richard Harrigan

“The upshot of this widespread failure to recognize that AIDS is an exceptional crisis and threat is that the response to the pandemic is not made commensurate to the challenges—and so the epidemic escalates even while it erodes our capacities to check it.”

Dr Peter Piot, UNAIDS Executive Director

International AIDS Society
Stronger Together

AIDS 2006
XVI International AIDS Conference
Time to Deliver

Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model

Reuben M Granich, Charles Gilks, Christopher Dye, Kevin M De Cock, Brian G Williams

Summary

Background  Roughly 3 million people worldwide were receiving antiretroviral therapy (ART) at the end of 2007, but an estimated 6·7 million were still in need of treatment and a further 2·7 million became infected with HIV in 2007. Prevention efforts might reduce HIV incidence but are unlikely to eliminate this disease. We investigated a theoretical strategy of universal voluntary HIV testing and immediate treatment with ART, and examined the conditions under which the HIV epidemic could be driven towards elimination.

Methods  We used mathematical models to explore the effect on the case reproduction number (stochastic model) and long-term dynamics of the HIV epidemic (deterministic transmission model) of testing all people in our test-case community (aged 15 years and older) for HIV every year and starting people on ART immediately after they are diagnosed HIV positive. We used data from South Africa as the test case for a generalised epidemic, and assumed that all HIV transmission was heterosexual.

Findings  The studied strategy could greatly accelerate the transition from the present endemic phase, in which most adults living with HIV are not receiving ART, to an elimination phase, in which most are on ART, within 5 years. It could reduce HIV incidence and mortality to less than one case per 1000 people per year by 2016, or within 10 years of full implementation of the strategy, and reduce the prevalence of HIV to less than 1% within 50 years. We estimate that in 2032, the yearly cost of the present strategy and the theoretical strategy would both be US$1·7 billion; however, after this time, the cost of the present strategy would continue to increase whereas that of the theoretical strategy would decrease.

Interpretation  Universal voluntary HIV testing and immediate ART, combined with present prevention approaches, could have a major effect on severe generalised HIV/AIDS epidemics. This approach merits further mathematical modelling, research, and broad consultation.
Breakthrough of the year 2011
A  Linked HIV Transmission

Cumulative Probability

Years since Randomization

No. at Risk

Early 893 658 298 79 31 24
Delayed 882 655 297 80 26 22

Delayed
Early
Transmission during therapy

- Starting antiretroviral therapy at higher CD4 counts results in 96% reduction of HIV transmission
  - Start at CD4 < 250 vs start at CD4 of 350 – 550

- Clinical benefits to patients
  - 41% reduction in opportunistic infections and mortality


Only one of 103 genetically-linked HIV transmissions from an individual who had started ART.

Transmission rate 0.37 per 100 person years vs. 2.24 in those who had not started ART: a 92% reduction.
Are we already seeing a benefit of treatment?

Global HIV trends, 1990–2011

NUMBER OF PEOPLE NEWLY INFECTED WITH HIV, GLOBAL, 1990–2011

Source: UNAIDS estimates.
Initiation of long-term treatment initiated at PHI leads to a significant frequency of viremia control.

http://www.plospathogens.org/article/info:doi/10.1371/journal.ppat.1003211
Treatment as Prevention (TASP) : is it going to be easy?

NO
Figure 2. The spectrum of engagement in HIV care in the United States spanning from HIV acquisition to being fully engaged in care, receiving antiretroviral therapy and achieving complete viral suppression. We estimate that only 19% of HIV infected individuals in the United States have an undetectable HIV viral load.
TasP: is it going to be enough?
TasP: maybe not enough, but critical!

It is clear that TasP should be scaled up in conjunction with other effective HIV prevention interventions.

But it is also clear that TasP is an essential component of the prevention package and should be rolled out as expeditiously as possible.
The truth of the matter is that virtually all HIV-infected individuals need to be treated anyhow for their own health.

It is best to do this in a way that maximizes both individual and public health benefits:

- which means as early as possible!
Earlier treatment?

- WHO recommends to start treatment at a CD4 < 500 cells/µl
  - Priority should be given to those with advanced disease or CD4 < 350 cells/µl

WHO, HIV treatment and prevention guidelines 2013
Earlier treatment?

- WHO recommends to start treatment at a CD4<500 cells/µl
  - Priority should be given to those with advanced disease or CD4<350 cells/µl

- Could earlier treatment lead to more resistance in the population and affect future treatment success?
Objective

- Can the benefits of earlier antiretroviral drug treatment be offset by increased drug resistance?
  - Current status of drug resistance
  - Predicted change in epidemiology resistance after implementation of early treatment
  - Strategies to reduce drug resistance
Drug resistance

- Meta-analyses report that transmitted drug resistance is increasing in “resource-limited” settings

Drug resistance

- Meta-analyses report that transmitted drug resistance is increasing in “resource-limited” settings
  - Increased access to antiretroviral drugs

Drug resistance

- Meta-analyses report that transmitted drug resistance is increasing in “resource-limited settings”
  - Increased access to antiretroviral drugs
  - No systemic results from Asia due heterogeneity between countries
  - Largest increase in East-Africa (29% per year)
    - Predominantly NNRTI

Averted HIV infections due to expanded antiretroviral treatment eligibility offsets risk of transmitted drug resistance: a modeling study

Brooke E. Nichols\textsuperscript{a}, Kim C.E. Sigaloff\textsuperscript{b,c}, Cissy Kityo\textsuperscript{d}, Kishor Mandaliya\textsuperscript{e}, Raph L. Hamers\textsuperscript{b,c}, Silvia Bertagnolio\textsuperscript{f}, Michael R. Jordan\textsuperscript{g}, Charles A.B. Boucher\textsuperscript{a}, Tobias F. Rinke de Wit\textsuperscript{b,c} and David A.M.C. van de Vijver\textsuperscript{a}

\textbf{Background:} Earlier antiretroviral therapy initiation can reduce the incidence of HIV-1. This benefit can be offset by increased transmitted drug resistance (TDR). We compared the preventive benefits of reducing incident infections with the potential TDR increase in East Africa.

\textbf{Methods:} A mathematical model was constructed to represent Kampala, Uganda, and Mombasa, Kenya. We predicted the effect of initiating treatment at different immunological thresholds (<350, <500 CD4 cells/\mu l) on infections averted and mutation-specific TDR prevalence over 10 years compared to initiating treatment at CD4 below 200 cells/\mu l.

\textbf{Results:} When initiating treatment at CD4 below 350 cells/\mu l, we predict 18 [interquartile range (IQR) 11–31] and 46 (IQR 30–83) infections averted for each additional case of TDR in Kampala and Mombasa, respectively, and 22 (IQR 17–35) and 32 (IQR 21–57) infections averted when initiating at below 500. TDR is predicted to increase most strongly when initiating treatment at CD4 below 500 cells/\mu l, from 8.3% (IQR 7.7–9.0%) and 12.3% (IQR 11.7–13.1%) in 2012 to 19.0% (IQR
Mathematical modelling

- Studying impact of earlier treatment on drug resistance will require epidemiological follow-up study
  - Time-consuming
  - Expensive

- Mathematical modelling may be helpful
Kampala, Uganda

• Data from PASER – PharmAccess

• Drug resistance in
  – Individuals starting treatment
  – Individuals who used treatment for 1 or 2 years

Hamers Lancet Inf Dis 2011, Hamers Lancet Inf Dis 2012
Kampala, Uganda

- Data from PASER – PharmAccess
- Drug resistance in
  - Individuals starting treatment
  - Individuals who used treatment for 1 or 2 years

<table>
<thead>
<tr>
<th>Transmission of resistance</th>
<th>8.6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquired resistance (1y)</td>
<td>10%</td>
</tr>
<tr>
<td>Zidovudine-based regimen</td>
<td></td>
</tr>
<tr>
<td>Tenofovir-based regimen</td>
<td>6%</td>
</tr>
</tbody>
</table>

Hamers Lancet Inf Dis 2011, Hamers Lancet Inf Dis 2012
Drug use

- Drugs that were used
  - Zidovudine, lamivudine, NNRTI
  - Tenofovir, emtricitabine/lamivudine, NNRTI
  - Second line based on boosted protease inhibitors
### Classification of resistance

<table>
<thead>
<tr>
<th>Antiretroviral</th>
<th>Class</th>
<th>Classification</th>
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</thead>
<tbody>
<tr>
<td>Zidovudine</td>
<td>NRTI</td>
<td>TAM</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>NRTI</td>
<td>M184V</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>NRTI</td>
<td>K65R</td>
</tr>
<tr>
<td>Efavirenz, nevirapine</td>
<td>NNRTI</td>
<td>NNRTI</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>Protease inhibitor</td>
<td>PI</td>
</tr>
</tbody>
</table>

Reversion to wild-type was included, ranges from weeks for M184V to years for NNRTI resistance.
Future prevalence of HIV drug resistance

Year

Transmitted Drug Resistance Prevalence (%)

Immediate

<500

<350

2015 2020 2025 2030 2035 2040 2045 2050
Absolute number HIV drug resistance

Year

Absolute Number of Yearly TDR Cases

<350

<500

Immediate
Transmission of drug resistance mutations in China

- Stanford HIV database collected sequences published on Genbank about transmission of drug resistance
  - Including 16 studies from China published between 2002 and 2013
    - 3 studies, including 136 patients published before 2008
  - 1360 patients
  - 17 excluded because protease-gene was missing
  - Resulting 1343 patients all had HIV-RT gene sequenced
HIV-1 Drug Resistance in ARV-naive Populations

Compendium of published virus sequences from 46,765 persons, 264 studies according to region, year and subtype

Publications

<table>
<thead>
<tr>
<th>Continent</th>
<th>Country</th>
<th>Publication</th>
<th>Resistance (%)</th>
<th>n</th>
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<tbody>
<tr>
<td>Asia</td>
<td>CHINA</td>
<td>Zhang10</td>
<td>2.1</td>
<td>47</td>
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<tr>
<td>Asia</td>
<td>CHINA</td>
<td>Wang08</td>
<td>2.6</td>
<td>36</td>
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<td>CHINA</td>
<td>Yang12</td>
<td>3.4</td>
<td>119</td>
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<td>Asia</td>
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<td>Han10</td>
<td>5.0</td>
<td>141</td>
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<td>CHINA</td>
<td>Li13</td>
<td>5.3</td>
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</tr>
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<td>CHINA</td>
<td>Han07</td>
<td>5.5</td>
<td>72</td>
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<td>GEORGIA</td>
<td>Zarandia08</td>
<td>9.3</td>
<td>48</td>
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<tr>
<td>Asia</td>
<td>INDIA</td>
<td>Sinha12</td>
<td>9.7</td>
<td>31</td>
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<td>Ravur06</td>
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<td>Asia</td>
<td>INDIA</td>
<td>Thorat11</td>
<td>2.1</td>
<td>47</td>
</tr>
</tbody>
</table>

% Resistance

- < 2.5
- 2.5 - 5
- 5 - 10
- >= 10

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China

- Prevalence transmission of drug resistance mutations
  - $43/1343 = 3.2\%$
  - Including 2 patients harboring a virus with mutations from two different classes of antiretrovirals
## Per class

<table>
<thead>
<tr>
<th>Class</th>
<th>Mutations</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protease inhibitors</strong></td>
<td>At least one M46I, M46L, L90M, I85V</td>
<td>19 (1.4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td><strong>NRTI</strong></td>
<td>At least one M184I/V, M41L, T215S</td>
<td>11 (0.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td><strong>NNRTI</strong></td>
<td>At least one K103N, Y181C, K101E</td>
<td>15 (1.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
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<td></td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>
Transmitted drug resistance by drug class or mutation

A. Kampala, Uganda

Nichols et al. AIDS 2013
So resistance increases a little …

- But at the same time many infections were prevented
  - Over 10 years, compared to a CD4<200
  - CD4<350, 12.6% infections averted
  - CD4<500, 28.8% infections averted
Prevention versus Resistance

Infections averted per drug resistant case gained

CD4 initiation threshold

Nichols et al. AIDS 2013
Strategies to reduce drug resistance
Can we limit drug resistance?

1. Viral load monitoring
2. Second-line treatment
3. Genotyping before start of treatment
1. Viral load monitoring

- Viral load monitoring allows to identify virological failure in a timely manner
  - Adherence counseling
  - Switch to alternative treatment
Viral load monitoring

Any thymidine analogue mutations
- NNRTI clinical trials
- Cohort (frequent monitoring)
- Cohort (infrequent or no monitoring)

M184V/I mutation
- NNRTI clinical trials
- Cohort (frequent monitoring)
- Cohort (infrequent or no monitoring)

Major NNRTI
- NNRTI clinical trials
- Cohort (frequent monitoring)
- Cohort (infrequent or no monitoring)

K65R mutation
- NNRTI clinical trials
- Cohort (frequent monitoring)
- Cohort (infrequent or no monitoring)

Percentage of all patients starting HAART with resistance at 48 weeks (95% CI)

Gupta et al. Lancet Infect. Diseases 2009
Viral load

- WHO recommends viral load monitoring
  - 6 months after start treatment
  - Every 12 months thereafter

WHO. Consolidated treatment and prevention guidelines. 2013
2. Increasing access to 2nd line

- Boosted protease inhibitors, have compared to NNRTI’s, a higher genetic barrier for resistance
  - Number of mutations required to overcome drug selective pressure
  - Drug resistance is therefore less common with protease inhibitors
Increase second-line

- Modelling study in Kampala, Uganda:
  - Only 33-50% of patients with continued failure on first-line make it onto second line
  - Increase to 80-100%?

Nichols et al. AIDS 2013
Increasing access to second-line

A. Kampala, Uganda: Overall transmitted drug resistance prevalence vs. increase in second-line access

Nichols et al. AIDS 2013
3. Baseline genotyping

- Resistance test to identify drug resistance associated mutations before start of treatment
  - Transmission of drug resistance is associated with increased risk of virological failure
Drug resistance

Wittkop et al. Lancet infectious diseases 2011
Baseline genotyping

- Optimize treatment based on results from baseline genotyping
  - Only when alternatives are available
  - 2nd line
But which strategy is the best?
But which strategy is the best?

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Reduction TDR</th>
<th>Infections averted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral load every six months</td>
<td>-3.3%</td>
<td>32</td>
</tr>
<tr>
<td>Increase second line</td>
<td>-11%</td>
<td>407</td>
</tr>
<tr>
<td>Baseline genotyping</td>
<td>-0.5%</td>
<td>18</td>
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- Over 40 years
- CD4<500
But which strategy is the best?

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- Viral load monitoring at least once a year
Is resistance unavoidable?

- In my view resistance will always be an issue
  - Adherence
  - Stock-outs

- But the benefits of treatment will outweigh the risk of drug resistance
Conclusion 1

- Earlier treatment initiation without good second line strategy will lead to a very small increase in prevalence of transmission of drug resistance
  - Especially NNRTI (first generation)
  - Far more infections averted than resistance gained
- Strategies to limit spread of drug resistance required!
  - Increase access to second line
Conclusion 2

- Earlier therapy combined with good monitoring and a good second line strategy will not lead to a significant increase in the prevalence of transmission of drug resistance.
- Early therapy may benefit patients and society by preventing new infections.
<table>
<thead>
<tr>
<th>Institution</th>
<th>Members</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erasmus Medical Centre</td>
<td>Brooke Nichols, Azzania Fibriani, David van de Vijver</td>
</tr>
<tr>
<td>Amsterdam Institute for Global health and development (AIGHD)</td>
<td>Kim Sigaloff, Raph Hamers, Tobias Rinke de Wit, Joep Lange</td>
</tr>
<tr>
<td>Radboud University Medical Centre</td>
<td>Rob Baltussen</td>
</tr>
<tr>
<td>Joint Clinical Research Centre, Kampala</td>
<td>Cissy Kityo</td>
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<tr>
<td>International Center for Reproductive Health, Mombasa</td>
<td>Kishor Mandaliya</td>
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<tr>
<td>Imperial College London</td>
<td>Tim Hallett</td>
</tr>
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<td>World Health Organization</td>
<td>Silvia Bertagnolio, Michael Jordan</td>
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