Dr Charles Boucher
Erasmus Medical Center Rotterdam, Netherlands

COMPETING INTEREST OF FINANCIAL VALUE ≤£1,000:

<table>
<thead>
<tr>
<th>Speaker Name</th>
<th>Statement</th>
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<tbody>
<tr>
<td>Dr Charles Boucher</td>
<td>Dr Boucher acts in a Consultancy capacity for <em>(Merck, Abbvie, Viiv)</em> and as a speaker at company-sponsored events for <em>(BMS)</em>. He has (also) received personal grants for attending conferences from <em>(Janssen)</em> end/or has received a personal grant for research from <em>(Merck, Roche)</em>.</td>
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Date: April 2013
HIV drug resistance in the future: a clinical virologist’s perspective

Charles Boucher
Erasmus Medical Center
Rotterdam, The Netherlands
Predicting the future

• Biological factors driving the emergence, persistence and transmission of drug resistant viruses

• The current situation

• Prediction by models
A truly (multi-class) drug resistant virus will be generated, which is as transmissible (or even more) and dominates the epidemic.
Viral quasispecies

![Diagram showing the relationship between variation and fitness for wild type, single mutations, and double mutations.]

- **Wild Type**: High fitness with minimal variation.
- **Single mutations**: Decreased fitness with increased variation.
- **Double mutations**: Further decreased fitness with even more variation.

The diagram illustrates how mutations can affect the fitness and variation of viral quasispecies.
Continuous genetic evolution

Non suppressive therapy

Selection pre-existing mutants

Generation additional resistance mutations

Generation compensatory mutations

Virus amount

- $10^4$
- $10^5$
- $10^6$

Days

- 10
- 20
- 30
- 40
- 50
- 60
- 70
- 80
- 90
- 100
- 110
A truly (multi-class) drug resistant virus will be generated, which is as transmissible (or even more) and dominates the epidemic.
Transmission of HIV drug resistance mutations

Treated patient
Multiple mutants

> 

Diagnosed patient
Limited profile
Trends over time in MSM

Prevalence of resistance over time in MSM

- any class
- NRTI
- NNRTI
- PI

Year:
- 1/2003
- 1/2004
- 1/2005
- 1/2006
- 1/2007

Prevalence:
- 0.19
- 0.22
- 0.008
- 0.006
# TDRM patterns

<table>
<thead>
<tr>
<th>NRTI-related mutations</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M41L</strong></td>
<td>73 (1.7)</td>
</tr>
<tr>
<td><strong>D67N</strong></td>
<td>16 (0.4)</td>
</tr>
<tr>
<td><strong>L210W</strong></td>
<td>27 (0.6)</td>
</tr>
<tr>
<td><strong>T215Y</strong></td>
<td>14 (0.3)</td>
</tr>
<tr>
<td><strong>T215rev</strong></td>
<td>118 (2.7)</td>
</tr>
<tr>
<td><strong>K219Q</strong></td>
<td>24 (0.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NNRTI-related mutations</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>K103N</strong></td>
<td>72 (1.7)</td>
</tr>
<tr>
<td><strong>G190A</strong></td>
<td>21 (0.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PI–related mutations</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>L90M</strong></td>
<td>10 (0.6)</td>
</tr>
</tbody>
</table>
Paradox of transmitted drug resistant viruses

- Continuous circulation/transmission of viruses with drug resistance mutations, which have been reported to reduce viral replication. (transmission)

- Drug resistance mutations found in new patients have not been selected by the use of modern HAART regimens (represent onwards transmission)
Persist study

33 patients:
- 4 countries: the Netherlands, Belgium, Slovenia, Greece
- 57 resistance mutations (IAS list)
- Diagnosed: 2001-2008
- HIV-RNA: 4.6log (SPREAD: 4.8log)
- CD4 count: 617 cells/mm³ (SPREAD: 343)

M. Pingen et al, preliminary data.
### Transmitted drug resistance profiles – one year

<table>
<thead>
<tr>
<th>NRTI</th>
<th>NNRTI</th>
<th>PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>M41L (3x)</td>
<td>K103N (2x)</td>
<td>M46L (5x)</td>
</tr>
<tr>
<td><strong>T69TP</strong></td>
<td>K103Q</td>
<td>L90M</td>
</tr>
<tr>
<td>L210LS</td>
<td>V179I</td>
<td></td>
</tr>
<tr>
<td>T215D (2x)</td>
<td>Y181C</td>
<td></td>
</tr>
<tr>
<td>T215S</td>
<td>G190A</td>
<td></td>
</tr>
<tr>
<td><strong>T215IT</strong></td>
<td><strong>Complex</strong></td>
<td></td>
</tr>
<tr>
<td>K219N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D67G T215C K219E (3x)</td>
<td>PR: <strong>G73S</strong> L90M RT: K103N</td>
<td></td>
</tr>
<tr>
<td>M41L T69S T210E T215ST (2x)</td>
<td>PR: <strong>F53FL</strong> I54V V82A L90M RT: M41L D67N L210W T215D</td>
<td></td>
</tr>
</tbody>
</table>

M. Pingen et al, preliminary data.
## Virus panels

<table>
<thead>
<tr>
<th>Site-directed mutants</th>
<th>Patient-derived virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>HXB2wt</td>
<td></td>
</tr>
<tr>
<td>M184V</td>
<td></td>
</tr>
<tr>
<td>M184I</td>
<td></td>
</tr>
<tr>
<td>M184T</td>
<td></td>
</tr>
<tr>
<td>M41L</td>
<td>pM41L</td>
</tr>
<tr>
<td></td>
<td>pM41L-T69S-L210W-T215S</td>
</tr>
<tr>
<td>K103N</td>
<td>pK103N</td>
</tr>
<tr>
<td>M46L</td>
<td>pM46L</td>
</tr>
<tr>
<td>M46I</td>
<td>pM46I</td>
</tr>
<tr>
<td>L90M</td>
<td>pL90M</td>
</tr>
<tr>
<td></td>
<td>pI54V-V82A-L90M</td>
</tr>
</tbody>
</table>

M. Pingen et al
Materials & Methods

Mutant/HXB2

HEK 293T cells

Cells: 5x10^6 PBMCs

Daily for 2 weeks:
Sample for p24 analysis

M. Pingen et al, preliminary data.
SDM viruses  Patient derived virus

M. Ping et al, preliminary data.
Compensatory fixation: a fitness valley blocks reversion to wild type
Compensatory fixation: a fitness valley blocks reversion to wild type
Compensatory fixation: a fitness valley blocks reversion to wild type
Continuous replication of HIV under non-suppressive therapy can generate drug resistant viruses with a compensated phenotype resulting in wild type level replication (transmission) and (compensatory) fixation leading to onwards transmission and thus fixation in (a proportion of) the epidemic.
A truly (multi-class) drug resistant virus will be generated, which is as transmissible (or even more) and dominates the epidemic.
"Widespread, unregulated access to ARV drugs in sub-Saharan Africa could lead to the rapid emergence of resistant viral strains, spelling doom for the individual, curtailing future treatment options, and leading to transmission of resistant virus."

"If compliance and careful follow-up of patients is not achieved, we will see a dramatic increase in multidrug-resistant HIV mutants..."

Global scale-up of ART

WHO public health model

- Standard ART regimens
- Restricted drug options
- Limited lab monitoring
- Decentralized service delivery and task shifting
HIVDR early Warning Indicators (EWI) Proportion of Clinics Achieving WHO-Recommended Targets

2107 clinics (2004-2009), >131,000 people, >50 countries

- Loss to follow-up ≤20%: 69%
- Retention on first-line ART ≥70%: 67%
- On time drug pick-up ≥90%: 17%
- On time appointment keeping ≥80%: 58%
- Drug supply continuity 100%: 65%
- Viral load suppression 12 months ≥70%: 85%

WHO HIV Drug Resistance Report 2012
Transmitted HIVDR in MSM and HSX is stabilizing in Europe

Prevalence of resistance over time

- any class
- NRTI
- NNRTI
- PI

Prevalence

Year


WHO 2009 Surveillance Drug Resistance Mutation list

P = 0.37
0.44
0.004 (increase in MSM only)

N = 4317

Wensing, on behalf of SPREAD
eacs-conference Oct 2011
Global trends in antiretroviral resistance in treatment-naive individuals with HIV after rollout of antiretroviral treatment in resource-limited settings: a global collaborative study and meta-regression analysis

Ravindra K Gupta, Michael R Jordan, Binta J Sultan, Andrew Hill, Daniel H J Davis, John Gregson, Anthony W Sawyer, Raph L Hamers, Nicole Ndombé, Deenan Pillay, Silvia Bertagnolio

26,102 patients from 191 datasets from 42 countries in Africa, Asia, Latin America
Prevalence of HIVDR in ARV-naïve individuals, by time since ARV rollout

Every circle is a study and the size of the circle is proportional to the precision of the estimate from the individual study.

Gupta et al. Lancet 2012
WHO transmitted HIVDR surveys
Mutation Prevalence
n=3588, pooled analysis from 82 surveys
Pretherapy HIVDR doubles 1\textsuperscript{st} year risk of VF and acquired HIVDR

\textit{PASER-M cohort in 6 African countries}

Multivariate analysis adjusted for sex, age, calendar year, WHO clinical stage, BMI, pretherapy HIVRNA and CD\textsubscript{4}, prior ARV use, type of NRTI and NNRTI.

\begin{itemize}
  \item No PDR (n=2404)
  \item PDR and fully-active ART (n=52)
  \item PDR and partially-active ART (n=123)
\end{itemize}

\begin{itemize}
  \item 91% Viral suppression
  \item 86% Viral suppression
  \item 75% Viral suppression
\end{itemize}

Hamers et al. Lancet Inf Dis 2012
Acquired HIVDR mutations in people failing ART at 12 Months from LMIC

WHO, pooled data
n=269
Lack of VL monitoring leads to loss of drug susceptibility

Cohort 1 (n=100)
Virological failure by routine pVL test, 12 mo ART

Cohort 2 (n=161)
Clinico-immunological failure, 26 mo ART

Hamers CID12; Sigaloff JID12
TDR reduced by implementing routine pVL monitoring to guide switches

Phillips A et al. AIDS 2011
Earlier treatment of HIV and transmitted HIV drug resistance in Sub-Saharan Africa

Brooke Nichols
Department of Virology
Erasmus MC
Rotterdam, The Netherlands
HIV Limited availability treatment

• Treating with three different drugs from two different classes is necessary, else resistance will develop

• In sub-Saharan Africa, limited HIV treatment regimens are available
  – Zidovudine-based (+lamivudine +NNRTI)
  – Tenofovir-based (+lamivudine +NNRTI)

  – A boosted protease inhibitor + 2 NRTIs
Potential issues with earlier treatment

- Resource limited settings
  - Already stretched thin, let alone with additional monitoring tests to detect drug resistance

- Viral load assays frequently not available
  - Expensive!
  - Without viral load assays, resistance emerges more quickly (Nichols J Intern Med 2011)

- Earlier treatment may also have adherence issues
  - Therefore- more resistance?
Kampala, Uganda

- Urban, government clinic
- **PASER-S: Surveillance 2010**
  - Transmitted drug resistance prevalence: 8.6%
- **PASER-M: Monitoring 2007-8 enrollment**
  - 10% acquired drug resistance after 12 months on zidovudine-based regimen
  - 6% acquired drug resistance after 12 months on tenofovir-based regimen
    - 40% of patients on tenofovir-based regimen
The Model: Simplified

Model calibrated to Kampala epidemic & Mombasa epidemic separately
Key model features

- Drug resistance by mutation or class - individuals can be infected with:
HIV Prevalence

Kampala, Uganda
- <200 cells/mm$^3$
- <350 cells/mm$^3$
- <500 cells/mm$^3$
Transmitted Drug Resistance Prevalence

Kampala, Uganda
- <200 cells/mm³
- <350 cells/mm³
- <500 cells/mm³

Year

TDR Prevalence (%)
0 5 10 15 20
Transmitted drug resistance by drug class or mutation

A. Kampala, Uganda

- NNRTI
- PI
- TAM
- M184V
- K65R

TDR Prevalence (%) vs Year

Year: 2012 to 2022
Transmitted drug resistance by drug class or mutation

A. Kampala, Uganda

NNRTIs part of ALL first-line regimens!
Where is it possible to intervene?

• Increase access to second-line!
  – Only 33-50% of patients with continued failure on first-line make it onto second line
  – Increase to 80-100%?
Increasing access to second-line

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

- Kampala, Uganda
- Increase in second-line
  - 200
  - 350
  - 500
Prevention of new infections vs. increase of transmitted drug resistance

• Kampala:
  – Treatment increase to CD4 <350: 18 infections averted for every additional case infected with a drug-resistant virus
  – When treatment at CD4 <500: 22 infections averted for every additional case infected with a drug-resistant virus
Previous papers have only shown the potential harms of increasing treatment and the issues with drug resistance. We have shown that the benefits of earlier treatment outweigh the risks associated with resistance! Starting second-line in a timely manner can eliminate this altogether!

Not the benefits of averting new infections!

We have shown that the benefits of earlier treatment outweigh the risks associated with resistance!
Starting second-line in a timely manner can eliminate this altogether!
Conclusions

• Increasing access to ART will increase the prevalence of drug resistant HIV among new infections, particularly NNRTI resistance

• The number of new infections is strongly reduced by increasing ART coverage
  – outweighs the risk of increased TDR

• Timely switching to second-line boosted PI regimens can actually reduce TDR over time
Pre-exposure profylaxis (PREP)?

Limited impact on HIVDR prevalence in sub-Saharan Africa
Conclusions – 1

• A possibilities that transmissible multidrug resistance will be generated

• Available evidence suggests that ART scale-up is driving TDR (NNRTIs) in east and southern Africa, which compromises response to first-line NNRTI-based ART
  - Of concern, but not at unexpected levels and rates
  - Lack of routine HIVDR surveillance data

• Current standard 1st and 2nd line regimens still effective for the majority of patients
Conclusions - 2

• Mathematical modelling predicts that:
  
  – Early ART initiation drives TDR, but outweighed by new infections averted
  – TDR can be eliminated by early failure detection and timely switch
  – HIVDR from treatment scale-up is expected to far exceed that from PrEP

• As novel ART strategies are being implemented, operational research needed to assess their impact in terms of adherence, retention and HIVDR development
Conclusions – 3

• HIVDR is a possible, but manageable, future threat to the success of the global HIV/AIDS control.
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16–19 April 2013

Manchester Central Convention Complex