Genotypic Resistance Testing in Routine Care in South Africa:

Is the Juice Worth the Squeeze?

Mark Siedner
Africa Health Research Institute
Harvard Medical School
Conflicts of Interest^*  

- No financial conflicts to report

^I am personally conflicted by my own argument

*Also I am not a modeler so I hope you did not come to this talk to see someone give you a convincingly derived, data-driven answer
The Case Against HIV GRT in SSA

• Resistance is not such a big deal
  • If it is now, it won’t be in the era of DTG

• Resistance testing is too expensive

• Resistance testing will not change outcomes
Resistance is Not Such a Big Deal
Not such a big deal: TDR

Gupta et al, Lancet HIV 2017
Not such a big deal: Resistance @ Failure

**Adults**
- Cytosine analogue
- NNRTI
- Tenofovir
  - Eastern Africa (n=159)
  - Southern Africa (n=461)
  - West and central Africa (n=82)

**Children**
- Any RAM
- NRTI
- NNRTI
- PI
  - Central and west Africa (n=134)
  - East Africa (n=132)
  - Southern Africa (n=479)

Not such a big deal: Resistance and outcomes

<table>
<thead>
<tr>
<th>Number of events</th>
<th>Multivariate</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline model</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>PDR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No PDR</td>
<td>174</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>PDR and fully active ART</td>
<td>6</td>
<td>1.01</td>
<td>0.55-1.87</td>
</tr>
<tr>
<td>PDR and partly active ART</td>
<td>21</td>
<td>2.13</td>
<td>1.44-3.14</td>
</tr>
</tbody>
</table>

Hamers et al, Lancet HIV, 2012
McCluskey et al, AIDS Pt Care and STDs, 2018
Not such a big deal: Resistance and outcomes

Detectable HIV RNA on first line ART
n = 90

Resistance Virus
n = 47/90
(52%)

Wild Type Virus
n = 43/90
(48%)

Continued first line ART

Average adherence >90%

n = 17/47
(36%)

n = 30/47
(64%)

Resuppress <400 copies/mL
n = 4/17
(24%)

n = 9/30
(30%)

Average adherence <90%

n = 22/43
(51%)

n = 21/43
(49%)

Resuppress <400 copies/mL
n = 20/22
(91%)

n = 16/21
(76%)

McCluskey et al, CROI, 2018
Not such a big deal: Deaths and costs

AIDS Deaths (millions)
- Total: 5 million
- Due to DR (<10%): 13%
- Due to DR (>10%): 16%

New HIV Infections (millions)
- Total: 5 million
- Due to DR (<10%): 7%
- Due to DR (>10%): 9%

ART Costs ($USD billion)
- Total: 80 billion
- Due to DR (<10%): 6%
- Due to DR (>10%): 8%
Will DTG Save Us from Resistance?
<table>
<thead>
<tr>
<th></th>
<th>SPRING-2&lt;sup&gt;1&lt;/sup&gt; (to Week 96)*</th>
<th>SINGLE&lt;sup&gt;2&lt;/sup&gt; (to Week 144)*</th>
<th>FLAMINGO&lt;sup&gt;3&lt;/sup&gt; (to Week 96)&lt;sup&gt;†&lt;/sup&gt;</th>
<th>ARIA&lt;sup&gt;4&lt;/sup&gt; (to Week 48)&lt;sup&gt;‡&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DTG + 2NRTI (n=411)</td>
<td>RAL + 2NRTI (n=411)</td>
<td>DTG + ABC/3TC (n=414)</td>
<td>DTG/ABC/3TC (n=248)</td>
</tr>
<tr>
<td>Subjects with persistent virologic failure, n (%)</td>
<td>20 (5)</td>
<td>28 (7)</td>
<td>39 (9)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Genotypic results at time of failure, n (%)</td>
<td>8</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INSTI-resistant mutations, n (%)&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>0 (0)</td>
<td>1 (6)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>RT genotypic results available at time of PDVF, n</td>
<td>12</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRTI-resistant mutations, n (%)&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>0 (0)</td>
<td>4 (21)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>NNRTI-resistant mutations, n (%)&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>–</td>
<td>–</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>PI-resistant mutations, n (%)&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>–</td>
<td>–</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

* INSTI-resistant mutations: 0 (0) 1 (6) 0 (0) 0 (0) – – 0 (0) 0 (0)

‡ RT genotypic results available at time of PDVF: 12 19 – – – – – –

NRTI-resistant mutations: 0 (0) 4 (21) 0 1 (K65K/R) 0 (0) 0 (0) 0 (0) 1 (M184V)

NNRTI-resistant mutations: 0 (0) 6 (K101E, K103N, K103K/N, G190G/A) 0 (0) 0 (0) – –

PI-resistant mutations: 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0)

**References:**

**Slide Courtesy of Ravi Gupta**
Can DTG Save Us from Resistance?

<table>
<thead>
<tr>
<th>Resistance analysis</th>
<th>DTG + 2 NRTIs (n=8)</th>
<th>LPV/RTV + 2 NRTIs (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INSTI</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NRTI</td>
<td>0</td>
<td>3*</td>
</tr>
<tr>
<td>K70R</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>M184V</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>K219Q</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>K219E</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>PI</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- No subject receiving DTG + 2 NRTIs developed INSTI or NRTI resistance-associated mutations.

Aboud et al, IAS, 2017
Can DTG Save Us from Resistance?

Cahn et al, Lancet HIV 2017
Can DTG Save Us from Resistance?

Can DTG Save Us from Resistance?

*Functional monotherapy in SSA?*  
- ~60% K65 + M184V at failure  
- >70% using NGS
Can DTG Save Us from Resistance?

*ACTUAL* monotherapy in SSA

Proportion of Facilities with at Least one HIV or TB Therapy Stockout

Second Annual Stock Out Report 2014 (MSF)
Can DTG Save Us from Resistance?

- Who’s line is it anyway?

<table>
<thead>
<tr>
<th>Population</th>
<th>First-line regimens</th>
<th>Second-line regimens</th>
<th>Third-line regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults and adolescents</td>
<td>Two NRTIs + DTG³</td>
<td>Two NRTIs + (ATV/r or lopinavir/ritonavir (LPV/r))</td>
<td>Darunavir/ritonavir (DRV/r)³ + DTG³ + 1–2 NRTIs (if possible, consider optimization using genotyping)</td>
</tr>
<tr>
<td>(including women and adolescent girls who are of childbearing potential or are pregnant)⁴</td>
<td>Two NRTIs + EFV⁴</td>
<td>Two NRTIs + DTG³</td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>Two NRTIs + DTG</td>
<td>Two NRTIs + (ATV/r or LPV/r)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Two NRTIs + LPV/r</td>
<td>Two NRTIs + DTG³</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Two NRTIs + NNRTI</td>
<td>Two NRTIs + DTG³</td>
<td></td>
</tr>
</tbody>
</table>

- Cabotegravir as a PrEP & DTG as ART?

Wijting et al, Lancet HIV 2017
Resistance Testing is Too Expensive
Resistance Testing is Too Expensive


d| Analysis Model | Population | Perspective | Time Horizon | Outcome | Sensitivity Analysis | Primary Result |
<table>
<thead>
<tr>
<th></th>
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<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost-Effectiveness of Preventing AIDS Complications state-transition model [24]</td>
<td>South Africa</td>
<td>Modified societal</td>
<td>Lifetime</td>
<td>Cost/year of life saved</td>
<td>Univariate and multiway</td>
<td>Very cost effective</td>
</tr>
<tr>
<td>Cost minimization model [25]</td>
<td>South Africa</td>
<td>Presumed Payer</td>
<td>5 years</td>
<td>Cost per strategy</td>
<td>Deterministic/Probabilistic</td>
<td>Cost Neutral</td>
</tr>
<tr>
<td>HIV synthesis transmission individual-based stochastic model [26]</td>
<td>Zimbabwe</td>
<td>Unstated</td>
<td>10 years</td>
<td>Cost/disability adjusted life year (DALY) averted</td>
<td>Several one way sensitivity analyses</td>
<td>Not cost-effective</td>
</tr>
</tbody>
</table>

Cost-Effectiveness of Dolutegravir

Philipps et al, Lancet HIV, 2017
Too expensive: In-house technology

Genotypic Resistance Testing Costs in sub-Saharan Africa

Hamers et al, Lancet ID, 2016
## Too expensive: Limited formulary

<table>
<thead>
<tr>
<th>South Africa</th>
<th>United States</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTIs</strong></td>
<td></td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate/FTC</td>
<td>Tenofovir alamfenamide fumarate/FTC</td>
</tr>
<tr>
<td>Zidovudine/3TC</td>
<td>Tenofovir disoproxil fumarate/FTC</td>
</tr>
<tr>
<td>Abacavir/3TC</td>
<td>Abacavir/3TC</td>
</tr>
<tr>
<td><strong>NNRTIs</strong></td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Rilpivirine</td>
</tr>
<tr>
<td></td>
<td>Doravirine</td>
</tr>
<tr>
<td></td>
<td>Efavirenz</td>
</tr>
<tr>
<td></td>
<td>Etravirane</td>
</tr>
<tr>
<td><strong>INSTIs</strong></td>
<td></td>
</tr>
<tr>
<td>Dolutegravir (any day/month now...)</td>
<td>Dolutegravir</td>
</tr>
<tr>
<td>Raltegravir (highly restricted)</td>
<td>Bictegravir</td>
</tr>
<tr>
<td></td>
<td>Elvitegravir</td>
</tr>
<tr>
<td></td>
<td>Raltegravir</td>
</tr>
<tr>
<td><strong>PIs</strong></td>
<td></td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>Darunavir/ritonavir</td>
</tr>
<tr>
<td>Atazanavir/ritonavir (restricted)</td>
<td>Atazanavir/ritonavir</td>
</tr>
<tr>
<td>Darunavir/ritonavir (highly restricted)</td>
<td></td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
</tr>
<tr>
<td>Maravaroc</td>
<td></td>
</tr>
<tr>
<td>Ibalizumab</td>
<td></td>
</tr>
</tbody>
</table>
Too expensive: Cost of not testing?
Resistance Testing Doesn’t Improve Outcomes
Resistance Testing Doesn’t Improve Outcomes

Resistance Testing Doesn’t Improve Outcomes

Proportion with Virologic Failure at 12 months

- ITT: n=803, P=0.56
- Wild Type: n=714, P=0.47
- Mutation 2-9%: n=27, P=0.47
- Mutation >10%: n=62, P=0.005

Chung et al, CROI 2016
Resistance Testing Doesn’t Improve Outcomes

Resistance Testing Doesn’t Improve Outcomes

Stockdale et al, CID
Resistance Testing Doesn’t Improve Outcomes

**HIV RNA**

- >1000 copies/mL
  - N = 64

\[ p = 0.89 \]

Average Adherence After Failure
Resistance Testing Will Not Change Outcomes

• Can a resistance test be an adherence intervention for patients?
Resistance Testing Will Not Change Outcomes

- Can a resistance test be an adherence intervention for clinicians?

![Pie chart showing distribution of outcomes]

- Changed to 2° Line (n=158, 6%)
- Re-suppressed on 1° Line (n=732, 20%)
- Remained on Failing Regimen (n=1,548, 63%)

Unpublished (Data analysis provided by Kathy Baisley, AHRI)
Resistance Testing Will Not Change Outcomes

- Can a resistance test be an adherence intervention for clinicians?

**Days on a Failing Regimen**

- Days on a Failing Regimen:
  - Remained on 1º Line
  - Switched to 2º Line

- Statistics:
  - Confirmed Death (n=124, 8%)
  - LTFU (n=588, 38%)
  - Censored on 1º Line (n=617, 40%)
  - Transferred Care (n=218, 14%)
  - Total (n=1548)
A GRT is not necessarily a GRT

<table>
<thead>
<tr>
<th></th>
<th>Pre DTG Era</th>
<th>Post DTG Era</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-ART GRT</td>
<td>Case 1</td>
<td>Case 1</td>
</tr>
<tr>
<td>GRT at First-Line Failure</td>
<td>Case 2</td>
<td>Case 3</td>
</tr>
</tbody>
</table>
Case 1

22 year old P1000 woman presents to care. She recently had a positive pregnancy test followed by a first ANC visit at ~10 weeks, where she was diagnosed with HIV. Her partner has been on treatment intermittently for 6 years with a one-pill/day regimen.

a. Which initial HIV regimen would you choose in the pre-DTG era?

b. Which initial HIV regimen would you choose in the post-DTG era

c. Should a routine HIV resistance test be available in this case?
Women presenting in pregnancy*

*After 28 weeks gestation

Orrell et al, AIDS 2018
Case 2

30 year old man, diagnosed with HIV in 2017, presented with CD4 10, recently completed 6 months of drug-susceptible pulmonary TB therapy. Truck driver, and picks up his medicines consistently, but often away 2-3 months at a time. First VL six months into treatment 25,000 copies/mL. Claims excellent adherence.

a. Should a routine HIV resistance test be available in this case?
Case 3

42 year old woman, diagnosed with HIV in 2000. Previously treated with triple nucleoside regimen, then D4T/3TC/EFV, then TDF/FTC/EFV, then switched to DTG/TDF/3TC 18 months ago. She initially suppressed on that regimen, but now has had three detectable VL of approximately 10,000 copies/mL over the past 12 months. She has thrush and has lost 4 kilograms in the past 6 months.

a. Which regimen would you choose?
b. Should a routine HIV resistance test be available in this case?
The Juice (might be) Worth the Squeeze

• Resistance is highly prevalent
  • Is resistance to INSTIs in SSA just a matter of time?

• Tradeoff between GRT and ART class step-up improving

• Resistance testing itself as an intervention to salvage lower cost-therapies

• Strong clinical rationale in key populations
Thank you

- Suzanne McCluskey
- Kathy Baisley
- Richard Lessells
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- Vince Marconi
- Ravi Gupta
- Kathy Baisley
- Francois Venter
- Conference Organizers