Routine 1\textsuperscript{st}-line resistance testing in the current treatment era: now is not the time

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XXVII International Workshop on HIV Drug Resistance and Treatment Strategies
October 23\textsuperscript{rd}, 2018

Supported by NHLBI (K01HL123349), NIAID (R01AI042006), and Claflin Distinguished Scholars Award
Financial disclosures

• I have no financial disclosures
Key points

• HIV DR testing can improve clinical outcomes but only after programmatic strengthening

• Rollout of DTG further reduces the benefits of routine HIV DR testing in the general population

• Resources can likely best be used by improving VL monitoring
Global objective

• To optimize the scale-up and sustainability of ART access and viral suppression worldwide to improve life expectancy and decrease transmissions

  1. Improve ART effectiveness and durability
  2. Utilize available resources efficiently
ART scale-up is unprecedented …

UNAIDS Global AIDS Update 2018
... Ongoing scale-up is still needed

UNAIDS/WHO estimates reported July 2018
Finding efficiencies in HIV care

PEPFAR 2018 Progress Report.
Roadmap

- Clinical impact of HIV DR testing
- Resource utilization
- Programmatic challenges
- Opportunity costs
Roadmap

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- Resource utilization
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- Opportunity costs
WHO regimen guidelines (July 2018)

1st Line
- EFV + 2 NRTI
- DTG + 2 NRTI

2nd Line
- DTG + 2 NRTI
- PI + 2 NRTI

3rd Line
- DTG (BID) + DRV/r (BID) + 1-2 NRTI

Start/switch regimen → Re-start regimen → INSTI genotype?

TLE initiation: no HIV DR testing

VL Monitoring

- **NNRTI-R 1\textsuperscript{st}-line ART**
- **Suppressed 1\textsuperscript{st}-line ART**
- **Failing 1\textsuperscript{st}-line ART**
TLE initiation: HIV DR testing

HIV DR Test

VL Monitoring

- NNRTI-R 1st-line ART
- Suppressed 1st-line ART
- Failing 1st-line ART
- Suppressed 2nd-line ART
Can NNRTI-R virus suppress with EFV?

- 837 patients initiated TDF/FTC/EFV in rural KZN and had at least 1 VL in follow-up
- Overall, 94.5% suppressed at 12 months

<table>
<thead>
<tr>
<th>PDR</th>
<th>N=</th>
<th>Time to suppression (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No PDR</td>
<td>765 (91%)</td>
<td>3.5</td>
</tr>
<tr>
<td>NNRTI-R</td>
<td>67 (9%)</td>
<td>4.1</td>
</tr>
<tr>
<td>NRTI/NNRTI-R</td>
<td>5 (&lt;1%)</td>
<td>11.7</td>
</tr>
</tbody>
</table>

Derache and Iwuji *et al.* CID 2018
Transmitted INSTI-R

• Very rare
• Not all INSTI-R mutations have clinical consequences
  – DTG will be active against many INSTI mutations

• Koulias et al. used simulation modeling to evaluate INSTI-R testing at ART initiation:
  – As long as 20% of transmitted INSTI-R mutations suppressed with DTG, it was not clinically beneficial or cost-effective to test before ART start in the US
  – Assumption: VL monitoring!

Koullias et al. CID 2017
HIV DR testing at 1\textsuperscript{st}-line ART initiation

- So many tests!
  - Benefits a small percentage of PWH
  - Insufficient laboratory capacity
  - \textbf{Will add delays to ART start for everyone}

- Minimal clinical benefit for patients starting TLD
  - Low PDR
  - Some INSTI mutations will suppress on DTG

- Alternative method to assess for failure
  - VL monitoring

- Costly
TLE failure: no HIV DR testing

NNRTI-R 1\textsuperscript{st}-line ART  Suppressed 1\textsuperscript{st}-line ART  Failing 1\textsuperscript{st}-line ART  Suppressed 2\textsuperscript{nd}-line ART
TLE failure: HIV DR testing

- **VL #1**: FF
- **VL #2**: FF
- **HIV DR Test**: FF
- **EAC**: FF
- **ART switch**: FF

- **NNRTI-R 1st-line ART**
- **Suppressed 1st-line ART**
- **Failing 1st-line ART**
- **Suppressed 2nd-line ART**
Benefits of HIV DR testing

• If susceptible virus:
  – Reduces unnecessary switch to later lines of ART
    • Monthly ART cost will be lower
    • Better tolerated ART regimens
    • Additional lines of ART reserved for future need

• If resistant virus:
  – Prompts appropriate regimen start/switch BUT
    • Genotype results must be interpreted
    • Someone must be empowered to make the switch
    • Next-line ART must be available
## CEA: genotype at 1st-line ART failure

<table>
<thead>
<tr>
<th>Country</th>
<th>Life expectancy</th>
<th>Cost</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosen 2011 South Africa</td>
<td>NA</td>
<td>--</td>
<td>Cost-neutral</td>
</tr>
<tr>
<td>Levison 2013 South Africa</td>
<td>↑ ↑</td>
<td>↑ ↑</td>
<td>Cost-effective ($900/YLS)</td>
</tr>
<tr>
<td>Phillips 2014 Zimbabwe</td>
<td>↑ ↑</td>
<td>↑ ↑</td>
<td>Not cost-effective</td>
</tr>
</tbody>
</table>
CEA: genotype at failure

• No analyses published regarding genotype after failure on INSTI regimen

• Genotype testing was cost-neutral or CE
  – ~80% of patients fail ART with resistant virus
  – Unnecessary switches are costly bc 2nd-line ART is 2-5x more expensive than 1st-line ART
  – HIV DR testing prompts *appropriate* switches but must not create delays (Not CE if >5 months)

• HIV DR testing not CE
  – Benefits of PI-based ART for poorly adherent
  – Not all switch to 2nd-line, even with HIV DR test

TLE failure: HIV DR testing – reality?

NNRTI-R 1<sup>st</sup>-line ART  Suppressed 1<sup>st</sup>-line ART  Failing 1<sup>st</sup>-line ART  Suppressed 2<sup>nd</sup>-line ART
HIV DR testing doesn’t solve inaction

• Why do patients fail 1st-line ART for prolonged periods of time?
  – Virologic failure goes unrecognized
  – Clinicians do not recommend 2nd-line despite VF
  – 2nd-line is not available (stockouts)
HIV DR testing doesn’t solve inaction

- Why do patients fail 1st-line ART for prolonged periods of time?
  - Virologic failure goes unrecognized
    - Improve VL monitoring
  - Clinicians do not recommend 2nd-line despite VF
    - Empower clinicians to advocate for 2nd-line ART after repeat VL remains detectable
  - 2nd-line is not available (stockouts)
    - Improve supply chains
Roadmap

Clinical impact of HIV DR testing

Resource utilization

Programmatic challenges

Opportunity costs
Test costs

• Usually described as “$XX/test”

• Such estimates rarely include many of the important contributors to what it takes to deploy a diagnostic test
Resource utilization

• Laboratory infrastructure
  – Capital costs
  – Maintenance costs

• Fixed versus marginal costs
  – Fixed: for test availability (machine, staff salaries, QC)
  – Marginal: per test (reagents, staff time)

• Additional costs
  – Transport of specimens
  – Communication of results with care providers
Resource utilization ≠ per test costs

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<th>Mobile clinic</th>
<th>Clinic</th>
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<td>Salary cost for QC ($/day)</td>
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<td>$4.41</td>
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<tr>
<td><strong>Total cost for QC ($/day)</strong></td>
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Roadmap

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- Resource utilization
- Programmatic challenges
- Opportunity costs
Anticipated challenges with DR testing

• New algorithm needed for providers
  – Who will be trained to interpret genotype results?
  – Who will be empowered to switch regimens?

• Avoid re-centralization
• Do not divert resources from VL scale-up
• Ensure accessibility and affordability of 2nd-line

• Given challenges surrounding DTG, now is not the time to add program complexity
Roadmap

- Clinical impact of HIV DR testing
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Opportunity costs

• What will not be funded if routine HIV DR testing is started?

• Would scale-up of VL monitoring slow?
  – Only 10% of focus countries report ≥90% of PWH on ART with annual VL

• Would ART availability be compromised?
  – 48% of focus countries reported ART stock outs in past year

Future steps

• Ongoing improvement in programmatic flow
  – Consistent viral load monitoring
  – Increased switch to 2\textsuperscript{nd}-line for patients failing 1\textsuperscript{st}-line
  – Reduce stock outs

• Special populations
  – Children

• Surveillance $\neq$ clinical decision-making
  – Further drug resistance data collected now to inform future guidelines

• Hope for the best, but anticipate the worst
  – Now is the time to develop a plan; simulation modeling can provide estimates and project outcomes
Key points

• HIV DR testing can improve clinical outcomes but only after programmatic strengthening

• Rollout of DTG further reduces the benefits of routine HIV DR testing in the general population

• Resources can likely best be used by improving VL monitoring
Thank You

**CEPAC-International Research Team**

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Valdilea Veloso, MD

**Côte d’Ivoire**
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**Supported by:**
National Heart, Lung, and Blood Institute (K01HL123349)  
National Institute of Allergy and Infectious Disease (R01AI042006, R37AI093269)
SUPPLEMENTARY SLIDES
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Start/switch regimen

Re-start regimen

INSTI genotype?

TLE Failure: HIV DR Testing

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TLD Failure: No HIV DR Testing

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TLD Failure: HIV DR Testing
Clinical Decision-Making

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<tr>
<th>ART Initiation</th>
<th>ART Switch</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLE</td>
<td>TLD</td>
</tr>
<tr>
<td>TLD</td>
<td>?</td>
</tr>
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** NRTI resistance pattern used to determine NRTI pair
Data Are on the Horizon

Inclusion criteria: patients failing NNRTI + 2NRTI

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAWNING</td>
<td>DTG vs LPV/r</td>
<td>Awaiting final data</td>
</tr>
<tr>
<td>D2EFT</td>
<td>DRV/r + 2NRTI, DTG + TDF/XTC, DRV/r + DTG</td>
<td>Enrolling</td>
</tr>
<tr>
<td>NADIA</td>
<td>DTG vs DRV/r + TDF/XTC vs AZT/3TC</td>
<td>Protocol finalization</td>
</tr>
</tbody>
</table>

Adapted from ClinicalTrials.gov
VL Monitoring is Essential

- Among PWH who have close follow-up with VL testing to assess response to ART, HIV DR testing
  - Reduce transmissions
  - Prompt adherence counseling
  - Trigger resistance testing or empiric ART switch
Clinical benefits of HIV DR testing

• Pretest probability of resistance:
  – Prevalence of pretreatment drug resistance
  – Likelihood of developing acquired drug resistance
    • Genetic barrier to resistance
    • Tolerability of regimens (adherence)
    • Frequency of stockouts

• Selection of optimal ART regimen
  – Depending on HIV DR test result