HIV Drug Resistance Training

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Welcome to the HIV Drug Resistance Module
Module Objectives

At the end of this module, participants will be able to:

- Discuss what Antiviral Drug Resistance means;
- Describe what factors influence HIVDR;
- Discuss how medication factors contribute to HIVDR;
- Discuss how systems factors can contribute to HIVDR;
- Discuss how patient factors can contribute to HIVDR;
- Discuss some of the elements of a National HIVDR Prevention and Assessment Strategy;
- Describe the HIVDR Early Warning Indicators (EWI);
- Discuss what response to take from surveys;
- Drug Resistance Testing for individual patient management;
- List the limitations of Resistance Testing.
Need for Population-based Therapies

- Need for rapid scale-up
- Need for standardized simplified treatment protocols
- Regimen selection not by clinicians but by national policy—first-line and second-line regimens
- Limitations in health infrastructure, trained personnel, facilities, lab capacity, drug transport and storage
Drug Resistance and HIV

HIV…

- evolves rapidly within human body
- has a high replication rate
- has a high mutation rate

↓

- Resistant strains can emerge within days if drug pressure is not sufficient to suppress replication.
- Resistant strains persist indefinitely and can re-emerge if same drugs are stopped and restarted (even if they are not detected by standard resistance assays).
What is Antiviral Drug Resistance?

- Drugs no longer prevent virus replication
- Cause:
  - Mutations in the viral genome
- One or more:
  - Specific for an antiviral drug OR
  - Affecting related drugs (cross-resistance)
- How much resistance? Which drugs?
  - Depends on type and number of mutations
HIV Drug Resistance is inevitable

- HIV DR is an inevitable consequence of ART, influenced by:
  - Adherence and tolerability of regimens
  - Low genetic barrier to resistance of some drug classes
  - Pharmacokinetics (IQ)
  - Availability/continuity of drug supply
  - Removal of barriers to access to care

- Therefore, efforts to minimize HIVDR should be focused on these factors
Medication Factors

- Use of appropriate drug regimens – all patients to be treated with 3 or more drugs from different drug classes
- Can and must suppress HIV replication to levels of <50 copies/ml
- Use of fixed-dose combinations to support adherence
In Which Conditions is DR Less Likely? (continued…)

System Factors

- Trained personnel, low turnover
- Appropriate supervision and monitoring
- Adequate lab services
- Effective drug supply and delivery systems
In Which Conditions is DR Less Likely? (continued…)

Patient Factors

- Optimal adherence to treatment regimen
- Avoiding interruption of treatment, even if only a few days
- Regular follow-up (going to clinic)
- Staying on uninterrupted first-line ART as long as possible
- Dialogue between care provider and patient to find optimal solution
- Community-based support
Elements of a National HIVDR Prevention and Assessment Strategy

A. Development of a national HIVDR Working Group, five year plan and budget
B. Regular assessment of HIVDR early warning indicators (EWI) from all ART sites (or representative sites)
C. Surveys to monitor acquired HIVDR and associated factors in patients receiving ART
D. HIVDR transmission / pretreatment surveys in areas where ART has been provided for > 3 years
E. HIVDR database development
F. Designation of an in-country or regional WHO-accredited HIVDR genotyping laboratory
G. HIVDR minimization activities review and support
H. Preparation of annual HIVDR report and recommendations; use of data for ART and planning

*Bennett, Bertagnolio, Sutherland and Gilks, Antiviral Therapy 13 Suppl 2:1–13, 2008*
### HIVDR EWI Site-Based Report Example

<table>
<thead>
<tr>
<th>Site</th>
<th>Months with no ARV drug stockouts</th>
<th>% appropriate Initial ART regimen prescriptions</th>
<th>% starting first line ART lost to follow up at 12 months</th>
<th>% on ART keeping all clinical appointments on time</th>
<th>% on ART picking up all ART drugs on time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>94/94 (100%)</td>
<td>4/96 (4%)</td>
<td>182/209 (87%)</td>
<td>184/192 (96%)</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>81/81 (100%)</td>
<td>9/74 (12%)</td>
<td>342/402 (85%)</td>
<td>176/220 (80%)</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>31/40 (78%)</td>
<td>12/37 (32%)</td>
<td>122/244 (50%)</td>
<td>144/206 (70%)</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>104/104 (100%)</td>
<td>10/99 (10%)</td>
<td>891/993 (90%)</td>
<td>483/508 (95%)</td>
</tr>
<tr>
<td>5</td>
<td>12</td>
<td>112/112 (100%)</td>
<td>13/105 (12%)</td>
<td>262/305 (85%)</td>
<td>184/202 (91%)</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>98/101 (97%)</td>
<td>2/90 (2%)</td>
<td>416/442 (95%)</td>
<td>254/359 (71%)</td>
</tr>
<tr>
<td>7</td>
<td>12</td>
<td>98/98 (100%)</td>
<td>9/88 (10%)</td>
<td>602/683 (88%)</td>
<td>369/402 (95%)</td>
</tr>
<tr>
<td>8</td>
<td>12</td>
<td>203/203 (100%)</td>
<td>43/195 (22%)</td>
<td>292/356 (82%)</td>
<td>254/284 (86%)</td>
</tr>
<tr>
<td>9</td>
<td>12</td>
<td>304/305 (99.7%)</td>
<td>117/260 (45%)</td>
<td>753/1506 (50%)</td>
<td>829/1202 (69%)</td>
</tr>
<tr>
<td>10...</td>
<td>12</td>
<td>94/94 (100%)</td>
<td>12/90 (13%)</td>
<td>271/305 (89%)</td>
<td>269/290 (93%)</td>
</tr>
<tr>
<td>152</td>
<td>12</td>
<td>33/33 (100%)</td>
<td>4/31 (13%)</td>
<td>147/180 (82%)</td>
<td>143/159 (90%)</td>
</tr>
<tr>
<td>153</td>
<td>10</td>
<td>26/34 (76%)</td>
<td>7/35 (20%)</td>
<td>148/224 (66%)</td>
<td>129/182 (71%)</td>
</tr>
<tr>
<td>154</td>
<td>12</td>
<td>73/73 (100%)</td>
<td>9/69 (16%)</td>
<td>178/203 (87%)</td>
<td>146/154 (95%)</td>
</tr>
</tbody>
</table>
Response to Results from Surveys

- When to consider changing standard 1<sup>st</sup> line regimen
- Monitor Early Warning Indicators for clues about what can be improved at a programmatic level
- If the patterns of resistance indicate reduced susceptibility to 2<sup>nd</sup> line drugs, surveys should be repeated in the original areas annually and extended to additional areas.
- Consider changing standard 2<sup>nd</sup> line regimen.
- Standardization of 3<sup>rd</sup> line regimen?

- **When to use:**
  - When options are available
  - To indicate drug exposure – NO!
  - At 2nd-line failure

- **What to consider:**
  - Treatment history, other reasons for therapy failure
  - Requires expert advice for optimal use
Only possible in case of a detectable viral load

Current assays do not pick up “minority species;” information is given on predominant strain

Assays have mostly been studied in “late” failures; what is their value in early failures?

Susceptibility is not equal to activity (clinical efficacy)

Clinical validation: more data necessary
Testing options

- US FDA-approved HIV-1 genotyping systems:
  - ViroSeq™ HIV-1 genotyping system ($150)
  - TRUGENE® HIV-1 genotyping system ($200)
- In-house, or “home-brew” genotyping systems ($120)
- ATCC
- Specific instruments: extraction, PCR and sequencing
- Specimen: EDTA plasma
- Viral load level: ≥1000-2000 copies/ml of plasma
- Extensive training for technicians
- Laboratory Biosafety level II working environment for sample preparation
Summary

HIV...

- evolves rapidly within human body
- has a high replication rate
- has a high mutation rate
- Resistant strains persist indefinitely and can re-emerge if same drugs are stopped and restarted (even if they are not detected by standard resistance assays).

HIV DR is an inevitable consequence of ART, influenced by:

- Adherence and tolerability of regimens
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- Pharmacokinetics (IQ)
- Availability/continuity of drug supply
- Removal of barriers to access to care
Monitor Early Warning Indicators for clues about what can be improved at a programmatic level.

If the patterns of resistance indicate reduced susceptibility to 2nd line drugs, surveys should be repeated in the original areas annually and extended to additional areas.

Limitations of Drug Resistance Testing:

- Only possible in case of a detectable viral load.
- Current assays do not pick up “minority species;” information is given on predominant strain.
- Susceptibility is not equal to activity (clinical efficacy).
- Clinical validation: more data necessary.
References

- Bennett, Bertagnolio, Sutherland and Gilks, Antiviral Therapy 13 Suppl 2:1–13, 2008
Wrap Up: Outcomes

Participants are now able to:

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