ARV Resistance
Learning Objectives

- Define drug resistance
- Identify factors that influence drug resistance.
- Identify strategies for minimizing development of drug resistance.
- Identify strategies for responding to detection of moderate to high levels of drug resistant HIV.
Impact of drug resistance

• Why is it important to measure drug resistance?

• How does it impact the success of large-scale treatment programs?
What is ARV drug resistance?

- Drugs no longer block 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
Types of drug resistance

Acquired drug resistance
- Develops when patients interrupt their treatment, do not take it according to prescription, or the drugs are not absorbed properly

Transmitted drug resistance
- People are infected from others who had HIV drug resistance and that carry resistant
Adults and children estimated to be living with HIV, 2014
By WHO region

Number of people, by WHO region

- Eastern Mediterranean: 330,000 [200,000–460,000]
- Western Pacific: 1,400,000 [1,200,000–1,800,000]
- Europe: 2,500,000 [2,200,000–2,800,000]
- Americas: 3,400,000 [2,500,000–4,400,000]
- South-East Asia: 3,500,000 [3,200,000–3,700,000]
- Africa: 25,800,000 [24,000,000–28,700,000]

Total: 36,900,000
[34,300,000–41,400,000]

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Information Evidence and Research (IER)
World Health Organization

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HIV Drug Resistance - unavoidable

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

- Ability of regimens to suppress replication completely
- Adherence and tolerability of regimens
- "Genetic barrier" to resistance
- Relative fitness of resistant variant(s)
- Pharmacokinetics (IQ)
- Availability/continuity of drug supply
- Removal of barriers to access to care

Therefore, efforts to minimize HIV DR should be focused on these factors
Need for population-based therapies

1. Need for rapid scale-up
   - Limitations in health infrastructure, trained personnel, facilities, lab capacity, drug transport and storage

2. Need for standardized simplified treatment protocols
   - Regimen selection not by clinicians but by national policy—first-line and second-line regimens
Need to maintain effectiveness

1. Limited number of regimens available
2. Need to minimize drug resistance
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.
Review

- Why is it important to measure drug resistance?
- How does it impact the success of large-scale treatment programs?
Factors that influence development of drug resistance

- What regimens influence drug resistance?
- What patient factors influence drug resistance?
- What public health approaches influence drug resistance?
In which conditions is DR more likely?

- Treatment with <3 drugs
- Inappropriate selection of drugs
- Adding one drug to a failing regimen
- Interruption of treatment (even for a few days)
- Prolonging a failing regimen
Virus related factors influencing resistance

- **High replication** rate of HIV
  - Turnover of 10 billion virions daily

- **Frequent errors** made during replication

- **High mutation rate**
  - 20 million mutations daily

- **Latent reservoirs** of HIV
  - Enable drug resistant HIV to hide for 20-30 years
Resistance can develop quickly, depending on the viral load.

<table>
<thead>
<tr>
<th>Viral Load</th>
<th>Days Before Mutation Arises</th>
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<tr>
<td>300,000</td>
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<tr>
<td>3,000</td>
<td>10</td>
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<tr>
<td>300</td>
<td>100</td>
</tr>
<tr>
<td>30</td>
<td>1,000</td>
</tr>
</tbody>
</table>

Siliciano, 2002
Drug related factors influencing resistance

- Inadequate **potency** (strength)
- **Drug interactions** leading to suboptimal drug levels
- Inadequate **durability** of drug potency (e.g., dual therapy)
- Poor **tolerability**
- **Inconvenience** of regimen
Adequate Drug Levels are Crucial to Control HIV Replication

- High drug levels delay or prevent development of resistance.

- Low drug levels encourage viral replication, ARV resistance, viral rebound and ultimate clinical deterioration.
Mutations and Resistance

- For certain ARVs, only one mutation is needed to stop the drug from working.

- For other ARVs, multiple, step-wise mutations must occur before the drug loses affect.
In which conditions is DR less likely?

**Medication Factors:**

- All patients treated with 3 or more drugs
- Use of appropriate drug regimens
- Can reliably suppress HIV replication to levels of <50 copies/ml
- Use of fixed-dose combinations to support adherence
In which conditions is DR less likely?

Systems Factors:

- Limited number of regimens
- Trained personnel, low turnover
- Supervision and monitoring
- Adequate lab services
- Drug supply and delivery systems
In which conditions is DR less likely?

**Patient Factors:**

- 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
Programmatic factors affecting patient adherence

- Cost of treatment to patient (not only money, but time)
- Distance patient must travel to get treatment
- Supply interruptions
- Availability of second-line regimens for patients whose first-line regimens fail
- Timing of use of second-line regimens
Discussion

- What regimens influence drug resistance?
- What patient factors influence drug resistance?
- What public health approaches influence drug resistance?
What regimens do we use in our country?

What systematic and programmatic challenges do we face?
Minimizing drug resistance

What can countries do to minimize or suppress drug resistance?
Strengthen existing programmes that minimize HIV DR

- Support for adherence and follow-up ➔ THIS IS YOU!
- Removal of barriers to ART access
- Drug supply continuity at the individual, ART site, and national levels
Monitor early warning indicators

- Routine collection of medical and pharmacy records
- Monitor for factors associated with HIV DR prevention or emergence
  - Extent to which prescribing practices meet national and international guidelines
  - % of patients still on first-line; % lost to follow-up
  - % patients with timely medication pick up and clinical follow-up
  - Drug supply continuity at site
  - Adherence and viral load → THIS IS YOU!
HIV DR Early Warning Indicators (EWIs)

- Proportion lost to follow-up during the first 12 months of ART
- Prescribing practices
- Drug supply continuity
- Viral load suppression @ 6 months
- ART appointment-keeping
- On-time ARV drug pick up
- Pill count/adherence
- Patient retention on first-line ART

Site-level ART Program Function
Key Messages

- Impact of HIV Drug Resistance
- Factors that Influence Development of Drug Resistance
- How to Minimize Drug Resistance