Symposium Stream:  
*HIV Resistance: Unavoidable or Preventable*

**Asia and Pacific**

**HIV Resistant Transmission:**

**Are We OK?**

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- **Speakers Bureau**
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  - Gilead, MSD, BMS, Daiichi

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**Categories of HIVDR**

- **Transmitted HIVDR:** previously uninfected individuals are infected with drug-resistant virus
  - Appropriately applied only to HIVDR detected in recently infected individuals

- **Acquired HIVDR:** resistance mutations are selected for by drug selective pressure in individuals receiving ART

- **HIVDR detected in individuals with chronic infection:** either transmitted or acquired

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**HIVDR Definitions**

- **Primary resistance**
  - Increase resistance of HIV to antiretroviral drugs seen in individuals who have never received treatment

  - Presumably have been infected with drug-resistant virus\(^1\,^2\)

  - Infected with a virus that is already resistant at baseline because of drug-resistant virus transmission\(^3\)

- **Secondary resistance\(^1\,^2\)**
  - Increase resistance of HIV to drugs seen in individuals already receiving treatment

  - Treatment failure

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\(^1\)http://www.phac-aspc.gc.ca/publicat/hiv1-vih1/pdf/Hiv-1-strain-01-e.pdf  

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Research Centre for Health Economics and Evaluation (ReCHEE)
Prevalence of HIVDR in Naïve Patients

- Systematic search for studies and conference abstracts published between January 2001 and July 2011
  - Included additional data from the WHO HIVDR surveillance program
- 5,635 patients from 50 studies in Asia
- Median no. of genotype per study: 61 (range, 11-676)
- 40% were recently infected population
- No difference between chronic and recent infection in the prevalence of >1 DR mutation


Characteristics of Studies from Asia

<table>
<thead>
<tr>
<th>Country and no. of study</th>
<th>Median sampling year (range)</th>
<th>Mean time since scale-up (year [range])</th>
<th>Weighted prevalence of DR mutation (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thailand (12)</td>
<td>2005 (2000-09)</td>
<td>4.3 (0.5-9.0)</td>
<td>0.5% (0.1-1.4)</td>
</tr>
<tr>
<td>China (15)</td>
<td>2006 (2001-10)</td>
<td>4.0 (0-7.5)</td>
<td>2.6% (1.4-4.1)</td>
</tr>
<tr>
<td>India (10)</td>
<td>2007 (1999-10)</td>
<td>2.7 (0-6.0)</td>
<td>2.7% (1.1-4.7)</td>
</tr>
<tr>
<td>Vietnam (9)</td>
<td>2010 (7-11)</td>
<td>1 (1.0-4.0)</td>
<td>4.5% (3.3-6.0)</td>
</tr>
</tbody>
</table>

The prevalence in east Africa at rollout was 1.0% (0.6 to 1.9), and 7.4% (4.3 to 12.7) 8 years later, increased 29% per year (95% CI 15 to 45; p=0.0001).


TDR in Asia by WHO HIVDR Threshold Survey Method

<table>
<thead>
<tr>
<th>Country</th>
<th>Year of survey</th>
<th>No. of patients</th>
<th>Patients characteristics</th>
<th>Subtype</th>
<th>Transmitted resistance rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Korea</td>
<td>2002-05</td>
<td>66</td>
<td>Early infection</td>
<td>B (all)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Thailand</td>
<td>2005-06</td>
<td>50</td>
<td>Blood donors and recent infection</td>
<td>CRF01_AE (80-87%)</td>
<td>0</td>
</tr>
<tr>
<td>Cambodia</td>
<td>2006-07</td>
<td>67</td>
<td>Median duration of infection 1.1 years</td>
<td>CRF 01_AE (95%)</td>
<td>(1.5%)</td>
</tr>
<tr>
<td>China</td>
<td>2009-11</td>
<td>182</td>
<td>Age 16-25 years</td>
<td>CRF01_AE (68.5%)</td>
<td>(4.4%)</td>
</tr>
<tr>
<td>China</td>
<td>2009-11</td>
<td>119</td>
<td>Newly diagnosis</td>
<td>CRF01_AE (70.6%)</td>
<td>8 (6.7%)</td>
</tr>
<tr>
<td>Malaysia</td>
<td>2003-04</td>
<td>100</td>
<td>Naive</td>
<td>CRF01_AE (64%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Vietnam</td>
<td>2006</td>
<td>49</td>
<td>Newly diagnosis, age 18-24 years</td>
<td>CRF01_AE (35%), CRF15_01B (20%)</td>
<td>1 (0.2%)</td>
</tr>
</tbody>
</table>


HIVDR in Treatment Naïve HIV with Recent Infection, Thailand

- 2003-6, Thammasat University Hospital
- 305 treatment naive with acute or recently HIV infection
- Median duration of HIV infection: 3 months
- 7 (2%) patients had HIV drug resistance
- Prevalence increased
  - From 0% to 5.8% (p=0.06)
- Sex partner had non-adherence


Research Centre for Health Economics and Evaluation (ReCHEE)
<table>
<thead>
<tr>
<th>Patient</th>
<th>CD4 (cells/mL)</th>
<th>Duration of HIV (months)</th>
<th>Mutation</th>
<th>Sexual partners (adherence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>404</td>
<td>6</td>
<td>K103N, M184C</td>
<td>VF on d4T/3TC/NVP (44%)</td>
</tr>
<tr>
<td>2</td>
<td>516</td>
<td>3</td>
<td>Y181C, M184V</td>
<td>VF on d4T/3TC/NVP (65%)</td>
</tr>
<tr>
<td>3</td>
<td>610</td>
<td>2</td>
<td>Y181C</td>
<td>VF on d4T/3TC/NVP (74%)</td>
</tr>
<tr>
<td>4</td>
<td>495</td>
<td>4</td>
<td>K103N, M184</td>
<td>VF on EFV-based (70%)</td>
</tr>
<tr>
<td>5</td>
<td>554</td>
<td>1</td>
<td>Y181C, M184V</td>
<td>VF on d4T/3TC/NVP (55%)</td>
</tr>
<tr>
<td>6</td>
<td>901</td>
<td>1</td>
<td>Y181C, M184V</td>
<td>VF on d4T/3TC/NVP (45%)</td>
</tr>
<tr>
<td>7</td>
<td>859</td>
<td>1</td>
<td>Y181C, M184V</td>
<td>VF on d4T/3TC/NVP (60%)</td>
</tr>
</tbody>
</table>

### Prevalence of HIVDR in Naïve Patients

- Data included in publications systematically reviewed by the WHO
- Cambodia (N=2), China (N=11), India (N=8), Thailand (N=7) and Vietnam (N=6)

### Reference

**Primary HIVDR in Asia**

<table>
<thead>
<tr>
<th>Duration of HIV infection</th>
<th>No. of patients (n)</th>
<th>No. of patients with drug resistance (n)</th>
<th>Prevalence of drug resistance (%)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent</td>
<td>458</td>
<td>28</td>
<td>6.11</td>
<td>0.065</td>
</tr>
<tr>
<td>Chronic</td>
<td>1,340</td>
<td>54</td>
<td>4.03</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1,798</td>
<td>82</td>
<td>4.56</td>
<td></td>
</tr>
</tbody>
</table>

- Patients with chronic HIV infection, heterosexual contact was less likely to be associated with primary HIVDR
  - OR 0.34, 95% CI 0.20-0.59, \( p < 0.001 \)

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**Resistant associated mutations**

<table>
<thead>
<tr>
<th>Resistance associated mutation</th>
<th>Frequency of RAMs (%)</th>
<th>Total n (%)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recent HIV infection, n (%)</td>
<td>Chronic HIV infection, n (%)</td>
<td></td>
</tr>
<tr>
<td>NRTI</td>
<td>24 (5.2)</td>
<td>49 (3.6)</td>
<td>73 (4.1)</td>
</tr>
<tr>
<td>NNRTI</td>
<td>13 (2.8)</td>
<td>29 (2.2)</td>
<td>42 (2.3)</td>
</tr>
<tr>
<td>PI</td>
<td>18 (3.9)</td>
<td>14 (1.0)</td>
<td>32 (1.8)</td>
</tr>
</tbody>
</table>

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Primary HIVDR in Asia

HIVDR Mutations among Naive HIV-infected Patients in Asia
- 682 patients initiating ART in a prospective, multicenter HIV drug resistance monitoring study, 2007-2009
- 8 sites in Hong Kong, Malaysia, and Thailand
- Heterosexual risk (75%) and median (IQR) CD4 count was 100 (34-201) cells/mm³
- Prevalence of patients with >1 RAMs was 13.8%
- RAMs to NRTIs 8.4%, NNRTIs 6.5%, and PIs 0.4%

HIVDR in Chronic Infection
- 330 patients who had ART initiation in 2010-2011
- Bamrasnaradura Infectious Diseases Institute
- CRF01_AE 73%, B 23.9%, and others 3.1%
- Median (IQR) CD4 count 66 (23-172) cells/mm³
- Prevalence of patients with 1 DRAMs was 17.6%
- DRAM prevalence was 17% for NNRTIs, 0.6% for NRTIs, and 0.6% PIs
- Risk: not subtype AE and lower CD4 percentage

Minority HIV Resistant Variants
- Conventional genotyping results showed no drug resistance-associated mutations
- Pyrosequencing assay was developed to detect and quantify minority Y181C and M184V variants
- Sensitivity of PSQ to detect minority variants was approx. 1%
GS 934: Baseline NNRTI Resistance Reduces Virologic Response

<table>
<thead>
<tr>
<th>HIV RNA &lt;400 cps/mL at week 48 (%)</th>
<th>No baseline NNRTI resistance</th>
<th>Baseline NNRTI resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF + FTC + EFV</td>
<td>84/206 (41%)</td>
<td>9/244 (3.7%)</td>
</tr>
<tr>
<td>ZDV/3TC + EFV</td>
<td>73/177 (41%)</td>
<td>9/243 (3.7%)</td>
</tr>
</tbody>
</table>

Preexisting Resistance to NNRTI Predicts Virologic Failure of an EFV-Based Regimen

- 220 subjects in the random cohort, 57 (26%) had virologic failure
- Prevalence of baseline NNRTI resistance was 5%
- Risk of virologic failure for subjects with baseline NNRTI resistance was higher than that for subjects without such resistance
- HR 2.27, 95% CI 1.15-4.49; P=0.018

Kaplan-Meier plot of time to protocol-defined virologic failure among subjects in the randomly selected subcohort with and without virus resistant to NNRTIs at baseline. Virologic failure was defined as a confirmed plasma HIV RNA level >200 copies/mL at week 16 or later.

HIV Drug Resistance Testing Recommendation

<table>
<thead>
<tr>
<th>Settings</th>
<th>IAS-USA 1</th>
<th>DHHS 2</th>
<th>European 3</th>
<th>Thai 4</th>
<th>WHO 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary/acute</td>
<td>Recommend</td>
<td>Recommend</td>
<td>Recommend</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Post-exposure prophylaxis</td>
<td>—</td>
<td>—</td>
<td>Recommend*</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Chronic and treatment naïve</td>
<td>Recommend</td>
<td>Recommend</td>
<td>Recommend</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Failure</td>
<td>Recommend</td>
<td>Recommend</td>
<td>Recommend</td>
<td>Recommend</td>
<td>—</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Recommend</td>
<td>Recommend</td>
<td>Recommend</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Especially if exposure to someone receiving antiretroviral drugs is likely or if prevalence of drug resistance in untreated patients ≥5% (European: ≥10%).

In Resource-limited Settings

- In most resource-limited settings, HIVDR testing is neither routinely available nor recommended
- Genotyping is expensive and complex
- ART continues to be scaled-up rapidly, routine surveillance of transmitted and acquired HIVDR should be performed
- Greater funding and infrastructure are urgently needed to support ongoing routine surveillance of HIVDR
- Lack of accessible HIVDR testing need never limit optimization of patient care and global efforts to minimize HIVDR


Recommendations for Surveillance of TDR in Countries Scaling Up ART

- WHO recommends countries begin surveillance and threshold survey method was developed
- HIV transmission depends on many factors
- Most important is ART...how long, coverage, and number of patients with failing ART
  - Absence of monitoring, esp. HIV VL testing
  - Limited availability of the second-line regimens
  - Behavioral prevention programs

Asia and Pacific HIV Resistant Transmission: Are We OK?

Conclusions

• Prevalence of TDR by WHO HIVDR threshold survey method is still low in Asia
• However, scaling up of ART in Asia is increased
• Primary HIV resistance in Asia is emerging with reported prevalence of 5-17%
• Monitoring of HIVDR in naïve patients is needed
• HIV genotype testing prior to ART initiation may be indicated in selected HIV-infected patients