HIV Drug Resistance in the Asia-Pacific

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HIVDR in Asia Pacific

- Transmitted resistance
- Resistance to first-line therapy
- TREAT Asia- response to resistance
- SECOND LINE
• **Transmitted resistance**

• **Resistance to first-line therapy**

• **TREAT Asia - response to resistance**

• **SECOND LINE**
HIV drug resistance survey method criteria

• Standard procedures should be specified so that results will be comparable from country to country over time

• The survey methods should be simple and require minimal resources

• Surveys should focus on small geographic areas

• The method should maximise the likelihood that participants will have been infected with HIV within the past 3 years and limit the likelihood of previous ART exposure

• The required sample size should be small

• Specimen collection and handling procedures must be feasible in areas with minimal laboratory resources

• Definition of transmitted resistance should be based on a list of resistance mutations developed and regularly updated as new data become available

Bennett et al., Antivir Ther 2008:13 Suppl 2.
Participant eligibility criteria for HIVDR threshold surveys

Mandatory criteria

• Laboratory confirmation of HIV infection
• Age <25 years at HIV diagnosis
• If female, no previous pregnancy

Criteria to be applied where information is routinely available

• If applicable to the survey group, first risk-defining event within the past 3 years (eg IDU or STI)
• Documented laboratory evidence of recent infection (if based on a method validated within the country and laboratory context)
• No previous positive HIV test
• No known exposure to antiretroviral drugs
• No presumptive or definitive diagnosis of a WHO Stage 3 or 4 clinical event
• CD4+ T-cell count >500 copies/ml

Bennett et al., Antivir Ther 2008:13 Suppl 2.
Site selection criteria for HIV drug resistance threshold surveys

Mandatory criteria

- At least 50-70 specimens expected in 3-6 months
- Every eligible person likely to be included
  - All individuals receive a routine HIV test, or
  - Specimens from other tested routinely tested as part of anonymous survey, or
  - Uptake of optional HIV tests is >95%
- Persons diagnosed with HIV are representative of the area
- Sufficient records to exclude a 2nd positive test
- Opportunity to provide remnant or second blood sample for testing
- Confidentiality safeguards
- Informed consent procedures possible

Recommended criteria

- Information on previous HIV tests available
- Information on CD4 count, WHO stage and ART eligibility recorded
- Site is part of national system that identifies previous HIV diagnosis and ART use

Bennett et al., Antivir Ther 2008:13 Suppl 2.
## Summary of drug resistance threshold surveys in Asia-Pacific

<table>
<thead>
<tr>
<th>Country</th>
<th>Site type</th>
<th>Number</th>
<th>Sequenced</th>
<th>Predominant HIV subtype</th>
<th>Transmitted resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaysia</td>
<td>HIV clinic</td>
<td>100</td>
<td>100</td>
<td>CRF01_AE</td>
<td>1 case (NNRTI)</td>
</tr>
<tr>
<td>Thailand</td>
<td>HIV clinic</td>
<td>305</td>
<td>305</td>
<td>CRF01_AE</td>
<td>7 cases (RT)</td>
</tr>
<tr>
<td>Thailand</td>
<td>Blood donor/ VCT</td>
<td>100</td>
<td>84</td>
<td>CRF01_AE</td>
<td>No cases</td>
</tr>
<tr>
<td>Vietnam</td>
<td>VCT</td>
<td>70</td>
<td>44</td>
<td>CRF01_AE</td>
<td>1 case</td>
</tr>
<tr>
<td>Thailand</td>
<td>HIV clinic</td>
<td>113</td>
<td>113</td>
<td>CRF01_AE</td>
<td>14 cases (NRTI)</td>
</tr>
</tbody>
</table>

1 Tee et al., *AIDS Res Hum Retroviruses*, 2006: 22(2).
HIVDR in Asia Pacific

- Transmitted resistance

- **Resistance to first-line therapy**

- TREAT Asia- response to resistance

- **SECOND LINE**
### Evaluation of WHO criteria for ART failure

Cohort of 324 participants with treatment failure from South Africa

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 cell count failure at 12 months</td>
<td>21.2</td>
<td>95.8</td>
<td>36.8</td>
<td>91.3</td>
</tr>
<tr>
<td>- with results from 6-month visit</td>
<td>21.2</td>
<td>90.6</td>
<td>20.6</td>
<td>90.9</td>
</tr>
<tr>
<td>WHO-defined clinical failure</td>
<td>15.2</td>
<td>88.1</td>
<td>12.8</td>
<td>90.0</td>
</tr>
<tr>
<td>- excluding TB</td>
<td>12.1</td>
<td>90.6</td>
<td>12.9</td>
<td>89.9</td>
</tr>
<tr>
<td>- excluding &gt;10% weight loss</td>
<td>9.1</td>
<td>93.0</td>
<td>13.0</td>
<td>89.9</td>
</tr>
<tr>
<td>CD4 cell count (12 months) or WHO-defined clinical failure</td>
<td>33.3</td>
<td>85.6</td>
<td>21.2</td>
<td>91.8</td>
</tr>
<tr>
<td>Clinical failure due to TB</td>
<td>3.0</td>
<td>96.5</td>
<td>9.1</td>
<td>89.6</td>
</tr>
</tbody>
</table>

Mee et al., *AIDS* 2008:22.
Summary of genotypic resistance at virological failure 48 weeks after start of first-line therapy

- from 20 studies in developed countries
- incorporating 7970 patients

Adapted from Gupta et al., CID 2008:47.
HIVDR in Asia Pacific- Resistance to first-line therapy

Development of HIVDR after PI-based first-line regimen in Thailand

Number of major reverse transcriptase codon mutations (%)

<table>
<thead>
<tr>
<th>Mutation</th>
<th>B-strain (n=14)</th>
<th>CRF01_AE (n=29)</th>
<th>Total (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M41L</td>
<td>3 (21.4)</td>
<td>3 (10.3)</td>
<td>6 (14.0)</td>
</tr>
<tr>
<td>D67N</td>
<td>3 (21.4)</td>
<td>5 (17.2)</td>
<td>8 (18.6)</td>
</tr>
<tr>
<td>K70R</td>
<td>2 (14.3)</td>
<td>1 (3.4)</td>
<td>3 (7.0)</td>
</tr>
<tr>
<td>M184V</td>
<td>5 (35.7)</td>
<td>9 (31.0)</td>
<td>14 (32.6)</td>
</tr>
<tr>
<td>L210W</td>
<td>4 (28.6)</td>
<td>7 (24.1)</td>
<td>11 (25.6)</td>
</tr>
<tr>
<td>T215Y/S</td>
<td>5 (35.7)</td>
<td>6 (20.7)</td>
<td>11 (25.6)</td>
</tr>
<tr>
<td>K129Q/E</td>
<td>3 (21.4)</td>
<td>6 (20.7)</td>
<td>9 (20.9)</td>
</tr>
</tbody>
</table>

Sukasem et al., Int J Antimicrob Agents 2008:31
HIVDR in Asia Pacific- Resistance to first-line therapy

Drug resistance mutations by viral load at failure

Sungkanuparph et al., CID 2007:44
Genotypic drug resistance in 1,880 HIV patients experiencing treatment failure in Thailand 2000-2005

Sukasem et al., Infection 2007:35
HIVDR in Asia Pacific- Resistance to first-line therapy

Multivariate analysis of variables associated with virological failure and at least 1 major drug resistance mutation in South Africa

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mutation rate, %</th>
<th>Multivariate analysis CR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
<td>92</td>
<td>3.27 (0.92– 11.63)</td>
<td>.068</td>
</tr>
<tr>
<td>≥35</td>
<td>77</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>CD4 cell count at study enrollment, cells/mm³</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>84</td>
<td>0.87 (0.23– 3.33)</td>
<td>.838</td>
</tr>
<tr>
<td>≥200</td>
<td>86</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Plasma HIV RNA level at study enrollment, copies/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5000</td>
<td>77</td>
<td>1.05 (0.23– 4.81)</td>
<td>.103</td>
</tr>
<tr>
<td>5000–29,999</td>
<td>90</td>
<td>3.91 (0.84– 18.15)</td>
<td></td>
</tr>
<tr>
<td>30,000–99,999</td>
<td>92</td>
<td>7.97 (0.82– 77.21)</td>
<td></td>
</tr>
<tr>
<td>≥100,000</td>
<td>71</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Recent CI (within 6 months before study enrollment)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>88</td>
<td>2.20 (0.70– 6.88)</td>
<td>.175</td>
</tr>
<tr>
<td>No</td>
<td>75</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

No significance seen in univariate analysis of sex; employment; recent symptoms; hemoglobin; WHO clinical stage; treatment adhere; traditional medicine use; d4T+3TC vs ZDV+3TC or prior vs first HAART.

Marconi et al., CID 2008:46
HIVDR in Asia Pacific

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- SECOND LINE
TREAT Asia Studies to Evaluate Resistance (TASER)

Objectives:

- evaluate HIVDR and build capacity for surveillance and monitoring of HIVDR in Asia

TASER-monitoring (TASER-M)

- assess prevalence of HIVDR in individuals initiating first-line therapy, and incidence of HIVDR at 12 months after initiation

- assess prevalence and incidence of HIVDR in individuals switching to second-line therapy

TASER-surveillance (TASER-S)

- assess prevalence of transmitted HIVDR in ART-naïve recently HIV-infected individuals
TREAT Asia Quality Assurance Scheme (TAQAS)

The goal of the TAQAS is to standardize and optimise the outcome of HIV genotyping among sequencing platforms and laboratories.

- Panels (3 plasma and 1 electropherogram) were sent to the 15 participating laboratories (13 Asian, 1 South African and 1 North American).
- Each laboratory carried out genotypic analysis and sent the results for external quality assessment.
- Nucleotide sequences and ARV susceptibility profiles generated by the participants were compared.
HIVDR in Asia Pacific- TREAT Asia

Level of agreement (%) in interpretation of ARV susceptibility between participants using

<table>
<thead>
<tr>
<th>TAQAS Panel</th>
<th>Various systems</th>
<th>Stanford Database</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>71</td>
<td>97</td>
</tr>
<tr>
<td>2*</td>
<td>64</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>76</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>ND</td>
<td>80</td>
</tr>
</tbody>
</table>

*Chi-squared p<0.01

The level of agreement in interpretation of ARV susceptibility was higher in TAQAS 1 and TAQAS 2 when all participants used the same system, the Stanford Database.
• Transmitted resistance

• Resistance to first-line therapy

• TREAT Asia- response to resistance

• SECOND LINE
Currently no evidence available
the default position is “give PI/r + 2NRTIs”
  - this is OK in developed countries
    - close monitoring, numerous options
  - this will not work in developing countries
    - clinical +/- CD4 monitoring only
    - presence of multiple resistance mutations
    - limited options
    - 3rd line cART is unlikely for public-sector funding in the short- to medium-term
• RCT of patients failing NNRTI+2NRTIs

• randomization:
  • PI/r + 2NRTI
    versus
  • PI/r + raltegravir

• 96-week trial
  • 48-week analysis for public disclosure
    • 1° endpoint: proportion <50 copies per ml
    • 2° endpoints include metabolic toxicity, LD, AEs and SAEs
HIVDR in Asia Pacific - SECOND LINE

- powered for non-inferiority (15% CIs)
  - 480 patients
  - Australia and UK
    - 10% enrolment
    - Africa, India, SE Asia, Latin America
      - 90% enrolment
- 3-4 years drug supply
  - 1-2 years post-trial depending on country
requests of pharmaceutical sponsors:
  - raltegravir and boosted-PI supply
    - 3-4 years
    - 2 years study and 1-2 years post study
  - partial financial support shared with other sponsors
    - a Public-Private Partnership model

NCHECR/UNSW
  - trial sponsor and study coordination

trial management
  - representatives from trial sponsor, industry partners, other funders and a PI from each region/country participating