HIV Drug Resistance Surveillance in the US

Diane Bennett, MD MPH
Coordinator, Antiretroviral Drug Resistance Monitoring
DHAP-SE NCHSTP CDC
**Public health surveillance systems**

**Good surveillance systems**
- Are simple, minimal, standardized, cheap, sustainable, representative, support public health action
- Utilize data recorded for routine purposes locally
- Serve the needs of the people recording the data as well as public health purposes at higher levels
- Provide timely feedback

**Poor surveillance systems:**
- Results are not representative, methods not standardized across areas
- Results are interesting but not used for public health action
- Utility is not clear to the people recording information
- The amount or nature of the data being recorded impedes routine clinical or public health work
- Expensive or labor-intensive -- not sustainable without “research-level” funding
HIV drug resistance (HIVDR) prevalence studies in persons newly diagnosed with HIV

• Original purpose: to investigate whether resistant HIV strains were being transmitted
  – To evaluate whether HIV with specific combinations of mutations seen in treated persons were seen in drug naïve untreated persons

• Later purpose: To estimate the prevalence of mutations associated with HIV drug resistance (HIVDR) among drug-naïve persons
  – Recently infected with HIV
  – Newly diagnosed with HIV
  – Ready to start antiretroviral treatment (ART)
Potential utility of HIVDR surveillance data

• Guide recommendations for clinical HIVDR testing before ART begins
  – For recently infected persons
  – For persons with infection of unknown duration

• Guide recommendations for pre- and post-exposure prophylaxis*
  – More important now that single-drug pre-exposure prophylaxis is being widely considered as a prevention tool

• Guide recommendations for regimens to prevent vertical transmission*

• Guide recommendations for initial ART regimens*

*Data are currently not used for these purposes
TB Drug Resistance (TBDR) Surveillance in Persons Newly Diagnosed with TB

- Generated recommendations for routine clinical TBDR testing at diagnosis in the US and Europe
- Data guide recommendations for preventive treatment of latent infection
- Data guide general recommendations for initial TB treatment regimens (on a population basis)
- Used to evaluate success of TB treatment programs (successful rx program in a geographic region = minimal transmission of TBDR)

Data were not widely used for these purposes until the late 1980s/early 1990s
**Current Global TBDR surveillance**

- Focuses either on a country or defined geographic regions within the country
- Either includes all individuals newly diagnosed with TB, or weighted proportionate cluster sampling to represent all persons newly diagnosed with TB in all diagnostic and clinical sites
- Data are not included in global report unless the methodology used meet criteria for representativeness
### Table 2. Prevalence of Primary Drug Resistance in 32 Countries and Regions.

<table>
<thead>
<tr>
<th>Country or Region</th>
<th>No. of Patients</th>
<th>Drug Resistance*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Isoniazid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Single</td>
</tr>
<tr>
<td>Argentina</td>
<td>606</td>
<td>2.0</td>
</tr>
<tr>
<td>Benin</td>
<td>333</td>
<td>3.3</td>
</tr>
<tr>
<td>Bolivia</td>
<td>498</td>
<td>6.8</td>
</tr>
<tr>
<td>Botswana</td>
<td>407</td>
<td>1.2</td>
</tr>
<tr>
<td>Brazil</td>
<td>2,095</td>
<td>3.8</td>
</tr>
<tr>
<td>Cuba</td>
<td>763</td>
<td>1.0</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>199</td>
<td>1.0</td>
</tr>
<tr>
<td>Dominican Republic</td>
<td>303</td>
<td>8.6</td>
</tr>
<tr>
<td>England and Wales</td>
<td>2,742</td>
<td>3.3</td>
</tr>
<tr>
<td>Estonia</td>
<td>266</td>
<td>4.1</td>
</tr>
<tr>
<td>France</td>
<td>1,491</td>
<td>0.8</td>
</tr>
<tr>
<td>Ivory Coast</td>
<td>320</td>
<td>3.1</td>
</tr>
<tr>
<td>Kenya</td>
<td>445</td>
<td>5.4</td>
</tr>
<tr>
<td>Latvia</td>
<td>347</td>
<td>5.5</td>
</tr>
<tr>
<td>Lesotho</td>
<td>330</td>
<td>5.2</td>
</tr>
<tr>
<td>Nepal</td>
<td>787</td>
<td>1.7</td>
</tr>
</tbody>
</table>

*percentage of patients
US TBDR surveillance

- All positive TB cultures from drug-naïve persons newly diagnosed with TB are tested for resistance to the drugs in the standard first and second-line regimens

- Standard TB case reports to CDC include TBDR data

- Annual estimates are produced
Resistance to Isoniazid with or without Rifampin Resistance in Reported TB Cases with No Previous TB by Origin: United States, 1993-2003

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Cases²</th>
<th>U.S.-born</th>
<th>Foreign-born³</th>
<th>Total Cases²</th>
<th>U.S.-born</th>
<th>Foreign-born³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>1993</td>
<td>1,400 8.4</td>
<td>804 6.8</td>
<td>580 12.4</td>
<td>410 2.5</td>
<td>302 2.6</td>
<td>105 2.3</td>
</tr>
<tr>
<td>1994</td>
<td>1,353 8.3</td>
<td>708 6.4</td>
<td>631 12.1</td>
<td>352 2.2</td>
<td>238 2.2</td>
<td>109 2.1</td>
</tr>
<tr>
<td>1995</td>
<td>1,173 7.3</td>
<td>554 5.4</td>
<td>618 11.0</td>
<td>253 1.6</td>
<td>168 1.6</td>
<td>85 1.5</td>
</tr>
<tr>
<td>1996</td>
<td>1,136 7.4</td>
<td>494 5.2</td>
<td>639 11.3</td>
<td>206 1.3</td>
<td>104 1.1</td>
<td>101 1.8</td>
</tr>
<tr>
<td>1997</td>
<td>1,079 7.5</td>
<td>436 5.0</td>
<td>639 11.2</td>
<td>155 1.1</td>
<td>76 0.9</td>
<td>79 1.4</td>
</tr>
<tr>
<td>1998</td>
<td>1,011 7.5</td>
<td>366 4.7</td>
<td>643 11.3</td>
<td>130 1.0</td>
<td>54 0.7</td>
<td>75 1.3</td>
</tr>
<tr>
<td>1999</td>
<td>899 7.1</td>
<td>283 4.0</td>
<td>614 11.0</td>
<td>127 1.0</td>
<td>39 0.6</td>
<td>88 1.6</td>
</tr>
<tr>
<td>2000</td>
<td>894 7.6</td>
<td>269 4.4</td>
<td>622 11.1</td>
<td>121 1.0</td>
<td>38 0.6</td>
<td>83 1.5</td>
</tr>
<tr>
<td>2001</td>
<td>797 7.0</td>
<td>241 4.4</td>
<td>555 9.5</td>
<td>113 1.0</td>
<td>34 0.6</td>
<td>79 1.4</td>
</tr>
<tr>
<td>2002</td>
<td>801 7.6</td>
<td>200 4.1</td>
<td>598 10.7</td>
<td>124 1.2</td>
<td>35 0.7</td>
<td>89 1.6</td>
</tr>
<tr>
<td>2003</td>
<td>784 7.9</td>
<td>204 4.6</td>
<td>577 10.6</td>
<td>90 0.9</td>
<td>25 0.6</td>
<td>65 1.2</td>
</tr>
</tbody>
</table>

CDC, US Tuberculosis Surveillance Report, 2004
Primary MDR TB in US-born vs. Foreign-born Persons
United States, 1993-1999

% Resistant


- US-born
- Foreign-born

Note: Based on initial isolates from persons with no prior history of TB.
MDR TB defined as resistance to at least isoniazid and rifampin.
Other public health surveillance information supports interpretation of TBDR surveillance data

• Prescribing practices
• Percentage of persons who take at least 90% of all doses of TB drugs over specified time period
• Measures of “treatment success”
  – Percentage of persons with “smear conversion” from positive to negative at 2-3 months
  – Percentage of persons with “culture conversion” from positive to negative at 6-12 months
# Central African Republic (Bangui)

**Year of Survey:** 1998

## Profile of the Country and Its Control Programme

### Country Profile

- **Population:** 620,000
- **World Bank Income Category:** Low-income
- **Tuberculosis Case Notification:** 139.9/100,000
- **Tuberculosis Estimated Incidence:** 237/100,000
- **Notified Incidence of New Sputum Smear Positive TB:** 2,637 cases 75.7/100,000
- **Treatment Success:** 65%
- **Previously Treated Cases:** 9.9% of all patients registered
- **MTB/HIV Estimated Co-infection Rate:** 2,119.0/100,000
- **HIV-positive TB Cases:** 48.5%

### Control Programme

- **WHO Control Category:** 1
- **Year N.T.P. was Established:** 1995
- **Year of Rifampicin Introduction:** 1980
- **Standardized Regimens:** Yes
- **Use of Short Course Chemotherapy:** 100%
- **Use of Directly Observed Therapy during 1st 2 months:** No
  - (0% of patients)
  - During continuation phase: No
- **Use of Fixed Dose Combination:** Yes (100% of patients)
- **Treatment In Private Sector:** Cat. 1
  - Category 1: virtually all TB patients public sector
  - Category 2: <15% in private sector
  - Category 3: 15% or more in private sector

---

**Source:** CDC

---
Multivariate Analysis: TB drug resistance among newly diagnosed cases vs TB treatment and poverty variables

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Any drug resistance*</th>
<th>MDR-TB*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficients</td>
<td>Standard errors</td>
</tr>
<tr>
<td>% of previously treated cases</td>
<td>0.021</td>
<td>0.002</td>
</tr>
<tr>
<td>GNP per capita income (US$)</td>
<td>-0.33</td>
<td>0.02</td>
</tr>
<tr>
<td>% of TB cases under SCC</td>
<td>-0.18</td>
<td>0.03</td>
</tr>
<tr>
<td>% of treatment success</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of TB cases under DOT</td>
<td>-0.44</td>
<td>0.04</td>
</tr>
<tr>
<td>% TB patients infected with HIV</td>
<td>-0.004</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

* R square for any drug resistance = 35%, for MDR-TB = 29%
** Significant at p < 0.05
US HIVDR prevalence studies: current published estimates

- Several studies mostly based in specialist clinical centers
- Target population is generally recently-infected persons
- Often based on referrals from specialist clinicians
- Impossible to adjust estimates using information about recently infected persons not included
- Consent is generally required
- Definition of recently infected:
  - Based on referral from clinicians recognizing acute infection signs/symptoms, and/or
  - Less sensitive EIA, and/or
  - Negative HIV test less than one year previously
- Most studies: 90% white men who have sex with men
### Participant Characteristics (N=1082)

<table>
<thead>
<tr>
<th>Category</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender:</strong></td>
<td>74</td>
</tr>
<tr>
<td>Male</td>
<td></td>
</tr>
<tr>
<td><strong>Race/ethnicity:</strong></td>
<td>46</td>
</tr>
<tr>
<td>Black</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>27</td>
</tr>
<tr>
<td>Hispanic</td>
<td>22</td>
</tr>
<tr>
<td><strong>Age group:</strong></td>
<td>71</td>
</tr>
<tr>
<td>24-44 years old</td>
<td></td>
</tr>
<tr>
<td><strong>Exposure category:</strong></td>
<td>44</td>
</tr>
<tr>
<td>Heterosexual</td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>46</td>
</tr>
<tr>
<td>IDU</td>
<td>10</td>
</tr>
<tr>
<td><strong>Recent HIV infection [N=949 ]</strong></td>
<td>19</td>
</tr>
</tbody>
</table>

*based on STARHS algorithm*

Weinstock, CID, 2004
Overall prevalence of drug resistance higher in Western than North-Eastern or Southern cities in this study.

Bennett D, et al. 2nd IAS, Paris 2003, #787
# Prevalence of HIVDR among recently infected persons, 1995-2001 US studies

<table>
<thead>
<tr>
<th>Resis</th>
<th>CDC 10 US cities</th>
<th>Grant San Francisco</th>
<th>Simon NYC</th>
<th>Little 10 NA cities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>4.6</td>
<td>13.2</td>
<td>11.0</td>
<td>13.2</td>
</tr>
<tr>
<td>NRTI</td>
<td>4.6</td>
<td>8.8</td>
<td>9.3</td>
<td>11.8</td>
</tr>
<tr>
<td>NNRTI</td>
<td>0</td>
<td>5.5</td>
<td>2.5</td>
<td>2.6</td>
</tr>
<tr>
<td>1º PI</td>
<td>0</td>
<td>2.2</td>
<td>2.5</td>
<td>1.3</td>
</tr>
<tr>
<td>≥ 2</td>
<td>0</td>
<td>3.3</td>
<td>3.4</td>
<td>2.5</td>
</tr>
</tbody>
</table>

The differences in blue are significant at the p=0.05 level.
Potential sources of variation

- Unrepresentative sampling methodology
- Estimates not adjusted
- Small numbers
- Different case definitions for recent infection
- Different proportions of “risk groups” represented
- Different proportions of private vs public settings
- Referrals vs “all-comers”
- Geographic variations
- Different sets of mutations used to define “resistance”

*Surveillance of larger representative groups in diverse geographical areas is needed for accurate national estimates.*
Target populations for HIVDR surveillance

- Persons newly diagnosed with HIV – estimated 70,000* per year in US
- Persons recently infected with HIV -- estimated 40,000* per year in US
  - Of these, only an estimated 7000* are diagnosed during the period of recent infection

*Unpublished estimates
CDC methodology for US HIVDR Surveillance

- Residual diagnostic sera from all persons newly diagnosed with HIV collected and used for genotyping
- Non-research determination received – operates as part of routine HIV surveillance performed by health departments
  - Results available for providers within 30 days
- Demographic and clinical data merged in from HIV surveillance system
- Evaluation of recent infection will be available for most participants
  - Date of last negative HIV test recorded routinely if available
  - Use of less sensitive EIA to evaluate recent infection still under an FDA IND, but results from consenting persons can be merged in from HIV surveillance system
HIV drug resistance (HIVDR) surveillance in persons newly diagnosed with HIV

- To estimate the prevalence of mutations associated with HIVDR among persons
  - Recently infected with HIV
  - Newly diagnosed with HIV
- To evaluate trends in HIVDR transmission
  - To provide data for models
- To evaluate risk factors for HIVDR
  - Geographic region
  - Exposure category
  - Race/ethnicity
  - Gender
  - Public vs private facility
  - Clinical vs counseling and testing facility
  - B vs non-B HIV-1 subtypes
Advantages of HIVDR surveillance using diagnostic sera or specimens taken at diagnosis

• Earliest possible specimen -- best chance to see mutations that may later become undetectable
• Potentially the most representative method
  – Includes individuals who do not return for results
  – Includes individuals who do not seek clinical care
  – Informed consent not required (public health surveillance)
  – No missing participants because of persons not asked or not referred
  – Population diagnosed at each participating center well-characterized
    • Numbers of new diagnoses in each center known
    • Demographic and clinical information available from HIV surveillance database
• Simultaneous operation of the HIV incidence project (HIS)
  – Recently infected subgroup will be identified

<table>
<thead>
<tr>
<th>Mutations associated with resistance to:</th>
<th>Pilot HIVDR (%)</th>
<th>Proj 1 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any drug class: RTI or PI</td>
<td>82 (15.2)</td>
<td>87 (19.1)</td>
</tr>
<tr>
<td>NRTI</td>
<td>38 (7.1)</td>
<td>54 (11.9)</td>
</tr>
<tr>
<td>NNRTI</td>
<td>49 (9.1)</td>
<td>44 (9.7)</td>
</tr>
<tr>
<td>PI</td>
<td>17 (3.2)</td>
<td>13 (2.9)</td>
</tr>
<tr>
<td>≥ 2 drug classes</td>
<td>17 (3.2)</td>
<td>23 (5.1)</td>
</tr>
</tbody>
</table>

Of 595 eligible specimens, 539 (91%) could be amplified for genotyping.
Limitations and Partial Solutions

- Residual diagnostic specimen volume not always adequate
  - At least half of non-amplified specimens were associated with insufficient volume (< 1 ml)
  - Participating HD generally supply or require 10 ml tubes and education has helped in getting tubes filled

- Specimens should be centrifuged, aliquoted, and frozen quickly
  - Specimen transport to HIV lab sometimes takes days from non-clinical centers
  - Provision of special transport not feasible for ongoing routine (vs special study)
  - Many HD have been able to speed up transport
  - Serum separator tubes used; centrifuge as early as possible
  - Aliquot and freeze after first reactive EIA
  - Reasonable amplification (>91%) achieved so far

- Rapid/oral HIV testing is becoming common
  - Confirmation by blood draw required in many states
  - Dried blood spot genotyping a partial solution
Limitations and Potential Solutions

• Estimation of “transmitted resistance” is problematic because most persons recently infected with HIV cannot be genotyped during the period of recent infection— they are diagnosed later
  – Even if all recently infected persons among the newly diagnosed were identified, their prevalence of resistance would not = the prevalence in all recently infected
  – No national estimates are available on the % recently infected among the newly diagnosed, but smaller studies estimate 5% - 30%

• In all available studies, persons diagnosed during recent infection differ from those diagnosed later in infection by race/ethnicity and exposure category
  – Their HIVDR patterns may also differ from those infected at the same time but diagnosed later

• Can we estimate HIVDR in recent infection by modeling that includes “back calculation” using information on HIVDR patterns in those diagnosed post-recent infection (as we used to do with AIDS statistics and HIV)?
  – What additional information is needed?
Other Limitations

• Current funding for most participating states and cities tied to HIV incidence surveillance (HIS) funding
  – Rapid implementation not possible
  – HIS is top priority (very high public health importance): HIVDR is an add-on; funding is limited

• Funding for genotyping generous but still limited
  – 5-year contract with Stanford + funding of selected state labs will not cover additional states once currently participating areas begin to send ≥50% of eligible specimens

• Limited availability of specimens HIV-tested in private labs
  – May not be handled optimally for amplification for genotyping
  – No incentive for large commercial labs to request sufficient volume from providers, aliquot, freeze, and ship
  – (Private labs owned by private clinical centers are very amenable)
The problem of resources

• Genotyping is expensive (and unlike TBDR surveillance, we can’t capture clinical results at diagnosis)
• Labor and resources for specimen collection are minimal, but not zero
• Private commercial labs would require payment for specimens
• CDC has higher surveillance priorities for the limited funds available
Potential strategies to address insufficient resources: Two-stage HIVDR testing

- Instead of initial genotyping:
  - Screen first with cheaper point-mutation assays (RT-PCR, OLA) for a limited number of positions;
  - Genotype only those that screen “positive”

1082 specimens

Absence of T215

Absence of T69

Absence of M46

Absence of M184

K70R

M41L

V108I

L90M

The Algorithm

Predicted 96% (86/90) resistant strains

96%

996

1014

86
Potential strategies to address insufficient resources: alternate sampling strategies

• Instead of all newly diagnosed persons, use a strategy requiring few specimens
  – In some geographic areas? or all geographic areas?
  – For all diagnostic sites in the area? or for diagnostic sites of a certain type?

• Weighted proportionate cluster sampling (international TBDR surveillance [WHO])
• Sentinel surveillance (US gonorrhea DR surveillance)
• HIVDR threshold surveys based on binomial sequential sampling technique
  (HIVDR surveillance for developing countries where HIV drug treatment is being scaled up [WHO])
Weighted cluster sampling

Example: International TBDR surveillance
- Based on all diagnostic sites in the geographic setting and proportion diagnosed in each site
- Sequential sampling of diagnostic sera (or dried blood spots) up to the number required in each site
- Advantages:
  - Specimens need only be collected for a small time period yearly
  - Fewer specimens = labor and funds for genotyping ↓
- Disadvantages:
  - Major selling point for HIVDR surveillance (HIVDR information for each newly diagnosed person) lost
- Appropriate for all sites – or only for sites where HIV testing is performed in private labs?
Sentinel surveillance

Example: Gonorrhea drug resistance surveillance
Limited number of centers chosen for representativeness
• Must ensure adequate numbers to represent all newly diagnosed persons in each area
• Include appropriate mix of counseling and testing centers, STD clinics, specialist clinics, private docs
• Advantages:
  – Often sentinel centers collect specimens for only a few months annually
  – Detailed information can be collected during this period
• Disadvantages:
  – Difficult to ensure good representation of all diagnostic sites
  – Major selling point for HIVDR surveillance (HIVDR information for each newly diagnosed person) would be lost
Potential strategies to address insufficient resources: acquire more resources

• Demonstrate increased public health relevance for HIVDR surveillance results
  – For TB, population DR surveillance results are used to guide recommendations for regimens – will HIV treatment guidelines ever recommend use of HIVDR surveillance data?
  – Collect additional information on treatment (as with TB: prescribing practices, continuity of HIV drug accessibility) to support interpretation of data, broaden potential public health recommendations

• Initiate collaborative efforts, not all funded by CDC
  – Could be difficult to agree on standard methodology
  – QA/QC for data/labs potentially difficult
  – Surveillance data are collected and reported by health departments – other initiatives could be considered “research” if not coordinated by health departments
Current Treatment Guidelines focus only on individual HIVDR testing

<table>
<thead>
<tr>
<th>HIV Infection</th>
<th>IAS-USA¹</th>
<th>DHHS²</th>
<th>EuroGuidelines Group³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary/Acute</td>
<td>Recommend</td>
<td>Recommend</td>
<td>Recommend^¹</td>
</tr>
<tr>
<td>Established</td>
<td>Recommend if &gt;5%</td>
<td>Consider if &lt;2 yr and &gt; 5%</td>
<td>Recommend^</td>
</tr>
<tr>
<td>Failure</td>
<td>Recommend</td>
<td>Recommend</td>
<td>—</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Recommend*</td>
<td>—</td>
<td>Recommend*</td>
</tr>
<tr>
<td>Pediatric</td>
<td>—</td>
<td>—</td>
<td>Recommend¹</td>
</tr>
</tbody>
</table>

^ Recommend if prevalence > 10 %  *Recommend only if mother is viremic.
†Recommend only if mother was viremic and on treatment at time of birth.
¹Hirsch. JAMA 2000;283:2417. ²DHHS. Guidelines (Adult and Adolescent); Feb 2002.
Some foci for the consultation

- Mutation list for epidemiology/surveillance
- Recommendations for strategies/combinations of strategies for representative surveillance
- The role of special studies to answer questions raised by surveillance/clinical results
- Discussion of the use of earliest possible HIVDR result vs result before treatment begins
- Strategies for modeling prevalence of transmitted HIVDR
- Utility of surveillance of HIVDR in treatment (vs research studies)?
- Potential for surveillance of prescribing practices, continuous access to drugs, other programmatic factors affecting HIVDR emergence?
- Public health uses for HIVDR surveillance data