Lessons from the Stanford HIV Drug Resistance Database

Bob Shafer, MD
Department of Medicine and by Courtesy Pathology (Infectious Diseases)
Stanford University
Outline

• Goals and rationale for HIVDB
• Representing data in HIVDB
• Obtaining data for HIVDB
• Similarities and contrasts with TB drug resistance.
Rationale

- Clinical:
  - Interpreting genotypic resistance tests

- Surveillance:
  - Which mutations should be used to track transmitted drug resistance?

- Drug development:
  - How can drugs be developed with improved cross-resistance profiles?
Types of Data in HIVDB

- Genotype-treatment correlations
  - HIV gene sequences from patients with well-characterized treatment history
    - "Darwinian" evidence for drug resistance
- In vitro susceptibility data
  - Site-directed mutants
  - Clinical isolates
- Virological response to therapy
Sequences from ARV-naïve patients: RT, PR, and IN

- There are many sequence polymorphisms.
- Many polymorphisms are accessory DRMs.
- No polymorphisms are clinically important DRMs.
- HIV-1 subtype influences the proportions of many polymorphisms.
Sequences From Patients Receiving ARVs

- Usually cross-sectional data from patients with detectable plasma viremia on ARV therapy.
- Selected mutations are in the gene targets of therapy.
- Mutations resemble but are more extensive than those selected in vitro during pre-clinical drug development.
- >240 nonpolymorphic ARV-selected mutations in patients.
- Most mutations occur in combinations.
Sequenced Viruses and their in vitro Susceptibilities

- Site-directed mutations alone and in combinations.
- Clinical isolates: statistical approaches are required to determine the contribution of individual mutations.
- Drugs differ widely in the fold-resistance associated with loss of clinical activity.
Many confounders interfere with the relationship between DRMs and the virological response to an ARV regimen:

- Response to therapy depends on baseline virus level, past treatments, the combination of drugs used for therapy, and patient adherence.
- In areas where genotypic resistance testing has been available, it has nearly always been used to guide therapy.
## Obtaining Data

<table>
<thead>
<tr>
<th>Data</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequences from ARV-naïve individuals</td>
<td>GenBank</td>
</tr>
<tr>
<td>Sequences from ARV-treated individuals</td>
<td>Papers, GenBank, Collaborations</td>
</tr>
<tr>
<td>In vitro susceptibility data</td>
<td>Papers, Collaborations</td>
</tr>
<tr>
<td>Genotype-virological response data</td>
<td>Collaborations, ACTG trials</td>
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Parallels to a TB Drug Resistance DB

• What is the genetic basis of M.TB drug resistance?

• How can this information be used to improve surveillance and develop rapid diagnostic tests?

• How can the presence of mutations in clinical isolates be used to guide therapy?

• Can these data be used to inform anti-TB drug development?
Differences from a TB Drug Resistance DB: HIV Factors

- HIV has three gene targets encompassing ~1,500 to 2,800 bp of information.
- HIV has much more genetic variation. Resistance is rarely all or none.
- HIV exists as complex populations containing innumerable related variants.
Differences from an HIV Drug Resistance
DB: TB Factors

• TB genome is much larger than HIV

• Many more genes involved in resistance to anti-TB therapy.

• In larger microorganisms, the determinants of resistance may be outside of the targets of therapy.

• Effect of molecular phylogeny not well studied.
Differences from an HIV Drug Resistance
DB: Data Sharing

• TB database is beginning with more stakeholders and a more organized plan for data sharing.

• The field will benefit from sharing data even prior to publication.
Implications for Database Design

- In contrast to HIVDB, a TB drug resistance database should represent point mutations, gene sequences, and full genomes.

- Database will require different levels of permission so that different investigators can benefit from the data in the database.