Lessons from the Stanford HIV Drug Resistance Database

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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

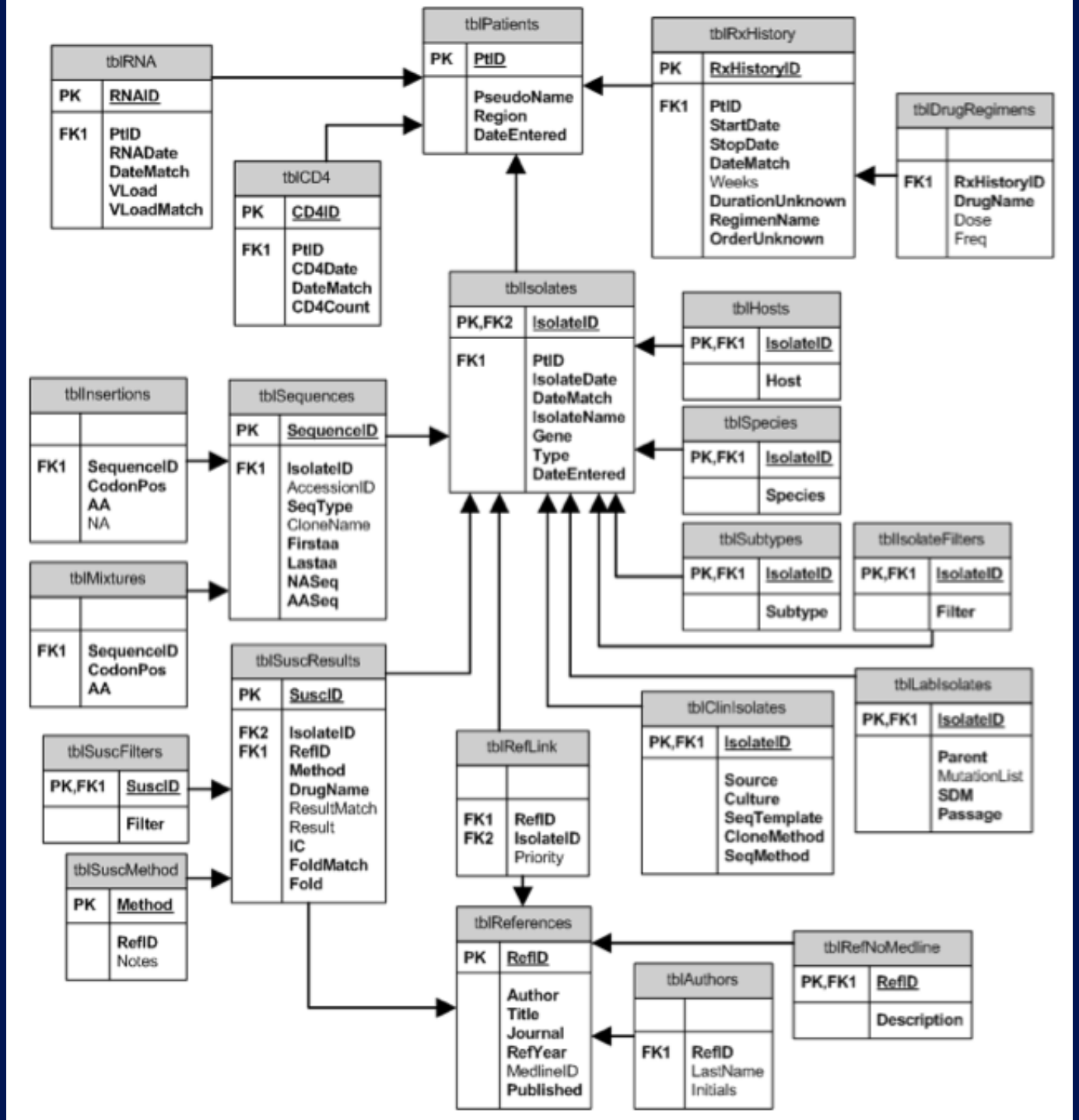
- Usually cross-sectional data from patients with detectable plasma viremia on ARV therapy.
- Selected mutations are in the gene targets of therapy.
- Mutations resemble but are more extensive than those selected in vitro during pre-clinical drug development.
- >240 nonpolymorphic ARV-selected mutations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

DRMs and the Virological Response to an ARV Regimen

- 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 be used to guide therapy.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Obtaining Data

Data	Source
Sequences from ARV-naïve individuals	GenBank
Sequences from ARV-treated individuals	Papers, GenBank, Collaborations
In vitro susceptibility data	Papers, Collaborations
Genotype-virological response data	Collaborations, ACTG trials

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 we 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.
- Proposed collaboration: “Establishing Minimal Information Reporting Guidelines for Studies of Antituberculosis and Antiviral Drug Resistance Studies.”