HIV-1 Antiretroviral Drug Resistance and Resistance Testing
Evolution of Viral Mutations

- Mutations arise because HIV-1 RT makes spontaneous errors (1 in $10^4$)
- HIV-1 genome is $10^4$ bases long, therefore 1 error each time the genome is replicated
- Production of virus = $10^9$ to $10^{10}$ virions per day → quasispecies
- Every possible mutation present in quasispecies before ARV therapy
Emergence of resistance

- Resistant mutants emerge as a result of
  - **genetic barrier (selective pressure of a regimen).**
  - **residual replication (potency of a regimen).**

- Drugs differ with respect to their genetic barrier and time it takes to develop resistance.
  - 1 nt change → aa change → resistance = LOW genetic barrier
  - >1 nt change at 1st and 2nd codon position → aa change → resistance = LOW genetic barrier, but slightly longer to emerge
  - >1 mutation (accumulation) → resistance = higher genetic barrier

- Escape mutants will continue to replicate and develop additional (secondary/compensatory) mutations to:
  - further increase resistance (decreased drug susceptibility)
  - increase viral fitness ("compensatory mutations")
Disappearance of resistance

- When treatment interrupted
- No drug selection of quasispecies
- Wild-type becomes dominant
- Drug-resistant strains no longer detected by genotyping assays
- Still minority population that can re-emerge if selection pressure re-applied
Antiretroviral drugs

- 5 classes drugs
  - PR Inhibitors (PIs) (9)
  - Nucleoside/nucleotide RT Inhibitors (NRTIs) (8)
  - Non-nucleoside RT Inhibitors (NNRTIs) (4)
  - Fusion Inhibitors (2)
  - Integrase Inhibitors (1)

- Current therapies imperfect because:
  - Regimen complexities
  - Toxicities
  - Drug resistance
- adequate drug concentrations are need in order to bring about desired pharmacological and virological effects.
PIs and Resistance

- Targets HIV-1 PR
  - Attaches to the PR binding cleft that recognizes and cleaves precursor polyproteins.
    - Most PR resistance mutations alter the structure of the substrate cleft
      - Causes resistance by reducing the binding affinity between the inhibitor and the mutant protease enzyme.
    - Mutations also occur in the flaps
      - compensate for loss of fitness
PI drug interactions

- PIs are metabolized by CYP 3A4 and P450 (the body’s drug clearance mechanisms).

- Ritonovir (RTV) is one of the most potent CYP 3A4 inhibitors known.

- Most PIs are co-administered with sub-therapeutic doses of RTV thereby increasing the plasma levels of the PI.

- Boosted PI levels can overcome small reductions in susceptibility conferred by early PI mutations, thus prolonging viral suppression.

- NNRTI’s (NVP and EFV) and TB drugs are inducers of CYP 450 and affect PI concentrations.
NRTIs

- NRTIs are ddNTPs
  - Phosphorylated NRTIs compete with natural dNTPs for incorporation into the newly synthesized DNA chains - cause chain termination

- Nucleosides require 3 phosphates; nucleotides require 2 phosphates
Chain termination with NRTIs

If AZT was the last nt added, then the RT enzyme cannot add new nucleotides
Pyrophosphorylation
• After incorporation of a nucleoside, two released phosphates may attack the link, causing the nucleoside to be released again.
NNRTIs and Resistance

- The non-nucleoside RT inhibitors (NNRTIs) bind to a hydrophobic pocket (called the NNRTI-binding pocket).

- NNRTIs inhibit replication by displacing the enzyme active site relative to the polymerase binding site.

- A single mutation in the NNRTI-binding pocket may result in high-level resistance to one or more NNRTIs (low genetic barrier).
Fusion Inhibitors

- During HIV-1 infection, the virus’s gp120 binds to both a CD4 and chemokine receptor (CCR5 or CXCR4) on the target cells
- causes a conformational change in gp120
- promotes the fusion of the viral and cellular membranes
Fusion Inhibitors

This class of drugs interferes with the binding, fusion and entry of an HIV virion to a human (host) cell.

Enfuvirtide (Fuseon)
• Binds to gp41 transmembrane protein and blocks fusion of hiv-1 to the host cell.

Maraviroc (Selzentry; Celsentri)
• Binds to CCR5, preventing an interaction with gp120.
Integrase Inhibitors

- Integrase is one of three viral enzymes necessary for HIV replication that integrates or blends HIV genetic material into the DNA of human CD4 cells.
  - This makes it possible for the infected cell to make new copies of HIV

**Isentress (raltegravir)**

- By interfering with integrase, the integrase inhibitors prevent HIV genetic material from integrating into the CD4 cell, thus stopping HIV replication.
# Mutations associated with resistance to PIs

Dr Michelle Gordon

October 2009


## PI Resistance Notes

Last updated on Jun 10, 2008

<table>
<thead>
<tr>
<th>Resistance Matrix</th>
<th>Resistance Mutation Comments</th>
<th>Resistance Mutation Scores</th>
<th>Drug Summaries</th>
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http://hivdb.stanford.edu/
## Mutations associated with resistance to NRTIs

### NRTI Resistance Notes

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### Multi-NRTI Resistance Mutations

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Last updated on Jun 10, 2008

Mutations associated with resistance to NNRTIs

NNRTI Resistance Notes

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# Mutations associated with resistance to Fusion Inhibitors

## Fusion Inhibitor Resistance Notes

Last updated on Jun 10, 2008

### Resistance Matrix

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http://hivdb.stanford.edu/
# Mutations associated with resistance to Integrase Inhibitors

## Integrase Inhibitor Resistance Notes

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<th>Resistance Matrix</th>
<th>Resistance Mutation Comments</th>
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<tr>
<td>Elvitegravir$</td>
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<td>Q</td>
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</table>

How do you measure drug resistance?

Genotyping:

Indirect assay: Detects drug resistance mutations that are present in the relevant virus genes.

Phenotyping:

Direct assay: Measures the ability of the virus to grow in various concentrations of antiretroviral drugs.
Resistance Testing

1. Genotypic Testing
   More commonly used in clinical settings
   wider availability, lower cost and quicker turnaround (1-2 weeks)

   - PI and RTIS
     - HIV-1 GenotypR PLUS (Specialty Laboratories)
     - TRUGENE HIV-1 genotyping test (Bayer)
     - VircoGEN II (Virco)
     - Viroseq HIV genotyping system (Abbott Diagnostics)
     - GeneSeq (ViroLogic)
     - HIV-1 Mutation Analysis (Focus Technologies)
     - HIV ViroTYPE (Rheumatology Diagnostoc Laboratory)
     - GenoSure (LabCorp and Virco)

   - Fusion Inhibitors
     - TRUGENE HIV-1 Envelope (gp41) Genotyping Assay (Bayer)
     - HIV GenoSure Fusion (LabCorp)
Genotyping: Advantages

- Identification of all nucleotides, amino acid differences, deletions & insertions
- Genotyping has the ability to detect resistant virus that constitutes only a small proportion (about 20%) of the viral population.
- This can provide “predictive” early warning of developing resistance before full resistance develops
- Faster and less expensive than phenotype assay
Genotyping: Disadvantages

- Reports may be difficult to interpret unless clinician is very experienced.

- Labs use different software programs to predict resistance - need a consensus on which mutations are important.

- There is a lot of variation in the quality of the “product” from different laboratories especially in the ability to detect minority species in the population.

- Current limitation of use is that viral load needs to $\geq 1000$ copies/ml - need greater sensitivity.
Phenotyping: Advantages

- Provides resistance information on each drug regardless of the presence of multiple mutations.
- Interpretation may be more intuitive than for genotype assay.
- Very useful in patients with complex drug history and complicated mutation profile.
- Very useful for deciphering cross-resistance.
- May be more useful than genotyping for new drugs until appropriate mutations are established by clinical data.
Phenotyping: Disadvantages

- If drug resistant population is minor the phenotypic effect may not be detected

- Current limitation of use is that viral load needs to $\geq 1000$ copies/ml - need greater sensitivity

- Very expensive and time-consuming

- The relevance of small changes in drug sensitivity not yet fully determined - drugs to which patient is actually still sensitive may be unnecessarily eliminated
In-house genotyping assays

- There is continued effort to develop cheaper in-house assays for resistance genotyping.

- However, there needs to be some mechanism of standardization between laboratories.

- Also, because all in-house methods are nested reactions (with an increased chance of contamination) there needs to be the same level of adherence to quality control.
Kits vs In-house assays

Genotyping kits
- Already optimized
- Standardized
- Built-in QC procedures
- Thus, prevent possible sample to sample contamination
- Very expensive
- Insensitive to presence of minor variants
- Interpretation requires prior knowledge of genetic determinants of resistance

In-house assays
- Most require optimization
- Not standardized btw labs
- Not usually have built-in QC
- Increased risk of contamination
- Much cheaper
- More sensitive, because a nested reaction
- Interpretation the same
Genotyping using the Viroseq Kit

1. Load samples onto ABI 3100
Sequence Analysis

File Edit Window Help

Protase

Reverse Transcriptase

L29_F_09_ab1
L29_A_01_ab1
L29_B_03_ab1
L29_G_11_ab1
L29_H_13_ab1
L29_C_05_ab1

L29_F_09_ab1
L29_A_01_ab1
Interpretation of Genotypic Resistance Tests

- Interpretation complicated by complex patterns of mutations

2 basic approaches:

i) Rules-based algorithms:

Developed by experts;

Based on published data on phenotypic impact and clinical significance of drug resistance mutations

- TruGene (Bayer)
- Viroseq (Celera)
- HIVdb (Stanford)
- ANRS (French)
- Rega (Belgium)
ii) Machine-learning algorithms

Contain rules discovered by a computer program by analyzing data linking genotype to phenotype or clinical outcome.

Learn from a training data set and test performance using a test data set

- Decision trees
- Categorical analysis and regression trees (CART)
- Neural networks
- Virtual phenotype
HIVdb Program Integrate Update
Mutation classification, Scores, Comments and References.

HIVdb User Guide (link to PDF)
Database query and reference pages, Interactive program,
Educational resources

Crystallographic Structures
RT, protease, and integrase

More news »

GENOTYPE-TREATMENT CORRELATIONS
- Retrieve sequences (and/or mutations) from persons receiving selected HIV drugs
- Retrieve sequences and treatments from viruses with specific mutations

GENOTYPE-CLINICAL CORRELATIONS
- Summaries of genotype-clinical outcome studies
- Genotype-clinical outcome datasets (download)

GENOTYPE-PHENOTYPE CORRELATIONS
- Retrieve drug susceptibility data for isolates with selected mutations
- Download genotype-phenotype research datasets

REFERENCES
- Published drug resistance studies in HIVRT&PrDB
- Published studies by Stanford database group

NEW SUBMISSIONS
- Fujisaki, et al. 11-year surveillance of HIV subtypes in Japan

SURVEILLANCE MUTATIONS
- World Health Organization 2009 Mutation List

MARVEL
MARVEL (Mutation ARV Evidence Listing) » Go To Program

ART-AIDE
Antiretroviral Therapy - Acquisition & Display Engine
» Go To Program

HIVseq Program
Provides mutation frequencies by subtype. » Go To Program

HIVAlg Program
Compare HIVdb, ANRS, Rega, or create custom list. » Go To Program

This program interprets user-entered mutations to infer the level of resistance to NRTIs, NNRTIs, PIs. Web Service is available.
HIVdb Program

Genotypic Resistance Interpretation Algorithm

HIVdb accepts user-submitted protease and RT sequences and returns inferred levels of resistance to 19 commonly used protease and RT inhibitors. Its purpose is educational and as such it provides extensive comments and a highly transparent scoring system that is hyperlinked to data in the HIV Drug Resistance Database. In clinical settings, genotypic data must be used in conjunction with a patient’s clinical history (including past treatments) and a solid understanding of the principles of antiretroviral treatment (http://www.aidsinfo.nih.gov/guidelines/).

The drug resistance interpretation system used here is similar to the one used by the Stanford University Hospital (SUH) Diagnostic.
Dr Michelle Gordon  
October 2009

**Drug Resistance Interpretation: PR**

**PI Major Resistance Mutations:**  M46I, I54V, V82A  
**PI Minor Resistance Mutations:**  L10F, T74S  
**Other Mutations:**  T12S, I15V, L19I, K20R, E35D, M36I, R41K, L63S, H69K, L89M, I93L

### Protease Inhibitors

- atazanavir/r (ATV/r)  Intermediate resistance  
- darunavir/r (DRV/r)  Potential low-level resistance  
- fosamprenavir/r (FPV/r)  Intermediate resistance  
- indinavir/r (IDV/r)  High-level resistance  
- lopinavir/r (LPV/r)  Intermediate resistance  
- nelfinavir (NFV)  High-level resistance  
- saquinavir/r (SQV/r)  Intermediate resistance  
- tipranavir/r (TPV/r)  Low-level resistance

### PR Comments

#### PI Major
- M46I/L decreases susceptibility to IDV/r, NFV, FPV/r, LPV/r, and ATV/r when present with other mutations.  
- I54V contributes resistance to each of the PIs except TPV/r and DRV/r.  
- V82A reduces susceptibility to IDV/r and LPV/r. With other mutations it is associated with reduced susceptibility to NFV, ATV/r, SQV/r, and FPV/r.

#### PI Minor
- L10I/W/F/R/Y are associated with resistance to most PIs when present with other mutations. L10I/W occur in 5-10% of untreated persons. L10F/R/Y are nonpolymorphic.  
- T74S is associated with reduced NFV susceptibility. It occurs in untreated persons with subtype C viruses.
HIValg Program

Comparison of Genotypic Resistance Algorithms

HIValg compares HIVdb results to those of 2 other algorithms: i. Rega Institute (rules), and ii. Agence Nationale de Recherches sur le SIDA (ANRS rules). However, it does not provide the HIVdb report. HIValg also allows users to interpret sequences using any algorithm created using the Algorithm Specification Interface (ASI). Users can create their own algorithm and then upload it with their sequence.

A detailed description of the program as well as all updates can be found in the Release Notes.
HIVAlg Program: Sequence Analysis

There are two methods for indicating which algorithms you would like to have run on your input sequences. You can use any of them in combination. Choose one or more of the default algorithms and/or upload a user-created algorithm in ASI format.

Algorithms

A  Selection Input
Select one or more previously published algorithms using the checkboxes below.
✓ ANRSV2008.07  ✓ HIVDB  ✓ RegaV8.0.1

B  The ASI grammar definition has been updated slightly and it is not backwards compatible so please bear with us and follow this link to the old website to submit your own rules defined in the previous ASI grammar. The new ASI grammar will be documented and available shortly.

Sequence information can be entered in FASTA, plain text, or GRF (Bayer Diagnostics) format. Sequences in FASTA format or plain text can be pasted in the text box (option A) or uploaded (option B). GRF files can only be uploaded (option C). Using options A or B, it is possible to analyze up to 100 sequences at a time (character limit: 600,000)
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**Gene Differences from Consensus B**


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**Controlled Vocabulary**

- AHRS
- 'SIR' interpretation
- HIVDB
- Scored Mutations
- REGA
- 'SIR' interpretation
- Scored Mutations
Limitations of Drug Resistance Testing

i) Relationship between drug resistance and clinical failure is complex
- Non-adherence
- Sub-optimal regimens
- Pharmacokinetics
- Host factors
- Many drug resistant variants are less fit

ii) Complex quasispecies

iii) Cross-resistance

iv) Potentially miss minor populations
Overcoming Resistance

- Adherance
- New Drugs
- Salvage Therapy
- Intensification
Conclusion

- Resistance-conferring mutations occur continuously, in absence and presence of drug therapy.
- Occur more rapidly when viral load is high: more replication, more mutations.
- Mutant strains become dominant under drug selection pressure.
- Resistance testing gives information on which drugs no longer potent in regimen.
- Resistance testing limited because relationship between drug resistance and clinical failure is complex; may miss minor populations; cross-resistance.
- Understanding resistance is important for optimal patient management!
References

- http://hivdb.stanford.edu
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Thank you