Primer 04

HIV Drug Resistance Primer

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DISCLOSURES

Financial Relationships with Relevant Commercial Interests

- GlaxoSmithKline - Consultant (HIV / ART)
- Janssen Biotech – Sponsored clinical trials (HIV / ART)
- Pfizer Pharmaceuticals – Sponsored clinical trials (HIV / ART)
- Viiv – Sponsored clinical research (HIV/ART)
HIV Drug Resistance Testing

- About 16% of HIV-infected people in the U.S. are infected with a drug-resistant viral strain.
- Current guidelines recommend an HIV genotype as part of screening **BEFORE** ART is started.
- Following failure of 1\textsuperscript{st} or 2\textsuperscript{nd} regimens, HIV genotype is recommended to use with the history to choose the optimal next regimen. Following failure of 3\textsuperscript{rd} and subsequent regimens, both HIV genotype **AND** HIV phenotype should be sent.
- If there is discordance between genotype and phenotype, use the geno result (more sensitive).
HIV Resistance

Nucleoside Reverse Transcriptase Mutations (NRTI)
Nucleoside Associated Mutations (NAMS)

• **M184V** (or **I**) confers COMPLETE resistance to lamivudine (3TC) and emtricitabine (FTC).
• **M184V** (or **I**) “re-sensitizes” both zidovudine (ZDV) and tenofovir (TDF), partially restoring virologic activity of these drugs.
• 4 or more of the 6 NAMS (at positions 41, 67, 70, 210, 215, 219) confers resistance to all NRTIs.
• **K65R** is selected by tenofovir (TDF) and confers resistance to ALL NRTI except zidovudine (ZDV).
• There are a few rare multi-NRTI mutations: **69SSS** (insertion) and **Q151M**.
HIV Resistance
Non-nucleoside Reverse Transcriptase Mutations (NNRTI)

- **K103N** is the signature mutation for efavirenz (EFV).
- **Y181C** is the signature mutation for nevirapine (NVP).
- Efavirenz and nevirapine have low genetic barriers (require only 1 mutation for resistance) and are COMPLETELY cross-resistant to one another.
- Etravirine and rilpivirine have higher barriers to resistance (require >1 mutation for resistance).
- **K103N** has no effect on etravirine susceptibility.
- Rilpivirine failure is associated with **E138K, K101E**, and/or **Y181C** consequent NNRTI class resistance.
HIV Resistance – Protease inhibitors (PI)

• In general, currently used protease inhibitors require multiple mutations for resistance (i.e. have a high genetic barrier).
  – Exception: I50L confers resistance to atazanavir (ATV).

• Patients experiencing failure on a 2 NRTI + boosted PI regimen most often have NO PI mutations.

• With significant prior protease inhibitor use, a phenotype is preferred to a genotype.
HIV Resistance – Other Drugs

• Enfuvirtide (ENF, T-20) has a low barrier to resistance (only 1 mutation in gp41 required). A history of ENF use with failure is enough to suggest drug resistance (even without a genotype).

• Resistance to maraviroc (MVC, the CCR5 antagonist) is very uncommon. The most common mechanism of virologic failure is selection of pre-existing X4 virus (X4 or D/M on tropism test).

• Raltegravir (RAL) and elvitegravir (EVG) have a low barrier to resistance. Patients failing RAL or EVG most commonly already have 2 or more integrase-associated mutations (N155H [with both], Q148H/R/K [with both], Y143C [with RAL], T66I [with EVG].)
Common Mutations To Memorize

- **M184V/I**
  - 3TC and FTC

- **M41L, D67N, K70R, L210W, T215Y, K219Q**
  - "TAMS"
  - 4 or more thymidine-analog mutations (TAMS) affect all approved nucleosides

- **65R**
  - tenofovir

- **Q151M, F77L, F116Y**
  - multi-NRTI
  - multi-NRTI mutations affect all nucleosides except tenofovir may retain activity against Q151M

- **K103N**
  - EFV (and NVP)
  - retains susceptibility to etravirine

- **Y181C**
  - NVP and other NNRTI

- **E138K, K101E**
  - RIL and other NNRTI

- **I50L**
  - ATV

- **N155H, Q148H/R/K**
  - RAL and EVG

- **Y143C**
  - RAL

- **T66I**
  - EVG