Primer 04

2012 HIV Drug Resistance Primer

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HIV Drug Resistance 2012
What you need to know (in 5 slides)
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 1st or 2nd regimens, HIV genotype is recommended to use with the history to choose the optimal next regimen. Following failure of 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).
- 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 mult-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 require >1 mutation for resistance.
• **K103N** has no effect on etravirine susceptibility.
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 X4 virus (X4 or D/M on tropism test).
- **Raltegravir (RAL)** has a low barrier to resistance and patients failing RAL most commonly already have 2 integrase-associated mutations.
Common Mutations To Memorize

- K65R  
  - Tenofovir
- M184V  
  - 3TC (ddC)
- K103N  
  - NNRTI
  - Remains ETRAVIRINE sensitive
- M41L, D67N, K70R, L210W, T215Y  
  - ”TAMS”*
- Q151M, F77L, F116Y  
  - Multi-NRTI**
    (Tenofovir may retain activity against Q151M)
- N155H, Y143C, Q148H/R/K  
  - Raltegravir

*Thymidine analog mutations (TAMS) affect all approved nucleosides

**MultiNRTI mutations affect all nucleosides except tenofovir

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