HIV Drug Resistance Primer

Roy M. Gulick, MD, MPH
Professor of Medicine
Chief, Division of Infectious Diseases
Weill Cornell Medical College

2/28/2019

HIV Drug Resistance Testing

- About 16% of treatment-naïve HIV-infected people in the U.S. are first 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 3rd and subsequent regimens, both HIV genotype AND HIV phenotype should be sent.
- If there is discordance between genotype and phenotype results, use the genotype result (more sensitive).

Nomenclature

- HIV drug resistance mutations are given in this format
  - LETTER-NUMBER-LETTER (e.g. M184V)
- The first LETTER is the code for the wild-type amino acid
  - (e.g., M = methionine)
- The NUMBER gives the amino acid position in the enzyme
  - (e.g., 184 = position #184 in HIV reverse transcriptase)
- The second LETTER is the code for the substituted (or “mutated”) amino acid
  - (e.g., V = valine)

HIV Resistance

Nucleoside Reverse Transcriptase Mutations (NRTI)

Nucleoside-Associated Mutations (NAMS)

- M184V (or I) confers COMPLETE resistance to lamivudine (3TC) and emtricitabine (FTC). These drugs have a low barrier to resistance.
- But, M184V (or I) also enhances the virologic activity of both zidovudine (ZDV) and tenofovir (TDF or TAF).
- Having 4 or more of the 6 NAMS (at reverse transcriptase positions 41, 67, 70, 210, 215, 219) confers resistance to all NRTIs.
- K65R is selected by tenofovir (TDF/TAF) and confers resistance to ALL NRTI except zidovudine (ZDV). (This is a testable fact!)
- There are a few rare multi-NRTI mutations: 69SSS (insertion) and Q151M (retains susceptibility to tenofovir [TDF or TAF].

HIV Resistance

Non-nucleoside Reverse Transcriptase Mutations (NNRTI)

- K103N is the signature mutation for efavirenz (EFV).
- Y181C is the signature mutation for nevirapine (NVP).
- Older NNRTIs, efavirenz and nevirapine, have a low genetic barrier (require only 1 mutation for resistance) and are COMPLETELY cross-resistant to one another.
- Newer NNRTIs, etravirine (ETR) and rilpivirine (RPV), have a higher barrier to resistance (require >1 NNRTI-associated mutation for resistance).
- E138K is the signature mutation for rilpivirine (RPV) and etravirine (ETR).

.

- K103N (alone) has no effect on RPV or ETR susceptibility.
- Rilpivirine or etravirine failure is associated with E138K, K101E, and/or Y181C and consequently, resistance to ALL NNRTIs.

HIV Resistance
Protease Inhibitors (PI)

- Currently used protease inhibitors require multiple mutations for resistance (i.e. have a high genetic barrier).
  - Exception: I50L alone confers resistance to atazanavir (ATV)
- Patients experiencing failure on a 2 NRTI + boosted PI regimen most often have NO PI (or nucleoside) mutations
- With significant prior protease inhibitor use, because of the multiple mutations, a phenotype is preferred to a genotype.

HIV Resistance – Integrase Inhibitors

- The first 2 approved HIV integrase inhibitors, raltegravir (RAL) and elvitegravir (EVG) have a low barrier to resistance (only 1 mutation required to confer resistance) and are cross-resistant to one another.

- Patients failing RAL or EVG most commonly already have selected 2 or more integrase-associated mutations: Q148H/R/K [with both], N155H [with both], Y143C [with RAL], T66I [with EVG].

- Dolutegravir (DTG) and bictegravir (BIC) have a higher barrier to resistance and are active against some RAL- or EVG-resistant strains

- The Q148 mutation decreases DTG or BIC activity.

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 strongly suggest drug resistance (even without getting a fusion inhibitor 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). (This is a testable fact!)

Common Mutations To Memorize

- M184V/I — 3TC and FTC
- M41L, D67N, K70R,L210W, T215Y, K219Q — ”TAMS” – all nucs
  4 or more thymidine-analog mutations (TAMS) confer resistance to all approved nucleosides
- K65R — tenofovir (TDF/TAF)
  Among nucleosides, only ZDV retains activity in the presence of K65R
- Q151M, 69SSS — Multi-NRTI
  Multi-NRTI mutations affect all nucleosides except tenofovir that may retain activity against Q151M
- K103N — EFV (and NVP)
  Retains susceptibility to rilpivirine and etravirine

Common Mutations To Memorize cont.

- Y181C — NVP (and EFV)
- E138K, K101E — RPV and ETR

- I50L — ATV

- Q148H/R/K — all integrase inhibitors
  only Q148 decreases virologic activity to DTG and BIC
- N155H, Y143C, T66I — RAL and/or EVG