HIV/HBV Drug Resistance: Lessons Learned

Douglas Richman

HCV DRAG

18 May 2007

CFAR
CENTER FOR AIDS RESEARCH
University of California San Diego

HIV,HBV and HCV: Similarities

- chronic infection with inadequate immune response
- quasi-steady state with massive rates of viral production and clearance
- complex genetic composition in each patient: quasispecies
- viral polymerase with ssRNA template
  - high mutation rate (~10^{-5} nucleotides/replication cycle). Thus, with 10^{10} - 10^{-12} virions generated daily, all possible mutations occur daily.
  - no proofreading mechanism
- complex dynamics in response to treatment
- variable host susceptibility that is probably genetically determined primarily but some contribution of variable agent virulence.

HIV,HBV and HCV: Differences

- Different host cells
  - different disease complications
  - different dynamics of response to treatment
- HIV cytopathic
- Overlapping reading frames: HBV>HIV>HCV
- Recombination: HIV>>HBV and HCV
- Anatomic and cellular compartmentalization: HIV > HBV and HCV (?)
- Chromosomal integration of HIV; potential curability of HCV

Practical Implications of the Biology of HIV/HBV/HCV Drug Resistance - 1

- **Genetic variants with single and probably double mutations preexist. (Why some regimens fail.)**
- **Genetic variants with 3 or more drug resistance mutations rarely exist. (Why some combination regimens succeed.)**
- **The prevention of the cumulative acquisition of drug resistance mutations requires the suppression of replication.**

Practical Implications of the Biology of HIV/HBV/HCV Drug Resistance - 2

- **Fitness and genetic variants**
  - **Some mutations have a fitness cost; some do not. (Invoking impaired fitness as an accomplishment is poor medicine and questionable marketing)**
  - **Unfit mutations may be compensated for by other mutations (Reversion of resistance is slowed and resistant mutants are more virulent)**
  - **Mixtures of variants will emerge with their complexity increasing as failing treatment continues. (More resistance and cross-resistance may exist than is readily appreciated with population sequencing)**
  - **All these resistant variants will be archived for life with HIV, HBV and HCV (unless it is cured)**

Practical Implications of the Biology of HIV/HBV/HCV Drug Resistance – 3: Implications for Drug Development

- **Preclinical evaluation**
  - **Multiple clinical isolates**
  - **Representatives of various groups (clades)**
  - **Representatives of relevant drug resistant variants**
  - **Selection in vitro for drug resistance (confirms target and predicts clinical resistance (imperfectly) and cross-resistance**

- **Clinical evaluation (Vertex set an example)**
  - **Monitor the dynamics of emergence of resistance (pheno and geno)**
  - **Clone to monitor for minority species**
  - **Test for cross-resistance**
  - **Monitor decay off drug**