Antiretroviral Prophylaxis and HIV Drug Resistance

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Outline

- Two minutes on terminology
- Origins of HIV drug resistance
- Lessons learned from ART
- Do these apply to ARP?
  - Yes, but…
- Other relevant considerations

Two Minutes on Terminology

"Microbicides" mean different things to different people:

- Kills all microbes (i.e., bleach)
- Kills some microbes including HIV
- Only blocks HIV replication (i.e. ARV)
- Anything put into the vagina or rectum

Prevention with Antiretrovirals

- ARV treatment of infected persons (ART)
  - prevent horizontal transmission
  - prevent vertical transmission (pMTCT)
- ARV prophylaxis (ARP) of uninfected persons
  - prevent horizontal transmission (M $\Leftrightarrow$ F; M $\Leftrightarrow$ M)
  - prevent vertical transmission (pMTCT)
- ARP approaches
  - Mucosal (topical) or systemic (oral, SC, IM) or both
  - Pre- or post-exposure or both

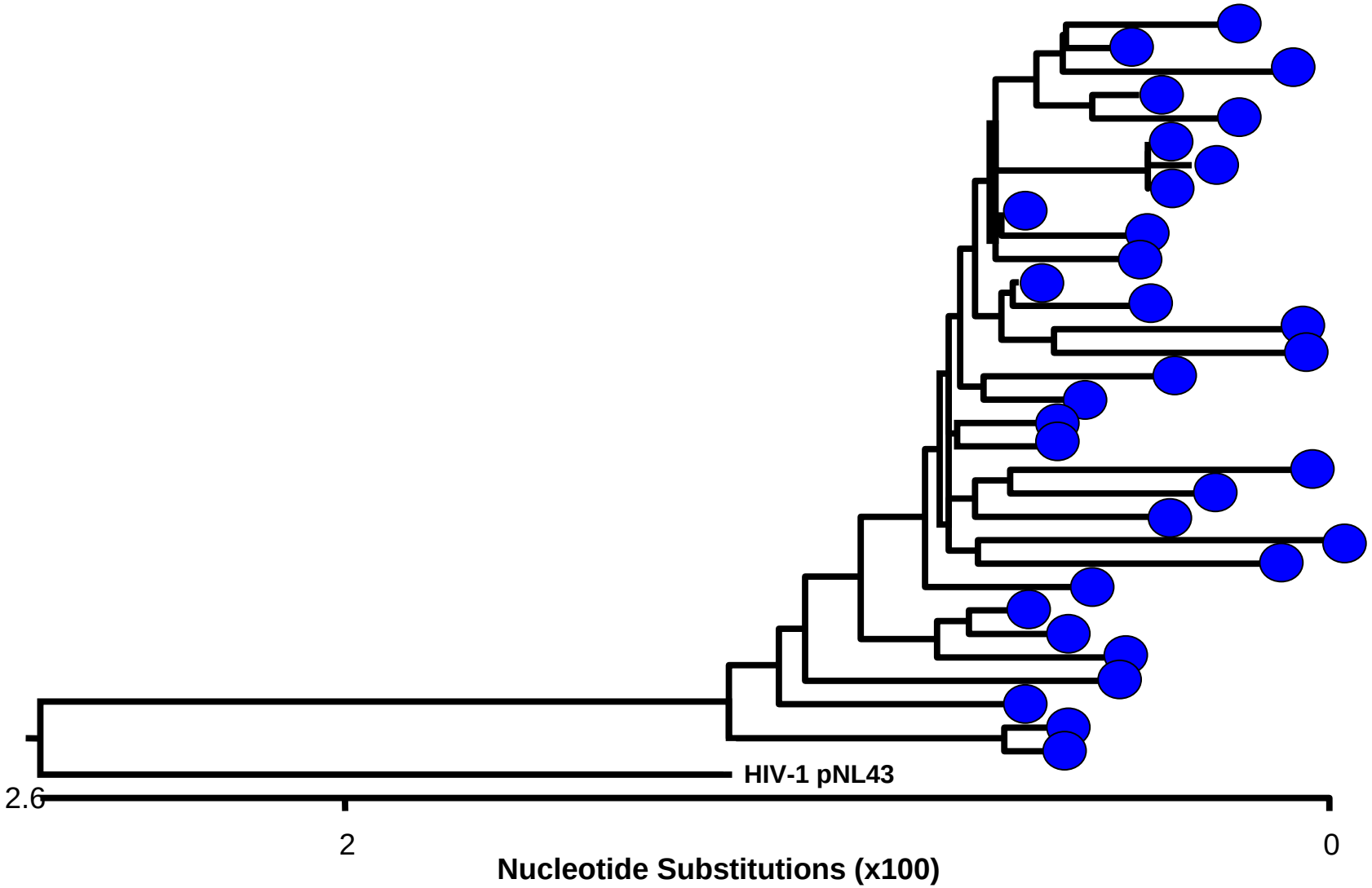
The Ideal ARV for Prevention

- Potent, specific HIV inhibitor
- Acts pre-integration (no provirus formation)
- High mucosal and submucosal exposure
- One dose daily – or less
- Well tolerated, safe for long term use
  - including pregnancy and breastfeeding!
- Gender neutral (empowers women and men)
- Not used for therapy - preserves treatment options!
- Affordable: drug and monitoring costs

Origins of HIV Drug Resistance

- Large, diverse population of HIV variants within a chronically infected individual
  - High viral replication: ~10^{11} virions produced per day
  - sloppy RT: ~3 errors per 100,000 bases copied
  - RT doesn't correct it's errors
  - No two genomes are the same!
  - Differ on average by one base out of ~10,000

HIV variants in one plasma sample (*Gag-pol* single genome sequences)



Billions of mutants produced daily!

Origins of HIV Drug Resistance

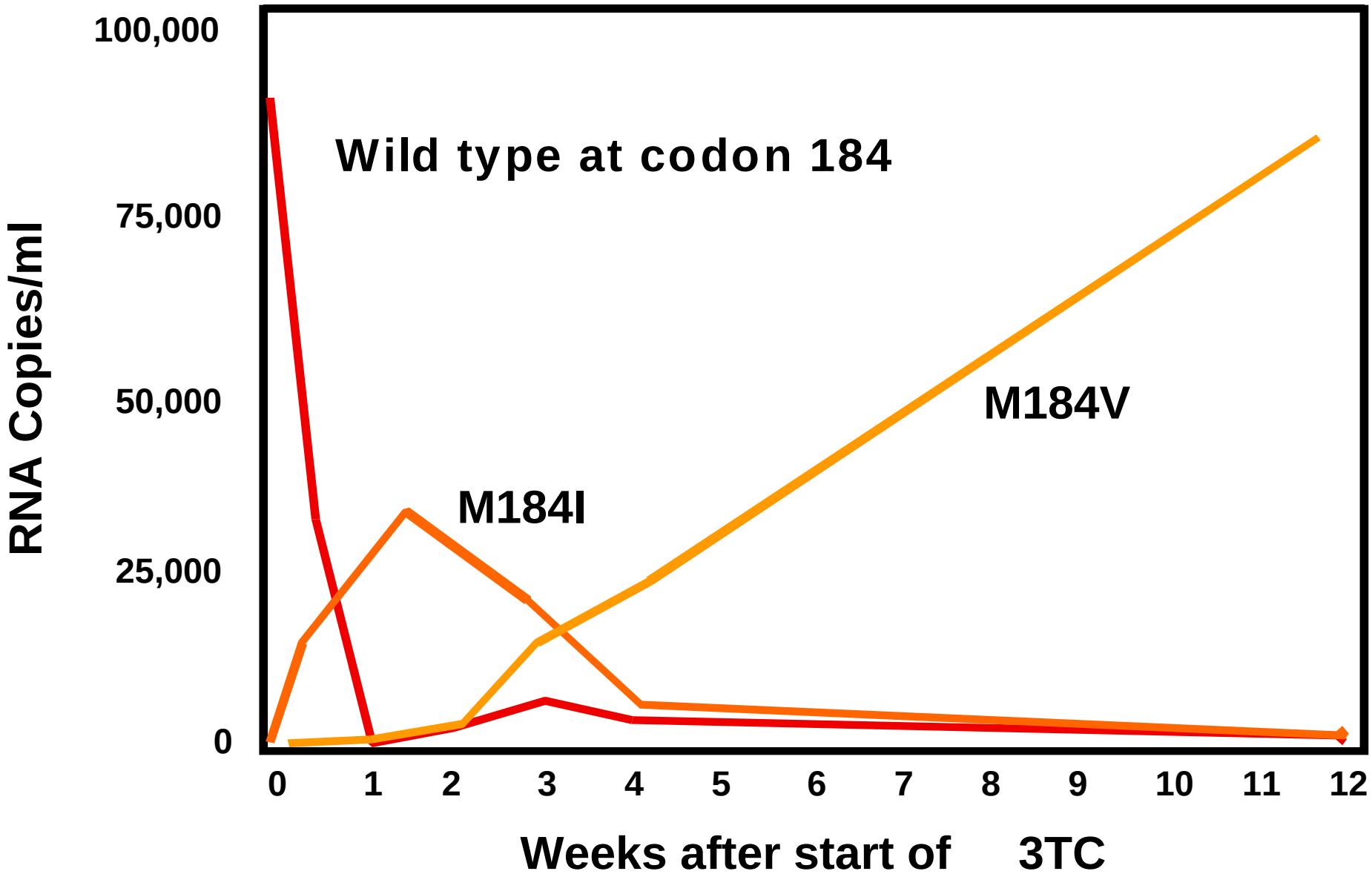
- For many ARV, a single nucleotide change results in resistance:
  - TNV (K65R): AAA to AGA
  - FTC (M184V): ATG to GTG
  - EFV (K103N): AAA to AAC
- With 10^{11} genomes produced daily:
  - All possible single mutants produced daily
  - Double mutants may also exist
  - Triple mutants probably do not
    - » $P = 10^{-12}$ (10^{-4} x 10^{-4} x 10^{-4}) < 10^{11} genomes/day

Lessons Learned from ART

- Resistant variants are rapidly selected by monotherapy with drugs for which 1 mutation confers resistance

Appearance of 3TC-Resistant Mutations in Treated Patients

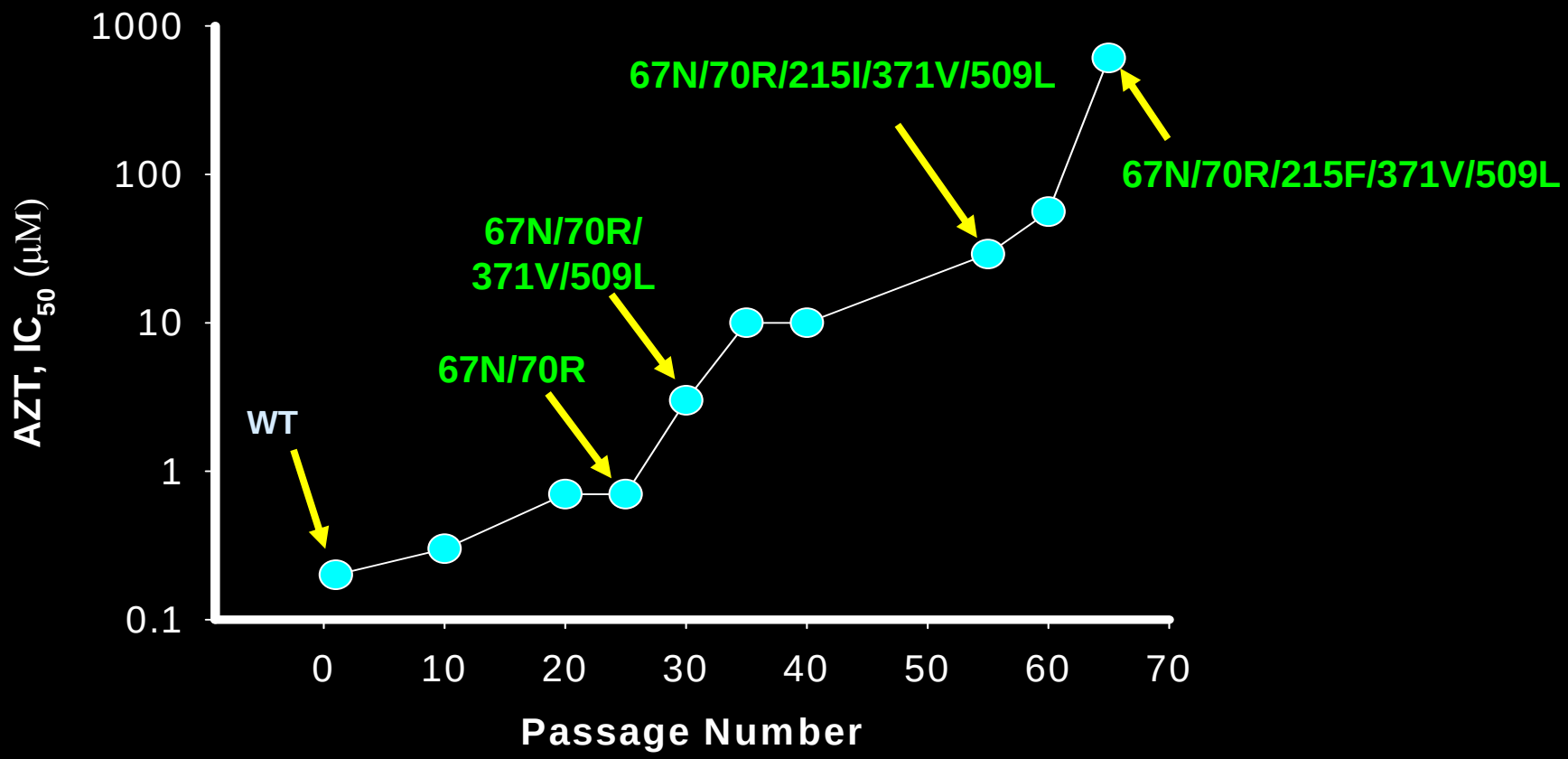
Schuurman et al, JID 1995; 171:1411



Lessons Learned from ART

- Resistant variants are rapidly selected by monotherapy with drugs for which 1 mutation confers resistance
- Incomplete suppression of viral replication results in accumulation of multiple mutations, more resistance and broader cross-resistance

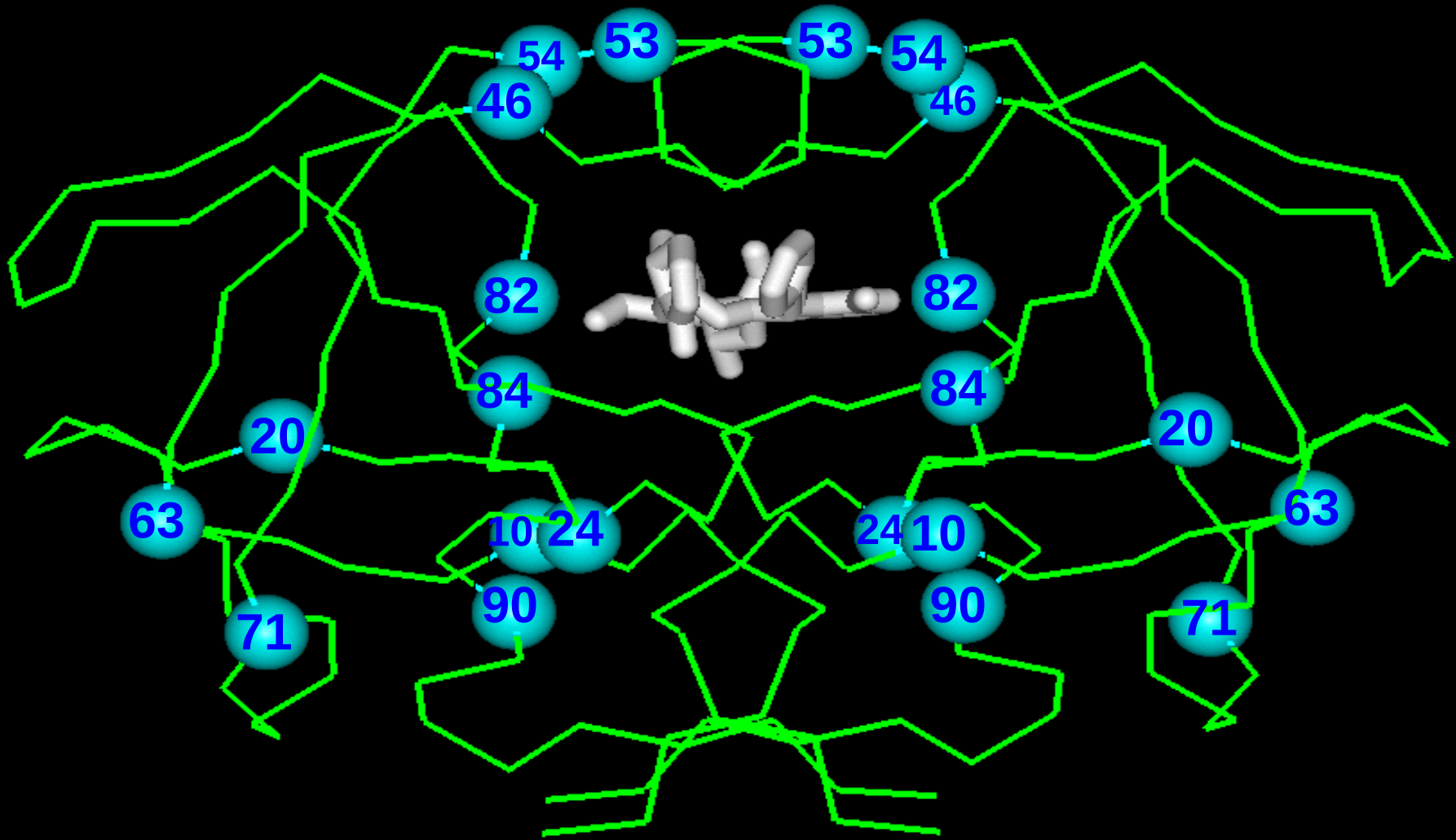
Accumulation of Multiple Mutations in HIV RT



Lessons Learned from ART

- Resistant variants are rapidly selected by monotherapy with drugs for which 1 mutation confers resistance
- Incomplete suppression of viral replication results in accumulation of multiple mutations, greater resistance and broader cross-resistance
- HIV proteins are amazingly flexible
  - Preserved function despite many substitutions
  - e.g., >25% of 99 amino acids in Protease can vary

Protease Mutations Associated with Reduced Susceptibility to Lopinavir



Principles of Successful ART

- Cover all pre-existing mutants
  - Single and double drug-resistant mutants
- Suppress new cycles of HIV replication
  - Plasma HIV RNA < 50 copies/ml
- Generally requires 3 potent drugs
  - With non-overlapping resistance mutations

ART MANTRA

No Replication = No Resistance

Caveats

- Not all three drug combinations are the same
  - TNV +3TC + ABC ⇒ rapid virologic failure in >50%
    - » Single mutant (M184V) affects two drugs: 3TC/ABC
    - » Failure virus has M184V ± K65R
  - TNV + 3TC + EFV ⇒ 75% long-term success
    - » No single mutant affects more than one drug
    - » M184V increases sensitivity to TNV!
- Can get away with 2 drugs requiring >2 mutations for viral escape
  - LPV/r + EFV = TNV/3TC/EFV (Riddler ACTG 5142)
- Choose combinations wisely
  - Consult your local resistance expert ☺

Relevant for ARP?

- Yes, but….***Warning, Entering Data Poor Zone***
  - Size and diversity of virus population in genital secretions is tiny compared with that in an infected individual
    - » 10^4-10^6 vs 10^{11} genomes
    - » Infectious titer probably much lower
    - » Probability of pre-existing resistant mutant is low
  - One drug may suffice (TNV in trials)
    - » Unless source of infection has resistance to that drug!
  - One drug requiring > 1 resistance mutation or 2 drugs with non-overlapping resistance mutations might be better
- Initial emphasis should be on potency and exposure at the site of infection to maximize efficacy….

ARP MANTRA

No Infection = No Resistance!

ARP Efficacy vs. Resistance

Number at Risk	Seroincidence	Efficacy of ARP	% Resistant w/ ARP Failure	Individuals with Resistance
100,000	5%	30%	50%	1750
100,000	5%	60%	50%	1000
100,000	5%	90%	50%	250
100,000	5%	95%	50%	125
100,000	5%	99%	50%	25

Other Relevant Issues

- Individuals who are put on ARP with undiagnosed HIV infection will develop resistance
  - Unless APR is equivalent to ART (impractical)
- Individuals who become infected on ARP will likely develop resistance unless it is stopped promptly
  - Impact of resistance on future response to ART?
- Ideally, agents used for ARP and ART will not overlap
  - Not possible today…a goal for the future

Questions?