# ARV Resistance and Microbicide Research

**John Mellors**

**University of Pittsburgh**

MTN
microbicide trials network

# Outline

- Origins of HIV-1 drug resistance
- Mechanisms of RTI action and resistance
- Clinical pathogenesis & consequences
- Review of key cenarios
- Implications for MTN trials

# Origins of HIV-1 Drug Resistance

- High viral replication (~$10^{11}$ virions/day)
  - Error prone RT (3 x $10^{-5}$/bp/cycle)
- All single & many double mutants likely pre-exist
  - Rapidly selected by monotherapy or dual therapy with drugs for which 1-2 mutations confer resistance
- Multiple mutations are selected and accumulate with continued viral replication during therapy
  - Resistance/cross-resistance to multiple drugs

# Origins of HIV-1 Drug Resistance (con't)

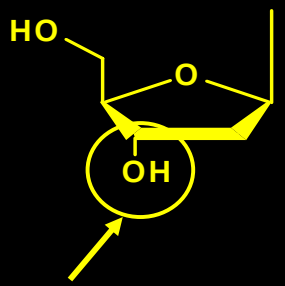
- Recombination between resistant variants
  - Speeds accumulation of mutations on the same genome
- HIV-1 target flexibility
  - Preserved function despite many substitutions
  - e.g., >25% of 99 amino acids in PR can vary

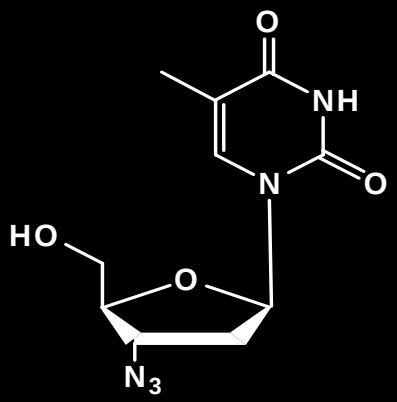
No ARV is Resistance Proof!

# Approved Antiretroviral Drugs 2007

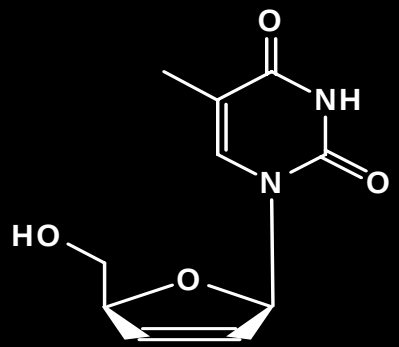
| NRTI | NNRTI | PI | FI |
|---|---|---|---|
| zidovudine | nevirapine | ritonavir | enfurvitide |
| didanosine | delavirdine | indinavir | |
| zalcitabine | efavirenz | nelfinavir | |
| stavudine | | saquinavir | |
| lamivudine | | amprenavir | |
| abacavir | | lopinavir/r | |
| tenofovir | | fosamprenavir/r | |
| emtricitabine | | tipranavir/r | |
| | | darunavir/r | |

# Nucleoside and Nucleotide RTIs (NRTI)

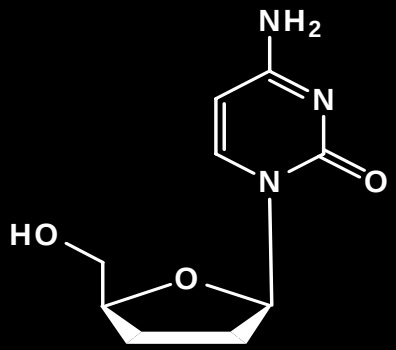


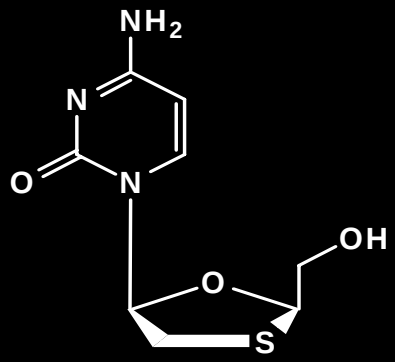

**Zidovudine (AZT)**



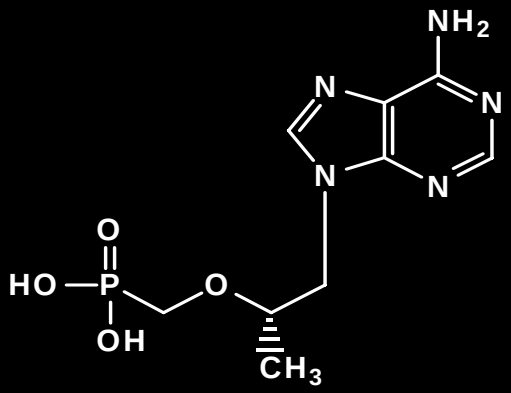

**Stavudine (d4T)**



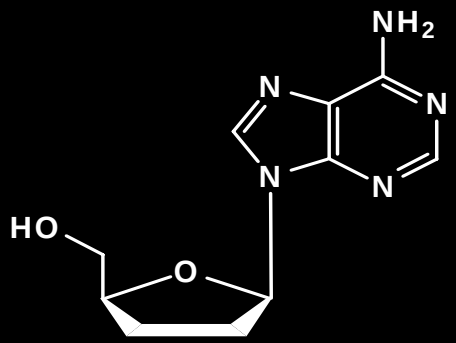

**Zalcitabine (ddC)**



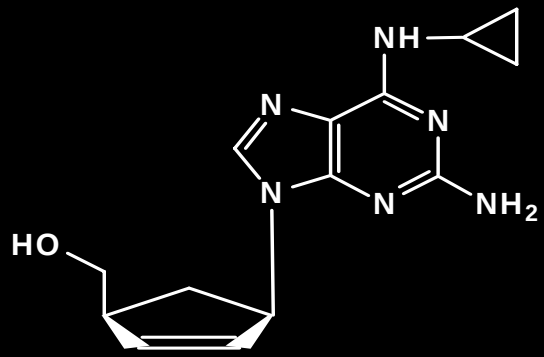

**Lamivudine (3TC)**



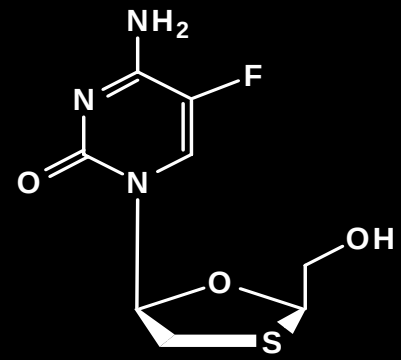

**Tenofovir (TDF)**




**Didanosine (ddI)**



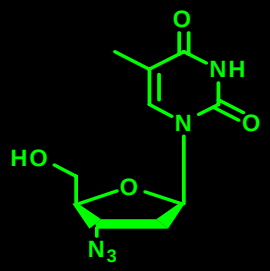

**Abacavir (ABC)**



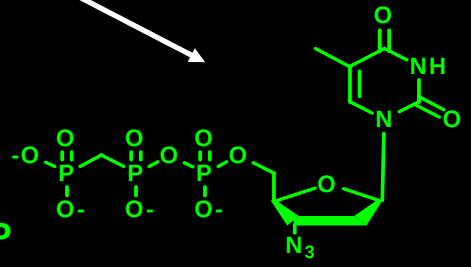

**Emtricitabine (FTC)**

# NRTI – Mechanism of Action

AZT
(Zidovudine)

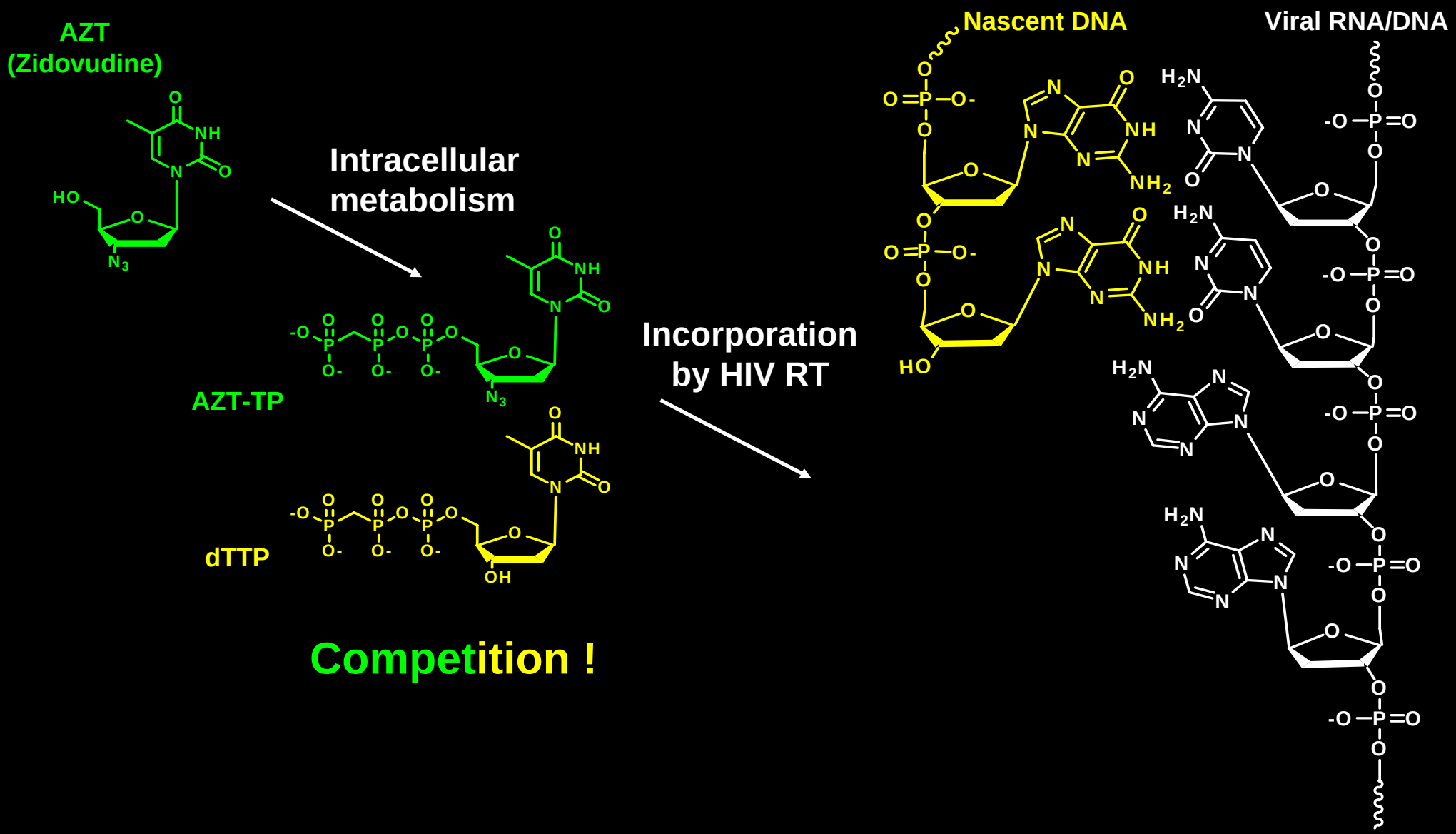



Intracellular
metabolism

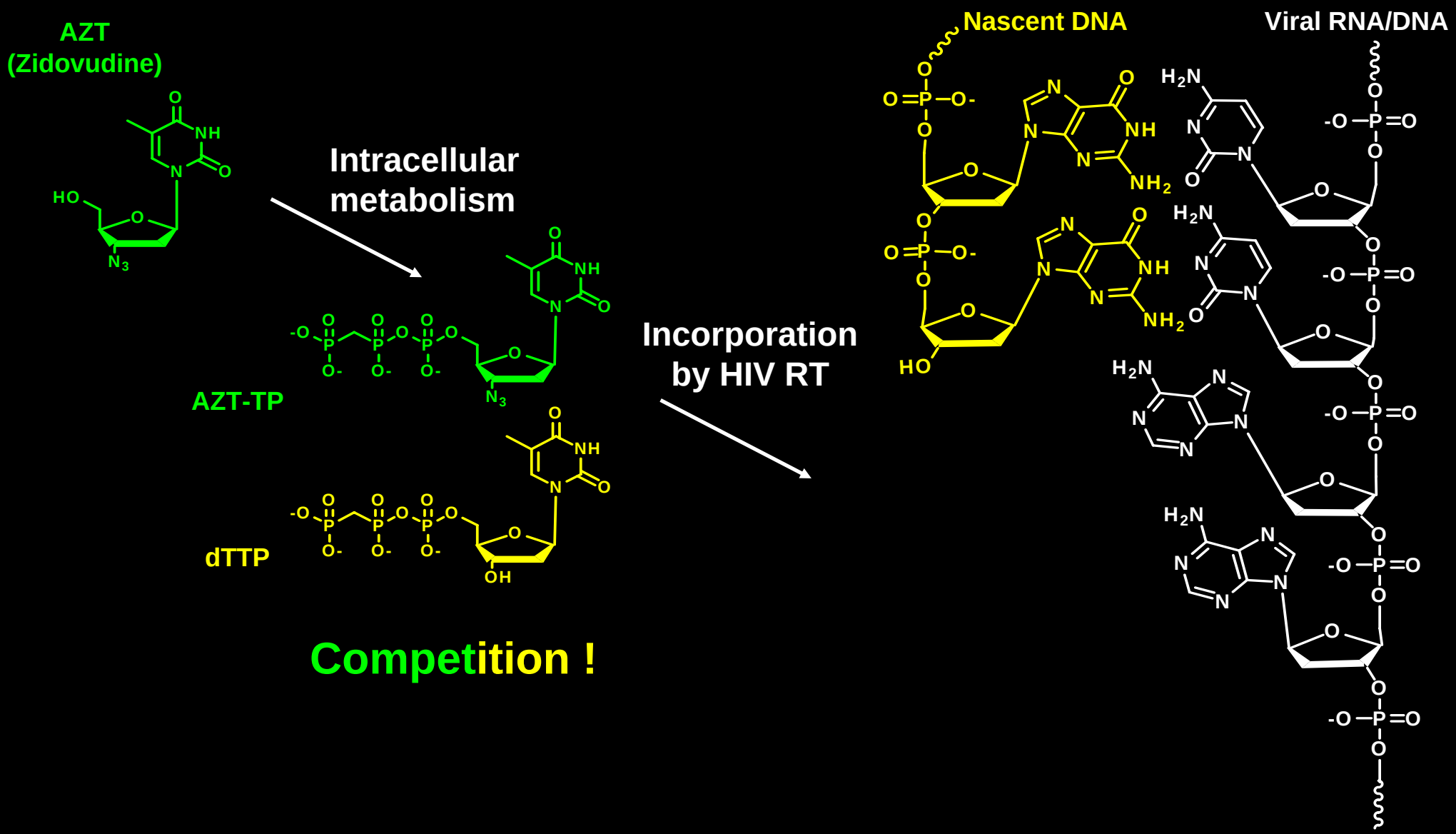



AZT-TP

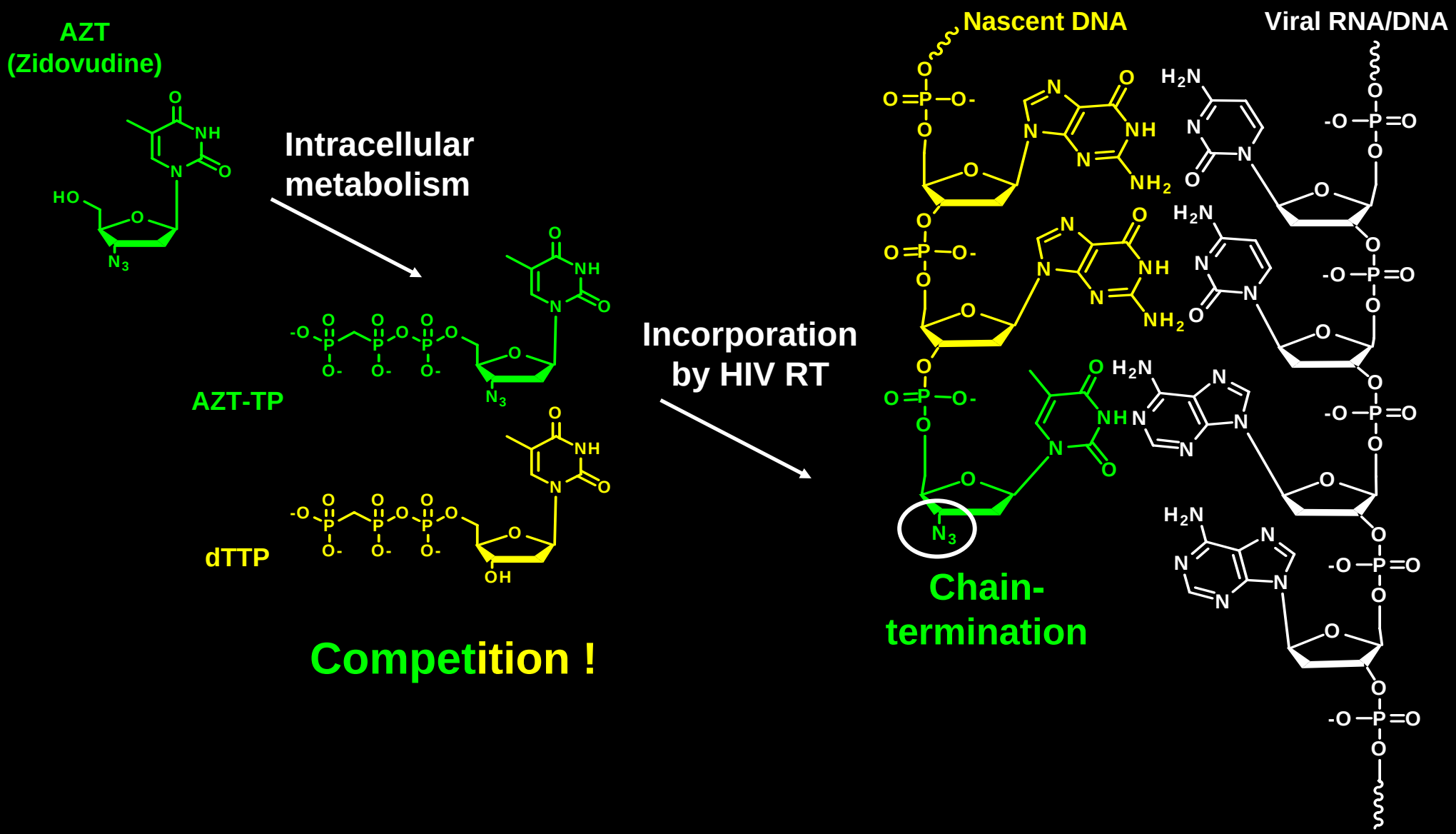
# NRTI – Mechanism of Action



# NRTI – Mechanism of Action



# NRTI – Mechanism of Action



# Molecular Mechanisms of NRTI Resistance

## 1. Discrimination:

Resistance mutations enable HIV-1 RT to preferentially incorporate the natural dNTP substrate over the NRTI-TP

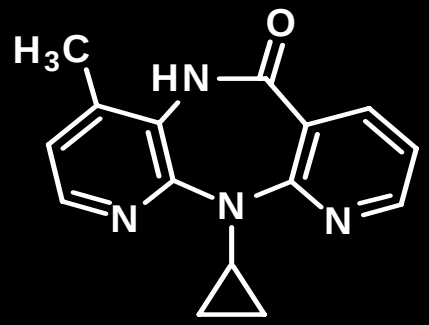
Mutations: K65R, K70E, L74V, M184V, Q151M

## 2. Excision:

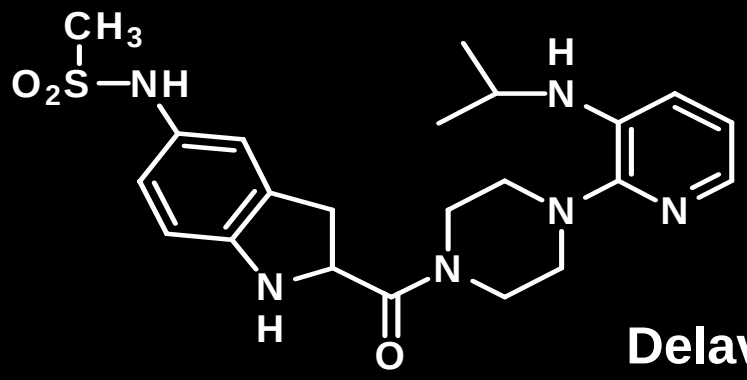
Resistance mutations facilitate excision or removal of the chain-terminating NRTI-MP from the 3'-terminus of the primer

Mutations: TAMs (M41L, D67N, K70R, L210W, T215F/Y, K219Q)

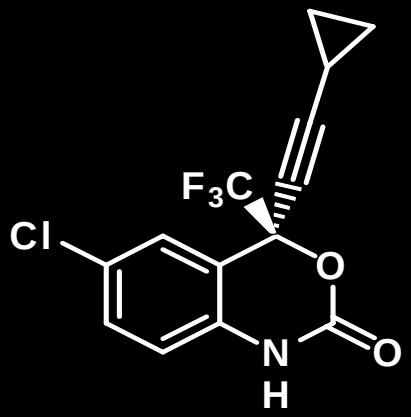
# Nonnucleoside RTIs (NNRTI)




Nevirapine
(Viramune)

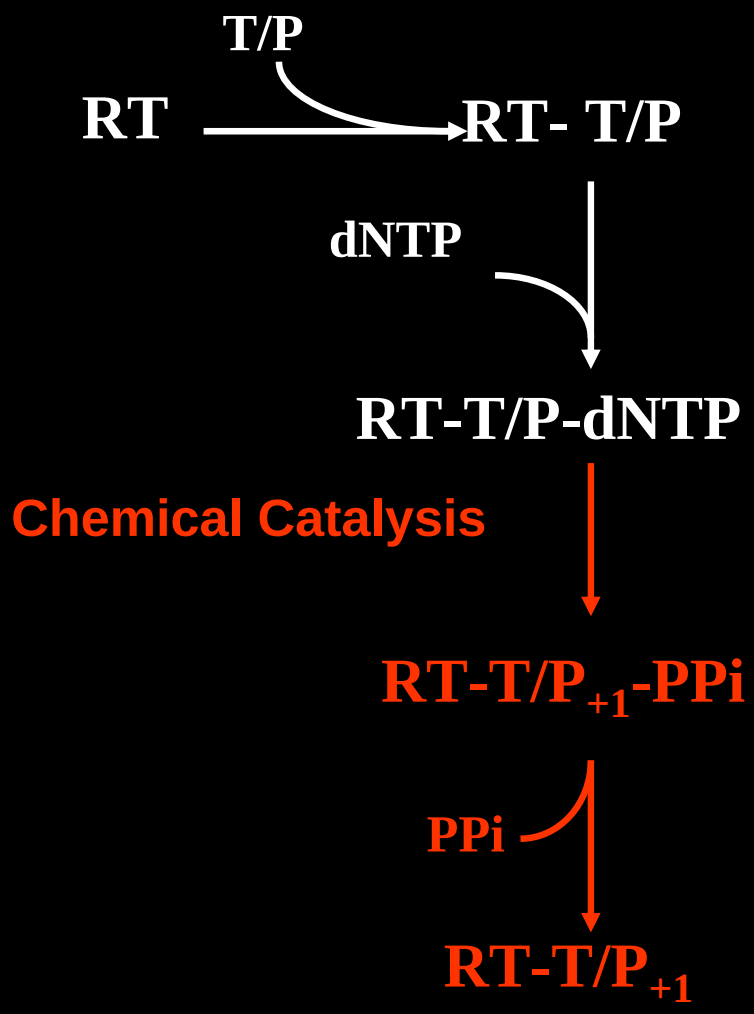



Delavirdine
(Rescriptor)

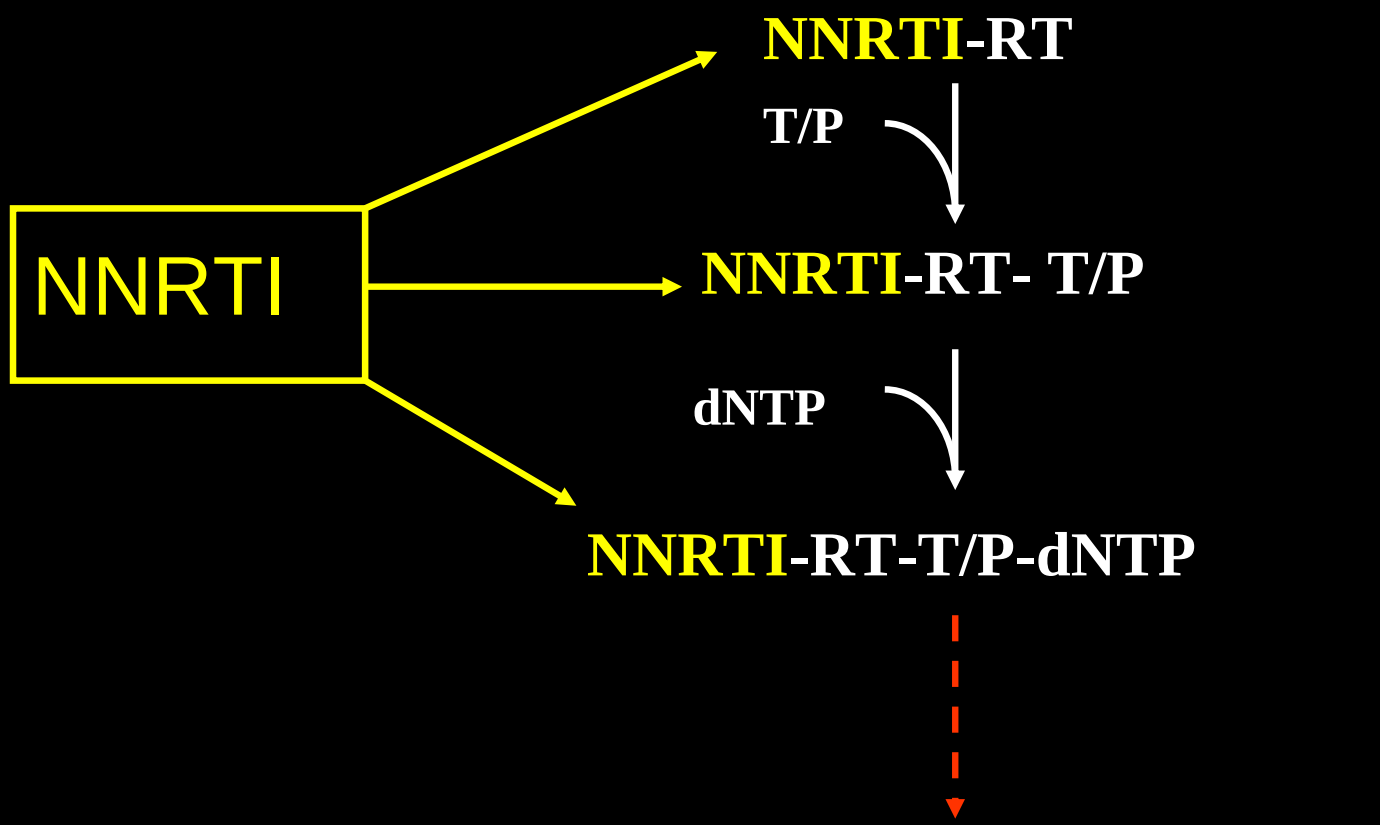



Efavirenz
(Sustiva)

# NNRTI – Mechanism of Action



# NNRTI – Mechanism of Action

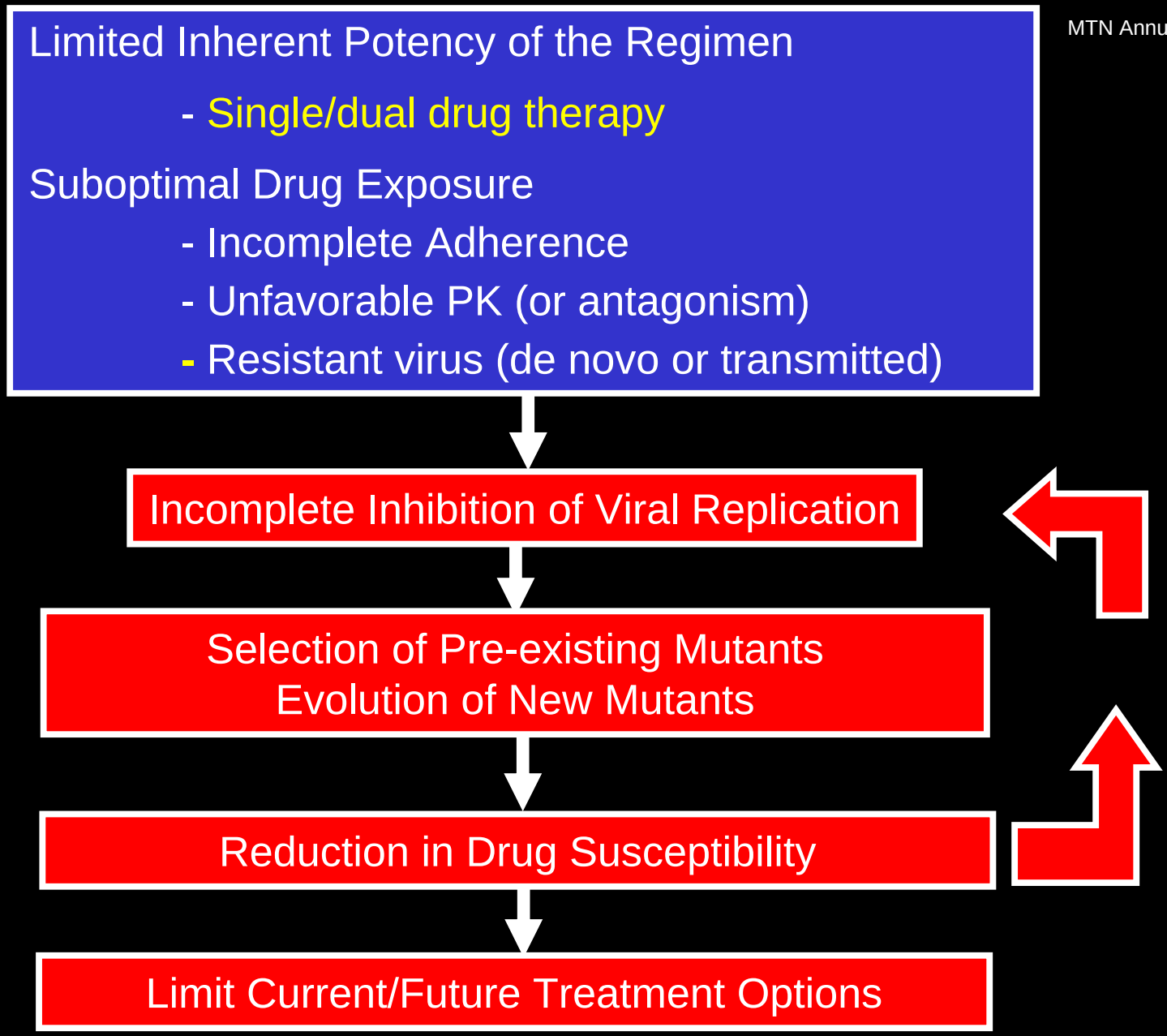



Spence et al. 1995. Science 267:988

# Mechanisms of NNRTI Resistance

Resistance mutations, such as K103N and Y181C, affect the association and dissociation constants of the NNRTI-RT binding interaction.

**Gietmann et al. 2006. J. Med. Chem. 49: 2367; Gietmann et al. 2006. J. Med. Chem. 49: 2375**

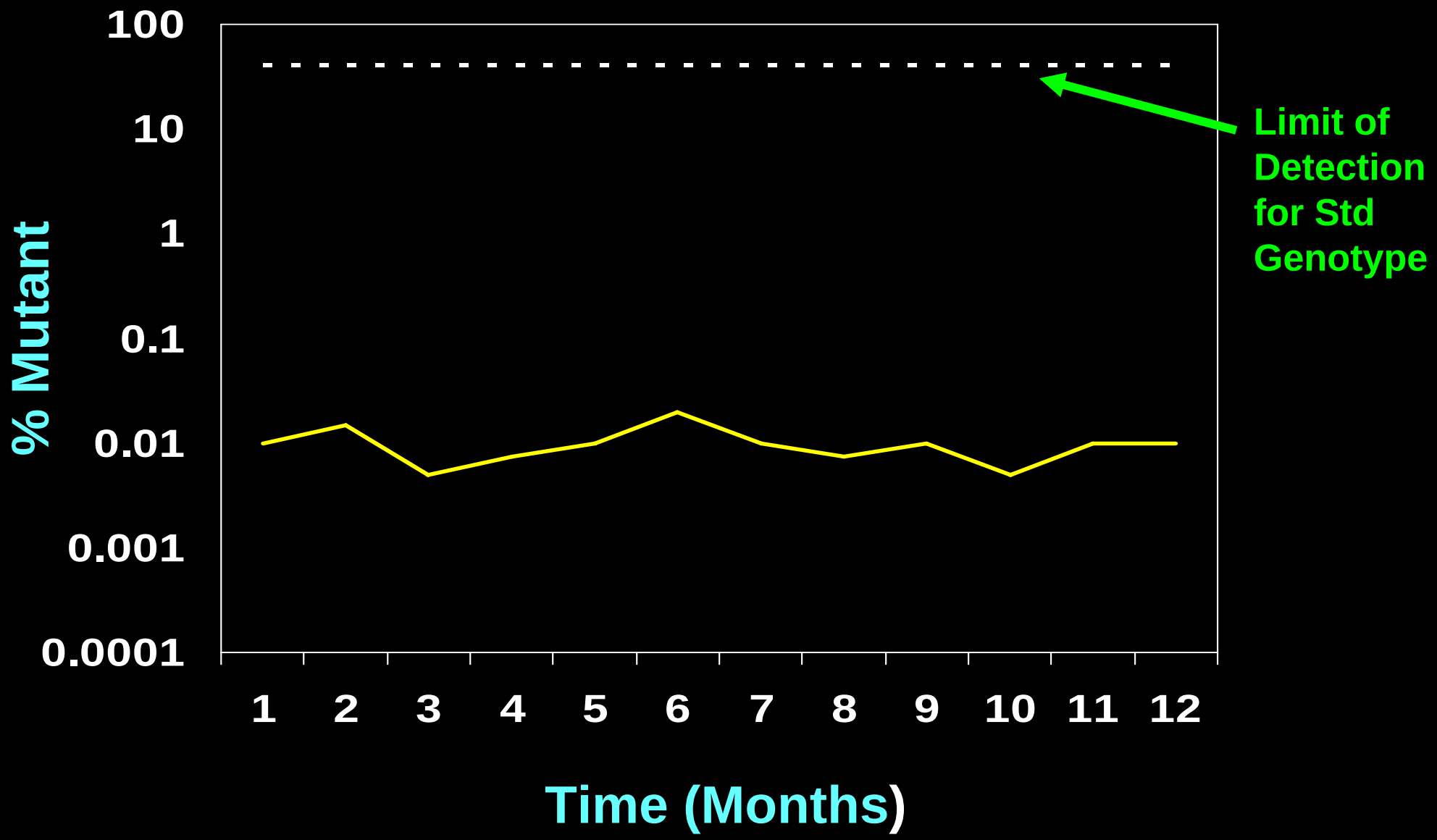

Limited Inherent Potency of the Regimen
- Single/dual drug therapy
Suboptimal Drug Exposure
- Incomplete Adherence
- Unfavorable PK (or antagonism)
- Resistant virus (de novo or transmitted)
Incomplete Inhibition of Viral Replication
Selection of Pre-existing Mutants
Evolution of New Mutants
Reduction in Drug Susceptibility
Limit Current/Future Treatment Options

# Fitness vs. Drug Resistance: Trade-off for Survival

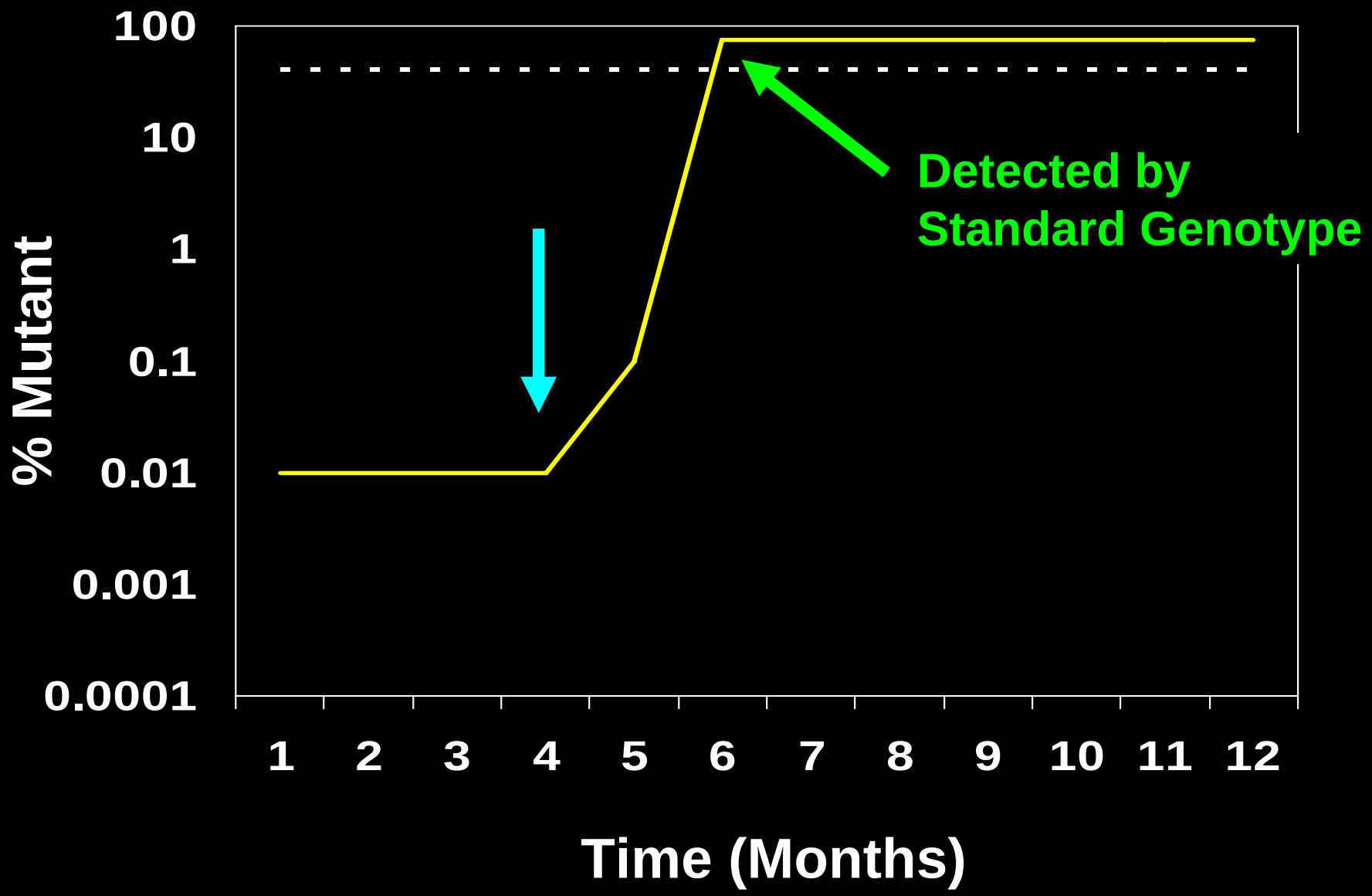
- Drug-resistant variants are less fit than wildtype when drug is absent
  - Leads to decay of resistant variants when drug is removed
- Drug-resistant variants are more fit than widtype when drug is present
  - Fitness advantage leads to emergence of the resistant variant
- Example
  - K65R: 3-10 fold resistance
  - 50% fitness of wildtype when drug is absent

# Review of Key Scenarios

## Chronic HIV-1 infection exposed to oral ARV PrEP?

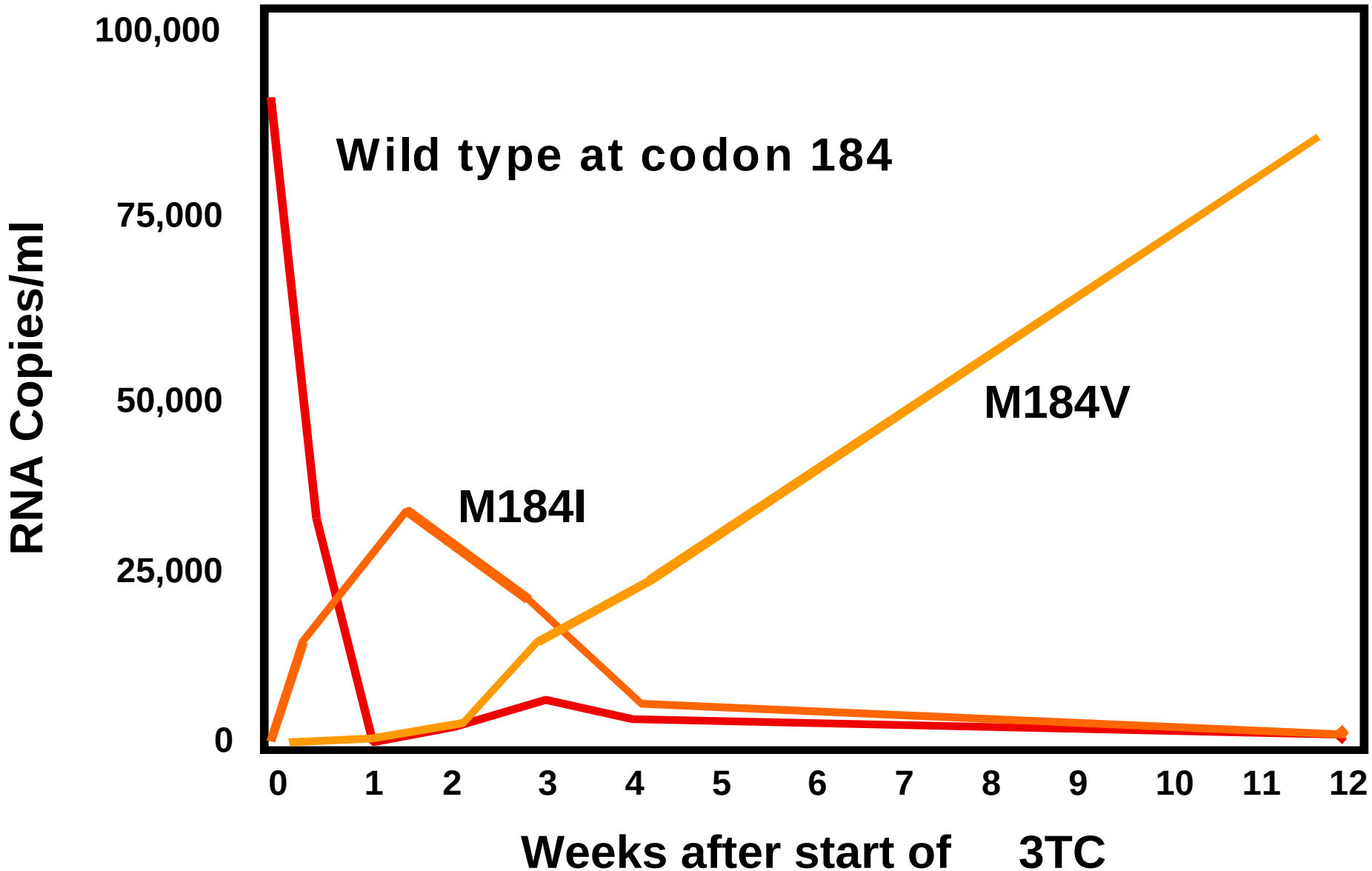

Pre-existing Mutant at ~0.01%
100
10
1
0.1
0.01
0.001
0.0001
% Mutant
1
2
3
4
5
6
7
8
9
10
11
12
Time (Months)
Limit of Detection for Std Genotype

# Monotherapy Selects Pre-existing Mutant



# Appearance of 3TC-Resistant Mutations in Treated Patients

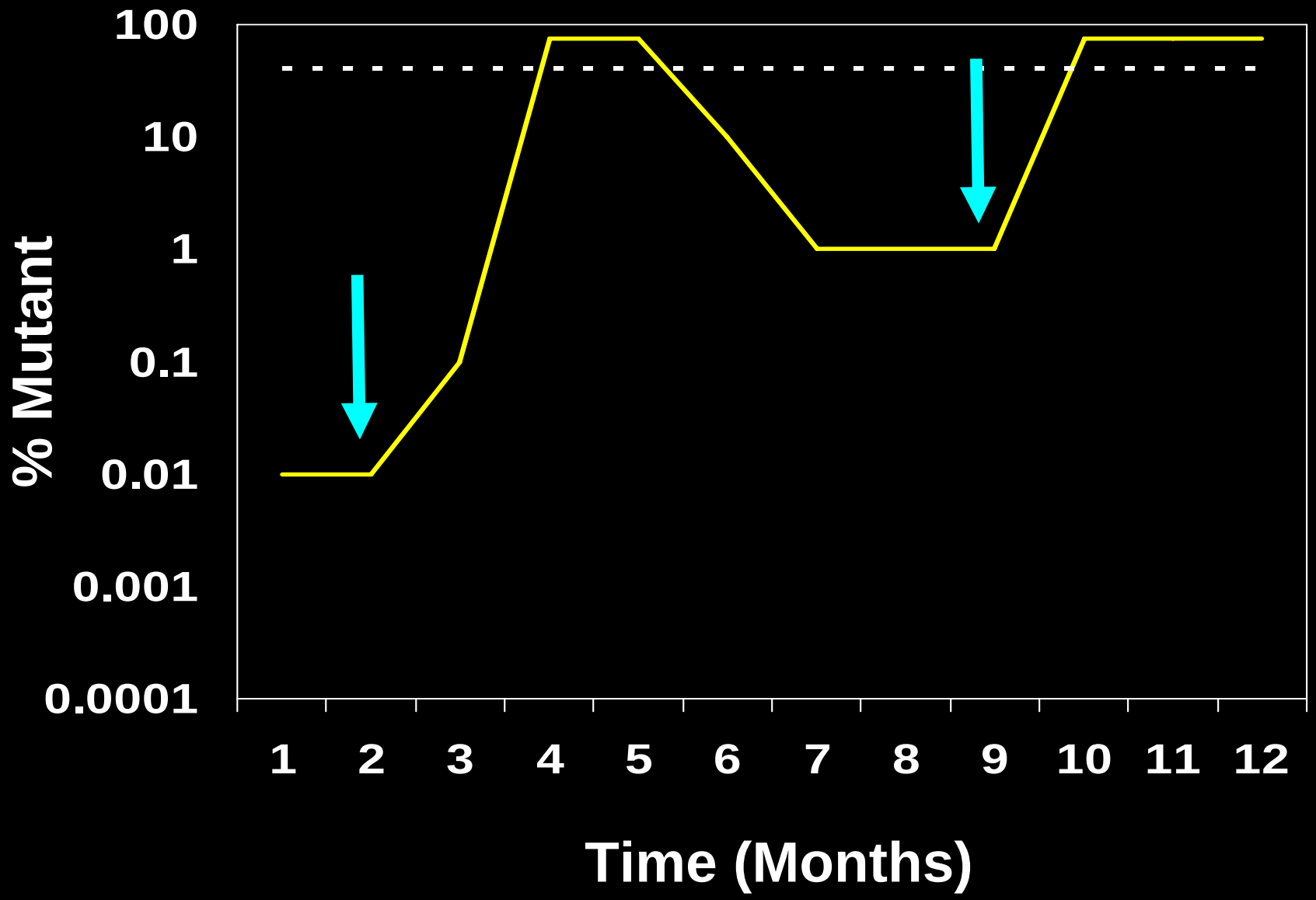
*Schuurman et al, JID 1995; 171:1411*



# Chronic HIV-1 infection exposed to oral ARV PrEP

- Rapid selection of resistant variants is likely with a single or dual ARV PrEP
  - Potential for horizontal or vertical transmission
- Resistant variants will likely decline in frequency with drug removal
  - May persist for NNRTI
- Impact on response to subsequent therapy unclear!

# Re-selection of “Low Frequency” Mutant



# Review of Key Scenarios

Chronic HIV-1 infection exposed to topical PrEP?

# Chronic HIV-1 infection exposed to topical ARV PrEP

- Local selection of resistant variants is likely with a single drug
  - Potential for systemic dissemination
  - Potential for horizontal or vertical transmission
  - May persist for certain drugs – NNRTI
- Systemic selection will depend on drug exposure
  - If low exposure likely to be a minor resistant population and not detected by standard genotype methods
- Impact on response to subsequent therapy unclear

# Review of Key Scenarios

Acute HIV-1 infection on to oral or topical ARV PrEP

# Acute HIV-1 infection on oral or topical ARV PrEP

- For NRTI PrEP, SIV/macaque studies show that initial breakthrough infection is wildtype! (unprotected cells)
  - Resistant virus will be selected with continued PrEP but not if PrEP is stopped in time
  - Should revert to wildtype with PrEP discontinuation unless transmitted virus was drug-resistant (no wildtype)
- Breakthrough infection of topical PrEP is likely to be wildtype with systemic dissemination related to systemic exposure
  - Risk of horizontal or vertical transmission of resistant virus if PrEP is continued

# Implications for MTN Trials

- Avoid inadvertent exposure of those with chronic HIV-1 infection to topical or oral ARV PrEP
  - Resistance selection is very likely
  - Subsequent transmission is possible
  - Could affect subsequent treatment response
- Detect acute HIV-1 infection on PrEP trials ASAP
  - Avoid selection of ARV-resistant virus
  - Could be transmitted
  - Could affect subsequent treatment response
- Study subsequent response to therapy carefully (MTN-015)

Discussion?