# Viral Resistance with Topical RT-Microbicides

Ian McGowan MD PhD FRCP
David Geffen School of Medicine
Los Angeles

MTN
microbicide trials network

# Overview

- What antiretrovirals (ARV) are being considered as candidate microbicides?
- How do they work?
- What is ARV resistance and how does it evolve?
- Could ARV resistance occur in microbicide trials?
- How might ARV resistance impact the design of MTN microbicide trials?
  - Phase 1/2
  - Phase 2B/3

MTN
microbicide trials network

# Approved Antiretroviral Drugs

| NRTI | NNRTI | PI | FI |
|---|---|---|---|
| Zidovudine | Nevirapine | Ritonavir | Enfurvitide |
| Didanosine | Delavirdine | Indinavir | (Maraviroc) |
| Zalcitabine | Efavirenz | Nelfinavir | |
| Stavudine | | Saquinavir | |
| Lamivudine | | Amprenavir | |
| Abacavir | | Lopinavir/r | |
| Tenofovir | | Fosamprenavir/r | |
| Emtricitabine | | Tipranavir/r | |
| | | Darunavir/r | |

MTN
microbicide trials network

# Microbicide Pipeline

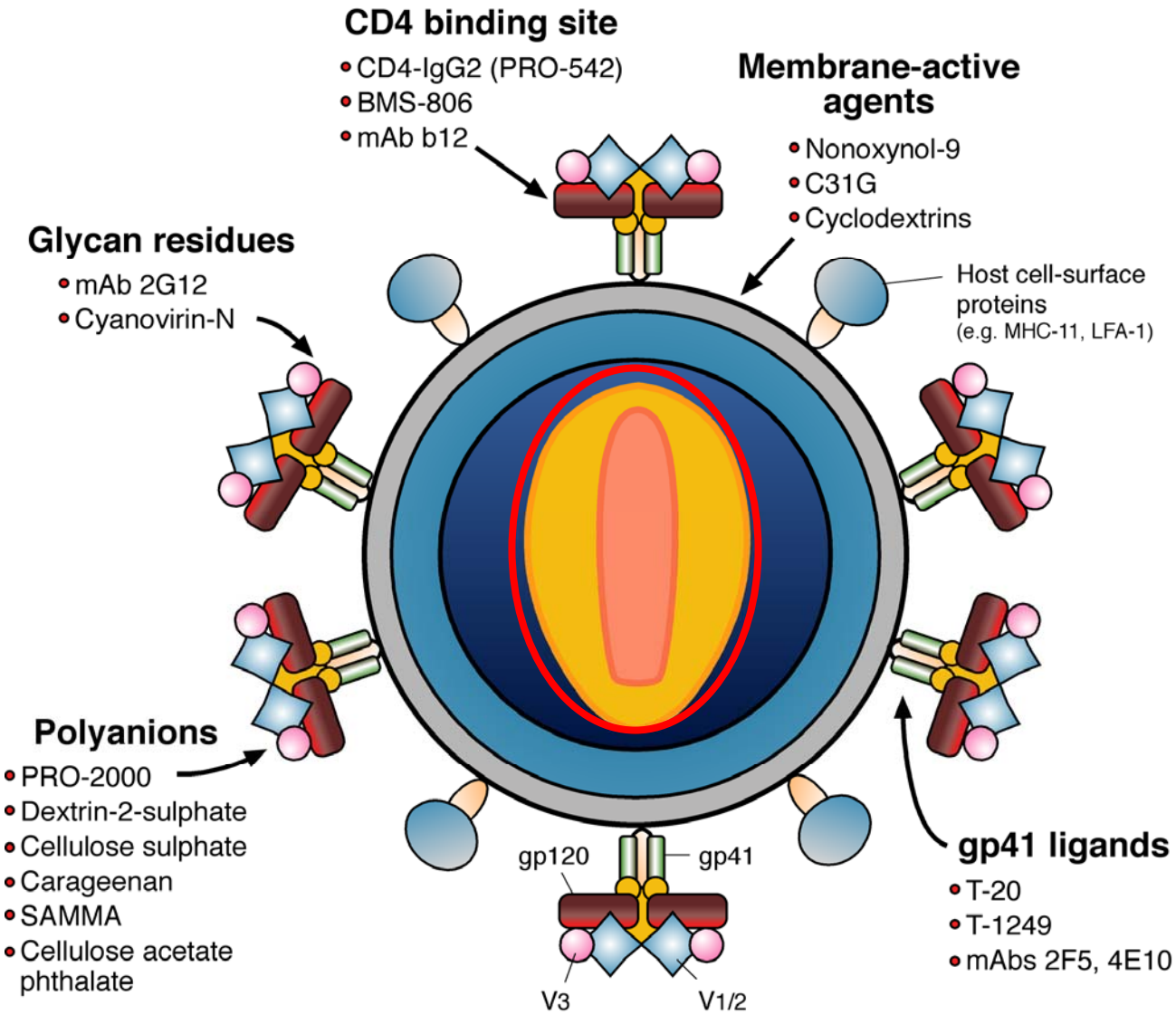
| | Pre-Clinical | Safety | Efficacy |
|---|---|---|---|
| Entry Inhibitors | Cyanovirin<br>BMS806<br>Plant lectins<br>New Polyanions | VivaGel<br>CAP<br>Polystyrene sulfate | Pro2000<br>Carraguard<br>Buffergel |
| NRTI | | PMPA | |
| NNRTI | DABO<br>MIV-150 | UC-781<br>TMC-120 | |
| Membrane active | | SLS | |
| Unclassified | Bacteria | Praneem | |
| Combination | PC-815<br>Truvada<br>NRTI/NNRTI<br>NRTI/P<br>NNRTI/P | | |

MTN
microbicide trials network

# RT-Inhibitor Microbicides

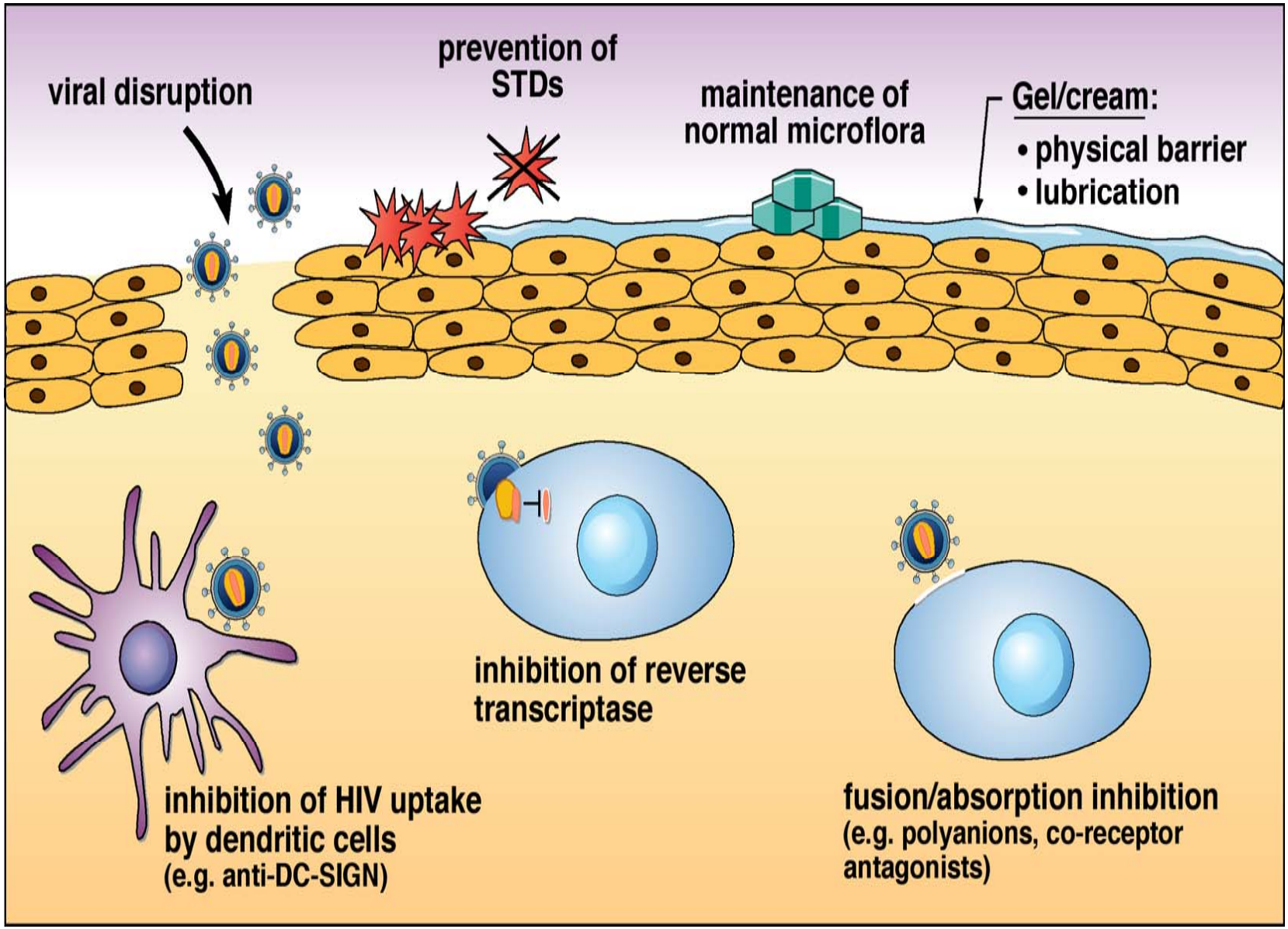
| Microbicide | Phase | Sponsor |
|---|---|---|
| PMPA (Tenofovir) | II | CONRAD/IPM |
| UC-781 | I | CONRAD |
| TMC-120 | I | IPM/Tibotec |
| PC-815 (MIV-150 + Carraguard) | Pre-clinical | Population Council |

MTN
microbicide trials network




Adapted from Shattock and Moore, Nat Rev Microbiol, 2003

MTN
microbicide trials network



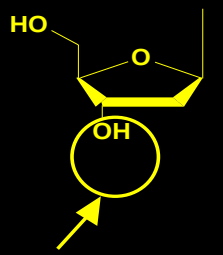

McGowan Biologicals 2006

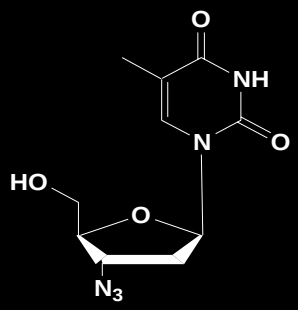
MTN
microbicide trials network

# Mechanism of Action

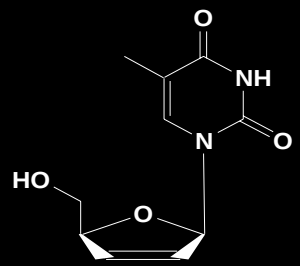
MTN
microbicide trials network

# Nucleoside and Nucleotide RTIs (NRTI)

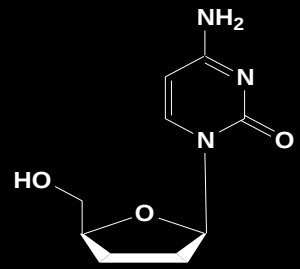


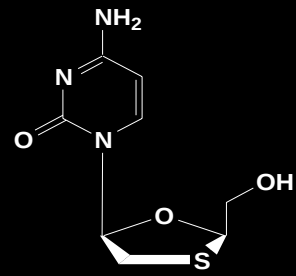

Zidovudine
(AZT)



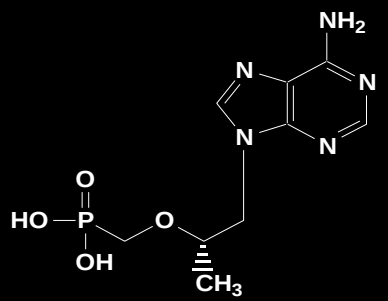

Stavudine
(d4T)



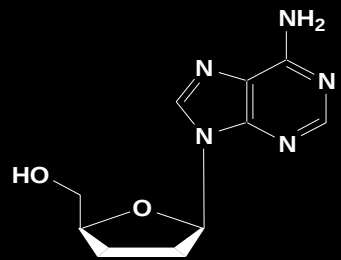

Zalcitabine
(ddC)



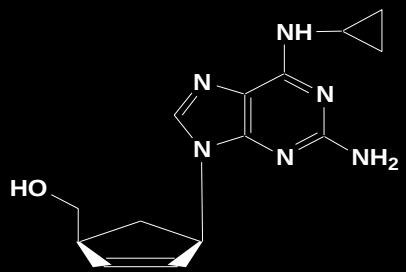

Lamivudine
(3TC)



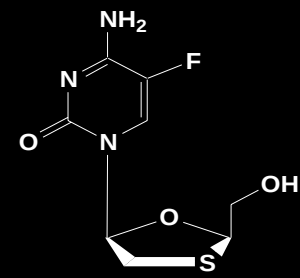

Tenofovir
(TDF)




Didanosine
(ddI)



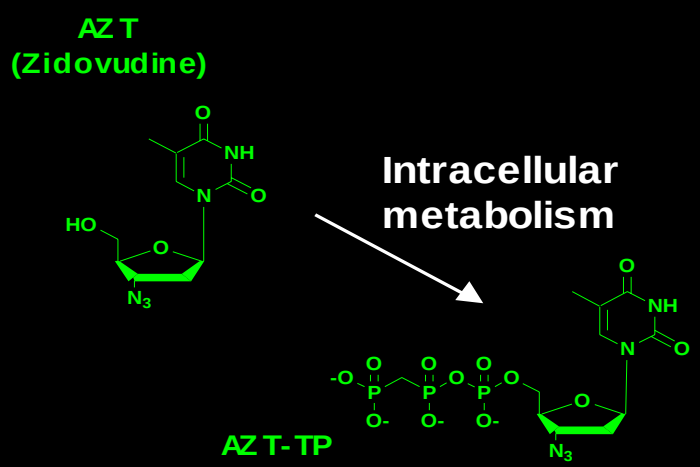

Abacavir
(ABC)



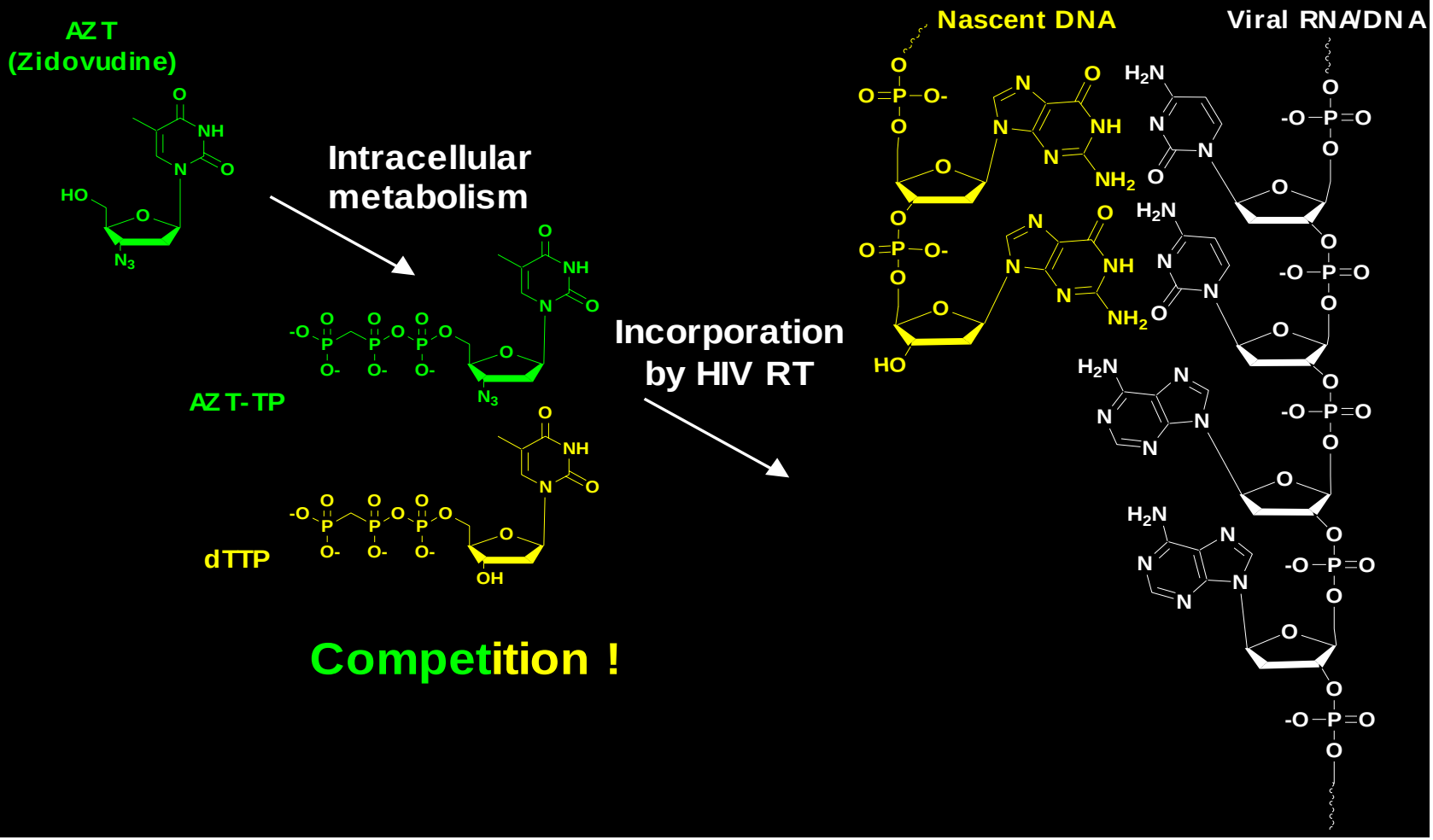

Emtricitabine
(FTC)

MTN
microbicide trials network

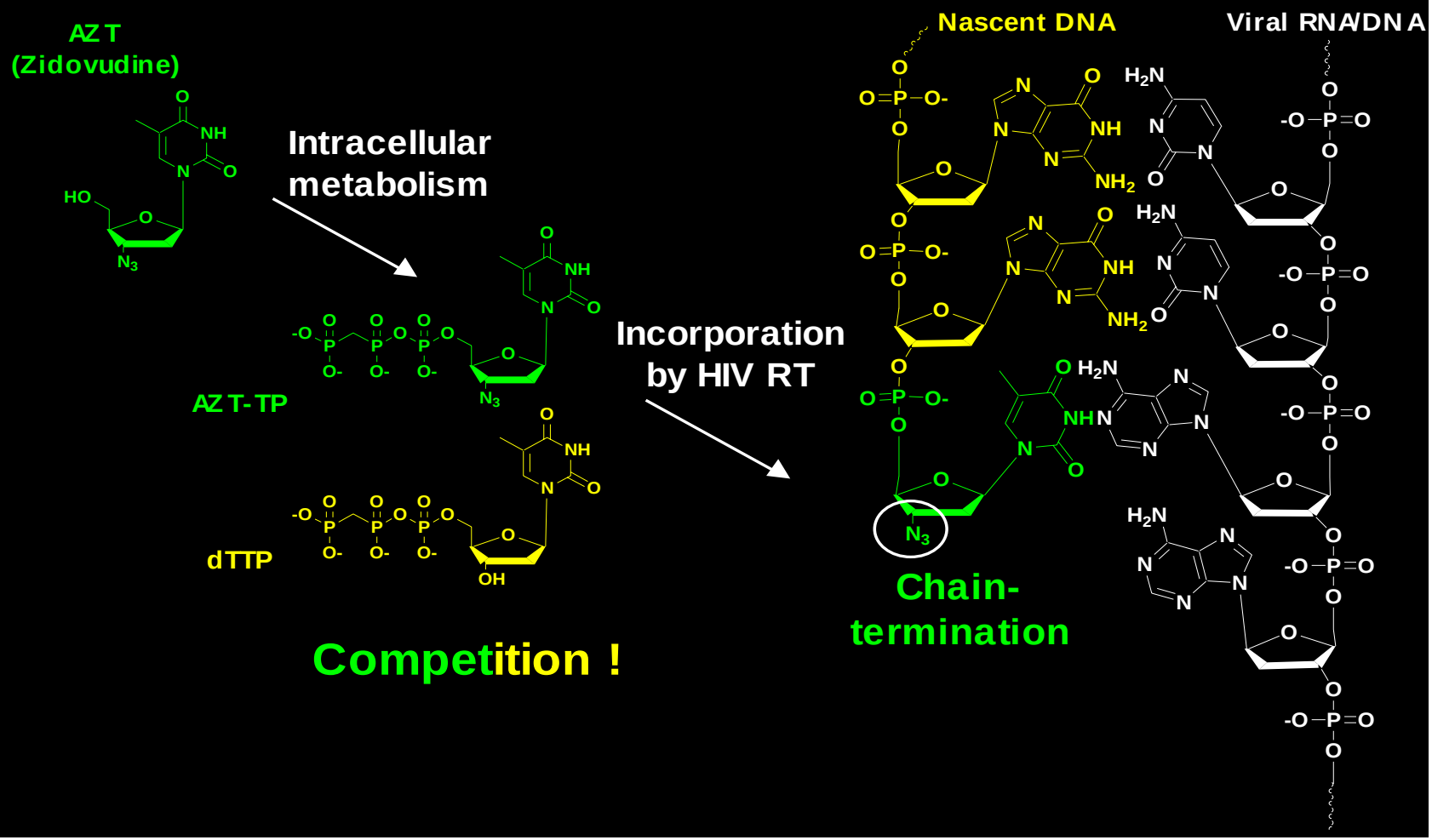
# NRTI – Mechanism of Action



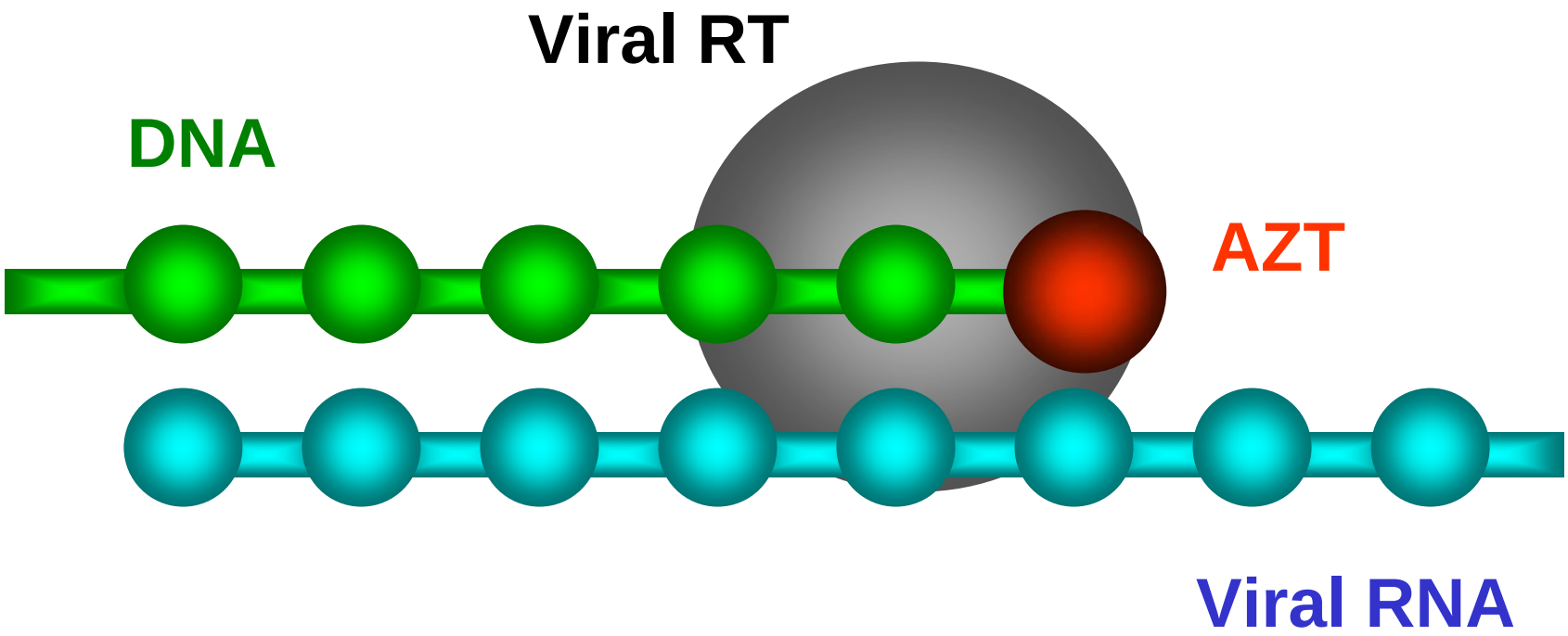
# NRTI – Mechanism of Action



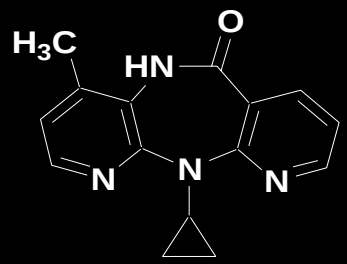
# NRTI – Mechanism of Action



# DNA Chain Termination by Nucleoside Analogues

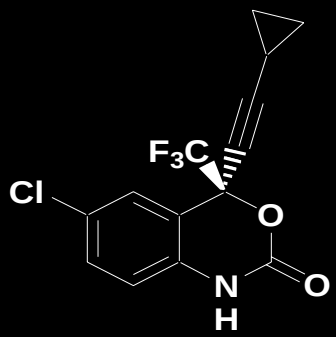


# Nonnucleoside RTIs (NNRTI)



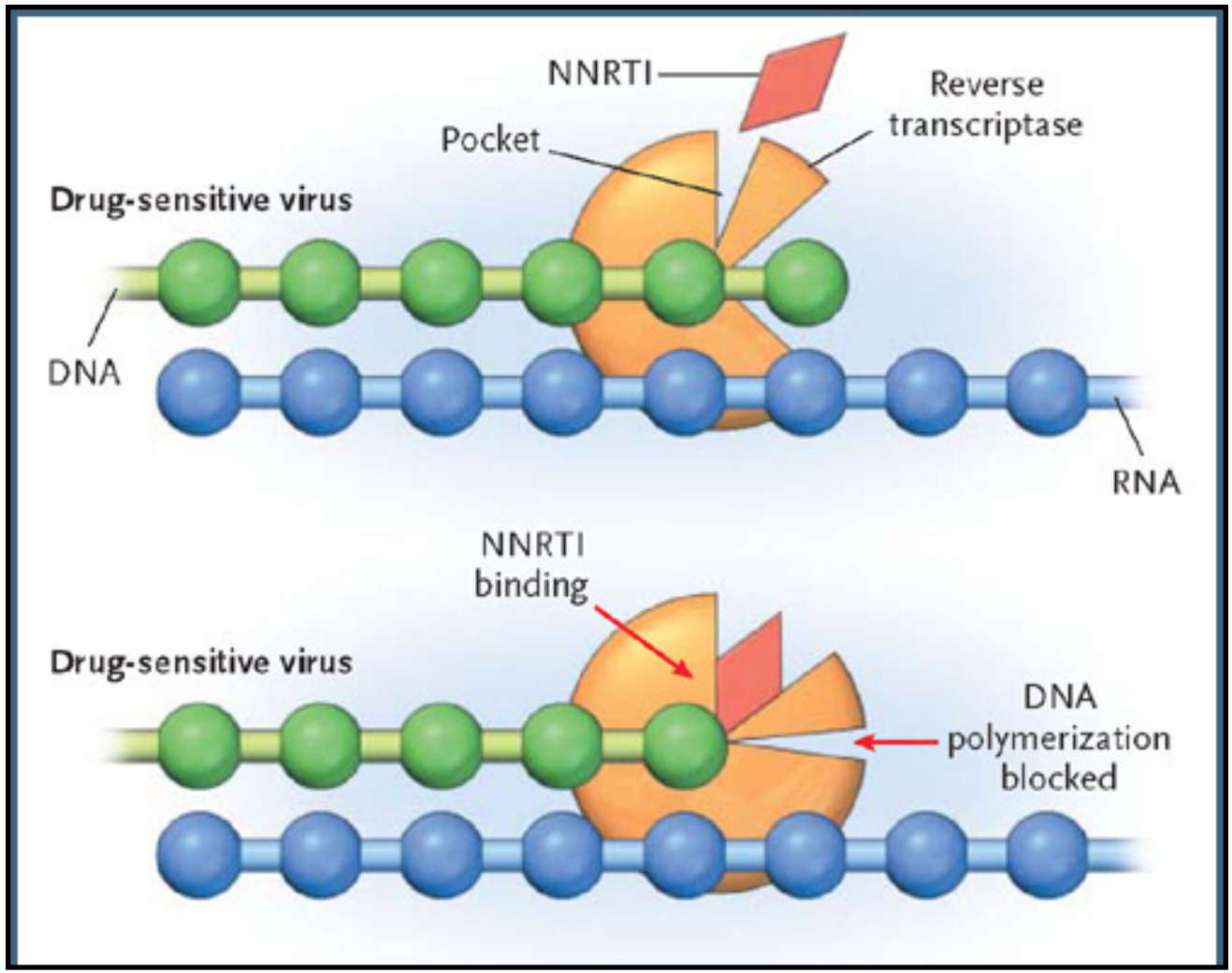

Nevirapine
(Viramune)


Delavirdine
(Rescriptor)




Efavirenz
(Sustiva)

# NNRTI Mechanism of Action




Clavel F, Hance AJ. N Engl J Med. 2004;350:1023-35

MTN
microbicide trials network

# 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

# HIV-1 Drug Resistance

- 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

MTN
microbicide trials network

# Fitness vs. Drug Resistance

- 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

MTN
microbicide trials network

# Mechanism of NRTI Resistance

- Discrimination
- Excision

# Discrimination

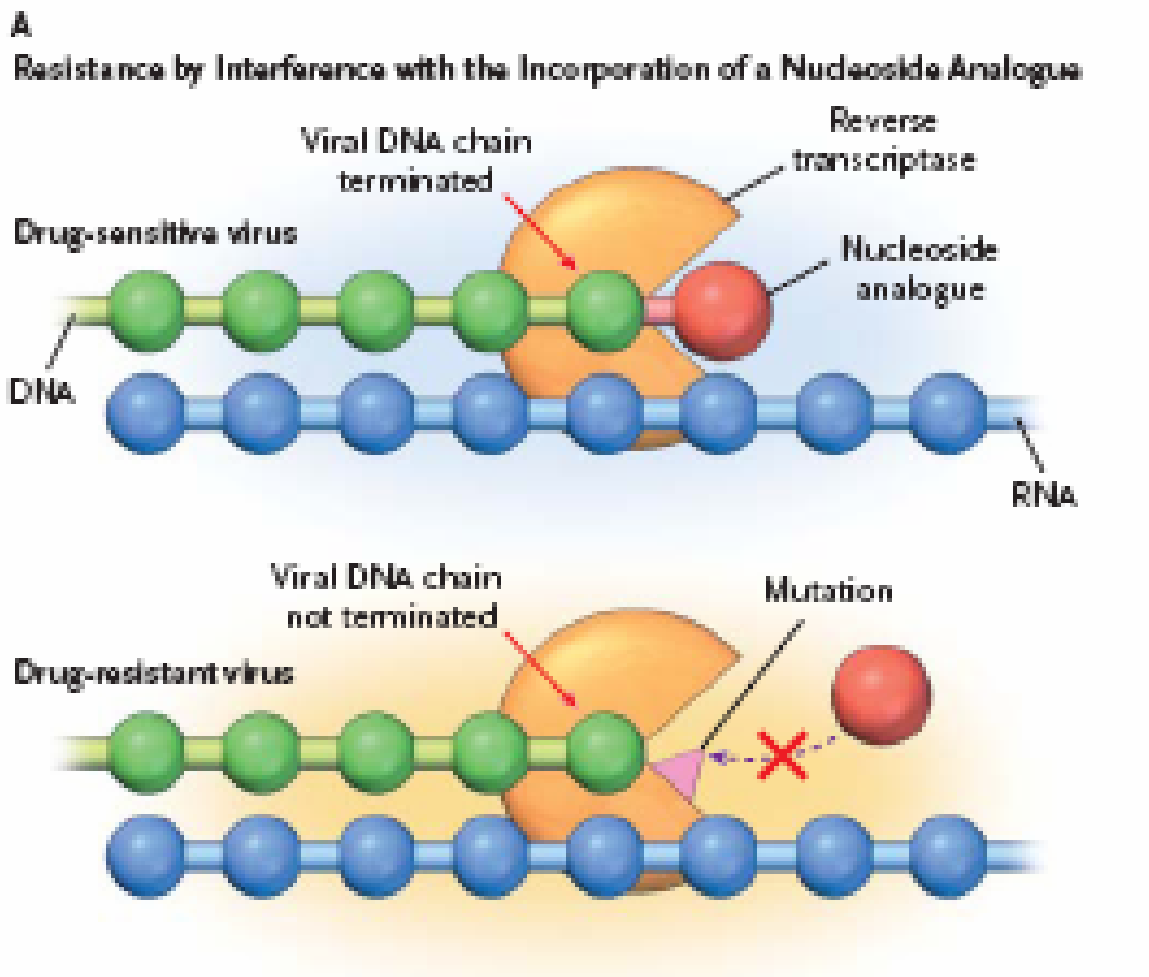
Resistance mutations enable HIV-1 RT to preferentially incorporate the natural dNTP substrate over the NRTI-TP

**Examples:** K65R, L74V, K70E, M184V

# Discrimination

Sensitive Virus

Resistant Virus




Clavel F, Hance AJ. N Engl J Med. 2004;350:1023-35

MTN microbicide trials network

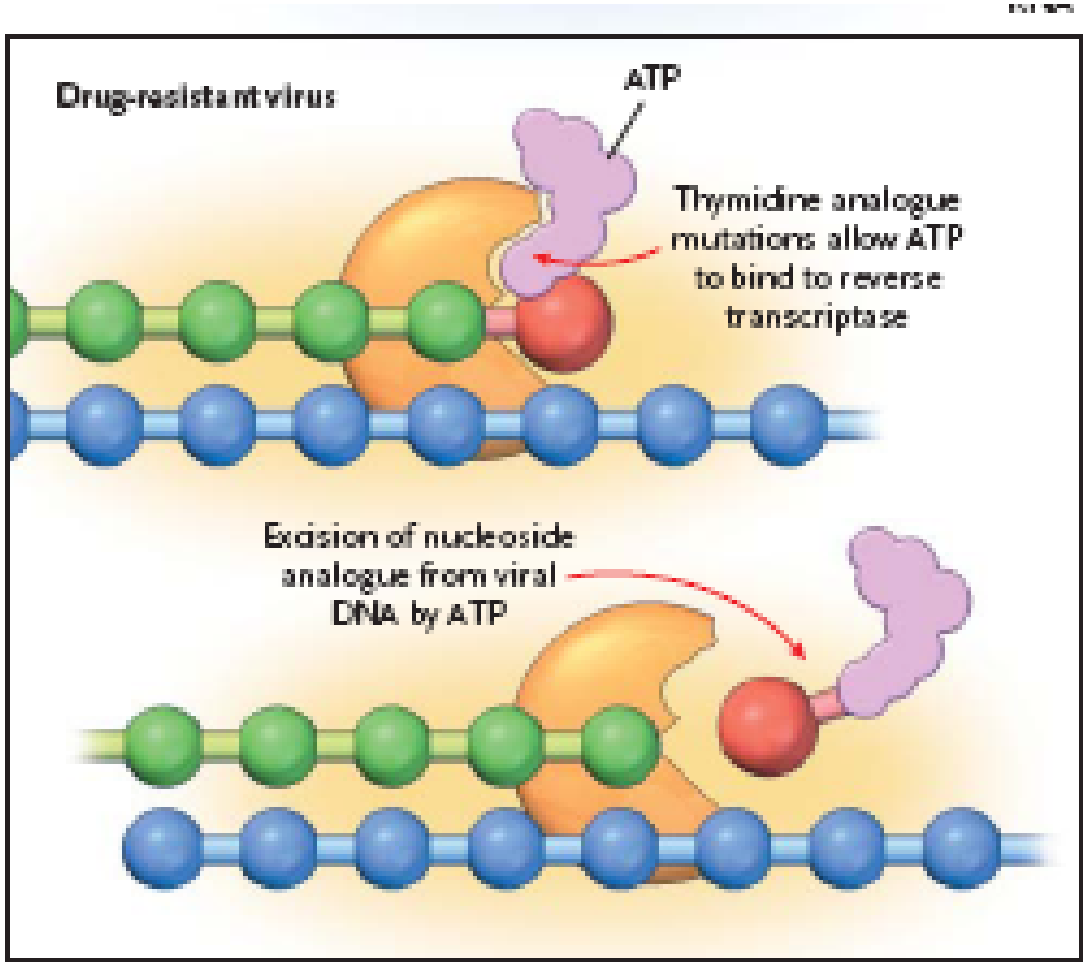
# Excision

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

**Examples:** Thymidine analogue mutations (TAMS)

# Excision

Resistant Virus




Clavel F, Hance AJ. N Engl J Med. 2004;350:1023-35

MTN microbicide trials network

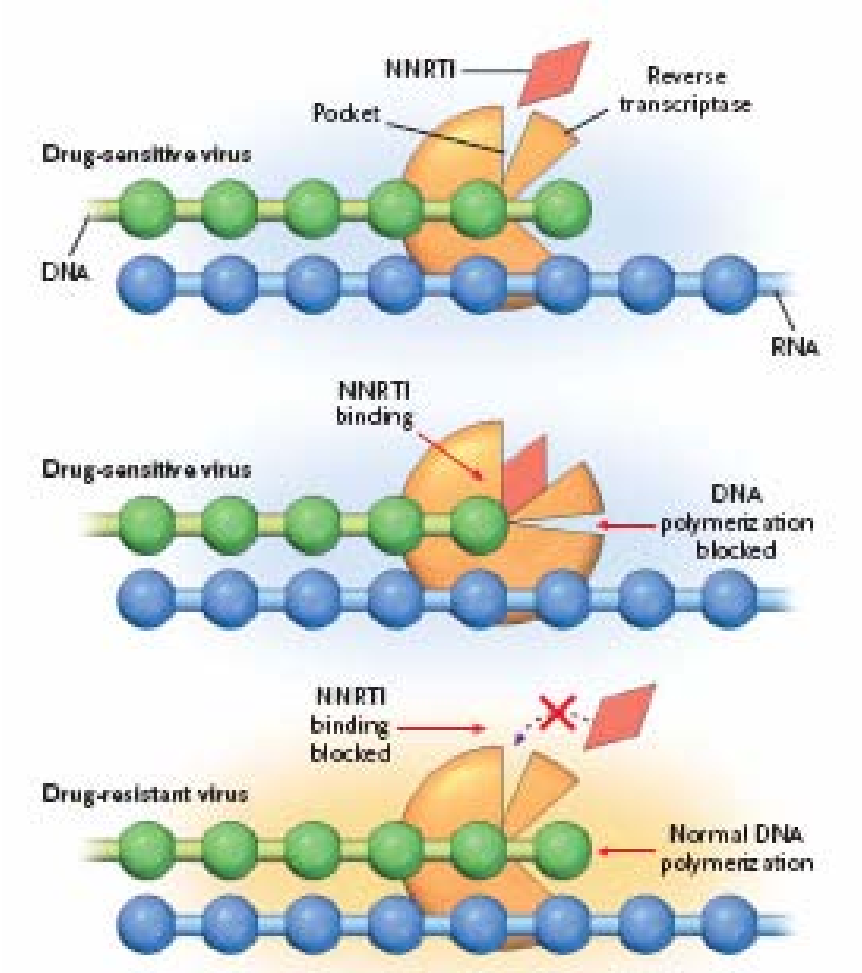
# Mechanism of NNRTI Resistance

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

# NNRTI Resistance

Sensitive Virus

Resistant Virus

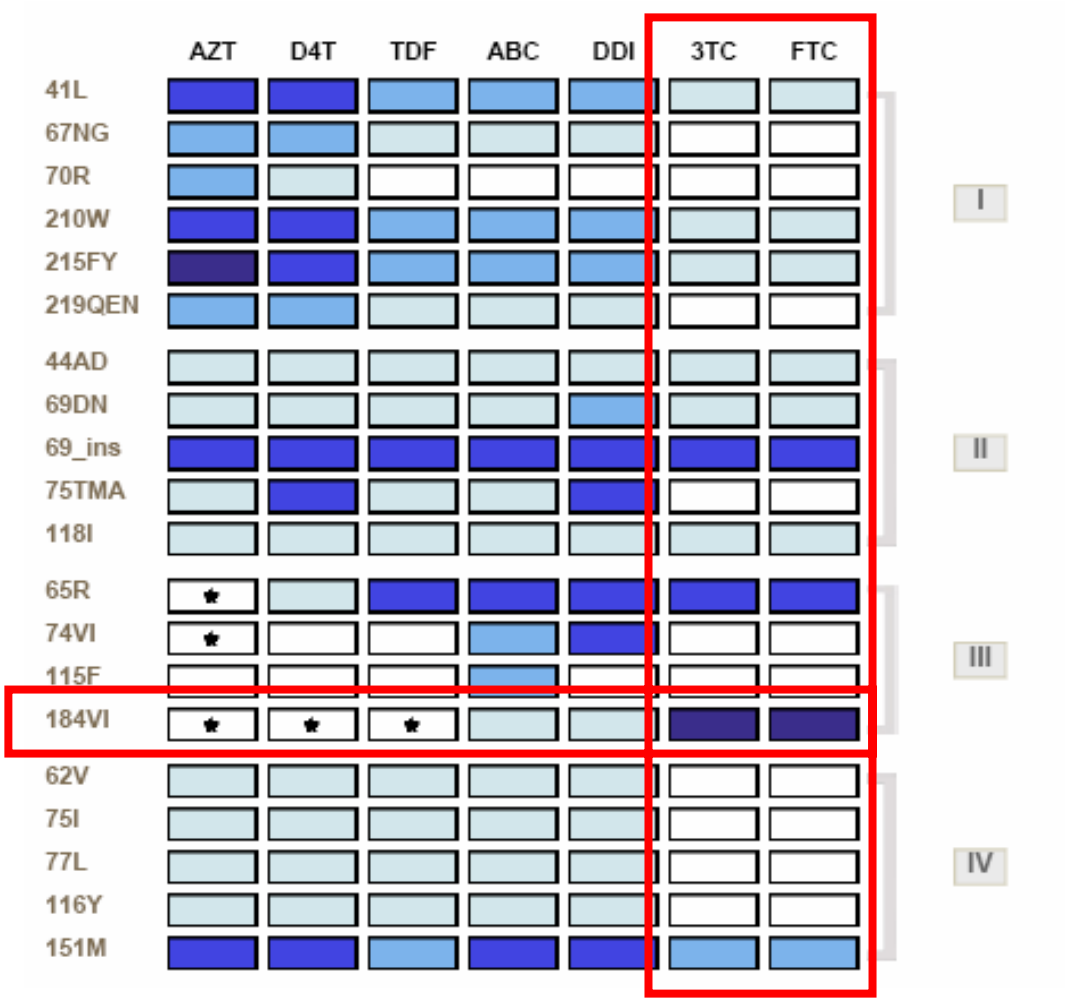



Clavel F, Hance AJ. N Engl J Med. 2004;350:1023-35

MTN microbicide trials network

# RT Resistance

3TC FTC

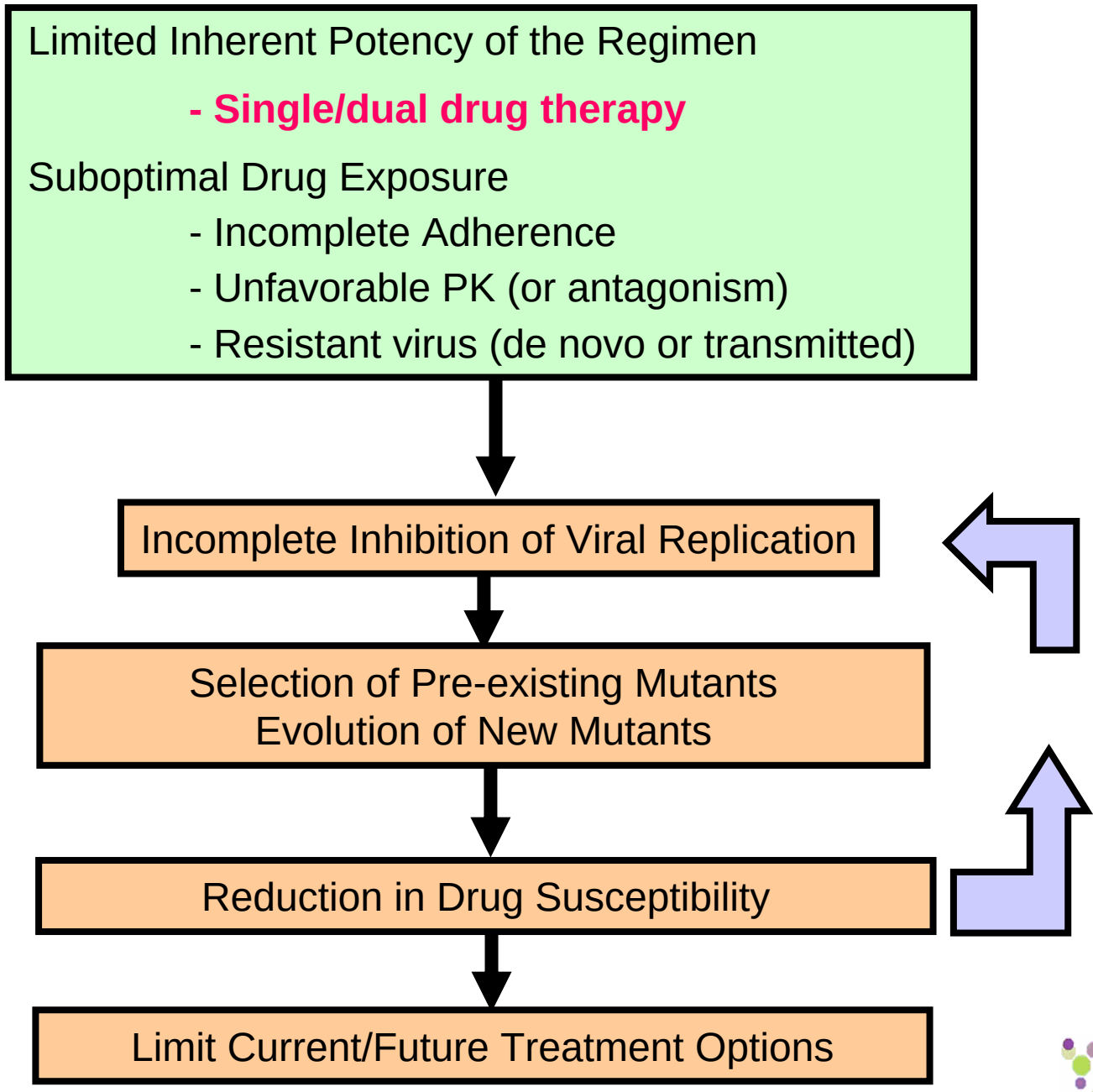



M184V

| Resistance | |
|---|---|
| | High-Level |
| | Intermediate |
| | Low-level |
| | Contributes |
| | None |

http://hivdb.stanford.edu/cgi-bin/NRTIResiNote.cgi

MTN microbicide trials network


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

# Antiretroviral Resistance in the Clinic

MTN
microbicide trials network

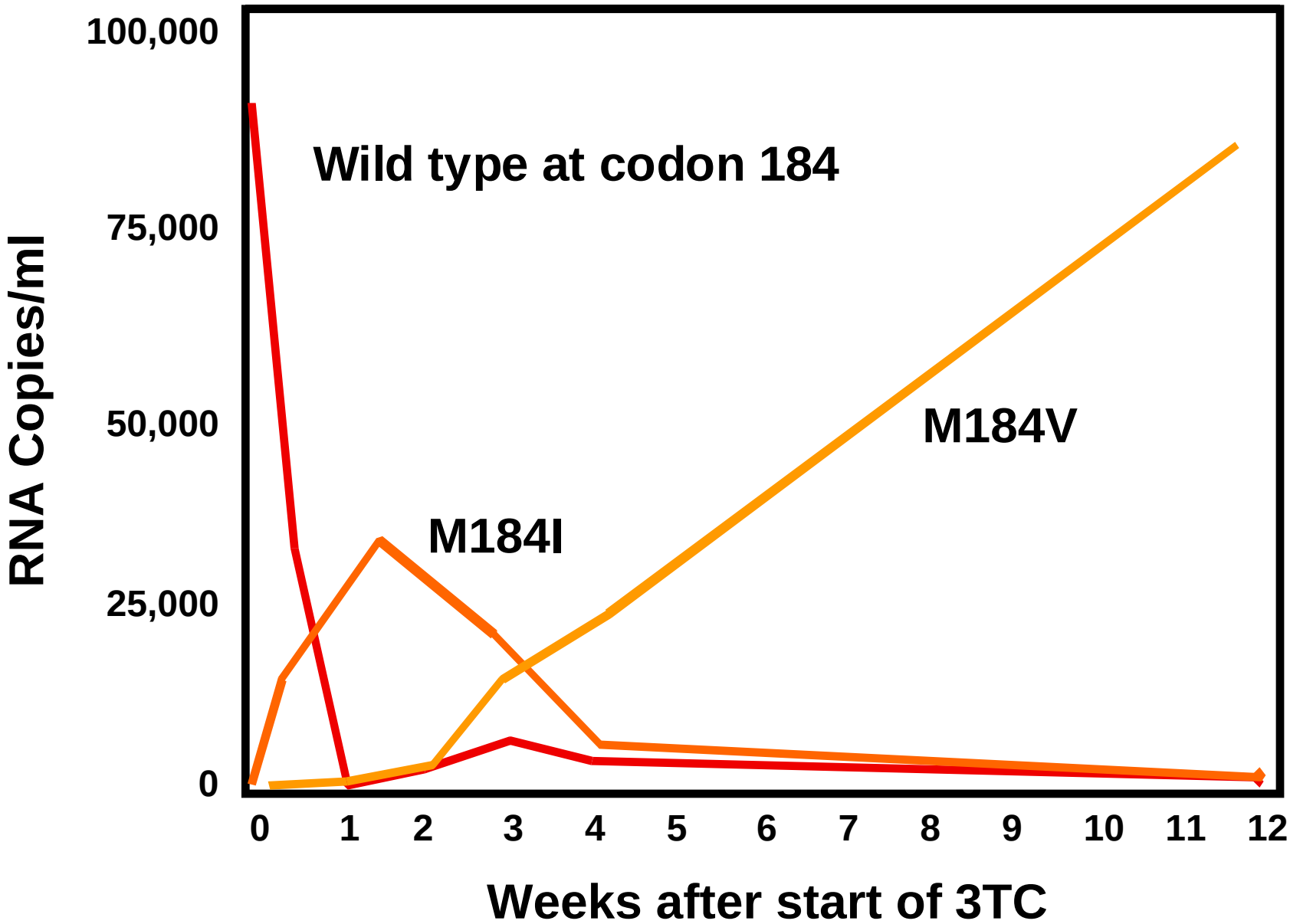
# Definitions are Important

- **Genotypic resistance**
  - Assay sensitivity
  - Single mutations
  - Multiple mutations
  - Use of Virtual Phenotype™
- **Phenotypic resistance**
  - Fold change in sensitivity (> 2.5, 5, or 10)
- **Virological response to ART**
  - Proportion with VL < 50, 400 copies per mL
  - Time to undetectable VL
  - Time to failure

MTN
microbicide trials network

# Appearance of 3TC-Resistant Mutations in Treated Patients

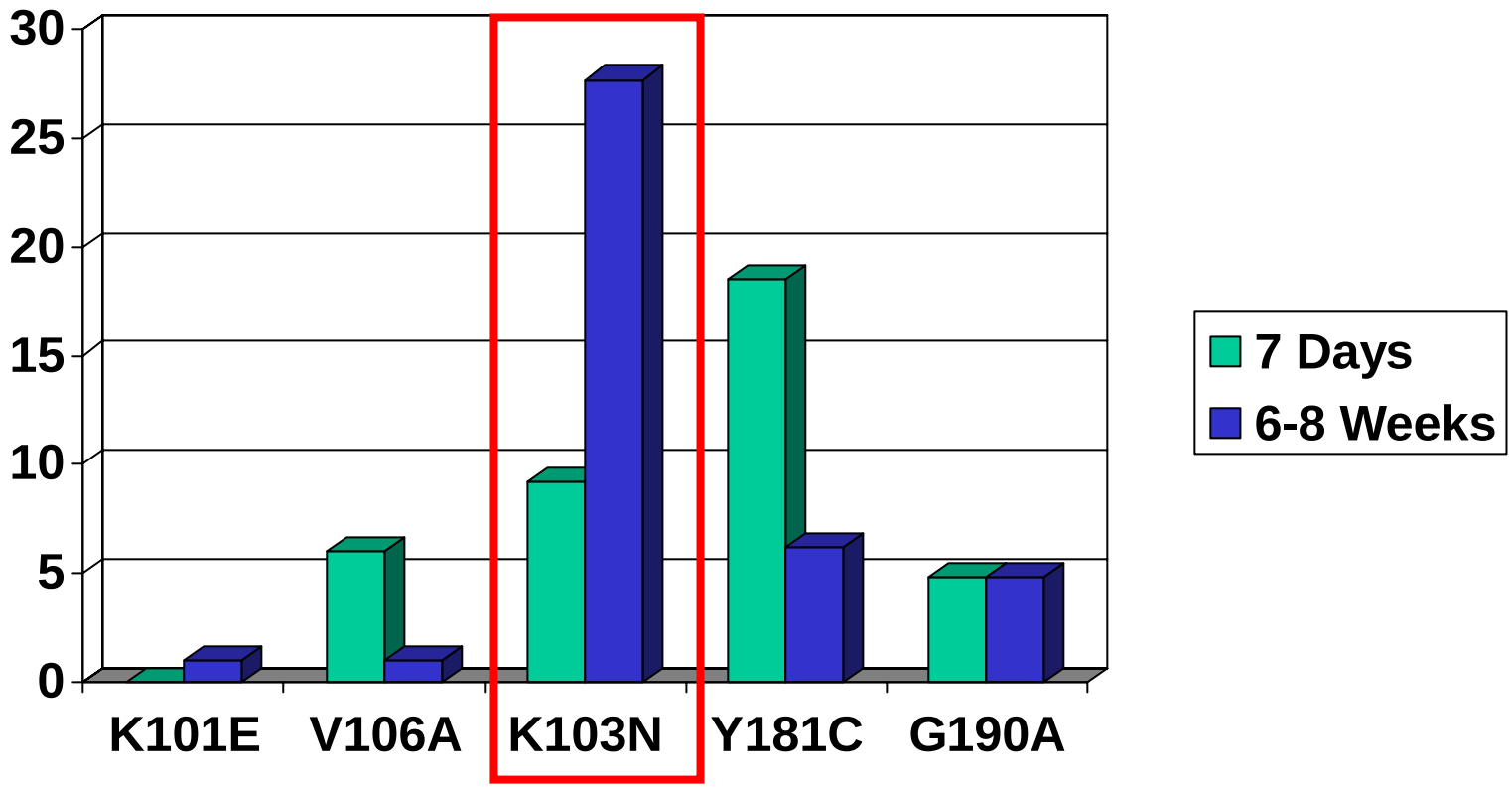
*Schuurman et al, JID 1995; 171:1411*



# Resistance Associated with Mother-to-Child Transmission Prevention Studies

MTN
microbicide trials network

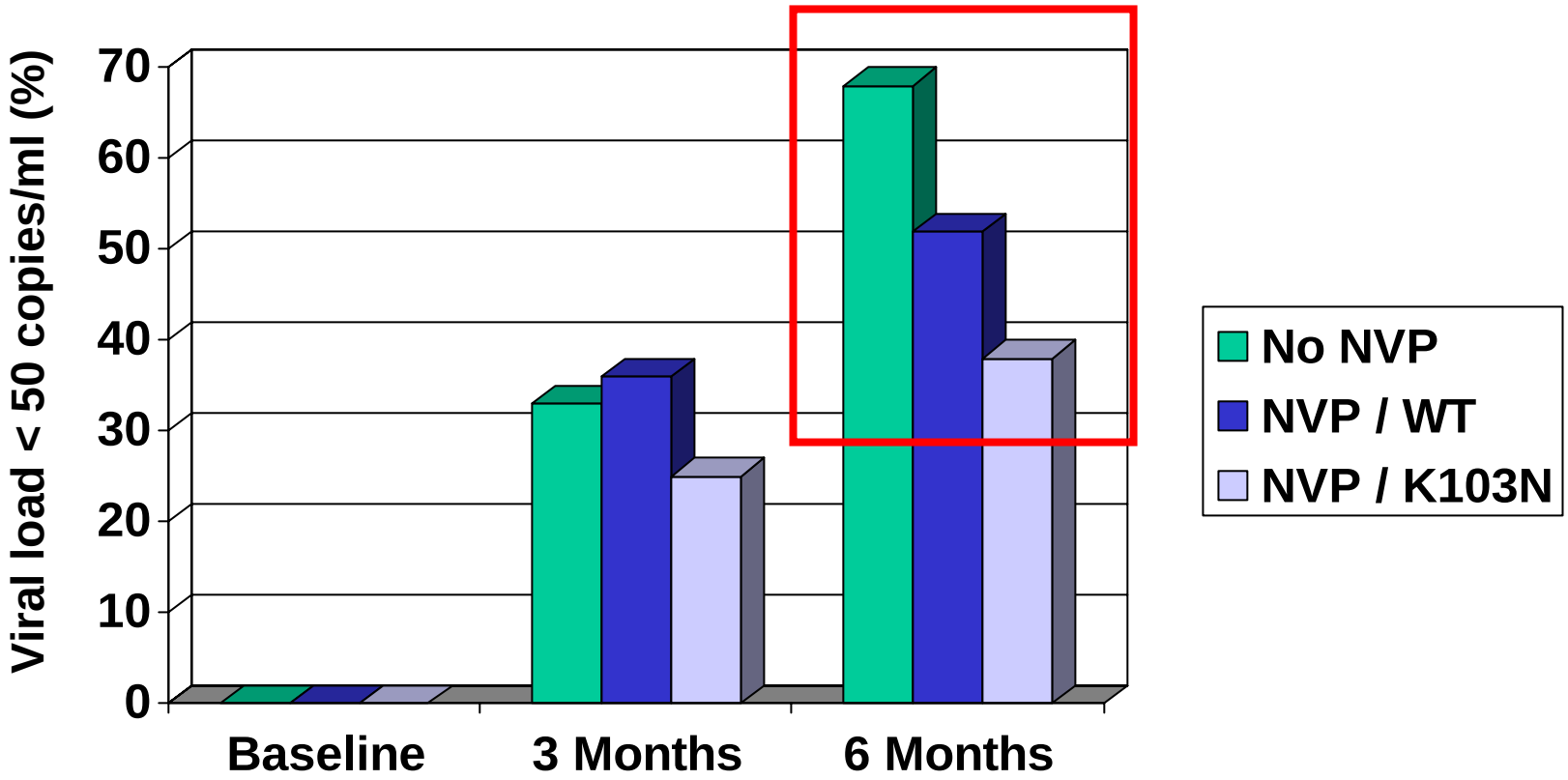
# Nevirapine Resistance




Eshleman S et al. AIDS Res Hum Retrovirol 2004

MTN
microbicide trials network

# Consequences of NVP Resistance




Jourdain et al. NEJM 2004

MTN
microbicide trials network

# ART Resistance in Treatment Naive Patients

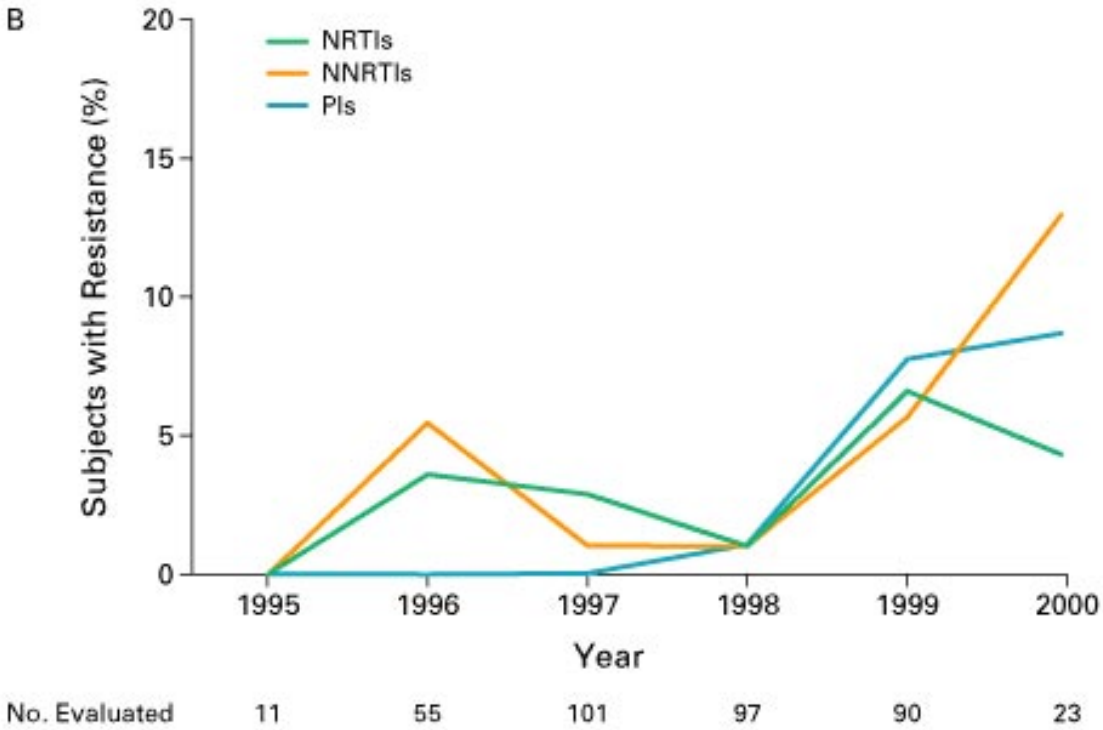
MTN
microbicide trials network

# Prevalence of Resistant Virus in Treatment Naive Patients

| Group | N | Prevalence | Reference |
|---|---|---|---|
| AIEDRP (USA: 1995 - 2000) | 377 | 12.4% | Little SJ et al. NEJM 2002 |
| CPCRA (USA: 1999 - 2001) | 491 | 11.6% | Novak RM et al. CID 2005 |
| CASCADE Europe, Canada, and Australia: 1987-2003) | 300 | 11% | Pillay D et al. AIDS 2006 |

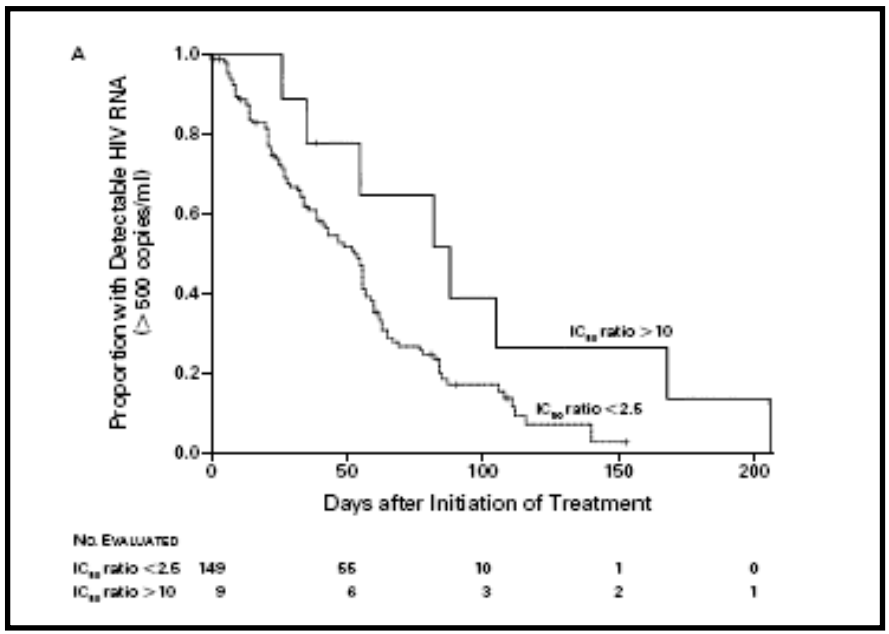
MTN
microbicide trials network

# Is Primary Resistance to ARV Increasing?

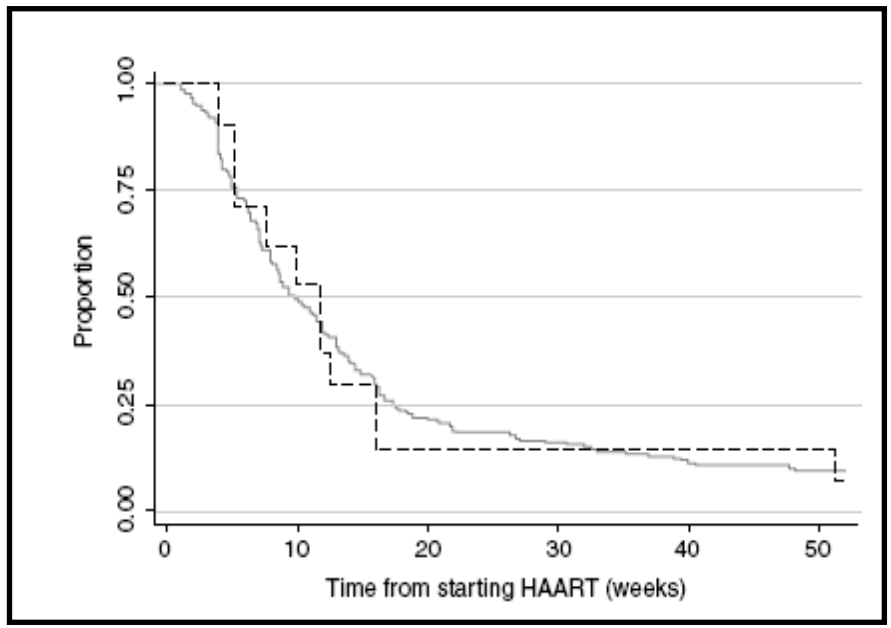



Little SJ et al. NEJM 2002

# Response* to ART in Subjects with Primary Resistance




Little SJ et al. NEJM 2002




Pillay D et al. AIDS 2006

*Proportion with HIV viral load > 500 copies mL plasma

MTN
microbicide trials network

# RT-Microbicide Resistance Scenarios

# Individuals with Chronic or Acute HIV Infection

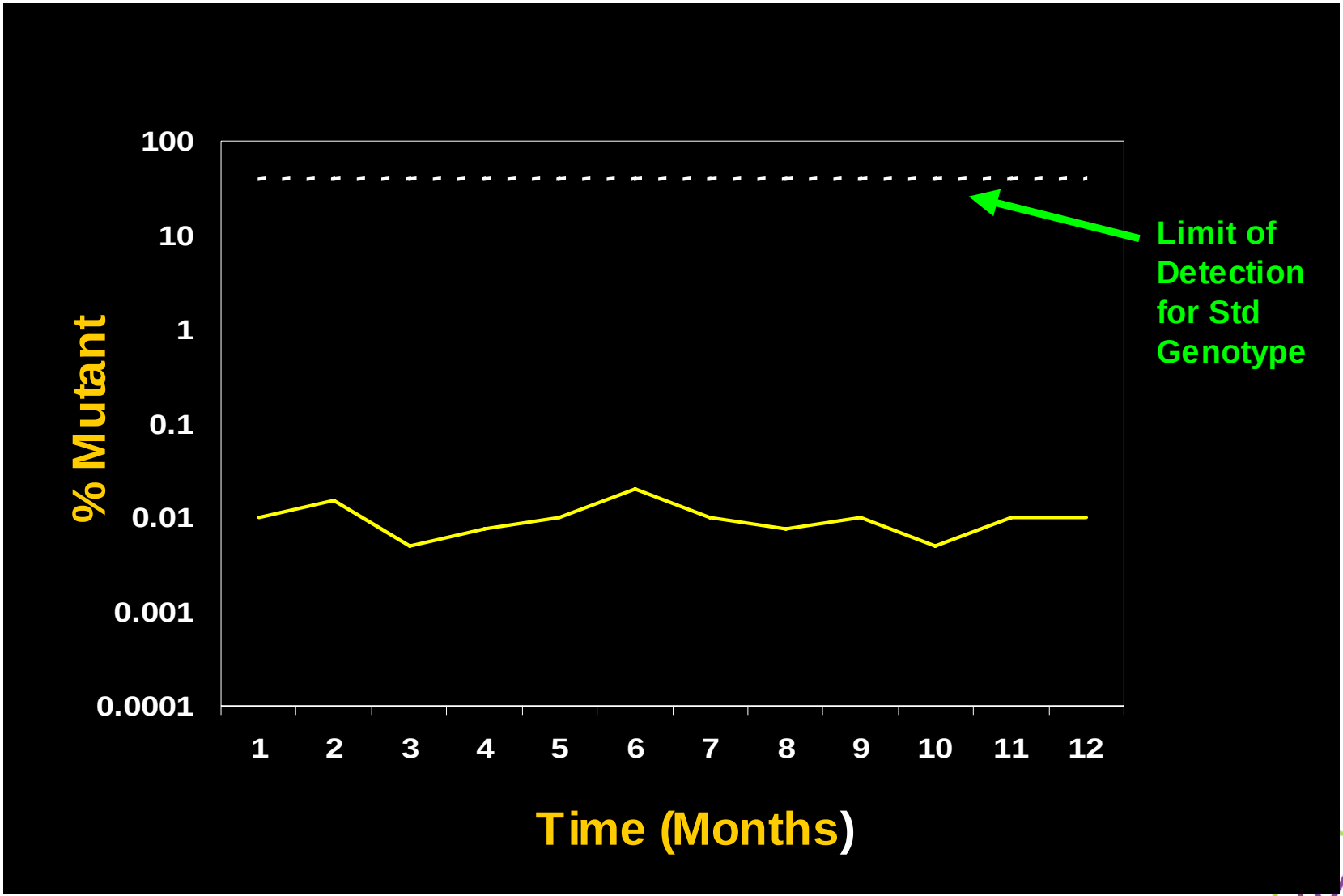
MTN
microbicide trials network

# Chronic HIV-1 infection Exposed to RT Microbicides

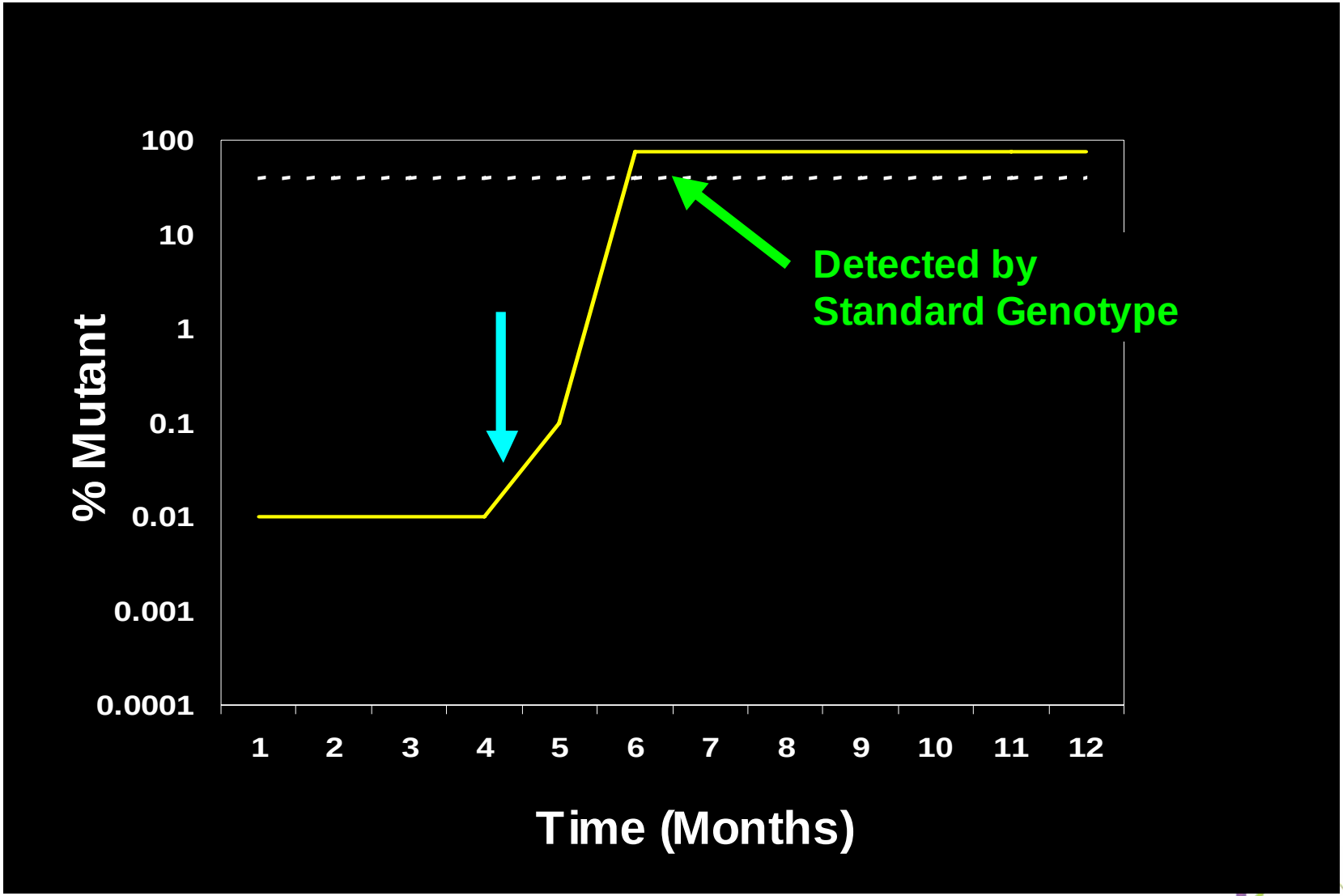
- Local selection of resistant variants is likely with a single drug
  - Potential for systemic dissemination
  - Potential for horizontal or vertical transmission
  - May persist for certain drugs – NNRTI
- Systemic selection will depend on drug exposure
  - If low exposure likely to be a minor resistant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

MTN
microbicide trials network

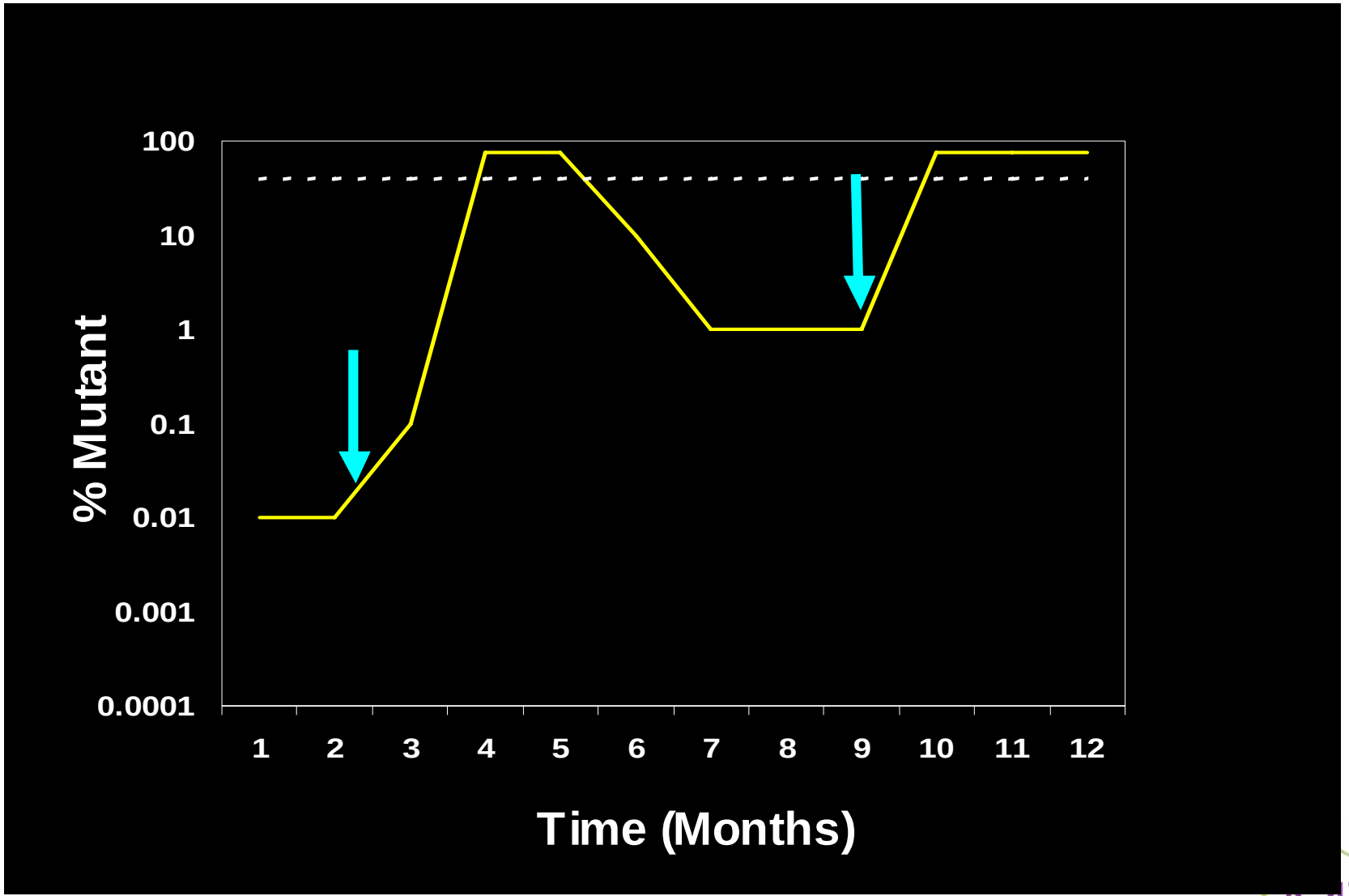
# Pre-Existing Mutant at 0.01%



# Monotherapy Selects Mutant



# Response to Treatment



# Acute HIV-1 infection with Oral or Topical ARV

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

MTN
microbicide trials network

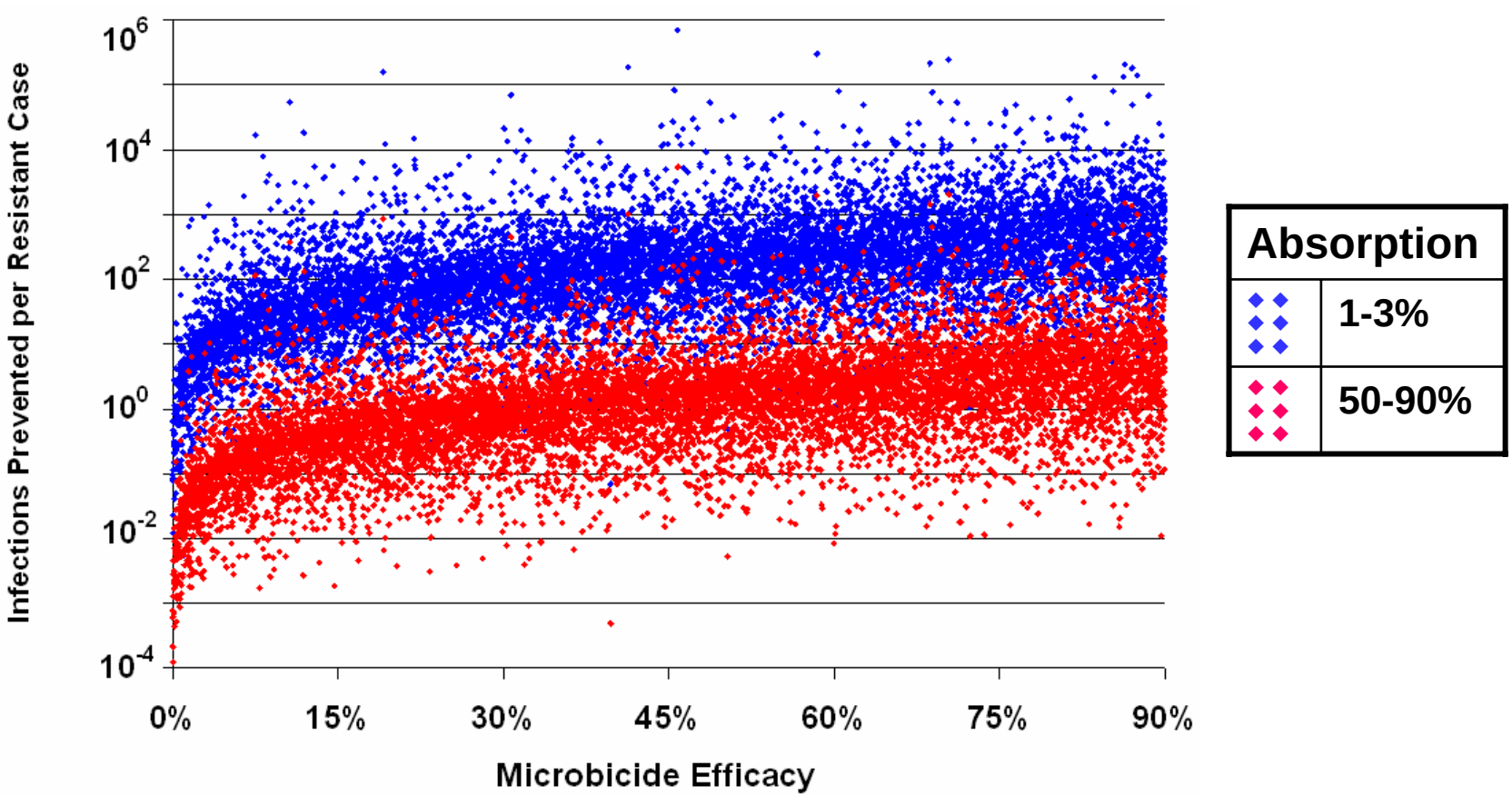
# Modeling RT Microbicide Resistance

- Phase III placebo controlled study
- 10,000 women followed for 12 months
- Monte Carlo Simulation (N = 10,000)
- Model parameters
  - Clinical efficacy (0-90%)
  - High absorption (50 – 90%)
  - Low absorption (1-3%)

Wilson et al. CROI 2007 Abstract 999

MTN microbicide trials network

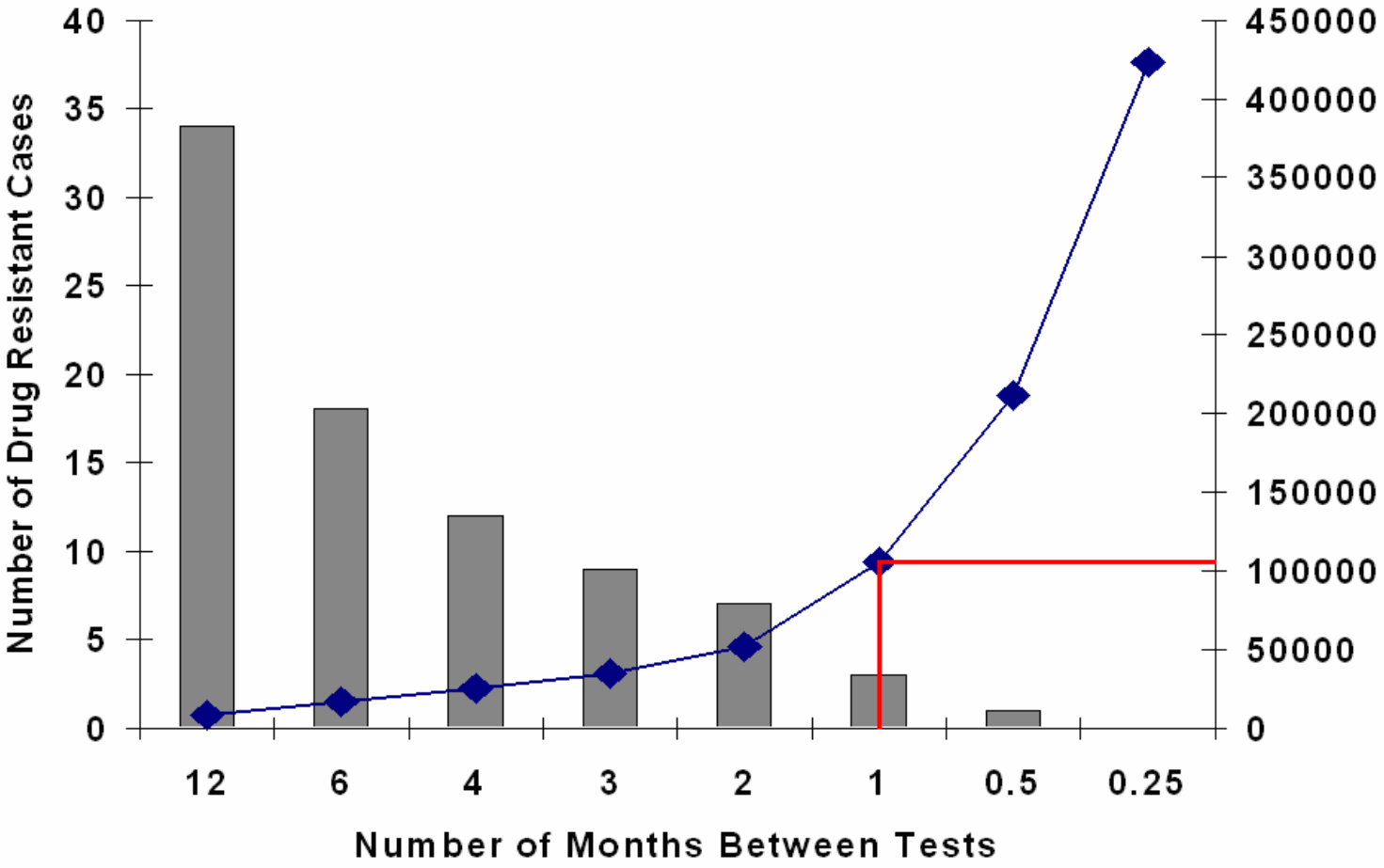
# Incidence of Resistance




Wilson et al. CROI 2007 Abstract 999

MTN microbicide trials network

# Frequency of HIV Testing




Wilson et al. CROI 2007 Abstract 999

MTN
microbicide trials network

# What do We Know From HPTN-050?

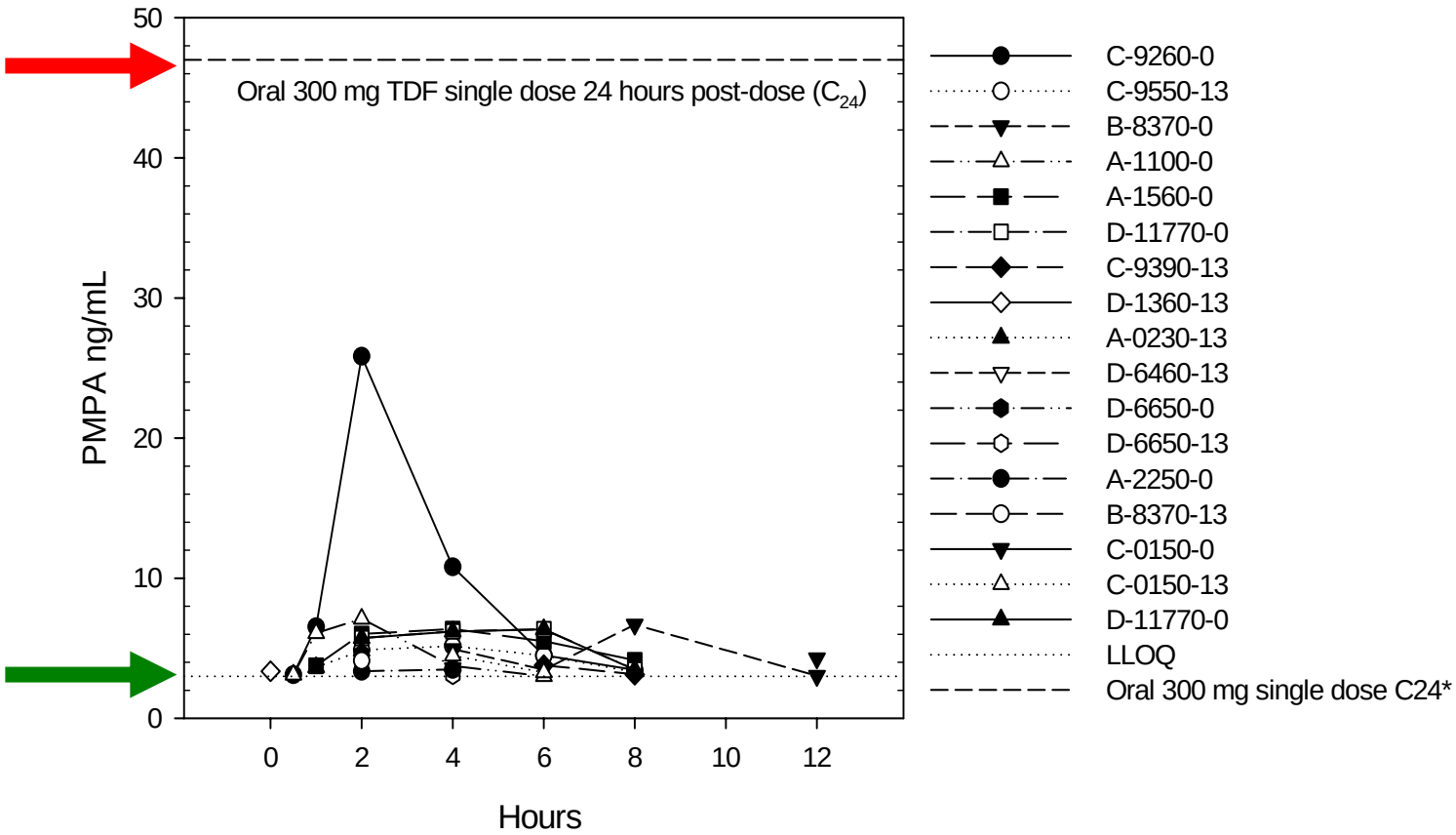
MTN
microbicide trials network

# HPTN-050

| Group | Category | PMPA | Dose | N |
|---|---|---|---|---|
| | | | | |
| A1 | Sexually abstinent HIV-negative | 0.3% | QD | 12 |
| A2 | | 1.0% | QD | 12 |
| A3 | | 0.3% | BID | 12 |
| A4 | | 1.0% | BID | 12 |
| B | Sexually active HIV-negative | 1.0% | BID | 12 |
| C | Sexually abstinent HIV-positive | 1.0% | BID | 12 |
| D | Sexually active HIV-positive | 1.0% | BID | 12 |

MTN
microbicide trials network

# HPTN-050 PK Data



# HPTN-050 Virology

- HIV was detected in the plasma of 13/24 HIV+ women at Day 0 and 12/24 at Day 14, but in CVL of only 2 women at Day 0 and none at Day 14.
- No new resistance mutations evolved in plasma or CVL after 14 days of TFV gel use.
- No pt. had high level TFV mutations e.g K65R

# Unanswered Questions

- What is the relationship between systemic absorption and the development of resistance?
- Will microbicide formulation or route of delivery alter risk of resistance?
- Could resistance occur during seroconversion?
- What about superinfection or viral recombination?

# Trial Design Issues

- Which patients should be studied?
  - Seroconverters
  - Chronically infected
- What assay should be used to assess viral resistance?
- What samples should be evaluated?
  - Plasma
  - Cervicovaginal or rectal secretions
  - Tissue
- What duration of study?

# Implications for MTN Trials (1)

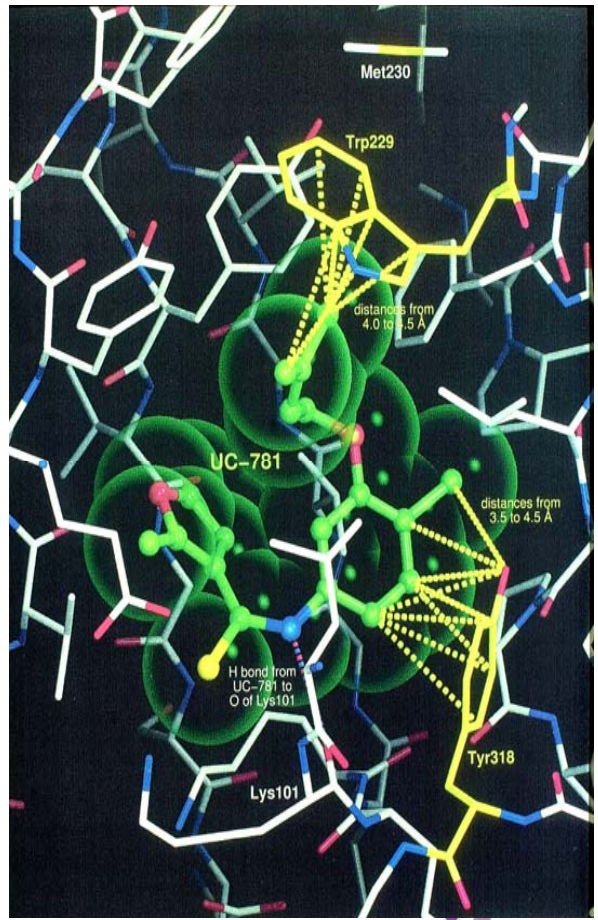
- Phase 1/2 studies in HIV positive participants
  - Avoid inadvertent exposure of those with chronic HIV-1 infection to topical or oral ARV PrEP
    - Resistance selection is very likely
    - Subsequent transmission is possible
    - Could affect subsequent treatment response

# Implications for MTN Trials (2)

- Detect acute HIV-1 infection on PrEP trials ASAP (HPTN-035, MTN-003)
  - Avoid selection of ARV-resistant virus
  - Could be transmitted
  - Could affect subsequent treatment response
- Possible need to increase frequency of HIV testing
- Study subsequent response to therapy carefully (MTN-015)

# Summary

- RT microbicide resistance is likely in participants with chronic HIV infection who should not be enrolled in Phase 1/2 studies
- Phase 2B studies using RT microbicides should identify seroconverters ASAP and stop therapy
- Long term follow-up of these seroconverters is very important




MTN
microbicide trials network

# Acknowledgements

John Mellors MD