

# Temporal Order of Resistance Emergence for Lamivudine/Emtricitabine, Efavirenz, and Raltegravir in Treatment-Naïve Patients

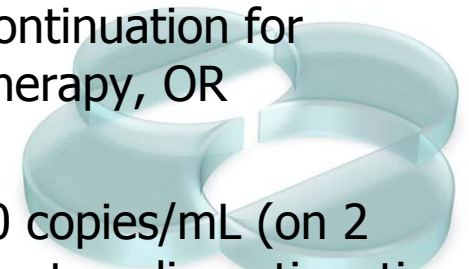
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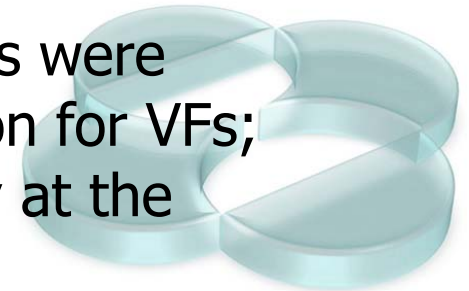
# Study Objectives

- Objective: Determine temporal order of resistance development to individual drugs in treatment-naïve patients with virologic failure (VF)
- Virologic Failure Definitions:
  - PN004: 2 consecutive measurements (at least 1 week apart)
    - HIV-1 RNA >400 copies/ml after initial response with plasma HIV-1 RNA <400 copies/ml; OR,
    - >1.0 log<sub>10</sub> increase in plasma HIV-1 RNA above the nadir level
  - PN021:
    - HIV-1 RNA >50 copies/mL at the time of discontinuation for patients who prematurely discontinue study therapy, OR
    - HIV-1 RNA >50 copies/mL at Week 24; OR
    - Virologic rebound for those with HIV RNA >50 copies/mL (on 2 consecutive measurements at least 1 week apart or discontinuation after one measurement >50 copies/mL) after initial response with HIV RNA <50 copies/mL.



# Patient population

- Patients were from Protocol 004 (Phase II) and Protocol 021 (Phase III), which had similar nucleoside backbones:
  - PN004: (RAL OR EFV) + 3TC + TDF
  - PN021: (RAL OR EFV) + FTC + TDF
- Patients who experienced VF by week 96 with resistance to any study drug were selected for longitudinal phenotypic and genotypic drug resistance analyses (Monogram Biosciences)
- In PN004 and PN021 protocols, investigators were encouraged to consider study discontinuation for VFs; however, patients could remain in the study at the investigator's discretion



# Longitudinal Resistance Analysis in Treatment-Naïve Patients

- Number of patients who had virologic failure (VF) with resistance to any study drug in PN004 and PN021 combined (by week 96)
  - 10 patients (of 441; 2%) failed a RAL arm with resistance to any study drug
  - 11 patients (of 320; 3%) failed an EFV arm with resistance to any study drug
- Number of time points with resistance tests per patient (post-VF):
  - Integrase (RHIN): Median = 7, Range = 2 to 15
  - RT (PRRT): Median = 5, Range = 1 to 15
- Tenofovir resistance was rare (2 patients with  $FCIC_{50} > 1.4$ , 2 additional patients with K65K/R but  $FCIC_{50} < 1.4$ ) and so was ignored for the current analysis

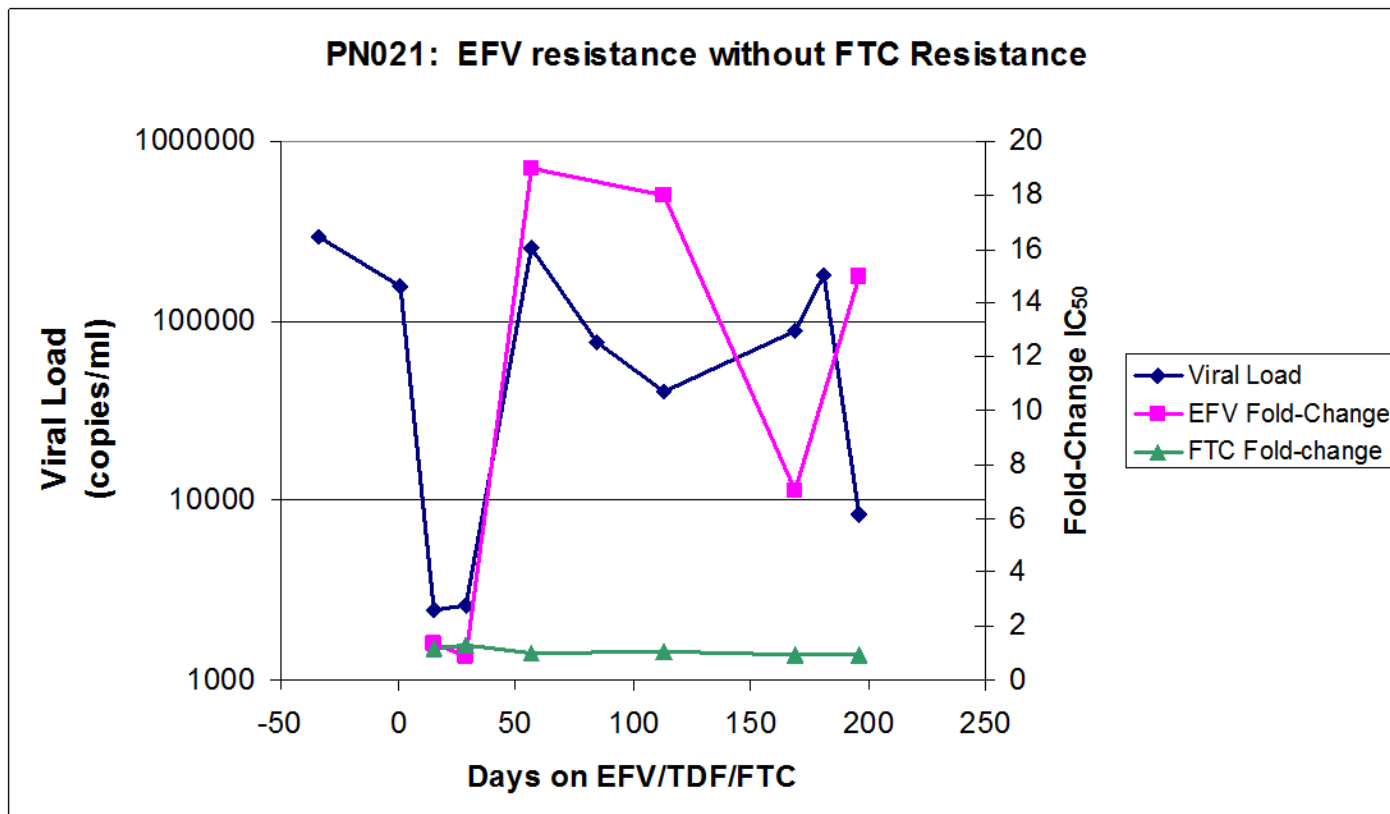


# 5 potential categories of resistance patterns

- Each patient's temporal order of resistance emergence (first time detected by either phenotype or genotype) was placed into one of five potential categories:
  1. RAL or EFV resistance appeared *without* FTC/3TC resistance
  2. RAL or EFV resistance appeared *before* FTC/3TC resistance
  3. RAL or EFV resistance appeared *simultaneously* with FTC/3TC resistance
  4. RAL or EFV resistance appeared *after* FTC/3TC resistance
  5. FTC/3TC resistance appeared *without* RAL or EFV resistance

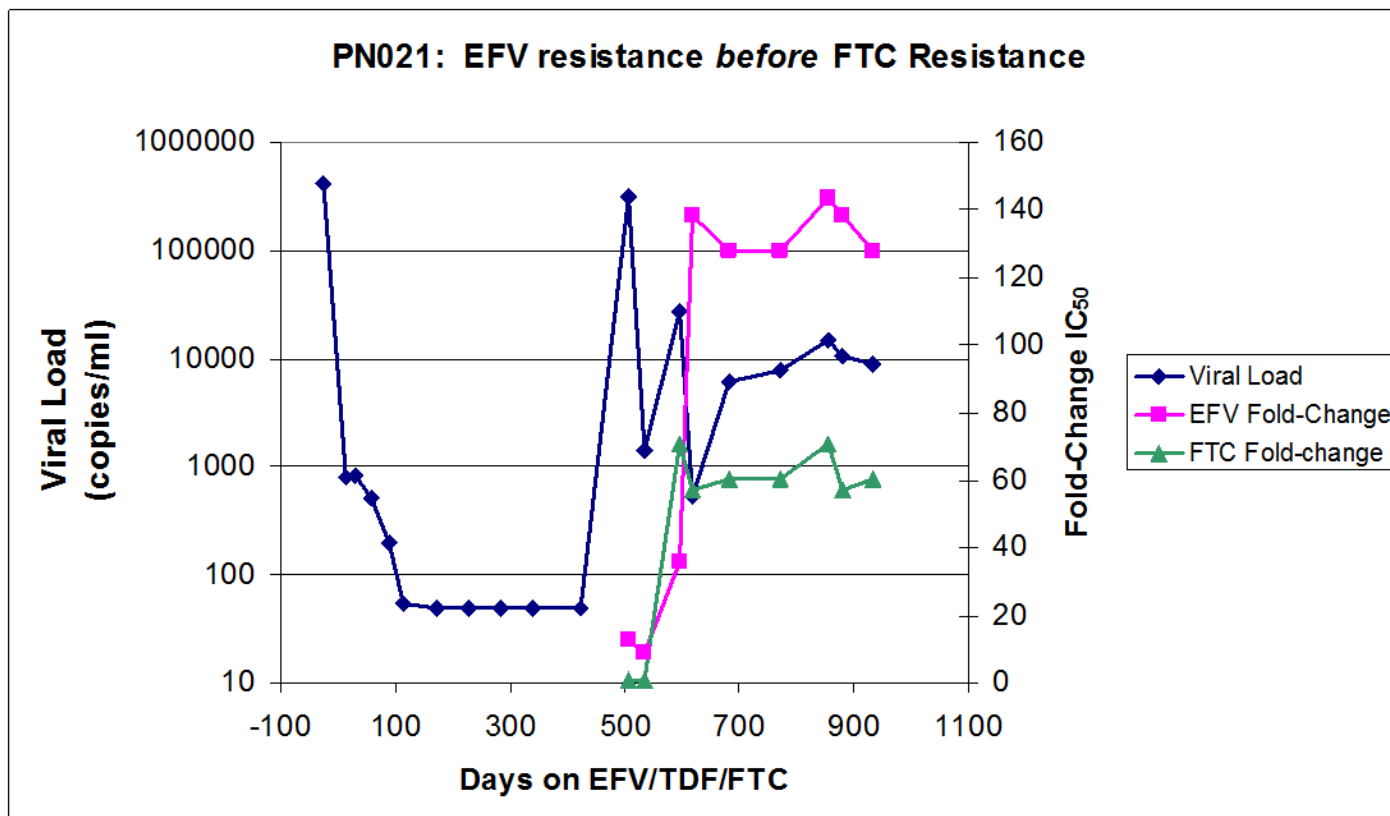


# Example 1: Patient with EFV resistance but without 3TC/FTC resistance



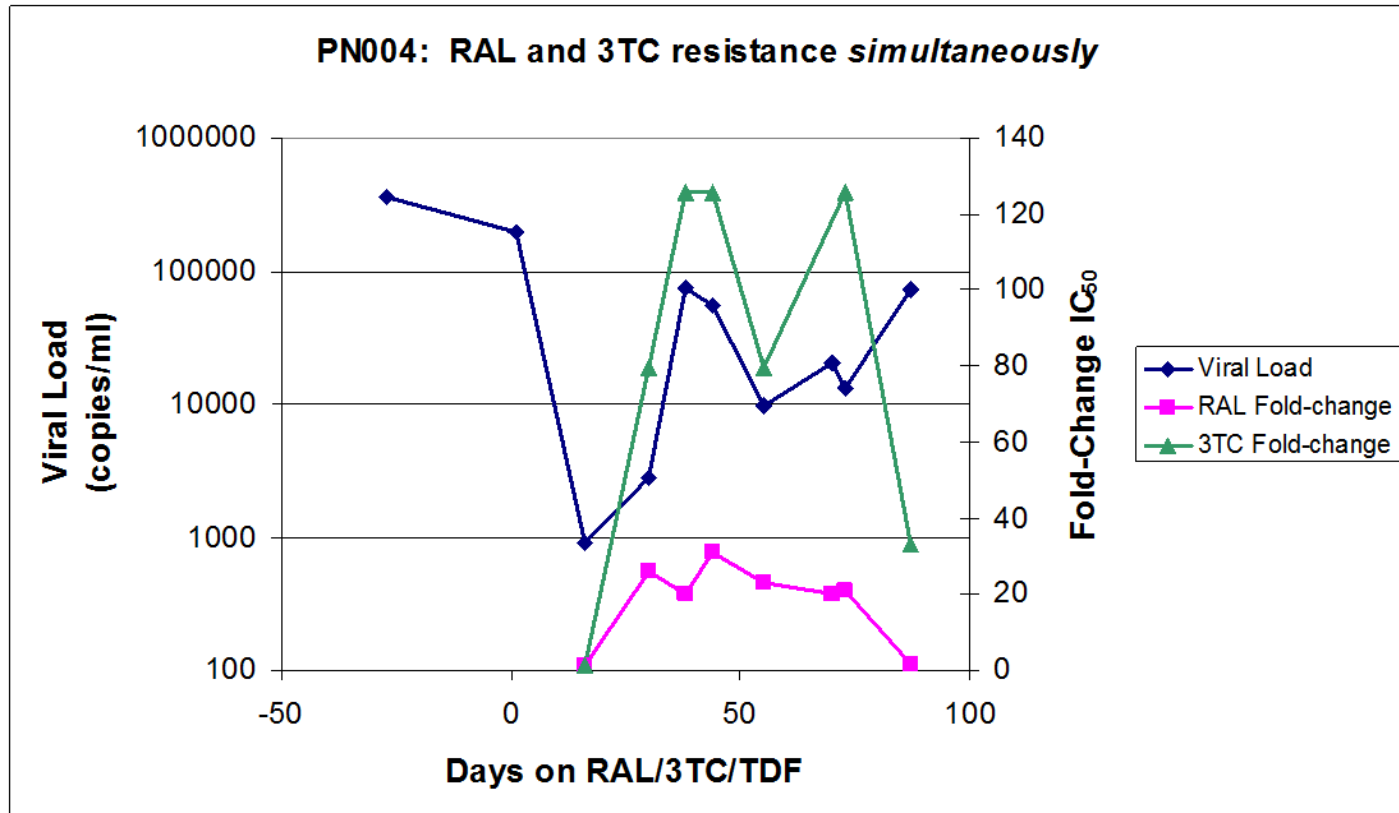
- Patient had EFV resistance without FTC resistance for ~20 weeks
- Genotypic data concordant (K103K/N/R/S + V106V/I/M → K103N)

# Example 2: Patient with EFV resistance appearing before FTC/3TC resistance



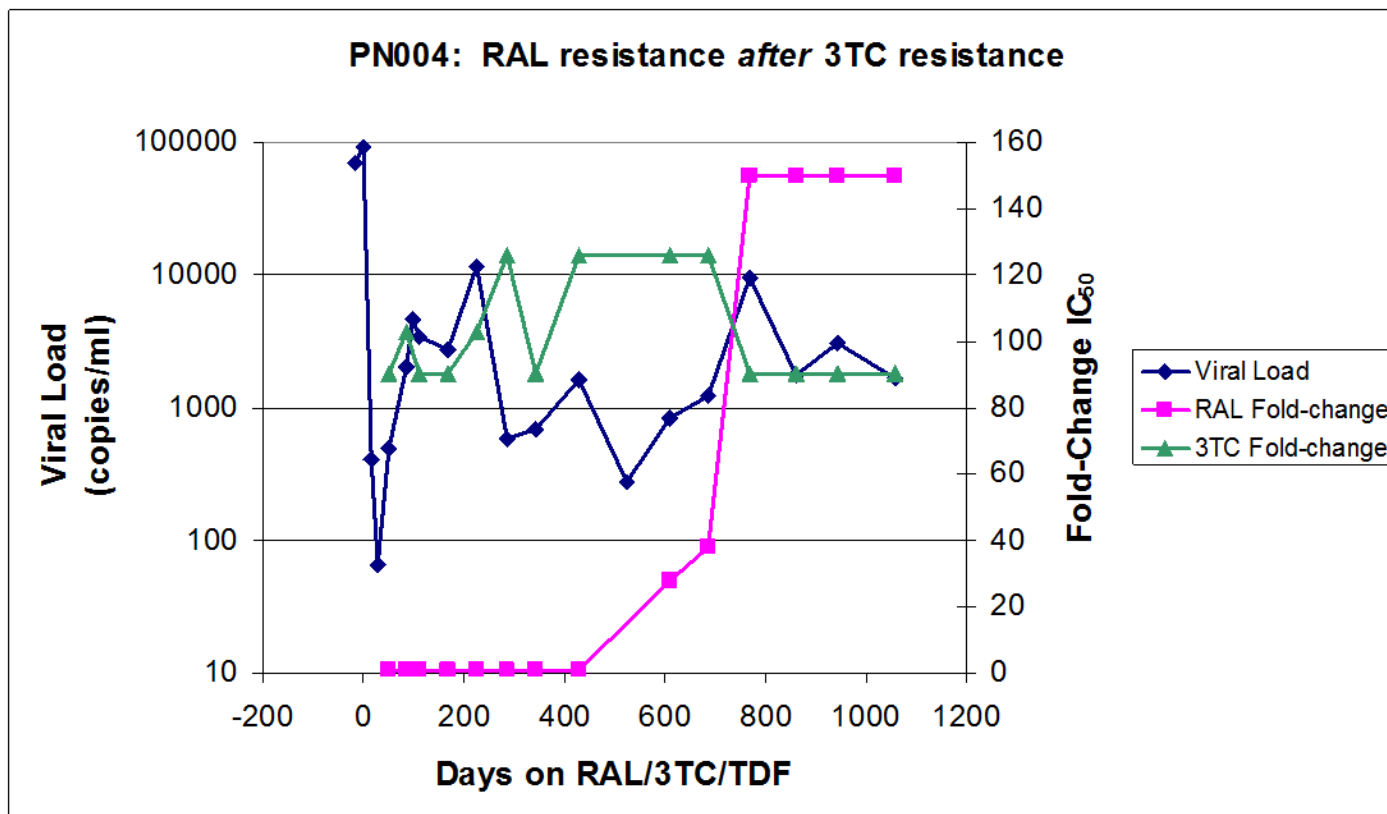
- Genotypic data concordant: K103K/N + V106V/M at day 508 (no M184V); M184V appeared at day 597 (~12 weeks)

# Example 3: Patient with RAL and FTC/3TC resistance appearing simultaneously



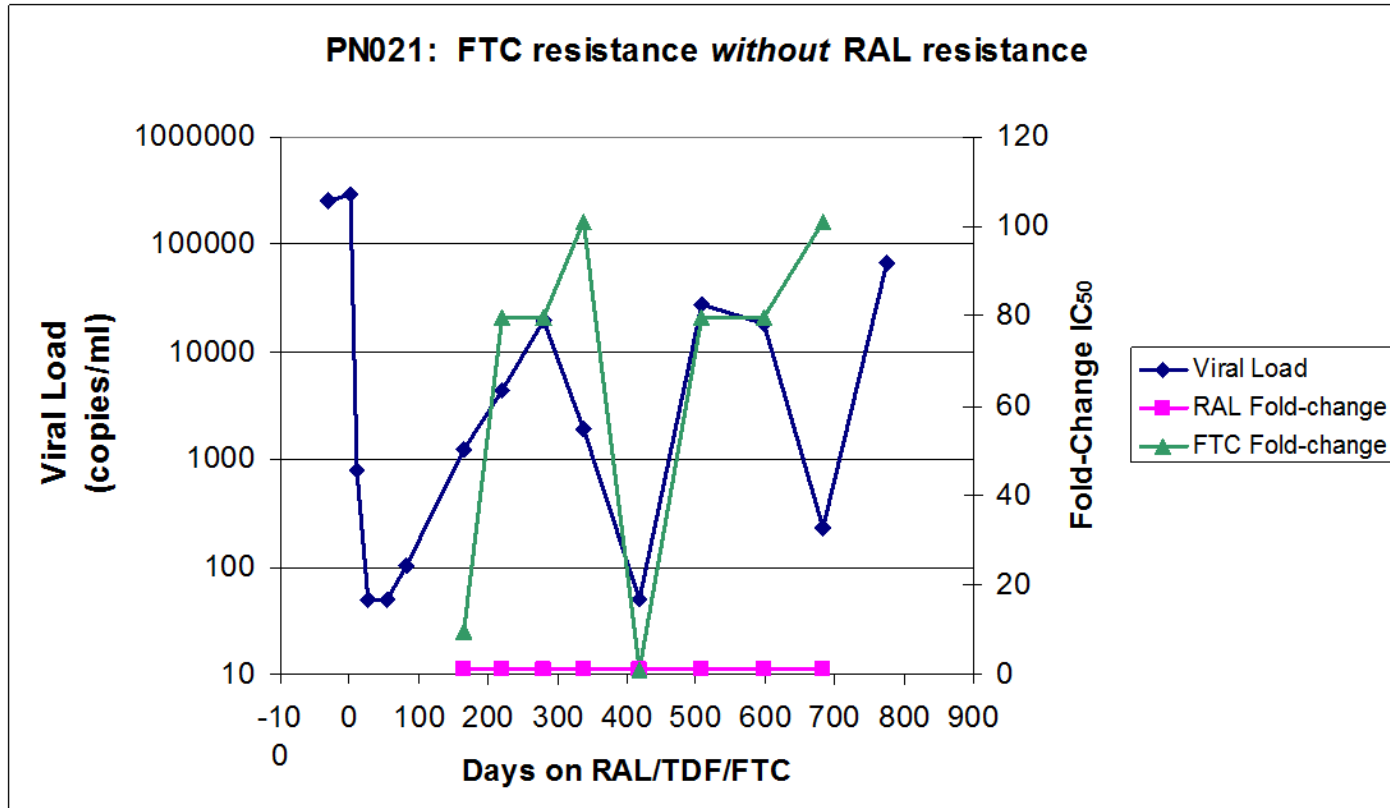
- Genotypic data concordant: M184M/I/V for 3TC resistance; N155H pathway for RAL resistance

# Example 4: Patient with RAL resistance appearing after FTC/3TC resistance



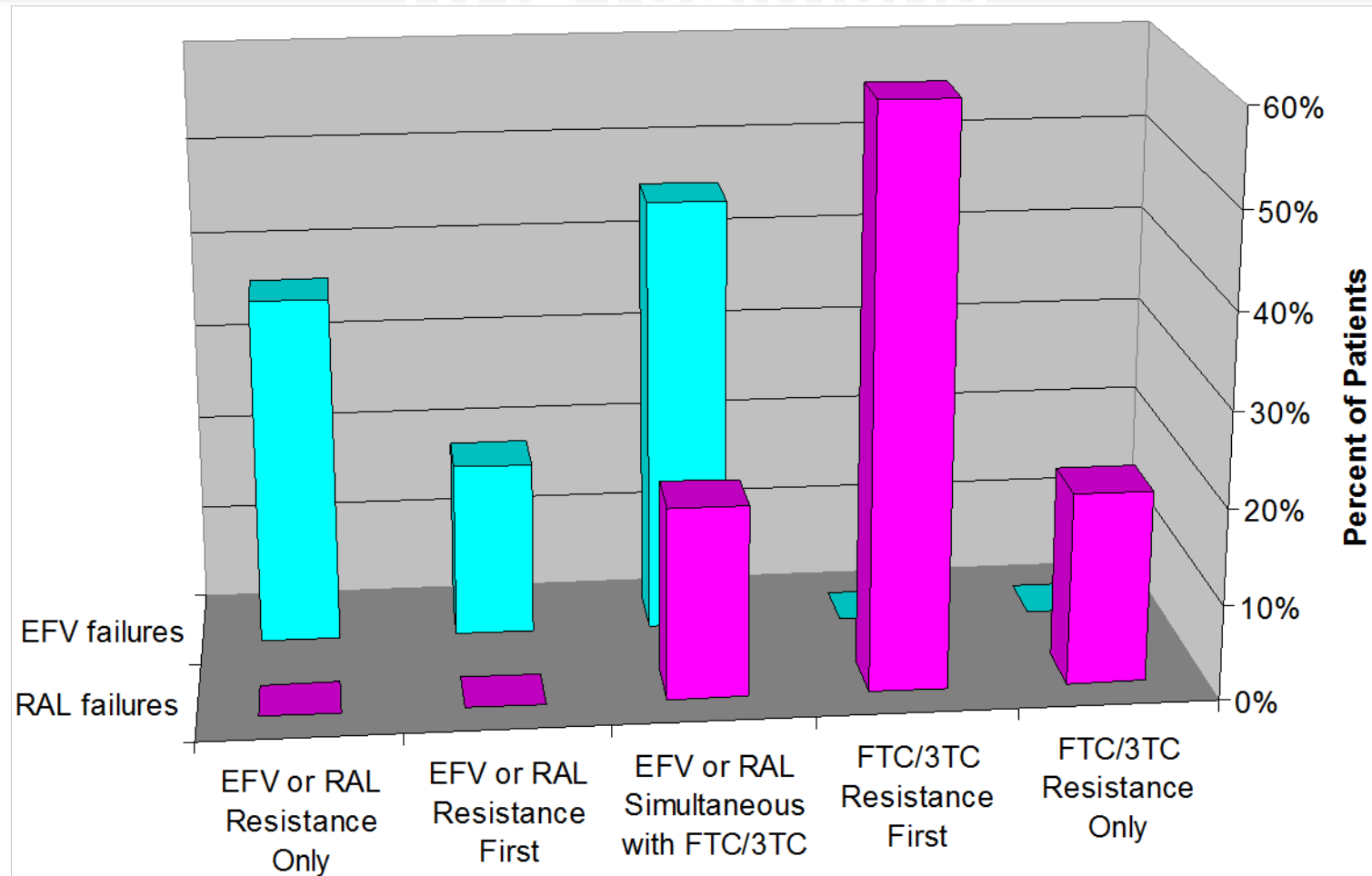
- Patient had 3TC resistance without RAL resistance for 80 weeks
- Genotypic data concordant: M184M/I/V → M184V; Y143 pathway for RAL resistance

# Example 5: Patient With FTC/3TC resistance appearing without RAL resistance

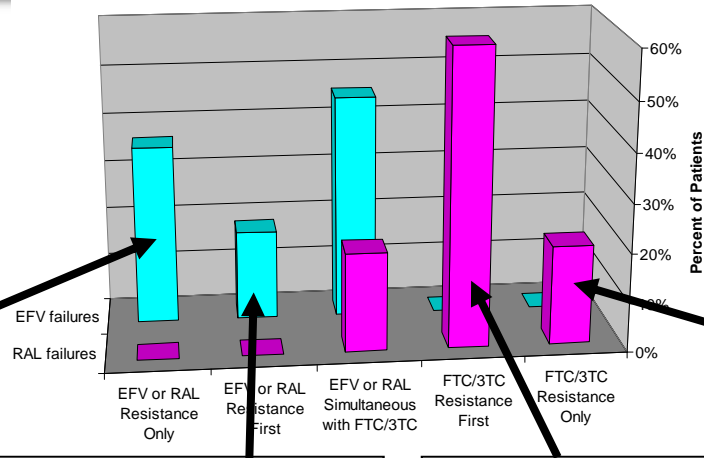


- Patient had 3TC resistance for >72 weeks without ever developing RAL resistance
- Genotypic data concordant: M184V; no RAL resistance mutations

# Temporal order of resistance appearance differs between EFV and RAL regimens



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Time with EFV resistance *without* FTC/3TC resistance (4 patients):

13 weeks

20 weeks

30 weeks

No data: pt discontinued just after EFV resistance developed

Time with EFV resistance *before* FTC/3TC resistance (2 patients):

12 weeks

49 weeks (VL resuppressed for 28 wks after K103K/N first emerged)

Time with 3TC/FTC resistance *before* RAL resistance (6 patients):

4 weeks

4 weeks

5 weeks<sup>†</sup>

6 weeks

12 weeks

80 weeks<sup>‡</sup>

Time with 3TC/FTC resistance *without* RAL resistance (2 patients):

5 weeks

74 weeks

<sup>†</sup> May be overestimated—1 untested intervening time point

<sup>‡</sup> May be overestimated—2 untested intervening time points

# Conclusions

- EFV and RAL resistance develop differently when administered with the same backbone regimen of 3TC/FTC and TDF
- EFV resistance usually emerged before or simultaneously with 3TC/FTC resistance
- RAL resistance usually emerged after 3TC/FTC resistance, in some cases with a large temporal disparity despite virologic failure
- This finding is consistent with previous observations comparing the barrier to these agents and suggesting the resistance barrier to RAL is distinct from that of EFV



# Acknowledgments

Protocol 004 Investigators

Protocol 021 Investigators

Patients who participated in  
Protocols 004 and 021

