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# Short-Term Raltegravir Monotherapy Does Not Predispose Patients to Develop RAL Resistance During Subsequent Combination Therapy: Analysis of Samples From Protocol 004

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## Abstract # M-187

**Background.** Raltegravir (RAL) is an HIV-1 Integrase Strand Transfer Inhibitor approved for treatment of HIV-1 infection. Protocol 004 was a Phase 2, multi-center, double-blind, 2-part randomized placebo-controlled dose-ranging study of RAL in treatment-naïve HIV-1 infected patients. Part 1 of this study enrolled 35 patients who received RAL monotherapy (at one of 4 doses) or placebo for 10 days. All Part 1 participants were eligible to enroll in Part 2, in which patients received tenofovir plus lamivudine in combination with RAL at their respective Part 1 dose or efavirenz (for patients who received placebo in Part 1). A total of 29 Part 1 participants (25 from RAL arms, 4 from placebo arm) were treated in Part 2. The goals of the current analysis were 1) to assess efficacy and durability of RAL combination therapy for patients who received RAL monotherapy, and 2) to use a sensitive 454 deep sequencing method to determine whether any minority RAL resistance mutations emerged during RAL monotherapy.

**Methods.** Virologic failure was defined as either non-response (viral load [VL] never reached <400 copies/ml) or virologic relapse (relapse defined as 2 consecutive VL > 400/ml after initially achieving VL<400/ml, or a >1 log10 increase in VL above the VL nadir. Deep sequencing of the integrase gene was performed by 454 Life Sciences using archived Part 1 plasma samples. When possible, for each patient, deep sequencing was attempted for 3 time points: Part 1 baseline (pre-therapy), an on-therapy sample with VL> 400/ml, and Part 2 baseline (or 14d after the end of monotherapy).

**Results.** Minority variants with RAL resistance mutations were observed infrequently by deep (454) sequencing in all Part 1 samples. Only one of 25 patients who received RAL monotherapy in Part 1 experienced virologic relapse during 96 weeks of RAL/TDF/3TC treatment in Part 2. At the time of failure, this patient's virus had no detectable genotypic resistance to RAL and no phenotypic or genotypic resistance to TDF or 3TC. Of the five patients who discontinued treatment prior to 96 weeks, 4 patients had VL<50/ml at the time of discontinuation (weeks 64 to 81) and 1 patient discontinued after 2 weeks of therapy.

**Conclusions.** Using 454 deep sequencing methods, mutations associated with RAL resistance were rarely detected in patients receiving RAL monotherapy and these minority variants did not result in virologic failure during subsequent combination therapy with TDF and 3TC.

## Introduction

Protocol 004 is an ongoing Phase 2, multi-center, double-blind, 2-part randomized placebo-controlled dose-ranging study of RAL in treatment-naïve HIV-1 infected patients with total 240 week duration. Safety and efficacy results through week 144 have been published or presented (Part 1: Markowitz, et al., 2006, *J Acquir Immune Defic Syndr*; 43:509; Part 2: Markowitz, et al., 2007, *J Acquir Immune Defic Syndr* 46:125; Markowitz, et al., 2009, *J Acquir Immune Defic Syndr* 52:350; Gotuzzo et al, 2009, IAS abstract MOPEB030). Week 192 results are presented at this meeting (Gotuzzo, et al, abstract #K-127).

The overall study design is shown in Figure 1. Part 1 of this study enrolled 35 patients who received RAL monotherapy (at one of 4 doses) or placebo for 10 days. All Part 1 participants were eligible to enroll in Part 2, in which patients received tenofovir plus lamivudine in combination with RAL at their respective Part 1 dose or efavirenz (for patients who received placebo in Part 1).

The goals of the present analysis were 1) to assess efficacy and durability of RAL combination therapy through week 96 specifically for patients who received RAL monotherapy, and 2) to use a sensitive 454 deep sequencing method to determine whether any minority RAL resistance-associated mutations emerged during RAL monotherapy.

## Methods

**Reanalysis of PN004 part 1 viral load change from baseline using an ultrasensitive assay.** Viral load change from baseline was originally assessed (Markowitz, et al., 2006, *J Acquir Immune Defic Syndr*; 43:509) using the Roche Amplicor Monitor Amplicor v1.5 assay with a nominal lower limit of quantification (LLOQ) of 400 cp/ml. In the original analysis, values of <400 cp/ml were imputed to 400 cp/ml (if RNA was detected) or 200 cp/ml (if RNA was not detected). This resulted in imputing of data from at least one time point for more than half of the patients receiving RAL monotherapy (15 of 28 patients; see Table 1). In the reanalysis, samples in which viral loads were <400 cp/ml by the Roche Amplicor Monitor v1.5 assay were reanalyzed using the Roche Ultrasensitive v1.5 assay (LLOQ = 50cp/ml). Values of <50 cp/ml were imputed to 50 cp/ml (if RNA was detected) or 25 cp/ml (if RNA was not detected); this resulted in imputing viral load for at least one time point from each of 5 patients (see Table 1).

**Table 1. Number and Percent of Patients with Plasma HIV-1 RNA**

<400 copies/ml or < 50 copies/ml
(Data As Observed Approach)
Protocol 004 part 1

| MK-0518 Treatment (Twice Daily) | N | HIV RNA <400 Copies/mL | | HIV RNA <50 Copies/mL | |
|---|---|---|---|---|---|
| | | n | % (95% CI) | n | % (95% CI) |
| 100 mg | 7 | 4 | 57 (18 to 90) | 1 | 14 (0 to 58) |
| 200 mg | 7 | 4 | 57 (18 to 90) | 2 | 29 (4 to 71) |
| 400 mg | 6 | 3 | 50 (12 to 88) | 1 | 17 (0 to 64) |
| 600 mg | 8 | 4 | 50 (16 to 84) | 1 | 13 (0 to 53) |
| Placebo | 7 | 0 | 0 (0 to 41) | 0 | 0 (0 to 41) |

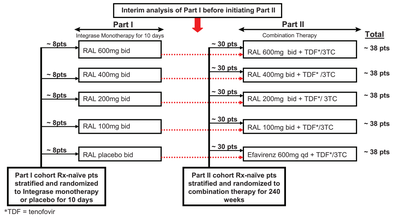
**Selection for patients for 454 sequence analysis.** Seventeen patients from Protocol 004 part 1 were chosen for further analysis based on the following criteria:

- Patients received RAL in part 1 and were subsequently treated in part 2 (28 of 35 patients in part 1)
- Patients had the following plasma samples available (17 patients):
  1. Baseline sample (pre-monotherapy)
  2. On-monotherapy sample – targeted samples with VL change from baseline between -0.5$\log_{10}$ and -3.0$\log_{10}$ so as to balance the need for observed viral suppression (indicating selective pressure has been applied) and need for sufficient virus to enable sampling of diversity
     - VL reduction from baseline for on-therapy testing samples: Mean = 1.37 $\log_{10}$; Range = 0.6 to 2.8 $\log_{10}$
     - VL of on-therapy testing samples : Geo Mean = 2034; Range = 226 to 12700
  3. Baseline sample (pre-combination therapy)
     - Time off RAL between parts 1 and 2: Mean = 100 days; Range = 48 to 168 days

**Detection of minority integrase (IN) variants by 454 pyrosequencing.** Viral RNA was isolated from ultracentrifuged plasma samples (~1ml) using a Qiagen QIAamp® Viral RNA Mini Kit or RNeasy Mini Kit. First strand cDNA was generated using a Transcriptor and a primer just upstream of IN. PCR was done using Fast Start HiFi polymerase and 6 primer sets to generate six different amplicons corresponding to partially overlapping fragments of IN. Amplicons were generated using primers that fused specific 454 immobilization and sequencing primers to the IN regions of interest. Fragments were immobilized on beads, subjected to water-in-oil amplification, and analyzed by pyrosequencing using a Genome Sequencer FLX with standard chemistry capable of nominal read lengths of 250 nucleotides. Data were analyzed to detect any of the following known RAL resistance-associated mutations: Y143C/H/R, Q148H/K/R, N155H (signature mutations); L74M, E92Q, T97A, E138A/K, G140A/S, V151I, S230R (secondary mutations). Only mutations observed in ≥0.5% of amplicons were reported.

## Results

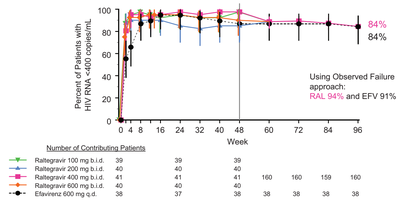
**Figure 1. Overall design of Protocol 004**




*TDF = tenofovir

See Markowitz, et al., 2007, *J Acquir Immune Defic Syndr* 46:125 for details.

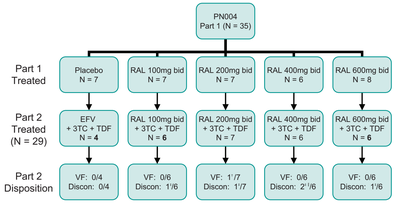
**Figure 2. Efficacy outcomes through week 96 of Part 2**




All patients received TDF and 3TC in addition to EFV or RAL. At week 48, all patients in RAL arms began receiving RAL 400mg bid. The figure shows the percent (95% CI) of patients with HIV RNA <400 copies/mL (noncompleter = failure approach). CI, confidence interval.

From: Markowitz, et al., 2009, *J Acquir Immune Defic Syndr* 52:350

**Figure 3. Patient accounting and disposition for patients participating in Part 1 of Protocol 004.**




VF, Virologic Failure by week 96. Discon, patient discontinued therapy.

[1]The one patient who met the protocol definition of virologic failure failed between 48 and 96 weeks, and virus analyzed after rebound displayed no resistance to RAL, 3TC, or TDF.

[2]Four patients discontinued therapy between 48 and 96 weeks, all had viral load <50 copies/ml at the time of discontinuation.

[3]One patient discontinued after 2 weeks of combination therapy (1 patient)

**Table 2. Change from Baseline in log10 HIV RNA**

(Data As Observed Approach)
Protocol 004, part 1

| Day | MK-0518 100mg b.i.d. | | MK-0518 200mg b.i.d. | | MK-0518 400mg b.i.d. | | MK-0518 600mg b.i.d. | | Placebo | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | mean (95% CI) | n | mean (95% CI) | n | mean (95% CI) | n | mean (95% CI) | n | mean (95% CI) |
| 2 | 7 | -0.42 (-0.74, -0.10) | 7 | -0.24 (-0.41, -0.07) | 6 | -0.39 (-0.58, -0.19) | 8 | -0.32 (-0.56, -0.08) | 7 | -0.13 (-0.33, 0.06) |
| 3 | 7 | -0.75 (-0.98, -0.52) | 7 | -0.65 (-0.79, -0.52) | 6 | -0.59 (-0.88, -0.30) | 8 | -0.66 (-0.92, -0.41) | 7 | -0.10 (-0.33, 0.13) |
| 4 | 7 | -0.93 (-1.09, -0.77) | 7 | -1.08 (-1.26, -0.89) | 6 | -0.92 (-1.22, -0.61) | 8 | -1.09 (-1.37, -0.81) | 7 | -0.08 (-0.15, -0.00) |
| 5 | 5 | -1.25 (-1.89, -0.61) | 6 | -1.40 (-1.75, -1.06) | 6 | -1.32 (-1.77, -0.88) | 7 | -1.36 (-1.76, -0.95) | 4 | -0.07 (-0.30, 0.15) |
| 8 | 7 | -1.81 (-2.22, -1.39) | 7 | -1.85 (-2.11, -1.58) | 6 | -1.78 (-2.22, -1.34) | 8 | -2.02 (-2.48, -1.57) | 7 | 0.00 (-0.24, 0.25) |
| 10 | 7 | -2.22 (-2.62, -1.82) | 7 | -2.22 (-2.45, -1.99) | 6 | -2.09 (-2.68, -1.49) | 8 | -2.22 (-2.61, -1.84) | 7 | -0.21 (-0.42, -0.00) |

Data at day 7 and 9 was treated as day 8, and last one was taken if multiple exists.

**Table 3. Detection of minority RAL resistance-associated mutations in patients receiving RAL monotherapy in Part 1 of Protocol 004**

| | | | | | % of sequences with this mutation:[2] | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient | Rx Group | Fate in Study Part 2[1] | STUDY VISIT | Viral Load (cp/ml) | L74M | E92Q | T97A | E138A | E138K | G140A | G140S | Y143R | Y143C | Y143H | Q148H/K/R | V151I | N155H | S230R |
| A | 100mg bid | Success | Baseline | 3.73 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | On monotherapy | 3.08 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | Pre-Part 2 baseline | 3.81 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| B | 100mg bid | Success | Baseline | 4.32 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | On monotherapy | 3.31 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | Pre-Part 2 baseline | 4.09 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| C | 100mg bid | Success | Baseline | 5.13 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | On monotherapy | 3.39 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | Pre-Part 2 baseline | 5.42 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| D | 100mg bid | Success | Baseline | 5.35 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3.16 |
| | | | On monotherapy | 2.56 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | Pre-Part 2 baseline | 5.37 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| E | 100mg bid | Success | Baseline | 5.03 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | On monotherapy | 4.10 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | Pre-Part 2 baseline | 4.77 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| F | 200mg bid | Success | Baseline | 3.84 | 0 | 0 | 0 | 1.83 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | On monotherapy | 3.25 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | Pre-Part 2 baseline | 4.02 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| G | 200mg bid | Success | Baseline | 4.64 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | On monotherapy | 3.54 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3.04 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | Pre-Part 2 baseline | 4.71 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| H | 200mg bid | Success | Baseline | 4.98 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | On monotherapy | 3.47 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | Pre-Part 2 baseline | 4.64 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| I | 200mg bid | Success | Baseline | 5.08 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | On monotherapy | 2.65 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | Pre-Part 2 baseline | 4.79 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| J | 400mg bid | Success | Baseline | 4.40 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | On monotherapy | 3.20 | 0 | 0 | 0 | No data | No data | No data | No data | No data | No data | No data | No data | No data | No data | No data |
| | | | Pre-Part 2 baseline | 3.49 | No data | No data | No data | No data | No data | No data | No data | No data | No data | No data | No data | No data | No data | No data |
| K | 400mg bid | Discon after 15 days; BL VL = 118,000 #15 VL = 1660 | Baseline | 4.88 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | On monotherapy | 3.66 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | Pre-Part 2 baseline | 5.07 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.55 | 0 | 0 | 0 |
| L | 400mg bid | Success | Baseline | 4.89 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | On monotherapy | 3.32 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | Pre-Part 2 baseline | 4.47 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| M | 600mg bid | Success | Baseline | 4.34 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | On monotherapy | 3.45 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | Pre-Part 2 baseline | 4.18 | 0 | 0 | 0 | 0.52 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| N | 600mg bid | Discon after 451 days (64 weeks) VL <50 at discon | Baseline | 4.85 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | On monotherapy | 3.91 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | Pre-Part 2 baseline | 4.38 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| N | 600mg bid | Success | Baseline | 4.26 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | On monotherapy | 2.35 | 0 | 0 | 0 | No data | No data | No data | No data | No data | No data | No data | No data | No data | No data | No data |
| | | | Pre-Part 2 baseline | 4.48 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.98 | 0 | 0 |
| O | 600mg bid | Success | Baseline | 5.28 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1.1 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | On monotherapy | 3.33 | 0 | 0 | 0 | No data | No data | No data | No data | No data | No data | No data | No data | No data | No data | No data |
| | | | Pre-Part 2 baseline | 4.76 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1.33 | 0 | 0 | 0 |
| P | 600mg bid | Success | Baseline | 5.54 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | On monotherapy | 3.68 | No data | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | Pre-Part 2 baseline | 5.08 | 0 | 0 | 0 | 1.4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

[1]Success means the patient did not meet the protocol definition of virologic failure by 96 weeks in part 2 of the study.

[2]Resistance-associated mutations analyzed were Y143C/H/R, Q148H/K/R, N155H (signature mutations); L74M, E92Q, T97A, E138A/K, G140A/S, V151I, S230R (secondary mutations). A threshold value of 0.5% of reads was applied, so any value listed as zero should be interpreted as <0.5% of all sequence reads. The following RAMs were not detected in any of these samples at >0.5% of reads: L74M, E92Q, E138A, G140A, Y143R, Q148H, Q148K, Q148R, N155H. "No data" indicates that there was no sequence coverage in the region for that specific mutation. Values in bold indicate the mutation was observed at a frequency of >0.5% of sequence reads. Values in bold red indicate mutations observed during or after treatment, which may have been selected by raltegravir monotherapy.

**RAL RAMs detected by Ultradeep (454) sequencing in 17 patients receiving RAL monotherapy in PN004**

- RAL resistance-associated mutations (RAMS) analyzed:
  - Signature mutations: Y143C/H/R, Q148H/K/R, N155H
  - Secondary mutations: L74M, E92Q, T97A, E138A/K, G140A/S, V151I, S230R
- RAMs not detected in any sample (LOQ = 0.5%):
  - L74M, E92Q, E138A, G140A, Y143R, Q148H, Q148K, Q148R, N155H
- RAMs detected in BL samples:
  - Signature mutation Y143C in 1 patient (1.1% of sequences)
  - Secondary mutation E138K in 1 patient (1.83% of sequences)
  - Secondary mutation S230R in 1 patient (3.16% of sequences)
- RAMs detected on therapy:
  - Secondary RAM G140S detected in 1 patient (3.04% at day 5; VL = 3460)
- RAMS detected in Part 2 BL but not in Part 1 BL:
  - Signature mutation Y143H in 1 patient (0.55% of sequences)
  - Secondary mutation V151I in 2 patients (0.96% and 1.33% of sequences)
  - Secondary mutation E138K in 2 patients (0.52% and 1.4% of sequences)

## Conclusions

- Reanalysis of viral load reduction in PN004 monotherapy using the Roche Ultrasensitive HIV assay showed that the mean VL decline across all 4 groups receiving RAL was about -2.19$\log_{10}$ at day 10.
- 24 of 25 patients who received 10d RAL monotherapy were treatment successes after 96 weeks of RAL+TDF+3TC combination therapy
  - The 1 patient with VF had NO resistance to RAL, TDF, or 3TC at VF
  - Low-level primary RAL resistance mutations appearing during PN004 monotherapy were rare and did not result in virologic failure during the combination therapy phase.
  - 1 patient selected Q148R during monotherapy (0.4%, below cutoff) but was a success in part 2.
  - 1 patient selected Y143H during monotherapy, but did not enroll in part 2
- RAL monotherapy did not reduce likelihood of treatment success
- Results here differ from efavirenz (EFV) monotherapy study (DMP-266-003, cohort 1; Bacheler, et al., 2000, *Antimicrob Agents Chemother*. 44(9):2475-84)
  - EFV resistance detected in 11 of 16 patients after 2 weeks of EFV monotherapy
  - Higher failure rate among patients who received EFV monotherapy

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