Selection of HIV Reverse Transcriptase (RT) Thymidine Analogue Mutations (TAMS) Rather than K65R is the Preferred Route of Resistance Seen in Patients with Virologic Failure on Once-Daily (QD) Trizivir (TZV) and Tenofovir (TDF)

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Introduction

COL40263 is a pilot 48 week, open-label, multicenter study evaluating the efficacy and safety of TZV + TDF QD in ART naive, HIV-infected subjects. This study was initiated at the time when ZDV QD was under clinical investigation.

A high virologic failure rate was noted in trials where TDF was combined with either ABC/3TC or ddI/3TC[1,2,3], with concomitant selection for the K65R and M184V mutation in the majority of subjects with virologic non-response. In this study, where TDF was combined with ABC/3TC/ZDV (TZV), we examined the sequence of drug resistance and mutation selection in subjects with virologic failure to determine if the presence of ZDV once daily would impact the selection for K65R in subjects with virologic failure.

Methods

Plasma HIV samples from baseline and from virologic failure (VF) time points through 48 weeks were analyzed by population genotype and phenotype (VIRCO). Virologic failures had confirmed HIV-1 RNA (RNA) ≥400 copies/mL at ≥24 weeks. Resistance mutations were as per IAS-USA Drug Resistance Mutations group guidelines, plus T215 reversion mutations which were also included in the resistance mutation assessment.

Results

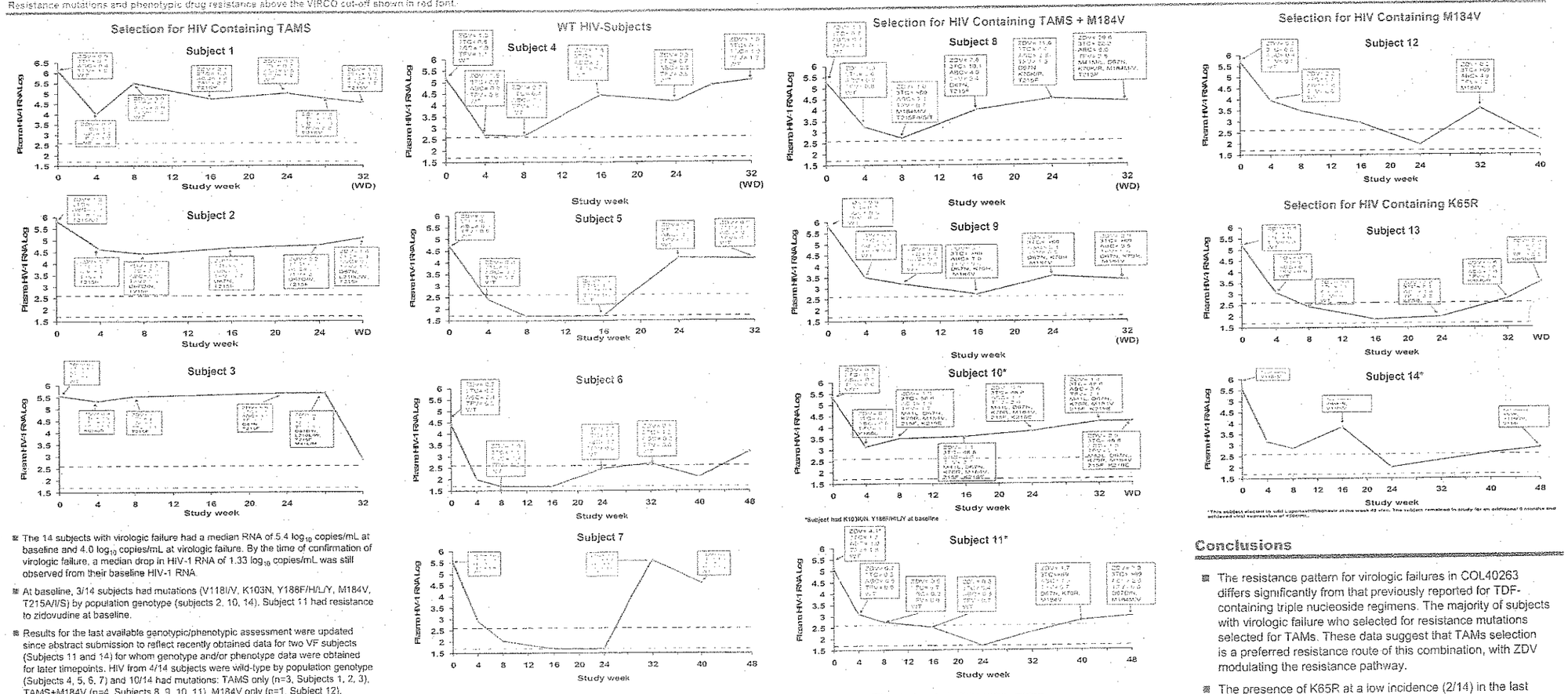
- 123 subjects were enrolled in the study. Through week 48, 14/123 (11%) met the protocol definition of virologic failure criteria (HIV-1 RNA ≥400 copies/mL at or after week 24, confirmed by a second draw within 2-4 weeks). Subject 14 optimized therapy by adding lopinavir/ritonavir at the week 48 visit.
- The demographics and baseline characteristics of the responder population (subjects who did not meet the protocol definition of virologic failure) compared to the group of subjects with virologic failure are shown in Table 1. The following differences are notable between these two groups - the proportion of subjects with baseline HIV-1 RNA ≥200,000 copies/mL in the virologic failure population was approximately twice the proportion in the responder population, the median baseline CD4+ in the virologic failure population was <200cells/mm^3 (vs. >200 cells/mm^3 for the responder population), and the proportion of subjects who were black were higher in the virologic failure population than in the responder population.

Table 1. Demographics and Baseline Characteristics of the Responder and Virologic Failure Population

	Responder Population (n=109)	Virologic Failure Population (n=14)
Median baseline $\log_{10}$ HIV-RNA	5.04 copies/mL	5.44 copies/mL
Baseline HIV-RNA ≥100,000 copies/mL	55%	86%
Baseline HIV-RNA ≥200,000 copies/mL	38%	64%
Median baseline CD4+	223 cells/mm^3	124 cells/mm^3
Median age (years)	38	36.5
Male	85%	64%
White	50%	21%
Black	36%	71%
American Hispanic	15%	0%

Figure 1. Longitudinal Profiles of Mutation Selection for Subjects with Virologic Failure Treated with Tenofovir + abacavir/lamivudine/zidovudine Once Daily as Detected by Population Genotyping

Resistance mutations and phenotypic drug resistance above the VIRCO cut-off shown in red font.



- The 14 subjects with virologic failure had a median RNA of 5.4 $\log_{10}$ copies/mL at baseline and 4.0 $\log_{10}$ copies/mL at virologic failure. By the time of confirmation of virologic failure, a median drop in HIV-1 RNA of 1.33 $\log_{10}$ copies/mL was still observed from their baseline HIV-1 RNA.
- At baseline, 3/14 subjects had mutations (V118I/V, K103N, Y188F/H/L/Y, M184V, T215A/I/S) by population genotype (subjects 2, 10, 14). Subject 11 had resistance to zidovudine at baseline.
- Results for the last available genotypic/phenotypic assessment were updated since abstract submission to reflect recently obtained data for two VF subjects (Subjects 11 and 14) for whom genotype and/or phenotype data were obtained for later timepoints. HIV from 4/14 subjects were wild-type by population genotype (Subjects 4, 5, 6, 7) and 10/14 had mutations: TAMS only (n=3, Subjects 1, 2, 3), TAMS+M184V (n=4, Subjects 8, 9, 10, 11), M184V only (n=1, Subject 12), K65R/K (n=2, Subjects 13 and 14).
- Phenotype was obtained for 13 virologic failures on therapy. Study drug resistance was seen in 1/13 subjects (Subject 11, zidovudine) at baseline. At the last available assessment, 5/13 (38%) subjects had phenotypic resistance to study drugs: 0/13 TDF, 3/13 ABC (Subjects 8, 9, and 12), 1/13 ZDV (Subject 8), and 5/13 3TC (Subjects 8, 9, 10, 11, and 12).

*Subject had K103N, Y188F/H/L/Y at baseline

*Baseline resistance to IDV was also observed and multiple secondary PI mutations

Conclusions

- The resistance pattern for virologic failures in COL40263 differs significantly from that previously reported for TDF-containing triple nucleoside regimens. The majority of subjects with virologic failure who selected for resistance mutations selected for TAMs. These data suggest that TAMs selection is a preferred resistance route of this combination, with ZDV modulating the resistance pathway.
- The presence of K65R at a low incidence (2/14) in the last available genotype suggests that the counter selection by ZDV towards TAMs may be lessened when administered QD.

References

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