EPB158

Low Level of Virologic Failure and Resistance in ART-Experienced, Integrase Inhibitor-Naive Participants Receiving Dolutegravir (DTG) and Nucleoside Reverse Transcriptase Inhibitors (NRTIs) Combined Regimens: 10-Year Follow-up in the SAILING Study

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Key Takeaways

- High virologic response rates and low PDVF occurrence were observed for DTG participants whose background regimen contained only NRTIs through 10 years
- Protocol-defined virologic failure (PDVF) occurred rarely in DTG participants receiving 2 fully active NRTIs as background regimens; 4 met PDVF criteria, including 1 with HIV-1 RNA <50 c/mL at the last on-study visit; 2 had treatment-emergent integrase (IN) substitutions with low impact on DTG susceptibility, and none developed treatment-emergent NRTI resistance
- Baseline thymidine analog mutations (TAMs) did not seem to impact virologic response for participants being treated with DTG plus a background regimen only containing NRTIs
- Durable virologic suppression was maintained for DTG participants harboring M184V and thus receiving inactive 3TC or FTC plus their second NRTI

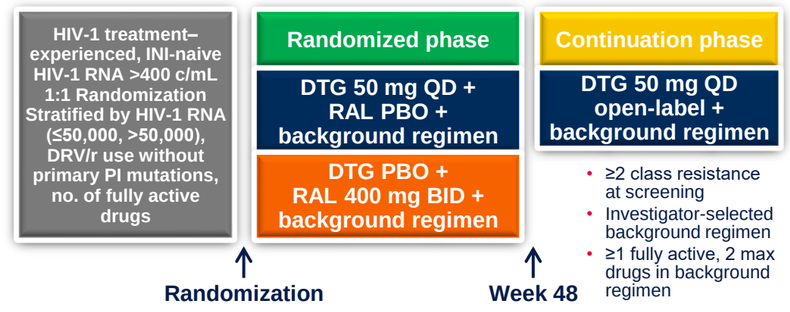
Introduction

- DTG demonstrated superiority to raltegravir (RAL) in the SAILING study at Week 48 (71% of participants on DTG vs 64% on RAL had HIV-1 RNA <50 c/mL [adjusted difference, 7.4%; 95% CI, 0.7-14.2]) in treatment-experienced, integrase inhibitor-naive participants (Pts) with HIV-1 who harbored resistance to ≥2 antiretroviral drug classes[1]
- A previous ad hoc analysis in subpopulations of SAILING reported that among participants receiving NRTI-only background regimens, none (0%, 0/32) in the DTG group experienced PDVF through Week 48 compared with 21.9% (7/32) of participants in the RAL group (P=0.005)[2]
- This 10-year follow-up assesses virologic outcomes and viral resistance in this subpopulation receiving DTG plus dual NRTIs through the end of study (EOS)

Methods

- Virologic outcomes were determined by last available on-treatment HIV-1 RNA (VL) through the EOS (up to Week 480)
- PDVF non-response was <1 $\log_{10}$ c/mL decrease by Week 16 unless <400 c/mL or ≥400 c/mL on or after Week 24
- PDVF rebound was ≥400 c/mL after confirmed <400 c/mL or >1 $\log_{10}$ c/mL above nadir of ≥400 c/mL
- Genotyping and phenotyping were performed by Monogram Biosciences on baseline and time of failure samples from participants meeting PDVF criteria
- While 295/357 DTG participants entered the open-label continuation phase post-Week 48, only 126/362 RAL participants continued in the study after completing Week 48 and withdrew more rapidly vs the DTG group, thus they are not included in the analysis
- 29 DTG participants receiving only NRTIs as background regimen (BR) throughout the study were analyzed

Figure 1. Study Design



Results

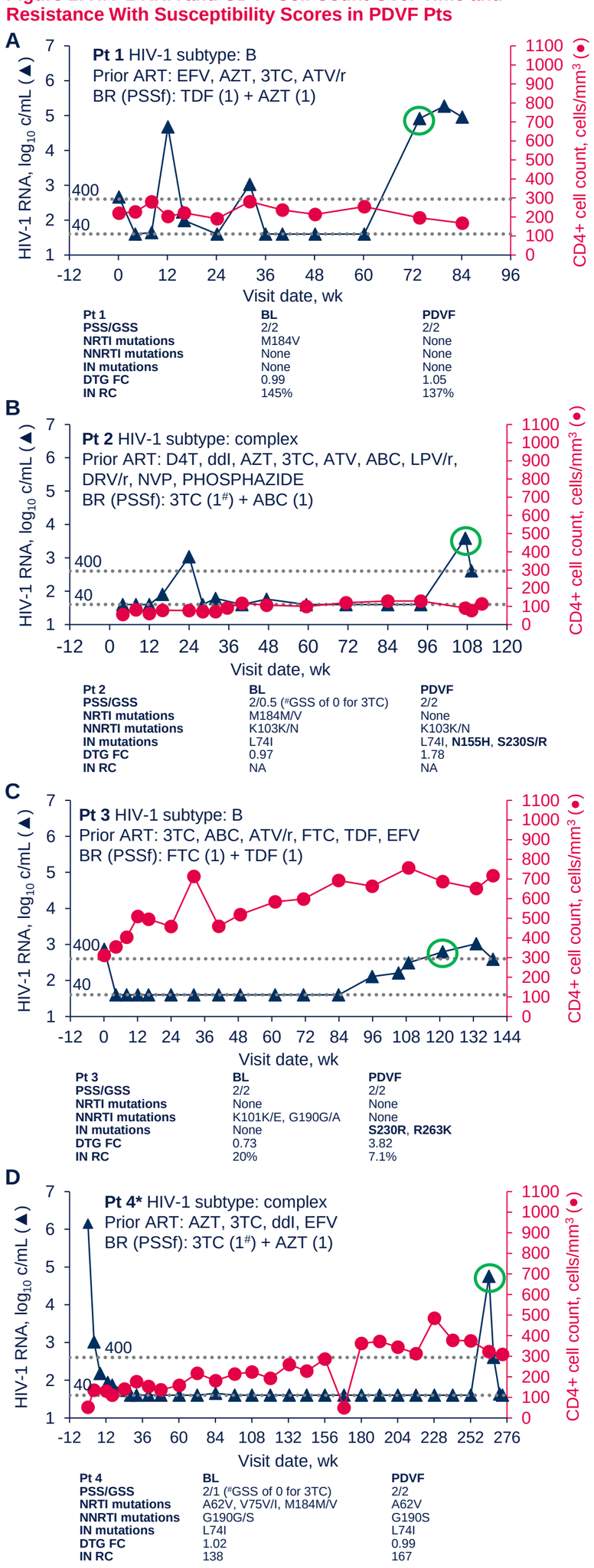
- Compared with overall study response at Week 48,[1] a high rate of virologic response (79%, 23/29) was observed for DTG participants receiving only NRTIs as BR through EOS, even without full backbone activity (Table 1)
  - Of the 28 participants entering the continuation phase, the virologic suppression rate (VL <50 c/mL) remained high (82%, 23/28)

Table 1. Virologic Response in DTG Pts Receiving NRTI-Only Background Regimen Across a 10-Year Follow-up

Participant characteristics	Last on-study VL <50 c/mL	Last on-study VL ≥50 c/mL
Received only NRTIs as BR (n=29[a])	23/29 (79%)	6/29 (21%)
2 fully active[b] (by PSSf)	*14/23 (61%)*	*4/6 (67%)*
1 fully active	*8/23 (35%)*	*1/6 (17%)*
Missing phenotypes	*1/23 (4%)*	*1/6 (17%)*
Baseline M184V receiving 3TC or FTC plus a 2nd NRTI (n=10)	8/10 (80%)	2/10 (20%)
M184V/I alone	*4/8 (50%)*	*2/2 (100%)*
M184V/I + ≥1 NRTI RAM[c]	*4/8 (50%)*	*0*

[a]Total of 32 participants were identified in this population from previous ad hoc analysis; however, 3 didn't have on-treatment VL for virologic outcome assessment, therefore they were excluded from this analysis. [b]Fully active based on phenotype as per Monogram Biosciences' PhenoSense assay using lower cutoff if upper and lower exist. [c]RAM = resistance-associated mutation.

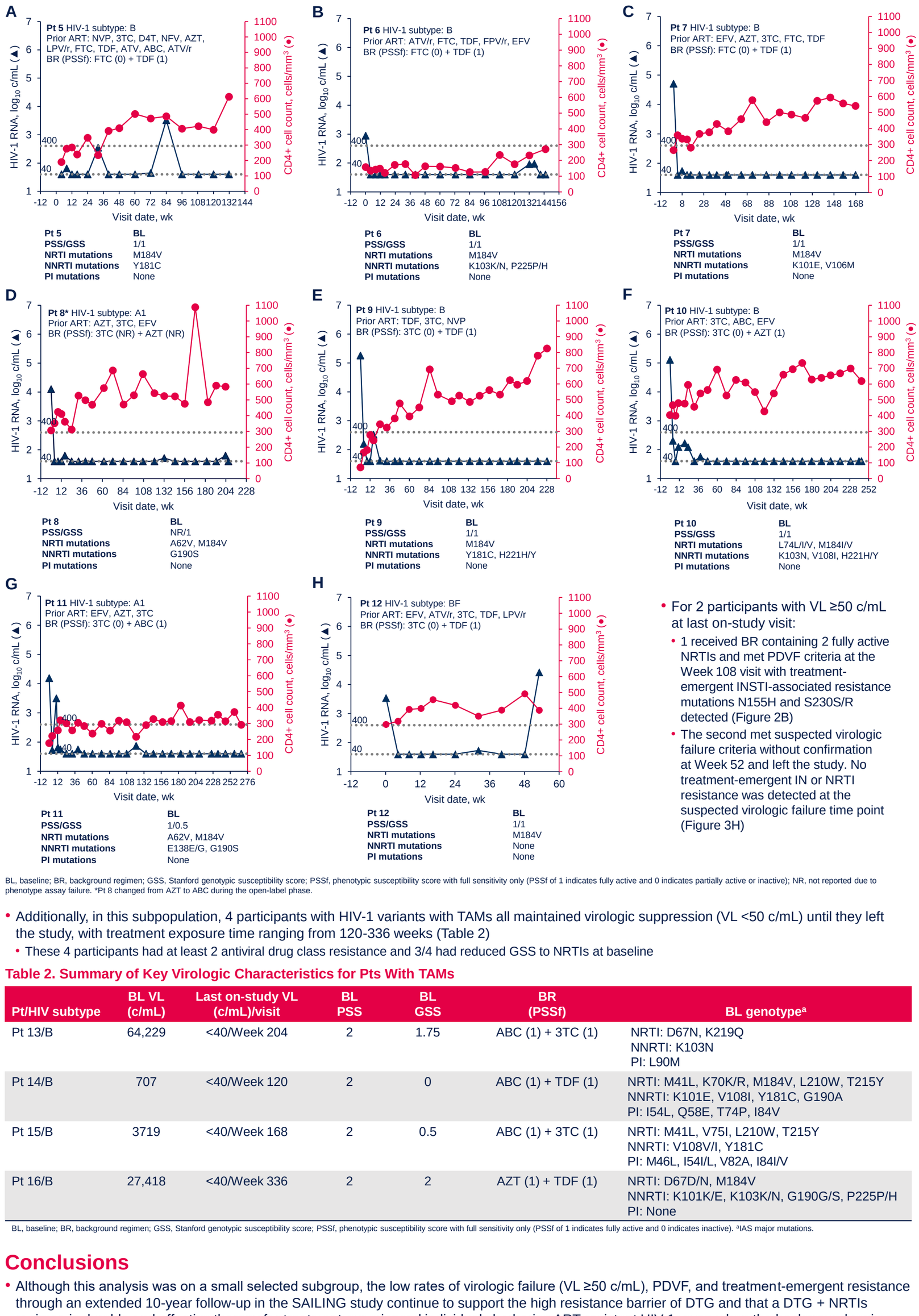
Figure 2. HIV-1 RNA and CD4+ Cell Count Over Time and Resistance With Susceptibility Scores in PDVF Pts



BR, background regimen; GSS, Stanford genotypic susceptibility score; PSS, phenotypic susceptibility score with full sensitivity only (PSS of 1 indicates fully active and 0 indicates partially active or inactive); RC, replication capacity. Green circles around dark blue triangles denote viral load at the week that each PDVF pt had resistance testing done. HIV-1 RNA 400 and 40 c/mL are indicated by dashed gray lines, respectively. *Pt 4 changed from AZT to ABC during the continuation phase.

- PDVF occurred in 4/29 participants with BR consisting of 2 fully active NRTIs. Treatment-emergent IN substitutions were detected in 2 PDVF participants (Figure 2):
  - Pt 4 met PDVF criteria at Week 264 but had plasma VL <50 c/mL subsequently at 2 visits through Week 276 and thus was considered a virologic responder at the last on-treatment study visit (Week 276)
  - Pt 2 had N155H and S230S/R at Week 108; Pt 3 had R263K and S230R at Week 120. Both demonstrated low fold change (FC <4) to DTG
  - None of them developed treatment-emergent NRTI resistance
  - PI mutation was only observed in Pt 1 at baseline with V82V/A
- High virologic response rate (80%, 8/10) was also observed in 10 DTG participants who had baseline M184V and received NRTI-only BR containing either 3TC or FTC along with a second NRTI (Table 1)
- Viral loads and other key virologic information for these 10 participants are shown in Figure 2B and 2D and Figure 3
- 8/10 participants with multiple baseline NRTI and NNRTI major mutations in addition to M184V maintained virologic suppression (VL <50 c/mL) through their last on-study visit (Figure 2D and Figure 3)
  - 6/8 received only 1 fully active NRTI as BR and 1/8 had missing phenotype on the baseline BR assessment
  - The duration of their treatment was 132-276 weeks

Figure 3. Key Virology Data in Non-PDVF Pts Harboring M184V With Background Regimen Containing 3TC or FTC Plus a Second NRTI



- For 2 participants with VL ≥50 c/mL at last on-study visit:
  - 1 received BR containing 2 fully active NRTIs and met PDVF criteria at the Week 108 visit with treatment-emergent INSTI-associated resistance mutations N155H and S230S/R detected (Figure 2B)
  - The second met suspected virologic failure criteria without confirmation at Week 52 and left the study. No treatment-emergent IN or NRTI resistance was detected at the suspected virologic failure time point (Figure 3H)

BL, baseline; BR, background regimen; GSS, Stanford genotypic susceptibility score; PSSf, phenotypic susceptibility score with full sensitivity only (PSSf of 1 indicates fully active and 0 indicates partially active or inactive); NR, not reported due to phenotype assay failure. *Pt 8 changed from AZT to ABC during the open-label phase.

- Additionally, in this subpopulation, 4 participants with HIV-1 variants with TAMs all maintained virologic suppression (VL <50 c/mL) until they left the study, with treatment exposure time ranging from 120-336 weeks (Table 2)
  - These 4 participants had at least 2 antiviral drug class resistance and 3/4 had reduced GSS to NRTIs at baseline

Table 2. Summary of Key Virologic Characteristics for Pts With TAMs

Pt/HIV subtype	BL VL (c/mL)	Last on-study VL (c/mL)/visit	BL PSS	BL GSS	BR (PSSf)	BL genotype[a]
Pt 13/B	64,229	<40/Week 204	2	1.75	ABC (1) + 3TC (1)	NRTI: D67N, K219Q NNRTI: K103N PI: L90M
Pt 14/B	707	<40/Week 120	2	0	ABC (1) + TDF (1)	NRTI: M41L, K70K/R, M184V, L210W, T215Y NNRTI: K101E, V108I, Y181C, G190A PI: I54L, Q58E, T74P, I84V
Pt 15/B	3719	<40/Week 168	2	0.5	ABC (1) + 3TC (1)	NRTI: M41L, V75I, L210W, T215Y NNRTI: V108V/I, Y181C PI: M46L, I54I/L, V82A, I84I/V
Pt 16/B	27,418	<40/Week 336	2	2	AZT (1) + TDF (1)	NRTI: D67D/N, M184V NNRTI: K101K/E, K103K/N, G190G/S, P225P/H PI: None

BL, baseline; BR, background regimen; GSS, Stanford genotypic susceptibility score; PSSf, phenotypic susceptibility score with full sensitivity only (PSSf of 1 indicates fully active and 0 indicates inactive). [a]IAS major mutations.

Conclusions

- Although this analysis was on a small selected subgroup, the low rates of virologic failure (VL ≥50 c/mL), PDVF, and treatment-emergent resistance through an extended 10-year follow-up in the SAILING study continue to support the high resistance barrier of DTG and that a DTG + NRTIs regimen is durable and effective therapy for treatment-experienced individuals harboring ART-resistant HIV-1, even when the background regimen had suboptimal activity.

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References: 1. Cahn et al. *Lancet*. 2013;382:700-708. **2.** Demarest et al. *AIDS Res Hum Retroviruses*. 2018;34:343-346.

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