High Level of Pre-existing NRTI Resistance Prior to Switching to B/F/TAF

Study GS-US-380-4030

Rima Acosta[1], Madeleine Willkom[1], Kristen Andreatta[1], Hui Liu[1], Ross Martin[1], Silvia Chang[1], Hal Martin[1], Sean Collins[1], Leena Sathia[2], and Kirsten L. White[1]

1. Gilead Sciences, Inc., Foster City, California, USA
2. Gilead Sciences, Ltd., London, UK

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Introduction

- Treatment guidelines recommend triple therapy with INSTIs including B/F/TAF and DTG + F/TAF as preferred initial regimens (EACS, DHHS, IAS-USA)
- Newer INSTIs (Dolutegravir, Bictegravir): potent, well tolerated, OD dosing, no food requirement, few drug-drug interactions
- Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) is approved for the treatment of HIV-1 infection (treatment-naïve and virologically suppressed without resistance)[1,2]
- B/F/TAF safety, efficacy, and lack of emergent resistance have been demonstrated in controlled clinical trials [3-10]

DTG, dolutegravir; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; INSTI, Integrase Strand Transfer Inhibitor; OD, once daily

1. Bictegravir, emtricitabine, and tenofovir alafenamide Tablets for Oral Use Prescribing Information. Gilead Sciences, Initial US Approval 2018. 2. B/F/TAF: EPAR – Product Information. European Medicines Association, 2018. 3. Gallant J, et al., *The Lancet* (2017) 390(10107): 2063-2072. 4. Sax PE, et al., *The Lancet* (2017) 390(10107): 2073-2082. 5. Wohl D, et al., ID Week (2018) Presentation #74246. 6. Stellbrink HJ, et al., HIV Glasgow (2018) Presentation #4185960. 7. Daar ES, et al., *The Lancet HIV* (2018) 5(7): e347-e356. 8. Molina JM, et al., *The Lancet HIV* (2018) 5(7): e357-e365. 9. Kityo C, et al., CROI (2018) Presentation #500. 10. Gaur AH, et al., CROI (2019) Presentation #46

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Does switching from DTG + F/TAF or F/TDF to the single tablet regimen B/F/TAF provide comparable virologic control in patients with or without pre-existing resistance?

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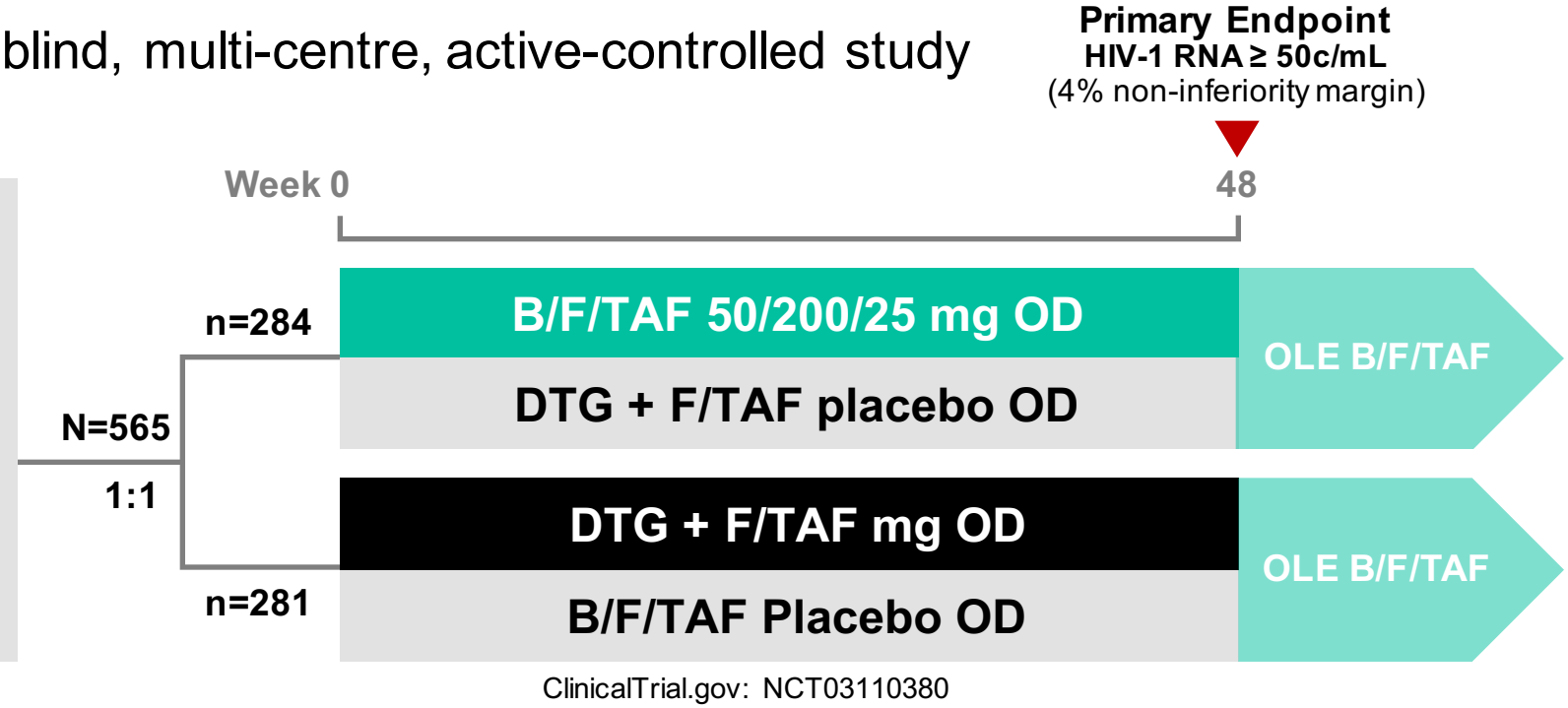
Study 380-4030: Design

- Phase 3, randomised, double-blind, multi-centre, active-controlled study

HIV-suppressed adults on regimen containing DTG + F/TAF or F/TDF

- HIV-1 RNA <50 copies/mL for ≥ 3 or 6 months*
- No documented INSTI resistance or virological failure on INSTI containing regimen

*6 months if known NRTI resistance



ClinicalTrial.gov: NCT03110380

NRTI-R	allowed
NNRTI-R	allowed
PI-R	allowed
INSTI-R	excluded

B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; DTG, dolutegravir; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; INSTI, Integrase Strand Transfer Inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-NRTI; OD, once daily; OLE open label extension; PI, protease inhibitor; R, resistance

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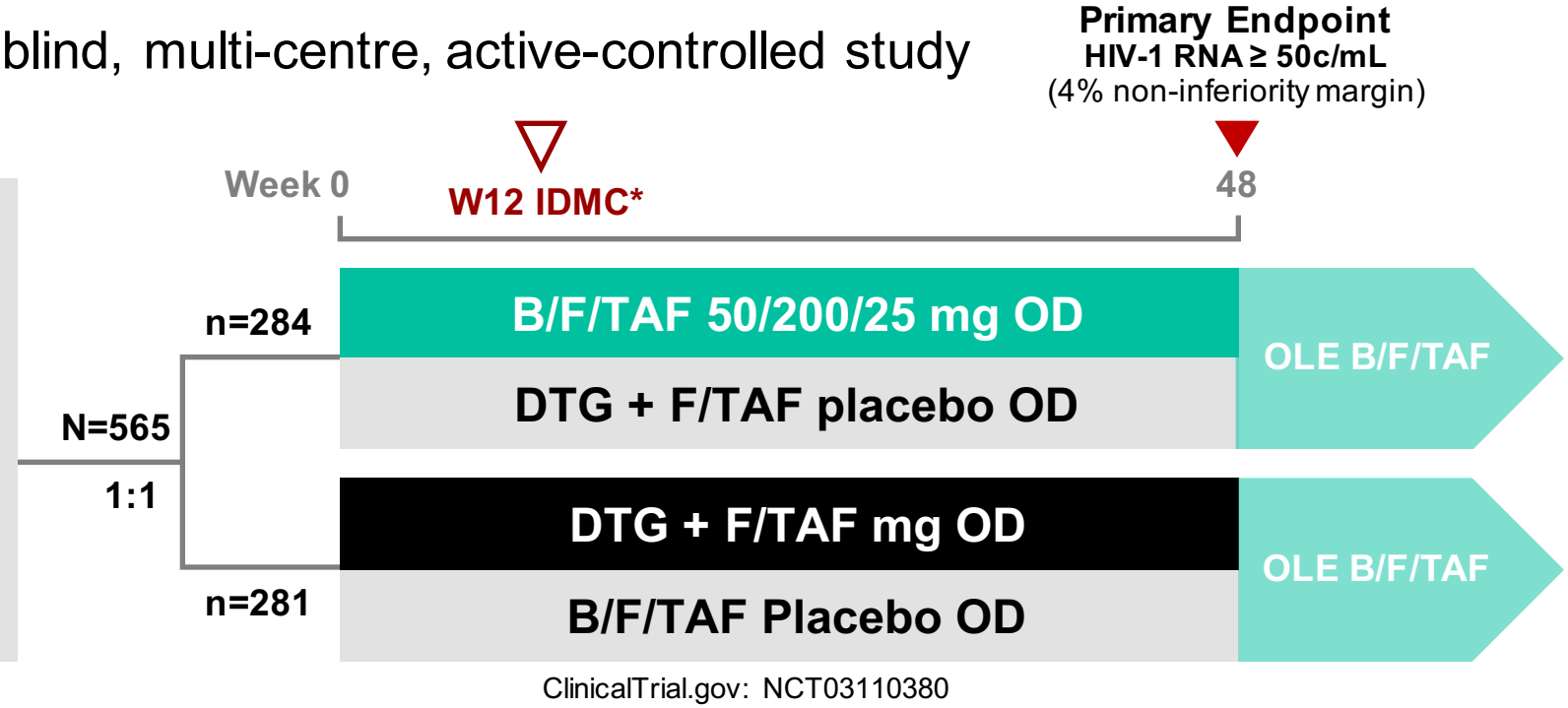

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Randomisation stratified by:
- F/TAF vs F/TDF at baseline
- Documented or suspected history of NRTI resistance

* Pre-specified Analysis by the IDMC, Independent Data Monitoring Committee

Methods: Baseline NRTI resistance categories

- At randomisation, the Investigator assigned the resistance category based upon HIV-1 historical genotype if available, and antiretroviral treatment history for “suspected” resistance
- NRTI resistance was stratified into 3 categories. For participants that qualified for more than one resistance category, stratification was prioritised by category 1, then 2, then 3:

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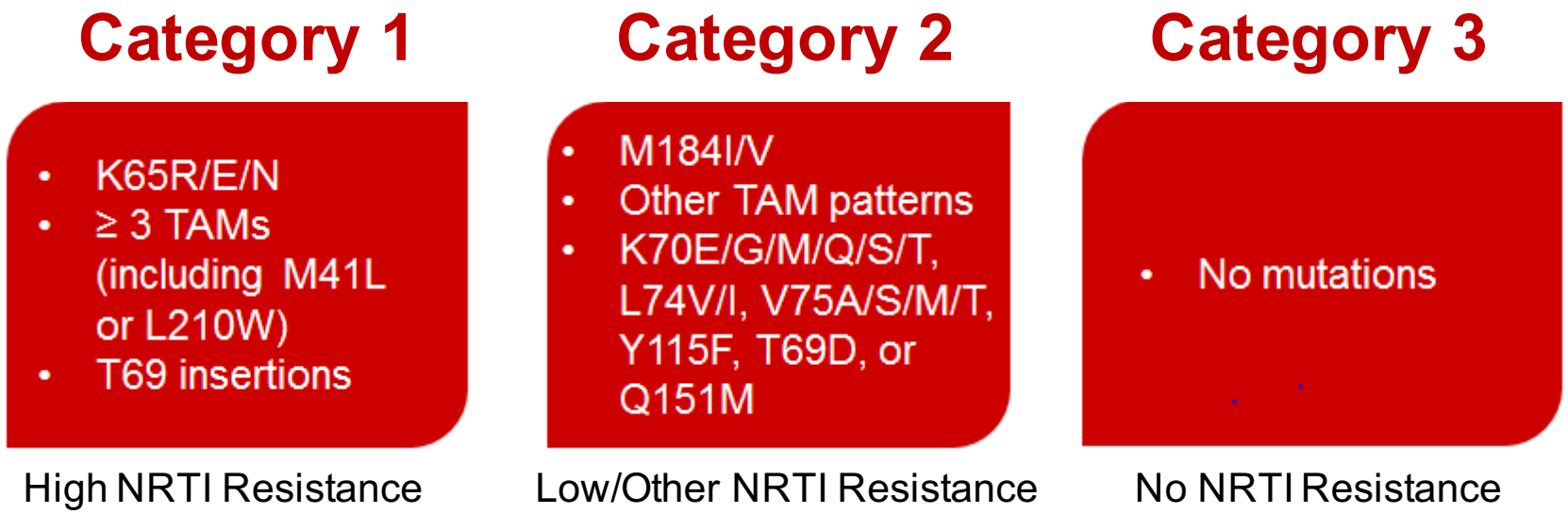

TAMs are M41L, D67N, K70R, L210W, T215F/Y, and K219Q/E/R/N

Methods

- Final resistance categories were assigned post-randomisation, based on:
  - historical data
  - Investigator suspicion of resistance
  - baseline genotyping using proviral HIV-1 DNA genotype*
- Randomisation assignments remained blinded
- Here we present baseline resistance analyses and blinded virological outcome data at the Week 12 IDMC data cut

*GenoSure Archive assay, Monogram Biosciences
IDMC, Independent Data Monitoring Committee

Results: Demographics

	B/F/TAF or DTG + F/TAF (N=565)
Median age, years (range)	51 (20-79)
Male, %	86
Black or African Race, %	23
Hispanic/Latino Ethnicity, %	20
Median CD4 cell count, cells/μL (IQR)	646 (474,830)
HIV-1 RNA < 50 copies/mL at baseline	98%
Median $eGFR_{CG}$, mL/min (IQR)	99 (81,119)
NRTIs at baseline	
F/TAF, %	69
F/TDF, %	31

$eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault; IQR, interquartile range.

Results: Baseline Genotypic Data Sources

Historical Genotype
HIV-1 RNA ≥400 c/mL

50% (285/565)

+

Proviral DNA
HIV-1 RNA <50 c/mL

69% (391/565)

=

Any Genotype

83% (470/565)

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Category	NRTI Mutation	Initial Categorisation by Investigators n (%)	Final Categorisation n (%)
1	K65R/E/N or ≥ 3 TAMs	15 (3%)	30 (**5%**)
2	Any Other Pattern	63 (11%)	108 (**19%**)
3	No NRTI Mutation	487 (86%)	427 (**76%**)

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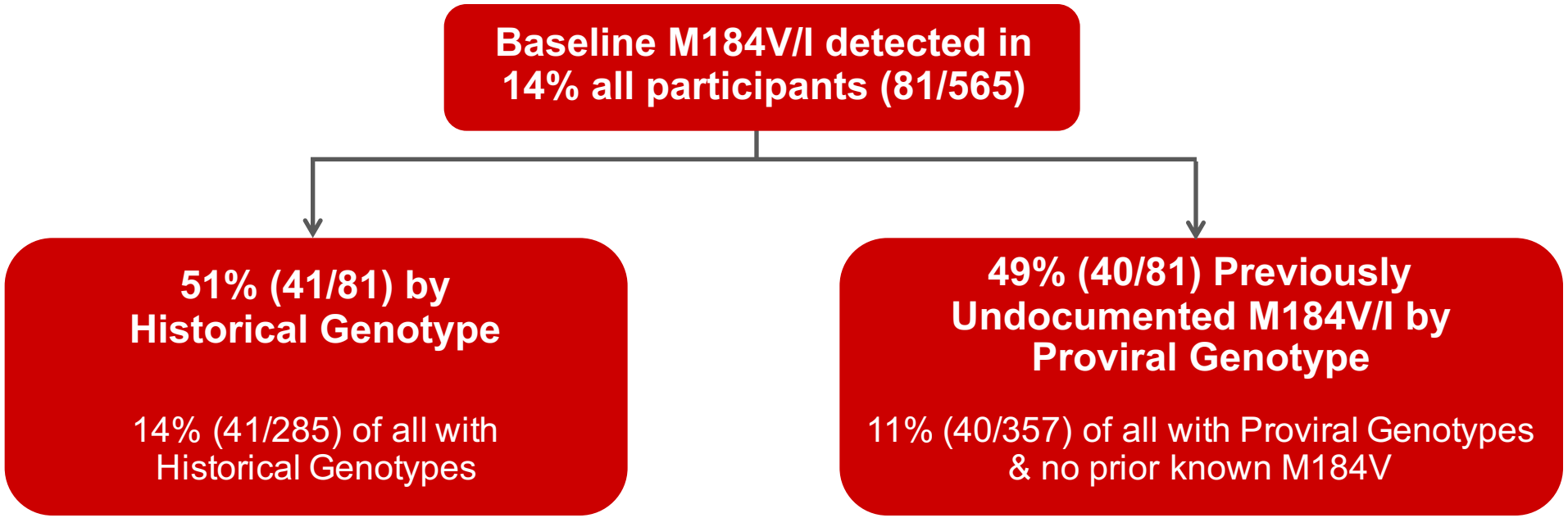
3	No NRTI Mutation	487 (86%)	427 (**76%**)
Additional Resistance Analysis Sets			
Any PI, NRTI, NNRTI, INSTI Resistance Mutation			222 (**39%**)
Any NRTI-R			138 (24%)
M184V/I (from Category 1 or 2)			81 (**14%**)
Any NNRTI-R			118 (21%)
Any PI-R			38 (7%)
Any INSTI-R			20 (4%)

M184V or M184I cause resistance to FTC and 3TC; the INSTI-R isolates are sensitive to BIC

Results: Detection of M184V/I in Baseline Genotypic Data



34/41 participants had both historical and Proviral genotypes

- 50% (17/34) of historical M184V/I was missed by Proviral
- 50% (17/34) of historical M184V/I was confirmed by Proviral

- 25% (10/40) had historical WT M184M but M184V/I found by Proviral
- 75% (30/40) found by Proviral in absence of historical data

HIV-1 RNA < 50 c/mL at Week 12 IDMC (Blinded) by Resistance Category

Category	NRTI Mutation	Baseline Drug Resistance (N=565)	Virologic Suppression (N=562)[a]
Final NRTI resistance category			
1. K65R/E/N or ≥ 3 TAMs		30 (**5%**)	**97%** (29/30)
2. Any Other Pattern		108 (**19%**)	**99%** (107/108)
3. No NRTI Mutation		427 (**76%**)	**99%** (421/424)
Additional Resistance Analysis Sets			
Any PI, NRTI, NNRTI, INSTI Resistance Mutation		222 (**39%**)	**99%** (220/222)
Any NRTI-R		138 (**24%**)	**99%** (136/138)
	M184V/I (from Category 1 or 2)	81 (**14%**)	**98%** (79/81)
Any NNRTI-R		118 (**21%**)	**99%** (117/118)
Any PI-R		38 (**7%**)	**97%** (37/38)
Any INSTI-R		20 (**4%**)	**100%** (20/20)

a. 3 participants from resistance category 3 had no post-baseline on-treatment data and were not included in the efficacy analysis

- High rates of virologic suppression maintained with switches to BFTAF or DTG + F/TAF through Week 12

Week 12 IDMC (Blinded) Resistance Analysis of Virologic Failures

	B/F/TAF or DTG + F/TAF (N=565)
Resistance analysis population	2[a]
Emergent resistance	0

Resistance analysis population was any participant with a confirmed viral rebound of HIV-1 RNA ≥ 50 copies per mL, with the confirmatory HIV-1 RNA ≥ 200 copies/mL through the Week 12 IDMC data cut, or without confirmation if at the last visit, who did not resuppress while on study drug.

a. Both participants were from resistance category 3, with no NRTI-R, NNRTI-R, PI-R, or INSTI-R detected at baseline or virologic failure

Association of M184V/I with Other Primary Resistance Mutations

	Percent of Participants (n/N)	
	Participants with Baseline M184V/I n=81	**HIV-1 RNA <50 c/mL at Week 12 IDMC (Blinded)**
M184V/I alone	**26% (21/81)**	**95% (20/21)[a]**
M184V/I + ≥ 1 primary resistance substitution	**74% (60/81)**	**98% (59/60)[b]**
M184V/I + PI-R	20% (16/81)	94% (15/16)
M184V/I + NNRTI-R	51% (41/81)	98% (40/41)
M184V/I + other NRTI-R	51% (41/81)	98% (40/41)
M184V/I + TAMs	42% (34/81)	97% (33/34)
M184V/I + primary INSTI-R	6% (5/81)	100% (5/5)

Two patients had virologic failure at Week 24, but neither met the protocol defined criteria for genotyping (HIV-1 RNA ≥ 200 c/mL)

a. One participant with M184V alone had a viral load of 120 c/mL and later resuppressed
b. One participant with M184I and M41L, L210W, and T215Y NRTI-R mutations; K101E, V106A, Y181C, and G190A NNRTI-R mutations; and D30N and L90M PI-R mutations had a viral load of 59 c/mL and later resuppressed

Summary

- **Resistance observed:**
  - Primary drug resistance to any class was present in 39% of participants
  - 14% had NRTI resistance known or suspected at screening, which increased to 24% using historical data and additional baseline proviral HIV-1 DNA genotyping
    - M184V/I was present in 14% of participants
  - Other studies using proviral DNA genotyping have also reported previously undocumented M184V/I[12] and missed documented M184V/I in ~50% of cases[13]

- **Virological efficacy maintained (blinded), with no emergent drug resistance:**
  - 99% of the 562 participants in the study maintained suppression
  - 99% of the 222 participants with any drug resistance maintained suppression
  - 98% of the 81 participants with M184V/I maintained suppression

12. Andreatta K, et al., HIV Glasgow (2018) Presentation #P298 13. Perez-Valero I, et al., IAC (2018) Presentation #TUAB0104.

Conclusions

- High levels of NRTI resistance may be seen in virologically suppressed patients
- Proviral DNA assays may provide valuable additional genotypic data
- HIV-1 RNA suppression was maintained with B/F/TAF or DTG + F/TAF through this blinded, preliminary Week 12 IDMC data cut in suppressed patients with pre-existing NRTI resistance including M184V/I
- 48 Week outcomes will be presented later this year
  - efficacy, safety, tolerability, PROs

Acknowledgements

- The individuals who participated in Study GS-US-380-4030
- The study site investigators and research teams
- Gilead study team (particularly Rima Acosta, Kirsten White, Sean Collins, and Neal Marshall)