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Achievement of Undetectable HIV-1 RNA in the B/F/TAF Treatment-Naïve Clinical Trials

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Introduction

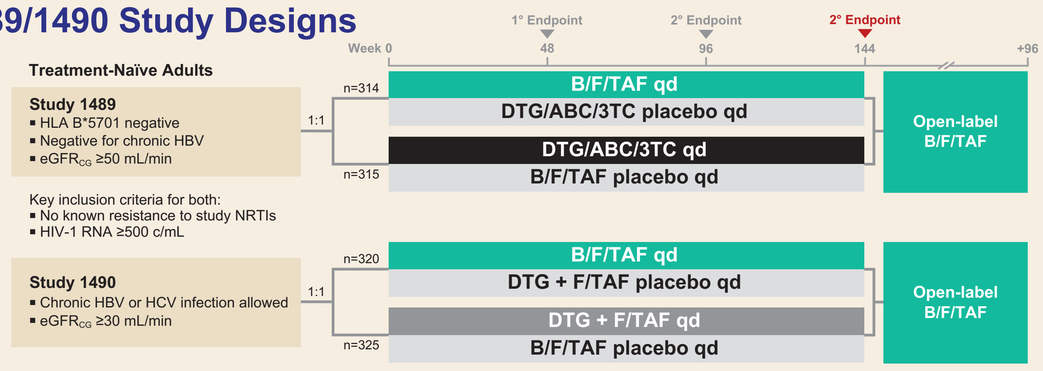
- The single-tablet regimen bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) is a guidelines-recommended regimen with demonstrated safety, efficacy, and a high barrier to resistance[1-5]
- Studies 1489 (ClinicalTrials.gov NCT02607930) and 1490 (NCT02607956) are two Phase 3 studies of B/F/TAF compared with dolutegravir (DTG)–containing regimens in treatment-naïve adults
  - B/F/TAF was noninferior to DTG/abacavir (ABC)/lamivudine (3TC) and DTG + F/TAF through 144 wk of treatment[6]
  - Ongoing open-label extensions are evaluating treatment with B/F/TAF for an additional 96 wk since completion of the blinded phase, encompassing a total of 5 y of follow-up[7]
- HIV-1 viral loads that are <50 copies (c)/mL, but still detectable, may be associated with virologic rebound[8]
  - In Studies 1489 and 1490, participants' viral loads were measured using the COBAS® TaqMan® HIV-1 Test, version 2 (Roche Diagnostics International AG, Rotkreuz, Switzerland), which quantitates HIV-1 RNA from 20 to 10,000,000 c/mL and for viral load <20 c/mL provides semiqualitative target detected (TD) or the lower target not detected (TND) results

Objectives

- To assess achievement of undetectable (TND) HIV-1 RNA in Studies 1489 and 1490, and understand potential predictors of TND achievement

Methods

1489/1490 Study Designs



eGFR$_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault equation; HBV, hepatitis B virus; HCV, hepatitis C virus; HLA, human leukocyte antigen; NRTIs, nucleoside reverse transcriptase inhibitors.

- Participants with ≥1 on-treatment postbaseline viral load value had treatment efficacy assessed by missing=excluded imputation at each study visit using a range of viral load endpoints through Week 144
- Associations with consistent TND were studied using a multivariate logistic regression analysis
  - Consistent TND: a defined percentage of visits between Weeks 48 and 144 that had viral load <20 c/mL TND for all HIV-1 RNA results collected
  - Intrinsic predictors: age group, sex, race, ethnicity, body mass index (BMI), and sexual orientation
  - HIV-specific variables: baseline CD4 count, baseline HIV-1 RNA, HIV disease status, adherence, and resistance at baseline by antiretroviral class to integrase strand transfer inhibitors (INSTIs), NRTIs, non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs)

Results

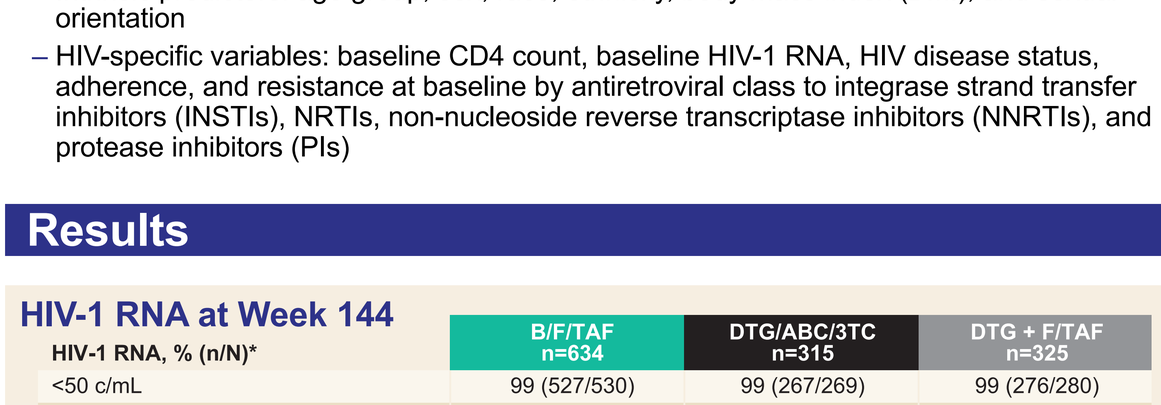
HIV-1 RNA at Week 144

HIV-1 RNA, % (n/N)*	B/F/TAF n=634	DTG/ABC/3TC n=315	DTG + F/TAF n=325
<50 c/mL	99 (527/530)	99 (267/269)	99 (276/280)
<20 c/mL	95 (501/530)	97 (260/269)	93 (260/280)
TD	23 (123/530)	23 (62/269)	21 (59/280)
TND	**71 (378/530)**	**74 (198/269)**	**72 (201/280)**

*Missing=excluded. TD, target detected; TND, target not detected.

- At Week 144, 99% of participants in the B/F/TAF, DTG/ABC/3TC, and DTG + F/TAF groups had HIV-1 RNA <50 c/mL
  - The percentages of participants with HIV-1 RNA <20 c/mL TND for each group were 71% for B/F/TAF, 74% for DTG/ABC/3TC, and 72% for DTG + F/TAF, and were not statistically different (p=0.5: B/F/TAF vs DTG/ABC/3TC; p=0.9: B/F/TAF vs DTG + F/TAF)

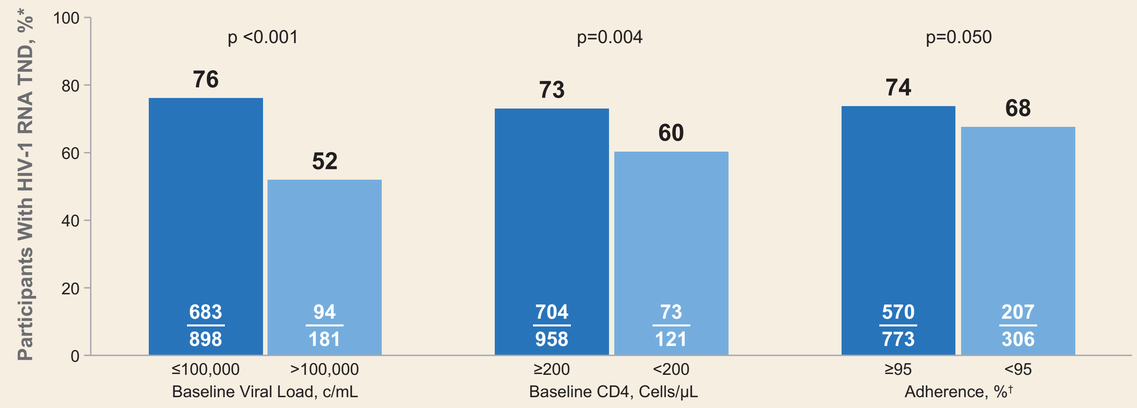
Longitudinal Analysis of HIV-1 RNA TND



*Missing=excluded.

- TND was rapidly achieved and maintained for participants treated with B/F/TAF, DTG/ABC/3TC, or DTG + F/TAF at all visit windows through Week 144

Achievement of TND at Week 144: Pooled Treatment Groups



*Missing=excluded; p-values calculated by Fisher exact test; †Adherence measured by pill count based on pills returned.

- TND was achieved at Week 144 in 777/1079 total participants (72%) who had HIV-1 RNA data at Week 144 in these studies
- TND achievement at Week 144 was higher for participants with baseline HIV-1 RNA ≤100,000 c/mL, baseline CD4 ≥200 cells/µL, and adherence by pill count ≥95%

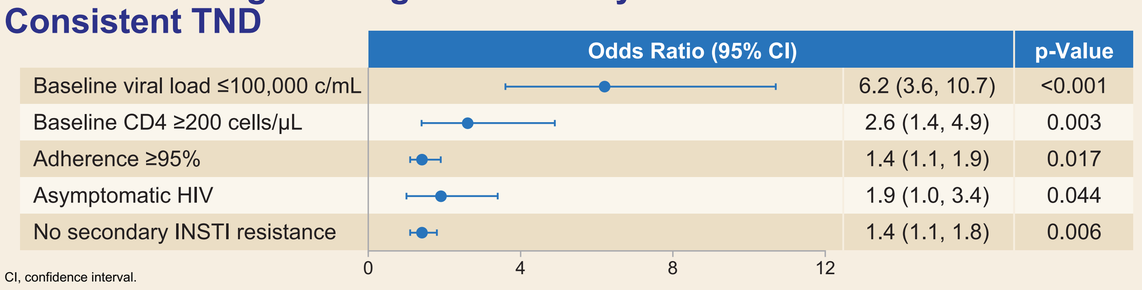
Achievement of Consistent TND Between Weeks 48 and 144, and Association With Baseline HIV-1 RNA and CD4 Count*

TND, %	B/F/TAF (n=591), % (n)	DTG/ABC/3TC (n=302), % (n)	DTG + F/TAF (n=308), % (n)	Overall (n=1201), % (n)	Overall: Median Baseline Viral Load, c/mL (Q1; Q3) [min; max]	Overall: Median Baseline CD4, Cells/µL (Q1; Q3) [min; max]
100	18 (108)	17 (52)	17 (53)	18 (213)	8680 (2940; 21,300) [19; 285,000]	535 (408; 717) [13; 1458]
≥95	18 (108)	17 (52)	17 (53)	18 (213)	8680 (2940; 21,300) [19; 285,000]	535 (408; 717) [13; 1458]
≥90	19 (111)	18 (54)	18 (55)	18 (220)	9060 (2995; 21,200) [19; 285,000]	530 (403; 715) [13; 1458]
≥85	33 (197)	30 (89)	35 (109)	33 (395)	11,100 (3590; 25,200) [19; 285,000]	492 (386; 688) [2; 1458]
≥80	35 (205)	32 (95)	37 (113)	34 (413)	11,500 (3610; 25,600) [19; 285,000]	492 (386; 682) [0; 1458]
≥75	48 (285)	47 (142)	50 (152)	48 (579)	15,100 (4840; 33,800) [19; 285,000]	480 (373; 655) [0; 1636]

*There were 9 scheduled visits between Weeks 48 and 144 at Weeks 48, 60, 72, 84, 96, 108, 120, 132, and 144; additional unscheduled visits were included in analysis. max, maximum; min, minimum; Q, quartile.

- 100% consistent TND at all visits at or after Week 48 (median 9 visits) was achieved in 17–18% of participants in each treatment group
  - ≥85% consistent TND (roughly 8/9 visits over 2 y) was achieved in 30–35% of participants and was used in the multivariate model
  - Less stringent consistent TND (TND at ≥75% of visits after Week 48) was achieved in 47–50% of participants
- The highest percentages of consistent TND were associated with lower baseline viral load and higher CD4 count

Multivariate Logistic Regression Analysis for Factors Associated With Consistent TND



CI, confidence interval.

- Further analyses sought to better understand achievement of ≥85% consistent TND, which would require ≥8/9 scheduled visits between Weeks 48 and 144 to have TND
- Independent associations for 85% consistent TND included baseline viral load ≤100,000 c/mL, baseline CD4 ≥200 cells/µL, ≥95% adherence by pill count through Week 144, asymptomatic HIV status, and no secondary INSTI resistance substitutions
- 85% consistent TND was achieved for:
  - 38% (380/996) vs 7% (15/205) of participants with baseline viral load ≤ vs >100,000 c/mL
  - 36% (381/1066) vs 10% (14/135) of participants with baseline CD4 ≥ vs <200 cells/µL

Restrictive Study Inclusion Criteria May Maximize Consistent TND

- Using Studies 1489 and 1490 as models, we sought to define study inclusion criteria that may maximize the potential to achieve ≥85% consistent TND
  - Could have potential for establishing cohorts with low viral burden for future cure studies
  - A subanalysis of participants with baseline HIV-1 RNA ≤11,100 c/mL and CD4 ≥492 cells/µL (median baseline viral load and CD4 count for those who achieved ≥85% TND at Week 144) was conducted for Studies 1489 and 1490
  - The percentages of participants who satisfied these restrictive study inclusion criteria and achieved ≥85% TND were evaluated

	Participants With ≥85% Consistent TND from Weeks 48 to 144, n/N (%)
Study 1489	56/94 (60)
Study 1490	68/103 (66)
Total	124/197 (63)

- The inclusion criteria doubled the percentage of participants who achieved ≥85% consistent TND between Weeks 48 and 144 from 33% to 63%

Conclusions

- Treatment with B/F/TAF, DTG/ABC/3TC, and DTG + F/TAF achieved HIV-1 viral loads <20 c/mL TND in 71–74% of participants at Week 144
  - Achievement of TND at Week 144 was associated with baseline HIV-1 RNA ≤100,000 c/mL, baseline CD4 ≥200 cells/µL, and ≥95% adherence by pill count; therefore, TND outcomes were influenced by study populations and study entry criteria
- Consistent TND at ≥85% of visits between Weeks 48 and 144 was associated with several factors, including lower baseline viral load, higher baseline CD4 counts, and high adherence
- These data can be used to design studies with enhanced frequency of TND outcomes, which could aid HIV cure research

References: **1.** Biktarvy [EPAR]. Foster City, CA: Gilead Sciences, Inc., 6/18; **2.** Biktarvy [package insert]. Foster City, CA: Gilead Sciences, Inc., 6/19; **3.** Dept of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV, 12/19; **4.** EACS European AIDS Clinical Society Guidelines Version 10.0, 11/19; **5.** Saag MS, et al. JAMA 2020;324:1651-69; **6.** Orkin C, et al. Lancet HIV 2020;7:e389-400; **7.** Workowski K, et al. CROI 2021, abstr 2268; **8.** Doyle T, et al. Clin Infect Dis 2012;54:724-32. **Acknowledgments:** We extend our thanks to the participants, their families, study investigators, and staff. These studies were funded by Gilead Sciences, Inc.

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