Unreturned Pill Bottles in the 1489 and 1490 Clinical Trials: An Important Measure of Poor Adherence That Is Often Ignored in Pill Count Calculations

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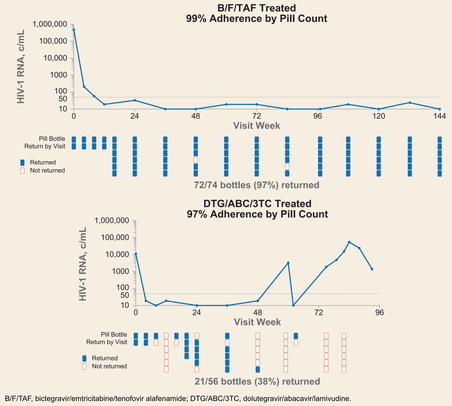
Introduction

- Adherence to antiretroviral therapy is important for HIV viral suppression
  - Durable viral suppression prevents emergence of drug resistance, improves HIV morbidity and mortality outcomes, and prevents transmission of HIV to others[1,2]
- There are several methods to assess medication adherence, all with advantages and limitations[3]:
  - Self-reported adherence
  - Prescription refill records
  - Pill count
- Most HIV clinical trials use pill count to measure participants' adherence
  - Limitations include:
    - Missing pills are not necessarily pills that were taken
    - Adherence pattern cannot be determined (eg, missing drug on consecutive days vs 1 missed dose/wk)
    - Adherence by pill count cannot assess causes of poor adherence (illness, vacation, busy, and other)
    - Pill count calculations do not include unreturned pill bottles

Figure 1. HIV-1 Viral Loads of 2 Participants With ≥95% Adherence by Pill Count Through Week 144



B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine.

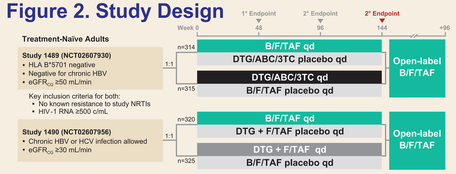
- Virologic suppression with ≥95% adherence by pill count can differ for individuals with unreturned pill bottles (Fig 1)
  - Virologic failure without resistance and multiple unreturned pill bottles suggests that poor adherence led to the failure

Objective

- To understand the relationship between unreturned pill bottles as a measure of poor adherence and the overall effect on virologic success

Methods

Figure 2. Study Design



eGFRCG, 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.

- **Studies 1489 and 1490:** Phase 3 studies of B/F/TAF compared with DTG-containing regimens in treatment-naïve studies; B/F/TAF was noninferior for efficacy to DTG/ABC/3TC and DTG + F/TAF through 144 wk of treatment (Fig 2)[4]
  - Participants with HIV-1 RNA <50 c/mL by FDA Snapshot at Week 144: 82% for B/F/TAF, 84% for DTG/ABC/3TC, and 84% for DTG + F/TAF
- **Study drug regimen adherence:** adherence (%) of study drug regimen through 144 wk was calculated as:

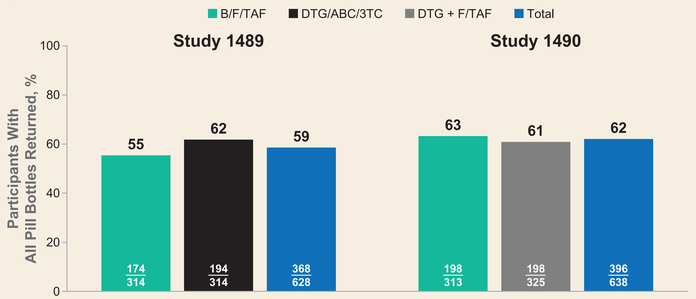
$$\text{Adherence (\%)} = 100 \times \frac{\text{Total no. of pills taken}}{\text{Total no. of pills prescribed}}$$

$$= 100 \times \frac{\sum \text{No. of pills taken at each dispensing period}}{\sum \text{No. of pills prescribed at each dispensing period}}$$

  - If any study drug bottle was not returned, all records in that dispensing period for that study drug were excluded from the calculation
- **Adherence by pill count and FDA Snapshot outcome in Studies 1489 and 1490:** median adherence in Studies 1489 and 1490 was ≥95%[4]
  - Participants with HIV-1 RNA <50 c/mL by FDA Snapshot at Week 144: 88% for those with calculated adherence ≥95% vs 74% with adherence <95%
- **Virologic events through Week 144:** included last on-treatment observation carried forward (LOCF) outcome through Week 144, inclusion in the resistance analysis population, and blip occurrence
  - Resistance analysis population included participants with confirmed HIV-1 RNA ≥200 c/mL or ≥200 c/mL at last visit, with no resuppression of HIV-1 RNA to <50 c/mL while on study drug
  - Viral blips were defined as HIV-1 RNA ≥50 c/mL preceded and followed by HIV-1 RNA <50 c/mL after achieving confirmed suppression (2 consecutive HIV-1 RNA <50 c/mL)
- **Pill bottle return category:** defined as all bottles returned or ≥1 bottle unreturned (including both study drug and placebo bottles) and calculated for all participants; association of bottle return category with virologic events through Week 144 was determined by Fisher exact test
- **Pill bottle return rate:** calculated for all participants; association of bottle return rate with virologic events through Week 144 was determined by Wilcoxon rank-sum test

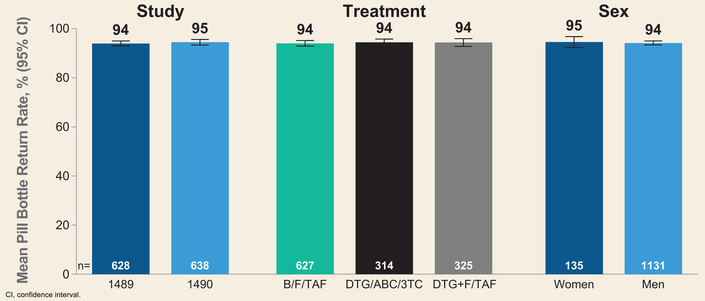
Results

Figure 3. Participants With All Pill Bottles Returned Through Week 144



- In these studies, 60% (764/1266) of participants returned all their pill bottles through Week 144; if 1 visit with ≥1 unreturned bottle was allowed, this percentage increased to 81% (Fig 3)

Figure 4. Pill Bottle Return Rates

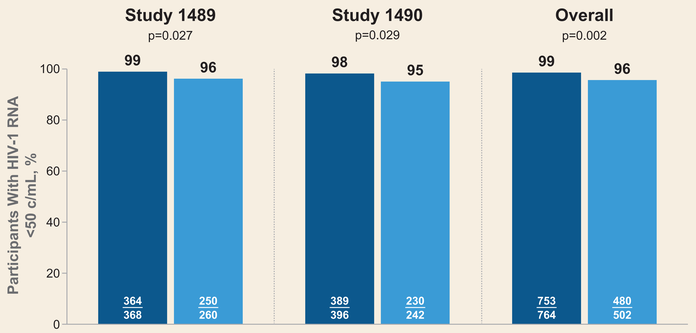


CI, confidence interval.

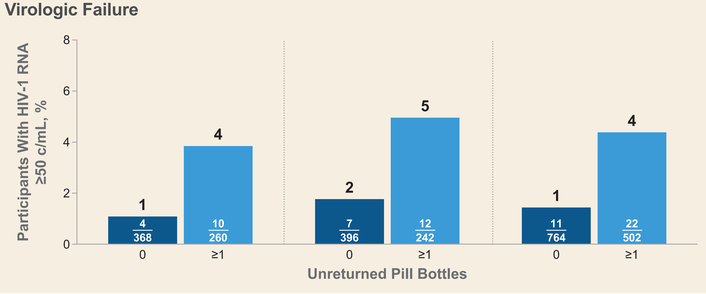
- Mean bottle return rate was 94% and did not differ by study, treatment arm, or sex (Fig 4)

Figure 5. LOCF Outcome at Week 144 by Pill Bottle Return Category

Virologic Suppression

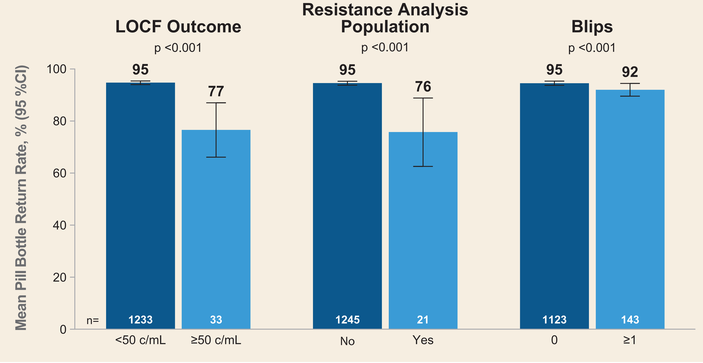


Virologic Failure



- Failure to return pill bottles was associated with lower suppression rates at last visit (Fig 5)

Figure 6. Virologic Events Through Week 144 and Average Pill Bottle Return Rate



- There was a significant association between different virologic events through 144 wk and fewer pill bottles returned (Fig 6)

Conclusions

- In these HIV-1 treatment-naïve clinical trials of integrase strand transfer inhibitor–based regimens, failure to return pill bottles was associated with lower HIV-1 RNA suppression rates
- Although the calculated adherence rates in these studies were relatively high (median ≥95%), these calculations did not account for unreturned pill bottles
- The results show that assessing adherence by both pill count and pill bottle return provides a more complete picture of adherence in HIV-1 clinical trials

References: 1. Bangsberg DR, et al. AIDS 2006;20:223-31; 2. Nachega JB, et al. Ann Intern Med 2007;146:564-73; 3. Lam WY, et al. Biomed Res Int 2015;2015:217047; 4. Orkin C, et al. Lancet HIV 2020;7:e389-e400.
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