

# Incidence and Prevalence of Diarrhea in HIV Clinical Trials in the Recent Post-cART Era: Analysis of Data From 38 Clinical Trials From 2008-2017 in Over 21,000 Patients

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## BACKGROUND:

- There is a general perception that gastrointestinal (GI) manifestations of HIV infection have declined over time, particularly with the introduction of cART
- While gastrointestinal opportunistic infections such as CMV and cryptosporidium are very rare manifestations of HIV disease in the post-cART era, patients will report multiple loose stools per day with significant urgency, bloating, and unwanted disruptions to their quality of life if queried directly about stool frequency<sup>1</sup>
- A 2014 survey conducted in a matched cohort of HIV subjects and their healthcare providers revealed that approximately 20% of subjects reported diarrhea/loose stools at the time of their visit<sup>2</sup>
- Studies have demonstrated that there is incomplete immune reconstitution of the GI mucosa, even with early intervention with cART<sup>3-6</sup>
- To examine whether the rate of HIV-associated diarrhea has changed over time, we interrogated the publicly available National Institutes of Health (NIH) database of clinicaltrials.gov for the reported frequency of diarrhea in HIV clinical trials from 2008 through 2016

## METHODS:

- The reported incidence of diarrhea as an adverse event in HIV clinical trials between 2008 and 2016 was accessed from the NIH database of clinicaltrials.gov
- All trials that met the following criteria were included in the analysis:
  - Pivotal efficacy intervention trials conducted in the United States (including multinational trials)
  - Trials with at least 100 participants
  - Comparative and switch studies
- Trials of select subpopulations, such as pediatric subjects or pregnant women, were excluded
- The incidence of diarrhea reported in each trial was examined for both the experimental arm and any comparator arms
- The reported values are not the treatment emergent rates but rather all grades reported throughout the duration of the clinical trial
- The incidence of diarrhea in clinical trials with select treatment regimens was compared to the rate of diarrhea reported as an adverse event in the US FDA-approved labeling (package inserts)
- The incidence of diarrhea reported was compared for subjects with no prior ART therapy (naïve) and those who were switched from or had failed prior ART therapy prior to entering the trial (experienced)

## RESULTS:

- 38 trials met the inclusion criteria, with 21,066 trial subjects receiving cART. 11,821 subjects received interventional therapy and 9,245 received a comparator regimen
- 21 of these trials enrolled naïve subjects, 11 enrolled treatment experienced subjects who were undetectable in a 'switch' strategy, and 5 enrolled subjects as treatment experienced failing their current regimen. 1 study had two arms – one naïve and one experienced (switch).
- The weighted average of reported diarrhea incidence in those who received interventional regimens vs. those who received comparator regimens was 17.50% and 17.88%, respectively (**Table 1**)
- The median incidence of reported diarrhea was similar at 17.53% and 17.86%, respectively (**Table 1**)

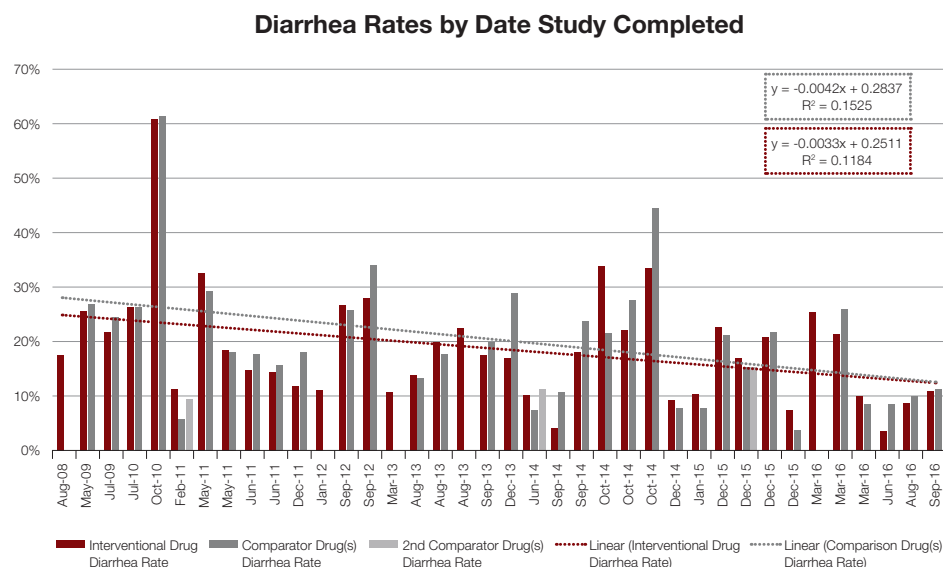
**Table 1: Incidence of Diarrhea in HIV Clinical Trials**

Diarrhea Incidence with Interventional Study Drugs		
# Receiving Interventional Drug (n)	Incidence of Diarrhea (weighted average)	Incidence of Diarrhea (median)
11,821	17.50%	17.53%

Diarrhea Incidence in Comparator Group		
# Receiving Comparator (n)	Incidence of Diarrhea (weighted average)	Incidence of Diarrhea (median)
9,245	17.88%	17.86%

- The linear regression of diarrhea rates by date of completion of the study reveals beta coefficients of -0.0042 and -0.0033 for the interventional drugs and the comparator regimens, respectively (**Figure 1**)



- When the single study containing lopinavir/ritonavir (Kaletra) was removed from the analysis, the beta coefficients were -0.0027 and -0.002 for the interventional drugs and comparator regimens, respectively
- These small beta coefficient values support the hypothesis that the rates of diarrhea have not changed over time



- There were differences in the incidence of diarrhea in clinical trials compared to the values reported for diarrhea as an adverse event in the US FDA-approved package inserts (**Table 2**)

**Table 2: Diarrhea Rates in Clinical Trials Compared to FDA-Approved Package Inserts (PI)**

Product	Components Studied	Diarrhea Rate in Clinical Trials	Diarrhea Rate in US Label
Atripla	EFV, FTC, TDF	22.2%	≥10% (all grades) 9.0% (≥ grade 2)
Complera	RPV, FTC, TDF	14.5%	>10%
Descovy	FTC, TAF + 3rd agent	8.7%	none listed
Evotaz	ATV, COBI, FTC, TDF	22.1%	11.0%
Genvoya	EVG, COBI, FTC, TAF	14.1%	7.0%
Stribild	EVG, COBI, FTC, TDF	20.6%	12.0%
Triumeq	DTG, ABC, 3TC	16.6%	<1% (≥ grade 2)
Isentress	RAL + NRTIs	17.2%	none listed
Prezcobix + Truvada	DRV, COBI, FTC, TDF	21.4%	P: ≥5% (≥ grade 2) T: 9% (≥ grade 2)
Prezcobix + Descovy	DRV, COBI, FTC, TAF	26.0%	P: ≥5% (≥ grade 2) D: none listed
Tivicay + 2NRTIs	DTG, 2NRTIs	16.7%	<1% (≥ grade 2)

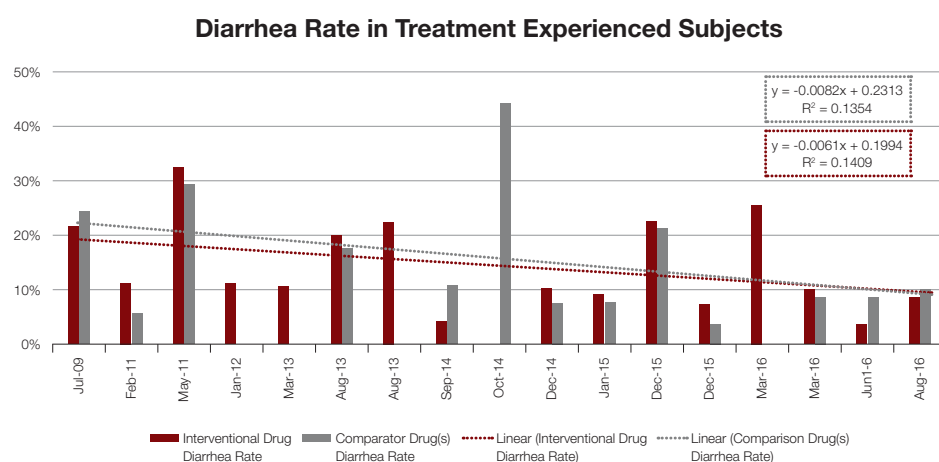
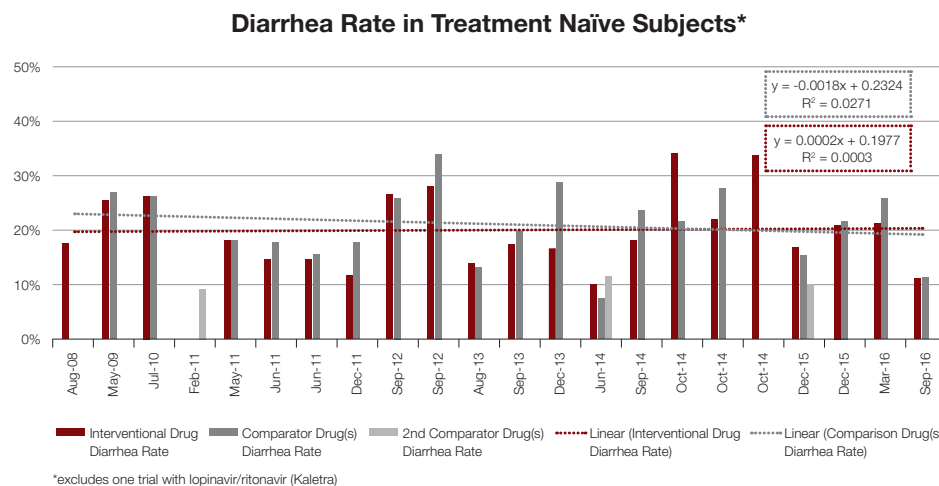
Glossary: 3TC (lamivudine), ABC (abacavir), ATV (atazanavir), COBI (cobicistat), DRV (darunavir), DTG (dolutegravir), EFV (efavirenz), EVG (elvitegravir), FTC (emtricitabine), RAL (raltegravir), RPV (rilpivirine), TAF (tenofovir alafenamide fumarate), TDF (tenofovir disoproxil fumarate)

- There were 13,839 treatment-naïve subjects and 7,227 treatment-experienced subjects in the trials
- The weighted average of reported diarrhea incidence was significantly higher for naïve subjects vs. experienced subjects, 19.72% vs 13.74%, respectively ( $P < 0.001$ ) (**Table 3**)
- The weighted average of reported diarrhea incidence in the experienced subjects was higher for treatment failure subjects than switch subjects, 18.81% vs 12.53%, but was not statistically significant ( $P = 0.107$ ) (**Table 3**)

**Table 3: Incidence of Diarrhea in Treatment-Naïve and Treatment-Experienced Subjects**

Diarrhea Incidence in Treatment-Naïve vs. Experienced Subjects			
Naïve Subjects (n=13,839)	Experienced Subjects (n=7,227)		
19.72%	13.74%		$P < 0.001$
Diarrhea Incidence in Switch vs. Treatment Failure Subjects			
Switch Subjects (n=5,829)	Treatment Failure Subjects (n=1,398)		
12.53%	18.81%		$P = 0.107$

- The linear regression of diarrhea rates by the study completion date reveals very small beta coefficients for the naïve and the experienced subjects, respectively (**Figures 2 and 3**)



## CONCLUSIONS:

- The incidence of diarrhea as an adverse event in HIV clinical trials has not declined significantly in the modern cART era
- Diarrhea remains a significant comorbidity in people with HIV. Even for those virally suppressed in clinical trials, the incidence of diarrhea was around 18%
- Treatment-naïve subjects had significantly greater incidence of diarrhea than did treatment-experienced subjects
- These findings emphasize the need for more targeted epidemiologic and interventional studies to characterize the residual morbidity of GI complaints in people living with HIV

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