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

David M Asmuth, MD[1]; Patrick Clay, PharmD[2]; Gary Blick, MD[3]; Pravin Chaturvedi[4], PhD; Katie MacFarlane, PharmD[4,5]

[1]University of California Davis Medical Center, Sacramento, CA; [2]University of North Texas Health Science Center, Fort Worth, TX; [3]Health Care Advocates International, LLC, Stratford CT; [4]Napo Pharmaceuticals, San Francisco, CA; [5]Purdue University School of Pharmacy, West Lafayette, IN

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[1]
- 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[2]
- Studies have demonstrated that there is incomplete immune reconstitution of the GI mucosa, even with early intervention with cART[3-6]
- 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)**

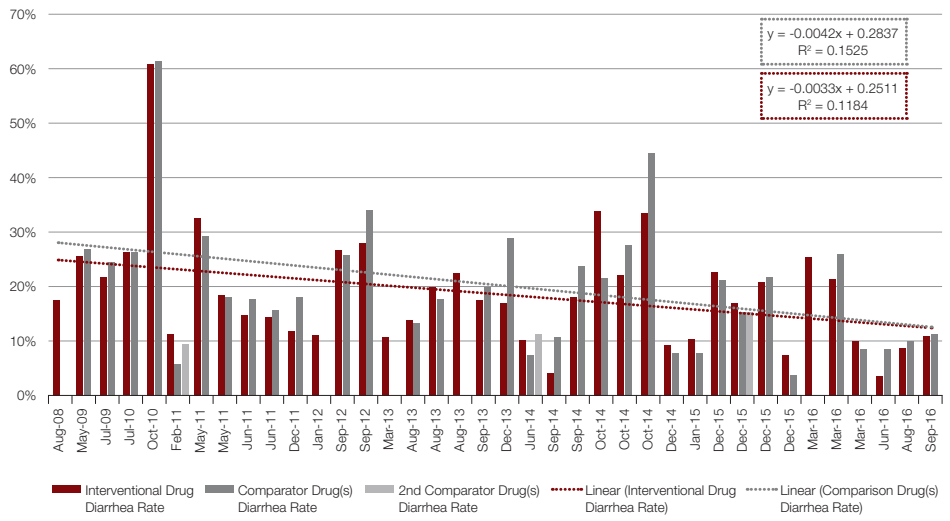
Table 1: Incidence of Diarrhea in HIV Clinical Trials

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)**

Diarrhea Rates by Date Study Completed



- 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)**

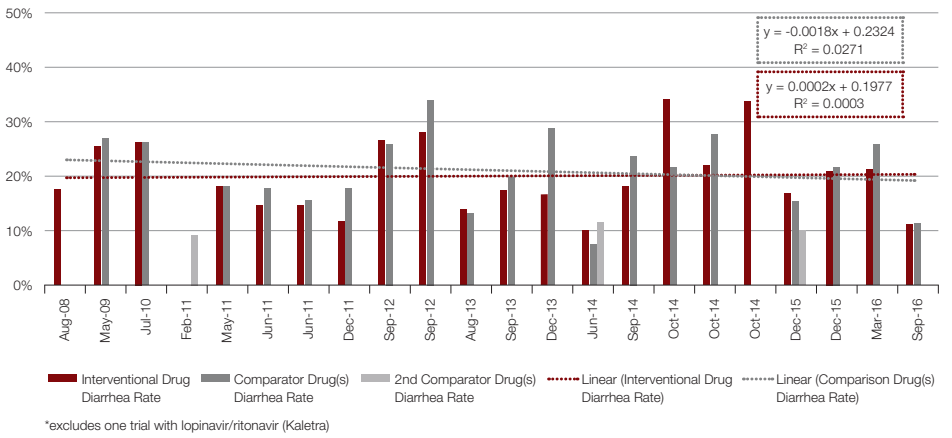
Table 3: Incidence of Diarrhea in Treatment-Naïve and Treatment-Experienced Subjects

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

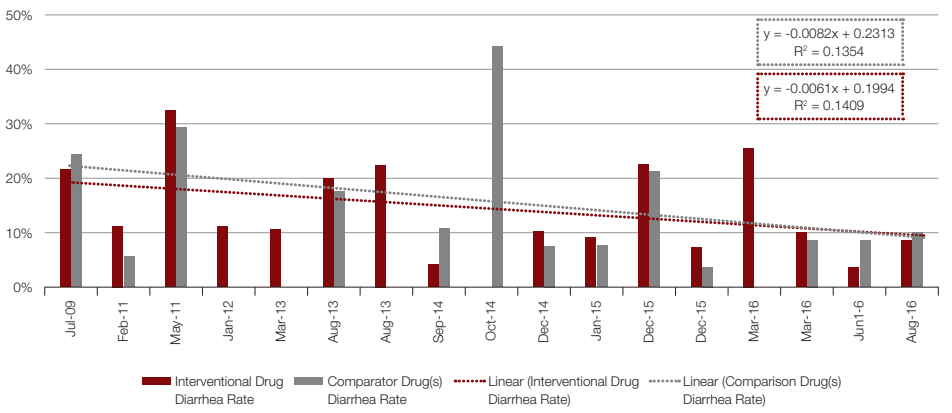
- The linear regression of diarrhea rates by the study completion date reveals very small beta coefficients for the naïve and the experienced subjects, respectively **(Figures 2 and 3)**

Diarrhea Rate in Treatment Naïve Subjects*



*excludes one trial with lopinavir/ritonavir (Kaletra)

Diarrhea Rate in Treatment Experienced Subjects



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

REFERENCES:

1. Siddiqui U, Bini EJ, Chandarana K, Leong J, Ramsetty S, Schiliro D, et al. Prevalence and impact of diarrhea on health-related quality of life in HIV-infected subjects in the era of highly active antiretroviral therapy. *J Clin Gastroenterol* 2007; 41:484–490. **2.** Gehrig M, Clay P, Perry R, et al. Actual versus perceived use of pharmacokinetic (primarily absorption) influential OTC agents and ART tolerability in a nationwide matched cohort of HIV subjects and their healthcare providers. Poster abstract presented at: ID Week 2016; October 26-30, 2016; New Orleans, LA. Abstract 1514. **3.** Kim C, Rousseau R, Huibner S, et al. Impact of intensified antiretroviral therapy during early HIV infection on gut immunology and inflammatory blood biomarkers. *AIDS.* 2017;31(11):1529-1534. **4.** Mehandru S, Poles M, Tenner-Racz K, et al. Lack of mucosal immune reconstitution during prolonged treatment of acute and early HIV-1 infection. *PloS Med.* 2006;3:2335-2348. **5.** Asmuth D, Ma Z, Mann S, et al. Gastrointestinal-associated lymphoid tissue immune reconstitution in a randomized clinical trial of raltegravir versus non-nucleoside reverse transcriptase inhibitor regimens. *AIDS.* 2012;26:1625-1634. **6.** Serrano-Villar S, Sainz T, Ma Z-M, et al. Effects of Combined CCR5/Integrase Inhibitors-based Regimen on Mucosal Immunity and HIV Persistence in HIV-infected Subjects Naïve to Antiretroviral Therapy. *PLoS Pathogens.* 2016;12(1): e1005381.

NP-312-2