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The Safety of Multiple Flexible Sigmoidoscopies with Mucosal Biopsies in Healthy Clinical Trial Participants

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Abstract

During Phase 1 pharmacokinetic/pharmacodynamics studies, participants may undergo multiple sigmoidoscopies, with a collection of 10–20 biopsies during each procedure. This article characterizes the safety of flexible sigmoidoscopies in clinical trial participants. We determined the number of flexible sigmoidoscopies and rectal biopsies that participants underwent and analyzed the frequency, duration, and severity of flexible sigmoidoscopy-related adverse events (AEs). During the study period, 278 participants underwent 1,004 flexible sigmoidoscopies with the collection of 15,930 rectal biopsies. The average number of procedures per participant was 3.6 (median 3; range 1–25), with an average time interval between procedures of 61.8 days (median 28 days; range 1–1,159). There were no serious AEs. Sixteen AEs were related to flexible sigmoidoscopy and occurred in 16 participants, leading to an overall 1.6% (16/1,004) AE rate per procedure and 0.1% (16/15,930) AE rate per biopsy. Of the 16 AEs, 8 (50%) involved abdominal pain, diarrhea, bleeding, flatulence, and bloating, with an average duration of 4.7 days (median 1 day; range 1–28). Most (14/16) AEs were categorized as Grade 1 (mild), whereas two of the AEs were Grade 2 (moderate). No participant withdrew due to procedure-related AEs. Overall, the number of AEs caused by flexible sigmoidoscopy with multiple biopsies was low and the severity was mild, suggesting that this procedure can be safely integrated into protocols requiring repeated intestinal mucosal sampling.

Keywords: endoscopy, intestinal biopsy, adverse events, clinical trials

Introduction

Flexible sigmoidoscopy is a common procedure in clinical trials requiring the collection of intestinal biopsy samples. The safety of flexible sigmoidoscopy has been evaluated in special populations, such as pregnant women,[1–4] patients with recent myocardial infarctions,[5,6] patients with recent colonic surgeries,[7] and patients undergoing colorectal cancer screening,[8–15] but not in healthy participants. Many flexible sigmoidoscopy studies focus on comparing the clinical outcomes performed by physicians, mid-level providers, and nurses[16–25] and adverse event (AE) rates among these studies were low (0%–0.03%).[26] However, most of these studies report procedure-related complications/AEs as secondary outcomes, documenting only severe complications such as perforations, bleeding episodes requiring transfusions, postprocedural infections, or death.

The majority of patients from other studies underwent one-time flexible sigmoidoscopies for diagnostic, therapeutic, or screening purposes, did not undergo multiple procedures in rapid successions, and had limited, if any, mucosal sampling performed. Therefore, they do not reflect the risks faced by healthy participants who volunteer in multiple clinical trials for research purposes that are usually investigating pathogenesis and/or prevention. The goal of this article is to characterize the safety of multiple flexible sigmoidoscopies with multiple biopsies in healthy clinical trial participants.

Materials and Methods

Ethics statement

The study was approved by the University of Pittsburgh IRB (IRB No. PRO15120023). All participants provided written informed consent for the studies.

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Table 1. Studies Included in the Analysis

Study number	*Study name*	*Number of participants for analysis*	*Study description*	*References/ comments*
PRO08030370	Aptamer Microbicide Development Program study	82	Single-visit tissue collection for assay development and screening of aptamers for *in vitro* activity against HIV-1 Number of procedures: 1–3; number of biopsies/procedure: 10–20; total number of biopsies: 1,914	28–35
PRO10090390	MIG-HVTN study	20	Single-visit tissue collection for flow cytometric analysis of gut-associated lymphoid tissue Number of procedures: 1; number of biopsies/procedure: 20; total number of biopsies: 380	36
PRO09050085	RMP-02/MTN-006 study	7	Multiple-visit Phase 1 study to assess the rectal safety, acceptability, pharmacokinetics, and pharmacodynamics of tenofovir 1% gel and oral tenofovir disoproxil fumarate Number of procedures: 8; number of biopsies/procedure: 13–17; total number of biopsies: 772	37–39
PRO09060060	MTN-007 study	21	Multiple-visit Phase 1 study to assess the rectal safety and acceptability of tenofovir 1% gel Number of procedures: 3; number of biopsies/procedure: 7; total number of biopsies: 441	40–42
PRO12030070	CHARM-01 study	3	Multiple-visit Phase 1 study to assess the rectal safety, acceptability, pharmacokinetics, and pharmacodynamics of three tenofovir gel formulations Number of procedures: 4; number of biopsies/procedure: 21; total number of biopsies: 231	43
PRO14060071	CHARM-03 study	20	Multiple-visit Phase 1 study to assess the safety, acceptability, pharmacokinetics, and pharmacodynamics of oral maraviroc, and rectal/vaginal maraviroc gel Number of procedures: 5; number of biopsies/procedure: 9–19; total number of biopsies: 1,552	Data analysis ongoing
PRO11100727	HPTN-069 study	32	Multiple-visit Phase 2 study to assess the safety, acceptability, pharmacokinetics, and pharmacodynamics of four oral pre-exposure antiretroviral prophylaxis groups Number of procedures: 4; number of biopsies/procedure: 14–20; total number of biopsies: 2,054	Data analysis ongoing.
PRO10010417	MICL study	114	Single-visit tissue collection for flow cytometric analysis of gut-associated lymphoid tissue Number of procedures: 1–4; number of biopsies/procedure: 20; total number of biopsies: 3,692	Manuscript in preparation.
PRO12080047	MTN-017 study	19	Multiple-visit Phase 2 study to assess the safety, acceptability, pharmacokinetics, and pharmacodynamics of oral tenofovir disoproxil fumarate and rectal tenofovir gel Number of procedures: 4; number of biopsies/procedure: 15–20; total number of biopsies: 1,385	44
PRO13050286	PASS study	31	Single-visit tissue collection for assay development and screening of microbicide candidates for *in vitro* activity against HIV-1 Number of procedures: 1–4; number of biopsies/procedure: 16–20; total number of biopsies: 666	PASS is a means to collect samples.
PRO12020292	MWRI-01 study	44	Multiple-visit Phase 1 study to assess the safety, acceptability, pharmacokinetics, and pharmacodynamics of long-acting rilpivirine injections Number of procedures: 5–7; number of biopsies/procedure: 14–18; total number of biopsies: 2,843	45

CHARM, combination HIV antiretroviral rectal microbicide; HPTN, HIV Prevention Trials Network; MICL, Mucosal Immunology Research Core Laboratory; MIG-HVTN, Mucosal Immunology Group-HIV Vaccine Trials Network; MTN, Microbicide Trials Network; PASS, Prevention Assays; RMP, Rectal Microbicide Program (MDP).

Table 2. Participants' Demographics

		Percentage	*Standard deviation*
Total no. of unique participants	278		
Female	111	39.9	
Male	166[a]	59.7	
Average age (year)	34.0		11.6
Female weight (kg)	71.6		17.1
Male weight (kg)	86.0		19.9
Ethnicity			
Caucasian	117	41.8	
African American	47	17.8	
Others/did not report	114	40.3	
Average no. of studies per participant	1.4		0.8
Total no. of flexible sigmoidoscopy	1,004		
Average no. of flexible sigmoidoscopy	3.6		3.3
Median of flexible sigmoidoscopy	3		
Mode of flexible sigmoidoscopy	1		
Maximum no. of flexible sigmoidoscopy by a single participant	25		
Average interval between flexible sigmoidoscopy (day)	61.8		
Total no. of biopsies	15,930		
Average no. of biopsies per participant	57.3		49.1
Median of biopsy	40		
Mode of biopsy	20		

[a]One participant did not specify gender.

Study population

Healthy participants in the 11 studies, all HIV seronegative, were screened for eligibilities based on the specific criteria of each study. Rectal biopsies were performed by using Radial™ 4 jumbo forceps (Boston Scientific, Marlborough, MA). The biopsy sites were between 10 cm and 15 cm measured from the anal verge. Enrolled participants, who underwent at least one flexible sigmoidoscopy, were included in the final analysis.

Data extraction and analysis

Archived source documentation from the studies listed in Table 1 were retrieved for analysis. Only participants enrolled at the University of Pittsburgh were included to minimize site variability. Individual charts for eligible participants were reviewed, and unique identification numbers were assigned to each eligible subject specifically for this study. Participant data were included, irrespective of the study randomization. All AEs were documented by registered nurses and reviewed by physicians who were involved in the studies. The severity of an AE was graded according to the guidelines on Division of AIDS Table of Grading the Severity of Adult and Pediatric Adverse Events and Addendum 3: Rectal Grading Table for Use in Microbicide Studies.[27] The severity was graded on a 4-point scale: 1 (mild), 2 (moderate), 3 (severe), and 4 (life threatening). Only AEs related to flexible sigmoidoscopies (procedures) were included in this analysis.

Results

Demographics

A total of 278 participants underwent at least one flexible sigmoidoscopy. Study demographics are listed in Table 2. Most participants (199/278; 71.6%) were only enrolled in one study. Fifty-five (19.8%) participants participated in two studies, and 17 (6.1%) participants participated in three studies. Only seven participants completed four or more studies (median 4; range 4–6). Participants who enrolled in two or more studies on average took part in 2.4 studies (median 2; range 2–6).

Single-visit studies

The Aptamer, Mucosal Immunology Group-HIV Vaccine Trials Network (MIG-HVTN), Mucosal Immunology Research Core Laboratory (MICL), and Prevention Assays (PASS) studies were single-visit studies that were designed to

Table 3. Characteristics of Single-Visit Studies (Aptamer, MIG-HVTN, MICL, and PASS)

No. of study visits[a]	*No. of participants*	*Total no. of flexible sigmoidoscopy*	*Average no. of biopsies/ participant/visit*	*Average time interval (days) between flexible sigmoidoscopy (SD)*	*Time interval range (days)*	*Adverse events related to flexible sigmoidoscopy*
1	117	117	19.4	N/A	N/A	3
2	45	90	20	151 (215)	1–1,159	0
3	23	69	19.7	195 (228)	26–1,153	0
4	5	20	19.7	179 (176)	14–504	0
>4	8	41	19.7	216 (278)	12–1,063	1

[a]Each study was a single visit, but participants could consent to come back for multiple visits over an extended period of time.

Table 4. Characteristics of Multiple-Visit Studies (MWRI-01, MTN-006, MTN-007, CHARM-01, CHARM-03, MTN-017, and HPTN-069)

No. of study visits with sigmoidoscopy	*No. of participants*	*No. of flexible sigmoidoscopies*	*Average no. of biopsies per participant*	*Average time interval (days) between flexible sigmoidoscopies*	*Adverse events related to flexible sigmoidoscopies*
0–5	82	318	55.7	56.3	6
6–10	25	192	107.5	29.9	2
11–15	11	135	158	30.2	3
>15	1	22	284	49.8	1
Total	119	667	78.0	42.6	12

collect tissue for assay development. Participants could return for repeat visits. One hundred ninety-eight participants were involved in single-visit studies, with 59% (117/198) participating once only and 41% participating in >1 single-visit study. The total number of flexible sigmoidoscopies in single-visit studies was 337, and the prevalence of flexible-sigmoidoscopy-related AEs was 4/337, or 1.2%. The total number of biopsies in single-visit studies was 6,672. The prevalence of flexible-sigmoidoscopy-related AEs per biopsy was 4/6,672, or 0.1%. Of the four events, three (0.9% per procedure or 0.1% per biopsy) were Grade 1 and one (0.2% per procedure or 0.02% per biopsy) was Grade 2. The number of biopsies per procedure in single-visit studies ranged from 10 to 20. The detailed analysis of these events is presented in Table 3.

Multiple-visit studies

The MWRI-01, RMP-02/MTN-006, MTN-007, CHARM-01, CHARM-03, MTN-017, and HPTN-069 studies were categorized as multiple-visit studies, because participants were scheduled to undergo multiple protocol-specified flexible sigmoidoscopies within each individual study. One hundred nineteen participants were involved in multiple-visit studies, with 82 out of 119 (69%) of the participants receiving five or fewer flexible sigmoidoscopies, and one subject undergoing 22 flexible sigmoidoscopies through participation in four multiple-visit studies. These 22 procedures were conducted over 6 years (2010–2016). The AE per procedure for this participant was 1/22, or 4.5%. The AE per biopsy for this participant was 1/284, or 0.44%. The total number of flexible sigmoidoscopies in multiple-visit studies was 667, and the prevalence of flexible-sigmoidoscopy-related AEs was 12/667 (1.8%).

The total number of biopsies in multiple-visit studies was 9,278. The prevalence of flexible-sigmoidoscopy-related AEs per biopsy was 12/9,278, or 0.1%. Of the 12 events, 11 (1.6% per procedure or 0.1% per biopsy) were considered Grade 1 and one (0.2% per procedure or 0.01% per biopsy) was considered Grade 2. The number of biopsies per procedure in multiple-visit studies ranged from 7 to 21. The details of these AEs are presented in Table 4.

The overall study retention rate was high at 95% (113/119) among multiple-visit study participants. MWRI-01, MTN-007, and CHARM-01 had no early study withdrawals. RMP-02/MTN-006 had one early withdrawal due to the participant requiring prednisone which was not allowed in the study. CHARM-03 had two withdrawals due to employment situations. MTN-017 had one withdrawal due to moving, and HPTN-069 had two withdrawals due to pre-existing mental health issues. None of the withdrawals was due to procedures or biopsies based on patient and study team report.

AEs related to flexible sigmoidoscopy

Combining both single-visit and multiple-visit studies, a total of 1,004 flexible sigmoidoscopies were performed. Sixteen AEs related to flexible sigmoidoscopy were recorded, leading to an overall 1.6% AE rate (Table 5). Of the 16 participants that reported AEs, eight (50%) took part in two or more studies. The study with the highest AE rate was CHARM-01 (multiple-visit study, 2/12; 16.7% per procedure, or 2/231; 0.9% per biopsy). Aptamer and PASS had no procedure-related AEs reported. Fourteen flexible-sigmoidoscopy-related AEs (87.5%) were gastroenterological in nature (abdominal pain $N=2$, bloating $N=2$, flatulence $N=3$, diarrhea $N=2$, rectal bleeding $N=4$, and anal pain or abrasions $N=1$; Table 6). The remaining two AEs were vasovagal episodes. The average duration for all AEs was 4.7 days (median 1 day; range 1–28), with the longest being 28 days (anal abrasion).

The majority of these events were of mild severity, with 14 episodes categorized as Grade 1 (14/16, 88%) and two (12%) episodes categorized as Grade 2 (one case was a combination of abdominal pain and rectal bleeding that lasted for 1 day, and the second case was a vasovagal syncope episode). Fourteen out of sixteen (88%) AEs required no treatment, the anal abrasion case was treated with warm compresses, and one of the abdominal pain cases was treated with pain medication. Of the 16 participants with AEs documented, 12 of them had additional flexible sigmoidoscopies performed afterward. One person had an AE on the last flexible sigmoidoscopy for the study (Grade 1), and he continued to have additional visits that did not require procedures. Three participants were involved in single-visit studies. No participant withdrew from any of the 11 studies due to flexible-sigmoidoscopy- or biopsy-related AEs.

Discussion

Flexible sigmoidoscopy is routinely utilized in gastrointestinal and HIV translational research studies. Based on data from >1,000 procedures, we have shown that flexible sigmoidoscopy with a collection of as many as 20 biopsies taken by using jumbo forceps has a low AE rate, even when performed repeatedly in clinical trial participants.

This is the first time that the safety of multiple sigmoidoscopies with mucosal biopsies has been documented in healthy clinical trial participants. Our AE rate in single-visit studies (1.2% per procedure or 0.1% per biopsy) was within the range found in other published studies (0%–8.7%).[8,9,11,14,15,18–24,26] An exact head-to-head comparison is challenging due to

Table 5. Adverse Events Related to Flexible Sigmoidoscopy

	Total no. of participants with at least one flexible sigmoidoscopy	*Total no. of flexible sigmoidoscopies*	*Total no. of adverse events related to flexible sigmoidoscopies*	*Percentage of adverse events due to flexible sigmoidoscopies*	*Average duration (day) (SD)*	*Grade*
Aptamer MDP study	82	99	0	0	N/A	N/A
MIG-HVTN study	20	20	1	5	N/A	Grade 1
RMP-02/MTN-006 study	7	48	2	4.2	1.5	All Grade 1
MTN-007 study	21	63	3	4.8	5.8 (9.5)	All Grade 1
CHARM-01 study	3	12	2	16.7	7 (7.1)	All Grade 1
CHARM-03 study	20	108	1	0.9	12 (0)	Grade 1
HPTN-069 study	32	112	1	0.9	4	Grade 1
MICL study	114	185	3	1.6	1.3 (0.4)	2 events were Grade 1; 1 event combining abdominal pain and bleeding was Grade 2
MTN-017 study	19	74	1	1.4	1	1 syncopal episode was Grade 2
PASS study	31	36	0	0	N/A	N/A
MWRI-01 study	44	251	2	0.8	5 (10.2)	All Grade 1
Total	393	1,008	16	1.6	4.7	

Table 6. Specific Symptom Breakdown of Flexible-Sigmoidoscopy-Related Adverse Events

Adverse event related to flexible sigmoidoscopy	*No. of events*
Abdominal pain	2
Grade 1	1
Grade 2	1
Diarrhea	2
Grade 1	1
Grade 2	1
Bleeding	4
Grade 1	3
Grade 2	1
Flatulence	3
Grade 1	3
Grade 2	0
Anal pain/abrasions	1
Grade 1	1
Bloating	2
Grade 1	1
Grade 2	1
Others	2
Grade 1	1
Grade 2	1

heterogeneity in study-specific elicitation and reporting of AEs. For example, some studies only measured major complications such as perforations,[14,21] whereas others focused on specific complications such as obstetrical and fetal outcomes.[1,2] One study included sleep disturbances,[12] which others did not report. Methods of reporting were also different. Some studies,[8,10,12] including ours, involved communication between participants and study coordinators to identify AEs, whereas the largest study, which involved >100,000 colorectal cancer screening patients, utilized hospitalization records to identify possible complications.[13] We used a rectal grading table specifically developed for microbicide studies,[27] whereas others did not.

Most studies also considered complications/AEs as secondary outcomes, and, thus, detailed breakdowns of each individual AEs were generally not available. Four studies provided breakdowns of postflexible-sigmoidoscopy complications,[8,10,12,13] though they did not have standardized definitions of each complication category.

In previous studies, abdominal pain due to flexible sigmoidoscopy/bowel preparation ranged from 4.2% to 19% (per procedure)[8,12] whereas questionnaire-elicited peri-procedural discomfort was 62%.[10] Our flexible-sigmoidoscopy-related abdominal pain rate was 0.2% per procedure (2/1,004). One study reported rates of flatulence between 24% and 50% per procedure,[12] whereas the rate in our study was 0.3% (3/1,004). Another study identified 11 cases of procedure-related bleeding that required hospitalization (0.01% per participant; 11/109,534), with two requiring transfusions[13]; we had a bleeding complication rate of 0.4% per procedure (4/1,004), and none of the four participants required hospitalization. Some studies explicitly stated that there was no complication or no major complication.[11,15,16,18–20,22–24]

Despite the heterogeneous nature of AE reporting and the different study populations (patients vs. healthy clinical trial participants), all studies did, however, conclude that flexible sigmoidoscopy procedures were safe. The overall AE rate in our single-visit studies was similar to that of multiple-visit

studies (1.2% per procedure or 0.1% per biopsy vs. 1.8% per procedure or 0.1% per biopsy). It is possible that the shorter intervals between sigmoidoscopies in multiple-visit studies (average 43 days) compared with those in single-visit studies (average 174 days) contributed to a higher AE rate. However, it is also possible that participants were more likely to report AEs due to more frequent interactions with clinical staff that occur during multiple-visit studies. The types of AEs were very similar between the single-visit study population and the multiple-visit study population.

Of the studies we examined in the literature, only one study scheduled participants to undergo >1 flexible sigmoidoscopy.[19] The participants ($N = 328$) in this study underwent two flexible sigmoidoscopies back to back within 5 min performed by nonphysicians and physicians to compare the rates of polyp detection. Biopsies were performed in this study, and any nonbleeding polyps identified in the second flexible sigmoidoscopy were identified as missing polyps. It had no complication in any patient. As far as we know, our study is the first study that examined AEs in multiple (>2) flexible sigmoidoscopies.

Of the 16 flexible-sigmoidoscopy-related AEs, two events were graded as 2 (moderate). The grading was based on guidelines described in the Methods section of this article.[27] The Grade 2 events involved one case of abdominal pain ''greater than minimal interference with usual social and/or functional activities'' and rectal bleeding ''persistent without transfusion'' and a second case of syncopal episode. It is important to note that all symptoms resolved within 1 day. The other 14 AEs were categorized as Grade 1, which generally indicated ''no or minimal interference with usual social and/or functional activities.'' Overall, the severities of most of the AEs (14/16; 88%) were Grade 1 on a 4-point scale.

None of the healthy clinical trial participants who experienced flexible-sigmoidoscopy-related AEs withdrew from the studies. It is possible that the participants continued to sign up for subsequent studies, even though they experienced AEs in previous studies. The retention rate among all healthy participants in multiple-visit studies, regardless of their AE status, was high at 95%. Data on retention rates are rare, most likely due to the fact that these studies involved diagnostic, therapeutic, or colorectal cancer screening purposes in patients and did not require patients to participate in multiple flexible sigmoidoscopies. One study asked through a telephone questionnaire whether a patient was willing to participate in flexible sigmoidoscopy again[10]; 10 out of 161 refused to participate again, so the theoretical retention rate was 94% (151/161), which is comparable to our study with healthy individuals.

This is the first large-scale analysis to examine safety records of multiple flexible sigmoidoscopy procedures in healthy, nonpatient clinical trial participants. Overall, the number of AEs caused by multiple flexible sigmoidoscopies was low. For the few AEs that occurred, the severity was mild and required little treatment. Therefore, we conclude that multiple flexible sigmoidoscopies with a collection of mucosal biopsies can be safely integrated into protocols requiring repeated mucosal sampling.

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Author Disclosure Statement

No competing financial interests exist.

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