

# The Effect of Dairy Product Ingestion on Human Immunodeficiency Virus–Related Diarrhea in a Sample of Predominantly Gay Men

## *A Randomized, Controlled, Double-blind, Crossover Trial*

Jill Tinmouth, MD, PhD, FRCPC; Gabor Kandel, MD, FRCPC; George Tomlinson, PhD; Sharon Walmsley, MD, MSc, FRCPC; A. Hillary Steinhart, MD, MSc, FRCPC; Richard Glazier, MD, MPH, CCFP

**Background:** In the highly active antiretroviral therapy (HAART) era, chronic diarrhea remains common in human immunodeficiency virus (HIV) illness. Empirical lactose avoidance is often advised despite lack of evidence of benefit in a population at risk for osteopenia and malnutrition.

**Methods:** The a priori hypothesis was that moderate lactose ingestion would not worsen diarrhea in this population. We used a double-blind, noninferiority, randomized crossover trial in a community setting of primary and tertiary care HIV clinics. The participants all had chronic diarrhea and were a volunteer sample of 49 predominantly white HIV-infected men who have sex with men. They ingested 240 mL of low-fat milk (12 g of lactose) and lactose-free milk during 2 separate study periods. The primary outcome was mean difference in stool weight between the 2 study periods in the 8 hours after milk ingestion. Lactose was judged not to worsen diarrhea if this difference did not exceed 167 g in 8 hours with 95% certainty.

**Results:** Forty-eight (98%) of 49 participants were male. Median age, CD4 cell count, and viral load were 42 years (range, 20–62 years), 390 cells/mL (range, 20–1100 cells/mL), and 112 copies/mL (range, <50 to >500 000 copies/mL), respectively. Thirty-nine participants (80%) were taking HAART medication. Ten participants (20%) were lactase deficient. The mean difference in stool weight between the 2 study periods was  $-41.3$  g/8 h (upper 95% confidence limit,  $-13.5$  g) for the entire group and  $+11.3$  g/8 h (upper 95% confidence limit,  $+47.4$  g) for the lactase-deficient group.

**Conclusions:** Moderate lactose ingestion does not worsen diarrhea in HIV-infected persons with chronic diarrhea, regardless of lactase status. Therefore, avoidance of modest quantities of milk may not be justified in this population.

*Arch Intern Med.* 2006;166:1178-1183

**D**IARRHEA REMAINS COMMON in persons with human immunodeficiency virus (HIV) despite the use of potent antiretroviral medications.<sup>1</sup> However, the cause of this problem is changing, with a decline in opportunistic infections and an increase in noninfectious causes.<sup>2</sup> Noninfectious HIV-related diarrhea has been attributed to HIV enteropathy,<sup>3</sup> medications,<sup>4</sup> and lactase deficiency (LD).<sup>5,6</sup>

Lactose intolerance is characterized by abdominal bloating, flatulence, diarrhea, and cramping abdominal pains after the ingestion of foods containing lactose. It is caused by a deficiency of lactase, a small bowel brush border enzyme essential to the digestion of lactose. Hydrogen breath testing is a highly sensitive and specific test for LD.<sup>7</sup> In the general population, it is well recognized that many persons with LD can

tolerate moderate quantities of lactose in their diet (eg, 12–18 g, which is equivalent to 1–1.5 cups of milk) without developing symptoms.<sup>8–10</sup> Conversely, subjective perception of milk intolerance is a poor predictor of true LD.<sup>9–11</sup>

Although LD is more prevalent in HIV-infected adults than in uninfected adults,<sup>12</sup> there are no blinded and controlled studies evaluating the effect of lactose ingestion on HIV-related diarrhea. Despite this lack of evidence and despite the potential risks of malnutrition<sup>13</sup> and osteopenia<sup>14</sup> in this population, avoidance of dairy products is often recommended in the management of HIV-related diarrhea.<sup>15–17</sup> In a survey of 21 HIV health care providers in the Toronto, Ontario, area, 15 reported that they recommend empirical lactose avoidance to their patients with HIV-related diarrhea (unpublished data, October 1999).

Author Affiliations are listed at the end of this article.

Our hypothesis was that moderate ingestion of lactose-containing milk would not worsen the diarrhea of HIV-infected persons with chronic noninfectious diarrhea compared with ingestion of lactose-free milk.

## METHODS

This was a randomized, double-blind, noninferiority, cross-over trial in which HIV-infected participants drank lactose-containing and lactose-free substrate followed by stool collection and hydrogen breath testing on 2 separate days. Outcomes were stool weight and symptom score. All participants were recruited and studied between September 2000 and March 2003.

HIV-infected persons between the ages of 18 and 80 years who reported at least 3 loose to watery bowel movements per day for the previous 4 weeks or more were eligible. Persons with fewer than 3 bowel movements daily but who required daily antidiarrheal medications were also eligible. The antiretroviral regimen had to be stable over the previous 4 weeks and for the duration of the study.

Exclusion criteria included pregnancy, LD preating the diagnosis of HIV, severe systemic illness, malignancy, hospitalization, use of antibiotics other than for prophylaxis against opportunistic infections in the month prior to study enrollment, any colon-cleansing procedure within 1 week of the first study period, or diagnosis of other causes of diarrhea such as inflammatory bowel disease.

Participants were recruited from primary care and tertiary care HIV clinics in Toronto as well as from the community using a variety of methods including newspaper advertisements, direct communication with treating physicians, and posters in clinics and AIDS advocacy agencies.

## PROTOCOL

The study protocol was approved by the research ethics boards at St Michael's Hospital, the University Health Network, and the University of Toronto. All participants gave written, informed consent. This investigation was carried out in accordance with the regulations set out in the Declaration of Helsinki.

Prior to study entry, infection and other non-HIV-related causes of diarrhea were ruled out with microbiologic studies (negative findings from 3 stool cultures, 3 microscopic examinations for ova and parasites with special stains for cryptosporidium, and 1 stool assay for *Clostridium difficile* toxin) and endoscopy.

For the 24 hours prior to each study period, participants followed a lactose-free diet and avoided all antidiarrheal medications. They ate an evening meal that was low in hydrogen-producing foods. Prior to each study period, they abstained from smoking for 3 hours and fasted for 12 hours. Human immunodeficiency virus medications were taken at the same time on both study days.

On both study days, participants ingested test substrate and underwent concomitant 5-hour hydrogen breath testing and an 8-hour stool collection period. They were randomized, using a computer-generated list created by the hospital research pharmacist, to the order in which they received the test substrates. The primary investigator (J.T.) obtained written informed consent and enrolled the participants. Study personnel and participants were blinded to the randomization schedule. There was a minimum 1-week washout period between the 2 study days, but both had to be completed within 6 weeks.

Alveolar breath samples were collected using an AlveoSampler (QuinTron Instrument Co, Milwaukee, Wis). A baseline breath specimen was taken; the test substrate was ingested; and

subsequent specimens were collected hourly. Concentrations of hydrogen and methane in the breath samples were measured by gas chromatography (model SC MicroLyzer; QuinTron). If the hydrogen concentration rose by 10 ppm or more from baseline<sup>9,18</sup> or if there was a rise of 100% or more in methane levels from baseline in participants with a baseline methane level of 5 ppm or more<sup>19</sup> on the lactose study day, a diagnosis of LD was made. Otherwise, participants were categorized as lactase persistent (LP).

At the start of each study period, participants drank 240 mL of test substrate. On the lactose-free study day, the test substrate was lactose-hydrolyzed 2% milk (Lactaid; Parmalat, Brampton, Ontario) and on the lactose study day, it was sweetened 2% milk containing 12.5 g of lactose. To render it indistinguishable from the lactose-free milk, which has a sweetened taste as a result of the lactose hydrolyzation, 0.23 g of aspartame was added to the lactose-containing milk. Using the sensory triangle test,<sup>20</sup> 30 untrained volunteers, who were not known to be HIV-infected, were not able to distinguish the 2 test substrates (data not shown).

## OUTCOMES AND STATISTICAL ANALYSIS

The primary outcome was the stool weight in grams over an 8-hour period after test substrate ingestion. This duration of stool collection was based on reported orofecal transit times after lactose ingestion.<sup>21</sup> To ensure that our collection period was not too short, participants completed the symptom questionnaire described below for the 16 hours after each study period.

The secondary outcome was self-reported participant symptoms, scored using a questionnaire previously used in the evaluation of lactose intolerance<sup>9</sup> in which 4 symptoms (abdominal bloating, flatulence, pain, and diarrhea) were evaluated on a 6-point Likert scale (0-5). The number of bowel movements and of flatuses during each study period were recorded.

For the primary outcome, a noninferiority boundary of an increase of 167 g in stool weight during the lactose period was selected, reflecting a change of approximately 50% in stool output for HIV-infected persons taking protease inhibitors.<sup>22</sup> Our hypothesis would be supported if the 1-sided upper 95% confidence limit (CL) of the mean difference in stool weight between the study periods was less than this noninferiority boundary.<sup>23-25</sup>

For the secondary outcome, the 4 symptom scores were tallied, and the mean difference in the total score between the 2 periods was calculated. Two subgroup analyses were performed by analyzing the subgroup-intervention interaction term.<sup>26</sup> The first subgroup analysis, which was prespecified, compared stool weight and symptom scores in the LD and LP groups. In the second subgroup analysis, stool weight and symptoms were compared for those who reported lactose avoidance or definite symptoms associated with lactose ingestion to determine whether lactose ingestion worsened their diarrhea.

Mean differences with 95% confidence intervals (CIs) are reported. Nonparametric bootstrapping techniques<sup>27</sup> were used for the CIs where the data were markedly skewed. Comparisons were made using the *t* test, the Wilcoxon signed rank test, or the Wilcoxon rank sum test depending on the distribution of the data. A *P* value of less than .05 was considered significant. All data were analyzed using the SAS statistical package, version 8.2 (SAS Institute, Cary, NC).

The sample size was calculated for a noninferiority type trial assuming no difference in stool weight between study periods, a standard deviation of 258 g in 8 hours,<sup>22</sup> and a moderate correlation between the 2 study periods ( $\rho=0.3$ ). For our sample size of 50 participants, there was a 96.4% probability that the 1-sided 95% upper CL for the mean difference in stool weight between study periods would exclude an increase of 167 g.

**Table. Baseline Characteristics of Study Participants\***

Characteristic	Overall Group (n = 49)	Lactase Deficient (n = 10)	Lactase Present (n = 39)
Age, median (range), y	42 (20-62)	40 (35-60)	43 (20-62)
Male	48 (98)	10 (100)	38 (97)
White	45 (92)	8 (80)	37 (94)
Risk factors for HIV infection†			
Homosexual activity	45 (92)	8 (80)	35 (95)
Heterosexual activity	4 (8)	2 (20)	2 (5)
IV drug use	3 (6)	1 (10)	2 (5)
Transfusion	1 (2)	1 (10)	0
Other	1 (2)	1 (10)	0
Duration of HIV infection, median (range), y	10.5 (1.0-17.6)	11.2 (3.4-17.4)	10.5 (1.0-17.6)
CD4 count, median (range), cells/mL	390 (20-1110)	350 (20-942)	390 (72-1110)
Viral load, median (range), copies/mL‡	112 (<50 to >500 000)	119 (<50 to >500 000)	52 (<50-257 607)
Viral load <50 copies/mL‡	21 (43)	2 (20)	19 (49)
Currently undergoing HAART	39 (80)	8 (80)	31 (80)
Never underwent HAART	4 (8)	1 (10)	3 (8)
Duration of current HAART regimen, median (range), mo	12 (1-84)	10 (2-6)	12 (1-84)
Duration of diarrhea, median (range), mo	36 (1-142)	45 (12-120)	35 (1-142)
BMs/d, median (range), No.	4 (1-18)	4 (3-9)	4 (1-18)
Symptoms in last month			
Urgency	38 (84)	6 (67)	32 (89)
Incontinence	33 (73)	5 (56)	28 (78)
Tenesmus	14 (31)	4 (44)	10 (28)
Abdominal cramps	30 (67)	7 (78)	23 (64)
Nocturnal BMs	23 (53)	6 (60)	20 (51)
Antidiarrheal medication use	42 (86)	9 (90)	33 (85)

Abbreviations: BM, bowel movement; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IV, intravenous.

\*Unless otherwise indicated, data are reported as number (percentage) of patients.

†Some participants had more than 1 risk factor.

‡Viral load tested using Chiron 3.0 assay (Chiron Corp, Emeryville, Calif).

## RESULTS

### PARTICIPANTS

Results are reported for only 49 of the 50 participants because 1 participant violated the study protocol. This person was unable to complete the protocol within a 6-week period because of hospital closures related to a public health emergency in Toronto.

Baseline demographics are reported in the **Table**. Forty-eight (98%) of the participants were male; 45 were white; 1 was African Canadian; 1 was Latino; and 2 were Aboriginal. The median CD4 count was 390 cells/mL, while the viral load was undetectable in 21 participants (43%). Thirty-nine (80%) of the participants were taking highly active antiretroviral therapy (HAART) medication while 42 (86%) were taking anti-diarrheal medications. Participants reported a median of 4 bowel movements per day.

Nineteen participants (39%) reported "definite gastrointestinal symptoms" with intake of lactose-containing foods, while 15 (31%) were unsure about this relationship, and the remaining 15 (31%) felt that there was no relationship. Eighteen (37%) of the participants reported avoiding lactose-containing foods.

The baseline characteristics of the 10 participants (20%) found to be LD did not appear to differ from the overall group (Table).

## OUTCOMES

In each study period, participants had a median of 2 bowel movements (range, 0-7) and 2 episodes of flatus (0-15 in lactose-free period; 0-16 in lactose period).

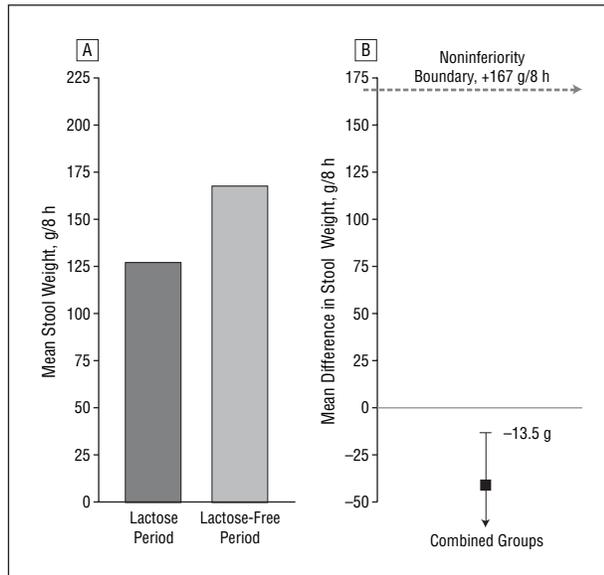
### Primary Outcome: Stool Output

For the entire group, the mean±SD stool weights were 126.3±132 g and 167.6±194 g during the lactose and lactose-free study periods, respectively. The correlation in stool weight between the study periods was  $\rho=0.12$ . The mean difference between the 2 periods (stool weight<sub>lactose-free</sub> - stool weight<sub>lactose</sub>) was -41.3 g, with a 1-sided upper 95% CL of -13.5 g, which was less than the +167-g noninferiority boundary (**Figure 1**).

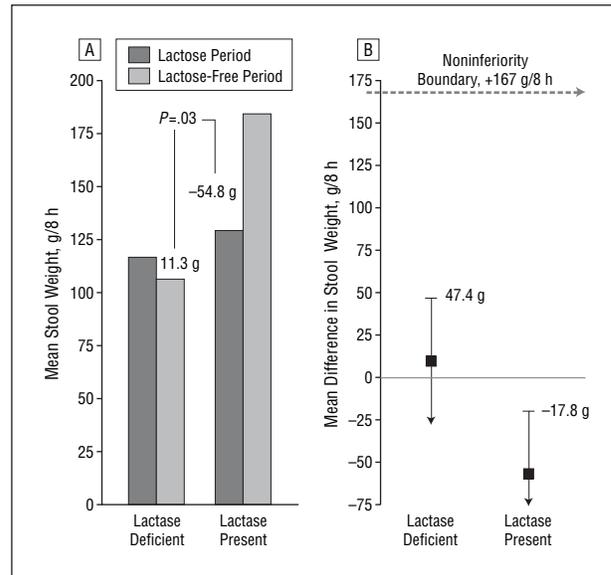
The LD group had a mean difference in stool output between the 2 periods of +11.3 g (upper 95% CL, +47.4 g), while in the LP group, the mean difference between the 2 periods was -54.8 g (upper 95% CL, -17.8 g). The stool output in the LD group differed significantly from the LP control group (66.1 g difference between groups; 95% CI, 11.84-122.3 g;  $P=.03$ ) (**Figure 2**).

### Secondary Outcome: Symptoms

For the entire group, the mean symptom scores were 4.7 and 5.5 during the lactose and lactose-free study peri-



**Figure 1.** Representations of stool weight measures. A, Mean stool weight for lactose and lactose-free 8-hour periods. The mean difference between the 2 periods is  $-41.3$  g. B, Mean difference in stool weight between lactose and lactose-free period, with upper 1-sided 95% confidence limit.



**Figure 2.** Representations of stool weight measures. A, Mean stool weight during lactose and lactose-free 8-hour periods for lactase-deficient and lactase-present groups. B, Mean difference in stool weight between lactose and lactose-free periods, with upper 1-sided 95% confidence limits for lactase-deficient and lactase-present groups.

ods, respectively. The mean difference between the 2 periods was  $-0.8$  (95% CI,  $-1.9$  to  $0.3$ ).

For the LD group, the mean difference in symptom scores between the 2 periods was  $1.0$  (95% CI,  $-2.5$  to  $4.5$ ), whereas for the LP group, the mean difference was  $-1.2$  (95% CI,  $-2.3$  to  $-0.1$ ). There was no significant difference in symptoms between the 2 groups ( $-2.2$  difference between groups; 95% CI,  $-5.0$  to  $0.5$ ;  $P = .11$ ).

There were no significant differences between the study periods in the total and diarrhea-specific symptom score for the 16 hours immediately following each period for the overall group or for the LP and LD subgroups.

Self-reported lactose avoidance and participant perception of symptoms were not significantly associated with a change in stool weight nor were they associated with increased symptoms during the lactose period (data not shown).

#### COMMENT

In this study, we have shown that empirical ingestion of moderate quantities of lactose-containing milk does not increase stool output or worsen symptoms in a sample of patients with diarrhea, predominantly white HIV-infected men who have sex with men, when compared with ingestion of lactose-free milk. In the subgroup analysis, there was a significant difference in stool output between the LD and the LP groups, largely due to a greater stool output in the latter group on the lactose-free study day (Figure 2). The reason for this finding in the LP group is unclear. We did not identify a missed lactose effect in this subgroup in the immediate poststudy period. Some might interpret our results to mean that lactose-hydrolyzed milk causes diarrhea in LP HIV-infected persons; however, there is no recognized biological mechanism to support this conclusion.

Despite the statistically significant difference in stool weight between the LD and LP groups, the clinical importance of this finding is questionable. The upper 95% CL of the mean difference in stool output between the 2 study periods suggests that at most, lactose would produce a mean increase of  $48$  g of stool in an 8-hour period in the LD group. This difference represents approximately 3 tablespoons of stool and is unlikely to be clinically significant. Similarly, the upper 95% CL of the difference in symptoms between the 2 study periods for the LD subgroup is small.

Our findings echo those from the non-HIV literature where moderate lactose ingestion has not been shown to worsen symptoms in otherwise healthy individuals.<sup>9,11</sup> In a nonblinded and uncontrolled study, Corazza et al<sup>12</sup> demonstrated an association between lactose ingestion and symptoms in the LD subset of a group of HIV-infected adults. Our findings are particularly robust because our randomized and controlled study was a noninferiority trial.<sup>23-25</sup> We can be 95% certain that the true difference in stool output between the 2 periods is no more than upper CL of this difference,  $-13.5$  g.

There are several limitations to this study. Primarily, there is no gold standard method to evaluate diarrhea. We used a change in stool weight as our primary measure because (1) it is easily quantifiable; (2) it is a logical choice for the osmotic diarrhea of LD; and (3) abnormal stool weight is generally agreed by clinicians to objectively define diarrhea.<sup>28</sup> Patient symptoms were also assessed because stool weight has been criticized as a criterion for failing to capture the more subjective symptoms associated with diarrhea such as stool frequency or abdominal cramps.<sup>29</sup> Our conclusion that lactose does not worsen HIV-related diarrhea is strong because it was consistent across 2 independent measures: one, objective and quantifiable; the second, subjective but patient centered.

The size of and the timing of the lactose load are also potential limitations. This is particularly a concern in a non-inferiority trial where a smaller lactose load could introduce bias (ie, toward a finding of no difference between the 2 test substrates). However, this dose is equivalent to that found in 1 glass of milk, which is representative of the amount of lactose that might be found in a normal diet; for this reason, this dose is extremely clinically relevant. Our choice of 12.5 g of lactose is in keeping with other studies where a similar physiologic dose of lactose was used.<sup>8,9,11,18</sup> Additionally, we evaluated the effects of lactose ingestion at a single point in time only. However, long-term lactose ingestion is likely to cause even fewer symptoms because persons with LD may develop tolerance to the effects of lactose (due to adaptation of colonic bacteria).<sup>30</sup>

The crossover design we used has some potential limitations, including period and sequence effects.<sup>31,32</sup> Formal statistical tests of period and sequence effects are discouraged because they are difficult to interpret.<sup>33</sup> We did not perform these tests but note that our study results appear similar when reported by order of intervention and study period (data not shown). We believe that the nature of the clinical problem being studied and the trial design we selected are appropriate to a crossover trial,<sup>33,34</sup> making important period or sequence effects unlikely.

Finally, the generalizability of our findings may be limited because our study sample was predominantly white men who have sex with men, with 80% taking antiretroviral medications. The composition of our sample may be of concern because the prevalence of LD is known to vary by racial group. In addition, most of our participants were taking antiretroviral medications; it is conceivable that LD related to HIV enteropathy may be more common in those who are not taking antiretroviral agents.

Deliberately, we evaluated the effect of lactose ingestion on a general population of HIV-infected individuals with diarrhea because we were interested in testing our hypothesis under the conditions that we had observed in clinical practice, that is, the recommendation of empirical lactose avoidance. In fact, we found that more than one third of our participants reported avoiding lactose, although in our sample, neither self-reported lactose avoidance nor perception of symptoms after lactose ingestion was associated with objective evidence of worsening diarrhea after lactose ingestion.

In summary, we have shown that moderate 1-time ingestion of lactose-containing milk does not worsen diarrhea significantly in HIV-infected persons, regardless of the presence or absence of LD. Therefore, avoidance of moderate quantities of milk (ie, 1 cup, equivalent to 12 g of lactose) may not be justified in this population. Further studies would be useful, specifically studies in different patient populations and with larger doses of lactose given over longer periods, to make more definitive recommendations.

It is well recognized that elimination diets such as a lactose-avoidance diet may lead to weight loss and that lactose avoidance is associated with osteoporosis.<sup>35</sup> In HIV-infected persons, diarrhea is also a risk factor for weight loss,<sup>36</sup> and even in the HAART era, weight loss remains a predictor of mortality.<sup>37</sup> Given the risks of malnutrition<sup>13</sup> and osteopenia in this population,<sup>14</sup> practitioners

may wish to encourage their HIV-infected patients with diarrhea to include moderate quantities of dairy products in their diets.

**Accepted for Publication:** January 24, 2006.

**Author Affiliations:** Departments of Medicine (Drs Tinmouth, Kandel, Tomlinson, Walmsley, and Steinhart) and Family and Community Medicine (Dr Glazier), University of Toronto; Division of Gastroenterology, Sunnybrook and Women's College Health Sciences Centre (Dr Tinmouth); Division of Gastroenterology (Dr Kandel) and Department of Family and Community Medicine and Centre for Research on Inner City Health (Dr Glazier), St Michael's Hospital; Department of Medicine (Dr Tomlinson) and Division of Infectious Diseases (Dr Walmsley), University Health Network; and Combined Division of Gastroenterology, Mount Sinai Hospital and University Health Network (Dr Steinhart), Toronto, Ontario.

**Correspondence:** Jill Tinmouth, MD, PhD, FRCPC, Division of Gastroenterology, Sunnybrook & Women's College Health Sciences Centre, 2075 Bayview Ave, Room HG40, Toronto, Ontario M4N 3M5, Canada (jill.tinmouth@sunnybrook.ca).

**Author Contributions:** Dr Tinmouth had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Financial Disclosure:** None.

**Funding/Support:** This study was funded by the Canadian Association of Gastroenterology, Oakville, Ontario; Canadian Institutes for Health Research, Ottawa, Ontario; Canadian HIV Trials Network, Vancouver, British Columbia; and Ontario HIV Trials Network, Toronto.

**Role of the Sponsor:** None of the study's funding agencies had a role in the study design or conduct; in the collection, analysis, or interpretation of data; in the preparation, review or approval of the final manuscript; or in the decision to submit the paper for publication.

**Acknowledgment:** We thank the Canadian Association of Gastroenterology, Canadian Institutes for Health Research, Canadian HIV Trials Network, and the Ontario HIV Trials Network for their support of this study. In addition, this study benefited tremendously from the expertise and assistance of Gail Stewart, RN, Laura Parsons, CPhT, Ann Kosinski, CPhT, APMR, Shawn Lauenders, BScPharm, and Cindy James, RN, BSCN.

## REFERENCES

1. Knox TA, Spiegelman D, Skinner SC, Gorbach S. Diarrhea and abnormalities of gastrointestinal function in a cohort of men and women with HIV infection. *Am J Gastroenterol*. 2000;95:3482-3489.
2. Call SA, Heudebert G, Saag M, Wilcox CM. The changing etiology of chronic diarrhea in HIV-infected patients with CD4 cell counts less than 200 cells/mm<sup>3</sup>. *Am J Gastroenterol*. 2000;95:3142-3146.
3. Heise C, Dandekar S, Kumar P, Duplanter R, Donovan RM, Halsted CH. Human immunodeficiency virus infection of enterocytes and mononuclear cells in human jejunal mucosa. *Gastroenterology*. 1991;100:1521-1527.
4. Sherman DS, Fish DN. Management of protease-inhibitor associated diarrhea. *Clin Infect Dis*. 2000;30:908-914.
5. Katabira ET. Epidemiology and management of diarrheal disease in HIV-infected patients. *Int J Infect Dis*. 1999;3:164-167.
6. Kapembwa MS, Batman PA, Fleming SC, Griffin GE. HIV enteropathy. *Lancet*. 1989;2:1521-1522.

7. Newcomer AD, McGill DB, Thomas PJ, Hofmann AF. Prospective comparison of indirect methods for detecting lactase deficiency. *N Engl J Med.* 1975;293:1232-1235.
8. Solomons NW, Garcia-Ibanez R, Viteri FE. Hydrogen breath test of lactose absorption in adults: the application of physiological doses and whole cow's milk sources. *Am J Clin Nutr.* 1980;33:545-554.
9. Suarez FL, Savaiano DA, Levitt ML. A comparison of symptoms after the consumption of milk or lactose-hydrolyzed milk by people with self-reported severe lactose intolerance. *N Engl J Med.* 1995;333:1-4.
10. Rosado JL, Allen LH, Solomons NW. Milk consumption, symptom response, and lactose digestion in milk intolerance. *Am J Clin Nutr.* 1987;45:1457-1460.
11. Johnson AO, Semenya JG, Buchowski MS, Enwonwu CO, Scrimshaw NS. Correlation of lactose maldigestion, lactose intolerance and milk intolerance. *Am J Clin Nutr.* 1993;57:399-401.
12. Corazza GR, Ginaldi L, Marani-Toro G, Di Giammartino D, Quaglino D. The impact of HIV infection on lactose absorptive capacity. *J Infect.* 1997;35:31-35.
13. AGA Patient Care Committee. AGA technical review: malnutrition and cachexia, chronic diarrhea and hepatobiliary disease in patients with human immunodeficiency virus infection. *Gastroenterology.* 1996;111:1724-1752.
14. Tebas P, Powderly WG, Claxton S, et al. Accelerated bone mineral loss in HIV-infected patients receiving potent antiretroviral therapy. *AIDS.* 2000;14:F63-F67.
15. Anastasi JK, Sun V. Controlling diarrhea in the HIV patient. *Am J Nurs.* 1996;96:35-41.
16. Rachlis A, Gill J, Baril J-G, et al. Effectiveness of step-wise intervention plan for managing nelfinavir-associated diarrhea: a pilot study. *HIV Clin Trials.* 2005;6:203-212.
17. Winson SKG. Management of HIV-associated diarrhea and wasting. *J Assoc Nurses AIDS Care.* 2001;12:55-62.
18. Strocchi A, Corazza GR, Ellis CJ, Gasbarrini G, Levitt M. Detection of malabsorption of low doses of carbohydrate: accuracy of various breath H<sub>2</sub> criteria. *Gastroenterology.* 1993;105:1404-1410.
19. Corazza GR, Benati G, Strocchi A, Malservisi S, Gasbarrini G. The possible role of breath methane measurement in detecting carbohydrate malabsorption. *J Lab Clin Med.* 1994;124:695-700.
20. Jellinek G. *Triangle Test: Sensory Evaluation of Food: Theory and Practice*. Chichester, England: Ellis Horwood Ltd; 1985:204-247.
21. Briet F, Pochart P, Marteau P, Flourie B, Arrigoni E, Rambaud JC. Improved clinical tolerance to chronic lactose ingestion in subjects with lactose intolerance: a placebo effect? *Gut.* 1997;41:632-635.
22. Holodniy M, Koch J, Mistal M, et al. A double blind, randomized, placebo-controlled phase II study to assess the safety and efficacy of orally administered SP-303 for the symptomatic treatment of diarrhea in patients with AIDS. *Am J Gastroenterol.* 1999;94:3267-3273.
23. Timmouth JM, Steele LS, Tomlinson G, Glazier RH. Are claims of equivalency in digestive diseases trials supported by the evidence? *Gastroenterology.* 2004;126:1700-1710.
24. Jones B, Jarvis P, Lewis JA, Ebbutt AF. Trials to assess equivalence: the importance of rigorous methods. *BMJ.* 1996;313:36-39.
25. Greene WL, Concato J, Feinstein AR. Claims of equivalence in medical research: are they supported by the evidence? *Ann Intern Med.* 2000;132:715-722.
26. Detsky AS, Naglie IG. Subgroup analyses: primary and secondary. *ACP J Club.* 1995;122:A12-A14.
27. Carpenter J, Bithell J. Bootstrap confidence intervals: when, which, what? a practical guide for medical statisticians. *Stat Med.* 2000;19:1141-1164.
28. Powell DW. Approach to the patient with diarrhea. In: Yamada T, ed. *Textbook of Gastroenterology*. 3rd ed. Philadelphia, Pa: Lippincott, Williams & Wilkins; 1999:858-909.
29. Fine K. Diarrhea. In: Feldman M, Scharschmidt BF, Sleisenger MH, Fordtran JS, Zorab R, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management*. 6th ed. Toronto, Ontario: WB Saunders Co; 1998:128-152.
30. Hertzler SR, Savaiano DA. Colonic adaptation to daily lactose feeding in lactose maldigesters reduces lactose intolerance. *Am J Clin Nutr.* 1996;64:232-236.
31. Louis TA, Lavori PW, Bailar JC, Polansky M. Crossover and self-controlled designs in clinical research. *N Engl J Med.* 1984;310:24-31.
32. Woods JR, Williams JG, Tavel M. The two-period crossover design in medical research. *Ann Intern Med.* 1989;110:560-566.
33. Senn SJ. Cross-over trials, carry-over effects and the art of self-delusion. *Stat Med.* 1988;7:1099-1101.
34. Fleiss JL. A critique of recent research on the two-treatment crossover design. *Control Clin Trials.* 1989;10:237-243.
35. Corazza GR, Benati G, Di Sario A, et al. Lactose intolerance and bone mass in postmenopausal Italian women. *Br J Nutr.* 1995;73:479-487.
36. Smit E, Skolasky RL, Dobs AS, et al. Changes in the incidence and predictors of wasting syndrome related to human immunodeficiency virus infection, 1987-1999. *Am J Epidemiol.* 2002;156:211-218.
37. Tang AM, Forrester J, Spiegelman D, Knox TA, Tchetgen E, Gorbach SL. Weight loss and survival in HIV-positive patients in the era of highly active antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2002;31:230-236.