

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

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OBJECTIVE: The aim of this study was to investigate the safety and effectiveness of orally administered SP-303 in patients with AIDS and diarrhea.

METHODS: This is a multicenter, phase II, randomized, double blind, placebo-controlled study. HIV-positive subjects with a history of a CD4 count <200 or an AIDS-defining illness were admitted to an inpatient study unit and screened for diarrhea defined as at least three abnormal (*i.e.*, soft or watery) stools and >200 g of abnormal stool weight over a 24-h period. Subjects discontinued all antidiarrheal agents >24 h before enrollment. Stool samples were studied for routine pathogens. Subjects received 500 mg *p.o.* of SP-303 or placebo every 6 h for 96 h (4 days). Stool frequency and weights were recorded. Subjects were monitored for symptoms and side effects and were seen 1 wk later in follow-up.

RESULTS: A total of 26 subjects received SP-303, and 25 received placebo. There were no significant demographic differences between treatment arms. A total of 41 subjects (80%) were receiving antiretroviral therapy and 39 subjects (77%) were receiving at least one protease inhibitor. Stool studies revealed no pathogens in 48 of 51 patients (94%). There were no serious adverse events or laboratory abnormalities. The SP-303 treatment group demonstrated a mean reduction from baseline stool weight of 451 g/24 h *versus* 150 g/24 h with placebo on day 4 of treatment ($p = 0.14$), and a mean reduction in abnormal stool frequency of three abnormal stools in 24 h *versus* two in 24 h in the placebo group ($p = 0.30$). Daily measures analysis over 4 days of treatment demonstrated that SP-303 subjects had a significant reduction in stool weight ($p = 0.008$) and abnormal stool frequency ($p = 0.04$) when compared to placebo-treated subjects.

CONCLUSIONS: SP-303 is safe and well tolerated. These results suggest that SP-303 may be effective in reducing stool weight and frequency in patients with AIDS and

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INTRODUCTION

Diarrhea is a frequent problem among patients infected with HIV-1 (1). Before the introduction of HIV-1 protease inhibitors, infectious causes were identified in approximately two-thirds of diarrheal episodes (2). Although the incidence of pathogen-associated diarrhea may be decreasing after highly active antiretroviral therapy (HAART) (3–5), many patients with AIDS continue to have chronic diarrhea with no identifiable pathogen despite an extensive evaluation (6).

Some of these patients may have unidentified pathogens, HIV-associated enteropathy, or medications as causes of diarrhea (7). In some studies, 30% of patients taking protease inhibitors experienced mild to severe diarrhea (8). In addition, the prevalence of diarrhea during HAART therapy may be underreported because of embarrassment and the widespread use of prescription and over-the-counter anti-diarrheal medications. Regardless of the cause, diarrhea has resulted in decreased quality of life (9, 10) and significantly greater economic costs (10) for affected patients with AIDS when compared to those without diarrhea. Therefore, evaluation of effective treatments for diarrhea in patients with AIDS is important for quality of life issues as well as nutritional concerns.

SP-303 (Provir) is a proanthocyanidin oligomer that has been isolated and purified from the latex of *Croton lechleri* (family *Euphorbiaceae*). This plant species is widely distributed throughout Western Amazonian South America (11). The red, viscous latex from this plant is widely known for its medicinal properties, including relief of diarrhea (12–15). According to ethnobotanists who have interviewed indigenous populations using this plant product, side effects are minimal after routine oral use (15, unpublished observations). Although the precise cellular mechanism of SP-

303 action remains to be fully elucidated, it has been found to decrease chloride ion secretion in gastrointestinal tract cells (16).

In the current study, we investigated the safety and efficacy (as measured by a decrease in stool weight and abnormal stool frequency) of SP-303 in the treatment of diarrhea in patients with AIDS.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board at each academic center. Informed consent was obtained from all subjects during an initial screening visit. Subjects were evaluated with routine screening laboratories including serum chemistry and hematology panels, urinalysis, and urine drug screen for illicit drugs. If not performed in the 3 months before enrollment, HIV plasma viral load (Quantiplex 2.0; Chiron, Emeryville, CA) and T cell subsets (PathLabs, San Jose, CA) were measured. Stool culture for pathogens including mycobacteria, ova, and parasite examination including *Cryptosporidium*, and *Clostridium difficile* toxin assay were also performed. Subjects could be either men or women. Subjects were required to be between 18 and 60 yr of age; to have HIV-1 infection confirmed by standard serological screening (positive ELISA and Western blot tests); to have a diagnosis of AIDS based on CDC criteria (17); and to be on a stable medical regimen for treatment of HIV disease and associated conditions for ≥ 2 wk before screening and for the duration of the trial. Subjects were not permitted in the study if they were pregnant (as determined by a serum pregnancy test) or nursing; if they had a neutrophil count less than 500 cells/ μ l; if they had decompensated liver disease (total bilirubin >3 mg/dl, protime >3 times control, and albumin <3 g/dl); if they had a creatinine clearance of $<25\%$ of predicted; or if they were previously enrolled in a study in which they received SP-303 or any investigational drug within 30 days before entrance into the study. Subjects with chronic diarrhea were recruited for this study, and all subjects were questioned regarding the average number of stools produced per day in the month, wk, and 24-h period before study enrollment. Subjects with a history of three or more abnormal stools (defined as soft or watery) per day and who met the above criteria were admitted to a clinical research ward at one of two academic medical centers. Subjects were required to discontinue all anti-diarrheal medications ≥ 24 h before entry into the study unit.

In the study unit, subjects were allowed to choose their diet from the selections offered by the institution. All bowel movements during a 24-h observation period were weighed and recorded to determine baseline daily stool weight and frequency. Study personnel also assessed the consistency of each bowel movement according to the following definitions: 1) watery: stool can be poured; 2) soft: stool takes the shape of the container; 3) formed: stool retains shape. Subjects with >200 g of abnormal stool weight and three or

more abnormal bowel movements documented during the baseline 24-h period were randomized into one of two groups; study medication was prepackaged in a blinded, randomized fashion using a table of sequential random numbers. Subjects were administered two capsules *p.o.* containing either 250 mg of SP-303 delayed release beads (total dose 500 mg) or placebo every 6 h, for a total of 16 consecutive doses or 32 capsules. Study personnel and subjects were blinded throughout the trial. Subjects remained in the study unit throughout the screening period (24 h), treatment period, and 6 h after the last dose of study medication (a total of 96 h after the first dose). During the course of this trial from the screening period until the end of treatment, subjects were not allowed to take anti-diarrheal medication (*e.g.*, antimotility agents, antisecretory agents, or bulking agents). Study personnel also recorded the weight and consistency of all bowel movements during the treatment phase. Once the subject was discharged from the study unit, they were allowed to resume self-administration of routine and any anti-diarrheal medications. All study subjects were instructed to return approximately one week (7–9 days) after the administration of the last dose of study medication for outpatient assessment of safety.

Adverse experiences were assessed by recording the subject's complaints and documenting physical examination observations as necessary during the treatment phase and 1 wk after the administration of the last dose of study drug. Routine physical examinations were performed at the screening visit, end of the treatment phase, and 1 wk after the administration of the last dose of study drug. In addition, laboratory studies relevant to safety (hematology, chemistry, and urinalysis panels) were performed at the screening visit, end of the treatment phase, and 1 wk after the administration of the last dose of study drug.

To determine stool chloride levels, approximately 2–4 g of stool was placed in a previously weighed 5-ml polypropylene tube. The tube was placed in an oven overnight to dehydrate the stool. The tube containing dried stool was then weighed. Stool weight was then calculated by subtracting the empty tube weight from the tube plus dry stool combined weight. A quantity of 2 ml of deionized, glass-distilled water was then added to each tube. The tubes were vigorously mixed to bring the dried stool into solution. Chloride concentration was determined from an aliquot of this solution using a chloride ion-selective electrode (Beckman Synchron Cx Delta System, Beckman Instruments, Brea, CA). The resulting millimolar concentrations were converted to milliequivalents (mEq) of chloride ion per gram of stool. Samples for which the chloride concentration was undetectable were assigned a value of one-half the lower limit of detection (10 mEq/L). If stool chloride measurements were missing for a stool that had a sample taken, the subject's average daily stool chloride concentration for that day was substituted for the missing value.

Statistical Analysis

The primary efficacy parameters were stool weight and abnormal stool frequency. Daily totals of stool weight and abnormal stool number were computed at baseline and on treatment days 1–4. If a stool was recorded but the weight was missing, the average daily weight of stools on that day was used to replace the missing value. Adjustments for baseline weights and baseline stool frequencies were made in the analysis models through the use of covariates or other means wherever possible. Tests were considered to be significant if the p value was <0.05 (two tailed).

Change from baseline was analyzed using both the Wilcoxon rank sum test and a daily measures approach, which employed random regression models (RRM) as described by Gibbons *et al.* (18). For each subject in the RRM analysis, a simple linear regression line was fit to the 24-h stool weights collected at baseline and treatment days 1–4 using least squares regression. The slope of the line represents the average daily change in stool weight or frequency during the study. Average daily change values were compared using a two tailed t test.

Secondary efficacy parameters were daily output of stool chloride and daily gastrointestinal index score (DGIS). Daily output of stool chloride was analyzed by comparing daily totals and daily mean concentrations between treatment groups as well as by analyzing change from baseline using the Wilcoxon rank sum test. To compute the gastrointestinal index score (GIS), the uniform score of 0 (none), 1 (mild), 2 (moderate), and 3 (severe) were assigned at 6-h intervals to each of the following seven gastrointestinal complaints: nausea, vomiting, abdominal pain/cramps, excess gas/flatulence, urgency tenesmus, and fecal incontinence. The DGIS is the sum of the four 6-h interval scores within a 24-h period for all seven gastrointestinal complaints and can range from a minimum of 0 to a maximum sum of 84. The percent change in DGIS from baseline was analyzed using the Wilcoxon rank sum statistic.

All other comparisons between the two treatment groups were calculated on means or frequency counts using Fisher's exact test for categorical data and the Wilcoxon rank sum statistic for continuous data.

RESULTS

The study enrolled 51 patients with AIDS and diarrhea (26 received SP-303 and 25 received placebo). Six of the 51 patients did not meet at least one entry criterion for the study (three were HIV-positive but did not have a confirmed AIDS diagnosis, and one of the three also had a creatinine clearance $<25\%$ predicted; two did not meet stool criteria; and one had a confounding medical condition). There were no significant differences between the treatment arms with respect to any of the baseline demographic variables examined, including age, gender, race, past medical history, stool output history, CD4 count, or viral load (Table 1). The mean

number of abnormal stools/day for all patients in the month before study entry was 5.7. Approximately 50% of patients were rated as moderate (five to eight abnormal stools) or severe (nine or more abnormal stools) in disease severity, based on the 24-h screening period. The mean (\pm SEM) baseline stool weight and abnormal stool frequency during the 24-h screening period were 865.4 (108.6) g and 5.2 (0.4) abnormal stools, respectively, and did not differ significantly between groups.

Of the 51 patients, 48 (94.1%) had no recognized pathogen identified from their screening stool sample (culture, microscopic examination, and toxin assay). Two subjects had a positive *C. difficile* toxin assay, and a third had a culture positive for *Campylobacter*. A total of 41 subjects (80%) were receiving antiretroviral therapy and 39 subjects (77%) were receiving at least one protease inhibitor. Treatment with SP-303 was well tolerated, with no major imbalance between groups in the occurrence of adverse events or in treatment-emergent laboratory abnormalities. There were no serious adverse events reported in either treatment group.

There was no difference between treatment arms in the pattern of gastrointestinal symptoms associated with diarrhea. The mean DGIS at baseline for all subjects was only 8.6 out of a possible maximum of 84. With respect to the mean daily gastrointestinal scores of the seven individual symptoms, all but two values were <2 out of a possible maximum of 12. The changes in the mean DGIS, as well as the individual mean daily gastrointestinal scores over the 4-day course of treatment, were not statistically different between the two treatment arms.

The SP-303-treated group demonstrated a mean reduction from baseline in daily stool weight of 451.3 g/24 h at day 4 of treatment, as compared to 150.7 g/24 h in the patients receiving placebo ($p = 0.14$; Fig. 1). Nine of 26 (35%) patients in the SP-303 group experienced a reduction of >500 g/24 h, as compared to two of 24 (8%) patients in the placebo group after 4 days of treatment (one patient in the placebo group dropped out on day 1 as a treatment failure). In addition, abnormal stool frequency, which was 5.2 abnormal stools/24 h in both groups at baseline, decreased at day 4 by a mean of 3.0/24 h in patients receiving SP-303, versus a mean reduction of 2.0/24 h in the placebo ($p = 0.30$; Fig. 2). An analysis of the treatment effect over 4 days based on evaluation of daily measurements by random regression models indicated that patients treated with SP-303 experienced a statistically significant reduction in stool weight ($p = 0.008$) and in abnormal stool frequency ($p = 0.04$) when compared with placebo.

Mean daily stool chloride concentration in the SP-303 group declined by a mean of 7.1 mEq/g after 4 days ($p = 0.037$), as compared to an increase of 3.4 mEq/g in the placebo group ($p = 0.41$). The difference in day 4 mean change from baseline values between the SP-303 and placebo groups bordered on significance ($p = 0.05$; Fig. 3).

Table 1. Baseline Demographics and Disease Severity

	SP-303	Placebo	<i>P</i> Value
No. patients*	26	25	
Age (yr)			0.074
Mean (SEM)	42.0 (1.7)	38.1 (1.5)	
Median	42	37	
Range	21-60	27-55	
Sex (% male)	96.2	96.0	1.000
Race (%)			0.332
Caucasian	73.1	52.0	
Hispanic	15.4	20.0	
African-American	11.5	20.0	
Other		8.0	
Unformed stools/day in last month	25	24	0.187
Mean (SEM)	5.4 (1.1)	6.0 (1.0)	
Median	4	5	
Range	0-30	0-25	
CD4 cell count (cells/ μ l)			0.962
Mean (SEM)	227.7 (43.4)	238.6 (45.6)	
Median	180	176	
Range	6-1015	4-836	
Viral load (\log_{10} /ml)			0.605
Mean (SEM)	3.6 (0.2)	3.8 (0.2)	
Median	3	4	
Range	3-6	3-6	
Baseline stool weight (g/24 h)			0.200
Mean (SEM)	914.8 (132.2)	813.9 (176.0)	
Median	763	568	
Range	280-3407	206-4701	
Baseline abnormal stool frequency (stools/24 h)			0.915
Mean (SEM)	5.2 (0.5)	5.2 (0.5)	
Median	5	5	
Range	1-14	3-12	

* Incomplete data were available for one patient in the SP-303 group and one patient in the placebo group.

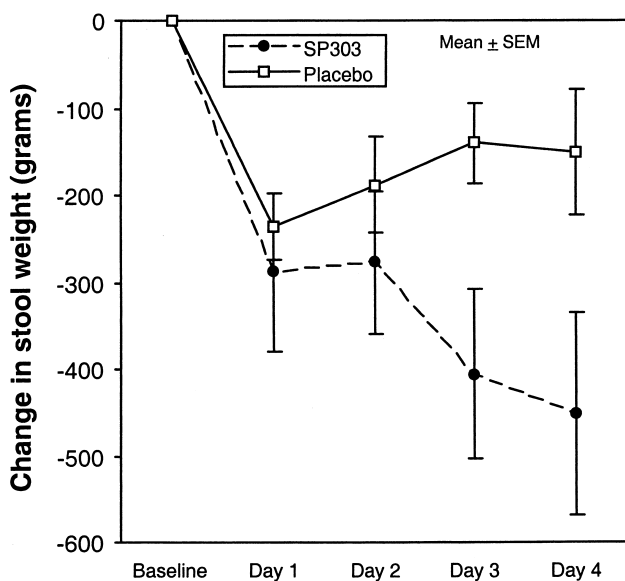


Figure 1. Change in daily mean stool weight (grams) for SP-303 (●) and placebo (□) groups. Comparison of baseline total weight to total weight on each day of treatment.

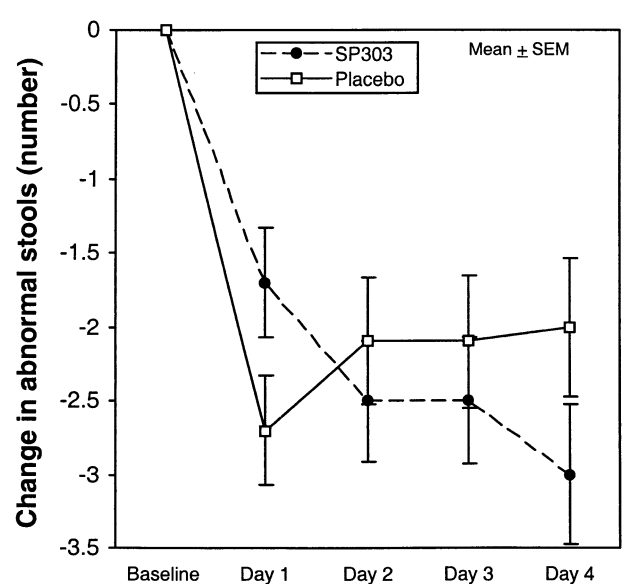


Figure 2. Change in mean abnormal stool number for SP-303 (●) and placebo (□) groups. Comparison of baseline abnormal stool number to total number on each day of treatment.

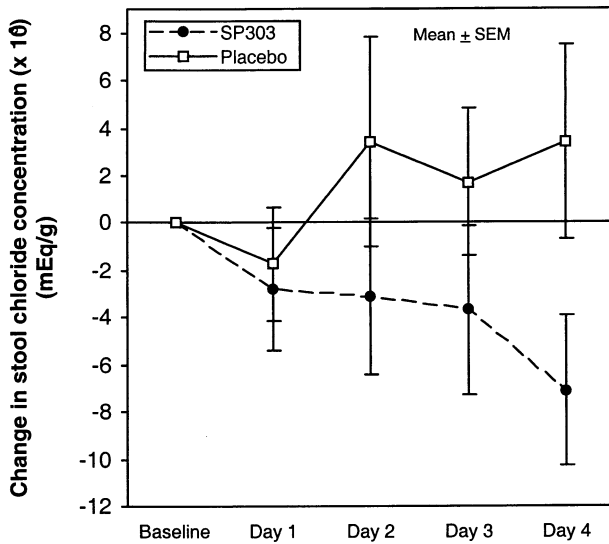


Figure 3. Change in daily mean stool chloride concentration (mEq/g) for SP-303 (●) and placebo (□) groups. Comparison of baseline mean chloride concentration to mean chloride concentration on each day of treatment.

DISCUSSION

The results of our study suggest that SP-303 may be effective in reducing stool weight and abnormal stool frequency in patients with AIDS and chronic diarrhea. Interestingly, a comparable decrease in abnormal stool frequency and in stool weight was seen in both treatment arms during the first 24 h of study drug administration. This may have been the result of several factors including dietary modification, decreased physical activity, and/or some degree of “placebo” effect associated with admission to a research ward and enrollment into a clinical study. Some subjects reported substantially different diets at home when compared to the diet they received in the study unit. After day 1, both mean daily stool weight and abnormal stool frequency continued to decrease further in the SP-303 group, but increased in the placebo group. When analyzed by daily measures over the 4-day course of treatment, the reductions in abnormal stool frequency and stool weight were significantly greater in patients treated with SP-303.

A potential pathogen was identified in only three subjects. This may be related in part to sampling sensitivity (only one stool sample was analyzed per subject) (2), the effectiveness of HAART therapy, antimicrobial prophylaxis, or the fact that invasive or special examinations required to identify some pathogens were not performed in this study (1). In addition, many patients in the study had undergone previous evaluations for diarrhea, at which time identified pathogens may have been treated. Diarrhea is a known side effect of many protease inhibitors as well as of other antiretroviral therapies (8). Our results emphasize that significant diarrhea, without an obvious pathogen, was still present even though >75% of patients were receiving HAART. The

number of subjects not receiving protease inhibitors was too small to analyze whether diarrhea differed clinically between subjects receiving protease inhibitors as compared to those who were not. In addition, the cohort size was too small to determine whether there were different responses between different protease inhibitor-containing regimens.

Classical infectious causes of secretory diarrhea are the result of bacterial toxins, which bind to apical receptors on epithelial cells in the small intestine (19, 20) and increase levels of intracellular cyclic nucleotides (21). This results in the opening of chloride ion channels and the secretion of excess chloride into the intestinal lumen down a concentration gradient (21). As the bacterial toxin also inhibits absorption of sodium chloride, the excess ions cause an osmotically driven flow of fluid into the intestinal lumen that results in watery diarrhea (22, 23). Therefore, agents that inhibit small bowel ion secretion may be effective in decreasing this form of diarrhea.

Although stool chloride concentrations are known in classical bacterial toxin-associated diarrhea, stool chloride concentrations have not been previously studied in AIDS-associated diarrhea. Our study demonstrated that diarrhea in patients with AIDS presents with a wide variability in stool frequency, weight, and consistency, and stool chloride concentrations were variable as well. Nevertheless, we found a statistically significant decrease in stool chloride concentration after 4 days of treatment with SP-303 when compared to placebo. Several agents have been found to inhibit chloride ion secretion *in vitro* or in animal models of secretory diarrhea (24–26). SP-303 has been shown to reduce basal and stimulated transmembrane chloride-dependent current flux across intestinal CaCo-2 cells *in vitro* as measured in an Ussing Chamber (16). SP-303 reverses the current stimulated by forskolin, a known stimulator of c-AMP-mediated chloride ion secretion. In addition, orally administered SP-303 reduces cholera toxin-induced intestinal fluid accumulation in a sealed-anus mouse model 3 h after cholera toxin had been administered (16). Whether the stool chloride findings in our study reflect a physiological effect of treatment with SP-303 is unknown.

The precise mechanism of diarrhea in patients with AIDS, particularly pathogen-negative syndromes, is not clear. The analysis of gastrointestinal tissue samples from subjects with AIDS and diarrhea, in general, reveal minor morphologic changes and a malabsorptive capacity (27). This malabsorption appeared worse in microsporidial disease when compared to pathogen-negative diarrhea (28). Clinically, diarrhea in patients with AIDS consists of water loss and stools containing little or no bulk. Certain factors such as tumor necrosis factor- α (TNF- α) have been shown to increase chloride ion secretion (29). In addition, increased stool levels of TNF- α have been found in pathogen-associated diarrhea in patients with AIDS (30). Elevated serum levels of vasoactive intestinal peptide (VIP), which promotes small intestine ion transport resulting in a secretory diarrhea, have been found in patients with AIDS and diar-

rhea (31). However, an injectable somatostatin analog (known to inhibit VIP secretion) was not significantly effective in reducing diarrhea in patients with AIDS (32). Thus, there is conflicting evidence regarding the secretory nature of diarrhea in patients with AIDS (33, 34), and the precise role of chloride ion secretion in the watery diarrhea syndrome of AIDS-associated diarrhea is not known.

In summary, 4 days of oral therapy with SP-303 resulted in a decrease in stool weight, frequency, and chloride secretion in patients with AIDS and diarrhea. Further studies to determine whether a longer duration of SP-303 treatment would be even more efficacious in AIDS-associated diarrhea are currently underway.

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REFERENCES

- Framm SR, Soave R. Agents of diarrhea. *Med Clin North Am* 1997;81:427-47.
- Sharpstone D, Gazzard B. Gastrointestinal manifestations of HIV infection. *Lancet* 1996;348:379-83.
- Carr A, Marriot D, Field A, et al. Treatment of HIV-1 associated microsporidiosis and cryptosporidiosis with combination antiretroviral therapy. *Lancet* 1998;351:256-61.
- Foudraine NA, Weverling GJ, van Gool T, et al. Improvement of chronic diarrhea in patients with advanced HIV-1 infection during potent antiretroviral therapy. *AIDS* 1998;12:35-41.
- Kim LS, Hadley WK, Stansell J, et al. Declining prevalence of cryptosporidiosis among patients with AIDS in San Francisco. *Clin Infect Dis* 1998;27:655-6.
- Blanshard C, Gazzard BG. Natural history and prognosis of diarrhea of unknown cause in patients with acquired immunodeficiency syndrome (AIDS). *Gut* 1995;36:283-6.
- DuPont HL, Marshall GD. HIV-associated diarrhea and wasting. *Lancet* 1995;346:352-6.
- McDonald C, Kuritzkes D. Human immunodeficiency virus type 1 protease inhibitors. *Arch Intern Med* 1997;157:951-9.
- Watson A, Samore MH, Wanke CA. Diarrhea and quality of life in ambulatory HIV-infected patients. *Dig Dis Sci* 1996;41:1794-1800.
- Lubeck DP, Bennett CK, Mazonson PD, et al. Quality of life and health service use among HIV-infected patients with chronic diarrhea. *J Acquired Immune Defic Syndr* 1993;6:478-84.
- Ubillas R, Jolad S, Bruening R, et al. SP-303, an antiviral oligomeric proanthocyanidin from the latex of *Croton lechleri* (Sangre de Drago). *Phytomed* 1994;1:77-106.
- McRae W, Hudson J, Towers F. Studies on the pharmacological activity of Amazonian Euphorbiaceae. *J Ethnopharmacol* 1988;22:143-72.
- Von Reis S, Lipp E. New plant sources for drugs and foods from the New York Botanical Garden. Cambridge: Harvard University Press, 1982.
- Vlietinck A. Biologically active substances from traditional drugs. In: Hostettmann K, Lea P, eds. *Biologically active natural products*. Oxford: Clarendon Press, 1987:33-47.
- Persinos-Perdue F, Blomster R, Blake D, et al. South American plants II: Taspine isolation and anti-inflammatory activity. *J Pharm Sci* 1979;68:124-6.
- Gabriel SE, Davenport SE, Steagall RJ, et al. A novel plant-derived inhibitor of cAMP-mediated fluid and chloride secretion. *Am J Physiology* 1999;276:658-63.
- CDC. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR* 1992, 41 (no. RR-17).
- Gibbons R, Hedeker D, Elkin I, et al. Some conceptual and statistical issues in analysis of longitudinal psychiatric data. *Arch Gen Psychiatry* 1993;50:739-50.
- Greenough, WB. *Vibrio cholerae* and cholera. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and practices of infectious diseases*, 4th ed. New York: Churchill Livingstone, 1995:1934-5.
- Guerrant RL. Principles and syndromes of enteric infection. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and practices of infectious diseases*, 4th ed. New York: Churchill Livingstone, 1995:945-62.
- Chao AC, de Sauvage FJ, Dong Y-J, et al. Activation of intestinal CFTR Cl⁻ channel by heat-stable enterotoxin and guanylin via cAMP-dependent protein kinase. *EMBO J* 1994;13:1065-72.
- Sears CL, Guerrant RL, Kaper JB. Enteric bacterial toxins. In: Blaser MJ, Smith PD, Ravdin I, et al., eds. *Infections of the gastrointestinal tract*. New York: Raven Press, 1995:617-34.
- Guerrant RL, Thielman NM. Types of *Escherichia coli* and enteropathogens. In: Blaser MJ, Smith PD, Ravdin I, et al., eds. *Infections of the gastrointestinal tract*. New York: Raven Press, 1995:687-707.
- Donowitz M, Levine S, Watson A. New Drug Treatments for diarrhea. *J Intern Med* 1990;228(suppl 1):155-63.
- Singh AK, Afink GB, Venglarik CJ, et al. Colonic Cl channel blockade by three classes of compounds. *Am J Physiol* 1991;260:C51-63.
- Rabbani GH. Mechanism and treatment of diarrhea due to *Vibrio cholerae* and *Escherichia coli*: Role of drugs and prostaglandins. *Dan Med Bull* 1996;43:173-85.
- Bjarnason I, Sharpstone DR, Francis N, et al. Intestinal inflammation, ileal structure and function in HIV. *AIDS* 1996;10:1385-91.
- Lambl BB, Federman M, Pleskow D, et al. Malabsorption and wasting in AIDS patients with microsporidia and pathogen-negative diarrhea. *AIDS* 1996;10:739-44.
- Schmitz H, Fromm M, Bode H, et al. Tumor necrosis factor-alpha induces Cl⁻ and K⁺ secretion in human distal colon driven by prostaglandin E2. *Am J Physiol* 1996;271:G669-74.
- Sharpstone DR, Rowbottom AW, Nelson MR, et al. Faecal tumor necrosis factor- α in individuals with HIV-related diarrhea. *AIDS* 1996;10:989-94.
- Manfredi R, Vezzadini P, Costigliola P, et al. Elevated plasma levels of vasoactive intestinal peptide in AIDS patients with

- refractory idiopathic diarrhea. Effects of treatment with octreotide. *AIDS* 1993;7:223-6.
32. Simon DM, Cello JP, Valenzuela J, et al. Multicenter trial of octreotide in patients with refractory acquired immunodeficiency syndrome-associated diarrhea. *Gastroenterology* 1995; 108:1753-60.
 33. Stockman M, Fromm M, Schmitz H, et al. Duodenal biopsies of HIV-infected patients with diarrhea exhibit epithelial barrier defects but no active secretion. *AIDS* 1998;12:43-51.
 34. Kelly P, Thillainayagam AV, Smithson J, et al. Jejunal water and electrolyte transport in human cryptosporidiosis. *Dig Dis Sci* 1996;41:2095-9.