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Chapter 5

“Improvement of chronic diarrhoea in patients with advanced HIV-1 infection during potent antiretroviral therapy”

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Summary

A substantial number of patients with advanced HIV infection suffer from intractable diarrhoea. The aim of this study was to evaluate whether potent antiretroviral therapy could alleviate such diarrhoea.

In an open randomized study the effect of the HIV protease inhibitor indinavir in combination with nucleoside analogue reverse transcriptase inhibitors on chronic HIV related diarrhoea was investigated in 14 late stage (CD4⁺ lymphocyte count ≤ 50 x 10⁶/l) HIV infected patients. Data concerning stool frequency, stool consistency and antidiarrhoeal drug use were collected in daily kept diaries over a 24-week period. Endpoints of the study were reduction of stool frequency, improvement of stool consistency, weight gain and in case of diarrhoea due to Enterocytozoon bieneusi or Cryptosporidium sp. disappearance of these parasites from stool.

Thirteen patients started the study drug indinavir. One patient died after 1 week and one patient withdrew prematurely after 18 weeks. Median stool frequency declined from 5.8 daily at baseline to 2.3 daily after 24 weeks (P=0.04). Stool consistency improved considerably over the study period: before treatment 56% of stools were watery and 0% were formed; at week 24 these figures were 0 and 33%, respectively. Body weight increased significantly with a median increment of 6.6 kg at week 24 (P=0.0006). In two out of six patients with microsporidiosis and both patients with cryptosporidiosis, stools were free of parasites at week 24. Five out of six patients who used non-specific antidiarrhoeal medication on a regular basis prior to the study had ceased to do so at the end.

The use of potent antiretroviral therapy in patients with advanced HIV infection can improve chronic HIV related diarrhoea and in some cases lead to disappearance of *E. bieneusi* and *Cryptosporidium sp.* from the stools.
Introduction

Patients with HIV-1 infection are prone to a wide range of opportunistic disease manifestations including diarrhoea, which is experienced by over 50% of patients with AIDS at some time during their illness, and is associated with a significant degree of morbidity and even mortality. In patients with chronic diarrhoea specific pathogens may be isolated in up to 75 - 80 percent [1], with the protozoal parasites Cryptosporidium and Microsporidium being particularly common, and preferentially causing diarrhoea in patients with severely depressed peripheral blood CD4⁺ lymphocyte counts [2,3]. Although anecdotal success has been reported with the use of various drugs such as albendazole and paromomycin for the treatment of intestinal crypto- and microsporidiosis, none of these agents has been found to be effective for the treatment of infection with Enterocytozoon bieneusi in controlled clinical trials [4-6]. In contrast, albendazole is very effective against the Microsporidium subspecies Encephalitozoonidae such as E. intestinalis. Thus, most patients with E. bieneusi depend on the use of non-specific antidiarrhoeal medication (loperamide, opioids, and octreotide) for the control of symptoms. In up to one-quarter of patients, no responsible causative microorganism is found and the diarrhoea is usually considered to be a non-specific manifestation of the underlying HIV infection.

The use of HIV-1 protease-inhibitors, especially in combination with nucleoside analogue reverse transcriptase inhibitors, has allowed the achievement of unprecedented degrees of suppression of HIV-1 replication in a substantial proportion of patients, which have been associated with marked increases in CD4⁺ lymphocyte count [7-9] improvement in T-lymphocyte function [10], and reduction in disease progression and mortality [11].

In view of these considerations, we decided to test the hypothesis of whether clinical benefit could be demonstrated by administering the protease inhibitor indinavir to patients with chronic uncontrolled cryptosporidial, microsporidial or unexplained diarrhoea when the protease inhibitor indinavir was made available for 14 patients in The Netherlands in the framework of an international compassionate use protocol for HIV-1-infected patients with fewer than 50 x 10⁶/ l CD4⁺ lymphocytes. In addition, in those with parasitic diarrhoea, the effect of treatment was evaluated on the shedding of Cryptosporidium and Microsporidium in stools.
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Methods

Patients

Patients could be enrolled in the study if they had a history of chronic diarrhoea that was associated with intestinal Cryptosporidium or Microsporidium infection, or was unexplained. Chronic diarrhoea was defined as the continuous presence for at least 1 month of at least twice daily watery or loose stools. Diarrhoea was considered to be unexplained if within a 3-month period prior to enrolment the following examinations had revealed no specific abnormalities: stool examination for culture of common bacterial diarrhoeal pathogens, stool examination for ova and parasites (three times or more), colonoscopy and mucosal biopsy for the presence of characteristic inclusions or specific antigen compatible with a diagnosis of cytomegalovirus (CMV) colitis. In addition, a stool culture for Mycobacterium avium intracellulare was obtained at the time of enrolment. Additional inclusion criteria included age 18 years or more, CD4+ lymphocyte count $\leq 50 \times 10^6/l$ on two determinations at least one week apart, haemoglobin $\geq 6.5$ g/dl, absolute neutrophil count $\geq 500 \times 10^6/l$ platelets $\geq 50 \times 10^9/l$, creatinine $\leq 6 \times$ the upper limit of normal, blood urea nitrogen $\leq 10 \times$ the upper limit of normal, aspartate aminotransferase and alanine aminotransferase $\leq 5 \times$ the upper limit of normal, and total bilirubin $\leq 2.5$ mg/dl. Women were excluded if pregnant or breast feeding. Other exclusion criteria were prior or concomitant use of protease inhibitors, use of any investigational drug fewer than 30 days before to or during the study, acute hepatitis of any cause, presence of central nervous system infections, CMV retinitis or active tuberculosis unless diagnosed and treatment initiated at least 2 weeks prior to enrolment, and unstable opportunistic infections defined as a change in the corresponding clinical condition or therapy less than 2 weeks before the start of indinavir therapy.

All investigators participating in the National AIDS Therapy Evaluation Center (NATEC) network for HIV clinical trials in the Netherlands were informed about the study and asked to refer eligible patients to the study coordinator (NF) at the Academic Medical Center in Amsterdam, who entered patients into the study after confirming their eligibility. All patients gave written informed consent before enrolment, and the protocol was approved by the ethics committees of all participating institutions as well as by the Scientific Advisory Board of NATEC.
Study design and treatment

Patients who fulfilled all inclusion criteria and none of the exclusion criteria were randomly assigned by a computer program to one of two treatment groups: (i) immediate treatment group, (ITG) comprising patients who started indinavir immediately after randomization; (ii) deferred treatment group, (DTG) comprising patients who documented the frequency and consistency of their stools for 2 weeks after randomization, and subsequently began treatment with indinavir. Prior to randomization, all eligible patients were instructed to keep a daily stool diary for 2 weeks in which they recorded each bowel movement, stool consistency (watery, loose or formed), and the use of non-specific antidiarrhoeal medication.

This design allows us to compare bowel movement frequency (all without indinavir treatment) between the 2-week period before and after randomization, respectively, in the DTG. A lack of significant change in the level of diarrhoea between these two 2-week periods, would strengthen the conclusion that changes in diarrhoea following the subsequent start of indinavir therapy indeed were the result of such therapy. To investigate a regression-to-the-mean phenomenon, which would show a decrease in stool frequency and improvement of consistency after patients have been randomized, mean daily frequency and consistency 2 weeks before and after randomization were compared using analysis of repeated measures among patients randomized to receive deferred therapy. In case no regression-to-the-mean was found, it was decided to define time point zero as the moment that indinavir therapy was started in order to investigate the influence of antiretroviral therapy on stool frequency and other parameters. The planned duration of the study was 24 weeks.

Indinavir was administered as 400 mg capsules at a dose of 800 mg three times daily on an empty stomach. Patients were recommended to drink at least 1.5 L of liquid daily. During the 2-week (ITG) or 4-week (DTG) period of observation, as well as during the initial 4 weeks of treatment with indinavir, no changes in background antiretroviral therapy or increases in the use of non-specific antidiarrhoeal medication were permitted.
Follow-up and outcome measures

Study visits were scheduled 1, 2, 3, 4, 12, 18 and 24 weeks after the start of indinavir. Patients were instructed to complete a stool diary for the 7-day period preceding each scheduled visit. In addition, during each of these visits patients were questioned about any adverse events, a full physical examination (including body weight) was performed, stool was obtained for culture and examination of ova and parasites, and blood was drawn for laboratory safety parameters and for measuring plasma HIV-1 RNA levels, T-lymphocyte subsets and in vitro T-lymphocyte functional capacity.

Stool samples were examined for routine culture and for ova and parasites according to standard procedures. Microsporidial spores were visualized using the Uvitex 2B stain, as previously described [12,13]. Electron microscopy was used for confirmation of *E. bieneusi* diagnosis. The presence of cryptosporidial oocysts and microsporidial spores in stool specimens was scored semiquantitatively by counting the number of parasites per high power field (1250 x magnification using a Leitz fluorescence microscope, Leitz, Wetzlar, Germany), according to the following grading system: grade 0, no spores/oocysts; grade 1, 1-5 spores/oocysts per slide; grade 2, 2-5 spores/oocysts per field; grade 3, 6-10 spores/oocysts per field; grade 4, > 10 spores/oocysts per field. All samples were examined and graded by the same technician and subsequently confirmed by one of the authors (TvG). Enumeration of CD4⁺ and CD8⁺ lymphocyte subsets, and determination of in vitro T-cell proliferation induced by phytohaemagglutinin (PHA) and the combination of CD3 and CD28 monoclonal antibodies, were performed according to previously described methods [14]. HIV-1 RNA plasma concentrations were measured using a commercial PCR-based assay (Amplicor HIV Monitor Test, Roche Diagnostic Systems Inc., Branchburg, New Jersey, USA).

The primary outcome measure was the change in frequency of bowel movement observed during 24 weeks of indinavir treatment. A beneficial response was defined as a reduction in stool frequency of 50% or more at week 24 compared to baseline. Additional outcome measures were changes in stool consistency, in body weight, and in the use of non-specific antidiarrhoeal medication. Secondary outcome measures included scoring of the degree of oocyst and spore shedding in stools, for patients with cryptosporidiosis and microsporidiosis, respectively.

For the assessment of durability of response the latest information available after week 24 was collected by contacting the patient’s physician. Data concerning
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diarrhoea, body weight, antiretroviral drug use, virologic and immunologic parameters were collected and described.

**Statistical analysis**

For each patient and at each time point (visit) the mean daily stool frequency was calculated as the total number of documented bowel movements divided by the total number of days of observation during the preceding week. In addition, patients categorized their stool consistency as watery, loose or formed, and hence stool consistency could be expressed as proportions of watery, loose and formed bowel movement for each time point.

The significance of change in body weight, absolute CD4⁺ lymphocyte count, log₁₀ plasma HIV-1 RNA copy number, mean stool frequency, and stool consistency was tested by analysis of repeated measures, using PROC MIXED of the SAS software package (version 6.11: SAS Institute, Cary, North Carolina, USA).

**Results**

*Pre-treatment*

Eight patients were randomized to receive immediate indinavir therapy (ITG) and six to receive therapy 2 weeks later (DTG). After being randomized to the DTG, one patient started treatment on his own account after one week and one patient withdrew 2 weeks after randomization but before the start of treatment. Since no follow-up data were available for this latter patient, he was excluded for the evaluation of treatment effect. Both treatment groups had comparable baseline characteristics at randomization (Table 1). In eight patients the cause of diarrhoea was unknown, whereas in six patients *Microsporidium* sp. *E. bieneusi* was found by light microscopy. This was confirmed by electron microscopy. In one patient who died after one week of treatment *E. bieneusi* could not be diagnosed with certainty by electron microscopy alone. Two of these patients had a concomitant infection with *Cryptosporidium*. Stool culture for *M. avium intracellulare* was negative in all patients.
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Table 1 Patient baseline characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Immediate treatment</th>
<th>Deferred treatment</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No patients</td>
<td>8</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Median (IQR) Age (years)</td>
<td>43 (38-51)</td>
<td>45 (39-49)</td>
<td>44 (38-50)</td>
</tr>
<tr>
<td>Male [n (%)]</td>
<td>8 (100)</td>
<td>5 (83)</td>
<td>13 (93)</td>
</tr>
<tr>
<td>Median [IQR]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4+ cell count (x 10^6/l)</td>
<td>10 (10-15)</td>
<td>10 (10-40)</td>
<td>10 (10-20)</td>
</tr>
<tr>
<td>CD8+ cell count (x 10^6/l)</td>
<td>450 (325-735)</td>
<td>230 (200-330)</td>
<td>330 (240-460)</td>
</tr>
<tr>
<td>HIV-1 RNA (log_{10} copies/ml)</td>
<td>5.1 (4.9-5.6)</td>
<td>5.1 (4.2-5.2)</td>
<td>5.1 (4.8-5.6)</td>
</tr>
<tr>
<td>No. (%) patients with non specific antidiarrhoeal drug use</td>
<td>3 (38)</td>
<td>3 (50)</td>
<td>6 (43)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of diarrhoea (months)</td>
<td>7 (5-11)</td>
<td>10 (5-12)</td>
<td>9 (5-11)</td>
</tr>
<tr>
<td>Median daily stool frequency</td>
<td>5.8 (4.1-7.4)</td>
<td>5.7 (4.6-7.1)</td>
<td>5.8 (4.6-7.1)</td>
</tr>
<tr>
<td>Pathogens present in stool [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptosporidium sp.</td>
<td>1 (13)</td>
<td>1 (17)</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Enterocytozoon bieneusi</td>
<td>4 (50)</td>
<td>2 (33)</td>
<td>6 (43)</td>
</tr>
<tr>
<td>Median (IQR) body weight (kg)</td>
<td>59 (54-64)</td>
<td>60 (46-63)</td>
<td>59 (54-64)</td>
</tr>
</tbody>
</table>

Both patients with cryptosporidiosis also had microsporidiosis. IQR, interquartile range.

No significant change in the mean daily stool frequency was observed in patients randomized to the DTG during the two weeks before randomization when compared with the 2-week observation period after randomization (P = 0.93), nor did the proportion of watery, loose and formed stool change after randomization (P-values 0.22, 0.18 and 0.84, respectively).

Since no change in stool frequency and consistency was found before and after randomization, data from both groups were pooled and the start of indinavir was considered as timepoint zero for evaluating the effect of treatment.

During treatment
All treated patients received indinavir 2400 mg daily added to their background medication. All patients had previously used nucleoside analogues. Three of the
patients had discontinued this treatment because of side-effects prior to starting indinavir. One patient died one week after starting indinavir due to euthanasia. One patient withdrew from the study at week 18 because of lack of response. Therefore, 11 patients completed at least 24 weeks of follow-up. Indinavir treatment was not changed during the study, but most of the patients had a change of their nucleosides after week 4.

Stool frequency had statistically significantly decreased from a median of 5.8 daily at baseline to 2.3 daily after 24 weeks of treatment (P = 0.04). At week 24, the median stool frequency, expressed as ratio from baseline, was 0.35 (interquartile range, 0.28-0.63, Fig. 1A). Seven patients had a clinical response defined as a reduction of ≥ 50% of stool frequency at week 24 (responders). Responders and non-responders did not differ in baseline characteristics (data not shown).

Stool consistency improved likewise. Of all stools at baseline, a median of 0% was formed, whereas a median of 35% were formed after 24 weeks of treatment (P = 0.01). The median proportion of watery stools was 56% at baseline and 0% after 24 weeks of treatment (P = 0.02), the percentages of loose stools did not change (44% and 50% respectively; Figure 1B). Body weight increased significantly in all patients with a median increment of 6.6 kg at week 24 (P = 0.0006; Figure 1C).

In two of the six patients with microsporidiosis, no parasites were detected in the stool at week 18 and 24. In one patient with a negative stool specimen for microsporidiosis after 12 weeks of treatment, a few parasites were seen again at week 24 (grade 1). In the stool specimens of two patients, a reduction of the amount of parasites excreted (grade 4 to 1) was observed, concurrent with a decrease in stool frequency. One patient with microsporidiosis died without a clinical or parasitological response 1 week after the start of treatment. In the stool specimens of the two patients with cryptosporidiosis at baseline no parasites were detected at the end of the study. One patient with Cryptosporidium and Microsporidium coinfection and associated signs of sclerosing cholangitis showed significant biochemical and radiologic improvement after 24 weeks of treatment. The diarrhoeal response did not differ between patients with unexplained diarrhoea and those with cryptosporidiosis/microsporidiosis (data not shown). Five out of six patients who used non-specific antidiarrhoeal medication on a regular basis prior to the study had ceased to do so at the end of the study.
Figure 1:
A] Stool frequency as ratio from baseline [median and interquartile range (IQR); P = 0.04].
B] Stool consistency as percentage of total bowel movements.
C] Change in body weight (kg) from baseline (median and interquartile range; P < 0.0006).
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Figure 1:
D: Plasma HIV-1 RNA levels ($\log_{10}$ copies/ml) as change from baseline, median and IQR; $P < 0.0002$).
E: $CD4^+$ and $CD8^+$ lymphocyte count ($x10^6/l$; median and IQR; $P < 0.0001$ and $P < 0.02$, respectively). Normal values: $CD4^+$ cell count 560-1490 $x10^6/l$; $CD8^+$ cell count, 260-990 $x10^6/l$.
F: T-lymphocyte function in whole-blood lymphocyte cultures as measured by responses to the combination of CD3 and CD28 monoclonal antibodies, and responses to phytohaemagglutinin (PHA; c.p.m.; median and IQR; $P < 0.0001$ and $P < 0.002$, respectively). Normal values: CD3 and CD28 monoclonal antibodies $\geq 17000$ c.p.m.; PHA $\geq 17000$ c.p.m.
Immunological and virological response

Plasma HIV-1 RNA levels had decreased with a median of 2.3 log_{10} at week 24 compared to baseline (P = 0.0002; Figure 1D). The median CD4^{+} and CD8^{+} lymphocyte count increased to a median of 100 x 10^6 cells/\mu l and 805 x 10^6 cells/\mu l, respectively at week 24 (CD4^{+} cells, P = 0.0001, CD8^{+} cells, P = 0.02; Figure 1E). In vitro T-cell function, as measured by the proliferative responses upon stimulation with the combination of CD3 and CD28 monoclonal antibodies, increased from a median of 165 to 11203 c.p.m. (P = 0.0001; normal range, ≥ 17000 c.p.m.). PHA responses improved from a median of 934 to 10724 c.p.m. (P = 0.002; normal range ≥ 17000 c.p.m.; Figure 1F).

Adverse events

Four serious adverse events were reported in three patients. One patient on anticoagulant and anti-epileptic therapy had a recurrent episode of deep venous thrombosis. Moreover he had experienced a tonic-clonic seizure possibly related to a low phenytoin serum level (5 mg/\mu l; therapeutic range, 8-18 mg/\mu l). A relationship with the use of indinavir was unlikely since his serum phenytoin concentration was already low (5.5 mg/\mu l) before the start of indinavir.

One other patient who had a history of nephrolithiasis had a single episode of severe flank pain and gross haematuria, although diagnostic procedures did not reveal a kidney stone. He admitted that his fluid intake was significantly lower than advised. He continued indinavir without a relapse of complaints. In one patient, disseminated CMV infection was diagnosed shortly after initiating indinavir. He recovered well with ganciclovir treatment. A moderate increase of unconjugated bilirubin was observed in most patients, but was never a reason to discontinue indinavir treatment.

Long term outcome

In order to evaluate the durability of the treatment response, patients' physicians were contacted 6-26 (median, 16 weeks) after the end of the study. Data about all eleven
patients were collected. Antiretroviral drug therapy had not been changed in any of the patients. Nine patients had no diarrhoea according to the prestudy definition. The median increase in body weight was 1 kg since week 24. CD4+ lymphocyte count had not significantly changed (105 versus 100 x 10^6 cells/l at week 24). Median plasma HIV-1 RNA level was 2.52 log_{10} copies/ml (2.81 log_{10} copies/ml at week 24). E. bieneusi was still found in the stools of two patients. Two patients in whom E. bieneusi could not be detected at week 24 were still free of and remained free until his last visit (week 46). No relapse of cryptosporidiosis was observed.

Discussion

Our study clearly demonstrated that signs and symptoms of chronic diarrhoeal disease even in patients with a very advanced stage of HIV-1 infection, may significantly improve with the use of potent antiretroviral treatment including a protease inhibitor. In 11 out of 14 patients with a median prior history of chronic diarrhoea of 9 months, 24 weeks of treatment with regimens including indinavir resulted in significant reductions of both the total number of daily bowel movements as well as the percentage of these that consisted of watery stools. This was mirrored by an increase in body weight of more than 6 kg. Three out of six patients who entered the study with E. bieneusi, and both patients with Cryptosporidium showed complete and persistent clearance of these parasites from their stools. In the two remaining evaluable patients a clear reduction of spore shedding was observed. This is remarkable because, at present, no proven curative antimicrobial therapy is available for E. bieneusi. Moreover, five out of six patients on non-specific antidiarrhoeal therapy were off these drugs after 24 weeks of antiretroviral therapy.

It is not likely that the observed decline of stool frequency can be explained by a regression-to-the-mean phenomenon. Our patients had a median duration of chronic diarrhoea of 9 months before protease therapy was started and spontaneous remission of long-lasting diarrhoea in end stage AIDS patients has rarely been described. Furthermore, no change in the diarrhoeal pattern was observed during the 4-week observation period in the DTG.

Although the small sample size of our study did not allow a formal analysis to be carried out of the relationship between improvement of immunologic markers and
amelioration of diarrhoea, it is likely that such a relationship exists. In general, chronic HIV-related diarrhoea, cryptosporidiosis and microsporidiosis occur at very advanced stages of HIV infection [3,12]. Moreover, response in diarrhoeal frequency was never observed as long as CD4$^+$ lymphocyte counts stayed below 40-50 x 10$^6$ cells/l.

Recently, case reports have been published concerning patients with a clinical improvement of other highly drug-resistant opportunistic diseases such as azole- and amphotericin B-resistant candidiasis [15], Kaposi’s sarcoma [16,17], progressive multifocal leukoencephalopathy [18] and microsporidiosis [19] with protease inhibitor-containing regimens. Together with our results this supports the concept that degrees of immune reconstitution can be accomplished by combination antiretroviral therapy including a HIV protease inhibitor that are associated with reversal of clinical signs and symptoms of opportunistic diseases, even in patients with advanced HIV infection.

We therefore suggest that initiation of potent combination antiretroviral therapy should be considered and further be explored as an approach to treat HIV-related opportunistic disease manifestations such as chronic diarrhoea, especially when specific effective therapy is not available or has failed. In addition, this approach allows the design of a new type of clinical endpoint trials, which over short time periods could elicit proof of clinical benefit for new antiretroviral treatments.

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