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Risk Factors for Gastrointestinal Adverse Events in HIV Treated and Untreated Patients

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Abstract

Advanced immunosuppression from HIV infection can lead to gastrointestinal symptoms such as diarrhea, nausea, vomiting, dysphagia, weight loss, and abdominal pain. There is a complex, combined effect of HIV infection plus antiretroviral treatment on the incidence of gastrointestinal symptoms, and, for some trials, the majority of gastrointestinal adverse events may not be related to antiretroviral treatment. Antiretroviral treatment can lead to improvements in gastrointestinal symptoms for patients with advanced immunosuppression. This was observed in the TORO trials of enfuvirtide and the DUET trials of etravirine, which were conducted in highly treatment experienced patients with low baseline CD4 counts.

While antiretroviral treatment can improve immune function, leading to fewer gastrointestinal symptoms, this could be counter-balanced by adverse gastrointestinal toxicity profiles from certain antiretrovirals. Ritonavir-boosted protease inhibitors show a range of gastrointestinal side effects; there are differences in tolerability within this class of antiretrovirals, influenced both by the dose of ritonavir used and the choice of boosted protease inhibitor. Overall, lopinavir/ritonavir and fosamprenavir/ritonavir tend to show the highest rates of drug-related grade 2-4 diarrhea, compared with atazanavir/ritonavir, darunavir/ritonavir, or saquinavir/ritonavir. Of the nucleoside analogs, zidovudine leads to a well-characterized problem of nausea.

Issues relating to gastrointestinal complications are often subjective, reliant upon patient reporting and perception, along with clinician interaction and intervention. In trial publications, many different systems are used to present gastrointestinal adverse events. Most are based on the US Division of AIDS Grading Scale, ranging from grade 1 (mild) to grade 4 (life-threatening). Clinical trials most commonly report grade 2-4 gastrointestinal adverse events, which are at least possibly related to study medication. In future, it is important for clinical trials to report gastrointestinal adverse events in a consistent way. The percentage of patients with drug-related grade 2-4 events should be reported. In addition, the percentage with any grade 2-4 gastrointestinal adverse event should be included, since there could be subjectivity in the assessment of drug relatedness in open-label clinical trials. The percentage of patients who use medications to lessen the symptoms of diarrhea and other gastrointestinal adverse events should also be reported. **(AIDS Rev. 2009;11:30-8)**

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Key words

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Introduction

Gastrointestinal (GI) manifestations of HIV disease can include diarrhea, nausea, vomiting, dysphagia, weight loss, abdominal pain, anorectal disease, hepatomegaly, GI bleeding, and GI tumors (Kaposi's sarcoma and non-Hodgkin's lymphoma). The most commonly experienced of these GI symptoms is diarrhea, affecting over half of HIV-positive people off-treatment[1]. Opportunistic infections of AIDS are associated with GI symptoms, in particular cryptosporidiosis, microsporidiosis and *Mycobacterium avium* complex[2].

Primary HIV infection is associated with a preferential depletion of CD4 cells in the GI tract, which is where more than 60% of the body's T lymphocytes reside. This suggests that HIV plays a pivotal role in early impairment of gut-associated lymphoid tissue. The precise pathogenic mechanisms are poorly understood, although it has been hypothesized that a breakdown of the GI mucosal barrier could contribute to chronic immune activation[3]. Exposure of peripheral immune cells to microbial products following gut injury may therefore result in the abnormal activation of these cells. HIV may also impair the GI barrier and affect the composition of gut microbiota: this can lead to a breakdown of GI mucosa, and peripheral lymphocytes would then be exposed to abnormal intestinal microbiota[3]. This hypothesis is supported by data showing lower levels of *bifidobacteria* and *lactobacilli* in HIV patients compared with HIV-negative controls; these bacteria are known to have a positive influence on mucosal immune function and general gut health[4-6].

Effects of antiretroviral treatment on gastrointestinal symptoms

Antiretroviral treatment can lead to improvements in GI symptoms for patients with advanced immunosuppression. In the TORO trials, there was a significant benefit for use of enfuvirtide (T-20) versus control treatment on CD4 counts and HIV RNA at week 48, and this was also associated with a 50% reduction in the incidence of diarrhea, nausea, and vomiting[7]. Summary results are shown in table 1. There were similar results in the DUET trials of the non-nucleoside etravirine, which included highly treatment-experienced patients with low baseline CD4 counts[8,9].

While antiretroviral treatment can improve immune function, leading to fewer GI symptoms, this could be counterbalanced by adverse GI toxicity profiles from certain antiretrovirals. Ritonavir-boosted protease inhibitors (PIs) show a range of gastrointestinal side effects; there are differences in tolerability within this class of antiretrovirals, influenced both by the dose of ritonavir used and the choice of boosted PI. In addition, certain nucleoside analogs (e.g. zidovudine) are associated with GI toxicities. Data from dose-ranging trials and randomized head-to-head studies provide the strongest evidence for the differential effects of antiretroviral combinations on GI tolerability.

As antiretroviral therapy has evolved, so too has the tolerability and patient acceptance of these treatments; impact on quality of life is now a major consideration for patients, especially as HIV is considered a long-term manageable condition. With a wider variety of treatments now available, switching due to "unacceptable" side effects has become a much-used option[10]. Conversely, evidence also suggests that GI toxicities are underreported by patients and are often self-managed (including the use of over-the-counter remedies)[11]. Gastrointestinal complications still remain one of the major reasons for discontinuing antiretroviral treatment.

Systems for classifying gastrointestinal adverse events

Issues relating to GI complications are often subjective, reliant upon patient reporting and perception, along with clinician interaction and intervention. Adverse events which may be problematic for one individual may not have the same effects on another. Clinical studies normally use a scale to grade adverse events, as either grade 1 (mild), 2 (moderate), 3 (severe), or 4 (potentially life-threatening). The grading scale intended for use is normally pre-specified in the protocol, and adverse events are graded prospectively at each patient visit. The most frequently used scale is produced by the US Division of AIDS[12]. The definitions of grade 1-4 diarrhea, nausea, and vomiting, typically the most common GI complications, are shown in table 2[12]. Within the DAIDS 2007 grading scale, some measurable outcomes are based on clinical expertise and evidence, while others rely on patient reporting[12].

In trial publications, many different systems are used to present GI adverse events, as evidenced in the results of a recent survey[13], shown in table 3. For example, three clinical trials, all evaluating zidovudine/lamivudine/efavirenz, have used different approaches for summarizing GI adverse events up to week 48. In the EPV20001 trial, where all drug-related grade 1-4

Table 1. TORO 1 and 2 trials: Grade 1-4 gastrointestinal adverse events at 48 weeks (all causality)

Adverse event	T-20 group n = 663	Control Group n = 334	Relative risk (95% CI)
Diarrhea nos	37.7% (n = 210)	73.4% (n = 119)	0.51 (0.40 to 0.63)
Nausea	27.1% (n = 151)	50.0% (n = 81)	0.52 (0.40 to 0.69)
Vomiting nos	15.1% (n = 84)	26.5% (n = 43)	0.60 (0.41 to 0.87)

Table 2. National Institute of Allergy and Infectious Diseases grading scale for gastrointestinal adverse events

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially life-threatening
Diarrhea	Transient or intermittent episodes of unformed stools OR increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR increase of 4-6 stools over baseline per 24-hour period	Bloody diarrhea OR increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences, e.g. hypotensive shock
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24-48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR aggressive rehydration indicated, e.g. IV fluids	Life-threatening consequences, e.g. hypotensive shock
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR aggressive rehydration indicated, e.g. IV fluids	Life-threatening consequences, e.g. hypotensive shock

Table 3. Methods used to report gastrointestinal adverse events in 53 clinical trials (from MEDLINE search)

Method for reporting gastrointestinal adverse events	Clinical trials using this method
Grade 2-4 treatment-related:	Abbott 418, Abbott 720, Abbott 730, Abbott 863, ALERT, ARTEMIS, BMS 034, BMS 043, BMS 045, BMS 089, CASTLE, CONTEXT, HEAT, KLEAN , REDUCE, SHARE, SOLO, TITAN
Grade 1-4 any cause:	CNA30021, DUET 1 and 2, GEMINI, KALEAD1, Gilead 902, MERIT, MOTIVATE 1 and 2, TMC125-C223, TORO 1 and 2
Grade 3-4 any cause:	ACTG 5095, ACTG 5142, Gilead 903, MERIT, MAXCMIN2, 2NN, POWER 1 and 2, RESIST 1, RESIST 2
Adverse events leading to discontinuation of treatment:	ACTG 384, ACTG 5095, ACTG 5142, Gilead 934, OK-01, OK-04, RAVE, TITAN
Grade 2-4 any cause:	CNA30024, Gilead 934, MONARK
Grade 1-4 treatment-related:	DMP-006, EPV20001, FTC 301, TMC278-C204, BENCHMRK 1, BENCHMRK 2
Grade 3-4 treatment-related:	Gilead 907

events are presented, the rates of diarrhea and nausea were 10 and 31%, respectively[14]. In the CNA30024 trial, where grade 2-4 events were presented, either related or unrelated to study medication, these rates fell to 6 and 11%[15]. In the Gilead 934 trial, the percentage of patients who discontinued trial medication for GI adverse events was 0% for diarrhea and 2% for nausea[16]. Similarly in the ALERT trial of fosamprenavir/

Table 4. Percentage of patients with at least one grade 2-4 gastrointestinal adverse event up to week 48, at least possibly related to study drug: clinical trials of two nucleoside reverse transcriptase inhibitors plus boosted protease inhibitor-based HAART in naive patients

Trial	Treatment arm	(n)	Grade 2-4, drug-related		
			Diarrhea	Nausea	Vomiting
ARTEMIS:	TDF/FTC + DRV/r	343	4%	2%	na
ARTEMIS	TDF/FTC + LPV/r (sgc)	346	10%	3%	na
CASTLE	TDF/FTC + ATV/r	441	2%	4%	na
CASTLE	TDF/FTC + LPV/r (sgc)	437	11%	8%	na
HEAT	TDF/FTC + LPV/r (sgc)	343	19%	6%	3%
HEAT	ABC/3TC + LPV/r (sgc)	345	18%	7%	3%
Abbott 730	TDF/FTC + LPV/r (M)	331	15%	5%	4%
Abbott 730	TDF/FTC + LPV/r OD (M)	333	17%	7%	3%
Abbott 418	TDF/FTC + LPV/r (sgc)	75	5%	8%	3%
Abbott 418	TDF/FTC + LPV/r OD (sgc)	115	16%	9%	3%
Abbott 863	d4T/3TC + LPV/r (sgc)	326	16%	7%	5%
KLEAN	ABC/3TC + fAPV/r	436	13%	6%	6%
KLEAN	ABC/3TC + LPV/r (sgc)	443	11%	5%	2%
REDUCE	ABC/3TC + fAPV/r 100	58	14%	3%	na
REDUCE	ABC/3TC + fAPV/r 200	57	18%	5%	na
SOLO	ABC/3TC + fAPV/r	322	9%	7%	2%

Missing data: GEMINI: grade 1-4 adverse events only reported; BMS-089: not reported; BI 1183: not reported; ACTG 5142: not reported; ALERT and SHARE: not reported.
TDF: tenofovir; FTC: emtricitabine; ATV: atazanavir; LPV: lopinavir; ABC: abacavir; 3TC: lamivudine; d4T: stavudine; fAPV: fosamprenavir; sgc: soft-gel capsule.

ritonavir 1,400/100 mg once daily, 53% of patients had any grade 1-4 adverse event of diarrhea up to week 48, whereas only 8% of patients showed a grade 2-4 adverse event of diarrhea judged to be related to study medication[17]. So, if results are to be compared across clinical trials, it is important to use a standardized approach to reporting this information; this may not be available across publications of clinical trials, even if conducted by the same sponsor.

The most common measure of GI adverse events is the percentage of patients with at least one grade 2-4 event at any time, judged by the clinical trial investigator to be at least possibly related to study treatment. Table 4 shows this measure for a range of clinical trials of first-line boosted PI-based HAART, while table 5 shows trials of PI-based HAART in treatment-experienced patients.

In addition to HIV-associated immunosuppression and antiretroviral treatment, other factors such as diet or hygiene could affect gastrointestinal symptoms. Also, dietary advice and over-the-counter treatments can help patients to manage gastrointestinal symptoms of antiretrovirals. Therefore, it can be difficult to compare and contrast studies conducted in different countries, even if the same protocol and grading scales have been adopted.

Effects of antiretroviral treatment on gastrointestinal adverse events

Nucleoside analogs

The main nucleoside analogs used in first-line treatment are tenofovir, abacavir, and zidovudine, used in combination with lamivudine or emtricitabine. Stavudine is still used widely in developing countries, but only rarely in developed countries. The problem in interpreting the trials data from nucleosides and non-nucleosides is that several different approaches have been used to summarize grade 1-4 GI adverse events, and

Table 5. Percentage of patients with at least one grade 2-4 gastrointestinal adverse event up to week 48, at least possibly related to study drug: clinical trials of boosted protease inhibitor-based HAART in pre-treated patients

Trial	Treatment arm	(n)	Grade 2-4, drug-related		
			Diarrhea	Nausea	Vomiting
TITAN	BR + DRV/r BID	298	8%	4%	na
TITAN	BR + LPV/r	297	15%	4%	na
BMS-045	BR + ATV/r	119	3%	3%	0%
BMS-045	BR + LPV/r	118	11%	2%	1%
CONTEXT	BR + fAPV/r BID	106	13%	3%	3%
CONTEXT	BR + LPV/r	103	11%	9%	5%

Missing data: GEMINI: grade 1-4 adverse events only reported; BMS-089: not reported; BI 1183: not reported; ACTG 5142: not reported; ALERT and SHARE: not reported.
BR: background regimen; DRV/r: darunavir/ritonavir; LPV/r: lopinavir/ritonavir; ATV/r: atazanavir/ritonavir; fAPV/r: fosamprenavir/ritonavir; BID: twice daily.

often adverse events not related to study medication have been included in the analyses.

Nausea was found to be associated with zidovudine treatment in one of the first placebo-controlled trials[18]. When zidovudine/lamivudine/efavirenz was compared with abacavir/lamivudine/efavirenz in the CNA30024 trial[15], the incidence of grade 2-4 nausea was higher for the zidovudine arm (11%) versus the abacavir arm (7%). The incidence of diarrhea was similar in both arms[15].

Tenofovir showed higher rates of grade 1-4 diarrhea (21-25%) relative to placebo in the dose-ranging trial Gilead 902[19]. When zidovudine/lamivudine/efavirenz was compared with tenofovir/emtricitabine/efavirenz in the Gilead 934 trial, the reported number of grade 2-4 GI adverse events was slightly higher for the tenofovir arm relative to the zidovudine arm; diarrhea was 7 versus 4%, and nausea was 8 versus 6%[16]. However these analyses included non treatment-related GI adverse events. In the Gilead 907 trial, where tenofovir or placebo was added to current HAART in treatment-experienced patients, the incidence of severe (grade 3 or 4) diarrhea was similar in the tenofovir and placebo arms. However, the rates of grade 1 or 2 diarrhea were not presented[20].

In the HEAT trial, abacavir/lamivudine and tenofovir/emtricitabine were compared in naive patients, who also received lopinavir/ritonavir 400/100 mg twice daily[21]. The incidence of grade 2-4 drug-related diarrhea, nausea, and vomiting were very similar in the two treatment arms: 18% for abacavir/lamivudine and 19% for tenofovir/emtricitabine[22]. In the FTC 301 trial, there was significantly more grade 1-4 diarrhea and nausea for patients receiving stavudine plus didanosine/efavirenz (34 and 24%), compared with the emtricitabine plus didanosine/efavirenz arm (24 and 14%)[22].

Didanosine is formulated in enteric coated tablets, and needs to be given on an empty stomach to optimize absorption. Diarrhea has been observed during the phase II and III trials of didanosine, but is a relatively minor side effect compared to pancreatitis and peripheral neuropathy, also seen with didanosine[23].

From the combined data of these trials, it appears that there could be a small background effect of nucleoside analogs on GI tolerability. However, the trials have been presented using different approaches, making it difficult to draw consistent conclusions about their relative GI safety profiles. Larger clinical trials of nucleoside reverse transcriptase inhibitor (NRTI)-sparing treatments will be required to investigate this further.

Non-nucleosides

Efavirenz and nevirapine rarely cause GI adverse events, but are associated with other issues, typically CNS adverse events for efavirenz, and rash plus hepatotoxicity for nevirapine. In the ACTG 5142 trial of naive patients[24], the arm of two NRTI plus efavirenz showed a higher percentage of patients with HIV RNA suppression below 50 copies/ml (89% at week 96), compared with the arm of two NRTI plus lopinavir/r (77%). However, there was no difference in rates of withdrawal for adverse events or in overall grade 3 or 4 adverse events between these two arms. A third arm of lopinavir/r plus efavirenz showed an 83% rate of HIV RNA suppression. The percentage of patients with grade 3 or 4 diarrhea was < 1% for the two NRTI plus

efavirenz arm, 3% for the two NRTI plus lopinavir/r arm, and 3% for the lopinavir plus efavirenz arm[24].

The non-nucleoside reverse transcriptase inhibitor TMC125 (etravirine) has been evaluated mainly in treatment-experienced patients. In the DUET trials, the incidence of GI adverse events was lower in the etravirine arms versus the placebo arms[8,9].

Protease inhibitors

Ritonavir

Boosting PIs with ritonavir is now an accepted method of achieving greater antiviral suppression. However, ritonavir itself shows dose-related increases in GI complications, as demonstrated in the first trials of ritonavir monotherapy[25,26]. The originally approved dose was 600 mg twice daily. Ritonavir is now used as a pharmacokinetic booster at doses of either 100 mg once daily (e.g. with darunavir or atazanavir), 100 mg twice daily (e.g. with lopinavir) or 200 mg twice daily (with tipranavir). Given the tolerability profile of ritonavir, minimizing the dose should lessen the incidence of GI adverse events. However, it is often difficult to know whether GI adverse events have been caused by the ritonavir component or by the higher plasma concentrations of the boosted PI being used. Unboosted PIs are now rarely used and are not included in this review.

Lopinavir/ritonavir

Gastrointestinal adverse events are the most common side effect of lopinavir/r, seen in the original comparative trial versus nelfinavir (Abbott 863)[27]. In this trial, 16% of patients taking lopinavir/r had grade 2-4 diarrhea and 7% showed grade 2-4 nausea by week 48. In a recent cohort study, diarrhea was the most frequent adverse event leading to discontinuation of lopinavir/r[28].

Five ritonavir-boosted PIs (atazanavir, darunavir, fosamprenavir, saquinavir, and tipranavir) have been compared with lopinavir/r in head-to-head randomized trials, either in naive or pre-treated patients. The percentage of patients with grade 2-4 GI adverse events in these trials are shown in table 4 and table 5. Gastrointestinal adverse events have been assessed in these trials. The dose of lopinavir/r in these trials was mainly 400/100 mg twice daily, using the original soft-gelatin capsule formulation. More recently, an 800/200 mg once-daily dose has been developed. However, the percentage of patients with diarrhea and nausea on the once-daily dose of lopinavir/r was the same or higher than the twice-daily dose in the Abbott 730 and Abbott 418 trials[29,30]. In addition, a heat stable Meltrex formulation of lopinavir/r has been developed. The new formulation produced plasma AUC levels of lopinavir and ritonavir 18 and 20% higher, respectively, compared with the soft gelatin formulation[31]. In the Abbott 730 trial, there was no statistically significant difference in the incidence of GI adverse events between the two formulations of lopinavir/r[30].

Atazanavir/ritonavir

In the CASTLE trial, treatment-naive patients were randomized to atazanavir/r 300/100 mg once daily versus lopinavir/r, with a backbone of tenofovir/emtricitabine. At 48 weeks, the treatments showed similar rates of full HIV RNA suppression[32]. The GI adverse event profile (grade 2-4, treatment-related) for atazanavir/r was significantly better than that for lopinavir/r: diarrhea 2 versus 11% and nausea 4 versus 8%[32].

In the BMS-045 trial, atazanavir/r and lopinavir/r were compared in treatment-experienced patients. The percentage of patients with treatment-related grade 2-4 diarrhea at week 48 was 3% for atazanavir/r versus 11% for lopinavir/r[33].

Boosted atazanavir has also been compared head-to-head with boosted fosamprenavir (both once daily) using the same backbone of tenofovir and emtricitabine in a small pilot study (ALERT). Similar rates of virologic and immunologic improvement were seen through 48 weeks with both drugs[34]. Diarrhea was more common in the fosamprenavir arm, with 8% of patients experiencing grade 2-4 adverse events versus 4% in the atazanavir arm.

Darunavir/ritonavir

Darunavir/r has been studied at the 800/100 mg once-daily dose for naive patients, and at the 600/100 mg twice-daily dose for treatment-experienced patients.

The ARTEMIS study compared darunavir/r 800/100 mg once daily head-to-head with lopinavir/r (800/200 mg once daily or 400/100 mg twice daily, according to regulatory approval and/or patient preference) in treatment-naive patients. After 48 weeks, a higher proportion of patients in the darunavir/r arm had an undetectable (< 50 copies/ml) viral load compared with the lopinavir/r arm, showing non-inferiority[35]. The incidence of all drug-related grade 2-4 GI adverse events was significantly lower for the darunavir/r arm (7%) versus lopinavir/r (14%). Grade 2-4 diarrhea was experienced by 4% of

patients in the darunavir arm and by 10% in the lopinavir/r arm ($p < 0.05$).

The TITAN study again put the two PIs head-to-head, both dosed twice daily (600/100 and 400/100 mg, respectively), in treatment-experienced patients[36]. At week 48, significantly more darunavir/r-treated patients achieved HIV RNA plasma levels < 50 copies/ml in the intent to treat analysis (71 vs. 60%). The most frequently reported adverse events were diarrhea and nausea: the percentage of patients with treatment-related grade 2-4 diarrhea was 8% in the darunavir/r arm versus 15% in the lopinavir/r arm ($p<0.05$). The incidence of grade 2-4 nausea was 4% in each treatment arm.

Fosamprenavir/ritonavir

Fosamprenavir/r has been assessed at a twice-daily dosage of 700/100 mg (the originally approved dose in Europe) and at two once-daily doses, 1,400/200 and 1,400/100 mg[37].

Fosamprenavir 700/100 mg twice daily has been compared in a head-to-head (KLEAN) study with lopinavir/r[38]. This study was conducted in treatment-naive patients and all received the same backbone of abacavir and lamivudine. The twice-daily dose of fosamprenavir/r was non-inferior versus lopinavir/r for HIV RNA suppression at week 48. Drug-related grade 2-4 GI adverse events were slightly higher in the fosamprenavir arm: diarrhea (13 and 11%) and nausea (6 and 5%).

In the CONTEXT trial[37], fosamprenavir/r 700/100 mg twice daily was compared with lopinavir/r in treatment-experienced patients. After 48 weeks, 46% of patients on fosamprenavir/r twice daily and 50% of those on lopinavir/r had HIV RNA levels < 50 copies/ml. The rates of grade 2-4 drug-related diarrhea were 13% for fosamprenavir/r and 11% for lopinavir/r.

In the REDUCE study[39], fosamprenavir/r was assessed at two doses: 1,400/200 mg once daily and 1,400/100 mg once daily. The rates of HIV RNA suppression were similar with both doses. The percentage of patients with grade 2-4 drug-related diarrhea was 14% in the lower ritonavir dose group and 18% in the 200 mg ritonavir dose group.

Saquinavir/ritonavir

Another PI, saquinavir, has also shown non-inferiority to lopinavir/r in head-to-head studies. The GEMINI study[40] randomized 337 treatment-naive patients to receive either saquinavir/r 1,000/100 mg twice daily or lopinavir/r twice daily with tenofovir/emtricitabine as a backbone. The incidence of reported grade 1-4 GI adverse events for saquinavir/r versus lopinavir/r was 7 vs. 14% for diarrhea, 6 vs. 9% for nausea, and 6% in both arms for vomiting. In the GEMINI trial, the 500 mg heat stable formulation of saquinavir was used. By contrast, in the MaxCmin2 trial the 200 mg soft-gelatin formulation was used, involving a daily pill count of 12 for the saquinavir/r 1,000/100 mg twice-daily arm. There was no significant difference in adverse events between the treatment arms in this trial[41].

Tipranavir/ritonavir

In the RESIST 1 and 2 trials, tipranavir was studied against an investigator-selected comparator PI. Data from the combined RESIST trials shows that tipranavir/r 500/200 mg twice daily was superior in efficacy to the comparator PI group. The adverse event profile is also reported as similar for tipranavir/r and control PIs through week 48, although only grade 3 or 4 GI adverse events have been reported[42]. Tipranavir/r 500/200 mg twice daily has also been compared with lopinavir/r in a large head-to-head trial of naive patients[43]. However, this trial was stopped owing to excess hepatic enzyme elevations in the tipranavir 500/200 mg twice-daily arm, and the rates of GI adverse events were not presented.

New drug classes

The integrase inhibitor raltegravir was not associated with GI toxicities in the initial trials of naive patients[44]. In treatment-experienced patients, the incidence of GI adverse events was similar to placebo, or lower[45]. The CCR5 antagonist maraviroc has not shown increased rates of GI adverse events in either the MERIT trial of naive patients[46] or the MOTIVATE trials of experienced patients[47].

Conclusions

Gastrointestinal adverse events, in particular diarrhea, are still a significant problem regardless of whether the patient is on treatment or which combination they are taking[1,10,11]. There is a complex, combined effect of HIV infection plus antiretroviral treatment on the incidence of GI symptoms, and, for some trials, the majority of GI adverse events may not be related to antiretroviral treatment. There are clinical trials where GI adverse events have improved during antiretroviral treatment of late-stage HIV infection as a result of improving immune function.

Randomized trials have shown significant differences in the incidence of GI adverse events between antiretrovirals. The reporting of these in clinical trials of ritonavir-boosted PIs has been fairly consistent, concentrating on the endpoint of grade 2-4 events at least possibly related to treatment. Overall, lopinavir/r and fosamprenavir/r tend to show the highest rates of drug-related grade 2-4 diarrhea, compared with atazanavir/r, darunavir/r, or saquinavir/r.

Since GI adverse events have not been reported consistently in clinical trials of nucleoside analogs, it is difficult to determine which drugs in this class affect GI tolerability the most. However, their effects are likely to be small. The exception is zidovudine, with its well-characterized profile of nausea.

In future, it is important for clinical trials to report GI adverse events in a consistent way. The percentage of patients with drug-related grade 2-4 events should be reported. In addition, the percentage with any grade 2-4 GI adverse event should be included, since there could be subjectivity in the assessment of drug relatedness in open-label clinical trials. The percentage of patients who use medications to lessen the symptoms of diarrhea and other GI complications should also be reported.

Gastrointestinal adverse events are one of the most common reasons for discontinuing antiretroviral therapy, and are most often seen with ritonavir-boosted PIs. However, the non-nucleosides, which are less likely to cause GI problems, can cause other adverse events. A large head-to-head trial is in progress, comparing efavirenz and atazanavir/r (ACTG 5202) in naive patients, with an NRTI backbone of either abacavir/lamivudine or tenofovir/emtricitabine. Other clinical trials are also being planned, comparing first-line once-daily boosted PIs (atazanavir/r and darunavir/r) with raltegravir. All of these combinations are likely to show high rates of efficacy, with a range of different adverse events from using different drug classes.

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