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Efficacy, Adherence and Tolerability of Once Daily Tenofovir DF-containing Antiretroviral Therapy in Former Injecting Drug Users with HIV-1 Receiving Opiate Treatment: Results of a 48-week Open-label Study

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Abstract
Objective: To assess efficacy, adherence and tolerability of once daily antiretroviral therapy containing tenofovir disoproxil fumarate (DF) 300 mg in HIV-1-infected former injecting drug users receiving opiate treatment (IVDU).
Methods: European, 48-week, open-label, single-arm, multicenter study. Patients were either antiretroviral therapy-naïve, restarting therapy after treatment discontinuation without prior virological failure or switching from existing stable treatment.
Results: Sixty-seven patients were enrolled in the study and 41 patients completed treatment. In the primary analysis (intent-to-treat missing=failure) at week 48, 34% of patients (23/67; 95% CI: 23%-47%) had plasma HIV-1 RNA <50 copies/mL. Using an intent-to-treat missing=excluded approach, the week 48 proportion of patients with plasma HIV-1 RNA <50 copies/mL increased to 56% (23/41; 95% CI: 40%-72%). Mean (standard deviation) increase from baseline in CD4+ cell count at week 48 was 176 (242) cells/mm^3. Although self-reported adherence appeared high, there were high levels of missing data and adherence results should be treated with caution. No new safety issues were identified.
Conclusions: Levels of missing data were high in this difficult-to-treat population, but potent antiretroviral suppression was achieved in a substantial proportion of HIV-infected IVDU-patients.
Key words: injecting drug users; tenofovir DF; HIV-1; methadone
Abbreviations: DF = disoproxil fumarate; MASRI = Medical Adherence Self Report Inventory

Introduction

Managing human immunodeficiency virus (HIV) infection in patients who are current or former injecting drug users poses several challenges that can impair effective clinical management. This population often expresses comorbidites and complicating mental health conditions. A range of viral infections (such as hepatitis B and C) and recurrent bacterial and fungal infections can lead to higher morbidity and mortality in these patients [1, 2]. Furthermore, use of illicit drugs is often linked with depression, which is itself associated with reduced levels of adherence that impair disease management [3-5]. There is also the potential for pharmacokinetic interactions between injected or substituted drugs, medication for comorbidities and prescribed antiretroviral therapies, which can further complicate clinical management [6-11]. Toxicities of the various substances taken by these patients can synergistically increase the occurrence of adverse events above rates that might be expected for any particular antiretroviral regimen. Potential pharmacokinetic interactions between opiate treatment and prescribed antiretroviral therapies may require patients to modify their opiate dose.

As a consequence of these challenges, injecting drug users infected with HIV have been underrepresented in or generally excluded from prospective studies of antiretroviral strategies. As such, current and former injecting drug users tend to receive HIV treatment regimens designed for, and tested in, individuals without such a history. Even in countries with health care systems providing antiretroviral therapy free of charge physicians still withhold this treatment in this difficult-to-treat population because of fears of non-adherence and consequent development of antiretroviral resistance, which impacts morbidity and mortality of these patients [12, 13].

We conducted a study in which we specifically optimised the study design to maximise patient participation and data collection in this difficult-to-treat population. Specifically, we selected former injecting drug users who were on stable opiate treatment, and used a once daily regimen containing the nucleotide reverse

transcriptase inhibitor tenofovir disoproxil fumarate (DF), which has been shown to have no effect on the pharmacokinetics of methadone and other substances for opiate treatment [14, 15], low hepatotoxicity [16] and to demonstrate highly effective antiretroviral activity combined with other antiretrovirals [17-20]. The aim was to assess the efficacy, adherence and tolerability of once daily antiretroviral treatment, including tenofovir DF.

Material, Methods and Statistics

Study Population

The study population comprised HIV-infected injecting drug users (adults ≥18 years) who were receiving stable opiate treatment with methadone, levomethadone or buprenorphine (stable opiate level for ≥2 weeks prior to entry into the study). Patients were either: (i) antiretroviral therapy naïve with a CD4+ cell count <351 cells/μL and/or HIV-1 plasma RNA concentration ≥30,000 copies/mL; (ii) restarting therapy after treatment discontinuation with no evidence of prior HIV virological failure; or (iii) receiving stable therapy with plasma HIV 1 RNA <400 copies/mL for at least 6 months but were experiencing adherence problems or side effects on current therapy and willing to switch regimens. Patients with a previous history of virological failure were ineligible. Patients were also excluded for a range of protocol-specific criteria relating to hypersensitivity, contraindications and resistance to previous or current treatments.

Study Design

This was a European, open-label, single-arm, multicentre study to evaluate the efficacy, adherence and tolerability to once-daily three-drug antiretroviral regimens containing tenofovir DF 300 mg in HIV-1-infected former intravenous drug users receiving opiate treatment. For all participating patients only tenofovir DF 300 mg was provided as the study drug by the sponsor. The other antiretroviral drugs of once-daily three-drug therapies were chosen and prescribed by the local investigators. The study was conducted from 9 December 2003 to 20 June 2006 at three centres in Germany, two in Portugal, one in Italy and one in Ireland. The study was conducted in accordance with the International Conference on Harmonization guideline for Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent and the protocol was approved by an Ethics Committee or Internal Review Board as appropriate.

Within 28 days of screening, patients attended an initial baseline study visit, followed by visits at weeks 4, 12, 24, 36 and 48 (all ±10 days) with a follow-up visit 30 days after the last visit (or within 72 h of stopping study drug for those who discontinued the study prematurely). At enrolment, patients were allocated to receive the study drug tenofovir DF 300 mg (supplied by Gilead Sciences), administered as a single tablet once daily with or without food, and two other antiretroviral drugs administered also once daily according to product labelling. Patients could switch from their starting therapy to an alternative once-daily regimen if they maintained tenofovir DF 300 mg in their treatment regimen.

Study data were entered into a central database (StudyWorks, PHT Corporation, Charlestown, MA, USA) via electronic case report forms completed by study sites and personal digital assistant (PDA) devices running Palm™ OS (Palm Europe Ltd, Windsor, United Kingdom) and LogPad® (PHT Corporation Sarl, Charlestown, MA, USA) that were completed by patients. Patients recorded and transmitted diary adherence data each day and Medical Adherence Self Report inventory (MASRI) questionnaire data once a month via their PDA devices. All other data were recorded via electronic case report forms by study site staff. Patients' LogPad devices were used to remind patients about their next study visit, the need to take study medication with them when leaving home, and to transmit adherence and MASRI data. The devices also reminded them to implement changes in medication in the diary MASRI and site visit and to state MASRI compliance at each visit.

Efficacy Assessments

The primary efficacy endpoints were the proportions of patients with plasma HIV-1 RNA <50 copies/mL and <400 copies/mL at week 48 (intent to treat, ITT, analysis missing=failure, M=F). All laboratory assessments, including plasma HIV-1 RNA and CD4+ cell counts were done in local laboratories using local methods. Quality of life assessments were collected using the 12-Item Short Form Health Survey (SF-12) [21].

Adherence Assessments

Adherence was evaluated using the MASRI questionnaire [22], and the daily diary (LogPad) entered via the patients' PDAs, and by pill counting of tenofovir DF tablets at each visit.

Safety Assessments

Safety and tolerability were assessed using physical examination (including vital signs) and assessment of standard haematology, clinical biochemistry and urinalysis endpoints at each study visit. Laboratories local to study sites were used to measure clinical laboratory parameters. Adverse events were assessed throughout the study. The investigator graded adverse event severity (according to the protocol-provided Gilead Sciences Toxicity Criteria; grades 1 to 4, with 4 being the most severe) and relationship to study drug. Any grade 3 or 4 value for serum creatinine, alkaline phosphatase, bilirubin, alanine aminotransferase, aspartate aminotransferase, or hypokalaemia was reported as a serious adverse event, even in the absence of associated signs or symptoms.

Definitions

Virological failure was defined in three different ways to account for the patient sub-groups as follows: (i) two consecutive measurements at least 4 weeks apart

with plasma HIV-1 RNA ≥400 copies/mL after achieving at least one HIV-1 <400 copies/mL; (ii) one measurement with plasma HIV-1 RNA ≥400 copies/mL after achieving at least one measurement <400 copies/mL but immediately followed by premature discontinuation; (iii) never achieving a plasma HIV-1 RNA value of <400 copies/mL during the study (only applicable for antiretroviral naïve patients and patients previously discontinued and then re-started on therapy who were treated for at least 24 weeks). Patients were considered to have discontinued from the study prematurely if they stopped taking tenofovir DF before study completion.

Statistical Methods

Enrolment of 60 patients was planned for this pilot study. The ITT (and safety) population included all study patients receiving opiate treatment and known to have taken at least one dose of study treatment (tenofovir DF). The study population was divided into three subgroups based on the study inclusion criteria described earlier: (i) the antiretroviral therapy-naïve sub-group; (ii) the restart sub-group; and (iii) the switch sub-group.

For the primary analysis of the primary efficacy endpoint, missing values for HIV-1 RNA at week 48 were estimated to be above the target limit (ITT M=F approach). In the secondary analysis, missing data were excluded (ITT missing=excluded, M=E, approach). For the analysis of CD4+ cell counts, a global model was used, which comprised a repeated measures analysis of variance (ANOVA) with subgroup, visit and interaction between subgroup and visit and estimates of two-by-two differences between subgroups included as factors. For individual visits, an ANOVA was used which included subgroup and estimates of two-by-two differences between subgroups as factors.

Results

Patient Disposition and Characteristics

Sixty-seven patients were enrolled and 30 patients completed the study by attending the follow-up visit (Fig. 1). The reasons for discontinuation were drug intolerability (n = 16), lost to follow-up (n = 11), subject noncompliance, Investigator's discretion and consent withdrawal (each n = 2) and virological failure, missing ≥2 visits without severe reason, resistance to lamivudine or stavudine; and protocol deviation (each n = 1). Data from 41 patients were included in week-48 assessment.

Demographic characteristics were generally similar across the three sub-groups (Table 1). Disease characteristics were similar for the treatment-naïve and restart sub-groups. The disease characteristics of the switch sub-group were generally consistent with a virologically suppressed sub-population. A total of eight antiretroviral drugs were taken in a total of six combination regimens by patients from baseline onwards (Table 1). Apart from tenofovir DF, the most frequently taken antiretroviral drugs were atazanavir (55 patients, 82%) and emtricitabine (51 patients, 76%). Nearly all patients in the study presented detectable levels of plasma hepatitis C virus RNA (60/67; 90%) and approximately half presented detectable levels of plasma hepatitis B virus DNA (35/67; 52%). As might be expected in this population, patients had a broad range of medical history including depression and psychological problems (14 patients, 21%).

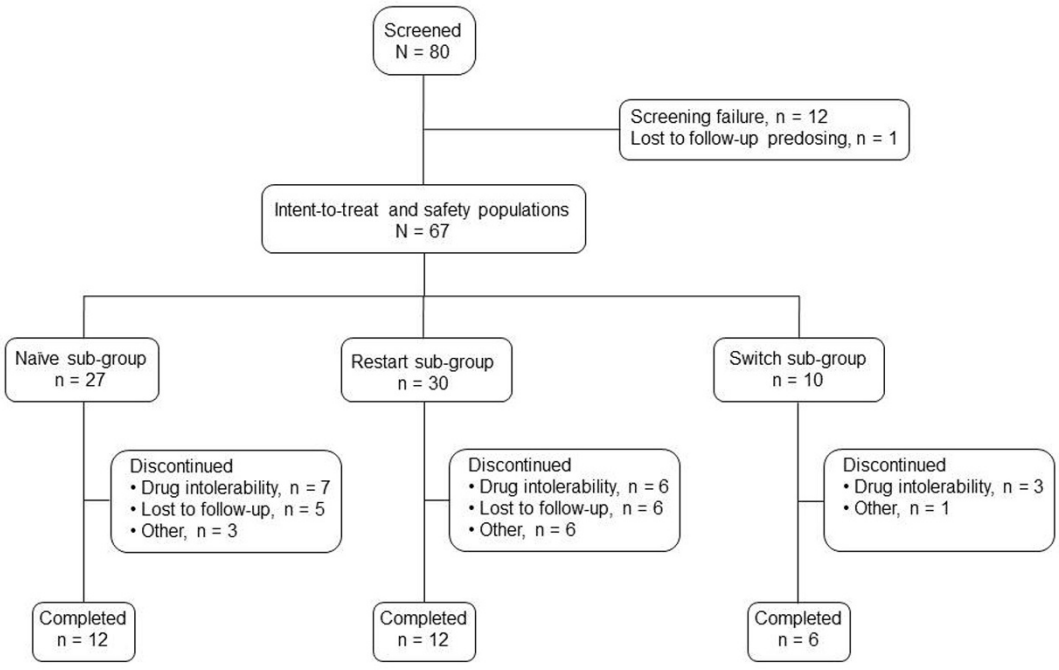


Fig. 1. Study flow chart. "Other" reasons for discontinuation included non-compliance, investigator's discretion, withdrawn consent (n = 2 each), resistant to lamivudine or stavudine, virological failure, protocol deviation and missing at least two visits without sufficient reason (n = 1 each).

Table 1. Demographics and patient characteristics (intent-to-treat population).

Parameter	Naïve (N = 27)	Restart (N = 30)	Switch (N = 10)	Total (N = 67)
Sex; n (%) male	17 (63%)	22 (73%)	6 (60%)	45 (67%)
Age (years); median [range]	34 [23-49]	38.5 [26-54]	40.5 [31-49]	37 [23-54]
BMI (kg/m^2); median [range]	21.77 [15.6-30.9]	21.90 [13.1-32.2]	24.44 [17.0-34.1]	22.13 [13.1-34.1]
Time since onset infection (years); median [range]	4.79 [0.1-23.8]	9.18 [2.4-19.3]	12.41 [3.6-16.3]	8.70 [0.1-23.8]
HIV-1 RNA ≥400 copies/mL; n (%)	24 (89%)[1]	28 (93%)[1]	0 (0%)	52 (81%)[1]
HIV-1 RNA (log_{10} copies/mL); median [IQR]	5.00 [4.7-5.6]	4.70 [4.1-5.3]	1.69 [1.69-1.69]	4.70 [3.50-5.21]
CD4+ cell count (cells/mm^3); median [IQR]	193 [54-256]	169 [91-285]	436 [289-694]	207 [100-297]
CD8+ cell count (cells/mm^3); median [IQR]	592 [455-1059]	879 [437-1329]	870 [490-1129]	764 [442-1190]
Antiretroviral medications started at baseline as part of combination regimen				
NRTI; n/N (%)				67/67 (100)
Tenofovir disoproxil fumarate (TDF); n (%)	27/27 (100)	30/30 (100)	10/10 (100)	67/67 (100)
Emtricitabine or Lamivudine (FTC/3TC)	27/27 (100)	27/30 (90)	10/10 (100)	64/67 (96)
Didanosine (DDI)	0	3/30 (10)	1/10 (10)	4/67 (6)
Tenofovir disoproxil fumarate	–	–	–	67/67 (100)
Emtricitabine	–	–	–	47/67 (70)
Lamivudine	–	–	–	15/67 (22)
PI; n/N (%)	–	–	–	55/67 (82)
Atazanavir/Ritonavir (ATV/r)	19/27 (70)	22/30 (73)	8/10 (80)	49/67 (73)
Atazanavir	1/27 (4)	4/30 (13)	1/10 (10)	6/67 (9)
NNRTI; n/N (%)	–	–	–	11/67 (16)
Efavirenz (EFV)	5/27 (19)	2/30 (7)	0	7/67 (10)
Nevirapine (NVP)	2/27 (7)	2/30 (7)	0	4/67 (6)
Regimen: n/N (%)				
PI + NRTI	20/27 (74)	26/30 (87)	9/10 (90)	55/67 (82)
TDF + FTC or 3TC + ATV/r	19/27 (70)	19/30 (63)	8/10 (80)	46/67 (69)
TDF + FTC or 3TC + ATV	1/27 (4)	4/30 (13)	1/10 (10)	6/67 (9)
TDF + DDI + ATV/r	0	3/30 (10%)	0	3/67 (4)
NNRTI + NRTI; n (%)	7/27 (26)	4/30 (13)	0	11/67 (16)
TDF + FTC or 3TC + EFV	5/27 (19)	2/30 (7)	0	7/67 (10)
TDF + FTC or 3TC + NVP	2/27 (7)	2/30 (7)	0	4/67 (6)
All NRTI; n (%)	0	0	1/10 (10)	1/67 (1)
TDF + FTC or 3TC + DDI			1/10 (10)	1/67 (1)
Opiate treatment at screening				
Time since onset opiate treatment (years); median [range]	3.01 [0.1-11.7]	6.03 [0.00-24.7]	8.24 [0.2-18.1]	5.26 [0.0-24.7]
Time since start stable dose (years); median [range]	–	–	–	1.6 [0-11.7]
Opiate treatment dose (mg); mean (SD)				
Methadone (n = 57; 85%)	84.1 (33.31)	98.2 (49.47)	70.0 (62.29)	88.8 (44.5 mg)
Levomethadone (n = 9; (13%)	70.0[2]	12.0 (20.41)	73.8 (39.45)	93.9 (36.8 mg)
Buprenorphine (n = 1; 1%)	–	12.0	–	12.0[2]

BMI = body mass index; IQR = interquartile range; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor

[1]Three patients had no HIV-1 RNA plasma concentration available at baseline, two patients in the treatment-naive subgroup and one in the restart subgroup; [2]n = 1

Table 2. Proportions of patients with plasma HIV-1 RNA <50 copies/mL and <400 copies/mL at week 48.

	Naïve (N = 27)	Restart (N = 30)	Switch (N = 10)	Total (N = 67)
<50 copies/mL (ITT M=F)				
n/N (%)	7/27 (26)	11/30 (37)	5/10 (50)	23/67 (34)
95% confidence interval[1]	[11-46]	[20-56]	[19-81]	[23-47]
<50 copies/mL (ITT M=E)				
n/N (%)	7/16 (44)	11/19 (58)	5/6 (83)	23/41 (56)
95% confidence interval[1]	[20-70]	[34-80]	[36-100]	[40-72]
<400 copies/mL (ITT M=F)				
n/N (%)	15/27 (56)	16/30 (53)	6/10 (60)	37/67 (55)
95% confidence interval[1]	[35-75]	[34-72]	[26-88]	[43-67]
<400 copies/mL (ITT M=E)				
n/N (%)	15/16 (94)	16/19 (84)	6/6 (100)	37/41 (90)
95% confidence interval[1]	[70-100]	[60-97]	[54-100]	[77-97]

ITT (M=F) = intent-to-treat missing equals failure analysis; ITT (M=E) = intent-to-treat missing equals excluded analysis
[1]Confidence interval on the percentage

Efficacy Results

In the primary analysis (ITT M=F approach) at week 48, 34% of patients (23/67; 95% CI: 23% - 47%) had plasma HIV-1 RNA <50 copies/mL and 55% of patients (37/67; 95% confidence interval, CI: 43% - 67%) had plasma HIV-1 RNA <400 copies/mL (Table 2). Using the ITT (M=E) approach at week 48, the proportion of patients with plasma HIV-1 RNA <50 copies/mL was 56% (23/41; 95% CI: 40% - 72%) and the proportion <400 copies/mL was 90% (37/41; 95% CI: 77% - 97%) (Table 2).

Overall, the proportion of patients with plasma HIV-1 RNA <50 copies/mL increased from 16% at baseline to 50% at week 24 (Fig. 2A; ITT (M=E)); proportions were maintained at 50% to 60% until the end of the study. At week 24, almost all patients achieved a plasma HIV-1 RNA level <400 copies/mL (Fig. 2B; ITT (M=E) analysis): 96% (46/48 patients) compared with 19% (12/64 patients) at baseline.

Median plasma HIV-1 RNA showed rapid reductions in the ITT population from baseline (4.7 $\log_{10}$ copies/mL) to week 4 (2.25 $\log_{10}$ copies/mL). From week 12 until the end of the study, median plasma HIV-1 RNA was at the lower limit of quantification (1.69 $\log_{10}$ copies/mL).

Mean (SD) CD4+ cell counts increased from the baseline value of 241 (220) cells/mm^3 to a week-48 value of 436 cells/mm^3 for the ITT (M=E) population (Fig. 3). Mean (SD) change from baseline to week 48 was +176 (242) cells/mm^3. For the treatment-naïve sub-group, the mean (SD) change from baseline to week 48 was +293 (282) cells/mm^3, for the restart group it was +149 (120) cells/mm^3 and -49 (269) cells/mm^3 for the switch group. Overall, there were statistically significant differences between the restart and switch subgroups ($p = 0.006$) and the treatment-naïve and switch subgroups ($p = 0.038$), but not between treatment-naïve and restart subgroups ($p = 0.311$) in absolute CD4+ cell counts at week 48. When compared by visit, there were no signifi-cant differences between the treatment-naïve and restart subgroups at any visit from baseline to week 48; there were significant differences between the switch and restart subgroups at all visits ($p < 0.05$).

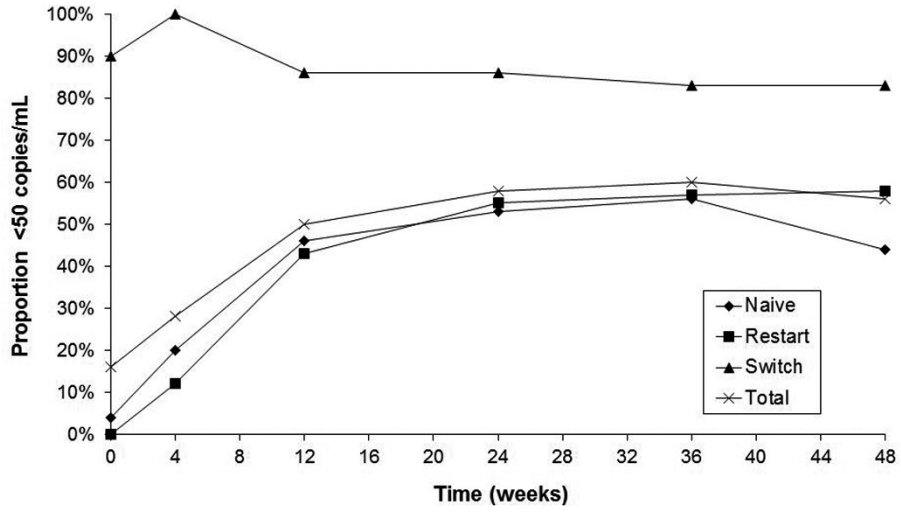
There were no marked changes from baseline to week 24 or week 48 in quality of life scores. Mean (SD) change from baseline was +0.11 (13.3) at week 24 and -2.95 (8.4) at week 48 for the mental component and +0.4 (8.1) at week 24 and +1.1 (7.2) at week 48 for the physical component.

Adherence Results

All five questions of the MASRI questionnaire showed 80-85% of patients to have 80-100% adherence. Patient diary data showed 93% of patients reported adherence between 80 and 100%. However, diary data were entered for fewer days than patients received treatment according to treatment stop and start dates (mean difference: 113 days). Fifteen patients did not provide any responses to the MASRI questionnaire and eight patients failed to enter any data into the patient diary. Tenofovir DF pill counts showed 68% of patients had ≥95% adherence.

Safety Results

Fifteen (22%) patients experienced events that led to discontinuation of all study medication. The most frequently occurring tenofovir DF related events leading to discontinuation were gastrointestinal events (5 patients), hepatic impairment (3 patients) and renal impairment/blood creatinine increased (2 patients). Almost all patients reported adverse events during the



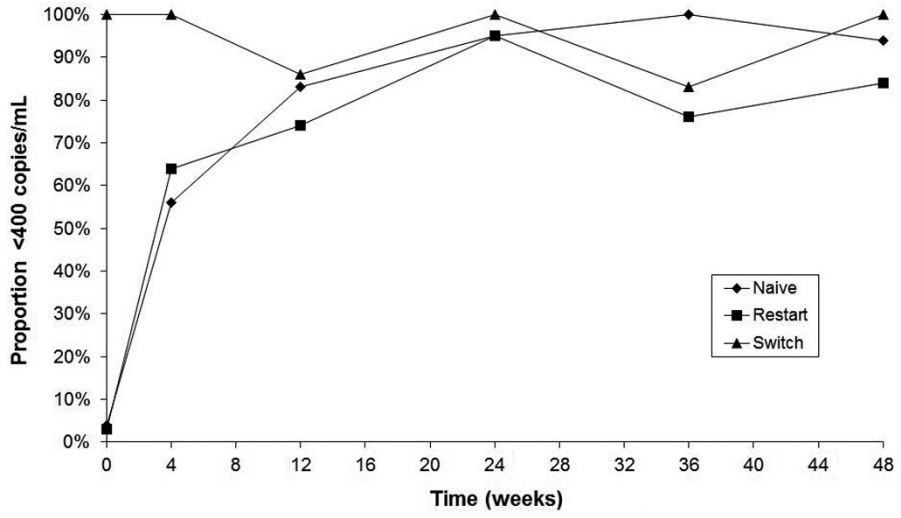


Fig. 2. Proportions of patients with plasma HIV-1 RNA <50 copies/mL (Panel A) and <400 copies/mL (Panel B) for the total intent-to-treat population (**X**), and for the treatment-naive (♦), restart (■) and switch (▲) sub-groups.

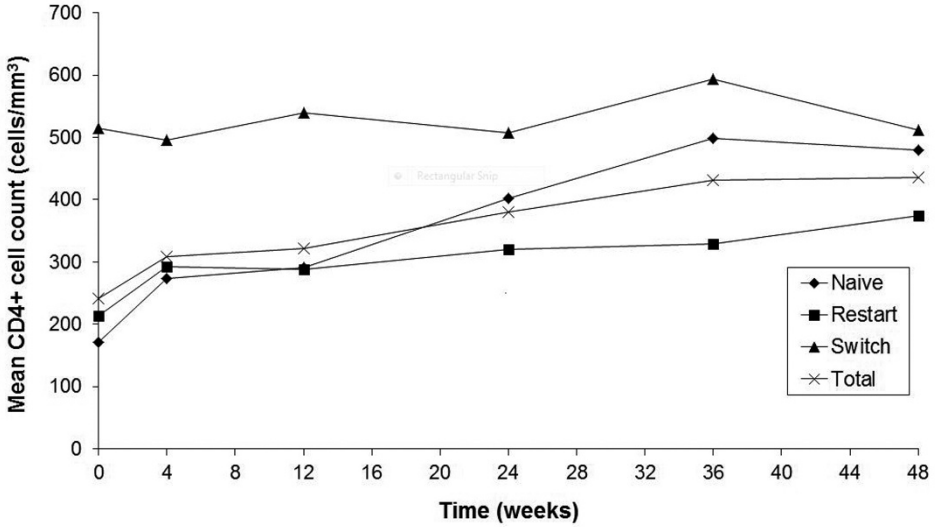


Fig. 3. Absolute CD4+ counts (cells/mm^3) for the total intent-to-treat population (**X**), and for the treatment-naive (♦), restart (■) and switch (▲) sub-group.

study (63 patients, 94%; Table 3), with approximately half of patients (36 patients, 54%) experiencing events judged to have a relationship to study medication. The most frequently occurring events (≥5% of patients) judged by the Investigator to have a relationship with study treatment were nausea (17 patients, 25%), vomiting (16 patients, 24%), diarrhoea (14 patients, 21%) and decreased weight (four patients, 6%). There were no deaths. Approximately half the patients in the study experienced adverse events that the Investigator judged to be serious (35 patients, 52%), with the most frequently reported events being elevated levels of bilirubin, coded as either increased blood bilirubin (nine patients, 13%) or hyperbilirubinaemia (five pa-

Table 3. Most frequently reported treatment-emergent adverse events (≥5% of patients; safety population).

Adverse event N = 67 n (%)	Safety population
Any adverse event	63 (94)
Vomiting	21 (31)
Nausea	19 (28)
Diarrhoea	17 (25)
Blood Bilirubin Increased	10 (15)
Fatigue	9 (13)
Hyperhidrosis	8 (12)
Insomnia	8 (12)
Influenza	7 (10)
Weight Decreased	7 (10)
Abdominal Pain	6 (9)
Abdominal Pain Upper	5 (7)
Constipation	5 (7)
Hyperbilirubinaemia	5 (7)
Sleep Disorder	5 (7)
Cheilitis	4 (6)
Gastritis	4 (6)
Headache	4 (6)
Hepatic Enzyme Increased	4 (6)
Lower Respiratory Tract Infection	4 (6)
Oral candidiasis	4 (6)

tients, 7%). All patients who experienced elevated levels of bilirubin that were regarded as adverse events received atazanavir as part of their antiretroviral regimen, which is known to increase serum bilirubin levels.

A number of patients experienced renal and urinary adverse events during the study: renal impairment (two patients; grade 2 and grade 3), dysuria (grade 1), haematuria (grade 1), pollakuria (abnormally high urinary frequency; grade 1) and increased serum creatinine (grade 1; one patient each). Two of these renal adverse events were considered by the Investigator to have a relationship to tenofovir DF. One patient who received tenofovir DF, emtricitabine and ritonavir-boosted atazanavir experienced increased serum creatinine at baseline (1.6 mg/dL; normal range: 0.8-1.5 mg/dL) and was diagnosed with serious renal impairment (grade 3) 2 weeks later, at which time his creatinine level was 3.0 mg/dL. He was discontinued from the study. His creatinine level returned to normal (1.3 mg/dL) within 3 weeks of discontinuing study drug, but increased above the normal range (2.3 mg/dL) when followed-up 2 months later. Another patient had increased serum creatinine (168 μmol/L; normal range: 50-115 μmol/L) after 29 days of treatment with tenofovir DF, emtricitabine and ritonavir-boosted atazanavir. The patient's serum creatinine value at screening was 132 μmol/L. Creatinine levels remained above the normal range but were not considered clinically significant until the patient's follow-up visit after his discontinuation on day 93 (148 μmol/L). No creatinine values were classed as grade 3 or 4 severity and neither of these patients had previous history of renal disorders.

Opiate Treatment Results

All patients received opiate treatment; methadone was the most frequently prescribed (57/67 patients, 85%), followed by levomethadone (9/67 patients, 13%) and buprenorphine (1/67 patients, 1%). Opiate treatment was adjusted according to patient symptoms of over- or under-dosing and, overall, 37 patients made changes to their opiate doses between screening and study end. There were no consistent patterns of dose changes for any of the opiates. Two thirds of the non-nucleoside reverse transcriptase inhibitor (NNRTI)-treated patients (n = 11) needed modifications of the opiate dose; except for one, all of these patients received increases. In contrast opiate dosage was adjusted in 52% of the protease inhibitor treated patients, (n = 55: opiate dosage modifications: none = 26/55, 47%; decrease = 13/55, 24%; increase = 11/55, 20%; decrease and increase = 5/55, 9%). No consistent differences between the different nucleoside reverse transcriptase inhibitor (NRTI) backbones were observed in context of opiate treatments. Despite opiate treatment 46.3 % of the patients reported the usage of other recreational drugs at baseline (cannabis: 21%; heroin: 3%, concomitant usage of different recreational drugs: 22%).

Discussion

This is one of few prospective multicentre studies conducted to assess the efficacy and tolerability of antiretroviral therapy in HIV-infected injecting drug users. Despite the proven benefits of antiretroviral therapy, many HIV-infected injecting drug users do not access treatment even in settings that provide free health care [23]. When they do receive treatment, it has been shown that injecting drug users show a weaker immunovirological response to initial therapy than other groups [24].

Our study showed that HIV suppression can be achieved in a substantial proportion of former injecting drug users, with a once daily antiretroviral regimen containing tenofovir DF co-administered with opiate treatment schemes. As expected from other studies that included injecting drug users, there were a lot of missing data [25]. A substantial number of patients prematurely discontinued their antiretroviral treatment because of adverse events or were lost to follow up. Nevertheless, in the on treatment analysis nearly two-thirds of the patients achieved HIV virological suppression at week 48 (<50 copies/mL). In contrast, the primary efficacy ITT analysis, which considered missing data to be equivalent to treatment failure, found only one third of patients to have plasma HIV-1 RNA <50 copies/mL at week 48. From week 12 until the end of the study, median plasma HIV-1 RNA levels

were below the limit of detection in all subgroups. Over the course of the study, CD4+ cell counts increased in the treatment-naïve and restart subgroups and, as predicted, CD4 counts were maintained in virologically suppressed patients who switched to the tenofovir DF 300 mg-containing once daily regimen. The increases in CD4+ cell counts were in line with previous studies of tenofovir DF-containing regimens in treatment-naïve and treatment experienced patients [19, 20].

This study had some limitations, for example, the number of patients was relatively low and 48 weeks was a relatively short observation period. Also resistance data and pharmacokinetic profiles were missing. The main limitation, however, was the open-label, single-arm design and the high number of early discontinuations.

There are little published data on the efficacy and safety of treatment of HIV-infected injecting drug users. A study of 1583 treatment-naïve, HIV-infected patients who initiated antiretroviral therapy over a 4-year period in British Columbia, Canada included 359 injecting drug users [26]. Response rates (defined as two consecutive plasma HIV RNA values <500 copies/mL) were reported to be 51% for injecting drug users and 70% for patients with no history of drug use. While the proportion of patients with plasma HIV RNA <500 copies/mL was not calculated in the current study, the proportion of patients with plasma HIV-1 RNA <400 copies/mL at week 48 was 55% in the most conservative analysis (ITT M=F), which was similar to that reported in the Canadian study.

A lot of data were missing in the current study, for example, only 61% of the total population provided data for the week 48 assessment of plasma HIV-1 RNA. Studies in injecting drug users generally have more missing data than those conducted in patients with no history of drug use. Injecting drug use, use of recreational drugs and episodes of depression (often associated with drug use) have been shown to increase the likelihood of non-adherence to antiretroviral regimens [3-5, 27, 28]. Therefore, adherence was an important variable in this study and it was anticipated that obtaining reliable estimates of adherence might be an issue in this population. A number of strategies were included to encourage good adherence and accurate measurement: patients were allocated to a once-daily treatment regimen; a simple one-touch, handheld electronic diary system was used [29]; reminders for patients to submit their adherence data were sent via their PDA device; and three methods of adherence assessment were used rather than just one. It appears, however, that these strategies were not sufficient to ensure the level of adherence more usually seen in populations lacking the additional complicating factor of injecting drug use as significant proportions of the population did not complete a single MASRI questionnaire (29%) or enter any diary data (14%). Pill counts, which are generally accepted to have a higher accuracy than diary card completion, indicated that a lower proportion of the population had >95% adherence than that indicated by the MASRI questionnaires and the diary data.

As expected, NNRTI containing antiretroviral regimen demanded more often increases of opiate dosage during this study. Usage of NRTI and protease inhibitors was not associated with specific dose modifications in opiate treatment. Most patients in this study were treated with ritonavir-boosted atazanavir once daily and methadone. Recently published data observed partial decreases in atazanavir plasma concentrations in patients concomitantly taking racemic methadone oral solution, which may have an impact on antiretroviral effectiveness [30].

Although safety data from studies assessing antiviral treatment of hepatitis C virus in HIV-infected injecting drug users are well represented in the scientific literature, there is a lack of studies that have specifically examined the safety of antiretroviral regimens in HIV-infected injecting drug users. High rates of adverse events associated with antiretroviral therapy were expected in this population because of potential comorbidities, coinfections and drug-drug interactions (although it should be noted only one patient was taking medication for Hepatitis C at screening). The results of the current study showed that almost all patients reported adverse events, although most of these did not lead to discontinuation of antiretroviral medication [16].

The reporting of adverse events seems to be broadly in line with other studies, that have reported gastrointestinal events as the most frequently reported events [17, 19, 20], and with the Summary of Product Characteristics [31]. No new safety issues were identified in this study. The reported rate of approximately 50% of patients who experienced serious adverse events was due largely to the requirement specified in the protocol that grade 3 or 4 abnormalities in a range of laboratory parameters had to be considered serious. The most prominent adverse event in the study was increased serum bilirubin / hyperbilirubinaemia. All subjects who experienced these events had received atazanavir, which is known to increase bilirubin levels [32]. Tenofovir DF has previously been associated with renal adverse events [33] and two patients were discontinued from this study after experiencing increased blood creatinine levels. These were judged by the investigator to be related to tenofovir DF. Quality of life scores were below those of the general population, but consistent with those of patients suffering from a chronic disease.

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