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ORIGINAL RESEARCH

Twenty-four-week efficacy and safety of switching virologically suppressed HIV-1-infected patients from nevirapine immediate release 200 mg twice daily to nevirapine extended release 400 mg once daily (TRANxITION)

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Objectives

Once-daily (qd) antiretroviral therapies improve convenience and adherence. If found to be effective, nevirapine extended release (NVP XR) will confer this benefit. The TRANxITION trial examined the efficacy and safety of switching virologically suppressed patients from NVP immediate release (NVP IR) 200 mg twice daily to NVP XR 400 mg qd.

Methods

An open-label, parallel-group, noninferiority, randomized (2:1 NVP XR:NVP IR) study was performed. Adult HIV-1-infected patients receiving NVP IR plus a fixed-dose nucleoside reverse transcriptase inhibitor (NRTI) combination of lamivudine (3TC)/abacavir (ABC), tenofovir (TDF)/emtricitabine (FTC) or 3TC/zidovudine (ZDV) with undetectable viral load (VL) were enrolled in the study. The primary endpoint was continued virological suppression with VL < 50 HIV-1 RNA copies/mL up to week 24 (calculated using a time to loss of virological response algorithm). Cochran's statistic (background regimen adjusted) was used to test noninferiority. Adverse events (AEs) were recorded.

Results

Among 443 randomized patients, continued virological suppression was observed in 93.6% (276 of 295) of NVP XR- and 92.6% (137 of 148) of NVP IR-treated patients, an observed difference of 1% [95% confidence interval (CI) −4.3, 6.0] at 24 weeks of follow-up. Noninferiority (adjusted margin of −10%) of NVP XR to NVP IR was robust and further supported by SNAPSHOT analysis. Division of Acquired Immunodeficiency Syndrome (DAIDS) grade 3 and 4 events were similar for the NVP XR and NVP IR groups (3.7 *vs.* 4.1%, respectively), although overall AEs were higher in the NVP XR group (75.6 *vs.* 60.1% for the NVP-IR group).

Conclusions

NVP XR administered once daily resulted in continued virological suppression at week 24 that was noninferior to that provided by NVP IR, with similar rates of moderate and severe AEs. The higher frequency of overall AEs with NVP XR may be a consequence of the open-label design.

Keywords: extended release, HIV, immediate release, nevirapine, noninferiority, switching, virologically stable

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Introduction

Adherence to therapeutic regimens for HIV-1 infection is a major factor in ensuring long-term successful treatment, in addition to the potency of antiviral agents [1–3]. Nonnucleos(t)ide HIV-1 reverse transcriptase inhibitor (NNRTI)-based combination antiretroviral therapies have been gaining popularity over protease inhibitor antiretroviral therapy, and have become preferred therapy options for treatment-naïve individuals as per treatment guideline recommendations [4]. In addition, recent publications have reported increased adherence to therapeutic regimens with the use of once-daily (qd) dosing [5–7].

The antiviral activity and safety of the NNRTI nevirapine (NVP) are well established [8–11]. NVP is a potent NNRTI with high bioavailability, a long half-life and no effect of food on its absorption [12]. It is available as an immediate release (IR) formulation, which is administered as 200 mg twice daily (bid). qd dosing will further simplify the administration of NVP and has the potential to improve adherence, which in turn should enhance long-term efficacy. A newly developed 400 mg NVP extended release formulation (NVP XR) administered qd has recently been investigated and found to be well tolerated and to have high and comparable efficacy to NVP immediate release (NVP IR) 200 mg bid in treatment-naïve individuals [13].

The current study investigated the efficacy, defined as continued virological response, at 24 weeks of follow-up, and the safety and tolerability of switching treatment-experienced patients from NVP IR bid to NVP XR qd.

Methods

Study design and patients

This trial is a multinational, open-label, Phase IIIb, randomized, parallel-group study to evaluate the efficacy and safety of switching HIV-1-infected patients, successfully treated with an NVP IR 200 mg bid regimen, to NVP XR 400 mg qd, in comparison to remaining on NVP IR 200 mg bid. The trial is continuing to collect data up to 144 weeks of follow-up. The study population is composed of adult (age $\geq$ 18 years) patients who were receiving NVP IR with a fixed-dose combination background therapy of lamivudine/abacavir (3TC + ABC), tenofovir/emtricitabine (TDF + FTC), or lamivudine/zidovudine (3TC + ZDV), or their individual components, for a preceding minimum of 18 weeks, with undetectable (< 50 HIV-1 RNA copies/mL) HIV-1 viral load (VL) in the previous 1–4 months and at screening.

Patients provided written consent and the trial (NCT00819052; TRANxITION) was conducted in accordance with good clinical practice and the ethical principles of the Declaration of Helsinki (1996 version) [14]. Trial protocol, amendments, informed consent and subject information were reviewed by the central or local institutional review board and independent ethics committees of the participating institutions.

Patients were stratified according to their background therapy and randomized within each stratum in a 2:1 ratio to either switch to NVP XR 400 mg qd or continue with NVP IR 200 mg bid. All data were recorded using electronic data capture methods. The database was maintained by the sponsor, but data were made available to all authors.

Viral load measurement

Plasma samples were obtained at every visit for safety laboratory and VL analyses. VL was routinely measured using the Roche Cobas TaqMan assay, which was subsequently shown to perform differently from the Roche Cobas Amplicor Ultrasensitive HIV-1 test (Roche Diagnostics, Risch, Switzerland). Data suggested that, at a low VL (< 48 copies/mL), the TaqMan assay may report detectable VL results at a higher frequency than the Amplicor test [15]. As the trial design was based on the test performance of the Amplicor test, plasma samples with TaqMan results $\geq$48 copies/mL and $\leq$200 copies/mL after randomization to week 24 inclusive were assayed using the Amplicor Ultrasensitive assay, in order to provide an Amplicor-based endpoint result. If the Amplicor Ultrasensitive assay detected virus (VL $\geq$ 50 copies/mL), the samples obtained before and after the index sample were also tested using the Amplicor Ultrasensitive assay. The VL recorded for the patient was the result using the Amplicor assay, whenever it was performed. For visits where the Amplicor assay was not performed, the result from the TaqMan assay was recorded.

Study endpoints

The primary study endpoint was the proportion of patients with continued virological response (< 50 copies/mL) at week 24, using the combined Amplicor–TaqMan results. Patients were classed as having treatment failure at the first occurrence of any one of the following:

i. two consecutive VLs of $\geq$50 copies/mL at least 2 weeks apart;
ii. missing VL measurement at week 24;
iii. change in background antiretroviral (ARV) therapy other than because of adverse events (AEs);
iv. death;
v. loss to follow-up; or
vi. study discontinuation.

Secondary efficacy endpoints included the proportion of patients with a continued virological response using a lower limit of quantification (LLOQ) of <400 copies/mL (as measured by Cobas Amplicor and Cobas TaqMan assay), and time to loss of virological response. Analyses were also performed where only the TaqMan data were used to define VL.

Adherence

Treatment adherence monitoring of study medication (tablet count and duration of medication intake) was performed using an adherence worksheet where tablet counts and treatment interruptions were documented. Adherence was calculated as the actual number of pills taken divided by the number of pills that should have been taken.

Safety

AEs, serious AEs (SAEs) including AIDS-defining events, Division of Acquired Immunodeficiency Syndrome (DAIDS) grade 3 or 4 AEs, laboratory abnormalities and change in baseline laboratory values to week 24 were recorded. When rashes that were possibly related to NVP or hepatic AEs occurred, specific rash and hepatic electronic case report forms were completed. Patients were assessed for changes in haematology, liver enzymes, bilirubin, coagulation parameters, renal function, glucose, amylase and lipase, and triglycerides.

NVP pharmacokinetics

Plasma trough concentrations of NVP were assessed at each visit for all patients using a validated method of tandem mass spectrometry. The relative bioavailability was assessed by comparing the NVP XR and IR trough concentrations at week 24 and the geometric mean of all weeks.

Statistical analyses

In determining the sample size, a planned noninferiority margin of 12% was selected for the difference in proportions between NVP XR and NVP IR in terms of continued virological response, assuming that 90% would be responders in both groups. A noninferiority test, with a one-sided $\alpha = 0.025$ and a randomization ratio of 2:1 for the NVP XR and NVP IR treatment arms, required 198 and 99 patients, respectively, in order to have 90% power to reject the null hypothesis.

The primary endpoint (proportion of patients with continued virological response at week 24) and its 95% confidence interval (CI) were estimated based on a time to loss of virological response (TLOVR) algorithm as specified by the US Food and Drug Administration (FDA) guidance [16]. Weighted treatment difference and corresponding variance were calculated based on Cochran's statistic [17] with continuity for variance calculation. Noninferiority to the control group in the primary endpoint was determined by comparing the lower 95% confidence limit of the difference in proportions of virological response for the two treatment arms (NVP XR *vs.* NVP IR) with the noninferiority margin of −12%. Because of the increased numbers of patients enrolled in this study, the noninferiority margin for the study was adjusted to −10%.

An additional approach (SNAPSHOT analysis) was also used to analyse the endpoint of continued suppression, as a key secondary analysis. In this approach, a patient with VL < 50 copies/mL at the 24-week time-point (± 4) was defined as a virological responder.

The secondary endpoint of TLOVR using an LLOQ of <400 copies/mL was analysed using the Cox proportional hazard model with baseline background therapy as a stratum variable. All safety data were analysed using descriptive statistical methods.

Results

Patient disposition and demographics

A total of 499 patients were enrolled in the study, an increase over the planned number of 300. This was a result of the unexpectedly rapid enrolment as a result of investigators pre-screening their patients. Of these, 445 were randomized, 295 to NVP XR and 148 to NVP IR; 54 patients were excluded primarily because they did not meet the eligibility criteria (Fig. 1). Two patients, one in each treatment group, were randomized but never received treatment, leaving 443 in the full analysis set.

Baseline demographic data, which are shown in Table 1, were similar for the two treatment groups. The baseline VL value was defined as the mean of the VLs at screening and at randomization; 27 patients had a VL > 50 copies/mL at the randomization visit, so 6.1% of patients had a 'detectable' baseline VL. As the results for VL at randomization were not available until several days after randomization, these patients were still included in the study and continued in the study based on the earlier nondetectable screening of VL.

Baseline CD4 cell counts were similar for male and female patients, with the majority of patients (76.5%) having CD4 counts >400 cells/μL; 1.8% had counts <200 cells/μL.

Efficacy

The results for the primary endpoint are summarized in Table 2a: continued virological suppression at week 24 was

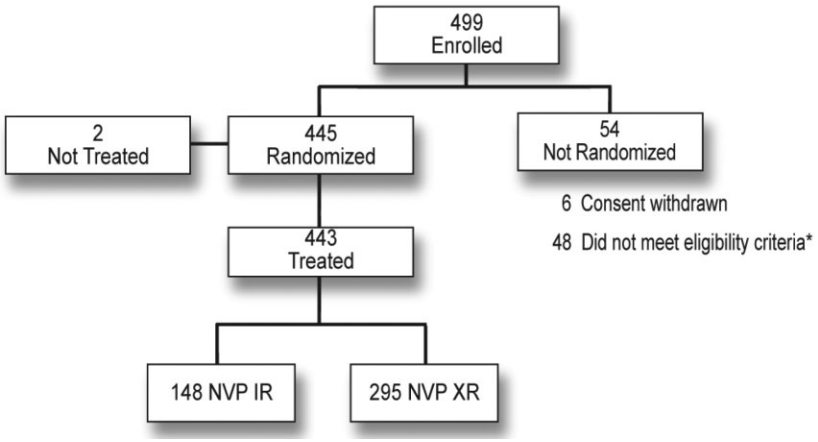

Fig. 1 Disposition of the study population. Of 499 patients who were enrolled in the study, 445 were randomized, 295 to nevirapine extended release (NVP XR) and 148 to NVP immediate release (NVP IR), with a total of 443 being treated; 54 patients were excluded primarily because they did not meet the eligibility criteria. *Some patients were not eligible for more than one reason. The most common reasons for ineligibility were detectable viral load at screening (12 patients), detectable viral load within 4 months preceding screening (nine patients), abnormal screening safety laboratory results (14 patients) and wrong antiretroviral background (seven patients).

Table 1 Baseline patient demographics

	NVP XR	NVP IR	Total
Number of patients	295	148	443
Male [*n* (%)]	244 (82.7)	128 (86.5)	372 (84.0)
Age [mean (SD)]	47.3 (9.6)	47.6 (9.8)	47.5 (9.7)
Region [*n* (%)]			
North America	98 (33.2)	46 (31.1)	144 (32.5)
Europe	197 (66.8)	102 (68.9)	299 (67.5)
Baseline HIV-1 RNA < 50 copies/mL [*n* (%)]	280 (94.9)	136 (91.9)	416 (93.9)
Baseline CD4 count (cells/μL) [mean (median; range)]	557.7 (530.0; 411.0–695.0)	569.7 (542.0; 411.5–668.0)	561.7
Background therapy [*n* (%)]			
TDF/FTC	158 (53.6)	82 (55.4)	240 (54.2)
3TC/ZDV	63 (21.4)	30 (20.3)	93 (21.0)
3TC/ABC	74 (25.1)	36 (24.3)	110 (24.8)
Duration of therapy with nevirapine [*n* (%)]			
< 1 year	52 (17.6)	30 (20.3)	82 (18.5)
1–3 years	101 (34.2)	44 (29.7)	145 (32.7)
3–5 years	75 (25.4)	35 (23.6)	110 (24.8)
> 5 years	67 (22.7)	39 (26.4)	106 (23.9)
History of AIDS-defining illness	74 (25.1)	30 (20.3)	104 (23.5)

3TC, lamivudine; ABC, abacavir; FTC, emtricitabine; IR, immediate release; NVP, nevirapine; SD, standard deviation; TDF, tenofovir; XR, extended release; ZDV, zidovudine.

observed in 93.6% of NVP XR-treated patients and 92.6% of patients in the NVP IR group. Adjusting for the strata of background treatment, the difference was 1.0% (95% CI −4.3, 6.0) using the TLOVR algorithm and Cochran statistic. NVP XR was noninferior to NVP IR in terms of virological response, using either the planned −12% or the modified −10% margin for noninferiority. This finding was consistent when virological responses were compared using an LLOQ of VL = 400 copies/mL, and was unaffected by gender, race or age (results not shown). As would be expected, continued virological response was slightly lower using the TaqMan-only analysis (91.2 and 89.9% for NVP XR and NVP IR, respectively) than with the Amplicor-corrected analysis. However, the observed difference in continued virological suppression of 1.3% favouring the NVP XR group is consistent with the difference observed using the Amplicor-corrected analysis.

Investigation of virological responses by ARV treatment stratum revealed an observed difference of −2.1% (95% CI −8.9, 4.6) for TDF + FTC; −3.0% (95% CI −11.8, 5.8) for 3TC + ZDV, and 11.2% (95% CI −0.7, 23.1) for 3TC + ABC, when comparing NVP XR with NVP IR

Table 2 Summary of continued virological response in the nevirapine (NVP) extended release (XR) and NVP immediate release (IR) treatment groups. (a) Primary analysis with Amplicor time to loss of virological response (TLOVR) (full analysis set); (b) secondary analyses with TLOVR and SNAPSHOT

(a)

	No. with virological response/total no. (%)		
	NVP XR 400 qd	NVP IR 200 bid	% difference (95% CI)
Total (all patients)	276/295 (93.6)	137/148 (92.6)	1.0 (–4.3, 6.2)
Subgroup response by background ARV therapy			
TDF + FTC	145/158 (91.8)	77/82 (93.9)	–2.1 (–8.9, 4.6)
3TC + ZDV	59/63 (93.7)	29/30 (96.7)	–3.0 (–11.8, 5.8)
3TC + ABC	72/74 (97.3)	31/36 (86.1)	11.2 (–0.7, 23.1)

(b)

	Secondary analyses using TLOVR and SNAPSHOT analysis				
Data set	Method/LLOQ (copies/mL)	Assay	NVP XR (*n*/*N*, %)	NVP IR (*n*/*N*, %)	% difference (95% CI)
FAS	TLOVR/50	TaqMan	269/295 (91.2)	133/148 (89.9)	1.3 (–4.7, 7.3)
FAS	SNAPSHOT/50	Amplicor	281/295 (95.3)	139/148 (93.9)	1.3 (–3.5, 6.1)
FAS	SNAPSHOT/50	TaqMan	279/295 (94.6)	137/148 (92.6)	2.0 (–3.2, 7.1)
FAS	TLOVR/400	TaqMan	285/295 (96.6)	140/148 (94.6)	2.0 (–2.5, 6.5)
PPS	TLOVR/50	Amplicor	274/293 (93.5)	136/147 (92.5)	1.0 (–4.3, 6.3)

3TC, lamivudine; ABC, abacavir; ARV, antiretroviral; bid, twice a day; CI, confidence interval; FTC, emtricitabine; IR, immediate release; LLOQ, lower limit of quantification; NVP, nevirapine; PPS, per-protocol set; qd, once a day; TDF, tenofovir; XR, extended release; ZDV, zidovudine.

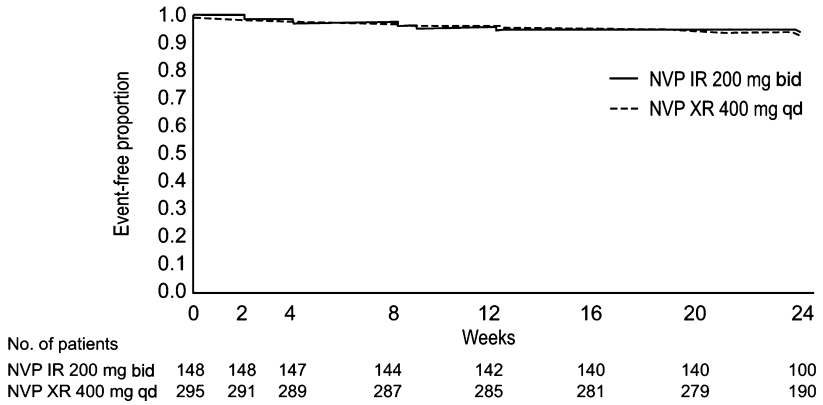

Fig. 2 Kaplan–Meier curves for time to loss of virological response (TLOVR) [lower limit of quantification (LLOQ) = 50 copies/mL by Amplicor; full analysis set (FAS)]. The Kaplan–Meier curves were very similar for the two treatment groups for the follow-up duration of 24 weeks. No significant difference in TLOVR was detected between the two treatment groups using the Cox model and adjusting for background antiretroviral therapy. IR, immediate release; XR, extended release.

(Table 2a). To determine if the large difference in the virological suppression rate of 11.2% between NVP XR and NVP IR in patients in the 3TC + ABC treatment stratum could be attributable to the length of time the patient received ARV therapy, the duration of ARV therapy prior to study enrolment was examined. However, no clear relationship was found between prior treatment duration and failure (data not shown). We must, however, bear in mind that the numbers of patients in each ARV treatment stratum were small.

Results of analysis of TLOVR are shown in Figure 2. The Kaplan–Meier curves were similar for the NVP XR and NVP IR treatment groups, with no significant difference. Using the Cox model adjusted for background ARV therapy, the TLOVR hazard ratio for loss of virological response of NVP XR *versus* NVP IR was 0.88 (95% CI 0.42, 1.86) for the Amplicor-corrected profile and 0.89 (95% CI 0.47, 1.68) for the TaqMan-only profile.

The SNAPSHOT approach was used to analyse both the Amplicor and TaqMan profiles (Table 2b). Using the

SNAPSHOT approach and results from the Amplicor assay with LLOQ = 50 copies/mL, the observed difference was 1.3% (95% CI −3.5, 6.1), and continued virological response was observed in 95.3% of patients in the NVP XR group and 93.9% in the NVP IR group (Table 2b). Analysis of the secondary endpoint of the proportion of patients with continued virological response using the TaqMan assay and LLOQ = 400 copies/mL, based on the TLOVR algorithm, revealed that 96.6% of those in the NVP XR group and 94.6% of those in the NVP IR group were responders at week 24, with a difference of 2.0% (95% CI −2.5, 6.5). The same difference of 2.0% (95% CI −3.2, 7.1) was obtained with the SNAPSHOT method and TaqMan assay using an LLOQ of 50 copies/mL.

The change from baseline to week 24 in CD4 cell count was 39.8 cells/μL in the NVP XR group and 32.5 cells/μL in the NVP IR group. Both treatment groups demonstrated a trend of increasing mean CD4 cell count after week 8, with no difference between the two treatment groups (data not shown).

Treatment exposure and adherence

In all, 98% of both treatment groups were exposed to study medication for at least 24 weeks. Adherence was similar between the treatment groups, the mean adherence with NVP XR being 99.6% [standard deviation (SD) 3.3] and that with NVP IR being 98.6% (SD 3.3).

Pharmacokinetics of NVP

All geometric mean NVP trough concentrations exceeded 3 μg/mL and were stable for both formulations during the reported 24-week period. The ratio of NVP XR to NVP IR trough geometric mean concentration for all visits was 89.7%. The relative bioavailability analysis showed that the NVP XR to NVP IR trough ratios were between 83.82 and 98.91%, within acceptable limits for week 24 and the geometric mean of all visits. Furthermore, when trough concentrations for the two formulations were compared, no clinically relevant differences were observed by gender, race, region or background ARV therapy.

Safety evaluations

Overall, AEs were observed in 75.6% (223 of 295) of patients in the NVP XR group and in 60.1% (89 of 148) of patients in the NVP IR group (Table 3a). The frequency of AEs of DAIDS grade 3 or 4 severity was similar between the two treatment groups: 3.7% (11 of 295) for NVP XR- and 4.1% (six of 148) for NVP IR-treated patients. SAEs were recorded in 21 patients altogether, 17 of 295 (5.8%) in the NVP XR group and four of 148 (2.7%) in the NVP IR group, none of which was considered drug related.

Investigator-defined study drug-related AEs occurred in 11.9% (35 of 295) and 2.0% (three of 148) of patients, respectively, for the NVP XR and NVP IR treatment groups. Grade 3 drug-related AEs occurred in one patient (0.3%) treated with NVP XR and two patients (1.4%) treated with NVP IR. There were no grade 4 or fatal clinical AEs in either study arm during the 24 weeks of follow-up.

Three patients (1.0%) had AEs leading to study discontinuation, all of whom were in the NVP XR group: one patient experienced tachycardia, dry mouth, indigestion, diarrhoea, olfactory intolerance, headache and a sense of impending doom (DAIDS grade 2); one patient had a rash (DAIDS grade 2); and the third experienced dizziness, lightheadedness and nausea (DAIDS grade 1).

When all the AEs were reviewed, it became apparent that the AEs occurring at numerically higher rates in the NVP XR group compared with the NVP IR group were related to gastrointestinal, general and administration site, nervous, psychiatric, and skin and subcutaneous disorders. These AEs were mainly of mild intensity, and there were no differences in the NVP XR and NVP IR groups in moderate or severe intensity events (Table 3b). Similar frequencies of AEs were observed for infections and infestations (36.6 and 33.1% for NVP XR and NVP IR, respectively) and for safety laboratory investigations (including aspartate aminotransferase, blood cholesterol and gamma-glutamyltransferase levels) (4.4 and 5.4%, respectively).

Rash and hepatic events were considered AEs of special interest and both were infrequently observed. Rash was reported in three patients (1.0%) in the NVP XR group – two with grade 1 and one with grade 2 intensity. The two patients with grade 1 rash continued NVP treatment, while the patient with grade 2 rash discontinued NVP treatment.

Hepatic events were observed in one NVP XR-treated patient, who acquired acute HCV infection during the course of the study. This patient experienced fatigue and transient liver enzyme elevation, which returned to normal after 6 weeks.

There were no differences between the two treatment groups in terms of safety laboratory tests or vital signs. The majority of abnormalities were mild (DAIDS grade 1). Moderate or severe (grade 2 or 3) aspartate transaminase (AST) and alanine transaminase (ALT) elevations were infrequent in both treatment groups (2.7 and 3.8% of NVP XR-treated patients, respectively, compared with 4.8 and 4.7% of NVP IR-treated patients, respectively). There was one occurrence of grade 4 ALT enzyme elevation in the NVP XR group (Table 3c).

Table 3 Adverse events and laboratory parameters. (a) Summary of all adverse events; (b) adverse events by system organ class and intensity; (c) summary of key laboratory test changes by worst Division of Acquired Immunodeficiency Syndrome (DAIDS) grade

(a)

	NVP XR 400 mg qd [*n* (%)]	NVP IR 200 mg bid [*n* (%)]
No. of patients	295 (100.0)	148 (100)
Any AE	223 (75.6)	89 (60.1)
Investigator-defined study drug-related AEs	35 (11.9)	3 (2.0)
AEs leading to discontinuation	3 (1.0)	0 (0.0)
SAEs	17 (5.8)	4 (2.7)
DAIDS grade 3 or 4 AEs	11 (3.7)	6 (4.1)
DAIDS grade 4 AEs	2 (0.7)	0 (0.0)
Any study drug-related DAIDS grade 3 AEs	1 (0.3)	2 (1.4)
Any study drug-related DAIDS grade 4 AEs	0 (0.0)	0 (0.0)

(b)

	NVP XR 400 mg qd (%)			NVP IR 200 mg bid (%)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Gastrointestinal disorders	61 (20.7)	9 (3.1)	0	7 (4.7)	4 (2.7)	0
General and administration site conditions	29 (9.8)	3 (1.0)	3 (1.0)	8 (5.4)	1 (0.7)	0
Nervous system disorders	25 (8.5)	7 (2.4)	1 (0.3)	5 (3.4)	4 (2.7)	0
Psychiatric disorders	23 (7.8)	7 (2.4)	1 (0.3)	7 (4.7)	1 (0.7)	0
Skin and subcutaneous tissue disorders	22 (7.5)	4 (1.4)	0	7 (4.7)	0	0

(c)

	NVP XR 400 mg qd				NVP IR 200 mg bid			
	Grade 1 (*n*/%)	Grade 2 (*n*/%)	Grade 3 (*n*/%)	Grade 4 (*n*/%)	Grade 1 (*n*/%)	Grade 2 (*n*/%)	Grade 3 (*n*/%)	Grade 4 (*n*/%)
AST	53/18.0	6/2.0	2/0.7	0/0	22/14.9	6/4.1	1/0.7	0/0
ALT	81/27.5	9/3.1	2/0.7	1/1.0	35/23.6	3/2.0	4/2.7	0/0
Triglycerides	0/0	11/3.7	4/1.4	2/0.7	0/0	8/5.4	2/1.4	2/1.4

AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; bid, twice a day; IR, immediate release; NVP, nevirapine; qd, once a day; SAE, serious adverse event; XR, extended release.

Discussion

The TRANxITION trial demonstrated that NVP XR was noninferior to NVP IR in maintaining virological suppression in NVP-experienced patients who switched from NVP IR bid to NVP XR qd. Continued virological suppression was high in both treatment groups, and the noninferiority of the NVP XR formulation was demonstrated through a treatment difference of 1.0% (95% CI −4.3, 6.0). This was well above the lower margin of −12%, such that, even using a −10% margin, noninferiority would be demonstrated in this study. In addition, the noninferiority of NVP XR qd to NVP IR bid was supported by all secondary analyses, including the SNAPSHOT approach analysis, different assays for VL, and different definitions of virological failure (one VL > 50 copies/mL or >400 copies/mL). The results with regard to the primary endpoint were consistent across subgroups, defined by race and gender.

Treatment adherence was high for both treatment groups in the present study (≥ 98%). The added convenience of qd dosing, especially in combination with a qd nucleoside reverse transcriptase inhibitor (NRTI) backbone, will be important to patients, especially those with drug adherence issues.

The NVP XR formulation was well tolerated. Although higher overall rates of AEs were associated with the NVP XR formulation, interpretation of this higher rate is difficult in the setting of an open-label, randomized trial in which both patients and investigators were aware of the new treatment that the patients on XR were receiving. Of note, the AEs occurring with higher frequency in the NVP XR treatment group were mainly of mild intensity and tended to be events that are subjective in nature. In contrast, AEs that were moderate or severe in intensity occurred at similar rates between the two treatment groups. It should be noted that patients were either staying on NVP IR, which they had already been taking (sometimes for several years), or switching to an investigational product – the NVP XR qd formulation. A weakness of the trial was its open-label design and it is possible that the differences in

mild and moderate AE rates resulted from such an open-label, change-over design.

Supporting this speculation is the observation that AE rates were very similar between the NVP XR and NVP IR groups in the VERxVE trial, which had a double-blind, double-dummy design. There was a nonsignificant trend towards lower AE rates for NVP XR 400 mg qd compared with NVP IR 200 mg bid at the 48-week analysis [13].

It has been observed in clinical studies that treatment-naïve patients with higher CD4 cell counts have a greater risk of hepatic events when they have a detectable VL ($\geq$ 50 copies/mL) in addition to CD4 cell counts above the thresholds of 400 cells/μL for men and 250 cells/μL for women. Consequently, it is recommended that treatment-naïve women with a CD4 count >250 cells/μL and men with a CD4 count >400 cells/μL should not take NVP [12,18]. However, the TRANxITION study involved treatment-experienced patients with suppressed VL (< 50 copies/mL); therefore, these patients could be considered suitable candidates regardless of CD4 cell count [12]. Furthermore, the study population had been receiving NVP for at least 18 weeks at the time they began the trial. The mean baseline CD4 cell count for patients in both treatment groups was >500 cells/μL, and continued to increase to week 24. Unlike treatment-naïve patients who are initiating therapy with NVP, cutaneous and hepatic hypersensitivity reactions were infrequent in the TRANxITION trial, suggesting that there is no increased risk of an immune-mediated reaction in those who switched between the two NVP formulations.

In conclusion, the results at week 24 of follow-up for this switch study demonstrate that NVP XR 400 mg qd was noninferior to NVP IR 200 mg bid in terms of virological efficacy in NVP treatment-experienced patients, and was well tolerated. This study supports the switch from NVP IR bid to the NVP XR qd formulation in patients who are virologically suppressed. These data are important as NVP is a widely used antiretroviral medication with which patients and physicians are familiar, and this new, once-daily, extended-release formulation is a more convenient presentation and a useful addition to HIV-1 therapy.

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Conflicts of interest: KA has received honoraria for consultancy work from Boehringer Ingelheim Pharmaceuticals Inc. DJW has received research grants from GlaxoSmithKline, Bristol-Myers Squibb, Boehringer Ingelheim Pharmaceuticals Inc, Merck, Gilead Sciences, Tibotec, Pfizer and ViiV. He has also been a consultant at advisory boards and speaker bureaus for GlaxoSmithKline, Bristol-Myers Squibb, Boehringer Ingelheim Pharmaceuticals Inc, Tibotec, Gilead Sciences and Pfizer. CO has received travel sponsorships from, provided advice to, and received research grants from Janssen, ViiV, GlaxoSmithKline, Merck Sharp & Dohme, Bristol-Myers Squibb, Gilead Sciences and Boehringer Ingelheim Pharmaceuticals Inc. AP, JML and CC do not have any conflicts of interest. AQ, EW, CLY, PR and JG are employees of Boehringer Ingelheim Pharmaceuticals Inc.

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