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TRANxITION 144 Week Results: Switching Virologically Stable HIV Patients from Immediate-release Nevirapine (NVP IR) to Extended-Release NVP (XR)

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Abstract

Purpose: TRANxITION compared efficacy and safety of switching virologically suppressed HIV-1 infected patients from nevirapine (NVP) immediate-release (IR) (200 mg twice-daily) to NVP extended-release (XR) (400 mg once-daily).

Methods: TRANxITION was an open-label, parallel-group, non-inferiority clinical trial where adult patients with undetectable viral loads, receiving NVP IR plus a fixed-dose NRTI combination, were randomized (2:1) to NVP XR or IR. After week 48, patients initially randomized to IR were allowed to switch to XR.

Summary of results: At week 48, proportions of patients with virologic response (LLOQ=50 copies/mL TaqMan, FAS) were 88.5% (131/148) in the IR arm, and 88.8% (262/295) in the XR arm, observed difference of 0.3% (95% CI -6.1, 6.7). DAIDS grade 3/4 adverse events were similar in the XR and IR arms at week 48: 6.4% (19/295) vs. 6.1% (9/148). After week 48, all but 13 patients in the IR arm switched to XR. At week 144, the proportions of patients with virologic response were 95.0% (115/121) in those switching from IR to XR after week 48 [IR-XR post48], and 95.2% (238/250) in those on XR throughout [XR-XR post48]). DAIDS grade 3 and 4 events at week 144 in IR-XRpost48 (7.7%, [10/130]) differed from the XR-XR post48 group (11.2%, [31/276]).

Conclusions: NVP XR QD resulted in continued virologic suppression at weeks 48 and 144. Up to week 144, rates of serious AEs were modestly higher than at week 24 in both post-week 48 XR arms, most likely due to the open-label design of the study.

Keywords: Nevirapine; Clinical trial; HIV; Extended-release formulation

Introduction

Treatment adherence is important to the long-term success of antiretroviral (ARV) regimens for the control of HIV infection [1-3]. Once-daily and, especially, single-tablet regimens have been shown to improve treatment adherence, leading to improved efficacy, safety, and regimen durability [4]. Therefore, new ARV formulations that allow once-daily dosing will provide important treatment options for HIV-infected patients.

As there have been countless advances in the treatment of HIV infection, patients can be expected to remain on ARV regimens for decades. Therefore, the metabolic consequences and management of chronic comorbidities associated with chronic HIV infection and ARV treatment gain importance. Various comorbidities of HIV infection, side effects of some ARVs, and non-HIV-related comorbidities can increase the overall risk of cardiovascular disease in the HIV-infected population.

The non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine (NVP) has been shown to have minimal untoward effects on serum lipids. Therefore, it is possibly an NNRTI of choice in patients who have hyperlipidemia or an otherwise elevated cardiovascular risk profile. The ArTEN trial recently demonstrated that a regimen of NVP plus tenofovir/emtricitabine (TDF/FTC) has similar safety and non-inferior efficacy compared with atazanavir/ritonavir plus TDF/FTC, in addition to having a less atherogenic lipid profile [5].

Recently, an extended-release version of NVP (NVP XR, 400 mg) has been approved for once-daily (QD) dosing, based on the VERxVE trial that demonstrated comparable efficacy to twice-daily (BID) regimens of the immediate-release formulation (NVP IR, 200 mg) in treatment-naïve individuals [6]. The present report describes the post-week 24 efficacy and safety results of switching patients who are virologically controlled on NVP IR 200 mg BID to NVP XR 400 mg QD.

Methods

The details of the methodology behind the TRANxITION study have been previously described in the original report of the week 24 results [7]; the methods are summarized here.

Study design

TRANxITION was an open-label, randomized, parallel-group study

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to assess the efficacy and safety of switching HIV-1-infected patients established on a NVP IR-based regimen to a NVP XR-based regimen. Upon meeting the screening criteria, patients were randomized 2:1 to either NVP XR 400 mg QD or continuing on NVP IR 200 mg BID. Baseline randomization was stratified by background NRTI therapy, which patients maintained throughout the trial. After week 48, patients initially randomized to NVP IR were allowed to switch to NVP XR.

Key study inclusion criteria included: HIV-1-infected patients aged ≥18 years who were stable on a NVP IR-based regimen for a minimum of 18 weeks. Permissible background NRTI regimens were specified combinations of NRTIs, such as lamivudine/abacavir (3TC/ABC), emtricitabine/tenofovir (FTC/TDF) or lamivudine/zidovudine (3TC/AZT). A further criterion was an undetectable HIV-1 viral load (lower level of detection<100 copies/mL) for a minimum of 4 months preceding enrollment and an HIV-1 viral load<50 copies/mL at screening.

Key study exclusion criteria included patients currently on an HIV protease inhibitor, participation in other clinical trials within the preceding 2 months, and baseline laboratory results that exceeded values of Division of AIDS (DAIDS) Grade 2 (coagulation, hematology, biochemistry) or Grade 3 (total triglycerides). Patients with hepatic cirrhosis of Child-Pugh class B or C were also excluded.

The primary endpoint in TRANxITION was the proportion of patients with sustained virologic response (SVR), defined as viral load<50 copies/mL (lower limit of quantification [LLOQ]=50 copies/mL, using Roche COBAS TaqMan or Amplicor Ultrasensitive Assay (RocheDiagnostics, Risch, Switzerland) [7], Full Analysis Set [FAS]) through week 24. Secondary endpoints for efficacy included the proportion of patients with SVR defined as viral load<50 copies/mL through week 144 (week 144 ± 6-week window), the proportion of patients with SVR with viral load<400 copies/mL, the time to loss of virologic response (TLOVR), and changes in viral load and CD4+ T-cell count from baseline at each visit. The secondary safety endpoints included treatment-related and treatment-unrelated adverse events (AEs), serious adverse events (SAEs) and AIDS-defining events, plus the occurrence of rashes or hepatic events, abnormal laboratory measurements, changes in laboratory test values from baseline to end-of-treatment (EOT), and the incidence of AIDS progression or death between baseline and EOT.

Statistics

The primary endpoint and the corresponding 95% confidence interval (CI) were analyzed using the TLOVR algorithm by Cochran's statistical test. A non-inferiority test for the primary endpoint (12% margin) was based on a 2-sided 95% CI for any difference in the virologic responses in the 2 treatment arms (NVP XR vs. NVP IR). All safety data were examined by descriptive statistical methods.

Results

Patient Disposition

Patient disposition is presented in Figure 1. After enrollment, 54 patients were excluded, primarily due to failure to meet trial eligibility criteria. Of the 499 patients enrolled, 445 were randomized and 443 were treated (n=148, NVP IR and n=295, NVP XR). After week 48, 130 of the 143 remaining patients in the IR arm exercised the option to switch to the XR ("IR-XR post48") formulation, while 13 patients continued on NVP IR ("IR-IR post48").

Baseline characteristics

Table 1 presents the baseline characteristics, including HIV viral loads, baseline CD4 T-cell counts, and the incidence of AIDS-defining illnesses, in patients who continued in TRANxITION beyond week 48. By inclusion criteria [7], all randomized patients received NVP-based regimens and had documented stable viral loads <50 copies/mL. Baseline CD4+ T-cell counts were similar across all groups: mean (±standard deviation [SD]), 564.2 (±213.7) cells/mm^3; range (SD), 559.2 (±212.8)-595.0 (±330.1).

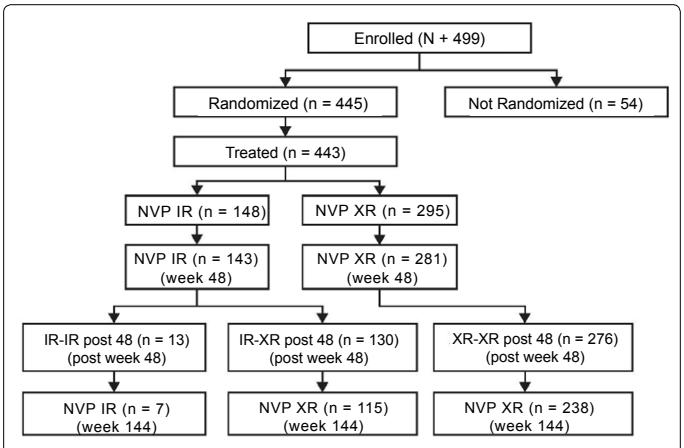

Figure 1: Patient disposition. IR-IR post48=remained on NVP IR twice daily after week 48; IR-XR post48=switched from NVP IR twice-daily regimen to NVP XR once-daily regimen after week 48; NVP IR=nevirapine immediate release; NVP XR=nevirapine extended release; XR-XR post48=remained on NVP XR once-daily regimen after week 48 (i.e., throughout study).

	IR-XR post48[a]	IR-IR post48[b]	XR-XR post48[c]	Total
Number of patients, n (%)	130 (100)	13 (100)	276 (100)	419 (100)
Baseline HIV-1 RNA, copies/mL,[d,e] n (%)				
<50	120 (92.3)	12 (92.3)	263 (95.3)	395 (94.3)
≥50	10 (7.7)	1 (7.7)	13 (4.7)	24 (5.7)
Baseline CD4+ T-cell counts, cells/mm,[d]				
n	129	13	276	418
Mean	571.9	595.0	559.2	564.2
SD	202.8	330.1	212.8	213.7
Baseline CD4+ T-cell counts, cells/mm,[d] n (%)				
>50 to 200	2 (1.5)	0 (0.0)	6 (2.2)	8 (1.9)
>200 to 350	13 (10.0)	2 (15.4)	38 (13.8)	53 (12.6)
>350 to <400	11 (8.5)	0 (0.0)	19 (6.9)	30 (7.2)
≥400	103 (79.2)	11 (84.6)	213 (77.2)	327 (78.0)
Missing	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)
History of AIDS-defining illness, n (%)				
No	105 (80.8)	8 (61.5)	200 (72.5)	313 (74.7)
Yes	25 (19.2)	5 (38.5)	76 (27.5)	106 (25.3)

Note: IR=immediate-release; NVP=nevirapine; XR=extended-release.
[a] Patients randomized to NVP IR and elected to change to NVP XR after week 48.
[b] Patients randomized to NVP IR and who chose to remain on NVP IR after week 48.
[c] Patients randomized to NVP XR who elected to remain on NVP XR after week 48.
[d] Baseline values are calculated as the average of the last 2 measurements prior to the start of randomized treatment.
[e] HIV-1 RNA viral load is based on TaqMan assay results.

Table 1: Baseline characteristics: post week 48.

Efficacy results

Primary endpoint-week 24*:* As measured by the primary endpoint, NVP XR was non-inferior to NVP IR, with 93.6% of patients in the NVP XR arm and 92.6% of patients in the NVP IR arm maintaining SVR through week 24, with an adjusted difference of 1.0% (95% CI, -4.3, 6.0), [7] using the TLOVR algorithm and Cochran statistic and with adjustment for all 3 background treatments. No significant between-group difference was seen in median change from baseline to week 24 in CD4+ T-cell count (NVP IR 32.5 cells/mm^3 vs. NVP XR 39.8 cells/mm^3) [7].

Post-week 48 efficacy analysis: At week 48, the proportion of patients with virologic response (LLOQ=50 copies/mL TaqMan, FAS) was 88.5% (131/148) treated with NVP IR BID and 88.8% (262/295) in those treated with NVP XR QD, with an observed difference of 0.3% (95% CI, -6.1, 6.7). Also, 96.2% (95% CI, 92.8%, 99.5%) of patients remaining in the IR-XR post48 group had viral loads<50 copies/mL (see Table 2). A total of 130 NVP IR patients switched to XR after week 48 (IR-XR post48). At follow-up visits, >90% of these patients had viral loads<50 copies/mL.

In XR-XR post48 patients (those initially on NVP XR and continued on XR), the proportion with virologic response was 97.1% (95% CI, 95.1%, 99.1%) at week 48. At week 144, 95.2% (95% CI, 92.6%, 97.8%) of XR-XR post48 patients had viral loads<50 copies/mL, whereas 95.0% (95% CI 91.2%, 98.9%) of patients remaining in the IR-XR post48 group had a virologic response.

At the last available observation for all patients, 93.8% had a viral load of <50 copies/mL. For the 276 patients in the XR-XR post48 group, similar rates were observed at each visit and, at week 144, 100% of all patients (i.e., all treatment groups) had a virologic response<400 copies/mL as the lower limit for virologic response.

Adverse events

Week 48*:* DAIDS grade 3 and 4 events were similar in the NVP XR and NVP IR groups at week 48: 6.4% (19/295) versus 6.1% (9/148), respectively. Serious AEs were slightly higher in the NVP XR group: 10.2% (30/295) vs. 8.1% (12/148) in the NVP-IR group.

Post-week 48: Adverse events were reported in all 3 treatment groups post-week 48. Considering any AE, there were 86.2% (112/130) of patients in the IR-XR post48 group and 90.6% (250/276) in the XR-XR post48 group with any reported AE. It should be noted that the total number of patients (n=13) who continued on IR post-week 48 (IR-IR post48) was too small to allow any meaningful analysis or interpretation of the data for this group.

The most common AEs among all 3 patient groups post-week 48 included nasopharyngitis (14.3%; 60/419), diarrhea (11.5%; 48/419), and bronchitis (10.7%; 45/419). The most common SAEs among all 3 patient groups were pneumonia (1.0%; 4/419) and depression (1.0%; 4/419). The 4 next most-common SAEs were anal fissures, hemorrhoids, myocardial infarction, and humerus fractures, each reported in 0.7% (3/419) of patients. A detailed listing of the most common AEs and SAEs post-week 48 is presented in Table 3.

Investigator-defined drug-related AEs were experienced by 3.1% (4/130) of patients in the IR-XR post48 group and 2.5% (7/276) of patients in the XR-XR post48 group (Table 4). The rate of SAEs was similar in the 2 treatment groups, with 13.1% (17/139) of patients in the IR-XR post48 group and 19.6% (54/276) of patients in the XR-XR post48 group reporting SAEs (Table 4).

Table 4 also presents the incidence of DAIDS Grade 3 or 4 AEs among the various patient groups. DAIDS Grade 3 or 4 AEs were reported in 7.7% of patients (10/130) in the IR-XR post48 group and in 11.2% (31/276) in the XR-XR post48 group. A total of 1.5% (2/130) of patients in the IR-XR post48 group and 2.9% (8/276) in the XR-XR post48 group had any DAIDS Grade 4 AEs. There were no patients in the IR-XR post48 group and 0.4% (1/276) patient in the XR-XR post48 group with any study drug-related DAIDS Grade 3 or 4 AEs. It is important to note that there were no patients with study drug-related DAIDS Grade 4 AEs in either group.

Four deaths occurred during the entire TRANxITION trial, none of which were determined to be related to NVP treatment. Fatal events of one suicide and one case of meningitis with endocarditis occurred in patients administered NVP XR. Of the patients receiving NVP IR, a case of Hodgkin's disease developed prior to week 48 that was later fatal; therefore, it is reported here. In addition, a fatal fall occurred post-IR treatment.

Discussion

High virologic efficacy was maintained throughout the TRANxITION trial in patients who switched from a NVP IR-based regimen to the NVP XR-regimen after week 48. It should also be noted that the safety findings reported out to week 144 were similar to those

	Number of patients with response/total number of patients, n/N (%)			
Visit Week	**IR-XR post48[a]**	**IR-IR post48[b]**	**XR-XR post48[c]**	**Total**
Week 48	125/130 (96.2)	11/12 (91.7)	268/276 (97.1)	404/418 (96.7)
Week 60	122/130 (93.8)	9/12 (75.0)	253/274 (92.3)	384/416 (92.3)
Week 72	124/130 (95.4)	9/9 (100)	265/271 (97.8)	398/410 (97.1)
Week 84	118/125 (94.4)	7/8 (87.5)	244/268 (91.0)	369/401 (92.0)
Week 96	117/124 (94.4)	9/9 (100)	242/263 (92.0)	368/396 (92.9)
Week 108	119/125 (95.2)	8/9 (88.9)	247/260 (95.0)	374/394 (94.9)
Week 120	112/121 (92.6)	7/8 (87.5)	235/258 (91.1)	354/387 (91.5)
Week 132	115/121 (95.0)	6/7 (85.7)	238/252 (94.4)	359/380 (94.5)
Week 144	115/121 (95.0)	7/7 (100)	238/250 (95.2)	360/378 (95.2)
Last available visit	121/130 (93.1)	11/13 (84.6)	261/276 (94.6)	393/419 (93.8)

Notes: FAS=full analysis set; IR=immediate release; LLOQ=lower level of quantification; NVP=nevirapine; XR=extended release.
[a] Patients who received NVP IR during the first 48 weeks, and then switched to NVP XR.
[b] Patients who remained on NVP IR after week 48.
[c] Patients who remained on NVP XR after week 48.

Table 2: Proportion of virologic response using LLOQ=50 copies/mL after week 48 by visit (FAS).

	IR- XR post48[a] n (%)	IR-IR post48[b] n (%)	XR-XR post48[c] n (%)	Total N (%)
Number of patients	130 (100)	13 (100)	276 (100)	419 (100)
AEs reported in >5% of patients				
Nasopharyngitis	15 (11.5)	1 (7.7)	44 (15.9)	60 (14.3)
Diarrhea	11 (8.5)	0 (0)	37 (13.4)	48 (11.5)
Bronchitis	10 (7.7)	1 (7.7)	34 (12.3)	45 (10.7)
Back pain	10 (7.7)	0 (0)	23 (8.3)	33 (7.9)
Sinusitis	9 (6.9)	0 (0)	22 (8.0)	31 (7.4)
Upper respiratory tract infection	9 (6.9)	1 (7.7)	20 (7.2)	30 (7.2)
Depression	7 (5.4)	0 (0)	22 (8.0)	29 (6.9)
Cough	6 (4.6)	1 (7.7)	20 (7.2)	27 (6.4)
Hypertension	7 (5.4)	0 (0)	15 (5.4)	22 (5.3)
SAEs in >0.5% of patients				
Total with SAEs	17 (13.1)	3 (23.1)	54 (19.6)	74 (17.7)
Pneumonia	1 (0.8)	1 (7.7)	12 (4.3)	4 (1.0)
Depression	3 (2.3)	0 (0)	1 (0.4)	4 (1.0)
Basal cell carcinoma	0 (0.0)	0 (0)	3 (1.1)	3 (0.7)
Anal fissure	1 (0.8)	0 (0)	2 (0.7)	3 (0.7)
Hemorrhoids	1 (0.8)	0 (0)	2 (0.7)	3 (0.7)
Myocardial infarction	0 (0.0)	0 (0)	3 (1.1)	3 (0.7)
Humerus fracture	1 (0.8)	0 (0)	2 (0.7)	3 (0.7)

Notes: AE=adverse event; FAS=full analysis set; IR=immediate release; NVP=nevirapine; SAE=serious adverse event; XR=extended release.
[a] Patients who received NVP IR during the first 48 weeks, and then switched to NVP XR.
[b] Patients who remained on NVP IR after week 48.
[c] Patients who remained on NVP XR after week 48.

Table 3: Most common adverse events and serious adverse events post week 48 (FAS).

	IR-XR post48[a] n (%)	IR-IR post48[b] n (%)	XR-XR post48[c] n (%)	Total N (%)
Number of patients	130 (100)	13 (100)	276 (100)	419 (100)
Patients with any AE	112 (86.2)	8 (61.5)	250 (90.6)	370 (88.3)
Patients with investigator-defined drug-related AEs	4 (3.1)	0 (0)	7 (2.5)	11 (2.6)
Patients with AEs leading to discontinuation of trial drug[d]	0 (0)	0 (0)	4 (1.4)	4 (1.0)
Patients with serious AEs[e]	17 (13.1)	3 (23.1)	54 (19.6)	74 (17.7)
Fatal	1 (0.8)	0 (0)	2 (0.7)	3 (0.7)
Immediately life-threatening	2 (1.5)	0 (0)	2 (0.7)	4 (1.0)
Disability/incapacitating	0 (0)	0 (0)	1 (0.4)	1 (0.2)
Required hospitalization	17 (13.1)	3 (23.1)	47 (17.0)	67 (16.0)
Prolonged hospitalization	0 (0)	0 (0)	1 (0.4)	1 (0.2)
Congenital anomaly	0 (0)	0 (0)	0 (0)	0 (0)
Other	0 (0)	0 (0)	7 (2.5)	7 (1.7)
Patients with DAIDS grade 3/4 AEs				
DAIDS grade 3 or 4 AEs	10 (7.7)	1 (7.7)	31 (11.2)	42 (10)
DAIDS grade 4 AEs	2 (1.5)	0 (0)	8 (2.9)	10 (2.4)
Any study drug-related DAIDS grade 3 or 4 AEs	0 (0)	0 (0)	1 (0.4)	1 (0.2)
Any study drug-related DAIDS grade 4 AEs	0 (0)	0 (0)	0 (0)	0 (0)

Notes: Notes: AE=adverse event; FAS=full analysis set; IR=immediate release; NVP=nevirapine; SAE=serious adverse event; XR=extended release.
Percentages are calculated using total number of patients per treatment as the denominator.
Medical Dictionary for Regulatory Activities (MeDRA) version 14.1 was used for reporting.
[a]Patients randomized to NVP IR and elected to change to NVP XR during the post-week 48 exposure.
[b]The post-week 48 exposure of patients randomized to NVP IR, who chose to remain on NVP IR after week 48.
[c]The post-week 48 exposure of patients randomized to NVP XR who elected to remain on NVP XR after week 48.
[d]Post-week 48, 4 patients (all in the NVP XR post48 group) experienced AEs leading to study drug discontinuation (n=2 infections and infestations; n=2 psychiatric disorders).
[e]A patient may be counted in >1 SAE category.

Table 4: Overall summary of adverse events post week 48 (FAS).

observed at the completion of week 48 of the trial. No new safety signals have been observed in patients in this long-term follow-up.

With regard to efficacy, 96% of patients in the IR-XR post48 group and 97% in the XR-XR post48 group had undetectable viral load (<50 copies/mL) at week 48. The results at week 144 were similar, with 95% of patients in the IR-XR post48 and 95% in the XR-XR post48 groups achieving undetectable viral load (<50 copies/mL). At the last available observation in all patients, 93.8% had a viral load<50 copies/mL.

Safety data post-week 48 showed that the frequencies of various AE categories were similar to but slightly lower for NVP IR patients who switched to NVP XR after week 48 compared with patients who received NVP XR from the beginning of the study. Higher overall rates of AEs were associated with the XR formulation in the initial 24 week report from the TRANxITION study [7]. While this trend continued through the 144 weeks of this extension study, the increases in AEs were generally modest. In the original report, these increases were attributed to the open-label design of the study, and this interpretation was supported by the observation that AE rates were actually numerically lower (no significant difference) in the XR arm of the VERxVE trial, which incorporated a double blind, double dummy design [6,8].

The most frequent AEs post-week 48 were consistent with those reported over the entire 144-week duration of the trial, with the majority of either mild or moderate intensity. Fewer than 3% of patients discontinued treatment due to an AE over the 144 weeks of the trial, possibly because all patients were receiving NVP IR for at least 18 weeks prior to initial randomization.

Overall, patients who switched post-week 48 from NVP IR 200 mg BID to NVP XR 400 mg QD had a similar safety profile compared with those patients who remained on NVP IR throughout the trial and patients who switched to NVP XR after 48 weeks of NVP IR treatment had similar frequencies of AEs as those patients treated with NVP XR from the beginning of the trial.

Conclusion

The NVP XR 400-mg QD formulation was generally well tolerated and safe and effective up to 144 weeks, both in patients who were randomized to switch from IR to XR in the initial phase (i.e., completing at least 144 weeks on XR), as well as in those who switched to XR after 48 weeks of IR treatment (i.e., completing at least 96 weeks on XR).

Disclosures

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