Published in final edited form as:
AIDS. 2010 January ; 24(Suppl 1): S27–S36. doi:10.1097/01.aids.0000366080.91192.55.

Non-Nucleoside Reverse Transcriptase Inhibitor Outcomes Among cART-Treated Adults in Botswana

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Abstract

Background—National initiatives offering NNRTI-based combination antiretroviral therapy (cART) have expanded in sub-Saharan Africa (SSA). The *Tshepo* study is the first clinical trial evaluating the long-term efficacy and tolerability of EFV- vs. NVP-based cART among adults in Botswana.

Methods—Three year randomized study (n = 650) using a 3×2×2 factorial design comparing efficacy and tolerability among: A: ZDV/3TC vs. ZDV/ddI vs. d4T/3TC; B: EFV vs. NVP, and C: Com-DOT vs. standard adherence strategies. This manuscript focuses on comparison B.

Results—There was no significant difference by assigned NNRTI in time to virologic failure with resistance (log-rank p = 0.14), NVP vs. EFV risk ratio (RR) = 1.54 [0.86-2.70]. Rates of virologic failure with resistance were 9.6% NVP-treated [6.8-13.5] vs. 6.6% EFV-treated [4.2-10.0] at 3 years. Women receiving NVP-based cART trended towards higher virological failure rates when compared to EFV-treated women, Holm-corrected log-rank p = 0.072, NVP vs. EFV RR = 2.22 [0.94-5.00]. 139 patients had 176 treatment modifying toxicities, with shorter time to event in NVP-treated vs. EFV-treated, RR = 1.85 [1.20-2.86], log-rank p = 0.0002.

Conclusions—*Tshepo*-treated patients had excellent overall immunologic and virologic outcomes, and no significant differences were observed by randomized NNRTI comparison. NVP-treated women trended towards higher virologic failure with resistance compared to EFV-treated women. NVP-treated adults had higher treatment modifying toxicity rates when compared to those receiving EFV. NVP-based cART can continue to be offered to women in SSA if routine safety monitoring chemistries are done and the potential risk of EFV-related teratogenicity is considered.

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Keywords

HIV/AIDS; HAART; non-nucleoside reverse transcriptase inhibitors (NNRTI's); nevirapine versus efavirenz; sub-Saharan Africa; randomized clinical trial

INTRODUCTION

The majority of the 3 million persons receiving combination antiretroviral therapy (cART) reside in resource-limited settings [1-2]. Large numbers of national initiatives offering public NNRTI-based cART have commenced in sub-Saharan Africa. Preliminary outcomes data from ARV pilot studies in Cote d'Ivoire [3], Senegal [4], Uganda [5], Khayelitsha, South Africa [6], and Botswana [7] as well as preliminary data from larger public cART initiatives in Malawi [8-9], Botswana [10], and Zambia [11] have documented impressive efficacy outcomes among the vast majority of cART-treated adults.

In resource-rich settings, based on available data from numerous clinical trials [12-14] efavirenz (EFV) is the NNRTI of choice, and is "*preferred*" for first-line cART, along with the NRTIs tenofovir (TDF) and emtricitabine (FTC) [12]. This recommendation is based on efficacy and more favorable tolerability data [12-18].

In resource-limited limited settings, the majority of cART-treated adults are female [6-7, 10-11] and have been prescribed nevirapine (NVP)-based cART regimens due to the potential teratogenic effects of EFV. Recent data has also shown that maternal NVP may be significantly compromised when administered to women who have recently received single-dose NVP for prevention of mother-to-child HIV transmission (PMTCT) purposes [19].

The 2NN trial [20], a large adult randomized trial, compared 1216 adults receiving stavudine (d4T) plus lamuvidine (3TC) with either NVP or EFV in North and South America, Australia, Europe, South Africa, and Thailand. The trial found non-inferiority (NVP vs. EFV) in their primary outcome of virologic failure. Additional 2NN analyses [20], however, showed an association between NVP and higher rates of serious toxicity. The CPCRA 058 and INSIGHT study team [21], reporting randomized data from NNRTI-treated adults, however, did show higher rates of virologic failure with and without resistance among NVP vs. EFV-treated patients. In that study, NNRTI allocation was determined by study-determined randomization or by patient choice. Significant numbers (75%) of CPCRA 058/ INSIGHT patients declined to participate in the study-determined randomization, and among those refusing, the majority (~62%) chose EFV over NVP (~38%). One recently published study among private-sector treated adults from South Africa [22] showed superiority of EFV over NVP, which was similar to reports from resource-rich settings. In this observational cohort of ~2800 adult patients, multivariate analysis showed that NVP-treated patients had a greater risk of virologic failure (HR 1.52 [1.24–1.86]), death (HR 2.17 [1.31-3.60]), and regimen discontinuation (HR 1.67 [1.32-2.11]) [22].

Family planning considerations in sub-Saharan Africa also strongly influence the choice of NNRTI especially as pregnancy rates among cART-treated women are high and EFV is limited to women committing to using at least two reliable contraceptive methods. One Botswana study [23] documented pregnancy rates as high as 7.9 per 100 person years of follow-up among cART treated women.

Data from randomized clinical trials conducted in Africa to evaluate first-line NNRTI outcomes are lacking [24-25]. The "*Tshepo*" study was initiated in December 2002 and completed in December 2007 to evaluate the efficacy, tolerability, development of drug

resistance, and the optimal means to sustain short- and long-term adherence among adults receiving various cART regimens in urban Botswana. "*Tshepo*" is the Setswana word for "hope".

METHODS

Study Design

The *Tshepo* study was an open-label, randomized, 3×2×2 factorial design study conducted at Princess Marina Hospital in Gaborone, Botswana to evaluate the efficacy, tolerability, and development of drug resistance of six different first-line cART regimens: ZDV/3TC/NVP (Arm A); ZDV/3TC/EFV (Arm B); ZDV/ddl/NVP (Arm C); ZDV/ddl/EFV (Arm D); d4T/3TC/NVP (Arm E), and d4T/3TC/EFV (Arm F). The study also compared two different adherence strategies: standard-of-care (SOC) versus SOC plus community-based supervision (Com-DOT) to determine the optimal means of promoting adherence among adults receiving first-line cART.

Participants were assigned in equal proportions (in an open-label, unblinded fashion) to one of 6 initial treatment arms and one of two adherence arms using permuted block randomization. Randomization was stratified by CD4+ cell count (less than 200 cells/mm^3, 201-350 cells/mm^3) and by whether or not the participant had an adherence assistant. Half of the participants were enrolled in each CD4+ cell count stratum, but there were no restrictions on whether or not they had an adherence assistant prior to study enrollment.

The primary endpoints of the study were: development of virologic failure with genotypic drug resistance and development of treatment-related toxicity, as defined by first incidence of a grade 3 or higher adverse event. Secondary endpoints were death for any reason and time to non-adherence, as estimated by an adherence rate of less than 90%.

ARV medication adherence was defined as being 'excellent' (>90 percent) based on a composite measure of three types of data: (i) patient four day and one month recall; (ii) patient verbal reporting on timing of doses, number of tablets per dose, and food requirements; and, (iii) ARV pill counts.

Initially, virologic failure was defined as a confirmed plasma HIV-1 RNA level >5,000 copies/mL at 16 or more weeks following cART initiation. An "intensified adherence intervention" occurred during the month after this first elevated plasma HIV-1 RNA determination, which involved both a home visit coupled with an extra clinic visit within a couple weeks of the elevated plasma HIV-1 RNA level, to counsel the patient and the patient's support community upon the importance of strict medication adherence. If a repeat plasma HIV-1 RNA level following this "intensified adherence intervention" still exceeded 5,000 copies/mL at the end of the month, the patient underwent a step change and was initiated on two different NRTIs and a PI in accordance with national treatment guidelines [26-27]. Effective 1 June 2007, the study virologic failure definition was changed to any confirmed viremia greater than the lower limit of detection, which was 400 copies/mL, in accordance with new medical literature [28-31] and national guidelines [27]. Genotypic resistance testing was done using *Roche ViroSeq v 2.0* as per the manufacturer's instructions.

An independent 8-member data safety and monitoring board (DSMB) was established prior to study initiation. The DSMB met prior to study opening and at least annually during the course of the study. On 6 April 2006, as part of the third interim analysis, the DSMB recommended discontinuing the two ZDV/ddI-containing study treatment arms due to inferiority in efficacy, as higher virologic failure rates were found among participants

receiving ZDV/ddI-containing cART compared to those receiving ZDV/3TC- and d4T/3TC-containing cART regimens. Based on the DSMB recommendation, all cART-treated patients who were receiving ZDV/ddl were switched to ZDV/3TC by 30 June 2006.

The study was approved by the institutional review boards of the Botswana Ministry of Health (Health Research Development Committee) and the Harvard School of Public Health (Human Subjects Committee) and written informed consent was obtained from all participants.

Study Population

Adult (≥18 years of age), HIV-1 infected, cART-naive Botswana citizens who attended one of the five ART screening clinics in Gaborone were approached for possible enrollment. All potentially eligible adults had to qualify for cART based on existing Botswana national ARV treatment guidelines [26-27] of having an AIDS-defining illness and/or CD4+ cell count ≤200 cells/mm^3 or meet the study's eligibility criteria of a CD4+ cell count between 201 and 350 cells/mm^3 with a plasma HIV-1 RNA level greater than 55,000 copies/mL. Inclusion criteria were: hemoglobin value >8.0 grams/dL; absolute neutrophil count ≥1.0 × 10^3/mm^3; aminotransferase levels less than five times the upper limit of the normal; and for women of child-bearing potential, a willingness to maintain active contraception throughout the duration of the study and a negative urine pregnancy test within 14 days of study enrollment. Exclusion criteria were: poor Karnofsky performance score (40 or below); an AIDS-related malignancy other than mucocutaneous Kaposi's sarcoma; grade 2 or higher peripheral neuropathy; major psychiatric illness; and for women, actively breastfeeding or less than six months post-partum. In our study catchment area, standard-of-care for pregnant women involved zidovudine prophylaxis beginning at 34 weeks (later changed to 28 weeks) of gestation. Single dose NVP for the prevention of mother-to-child transmission (PMTCT) was available in the study catchment area, but the vast majority of randomized females had not received it prior to study enrollment. Furthermore, women were excluded if they had received prior single dose NVP within 6 months of recruitment. Over the course of the study, protease-inhibitor (PI)-containing regimens were available for all participants with confirmed virologic failure, toxicities, or concomitant medical conditions that required the use of PI's.

Data Collection and Follow-up

Clinical and adherence assessments were done monthly at the study clinic. To monitor treatment efficacy, CD4+ cell counts (*FACS Calibur* flow cytometer, Becton Dickinson, San Jose, CA, USA) and plasma HIV-1 RNA levels (*Amplicor* HIV-1 Monitor test, version 1.5 Roche Diagnostics Systems, Branchburg, NJ), were obtained at enrollment and then every two months for the duration of the study. Laboratory safety monitoring included comprehensive chemistry and full blood count specimens at study enrollment, then every month for the first six months of the study, every two months during months 6-12 of study participation, and every four months during the remainder of participation. In addition, all patients had lipid chemistries performed at baseline and then every six months. Laboratory values were graded according to the 1994 Division of AIDS (DAIDS) laboratory grading scale [32], except lipid chemistry values which were graded using the DAIDS December 2004 grading scale [33]. Additional routine clinical assessment included peripheral neuropathy assessments every two months, lipodystrophy and performance assessments every six months, and annual screening for the presence of other sexually transmitted infections (hepatitis B and syphilis), and chest x-ray abnormalities. All women of reproductive potential had monthly urine pregnancy tests performed.

Comprehensive care for study participants was provided in accordance with existing national policy and was free of charge [26-27]. Opportunistic infections were diagnosed using available laboratory, imaging, and histopathologic services as well as specialist consultation. Prophylaxis for opportunistic infections included 6 months of isoniazid preventative therapy if determined that participant was without clinically active tuberculosis disease and 0week (or once daily) for the prevention of *Pneumocystis jiroveci* (PCP) pneumonia) when CD4+ cell counts were < 200 cells/mm^3.

A "*Dear Healthcare Professional*" letter was issued by Boehringer-Ingelheim Pharmaceuticals, Inc. on 5 February 2004 detailing new data pertaining to the risk of hepatotoxicity among adults initiating NVP-based cART [34]. This letter was adapted into a "*Dear Participant*" letter and was disseminated to all enrolled study participants in April 2004.

Statistical Considerations

To determine the sample size, a calculation was done for each of the primary objectives. Based on data from the DMP-006, DMP-043, Atlantic, and COMBINE studies, we assumed that > 50% of study participants would maintain HIV-1 plasma RNA levels < 400 copies/ml at 1 year. We also assumed a loss-to-follow-up rate of 10% over 3 years. With 600 evaluable subjects, if 50% of participants had not reached the primary endpoint by year 3 in the inferior level of two groups, we have 80% power to detect a treatment difference if the true percentage who have not failed in the superior level of the factor is 63.9% or greater; this is equivalent to a hazard ratio of 1.55 of the inferior to the superior level of the factor. With 600 evaluable subjects, if 60% (40%) of participants had not failed with resistance by year 3 in the inferior group, we had 80% power to detect a treatment difference if the true percentage who have not failed with resistance in the superior level is 73.4% (53.9%); this is equivalent to a hazard ratio of 1.65 (1.48). To assure that there would be at least 600 evaluable participants at the end of the study, we enrolled 650 participants, allowing for the possibility of a small amount of loss to follow-up.

Primary analyses of efficacy endpoints were performed on an "*intent-to-treat*" basis. Primary analyses of toxicity endpoints were performed on an "*as-treated*" basis. Time-to-event methods (Kaplan-Meier (K-M) survival curves including Kaplan-Meier estimates with 95% confidence intervals at one, two, and three years and Cox proportional hazards models) were used to compare study participants receiving NVP- versus EFV-containing cART with respect to event rates for virologic failure, death, and toxicity. Comparisons for continuous outcomes were done using repeated-measures ANOVA. All statistical analyses were conducted using SAS statistical software.

RESULTS

Study Recruitment

Between December 2002 and December 2004, 2188 patients were screened for possible enrollment at the adult Infectious Disease Care Clinic (IDCC) of Princess Marina Hospital and four designated local Gaborone City Council "*CD4+ screening*" clinics. Study eligibility visits and consent procedures were initiated in 898 patients. 248 patients were ineligible for the following reasons: CD4+ cell count between 201 and 350 cells/mm^3 but plasma HIV-1 RNA <55,000 copies/ mL (109), CD4+ cell count >350 cells/mm^3 (35), active medical conditions (65) including neutropenia (19), anemia (18), active tuberculosis infection (9) not on appropriate therapy and/or not deemed medically stable; other health related conditions such as grade 2 or greater peripheral neuropathy, elevated liver enzymes,

and active/recent pregnancy (19). 36 patients declined study participation and 3 were lost to follow-up during the screening process. 650 total adults were enrolled in the study.

Baseline Characteristics

Overall, 650 adults were enrolled, 451 (69.4%) of whom were female. Median age was 33.3 years [IQR 28.9 – 38.7]. Forty-three percent had advanced WHO clinical disease (Stage 3 or 4) at the time of enrollment. 330 (50.9%) patients were enrolled in the lower CD4+ stratum with a median CD4+ of 137 cells/mm^3, and 320 (49.1%) patients were enrolled in the upper CD4+ cell count stratum (CD4+ cell count value between 201 and 350 cells/mm^3 and plasma HIV-1 RNA >55,000 copies/mL) with a median CD4+ of 252 cells/mm^3 (Table 1). Baseline characteristics of patients in the NVP vs. EFV arms were evenly balanced at entry, with 325 patients randomized to each NNRTI arm, and within these 108 or 109 randomized to each dual-NRTI arm. 325 participants were randomized to the intensified adherence (Com-DOT) arm.

Follow-Up

Study follow-up was approximately 1960 person-years, with a median follow-up time of 156 weeks [IQR 155-156]. Ninety-eight percent of all scheduled follow-up visits were attended. During the study, 54 (8.3%) of the 650 enrolled patients were lost to follow up with regard to primary endpoint information. 26 (48%) of the 54 had moved out of the study catchment area, 9 (16.7%) declined further participation, and for 19 (35.2%), no further information was available despite repeated attempts by the study team to contact them. The sociodemographic and clinical characteristics of participants who were lost to follow-up did not differ from those who completed the trial.

Combination ART Outcomes

Analyses presented below focus on the NNRTI comparison between EFV and NVP. In all cases, the interaction terms for NNRTI *x* NRTI and NNRTI *x* adherence stratum did not approach statistical significance (all p-values > 0.10).

Virologic Failure/Development of Genotypic Resistance

The difference by assigned NNRTI in time to the primary outcome, virologic failure with resistance was not statistically significant, log-rank p = 0.14, NVP vs. EFV risk ratio = 1.54 [0.86 – 2.70]. Rates of virologic failure with resistance for patients assigned to NVP were 4.2% [2.5% - 7.1%], 7.9% [5.3% - 11.5%], and 9.6% [6.8% - 13.5%] at 1, 2, and 3 years respectively, and for patients assigned to EFV were 0.6% [0.1% - 2.6%], 4.0% [2.3% - 7.0%], and 6.6% [4.2% - 10.0%] at 1, 2, and 3 years respectively.

Among patients with confirmed virologic failure and documented genotypic resistance mutations, the most common major NNRTI-associated mutations were as follows: K103N (34.8%), G190A (28.3%), V106M (17.4%), Y181C (13.0%), and V108I (4.8%).

Adding death to the primary endpoint (i.e. time to virologic failure with resistance *or death*) had no qualitative impact on the treatment comparisons. There was no difference in this endpoint for patients assigned to NVP compared to EFV; p = 0.56, NVP vs. EFV risk ratio = 1.14 [0.74 – 1.75]. Similarly, the comparison of time to any virologic failure regardless of resistance for patients assigned to NVP vs. EFV was not statistically significant: log-rank p = 0.61, risk ratio = 1.12 [0.71, 1.79]

When time to virologic failure with resistance was analyzed by NNRTI assignment and gender, there was a statistical trend towards an interaction, log-rank p = 0.09. There was a trend for women receiving NVP-based cART to have higher virologic failure rates than did

women receiving EFV-based cART, Holm-adjusted [35] log-rank p = 0.074, NVP vs. EFV risk ratio = 2.22 [0.94 – 5.00]. There was no difference in virologic failure rates by NNRTI assignment among males, Holm-adjusted log-rank p = 0.063, NVP vs. EFV risk ratio = 1.28 [0.41 – 4.00] (Figure 1).

In a post-hoc analysis, the rate of virologic failure with resistance for 152 (23.4%) patients with baseline plasma HIV-1 RNA levels >500,000 copies/mL tended to be greater when compared to the 498 (76.6%) patients with baseline plasma HIV-1 RNA levels below this value: p = 0.078, relative risk 1.74 [0.94 – 3.23] (Figure 2.)

Virologic suppression rates were similar among NVP vs. EFV-assigned patients, Among NVP-assigned patients, 92.4% [89.4% – 95.4%], 88.2% [84.4% – 91.9%], and 90.6% [86.9% - 94.2%] had undetectable plasma HIV-1 RNA levels at 1, 2, and 3 years, respectively. Among EFV-assigned patients, 91.5% [88.4% – 94.7%], 94.0% [91.2% – 96.8%], and 93.6% [90.5% - 96.7%] had undetectable plasma HIV-1 RNA levels at 1, 2, and 3 years, respectively. The rate of early virologic suppression (undetectable plasma HIV-1 RNA by week 8) for patients assigned to NVP was 84.7% [80.8% – 88.7%] and for patients assigned to EFV was 88.0% [84.4% – 91.5%], and also did not differ by gender or baseline CD4 stratum.

Survival/Death Outcomes

In total, there were 37 deaths on study. Seven of the 37 deaths (18.9%) were described as being "*possibly related to study treatment*". Of the remaining 30 deaths, 16 (43.2%) were due to HIV-related illnesses, 11 (29.7%) were from diseases unrelated to HIV, 2 (5.4%) were from accidents, and 1 (2.7%) was due to unknown causes. There was not a statistically significant difference in time to death between NVP-treated and EFV-treated patients, log-rank p = 0.42, NVP vs. EFV relative risk = 1.46 [0.72 – 2.97]. The 3-year survival rates for NVP vs. EFV were 94.7% [91.5% – 96.4%] and 93.1% [89.7% 95.5%], respectively.

Immunologic Recovery

Median annual CD4+ increases from baseline were similar among EFV- vs. NVP-treated adults at 1, 2, and 3 years (p = 0.56). Among NVP-assigned patients, median CD4+ gains from baseline were 144 [IQR 75 – 228], 210 [IQR 115 – 331], and 259 [IQR 145 387] at 1, 2, and 3 years, respectively. Among EFV-assigned patients, median CD4+ gains from baseline were 135 [IQR 65 – 223], 225 [IQR 133 – 332], and 257 [IQR 149 – 388] at 1, 2, and 3 years, respectively. There was a gender difference in immunologic outcomes over time, with females experiencing greater CD4+ cell count increases than males (p = 0.0002). Among women, median CD4 gains from baseline were 140 [IQR 78 – 236], 235 [IQR 134 – 352], and 274 [IQR 162 – 416] at 1, 2, and 3 years, respectively. Among men, median CD4 gains from baseline were 132 [IQR 59 – 194], 205 [IQR 114 – 279], and 213 [IQR 120 – 342] at 1, 2, and 3 years, respectively.

Tolerability/Toxicity

139 patients had 176 treatment modifying toxicities (90 (27.7%) NVP vs. 49 (15.1%) EFV while on their initially assigned NNRTI. NVP-treated patients had a shorter time to first treatment-modifying toxicity than EFV patients (log-rank p=.0002), RR 1.85 [1.20 – 2.86] (Figure 3). Table 2 shows the number of patients with toxicities, by assigned NNRTI. EFV-treated patients did have significantly higher rates of central nervous system (i.e. neuropsychiatric symptoms) when compared to NVP-treated adults, which is consistent with existing data among HIV-1 infected, subtype B, HAART-treated adults. Rates of lactic acidosis were slightly higher among EFV-treated vs. NVP-treated adults, additional analyses are ongoing to further elucidate these findings. The vast majority of grade 3 or 4 NVP-

related cutaneous reactions (19 of 21, 90.5%) occurred within the first 3 months following cART initiation, with the majority occurring within the first month (18 of 19, 94.7%).

Additional subset analyses revealed no significant differences in rate of serious hepatotoxic (grade 3 or 4) events by NNRTI assignment among females initiating NVP-based cART with baseline CD4+ cell counts ≥250 cells/mm^3 (n = 45), 2.51 per 100 PY) versus those initiating at baseline CD4+ cell counts <250 cells/mm^3 (n = 185), 1.65 per 100 PY (p = NS). All 45 of these females initiating NVP-based cART did so prior to the issuance of the Boehringer-Ingelheim "*Dear Participant letter*" in February 2004.

DISCUSSION

Our study compared the effectiveness of NVP- versus EFV-based cART among a large group of adults in Botswana. Similar to 2NN findings [20], *Tshepo* study participants receiving NVP-based cART had non-inferior immunologic and virologic outcomes when compared to those receiving EFV-based cART. Results from the 2NN study evaluating comparable numbers of NNRTI-treated patients did not show inferiority of nevirapine versus efavirenz, but patients in that study had significantly higher overall virologic failure rates (i.e. in the 37-44% range) compared to *Tshepo* study treated patients. When analyzed separately, the 2NN team [20] did find that NVP-treated patients from South Africa had higher virologic failure rates (50.0%) when compared to EFV-treated patients (38.3%) with lower overall study completion by NNRTI assignment as well (48.4% vs. 36.2%, respectively). The study inclusion/exclusion criteria were similar between both studies, but 2NN presented 48 week data, compared to longer-term, 3 year outcomes in *Tshepo*. In addition, 2NN reported regional failure rates were approximately 5-fold higher than rates reported in *Tshepo*.

The reasons for these higher failure rates in 2NN are most likely multifactorial and may be related to significant single-dose NVP exposure among female patients which compromised efficacy, lower visit intensity, definition of virologic failure (i.e. lower limit of detection, greater than 50 copies/mL), and regional/site differences in management of virologic failure patients. In addition, 2NN was a multi-site trial compared to *Tshepo*, which was conducted only at one site. In *Tshepo* enrolled patients had to reside and be initially committed to remain to reside within 20 kilometers of the study clinic for all 3 years of the study. 2NN did not appear to have a similar requirement, which may have contributed to their higher virologic failure rates.

Unlike 2NN, *Tshepo* results showed a statistical trend in virologic failure with resistance rates by gender and NNRTI together, with women receiving NVP-based cART having higher rates of failure than those who receiving EFV-based cART. This gender by treatment interaction was only marginally significant (Holm adjusted p = 0.074). To investigate the sensitivity of these results to the change in primary endpoint definition (effective 01 June 2007; 7 months prior to study completion), we performed a separate analysis including as virologic failures only those patients who met the failure definition using our initial/old definition, namely having a confirmed plasma HIV-1 RNA level of greater than 5,000 copies/mL. In this analysis, the gender by treatment interaction was no longer even marginally significant. There were 6 patients who met the new definition, by having a confirmed plasma HIV-1 RNA level of greater than 400 copies/mL, 4 NVP-treated and 2 EFV-treated. Only two of these patients, both EFV-treated, met our old virologic failure definition (> 5,000 copies/mL) while the remaining 4 NVP-treated patients did not.

Reasons for the statistical trend towards gender differences in the *Tshepo* study may also be related to NNRTI tolerability, as higher proportions of females experienced moderate/severe

NVP-associated toxicity. This toxicity could have negatively influenced ARV medication adherence rates. The genotypic resistance patterns among patients failing NNRTI-based cART were similar to published literature from resource-rich settings [36-37]. These findings show a trend towards higher virologic failure rates among women receiving NVP-based treatment. The findings must be balanced, however, with the potential risk of EFV-related teratogenicity, especially in light of the high pregnancy rates which are being reported among cART-treated females in the region [23].

Approximately 13% of deaths on study were deemed "*possibly related to study medication*", and of these, lactic acidosis was the major cause. All 3 females who died as a result of severe lactic acidosis were overweight (BMI >25) [38] and received EFV. Additional gene association studies and the contribution of oxidant stress as it relates to adipogenesis are ongoing in order to better characterize these potentially "*at risk*" individuals.

There were also significant tolerability differences. NVP-treated adults had higher rates of treatment modifying toxicity compared to EFV-treated adults. The most common NVP-associated treatment modifying toxicities were cutaneous hypersensitivity reactions and hepatotoxicity, with rates of each being higher than expected when compared to cART treated adults in Western Europe and the United States. Additional studies are planned looking more in-depth at the risk factors associated with the development of hepatotoxicity.

This current study has certain limitations. The rates of virologic failure were most likely influenced by certain key factors: namely, inferiority of ZDV/ddl, as identified by the DSMB and our change in virologic failure definition after the majority of patients had reached greater than 2/3rds of their total study follow-up. In addition, our study was under-powered to detect significant differences as our original power calculations were based on anticipated virologic failure rates of ~ 50% (based on available published literature from resource-rich settings), and our actual event rates were lower than predicted. The effects of ZDV/ddl should have been equally distributed between NNRTI arms in our randomized design.

CONCLUSION

Tshepo-treated patients had impressive immunologic and virologic outcomes, and no significant differences were observed by randomized NNRTI. NVP-treated females, however, had a marginally statistical trend towards higher virologic failure rates with resistance when compared to EFV-treated females. There were no differences among men. There were also significant tolerability differences, with NVP-treated adults having higher treatment modifying toxicity rates when compared to those receiving EFV-based cART. NVP-based cART can continue to be offered to women in the region as long as routine safety monitoring chemistries are done and ideally periodic plasma HIV-1 RNA levels can be performed. EFV-treated women have a trend towards more favorable virologic outcomes, but this must be balanced with the potential risk of EFV-related teratogenicity, especially in light of the high pregnancy rates being reported among cART-treated females in the region.

Acknowledgments

We would like to formally acknowledge the Botswana Ministry of Health, the Princess Marina Hospital administration, outpatient adult Infectious Disease Care Clinic (IDCC), and inpatient Medical Ward teams, the entire Adult Antiretroviral Treatment and Drug Resistance (*Tshepo*) study team and our funder, the Bristol-Myers Squibb foundation for their support of this research initiative.

We also want to formally acknowledge and thank all adult study participants.

The project described was also supported by the following research grants from the National Institute of Allergy and Infectious Diseases, K23AI073141 (PI: C. William Wester, M.D.) and P30AI 060354 (PI: C. William Wester, M.D.), Harvard Center for AIDS Research (CFAR) grant evaluating the *Risk Factors for the Development of Nevirapine-Associated Toxicity in Southern Africa*. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases or the National Institutes of Health.

Lastly, we would like to thank Erika Färdig and Meredith Feir (Administration, Harvard School of Public Health, Boston, MA, USA) for their assistance with this manuscript.

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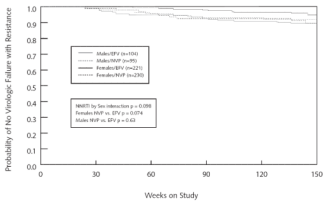

Figure 1.
Time to Virologic Failure With Resistance by NNRTI and Sex

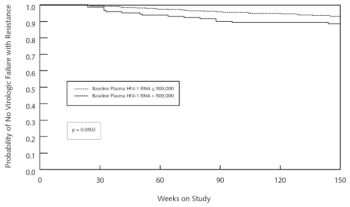

Figure 2.
Time to Virologic Failure With Resistance by Baseline Plasma HIV-1 RNA

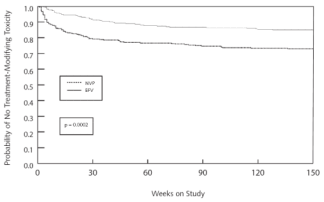

Figure 3.
Time to First Treatment-Modifying Toxicity by NNRTI

Table 1

Baseline Characteristics of Study Population

Characteristic		NVP (n = 325)	EFV (n = 325)	Total (n = 650)
Age of participant	Median	33.2	33.7	33.3
	[IQR]	29.0, 38.3	28.8, 39.1	28.9, 38.7
	Age < 40	261 (80.3%)	255 (78.5%)	516 (79.4%)
	Age >= 40	64 (19.7%)	70 (21.5%)	134 (20.6%)
Gender	Male	95 (29.2%)	104 (32.0%)	199 (30.6%)
	Female	230 (70.8%)	221 (68.0%)	451 (69.4%)
Weight	Median	57.50	57.0	57.0
	[IQR]	51, 66	50.25, 65.50	51, 66
Baseline BMI	Median	21.2	21.4	21.3
	[IQR]	19.2, 24.3	19.2, 24.1	19.2, 24.3
	< 18.5	61 (18.8%)	60 (18.5%)	121 (18.6%)
	18.5 - 24.99	187 (57.5%)	199 (61.2%)	386 (59.4%)
	25 - 29.99	52 (16.0%)	46 (14.2%)	98 (15.1%)
	>= 30	22 (6.8%)	19 (5.8%)	41 (6.3%)
Baseline HIV-1 RNA	Median	183,000	204,000	195,000
	[IQR]	61,900, 466,000	84,700, 499,000	70,100, 477,000
Baseline CD4+ cell count	Median	199	199	199
	[IQR]	138, 243	131, 260	136, 252
	CD4 < 201	165 (50.8%)	165 (50.8%)	330 (50.8%)
	CD4 = 201-350	160 (49.2%)	160 (49.2%)	320 (49.2%)
WHO Clinical Stage	Stage 1	90 (27.7%)	108 (33.2%)	198 (30.5%)
	Stage 2	84 (25.8%)	77 (23.7%)	161 (24.8%)
	Stage 3	117 (36.0%)	99 (30.5%)	216 (33.2%)
	Stage 4	25 (7.7%)	33 (10.2%)	58 (8.9%)
Baseline Diagnostic History				
Pulmonary TB		27 (8.3%)	32 (9.8%)	59 (9.1%)
Extra-pulmonary TB		2 (0.6%)	8 (2.5%)	10 (1.5%)
Herpes Zoster (Shingles)		29 (8.9%)	24 (7.4%)	53 (8.2%)
P. jiroveci (PCP) pneumonia		3 (0.9%)	3 (0.9%)	6 (0.9%)
Kaposi's sarcoma		4 (1.2%)	5 (1.5%)	9 (1.4%)
Wasting syndrome		61 (18.8%)	60 (18.5%)	121 (18.6%)
Anemia		15 (4.6%)	13 (4.0%)	28 (4.3%)

Table 2

Number of Patients with Treatment-Modifying Toxicities (n and %)

Toxicity	NVP (n=325)	EFV (n=325)	Total
Neutropenia	23 (7.1%)	9 (2.8%)	32 (4.9%)
Anemia	14 (4.3%)	11 (3.4%)	25 (3.8%)
Hypersensitivity Reaction/Rash	19 (5.8%)	0	19 (2.9%)
Lipodystrophy/atrophy	6 (1.8%)	8 (2.5%)	14 (2.2%)
Hepatotoxicity (not lactic acidosis)	11 (3.4%)	3 (0.9%)	14 (2.2%)
Lactic Acidosis	4 (1.2%)	7 (2.2%)	11 (1.7%)
Pancreatitis	10 (3.3%)	0	10 (1.5%)
Neuropsychiatric Symptoms	1 (0.3%)	7 (2.2%)	8 (1.2%)
Peripheral Neuropathy	4 (1.2%)	4 (1.2%)	8 (1.2%)
Diarrhea	3 (0.9%)	4 (1.2%)	7 (1.1%)
Vomiting	2 (0.6%)	2 (0.6%)	4 (0.6%)
Nephrotoxicity	2 (0.6%)	0	2 (0.3%)
Fever	0	1 (0.3%)	1 (0.1%)
Headache	1 (0.3%)	0	1 (0.1%)
Pancytopenia	1 (0.3%)	0	1 (0.1%)
Total*	**87 (27.7%)**	**49 (15.1%)**	**136 (20.9%)**

NOTE:

*Total number of patients experiencing at least one treatment-modifying toxicity. Columns do not add up because patients could experience more than one treatment modifying toxicity.