

NNRTI Outcomes Among HIV-1C Infected Adults Receiving First-Line HAART in Botswana: Results from a Randomized Clinical Trial

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ABSTRACT

BACKGROUND | National initiatives offering NNRTI-based antiretroviral therapy (ART) have recently commenced in sub-Saharan Africa, the first being in Botswana. Current studies show compromised efficacy among women later treated with NVP-based ART after recently receiving single dose (sd) NVP for PMTCT. The 2NN trial showed equivalent outcomes among those receiving EFV vs. NVP. The Tshepo Study is the first clinical trial evaluating long-term efficacy, tolerability, drug resistance, and adherence in Botswana.

METHODS | Completed, open-label, randomized study of 650 ARV-naïve adults treated for 3 years, using a 3x2x2 factorial design comparing efficacy and tolerability among factors: A. ZDV/3TC vs. ZDV/ddI vs. d4T/3TC; B. EFV vs. NVP, and C. Community-based DOT vs. Standard of Care. This abstract focuses on Factor B (EFV vs. NVP). Baseline viral load >55000 and 2 CD4+ strata: < 201 vs. 201-350. Intent-to-treat analyses included survival analyses, longitudinal ANOVA and logistic regression. Results are preliminary.

RESULTS | Baseline: 451 females (69.4%) and 199 males; median age 33.3 years, median baseline CD4+ 199 [IQR 134-239], plasma HIV-1 RNA 204,000 [IQR 81,000-447,000]. Median follow-up 151 weeks [IQR 125-156] and overall loss to follow-up 8.3%. EFV vs. NVP treated patients had equivalent immunologic and virologic suppression rates: at 1, 2, and 3 years, respectively, median CD4+ increase from baseline were 138 [IQR 74-223], 217 [IQR 122-332], and 258 [IQR 146-387], and 92.5%, 91.7%, and 91.1% had undetectable HIV-1 RNA levels. The 3 year Kaplan-Meier survival estimate was 94.0%, with no difference by NNRTI. Rates of virologic failure with genotypic resistance mutations were 8.9% NVP vs. 5.2% EFV, logrank p = 0.077. 140 patients had 178 treatment modifying toxicities (27.7% NVP vs. 15.7% EFV, p = 0.0001; with 20 (6.2%) NVP-treated patients developing cutaneous hypersensitivity reactions, 7 (2.2%) EFV-treated patients developing neuropsychiatric symptoms and 11 (3.4%) of NVP-treated and 3 (0.9%) EFV-treated patients developing hepatotoxicity (excluding lactic acidosis).

CONCLUSIONS | Tshepo-treated patients had excellent overall immunologic and virologic outcomes, with non-inferiority by randomized NNRTI (EFV vs. NVP), although NVP-treated adults had a marginally statistical trend towards higher virologic failure rates (p-value = 0.077) when compared to EFV-treated adults. There were significant tolerability differences, with NVP-treated adults having higher treatment modifying toxicity rates when compared to those receiving EFV-based cART. NVP-based cART should continue to be offered to adults qualifying for cART in the region where intensive plasma HIV-1 RNA monitoring is routinely available with the exception of females receiving recent sd NVP for PMTCT purposes. The majority of risk-benefit considerations relating to NVP are female specific, therefore, in resource-limited settings where cost is often a major issue, policymakers should consider widespread NVP-use among males while evaluating other sustainable non-EFV or NVP-containing alternatives for women.

BACKGROUND

- Preliminary data from numerous public initiatives within sub-Saharan Africa have documented impressive efficacy outcomes among the vast majority of combination antiretroviral therapy (cART)-treated adults.
- In resource-limited settings, the majority of cART-treated adults are female and are being placed on nevirapine-based cART regimens due to the reduced cost and widespread availability of generic *Triumeq*[™] (d4T/3TC/NVP), balanced by the potential teratogenic effects of its alternative, namely EFV.
- In addition, recent data has also shown that maternal NVP efficacy may be significantly compromised when administered to women recently receiving single-dose NVP for prevention of mother-to-child HIV transmission (PMTCT) purposes.
- The 2NN trial compared HIV-1 infected adults (n = ~1200) receiving d4T plus 3TC with either NVP or EFV in multiple sites including South Africa and Thailand. They found no significant differences in efficacy with NVP vs. EFV-treated patients experiencing similar rates of virologic failure. Additional 2NN analyses, however, did demonstrate that NVP was associated with higher rates of serious toxicities.
- One recently published study among private-sector treated adults from 9 sub-Saharan Africa countries has shown superiority of EFV when compared to NVP. In this observational cohort of ~ 2800 adult patients, multivariate analysis showed that NVP-treated patients had a greater risk of virologic failure, death, and regimen discontinuation.
- The Tshepo Study is the first clinical trial evaluating the long-term efficacy and tolerability of adults randomized to receive EFV vs. NVP-based cART in the region.

METHODS

- Completed, open-label, randomized study of 650 ARV-naïve adults followed for 3 years.
- 3x2x2 factorial design comparing efficacy and tolerability among:
 - (A) NRTI: ZDV/3TC vs. ZDV/ddI vs. d4T/3TC
 - (B) NNRTI: EFV vs. NVP
 - (C) Adherence: Community-based DOT vs. Standard of Care adherence strategies
- This manuscript focuses on Factor (B); namely EFV vs. NVP.
- 2 balanced CD4+ cell count strata at the time of enrollment, namely those having CD4+ cell counts <201 cells/mm³ vs. 201-350 cells/mm³ (having a viral load of > 55,000 copies/mL).
- Initially, virologic failure (VF) was defined as a confirmed plasma HIV-1 RNA level of greater than 5,000 copies/mL at 16 or more weeks following cART initiation. Effective 01 June 2007, the VF definition was changed to any confirmed viremia (greater than 400 copies/mL) in accordance with new literature and existing national guidelines.
- All analyses were "intent-to-treat." Time-to-event methods Kaplan-Meier (K-M) survival curves including K-M estimates with 95% CI's at 1, 2, and 3 years were used to compare patients receiving NVP- vs. EFV-containing cART with respect to virologic failure, death, and toxicity. Comparisons for continuous outcomes were done using repeated-measures ANOVA. All statistical analyses were conducted using SAS statistical software.

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Table 1. Baseline Characteristics

Characteristic		NVP (n = 325)	EFV (n = 325)	Total (n = 650)
Age of participant	Median [IQR]	33.2 29.0, 38.3	33.7 28.8, 39.1	33.3 28.9, 38.7
Gender	Male Female	95 (29.2%) 230 (70.8%)	104 (32.0%) 221 (68.0%)	199 (30.6%) 451 (69.4%)
BMI	Median [IQR]	21.2 (19.2, 24.3)	21.4 (19.2, 24.1)	21.3 (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%)
HIV-1 RNA	Median [IQR]	183,000 (61,900, 466,000)	204,000 (84,700, 499,000)	195,000 (70,100, 477,000)
CD4+ Cell Count	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%)
Opportunistic Infections				
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. NNRTI Genotypic Resistance Mutation Patterns among Tshepo Study Treated Adults with Virologic Failure on First-Line HAART

Location	Mutations	NVP-treated patients (n%)	EFV-treated patients (n%)	Total (n%)
G190	A, A/G, S	10 (34.5%)	6 (31.6%)	16 (33.3%)
K103	K/N, N	9 (31.0%)	11 (57.9%)	20 (41.7%)
Y106	M/V, M	6 (20.7%)	6 (31.6%)	12 (25.0%)
V108	I	2 (6.9%)	2 (10.5%)	4 (8.3%)
Y181	C/Y, C	11 (37.9%)	1 (5.3%)	12 (25.0%)
Y188	L	0	2 (10.5%)	2 (4.2%)

Table 3. 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	20 (6.2%)	0	20 (3.1%)
Lipodystrophy/Atrophy	7 (2.2%)	9 (2.8%)	16 (2.5%)
Hepatotoxicity (not lactic acidosis)	11 (3.4%)	3 (0.9%)	14 (2.2%)
Lactic Acidosis	4 (1.2%)	8 (2.5%)	12 (1.8%)
Pancreatitis	11 (3.4%)	0	11 (1.7%)
Neuropsychiatric Symptoms	1 (0.3%)	7 (2.2%)	8 (1.2%)
Peripheral Neuropathy	4 (1.2%)	4 (1.2%)	8 (1.2%)
Diarrhea	2 (0.6%)	4 (1.2%)	6 (0.9%)
Vomiting	3 (0.9%)	2 (0.6%)	5 (0.7%)
Other Toxicity *	4 (1.2%)	3 (0.9%)	7 (1.1%)
Total**	89 (27.7%)	51 (15.7%)	140 (21.5%)

* First toxicities with 2 or fewer patients
 ** 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.

Figure 1: Time to Virologic Failure with Resistance, NVP vs. EFV

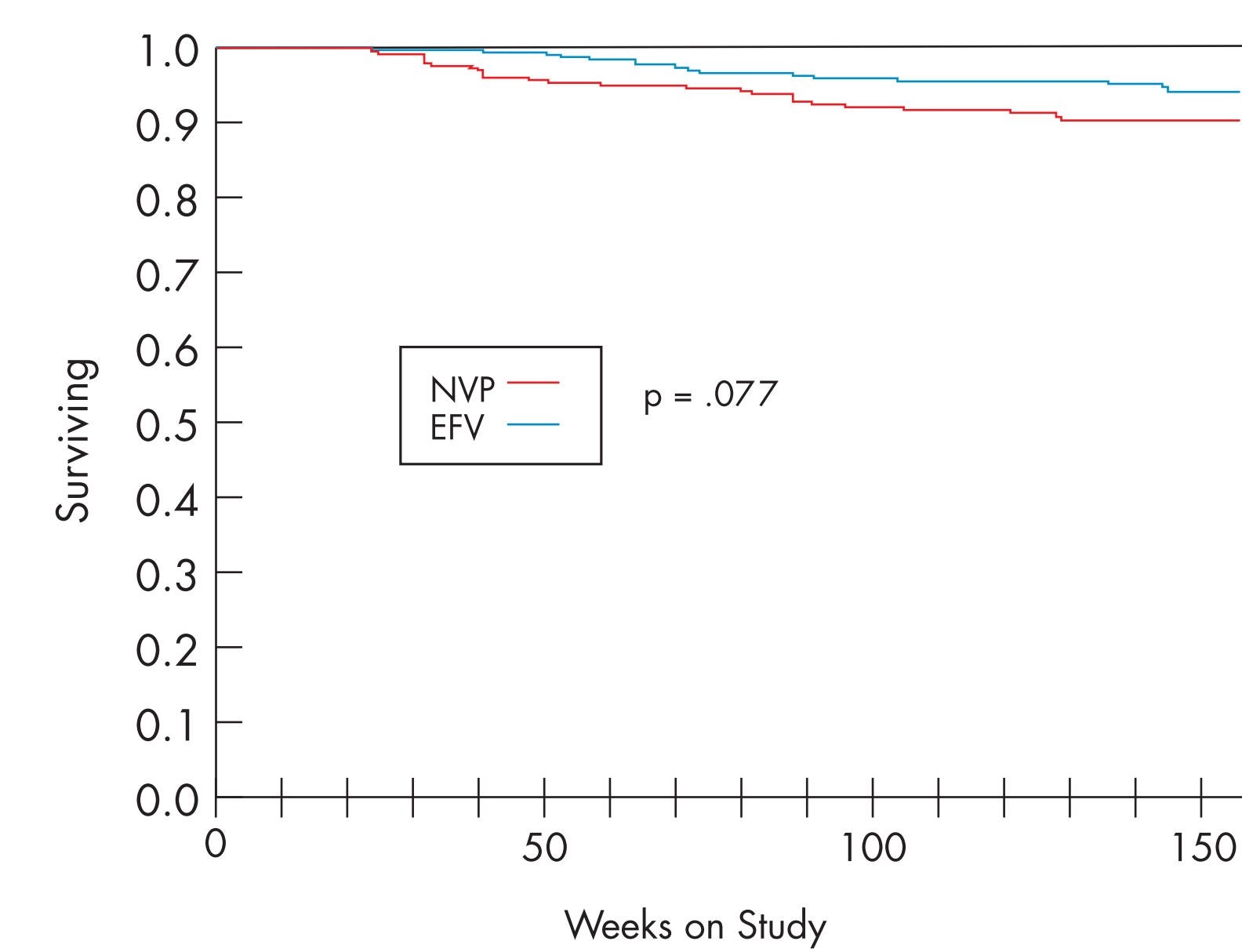
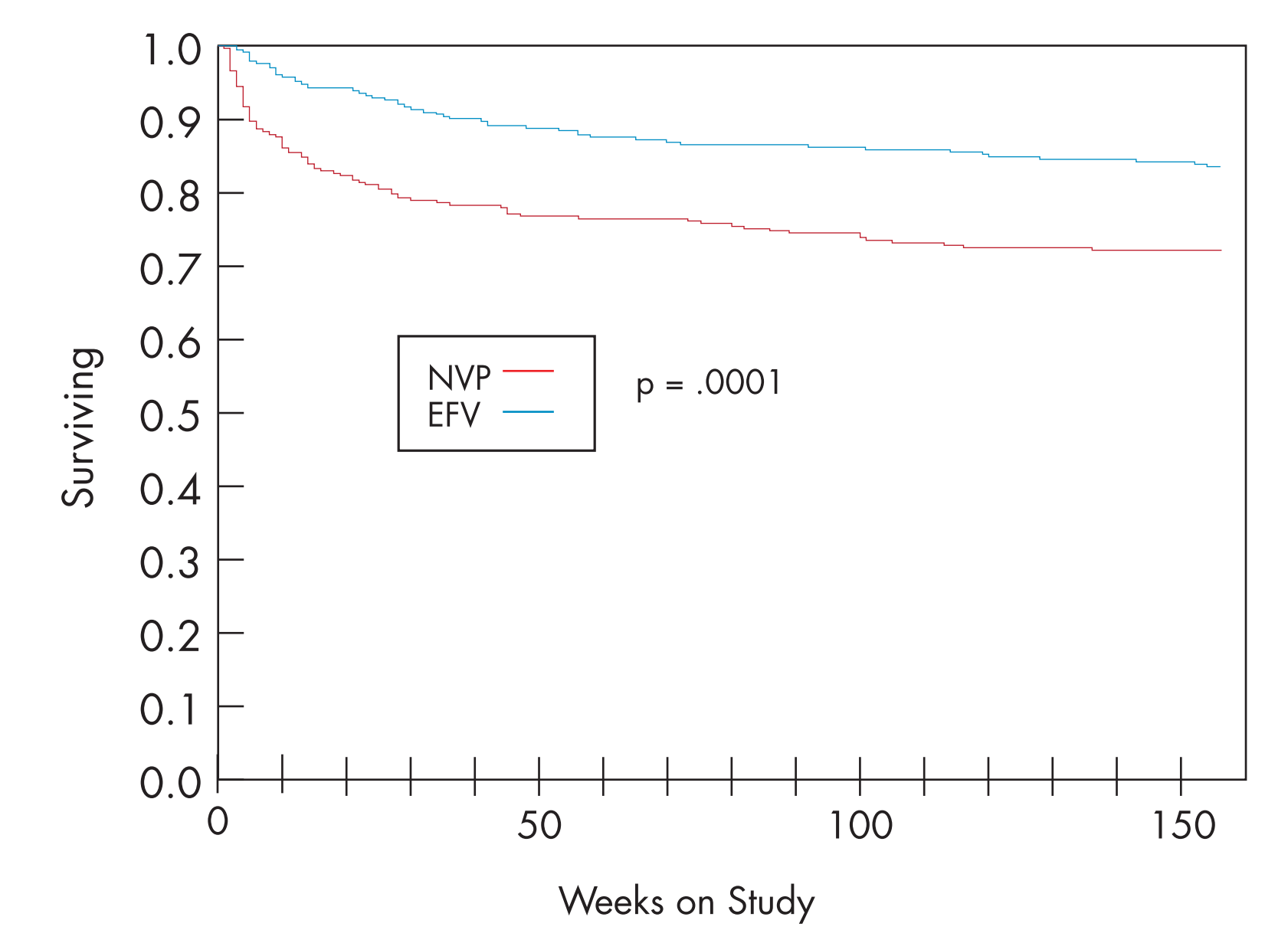


Figure 2: Time to First Treatment-Modifying Toxicity, NVP vs. EFV



RESULTS

- Table 1 shows demographic and clinical characteristics of patients at baseline.
- Median follow-up 156 weeks [IQR 155-156], with an overall lost to follow-up rate of 8.3%.
- EFV vs. NVP treated patients had equivalent immunologic recovery rates. Median CD4+ increase from baseline was 138 [IQR 74-223], 217 [IQR 122-332], and 258 [IQR 146-387], at 1, 2, and 3 years, respectively.
- EFV vs. NVP treated patients had equivalent virologic suppression rates. 92.5%, 91.7%, and 91.1% had undetectable plasma HIV-1 RNA levels at 1, 2, and 3 years, respectively.
- Rates of virologic failure were equivalent for NVP treated and EFV-treated patients, at 10.5% (N=34) and 10.2% (N=33) respectively.
- Rates of virologic failure with genotypic resistance mutations were 8.9% (N=29) for NVP-treated vs. 5.2% (N=17) for EFV-treated patients, logrank p = 0.077 (Figure 1).
- Among study patients with confirmed virologic failure with the presence of documented major genotypic resistance mutations, the most common major NNRTI-associated mutations are displayed in Table 2.
- In total, there were 32 deaths (4.9% of all subjects) among patients receiving first-line cART. 4 of the 32 deaths (13%) were "possibly related to study treatment". Among these 4 patients, lactic acidosis syndrome was the primary cause of death in 3 (57%), all EFV-treated, and 1 died from hepatotoxicity following 2 weeks of NVP-based cART possibly exacerbated by concomitant isoniazid which this female study participant received for TB prophylaxis.
- 140 patients had 178 treatment modifying toxicities (27.7% NVP vs. 15.7% EFV, p = 0.0001; with 20 (6.2%) of NVP-treated patients developing cutaneous hypersensitivity reactions, 7 (2.2%) of EFV-treated patients developing neuropsychiatric symptoms and 11 (3.4%) of NVP-treated and 3 (0.9%) of EFV-treated patients developing hepatotoxicity (excluding lactic acidosis). In addition, 11 (3.4%) of NVP-treated patients developed pancreatitis compared to no EFV-treated patients, and 25 (3.8%) patients overall developed anemia with 32 (4.9%) overall patients developing neutropenia (Table 3).

CONCLUSIONS

- Our large randomized clinical trial conducted among cART naïve adults in Botswana showed lack of inferiority in primary endpoint, namely virological failure among nevirapine versus efavirenz-treated patients, although NVP-treated adults had a marginally statistical trend towards higher virologic failure rates (p-value = 0.077) when compared to EFV-treated adults.
- This data is similar to that reported in the 2NN trial.
- The risk for treatment modifying toxicity is greater among NVP-treated adults, and for some patients, these cutaneous and/or hepatic toxicities may be life-threatening. Due to these safety concerns, therefore, the majority of which manifest within the first 18 weeks on treatment, it is recommended that all NVP- treated patients undergo intensive clinical and laboratory (ALT/SGPT) safety monitoring.
- NVP-based cART should continue to be offered to adults qualifying for cART in the region where intensive plasma HIV-1 RNA monitoring is routinely available with the exception of females receiving recent single-dose NVP for PMTCT purposes.
- The majority of risk-benefit considerations relating to NVP are female specific, therefore, in resource-limited settings where cost is often a major issue, policymakers should consider widespread NVP-use among males while evaluating other sustainable non-EFV or NVP-containing alternatives for HIV-1 infected women in the region.

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