Injectable contraception and HIV-1 acquisition in the VOICE study (MTN-003)

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Background

- Injectable hormonal contraception (HC) constitutes a large proportion of modern contraceptive use globally
- Several observational studies have reported an increased risk of HIV acquisition among women using injectable HC, particularly depot medroxyprogesterone acetate (DMPA), compared to women using non-hormonal methods
  - Few studies have disaggregated specific injectable type
  - Norethisterone enanthate (NET-EN) is a different type of injectable HC commonly used in South Africa
- Examining the association of HC type with HIV acquisition within a single delivery method (injection) may reduce behavioral confounding (e.g., differential condom use) present when comparing HC users with non-users
  - Comparing injectable HC methods to each other may have utility for women who elect to use effective contraception
- ***Objective: To compare the impact of DMPA to NET-EN exposure on HIV-1 acquisition among women enrolled at South African sites in the VOICE Study***

Methods

- The MTN-003 (VOICE) trial was a Phase 2B, multi-site, randomized, placebo controlled trial conducted between 2009 – 2012 that assessed the safety and effectiveness of tenofovir-based oral and topical HIV-1 chemoprevention in women
- Participants using protocol-defined effective contraception (HC, intrauterine device or sterilization) were eligible for enrollment
- Contraceptive use, pregnancy status and HIV status were assessed monthly during 1 – 3 years of participant follow-up
- Condom use and other behaviors related to HIV risk were assessed by interview-administered questionnaire and audio computer assisted self-interview (ACASI)
- Midpoint between last negative and first confirmed positive test was used to calculate estimated time of HIV-1 seroconversion
- In a planned secondary analysis of data from VOICE, we used a Cox proportional hazards model to compare directly the rates of HIV acquisition between women using DMPA and those using NET-EN at 11 South African VOICE sites
- We conducted additional comparisons stratifying by baseline (BL) herpes simplex virus type 2 (HSV-2) status

Results

- 3,163 women were enrolled at South African sites and met other pre-specified criteria for inclusion **(Figure 1)**
- Of injectable HC users included in the analysis, 2,055 (65.0%) used DMPA, 1,363 (43.1%) used NET-EN and 255 (8.1%) used both DMPA and NET-EN during follow-up
- Proportion of DMPA users (27 – 73%) and HIV-1 incidence (1.7 – 8.9/100 person-years) varied by site
- Median (IQR) age at baseline for DMPA users was 24 (21 – 27) and for NET-EN users was 23 (20 – 26) years old
- DMPA and NET-EN users differed with respect to marital status, HSV-2 status at BL, and several other factors that may have impacted risk for HIV acquisition **(Table 1)**
- No significant difference at baseline in risk of gonorrhea, chlamydia, or trichomonas diagnosis, or in report of condom use at last intercourse

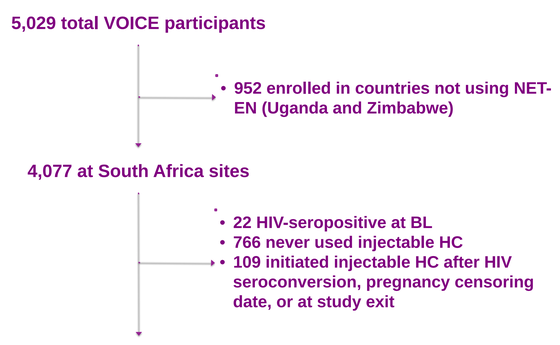


Figure 1. Study population

Table 1. Baseline characteristics of injectable HC users

Characteristic	Total n = 3,163*	Used DMPA n = 2,055	Used NET-EN n = 1,363	p value*
Under 25 years old	1,905 (60.2)	1,176 (57.2)	729 (65.8)	<0.001
Married or cohabitating	608 (19.2)	437 (21.3)	171 (15.4)	<0.001
Has one or more children	2,650 (83.8)	1,895 (92.2)	755 (68.1)	<0.001
Completed some high school	3,038 (96.2)	1,962 (95.7)	1,076 (97.1)	0.043
Chlamydia, gonorrhea or trichomonas diagnosis	670 (21.2)	440 (21.4)	230 (20.8)	0.668
HSV-2 seropositive	1,451 (46.7)	1,032 (50.6)	419 (39.2)	<0.001
Condom at last intercourse	2,150 (74.7)	1,392 (74.6)	758 (74.9)	0.840
Has more than one sexual partner	119 (3.8)	62 (3.0)	57 (5.3)	0.002
Partner has other partners	286 (9.4)	183 (9.1)	103 (9.8)	0.130
Anal sex in past 3 months	634 (20.4)	396 (19.5)	238 (21.9)	0.122
Exchanged sex for money in past year	159 (5.1)	99 (4.8)	60 (5.5)	0.432

Data are number (%). DMPA and NET-EN do not sum to total, because 255 (8.1%) women used both methods at different times during follow-up, *Statistical comparisons were made with χ^2 test.

Table 2. Results of Cox proportional hazards models

	HIV-1 seroconversions/ person-years (p-yrs)	HIV-1 Incidence/100 p-yrs	Unadjusted Cox proportional hazards regression		Adjusted Cox proportional hazards regression*	
			Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
All women	204/2,892	7.05				
NET-EN	54/1,008	5.36	Reference	Reference	Reference	Reference
DMPA	150/1,885	7.96	1.35 (0.97 to 1.88)	0.077	1.43 (1.04 to 1.97)	0.026
HSV-2 negative at BL	88/1,502	5.86				
NET-EN	33/582	5.67	Reference	Reference	Reference	Reference
DMPA	55/919	5.98	0.96 (0.66 to 1.39)	0.822	1.08 (0.75 to 1.56)	0.669
HSV-2 positive at BL	115/1,350	8.52				
NET-EN	20/399	5.02	Reference	Reference	Reference	Reference
DMPA	95/952	9.98	1.95 (1.04 to 3.67)	0.038	2.06 (1.12 to 3.79)	0.020

*Multivariate Cox proportional hazard regression model, adjusted for age, married/cohabiting, education, BL HSV-2, time-varying partners, partner has other partners, and unprotected sex, stratified by site, with censoring at pregnancy. Multivariate models stratified by BL HSV-2 include above as covariates except BL HSV-2. Additional covariates did not substantially change the above estimates.

Conclusions

- This observational study is the first specifically designed to compare risk of HIV-1 acquisition between DMPA and NET-EN use.
- Lack of a non-HC comparator group prevented estimation of risk associated with either method compared to non-use.
- Among women willing to use effective contraception while participating in an HIV prevention trial, we observed an overall increased risk of HIV-1 acquisition among women currently using DMPA compared to those using NET-EN.
- This observed difference in HIV acquisition was modified when stratifying by baseline HSV-2 status. However, findings in observational analyses, especially those in select sub-groups, are subject to bias and should be interpreted with caution.
- Site-based variation in distribution of injectable types and HIV-1 incidence also may have impacted our results.
- While results of this analysis show a weak association between injectable type (DMPA compared to NET-EN) and HIV-1 acquisition, lack of data on actual HIV-1 exposure limits inferences from these data.
- As HIV-1 incidence was high among injectable HC users, our results support current WHO recommendations that women using injectable progestin contraception should be advised to also use condoms and other HIV preventive measures.

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