Published in final edited form as:

Lancet HIV. 2015 July 1; 2(7): e279–e287. doi:10.1016/S2352-3018(15)00058-2.

Risk of HIV-1 acquisition among women who use different types of injectable progestin contraception in South Africa: a prospective cohort study

Lisa M. Noguchi, PhD, **Prof. Barbra A. Richardson, PhD**, **Prof. Jared M. Baeten, MD**, **Prof. Sharon L. Hillier, PhD**, **Jennifer E. Balkus, PhD**, **Prof. Z. Mike Chirenje, MD**, **Katherine Bunge, MD**, **Gita Ramjee, PhD**, **Gonasagrie Nair, MBChB**, **Thesla Palanee-Phillips, PhD**, **Pearl Selepe, MBChB**, **Prof. Ariane van der Straten, PhD**, **Urvi M. Parikh, PhD**, **Kailazarid Gomez, MPM**, **Jeanna M. Piper, MD**, **D. Heather Watts, MD**, and **Jeanne M. Marrazzo, MD for the VOICE Study Team**

Department of Epidemiology, Johns Hopkins University, Baltimore, MD, USA (L M Noguchi PhD); Department of Biostatistics, (Prof B A Richardson PhD), Department of Global Health (Prof J M Baeten MD), Department of Medicine (Prof J M Baeten, Prof J M Marrazzo MD), and Department of Epidemiology (Prof J M Baeten), University of Washington, Seattle, WA, USA; Department of Obstetrics, Gynecology, and Reproductive Sciences, Magee-Womens Hospital of UPMC and University of Pittsburgh, Pittsburgh, PA, USA (Prof S L Hillier PhD, K Bunge MD); Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA (J E Balkus PhD); UZ-UCSF Collaborative Research Programme, Belgravia, Harare, Zimbabwe (Prof Z M Chirenje MD); South African Medical Research Council, HIV Prevention Research Unit, Durban, KwaZulu-Natal, South Africa (G Ramjee PhD); Centre for the AIDS Programme of Research in South Africa, Durban, South Africa (G Nair MBChB); Wits Reproductive Health and HIV Institute, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa (T Palanee-Phillips PhD); The Aurum Institute, Klerksdorp, South Africa (P Selepe MBChB); RTI International, Women's Global Health Imperative, San Francisco, CA, USA (Prof A van der Straten PhD); Department of Medicine, University of Pittsburgh, Pittsburgh, PA, USA (U M Parikh PhD); FHI 360, Durham, NC, USA (K Gomez MPM); National Institute of Allergy and Infectious Diseases Division of AIDS, Bethesda, MD, USA (J M Piper MD); and US Department of State and Office of the Global AIDS Coordinator and Health Diplomacy, Washington, DC, USA (D H Watts MD)

Summary

Correspondence to: Dr Lisa M Noguchi, Department of Epidemiology, Johns Hopkins University, Baltimore, MD 21205, USA, lnoguch1@jhu.edu.

Contributors

LMN, BAR, and JMB conceptualised the Article and analysis plan. LMN did the analyses in collaboration with BAR. LMN drafted the initial report, and BAR, JMB, SLH, JEB, ZMC, KB, GN, TP-P, AvdS, UMP, JMP, DHW, and JMM contributed to the content and revisions. GR, GN, TP-P, and PS contributed to data collection. KG contributed to study operations. All authors contributed to article content.

Declaration of interests

BAR has received consultancy fees from Tobira Therapeutics and Theratechnologies. SLH has received consultancy fees from Merck and Symbiomix. JEB has received consultancy fees from Symbiomix. JMM has received consultancy fees from Merck. All other authors declare no competing interests.

Background—Several observational studies have reported that HIV-1 acquisition seems to be higher in women who use depot medroxyprogesterone acetate (DMPA) than in those who do not use hormonal contraception. We aimed to assess whether two injectable progestin-only contraceptives, DMPA and norethisterone enanthate (NET-EN), confer different risks of HIV-1 acquisition.

Methods—We included data from South African women who used injectable contraception while participating in the VOICE study, a multisite, randomised, placebo-controlled trial that investigated the safety and efficacy of three formulations of tenofovir for prevention of HIV-1 infection in women between Sept 9, 2009, and Aug 13, 2012. Women were assessed monthly for contraceptive use and incident infection. We estimated the difference in incident HIV-1 infection between DMPA and NET-EN users by Cox proportional hazards regression analyses in this prospective cohort. The VOICE trial is registered with ClinicalTrials.gov, NCT00705679.

Findings—3141 South African women using injectable contraception were included in the present analysis: 1788 (56·9%) solely used DMPA, 1097 (34·9%) solely used NET-EN, and 256 (8·2%) used both injectable types at different times during follow-up. During 2733·7 person-years of follow-up, 207 incident HIV-1 infections occurred (incidence 7·57 per 100 person-years, 95% CI 6·61–8·68). Risk of HIV-1 acquisition was higher among DMPA users (incidence 8·62 per 100 person-years, 95% CI 7·35–10·11) than among NET-EN users (5·67 per 100 person-years, 4·35–7·38; hazard ratio 1·53, 95% CI 1·12–2·08; p=0·007). This association persisted when adjusted for potential confounding variables (adjusted hazard ratio [aHR] 1·41, 95% CI 1·06–1·89; p=0·02). Among women seropositive for herpes simplex virus type 2 (HSV-2) at enrolment, the aHR was 2·02 (95% CI 1·26–3·24) compared with 1·09 (0·78–1·52) for HSV-2-seronegative women ($p_{interaction}$=0·07).

Interpretation—Although moderate associations in observational analyses should be interpreted with caution, these findings suggest that NET-EN might be an alternative injectable drug with a lower HIV risk than DMPA in high HIV-1 incidence settings where NET-EN is available.

Funding—National Institutes of Health, Mary Meyer Scholars Fund, and the Ruth Freeman Memorial Fund.

Introduction

Although benefits of contraception generally outweigh potential risks to women's health, [1,2] results of observational studies that assessed the effect of hormonal contraception on HIV-1 acquisition are mixed.[3] In light of findings that suggest increased HIV risk in women who use the injectable progestin depot medroxyprogesterone acetate (DMPA), WHO recommended "women using progestogen-only injectable contraception should be strongly advised to also always use condoms, male or female, and other HIV preventive measures".[4] WHO also recommended that injectable contraceptive alternatives to DMPA be investigated for associations with HIV acquisition in women.[5] Updated WHO guidance acknowledged these mixed findings and the need for further research.[6] This uncertainty is especially problematic in sub-Saharan Africa, where HIV incidence among young women is high and use of injectable contraception is common.[7–9]

In eastern and southern Africa, injectable methods are the most popular contraceptives, accounting for over 40% of use.[10] South African women are increasingly using injectables:[9,11,12] about half of women using contraception use injectable progestin methods, although estimates reach nearly 90% in some areas.[11] The two commonly used methods are DMPA 150 mg, a progesterone derivative used every 3 months,[13] and norethisterone enanthate (NET-EN) 200 mg, a first-generation synthetic progestin used every 2 months.[14,15] Although more South African women use DMPA than use NET-EN,[11] both are highly effective (97%, typical use); are available in the public sector, where most women obtain contraception;[9] have the same medical eligibility criteria;[16] and are treated similarly in policy guidance.[16] However, their pharmacokinetic profiles differ and amenorrhoea and delayed return to ovulation seem to be more common in DMPA users than in NET-EN users.[17,18] Findings from in-vitro studies that showed different progestins affect immune cells differently suggest risk of HIV-1 acquisition could differ between these two methods.[19,20] In a recent systematic review[21] and an individual participant data meta-analysis,[22] hazard ratios (HRs) for HIV acquisition were higher for DMPA (1·40, 95% CI 1·16–1·69;[21] and 1·50, 1·24–1·83)[22] than for NET-EN (1·10, 0·88–1·37;[21] and 1·24, 0·84–1·82)[22] when either method was compared with no hormonal contraception. So far, no published studies assessing separate progestin types have implicated NET-EN in HIV acquisition, although a recent systematic review reported an unpublished reanalysis of study data suggesting increased risk of HIV-1 infection associated with NET-EN, compared with use of no hormonal contraception.[3] However, NET-EN-specific data are limited.

Most analyses of hormonal contraception and HIV-1 acquisition have used comparator groups of women who do not use hormonal contraception.[3] However, a limitation of this approach is that it compares groups with potentially different HIV-related risk behaviours, including un protected intercourse and coital frequency.[23,24] These differential risks of exposure could confound associations between contraceptive type and HIV acquisition. However, restricting analysis to one delivery system (ie, injection) might address potential behavioural confounding by contraceptive type and allow more direct comparison between two hormonal contraception types of interest. A proposed randomised controlled trial of contraceptive methods would have no comparison group of women not taking contraception, similar to our approach.[25] Herein, we sought to quantify the difference in HIV-1 acquisition in DMPA and NET-EN users.

Methods

Study design and participants

We analysed prospective data from the VOICE trial (MTN-003), a randomised, placebo-controlled trial that investigated the safety and efficacy of three formulations of tenofovir for prevention of HIV-1 infection in women (NCT00705679). Women were enrolled from South Africa (Durban, Johannesburg, and Klerksdorp), Uganda, and Zimbabwe from Sept 9, 2009, to June 7, 2011, and were followed up until Aug 13, 2012.[26] Women who were HIV uninfected, sexually active, not pregnant, without curable genitourinary infection, and willing to use effective contraception (hormonal method, intrauterine device, or sterilisation) were eligible for inclusion. Women who were breastfeeding, or who had abnormal renal,

haematological, or hepatic function were excluded. Adherence to VOICE study drugs was low, and no regimen significantly reduced HIV-1 acquisition compared with placebo.[26] In the present study, we restricted analysis to participants in South Africa, where both DMPA and NET-EN are used. We postulated there would be no difference in acquisition between DMPA and NET-EN users.

Participants provided written informed consent before enrolment into the VOICE trial. Institutional review boards in South Africa, Uganda, the USA, and Zimbabwe approved the VOICE trial, with additional approval for this analysis provided by Johns Hopkins Bloomberg School of Public Health Institutional Review Board.

Procedures

Women attended monthly visits for study product management, completion of standardised questionnaires, documentation of contraceptive use, pregnancy testing, and HIV testing. Sensitive questions (eg, on sexual practices) were also asked via audio computer-assisted self-interview (ACASI). All participants were provided condoms and standard risk reduction counselling. Testing for HIV was done according to protocol-defined algorithms. Screening for chlamydia, gonorrhoea, and trichomonas infection was done at baseline, annually, and when clinically indicated, with treatment provided on site. Herpes simplex virus type 2 (HSV-2) status at baseline and study end was determined via FOCUS EIA (Focus Technologies, Cypress, CA, USA).

Statistical analysis

The VOICE protocol prespecified an analysis of contraceptive use and HIV-1 acquisition; the primary comparison of DMPA versus NET-EN use was designed Nov 9, 2012, after completion of the VOICE trial, but before data unmasking and primary data analysis. On the basis of anticipated number of HIV endpoints in the VOICE trial, we estimated 80–90% power to detect a 50% difference in hazard of acquisition between DMPA and NET-EN users. To compare baseline characteristics between DMPA and NET-EN users, we grouped participants according to initial exposure after enrolment. We estimated exposure using injection dates, which were recorded in clinic charts for on-site injections and transcribed from contraception cards for off-site injections. Exposure lengths per injection (17 weeks for DMPA and 10 weeks for NET-EN) were based on WHO guidelines for duration of contraceptive coverage.[27] We did not assume continued administration of injections during missed visits. Separate binary variables were created for DMPA and NET-EN. Person-time was set to unexposed when modelled exposure lengths ended; unexposed person-time was excluded. We identified and adjusted for periods when combined oral contraceptive pill (binary variable) and injectable exposure overlapped (eg, to treat breakthrough vaginal bleeding). Date of HIV-1 infection was estimated by calculation of the midpoint between last negative test and first confirmed positive test.

We used a Cox proportional hazards model with time-varying exposure to compare HIV acquisition between DMPA and NET-EN users. Follow-up time was from enrolment until estimated date of HIV-1 infection, pregnancy, loss to follow-up, or last negative HIV test. The time origin for the model was the date of first contraceptive injection resulting in

exposure during follow-up. We included person-time for both injectable types, including those participants who switched types during follow-up. We adjusted for baseline age, marriage or cohabitation, education, and HSV-2 serostatus; time-varying factors included combined oral contraceptive pill use, condom use at last sex (ACASI), and whether primary partners had other partners (ACASI). Because of overall low adherence to VOICE study products, we did not adjust by trial arm. Potential confounding variables were selected on the basis of clinical relevance. We calculated a multilevel, site-stratified estimate in the adjusted model because of variable HIV-1 incidence by site. We used clustering of variance–covariance estimation methods to calculate SEs, allowing for intragroup correlation at site level. Use of a marginal structural model to address time-dependent confounding was considered; however, intermittent combined oral contraceptive pill use and pregnancy were deemed potential violations of the positivity assumption requisite for marginal structural model validity.[28]

We did three prespecified subgroup analyses: women who reported at baseline not using condoms for vaginal sex in the past week (ACASI), women aged less than 25 years, and women with HSV-2 versus those without HSV-2 at baseline. We used the likelihood ratio test to assess the interaction between injectable type and HSV-2 serostatus in the adjusted model. We tested model sensitivity to censoring at pregnancy detection via an additional analysis omitting all pregnant person-time, but with allowance for return to assessment after pregnancy outcomes (subgroup analysis, not prespecified). We also assessed results in those with baseline chlamydia, gonorrhoea, or trichomonas infection, as potentially objective markers for recent unprotected sex (subgroup analysis, not prespecified). Lastly, as a strategy to investigate potential provider bias in prescriptive patterns, we repeated the model, restricting to, and then omitting, participants who used both injectable methods at different times during follow-up (subgroup analysis, not prespecified). All analyses were done with Stata version 13.1. All statistical tests were two-sided with a probability of type I error of 0·05.

The VOICE trial is registered with ClinicalTrials.gov, NCT00705679.

Role of the funding source

The National Institutes of Health participated in study design and oversight, data interpretation, and writing of the report, and provided an independent data and safety monitoring board to review the VOICE trial every 6 months; they had no role in data collection or data analysis. Mary Meyer Scholars Fund and the Ruth Freeman Memorial Fund had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study. Protocol chairs (ZMC and JMM) and sponsor representatives (JMP and DHW) had final responsibility for the decision to submit for publication.

Results

Of 5029 participants in the VOICE trial, 3141 South African injectable contraception users were included in the present analysis. Of the 1888 excluded participants, 33 were missing data for injectable contraceptive type and 22 were identified by plasma HIV-1 RNA PCR as

infected at enrolment (figure). Of 3141 participants included in the secondary analyses, 1788 (56·9%) solely used DMPA, 1097 (34·9%) solely used NET-EN, and 256 (8·2%) used both injectable types at different times during follow-up (figure). Because most participants did not switch injectable type, the first injectable was DMPA in 1927 women (61·3%) and NET-EN in 1214 (38·7%). Most women were young and unmarried (table 1). Women whose first injectable was DMPA were older (p<0·0001), more likely to be married or cohabitating (p=0·0004), more likely to be parous (p<0·0001), and less likely to report multiple partners (p=0·0001) or circumcised partners (p<0·0001). The median number of sex acts in the past week was similar, but the distribution was weighted toward fewer among NET-EN users (p=0·004). Recent anal sex was more commonly reported by those whose first injectable was NET-EN (p=0·04). Baseline seropositivity for HSV-2 was higher for those whose first method was DMPA (p<0·0001).

Overall median follow-up for women was 13·3 months (IQR 9·4–16·5) and was similar between groups (p=0·3). Women whose first injectable was DMPA more frequently continued participation until originally scheduled termination of study participation (1786 of 1925 [92·8%] *vs* 1085 of 1214 [89·4%]; p=0·001). Reasons for 268 women with early termination were death (three), refusal of further participation (127), relocation (61), loss to follow-up (41), investigator decision (one), and other reasons (35).

629 (20·0%) of 3141 participants had three or more consecutive missed visits during follow-up. 268 users of DMPA (13·9%) used combined oral contraceptive pills (alone or concurrently with injectable) during follow-up compared with 333 NET-EN users (27·4%; p<0·0001). Among those who started injectable use with DMPA, 32 (1·7%) became pregnant during follow-up compared with 38 (3·1%) NET-EN users (p=0·007); overall pregnancy incidence (0·5% for both methods) did not differ during DMPA and NET-EN exposure (p=0·9). Condom use was more frequently reported at quarterly follow-up visits for DMPA than for NET-EN users (p=0·01; table 2).

Overall, 207 new HIV-1 infections occurred over 2733·7 person-years of follow-up, resulting in an incidence of 7·57 per 100 person-years (95% CI 6·61–8·68; table 3): 152 during 1763·0 person-years of DMPA use (8·62 per 100 person-years, 7·35–10·11) and 55 during 970·8 person-years of NET-EN use (5·67 per 100 person-years, 4·35–7·38). Overall risk of HIV-1 infection was higher in DMPA users than in NET-EN users (HR 1·53, 95% CI 1·12–2·08; p=0·007). This association persisted in a site-stratified, multivariable model adjusted for baseline and time-varying factors (adjusted HR [aHR] 1·41, 95% CI 1·06–1·89; p=0·02). Additional adjustment for number of sexual partners and receptive anal sex did not substantially alter results. Use of a categorical variable for HSV-2 (remained HSV-2 seronegative, acquired HSV-2, or HSV-2-seropositive at baseline) also resulted in a similar estimate (aHR 1·42, 95% CI 1·06–1·90; p=0·02). HIV-1 incidence varied by site (2·18–10·40 per 100 person-years). We did not find evidence of a statistical interaction by study site ($p_{interaction}$=0·6).

Among women who were seronegative for HSV-2 at baseline, no significant difference in risk of HIV was noted between DMPA and NET-EN users (p=0·6; table 3). However, among women who were seropositive for HSV-2 at baseline, we noted a higher risk of

incident HIV infection in DMPA compared with NET-EN users (aHR 2·01, 95% CI 1·12–3·63 *vs* 1·09, 0·78–1·52; $p_{interaction}$=0·07). Repeating the primary comparison in the whole cohort, with the addition of injection exposures and person-time after pregnancy outcomes, did not substantially alter the results. Results were similar if analysis was restricted to those diagnosed with trichomonas, chlamydia, or gonorrhoea infection at baseline. Lastly, when we restricted analysis to women who used both DMPA and NET-EN (at different times) during follow-up, DMPA was associated with higher risk of HIV than was NET-EN (aHR 4·76, 95% CI 2·15–10·52; p=0·0001).

Discussion

In this large prospective study of South African women who use injectable progestin-only contraception, those using DMPA had about a 50% increase in incident HIV-1 infection compared with those using NET-EN; increased risk persisted after controlling for important demographic and behavioural factors and in several sensitivity analyses. Present WHO recommendations suggest progestin-only injectable methods have the potential to increase risk of HIV acquisition;[6] our results suggest risk might differ across different progestin-only injectable types.

As VOICE required all participants to be using contraception at enrolment, our analyses cannot address whether DMPA or NET-EN increases risk of HIV-1 acquisition in women compared with no use of hormonal contraception. We are also unable to assess potential HIV infection risk associated with combination injectable methods (oestrogen plus progestin in a single formulation) because those methods were not used by any VOICE participants. However, these results might offer clinically relevant information for the millions of women at risk for HIV who want to use progestin-only injectable contraception, particularly those unable to negotiate condom use or who live where non-hormonal alternatives are scarce. The more common comparison of DMPA versus no hormonal contraception is appropriate when estimating the effect of DMPA on HIV acquisition,[23] but comparisons between methods have greater utility for women who want to avoid pregnancy and for contraceptive providers. Moreover, a comparison between two different injectable methods is less likely to be confounded by behavioural differences (eg, condom use, coital frequency, or partner selection) than are comparisons between hormonal and non-hormonal methods of contraception. In view of the high incidence of HIV-1 in this cohort, our findings support WHO recommendations[6] that condoms are available to couples in which the woman is using injectable progestogen contraception. However, condom use is frequently outside women's control, and this persistent inequity contributes to demand for injectable contraceptives, which can be used independent of partners' knowledge or consent. In this cohort, women not using condoms at baseline had overall lower HIV risk than the whole cohort, which might be related to both risk perception and partner choice. Scale-up is needed for alternatives to injectable methods such as implants and non-hormonal methods (eg, the copper intrauterine device), although the effect of implants on HIV risk has been estimated in only a few analyses.[29] Development of multipurpose technologies for prevention of both HIV infection and undesired pregnancy is also needed.

Among women who were seropositive for HSV-2 at baseline, DMPA was associated with a two times increased risk of HIV acquisition compared with NET-EN, whereas this association was not noted among women who were seronegative for HSV-2 at baseline. Our findings differ from those of previous studies that compared DMPA or pooled hormonal contraception versus no hormonal contraception, which reported either an increased risk of HIV acquisition among HSV-2 seronegative women[30] or no suggestion of modification of effect by HSV-2 status.[31–33] Thus, data are insufficient to inform clinical guidance specifically for women with known or suspected HSV-2 infection.

Because analysis of hormonal contraception and HIV-1 acquisition was planned in the VOICE trial, we prospectively implemented robust data collection and site monitoring strategies for this cohort, one of the largest so far with regard to person-time and HIV infection. Measurements of contraceptive exposure, sexual behaviour, pregnancy, and HIV status were frequent for a study of this type. Contraception was offered on site, and injection types and dates were directly reported or identified from family planning cards, rather than self-report. Frequent measurement of contraceptive use allowed precise characterisation of exposures relative to HIV outcome, reducing but not eliminating potential exposure misclassification. The design of the VOICE trial also permitted simultaneous investigation of genital tract infection, and frequency of prevalent or incident gonorrhoea or chlamydia did not differ between DMPA and NET-EN users, as might be expected if the reported increase in HIV acquisition were related solely to differences in behaviour (eg, condom use).[34]

Although our results seem to be consistent with those of in-vitro analyses that suggest proinflammatory effects of DMPA compared with NET-EN[19,20] and a recent meta-analysis that suggests higher risk of HIV in users of DMPA than in users of NET-EN,[22] ultimately our findings do not identify potential mechanisms for differences in HIV-1 acquisition. The main limitation of this study is possible bias—a substantial risk in all observational analyses, which have limited capacity to detect slight associations reliably.[35] In this cohort, in which partners' HIV serostatus was not assessed, true exposure levels to infection are unknown and potentially differed between injectable groups. The inclusion of only clinical trial participants limits the generalisability of our results. Social desirability might have affected measurement of self-reported covariates, such as condom use. Although we postulated that DMPA and NET-EN users were more similar to each other with regards to HIV risk than to women not using hormonal contraception, we noted differences between women in the two contraceptive groups that suggest we cannot completely circumvent analytical challenges related to possible confounding and group comparability. First, DMPA users were more likely to continue follow-up until scheduled termination, which potentially affected estimates for comparative risk of HIV acquisition. Some factors, such as partner's circumcision status, uncertainty about a partner's other partners or HIV status, and participant's HSV-2 serostatus, might suggest higher HIV risk for DMPA than for NET-EN users. However, other differences between groups (eg, age, and knowing a primary partner had other partners or HIV) potentially suggest higher HIV risk in NET-EN users, although we did not identify this in our results. Thus, demographic and behavioural differences between DMPA and NET-EN users do not suggest a consistent direction for bias. Some differences between DMPA and NET-EN users, particularly age, have been reported

previously and are probably a result of misperceptions that NET-EN is more appropriate for younger women who want future fertility,[36] which suggests that socio-demographic differences between injectable users persist despite contemporary messaging to discourage age-based prescribing.[37,38] Lastly, pharma cokinetic profiles differ between progestin types and among women, and physiological effects are known to outlast detectable drug in some women;[39] thus, our exposure definitions might not demarcate the most relevant exposure periods.

HIV-1 infection does not exist in isolation from other substantial health risks for women in sub-Saharan Africa, including maternal mortality. In South Africa, modern contraception has averted an estimated 58% of potential maternal deaths.[1] Benefits of contraception also include reduced deaths of newborn babies, improved child health, and increased household income.[40] Thus, concerns about possible increased HIV risk with DMPA use must be weighed against the beneficial effects of contraception on a broad range of outcomes. Despite findings that might implicate DMPA in HIV acquisition, evidence remains mixed, and withdrawal of any common effective contraceptive could increase maternal mortality rates.[41] The present data suggest that NET-EN might be an alternative injectable drug with a lower HIV risk than DMPA, and policy makers, clinician scientists, and community stakeholders should continue to assess emerging evidence to establish whether women who prefer an injectable, in consultation with providers, should consider switching from DMPA to NET-EN in high HIV incidence settings where NET-EN is available.

Acknowledgments

LMN, BAR, JMB, SLH, JEB, ZMC, KB, GR, GN, TP-P, PS, AvdS, UMP, KG, and JMM report support from the National Institutes of Health (NIH). LMN reports support from the Johns Hopkins Training Program in Sexually Transmitted Infections (T32-AI050056). The Microbicide Trials Network is funded by the National Institute of Allergy and Infectious Diseases (UM1AI068633, UM1AI068615, UM1AI106707), with cofunding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the NIH. The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the official views of the NIH, the Office of the Global AIDS Coordinator, or the US Department of State. We thank all team members and participants in the VOICE study. LMN additionally thanks Matthew Reeves, Taha E Taha, and Ron Gray.

References

1. Ahmed S, Li Q, Liu L, Tsui AO. Maternal deaths averted by contraceptive use: an analysis of 172 countries. Lancet. 2012; 380:111–25. [PubMed: 22784531]
2. Cleland J, Conde-Agudelo A, Peterson H, Ross J, Tsui A. Contraception and health. Lancet. 2012; 380:149–56. [PubMed: 22784533]
3. Polis CB, Phillips SJ, Curtis KM, et al. Hormonal contraceptive methods and risk of HIV acquisition in women: a systematic review of epidemiological evidence. Contraception. 2014; 90:360–90. [PubMed: 25183264]
4. WHO. [accessed April 29, 2014] Hormonal contraception and HIV: technical statement. Feb 16. 2012 http://whqlibdoc.who.int/hq/2012/WHO_RHR_12.08_eng.pdf
5. WHO. [accessed May 9, 2014] Programmatic and research considerations for hormonal contraception for women at risk of HIV and women living with HIV. 2012. http://whqlibdoc.who.int/hq/2012/WHO_RHR_12.09_eng.pdf
6. WHO. Hormonal contraceptive methods for women at high risk of HIV and living with HIV: 2014 guidance statement. Geneva: World Health Organization; 2014.

7. UNAIDS. [accessed July 15, 2014] Getting to zero: HIV in eastern & southern Africa. 2013. http://www.unicef.org/esaro/Getting-to-Zero-2013.pdf
8. UNAIDS. [accessed May 14, 2014] HIV and AIDS estimates. 2013. http://www.unaids.org/en/regionscountries/countries/southafrica
9. Department of Health, Republic of South Africa. National contraception and fertility planning policy and service delivery guidelines. Pretoria: Department of Health; 2012.
10. UNFPA. World contraceptive patterns. Geneva: United Nations Population Fund; 2013.
11. Department of Health, Medical Research Council, OrcMacro. South Africa Demographic and Health Survey 2003. Pretoria: Department of Health; 2007.
12. IPFF. [accessed May 9, 2014] Directory of hormonal contraceptives. 2014. http://contraceptive.ippf.org/search
13. Pfizer. [accessed March 23, 2014] Product monograph: DEPO-PROVERA: medroxyprogesterone acetate injectable suspension. http://www.pfizer.ca/en/our_products/products/monograph/181
14. Malahyde Information Systems. [accessed May 14, 2014] Nur-Isterate. http://home.intekom.com/pharm/schering/nur-ist.html
15. Sitruk-Ware R. New progestagens for contraceptive use. Hum Reprod Update. 2006; 12:169–78. [PubMed: 16291771]
16. WHO. Medical eligibility criteria for contraceptive use. Geneva: World Health Organization; 2010.
17. Garza-Flores J, Cardenas S, Rodriguez V, Cravioto MC, Diaz-Sanchez V, Perez-Palacios G. Return to ovulation following the use of long-acting injectable contraceptives: a comparative study. Contraception. 1985; 31:361–66. [PubMed: 3159544]
18. Garza-Flores J, Hall PE, Perez-Palacios G. Long-acting hormonal contraceptives for women. J Steroid Biochem Mol Biol. 1991; 40:697–704. [PubMed: 1958567]
19. Tomasicchio M, Avenant C, Du Toit A, Ray RM, Hapgood JP. The progestin-only contraceptive medroxyprogesterone acetate, but not norethisterone acetate, enhances HIV-1 Vpr-mediated apoptosis in human CD4+ T cells through the glucocorticoid receptor. PloS One. 2013; 8:e62895. [PubMed: 23658782]
20. Huijbregts RP, Michel KG, Hel Z. Effect of progestins on immunity: medroxyprogesterone but not norethisterone or levonorgestrel suppresses the function of T cells and pDCs. Contraception. 2014; 90:123–29. [PubMed: 24674041]
21. Ralph LJ, McCoy SI, Shiu K, Padian NS. Hormonal contraceptive use and women's risk of HIV acquisition: a meta-analysis of observational studies. Lancet Infect Dis. 2015; 15:181–89. [PubMed: 25578825]
22. Morrison CS, Chen PL, Kwok C, et al. Hormonal contraception and the risk of HIV acquisition: an individual participant data meta-analysis. PLoS Med. 2015; 12:e1001778. [PubMed: 25612136]
23. Polis CB, Westreich D, Balkus JE, Heffron R. Assessing the effect of hormonal contraception on HIV acquisition in observational data: challenges and recommended analytic approaches. AIDS. 2013; 27(suppl 1):S35–43. [PubMed: 24088682]
24. Aklilu M, Messele T, Tsegaye A, et al. Factors associated with HIV-1 infection among sex workers of Addis Ababa, Ethiopia. AIDS. 2001; 15:87–96. [PubMed: 11192872]
25. Cates W. for the Evidence for Contraceptive Options and HIV Outcomes (ECHO) Consortium. Research on hormonal contraception and HIV. Lancet. 2014; 383:303–04. [PubMed: 24461116]
26. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2015; 372:509–18. [PubMed: 25651245]
27. WHO. [accessed May 19, 2014] Selected practice recommendations for contraceptive use: 2008 update. http://whqlibdoc.who.int/hq/2008/WHO_RHR_08.17_eng.pdf
28. Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. Am J Epidemiol. 2008; 168:656–64. [PubMed: 18682488]
29. Lutalo T, Musoke R, Kong X, et al. Effects of hormonal contraceptive use on HIV acquisition and transmission among HIV-discordant couples. AIDS. 2013; 27 (suppl 1):S27–34. [PubMed: 24088681]
30. Morrison CS, Richardson BA, Mmiro F, et al. Hormonal contraception and the risk of HIV acquisition. AIDS. 2007; 21:85–95. [PubMed: 17148972]

31. Baeten JM, Benki S, Chohan V, et al. Hormonal contraceptive use, herpes simplex virus infection, and risk of HIV-1 acquisition among Kenyan women. AIDS. 2007; 21:1771–77. [PubMed: 17690576]
32. Heffron R, Donnell D, Rees H, et al. Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study. Lancet Infect Dis. 2012; 12:19–26. [PubMed: 21975269]
33. McCoy SI, Zheng W, Montgomery ET, et al. Oral and injectable contraception use and risk of HIV acquisition among women in sub-Saharan Africa. AIDS. 2013; 27:1001–09. [PubMed: 23698064]
34. Noguchi L, Marrazzo J, Richardson BA, et al. Injectable progestin contraception and chlamydia and gonorrhea acquisition among South African women in VOICE. Sex Transm Dis. 2014; 41:8.
35. Shapiro S. Bias in the evaluation of low-magnitude associations: an empirical perspective. Am J Epidemiol. 2000; 151:939–45. [PubMed: 10853631]
36. Smit J, Gray A, McFadyen L, Zuma K. Counting the costs: comparing depot medroxyprogesterone acetate and norethisterone oenanthate utilisation patterns in South Africa. BMC Health Serv Res. 2001; 1:4. [PubMed: 11401729]
37. Morroni C, Myer L, Moss M, Hoffman M. Preferences between injectable contraceptive methods among South African women. Contraception. 2006; 73:598–601. [PubMed: 16730491]
38. IPPF. [accessed May 13, 2014] IPPF medical bulletin: comparing injectable contraceptives. http://www.ippf.org/sites/default/files/tks_medbulletin_july13_en.pdf
39. Mishell DR Jr. Pharmacokinetics of depot medroxyprogesterone acetate contraception. J Reprod Med. 1996; 41:381–90. [PubMed: 8725700]
40. Carr B, Gates MF, Mitchell A, Shah R. Giving women the power to plan their families. Lancet. 2012; 380:80–82. [PubMed: 22784540]
41. Rodriguez MI, Reeves MF, Caughey AB. Evaluating the competing risks of HIV acquisition and maternal mortality in Africa: a decision analysis. BJOG. 2012; 119:1067–73. [PubMed: 22676150]

Research in context

Evidence before this study

We searched PubMed for articles published before March 18, 2015, using the terms "hormonal contraception", "HIV/acquisition", "injectable", "progestin", "progestogen", "depot medroxyprogesterone acetate", "DMPA", "norethisterone enanthate", and "NET-EN", in different combinations. We also reviewed systematic reviews and meta-analyses on this topic. Recent findings from a systematic review and an individual participant data meta-analysis showed higher hazard ratios for depot medroxyprogesterone acetate (DMPA) than norethisterone enanthate (NET-EN) when either method was compared with use of no hormonal contraception. No published studies that disaggregated type of progestin have implicated NET-EN in HIV-1 acquisition, although a recent systematic review reported an unpublished reanalysis of study data that suggested an increased risk of infection associated with NET-EN, compared with no hormonal contraception. When assessed in the same study, some unpublished point estimates for HIV-1 risk were larger for NET-EN than for DMPA.

Added value of this study

Most analyses of hormonal contraception and HIV-1 acquisition have used comparator groups of women who do not use hormonal contraception. However, a limitation of this approach is comparison between groups with potentially different HIV risk behaviours, including unprotected intercourse and coital frequency. Restricting analysis to one delivery system (ie, injection) might address potential behavioural confounding by contraceptive type and allow more direct comparison between hormonal contraception types of interest. Our results might offer clinically relevant information for women at risk of HIV who want to use progestin-only injectable contraception, particularly those unable to negotiate condom use or who live where non-hormonal alternatives are scarce.

Implications of all the available evidence

Concerns about possible increased HIV-1 risk with DMPA use must be weighed carefully against the beneficial effects of contraception on public health. Despite observational findings that seem to implicate DMPA in HIV acquisition, evidence remains mixed, and withdrawal of any common effective contraceptive could increase maternal mortality ratios. A broad range of stakeholders should continue to assess emerging evidence to establish whether women, in consultation with providers, should consider switching from DMPA to NET-EN in high HIV incidence settings where NET-EN is available.

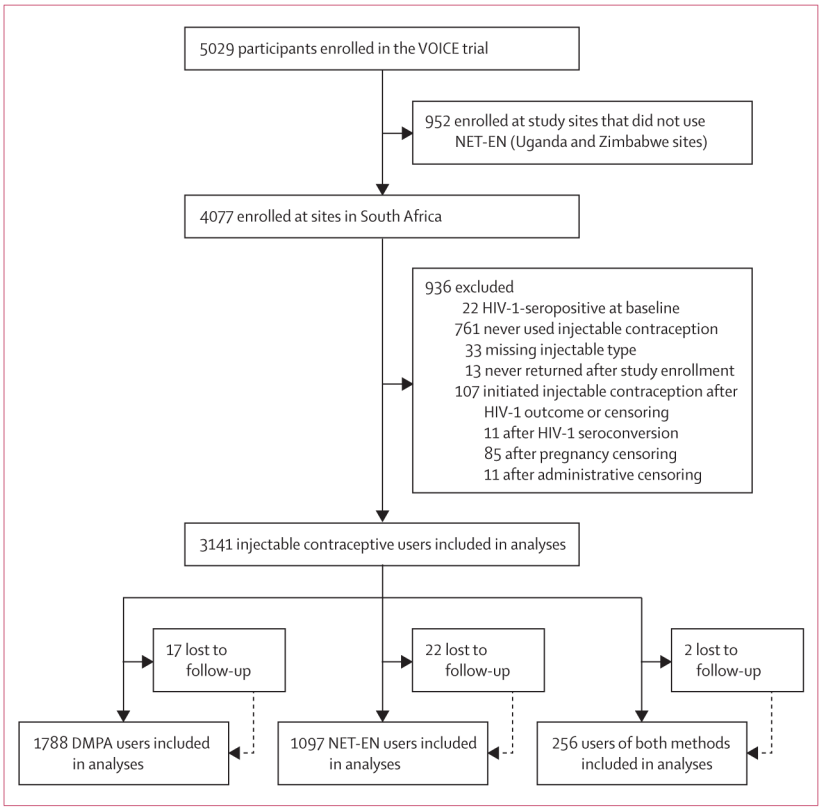

Figure. Cohort profile

DMPA=depot medroxyprogesterone acetate. NET-EN=norethisterone enanthate.

Table 1

Demographics and baseline characteristics of women by first injectable method type

	Whole cohort (n=3141)	DMPA first (n=1927)	NET-EN first (n=1214)	p value DMPA first *vs* NET-EN first
Demographics				
Age (years)*	23 (21–27)	24 (21–27)	23 (20–26)	<0·0001
Married or cohabitating	603/3141 (19·2%)	408/1927 (21·2%)	195/1214 (16·1%)	0·0004
Parous	2632/3141 (83·8%)	1786/1927 (92·7%)	846/1214 (69·7%)	<0·0001
Any secondary education	3017/3137 (96·2%)	1839/1924 (95·6%)	1178/1213 (97·1%)	0·03
Formal employment	299/3138 (9·5%)	178/1925 (9·2%)	121/1213 (10·0%)	0·5
Home ownership	2585/3139 (82·4%)	1585/1926 (82·3%)	1000/1213 (82·4%)	0·9
Sexual behaviours				
>1 sexual partner	118/3101 (3·8%)	53/1912 (2·8%)	65/1189 (5·5%)	0·0001
Number of sex acts in the past week*	2 (1–3)	2 (1–3)	2 (0–3)	0·004
Condom used at last sex	2132/2858 (74·6%)	1299/1748 (74·3%)	833/1110 (75·0%)	0·7
Anal sex in the past 3 months	628/3090 (20·3%)	364/1900 (19·2%)	264/1190 (22·2%)	0·04
Sex for money in the past year	155/3112 (5·0%)	93/1917 (4·9%)	62/1195 (5·2%)	0·7
Primary partner				
Any secondary education	2891/3119 (92·7%)	1764/1917 (92·0%)	1127/1202 (93·8%)	0·07
Has other partners				0·03
Yes	285/3038 (9·4%)	163/1889 (8·6%)	122/1149 (10·6%)	··
No	801/3038 (26·4%)	479/1889 (25·4%)	322/1149 (28·0%)	··
Don't know	1952/3038 (64·3%)	1247/1889 (66·0%)	705/1149 (61·4%)	··
Circumcised				<0·0001
Yes	1001/3120 (32·1%)	556/1918 (29·0%)	445/1202 (37·0%)	··
No	1727/3120 (55·4%	1123/1918 (58·6%)	604/1202 (50·2%)	··
Don't know	392/3120 (12·6%)	239/1918 (12·5%)	153/1202 (12·7%)	··
HIV infected				0·0006
Yes	104/3036 (3·4%)	61/1887 (3·2%)	43/1149 (3·7%)	··
No	2039/3036 (67·2%)	1224/1887 (64·9%)	815/1149 (70·9%)	··
Don't know	893/3036 (29·4%)	602/1887 (31·9%)	291/1149 (25·3%)	··
Genital tract infections				
Bacterial vaginosis†	1246/3137 (39·7%)	762/1925 (39·6%)	484/1212 (39·9%)	0·9
Trichomoniasis	174/3141 (5·5%)	114/1927 (5·9%)	60/1214 (4·9%)	0·2
Chlamydia	468/3141 (14·9%)	289/1927 (15·0%)	179/1214 (14·7%)	0·8
Gonorrhoea	110/3141 (3·5%)	67/1927 (3·5%)	43/1214 (3·5%)	0·9
Herpes simplex virus type 2	1459/3130 (46·6%)	985/1926 (51·1%)	474/1204 (39·4%)	<0·0001

Data are median (IQR) or n/N (%). Comparisons between participants were calculated with the Wilcoxon rank-sum test for continuous variables and Pearson's χ^2 test for categorical variables. Some percentages do not add up to 100 because of rounding.

*Reported as median (IQR) because of right-skewed distributions.

[†]Nugent score ≥7 for Gram-stained vaginal smear.

Table 2

Sexual behaviour during quarterly follow-up intervals for analysis of HIV-1 acquisition with DMPA and NET-EN use (n=3141 seronegative women)

	DMPA	NET-EN	p value*
Condom use at last vaginal sex act	4934/5999 (82·3%)	2527/3233 (78·2%)	0·002
More than one sex partner	148/6571 (2·3%)	93/3521 (2·6%)	0·3
Change in primary partner	618/7136 (8·7%)	404/3767 (10·7%)	0·06
Anal sex in the past 3 months	1133/7498 (15·1%)	545/3936 (13·9%)	0·4
Sex for money in the past year	349/7466 (4·7%)	222/3892 (5·7%)	0·4

Data are number of reports/number of quarterly visits with each characteristic (assessed by ACASI) during study follow-up (%), unless otherwise specified.

*Comparisons among contraceptive exposure groups are adjusted for correlation by multiple measures from the same woman with generalised estimating equations.

Table 3

Incidence and risk of HIV-1 infection, by injection type

	Number of HIV-1 seroconversions/person-years	Incidence per 100 person-years (95% CI)	Unadjusted Cox proportional hazards regression analysis		Adjusted Cox proportional hazards regression analysis	
			Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Primary comparison in whole cohort (n=3141)						
NET-EN	55/970·8	5·67 (4·35–7·38)	Reference	..	Reference	..
DMPA	152/1763·0	8·62 (7·35–10·11)	1·53 (1·12–2·08)	0·007	1·41 (1·06–1·89)*	0·02
Total	207/2733·7	7·57 (6·61–8·68)	..	..	..	..
Women who reported no condom use for vaginal sex at baseline (n=304)						
NET-EN	1/104·8	0·95 (0·13–6·77)	Reference	..	Reference	..
DMPA	7/163·2	4·29 (2·05–9·00)	4·80 (0·59–39·13)	0·1	3·92 (1·36–11·28)†	0·01
Total	8/268·0	2·98 (1·49–5·97)	..	..	..	..
Women under 25 years old at baseline (n=1890)						
NET-EN	41/625·1	6·56 (4·83–8·91)	Reference	..	Reference	..
DMPA	104/975·7	10·66 (8·80–12·92)	1·63 (1·14–2·35)	0·008	1·40 (1·01–1·95)	0·05
Total	145/1600·8	9·06 (7·70–10·66)	..	..	..	..
Women who were HSV-2 seronegative at baseline (n=1671)‡						
NET-EN	34/578·5	5·88 (4·20–8·23)	Reference	..	Reference	..
DMPA	55/866·6	6·35 (4·87–8·27)	1·08 (0·70–1·65)	0·7	1·09 (0·78–1·52)§	0·6
Total	89/1445·0	6·16 (5·00–7·58)	..	..	..	..
Women who were HSV-2-seropositive at baseline (n=1459)‡						
NET-EN	21/387·2	5·42 (3·54–8·32)	Reference	..	Reference	..
DMPA	97/895·4	10·83 (8·88–13·22)	2·02 (1·26–3·24)	0·003	2·01 (1·12–3·63)§	0·02
Total	118/1282·5	9·20 (7·68–11·02)	..	..	..	..
Whole cohort plus women with injectable exposure and person-time following pregnancy outcomes (n=3208)						
NET-EN	56/983·1	5·70 (4·38–7·40)	Reference	..	Reference	..
DMPA	155/1787·8	8·67 (7·41–10·15)	1·53 (1·13–2·08)	0·006	1·42 (1·04–1·95)*	0·03

	Number of HIV-1 seroconversions/person-years	Incidence per 100 person-years (95% CI)	Unadjusted Cox proportional hazards regression analysis		Adjusted Cox proportional hazards regression analysis	
			Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Total	211/2770·9	7·61 (6·65–8·71)	..	..	..	..
Women with trichomonas, chlamydia, or gonorrhoea infection at baseline (n=671)						
NET-EN	17/201·0	8·46 (5·26–13·60)	Reference	..	Reference	..
DMPA	59/376·8	15·66 (12·13–20·21)	1·86 (1·08–3·19)	0·02	1·79 (1·16–2·75)*	0·008
Total	76/577·8	13·15 (10·51–16·47)	..	..	..	..
Women who used both DMPA and NET-EN at different times during follow-up (n=256)						
NET-EN	3/104·2	2·88 (0·93–8·92)	Reference	..	Reference	..
DMPA	18/146·5	12·29 (7·74–19·50)	4·82 (1·41–16·51)	0·01	4·76 (2·15–10·52)*	0·0001
Total	21/250·7	8·38 (5·46–12·85)	..	..	..	..
Women who did not switch between DMPA and NET-EN during follow-up (n=2885)						
NET-EN	52/866·6	6·00 (4·57–7·87)	Reference	..	Reference	..
DMPA	134/1616·5	8·29 (7·00–9·82)	1·40 (1·01–1·92)	0·04	1·29 (0·94–1·76)*	0·1
Total	186/2483·0	7·49 (6·49–8·65)	..	..	..	..

DMPA=depot medroxyprogesterone acetate. HSV-2=herpes simplex virus type 2. NET-EN=norethisterone enanthate.

*Adjusted for baseline age, marriage or cohabitation, education, and HSV-2 status, and time-varying oral contraceptive pill use, primary partner has other partners, and condom use at last sex, with stratification by study site.

†Adjusted for baseline age, marriage or cohabitation, education, and HSV-2 status, and time-varying oral contraceptive pill use, and primary partner has other partners, with stratification by study site.

‡Baseline HSV-2 status was available for 3130 (99·6%) of the cohort.

§Adjusted for baseline age, marriage or cohabitation, and education, and time-varying oral contraceptive pill use, primary partner has other partners, and condom use at last sex, with stratification by study site.