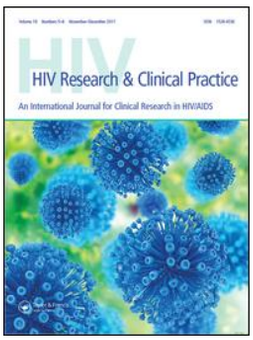

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Original Article

Implementation of a prospective pregnancy registry for antiretroviral based HIV prevention trials

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Background: Safety data on pregnancy and fetal outcomes among women in HIV prevention trials are urgently needed to inform use of effective antiretroviral agents for HIV prevention. We describe an effective, efficient, and novel method to prospectively collect perinatal safety data concurrent with on-going parent clinical trials.
Methods: The Microbicide Trials Network (MTN)-016 study is a multinational prospective pregnancy exposure registry designed to capture pregnancy and neonatal outcomes. Studies currently contributing data to this registry included phase I and II safety trials with planned exposures to candidate HIV prevention agents, as well as phase IIB and III efficacy trials capturing data on pregnancy and infant outcomes following inadvertent fetal exposure during study participation.
Results: To date, participants from two phase I studies and two effectiveness trials have participated in MTN-016, resulting in 420 pregnant women and 381 infants enrolled. Infant retention has been high, with 329 of 381 (86%) infants completing the 12-month follow-up visit.
Conclusion: In a research setting context, it is feasible to establish and implement a prospective, multinational HIV chemoprophylaxis pregnancy registry that will generate pregnancy exposure data in a robust fashion.

Keywords: HIV, ARV-chemoprophylaxis agents, registry, congenital malformation, pregnancy

Introduction

Large-scale clinical trials assessing the safety and effectiveness of topical and oral antiretroviral (ARV) agents for HIV prevention have been undertaken to identify new tools to curb the epidemic.[1–4] Given the high burden of HIV among young women globally, reproductive-aged women are a target population for recruitment into clinical trials of novel biomedical HIV prevention interventions. Such trials have typically excluded women who are currently pregnant or those planning pregnancy during the period of investigation due to uncertainties about safety of exposure to investigational products during pregnancy. Despite counseling and provision of highly effective contraceptive methods during HIV prevention trials, pregnancies occurred among 6–27% of participants while under study.[5] In many trials, study product use was stopped once pregnancy was diagnosed; therefore, exposure to the investigational products is limited to early pregnancy. Because pregnant women are also an important target population for effective HIV prevention interventions, several phase I and II trials have been implemented to evaluate the safety of ARV-based HIV prevention in pregnancy at later gestational ages.[6,7] The safety profile of candidate ARV-based prevention agents for use by HIV-uninfected pregnant women has not been fully characterized; therefore, all opportunities to assess safety in pregnancy should be undertaken.

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Data on approved ARV agents used for HIV treatment or pre-exposure prophylaxis (PrEP) are submitted to the Antiretroviral Pregnancy Registry and, for most agents, the data suggest that they are safe for use in pregnancy.[8] However, active surveillance strategies (relying on voluntary provider reports) may result in biased reporting as well as the inability to control for confounders related to teratogenicity.[9] Several new ARV agents are being evaluated for HIV prevention with limited data on their use in early pregnancy, including dapivirine delivered within a vaginal ring.[3,4] Considering the ethical and regulatory barriers to enrolling pregnant women into clinical trials and the more limited scientific rigor that post-licensure surveillance offers, a prospective pregnancy registry represents an efficient use of resources and offers a promising solution for the collection of safety data on pregnancy and neonatal outcomes following use of ARV-based agents for HIV prevention during early pregnancy. These data are critical for informing prescribing practices should products become more widely available for use in pregnancy, especially considering the evidence from observational studies suggesting that pregnancy increases risk for HIV acquisition.[10]

The Microbicide Trials Network (MTN)-016 study is a novel prospective registry designed specifically to capture pregnancy and infant outcomes for women who may have been exposed to investigational ARV-based HIV prevention agents during participation in on-going clinical trials. Below we describe the methodology used in its development, delineate its successful implementation, and report on feasibility in terms of enrollment and retention of the study population.

Methods and results

Study design

MTN-016 is a prospective cohort study designed to assess the potential impact of exposure to investigational ARV-based HIV prevention agents on pregnancy and infant outcomes during the first year of life. The study was designed to capture women currently or recently enrolled in MTN studies evaluating ARV-based HIV prevention agents for safety, acceptability, and effectiveness. Accrual into the registry began in Pittsburgh, Pennsylvania (USA) in September 2009. Other study sites are located in the USA (University of Alabama, Birmingham), Malawi, Uganda, South Africa, and Zimbabwe. The study has been reviewed and approved by ethical review boards in each of these countries.

Two groups of women are eligible to enroll in MTN-016: (1) women participating in MTN phase I or II studies with planned exposure to investigational ARV-based prevention agents in late pregnancy (see Table 4 for details); or (2) women who become pregnant, while participating in double-blinded, placebo-controlled, randomized effectiveness trials of ARV-based HIV prevention agents evaluated by the MTN. An important feature of this pregnancy exposure registry is that it enrolls women who were inadvertently exposed to both product and placebo, thereby providing a built-in comparison group for analysis. Women enrolling from planned exposure studies have well established pregnancies and were given the option to enroll into MTN-016 at the time of participation in the parent study. However, for participants enrolling following inadvertent study product exposure, MTN-016 eligibility criteria include multiple strategies for pregnancy diagnosis (Table 1). These criteria are aimed at diagnosing established pregnancies and to purposely avoid enrolling pregnancies that are considered early losses (including early spontaneous abortions, and planned terminations) for which MTN-016 would not provide additional data of any value beyond what was already being captured in the parent protocol. In MTN effectiveness trials, monthly urine β-human chorionic gonadotropin pregnancy tests were performed throughout study participation. Product use was stopped following the initial pregnancy diagnosis. Women who became pregnant, while participating in effectiveness trials were informed about MTN-016 and offered enrollment once eligibility criteria were confirmed. At enrollment, all women provided informed consent for participation of themselves and their infants. Women were ineligible to enroll if more than one year had passed since their pregnancy outcome.

Study procedures

Women were co-enrolled in both the parent study and then continued follow-up in MTN-016 if the parent protocol ended before completion of MTN-016 follow-up. When appropriate, study visits for the parent protocol and MTN-016 were combined and laboratory test results were shared between studies and minimize participant burden. At enrollment, study staff collected data on participant demographics, medical and obstetric history, and history of genetic disease in the family as well as concomitant medications and recreational drug use. Maternal follow-up visits in MTN-016 occurred quarterly until completion of the pregnancy. HIV testing was performed monthly, regardless of pregnancy status, which allowed for diagnosis of maternal HIV infection as well as appropriate counseling and referrals to prevent vertical HIV transmission at delivery. Pregnant participants were referred to local health facilities of their choice for antenatal care as this care was not part of participation in MTN-016. If a pregnancy did not result in a live birth, MTN-016 participation ended with collection of information regarding the outcome of the pregnancy. A single maternal enrollment/outcome visit occurred for those who enrolled subsequent to a known pregnancy outcome. Gestational age was estimated using a combination of date of last menstrual period (LMP), physical examination, and/or ultrasound

scan information. When participants were between 20 and 28 weeks of gestation, an ultrasound scan was provided by the study to verify gestational age and evaluate for any potential fetal abnormalities.

Infant follow-up schedule and strategies

Enrolled infants were followed as outlined in Table 2. The initial infant visit was conducted within 10 days of delivery. To maximize peripartum retention, expectant mothers were given contacts to alert study staff of their admission to the maternity ward. A variety of communication methods were used to facilitate communication between participants and study staff around the time of delivery, including short message text service, phone calls, and instant messaging platforms like WhatsApp®. All sites had prior arrangements with local health facilities to facilitate access to labor and delivery records. In anticipation of local customs or medical conditions that could prohibit a visit to the research site during the first 10 days following delivery, in-home visits were conducted when necessary by trained study physicians and research nurses.

Trained clinicians with capacity to characterize birth defects performed infant physical examinations. Across all sites, the same approach was used to document any suspected malformations/anomalies (see Table 3). Photographic documentation of suspected anomalies was uploaded to a secure database maintained by the MTN Statistical and data management center. Independent

Table 1 Inclusion criteria for enrolling into MTN-016 for women participating in MTN effectiveness trials of HIV chemoprophylaxis

Eligibility criteria for pregnant women[a]	
1. Able and willing to provide written informed consent for study participation	
2. During participation in a parent protocol, has/had a known confirmed pregnancy, meeting at least one of the following sets of criteria in A or B:	
Criteria A	Two consecutive monthly study visits, at least 14 days apart, with positive pregnancy tests, in the absence of signs/symptoms of miscarriage or participant report of pregnancy termination
Criteria B	One or more of the following assessments: • Auscultation of fetal heart tones • Positive pregnancy test confirmed by clinic staff in the presence of clinically confirmed enlarged uterus • Positive pregnancy test confirmed by clinic staff in the presence of missed menses (no menses occurring at least 60 days from the first day of the last menses) by participant report • Clinical assessment of fetal movement • Demonstration of pregnancy by ultrasound
Eligibility criteria for infants	
• Born to a mother from a pregnancy concurrent with participation in a parent study and had not reached one year of age • Has written informed consent provided by parent(s)/guardian	

[a]Pregnant women were also ineligible to participate if they had any condition that, in the opinion of the investigator or designee, would complicate interpretation of study outcome data, make participation in the study unsafe, or otherwise interfere with achieving the study objectives. In addition, women were no longer eligible to enroll if it had been more than one year since their pregnancy outcome.

Table 2 Schedule of infant visits in MTN-016

Type of visit	Administrative	Clinical
New-born/Initial visit Conducted on day 10 post-delivery.	• Eligibility assessment • Locator information • Schedule next visit	• Medical history • Medication history • Weight measurement • Length measurement • Head circumference measurement • Abdominal circumference measurement • (preferably within 10 days, but no later than Month 1 Visit) • Physical exam • If specific consent for this has been obtained, photographic documentation of suspected or confirmed anomalies as clinically indicated
Months 1, 6, and 12	• Locator information • Schedule next visit (1 and 6 months only; if indicated for month 12)	• Update medical history • Update medication history • Weight measurement • Length measurement • Head circumference measurement • Physical examination • If specific consent for this has been obtained, photographic documentation of suspected or confirmed anomalies as clinically indicated. • Laboratory investigations; As clinically indicated to follow a previous abnormal finding at the new-born/initial visit, for example, HIV testing in exposed infants.

Table 3 Maternal and infant outcome measures utilized by the pregnancy registry.

Infant outcomes	Maternal outcomes
(1) Major malformations Defined as structural abnormalities with surgical, medical, or cosmetic importance Note: The conditions listed below were excluded as major malformations (1) Minor physical features (2) Deformities that represent the normal response of fetal tissue to mechanical forces, e.g.positional plagiocephaly, (3) Physical features at birth in a preterm infant that are normally present before 37 weeks of gestation (4) Findings on prenatal ultrasonography but not on physical examination (5) Genetic disorders (2) Secondary end points • Weight, length, and head circumference at birth, one month, six months and 12 months. • HIV-1 drug resistance mutations among infants who acquire HIV-1 infection	• Delivery prior to 37 completed weeks of gestation • Stillbirth or intrauterine fetal demise (≥20 weeks) • Spontaneous abortion (<20 weeks) • Ectopic pregnancy • Intrapartum hemorrhage • Postpartum hemorrhage • Non-reassuring fetal status • Chorioamnionitis • Hypertensive disorders of pregnancy • Gestational diabetes • Intra-uterine growth restriction

experts in fetal malformations and genetics accessed the password-protected data in the secure database to review the information. These experts who were blinded to maternal exposure status in the parent protocol, independently reviewed all cases and provided a standardized assessment of whether any given abnormality met criteria for a major malformation as outlined in Table 3. If there was disagreement as to whether or not something was considered a major malformation, the genetics experts discussed the case together to come to a consensus. In the case of identified structural anomalies or other potential deviations from normal health, all efforts were made by study staff to communicate directly with the referral entity providing clinical management of the condition.

Infants were first assessed within 10 days of birth and followed through the first year of life with follow-up visits at months 1, 6, and 12. Interim visits were scheduled, as needed, to evaluate new findings prior to the next scheduled visit. Growth was assessed using serial measurements of length, weight, head/abdominal circumference and the WHO growth charts at all scheduled study visits.[11] Infants born to HIV-infected mothers were tested for HIV using the Roche Amplicor HIV-1 DNA test. Infant whole blood specimens were collected via heel prick up to 6 weeks following cessation of breastfeeding. HIV-1 DNA positive tests were confirmed through Abbott RealTime HIV-1 Assay with viral load determination. MTN-016 had capacity to test for HIV-1 drug resistance mutations among HIV-infected infants as soon as possible after diagnosis using the Viroseq platform, as the potential for resistance was a concern particularly with use of single agents for HIV prevention and could lead to future treatment failure.[12]

Study populations, enrollment and retention

To date, four MTN studies have enrolled participants into MTN-016 as summarized in Table 4. In total, 420 (87%) of 485 eligible women across 20 sites in five countries have been enrolled. The registry remains open to further enrollments from ongoing and future MTN studies. Among women participating in phase-I trials with planned exposure to ARV prevention agents (MTN-002 and MTN-008), 104 (90%) pregnant women and 101 (97%) infants were enrolled. One-year infant retention rates were 88% for MTN-002 and 73% for MTN-008.

In the VOICE/MTN-003 trial[2], which had a total of 452 pregnancies, 212 (82%) of 260 eligible pregnant women enrolled in MTN-016. Pregnancy outcome data were available for 213 of 215 (99%) pregnancies. Of 199 live births that occurred among VOICE participants who enrolled in MTN-016, 181 (91%) infants were enrolled into the registry. The proportion of infants attending the 12 months visit was 89%.

In the ASPIRE/MTN-020 trial[3] there were a total of 187 pregnancies, of which 104 of 110 (95%) eligible women enrolled in MTN-016. Of 102 live births that occurred among ASPIRE participants who enrolled in MTN-016, 99 (97%) infants were enrolled into the registry. Infant follow-up was completed in December 2016 and the proportion of infants presenting for their 12 month visit was 93%.

Discussion

MTN-016 is an innovative prospective cohort study that combines participants from large effectiveness trials with women participating in planned pregnancy exposure investigations in the third trimester. The registry is both feasible and acceptable based on the high rate of enrollment from parent studies as well as the high retention of both pregnant women and infants. Among women enrolled from studies where exposure to ARV-based prevention interventions was randomized, maternal and infant outcomes are assessed based on the maternal treatment assignment (active vs. placebo) from the

Table 4 Summary of parent protocols linked to the MTN 016 pregnancy registry.

Study name and reference	Type	Sample size of parent study	Dates	Summary	Sites	Mother/infant pairs enrolled statistics
Studies with planned exposures						
MTN-002[7]	Phase I	16	Aug 2008 to Dec 2009	Assessed pharmacokinetic parameters and placental transfer among women given Tenofovir 1% vaginal gel at term within two hours prior to an elective cesarian delivery	Pittsburgh, PA, USA	All 16 mothers and infants were enrolled. Infant retention at one year was 88%
MTN-008[6]	Phase I	99	Apr 2011 to Jul 2013	Assessed the safety and tolerability of Tenofovir 1% gel used daily for 7 days by healthy women aged 18–40 years in third trimester pregnancy and during lactation	Pittsburgh, PA USA. Birmingham, Alabama, USA	Eighty-eight of 99 (89%) pregnant women and 85 (97%) infants enrolled. Infant retention at 12 months was 73%
Effectiveness studies						
MTN-003[2] (VOICE)	Phase IIb	5029	Sep 2009 to Jun 2011	Double-blinded, five arm safety and effectiveness trial assessing Tenofovir (TDF) 300 mg tablets, Emtricitabine (FTC)/TDF 200/300 mg tablet (Truvada), Tenofovir 1% gel vs. oral placebo tablet and HEC placebo gel for HIV prevention	South Africa, Uganda, and Zimbabwe	Enrolled 213 of 260 (82%) eligible pregnant women and 181 (91%) infants. The 12-month infant retention rate was 89%
MTN-020[3] (ASPIRE)	Phase III	2629	Aug 2012 to Jun 2014	Double-blinded trial evaluating the safety and effectiveness of the 25 mg Dapivirine vaginal ring compared to its placebo for HIV prevention. The ring was changed every 28 to 35 days	Malawi, South Africa, Uganda, and Zimbabwe	Enrolled 104 of 110 (95%) of eligible pregnant women and 99 (97%) infants. The 12 month infant retention rate was 93%

parent study. Although pregnant women are a subset of all randomized women, their exposure is independent of their pregnancy status. This allows for assessment of the possible impact of exposure to investigational ARV-based prevention products in early pregnancy on maternal and infant outcomes (until 1 year of age) with minimal bias. Infant follow-up until one year age has the strength of gathering additional data above and beyond what is typically assessed in the parent trial.

Our registry study has several unique features. It is prospective with standardized data capture tools recording important maternal health information like gestational age at enrollment, medical conditions, and timing of concomitant medications. This provides critical information to characterize possible teratogenicity of ARV-based agents with decreased risk for recall bias. Data validity is enhanced in comparison with other pregnancy exposure registries whose attention to detail may not be as thorough.[8,13] Importantly, we used outcome measures that mirrored those used in everyday clinical practice and therefore had a seamless interface with local standard of care for antenatal and pediatric care as well as with parent protocols. This model may be transferred to normal clinical care with ease in some higher capacity settings in low resource countries. In addition, aggregate data from women randomized to placebo arms represents a valuable source of obstetric and pediatric surveillance data in sub-Saharan Africa, informing background rates of infant malformation and pregnancy outcomes which could be used as a benchmark for comparison in future studies.

MTN-016 utilizes basic technology that allows for access and efficient review of possible congenital anomalies by fetal experts through the examination of uploaded and internationally transmitted photographs. This flexibility is essential in a registry and allows for robust complete data and represents an efficient and cost-effective approach for evaluating potential abnormalities in settings where this expertise may be limited. To maximize data captured from participants, we were able to establish mechanisms for women to alert us of impending labor and delivery. Official agreements with local delivery institutions were easily put in place prior to pregnancy outcomes, thereby facilitating access to labor and delivery records. This approach enhanced data quality by minimizing reliance on historical self-reported outcome data. Coupled with allowing for home visits, we minimized loss to follow-up and its negative effects on data quality.

Despite these strengths, MTN-016 includes some limitations. Our eligibility criteria restrict study enrollment to relatively healthy women, which impacts the generalizability of the registry's findings. In addition, per protocol, we are unable to provide or fund postmortem examinations following intrauterine deaths or infant deaths, limiting our full understanding of the etiology of these events. Lastly, for analyses comparing maternal and infant outcomes by study arm assignment in the parent protocol, the strength of the analysis is dependent upon adherence to study product during the trial. Variable adherence to study product limits the ability to accurately characterize exposure to ARV-based prevention agents in early pregnancy and assess the relationship between exposure to study product and pregnancy and infant outcomes.[2,14]

To our knowledge, this is the first multinational prospective cohort study for women participating in biomedical HIV prevention trials and their infants that performs follow-up on infant outcome data up to one year of age, in a similar fashion across parent protocols, allowing for cross-protocol analyses. Using a registry format, MTN-016 contributes valuable information to support a possible pregnancy/lactation indication for ARV-based prevention products that are shown to be efficacious in preventing HIV infection. Data from several additional MTN studies of the dapivirine vaginal ring, including those with planned exposures in pregnancy, will be integrated into MTN-016 (MTN-025, MTN-042, MTN-043) and may allow for a sufficiently powered statistical analysis of pregnancy and infant outcomes.[15] This is particularly important considering that alternatives such as post-marketing surveillance, may take several years to demonstrate harmful effects of a new product, such as occurred with thalidomide use for treatment of nausea in pregnancy.[16] It is also the first pregnancy registry designed to explore possible development of HIV resistant mutations among infants infected with HIV at birth whose mothers used HIV chemotherapeutic drugs.

Conclusion

We demonstrate that it is feasible to establish and operationalize a prospective, multinational HIV chemoprophylaxis pregnancy registry in a research context in low resource settings. This registry model may offer an additional and potentially less biased approach in which to collect pregnancy and infant outcome data from large-scale efficacy trials enrolling women of reproductive potential, regardless of therapeutic class of investigation.

Author contributions

JEB and RB conceptualized the article and analysis plan. FGM drafted the initial report and all authors LN, SK, RS, JP, HW, KT, EB and SLH contributed to article content and approved the final manuscript.

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Conflict of interest

No potential conflict of interest was reported by the authors.

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References

1 Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science. 2010;329(5996):1168–1174. https://doi.org/10.1126/science.1193748.

2 Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-Based Preexposure Prophylaxis for HIV Infection among African Women. N Engl J Med. 2015;372(6):509–518. https://doi.org/10.1056/NEJMoa1402269.

3 Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women - NEJMoa1506110. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1506110. Accessed March 10, 2016.

4 Nel A, van Niekerk N, Kapiga S, Ring study team. Safety and efficacy of a dapivirine vaginal ring for HIV prevention in women. N Engl J Med. 2016;375(22):2133–2143. https://doi.org/10.1056/NEJMoa1602046.

5 Musekiwa A, Muchiri E, Manda SOM, et al. Pregnancy incidence and risk factors among women participating in vaginal microbicide trials for hiv prevention: systematic review and meta-analysis. PLoS ONE. 2013;8(10):e77014. https://doi.org/10.1371/journal.pone.0077014.

6 Beigi RH, Noguchi LM, Montgomery E, et al. A randomized safety and pharmacokinetic trial of daily tenofovir 1% gel in term and near-term pregnancy. J Int AIDS Soc. 2016;19(1). https://doi.org/10.7448/IAS.19.1.20990.

7 Beigi R, Noguchi L, Parsons T, et al. Pharmacokinetics and placental transfer of single-dose tenofovir 1% vaginal gel in term pregnancy. J Infect Dis. 2011;204(10):1527–1531. https://doi.org/10.1093/infdis/jir562.

8 For Health Care Providers. Available from: http://www.apregistry.com/HCP.aspx. Accessed December 14, 2016.

9 Williams PL, Crain MJ, Yildirim C, et al. Congenital anomalies and in utero antiretroviral exposure in human immunodeficiency virus-exposed uninfected infants. JAMA Pediatr. 2015;169(1):48–55. https://doi.org/10.1001/jamapediatrics.2014.1889.
10 Drake AL, Wagner A, Richardson B, et al. Incident HIV during pregnancy and postpartum and risk of mother-to-child HIV transmission: A systematic review and meta-analysis. PLOS Med. 2014;11(2):e1001608. https://doi.org/10.1371/journal.pmed.1001608.
11 WHO. The who child growth standards. Available from: http://www.who.int/childgrowth/en/. Accessed July 6, 2016.
12 Palmer S, Boltz V, Martinson N, et al. Persistence of nevirapine-resistant HIV-1 in women after single-dose nevirapine therapy for prevention of maternal-to-fetal HIV-1 transmission. Proc Natl Acad Sci. 2006;103(18):7094–7099. https://doi.org/10.1073/pnas.0602033103.
13 AED Pregnancy Registry. Available from: http://www.aedpregnancyregistry.org/. Accessed December 14, 2016.
14 FACTS 001 Phase III Trial of Pericoital Tenofovir 1% Gel for HIV Prevention in Women. CROI Conference. Available from: http://www.croiconference.org/sessions/facts-001-phase-iii-trial-pericoital-tenofovir-1-gel-hiv-prevention-women. Accessed March 10, 2016.
15 Microbicide Trials Network. Available from: http://www.mtnstopshiv.org/. Accessed August 28, 2017.
16 History of Thalidomide - Thalidomide. Available from: http://www.thalidomide.ca/history-of-thalidomide/. Accessed June 14, 2016.