Successful Discontinuation of the Placebo Arm and Provision of an Effective HIV Prevention Product After a Positive Interim Efficacy Result: The Partners PrEP Study Experience

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Background: Dissemination of research results to study participants and stakeholders and provision of proven effective products in the immediate post-trial period are core elements of the conduct of biomedical HIV prevention clinical trials. Few biomedical HIV prevention trials have demonstrated HIV protection with novel interventions, and thus, communication of positive trial results and provision of an effective product have not been tested in many situations.

Methods: In July 2011, the independent Data and Safety Monitoring Board of the Partners PrEP Study, a randomized, placebo-controlled efficacy trial of daily oral antiretroviral preexposure prophylaxis (PrEP) for HIV prevention among 4747 African heterosexual HIV serodiscordant couples, recommended discontinuation of the trial's placebo arm due to demonstration of PrEP efficacy. We describe dissemination of results, discontinuation of the placebo arm, and provision of active PrEP to participants' formerly assigned placebo.

Results: Within 72 hours, of the Data and Safety Monitoring Board meeting the study results were publicly released and disseminated to stakeholders and study participants. Within 3 months, the study protocol was modified to permit participants initially assigned to the study's placebo arm to be offered active PrEP. Of the 1418 participants initially randomized to placebo who were clinically eligible to receive PrEP, 89.1% (1264/1418) consented.

Conclusions: Prompt dissemination of a positive HIV prevention trial result and subsequent provision of effective product to research participants was feasible and efficient for >4700 HIV serodiscordant couples in East Africa. The extent to which study sponsors can assure continued product access to research participants remains a subject of discussion for future HIV prevention clinical trials.

Key Words: HIV prevention trials, Africa, ethics

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INTRODUCTION

Recently, clinical trials of novel biomedical HIV prevention interventions, including vaccines,[1] microbicides,[2] and the use of antiretroviral medications for treatment[3] and as preexposure prophylaxis (PrEP),[4–6] have demonstrated that these strategies hold significant promise for reducing the scale of the HIV epidemic. These biomedical HIV prevention trials have been conducted in the context of guidance documents that address scientific and ethical performance of research, including Good Clinical Practice,[7] Good Clinical Laboratory Practice,[8] the Declaration of Helsinki,[9] The Belmont Report,[10] Joint United Nations Programme on HIV/AIDS (UNAIDS)/World Health Organization (WHO) ethical considerations in biomedical HIV prevention trials,[11] UNAIDS/AVAC Good Participatory Practice (GPP),[12] and numerous local and national guidelines on the regulatory, ethical, and logistical conduct of research.

GPP guidelines provide systematic guidance on the roles and responsibilities of trial sponsors and implementers toward participants and their communities.[12] Two core issues

addressed by GPP are dissemination of trial results to study participants and stakeholders and post-trial access to proven effective HIV prevention products in the immediate post-trial period; these issues are also core to UNAIDS/WHO guidance on the ethical conduct of biomedical prevention trials.[11] To date, however, there have been few examples of communication of positive trial results and ability to promptly provide novel effective product to study participants, and few examples how communication and provision were done.

The Partners PrEP Study was a randomized, phase III, 3-arm, placebo-controlled clinical trial of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC)/TDF PrEP for HIV prevention among African heterosexual HIV serodiscordant couples.[4] In July 2011, the trial's placebo arm was discontinued and the results were reported publicly, after an interim data review demonstrated substantial HIV protection efficacy due to PrEP. We describe the timely execution of our preplanned strategies for results dissemination, discontinuation of the placebo arm, and provision of active PrEP to former placebo arm participants.

METHODS

Ethics Statement

The study protocol was approved by the University of Washington Human Subjects Review Committee and ethics review committees at each of the study sites. All participants provided written informed consent in English or their local language.

Study Population and Procedures

Between July 2008 and November 2010, 4747 heterosexual HIV serodiscordant couples were enrolled in the Partners PrEP Study and followed up at 9 research sites in Kenya and Uganda.[4] The primary aims of the study were to determine the efficacy and safety of TDF and FTC/TDF PrEP, each compared to placebo, for prevention of HIV acquisition. Both single-agent TDF and combination FTC/TDF PrEP were tested because of potential differences in cost and side effects for 2 compared to 1 antiretroviral medication for PrEP and based on preclinical animal model studies that suggested that FTC/TDF may provide greater HIV protection than TDF alone.[13]

Trial eligibility criteria included that couples be sexually active and intending to remain as a couple. HIV-seronegative partners were required to have normal renal function and be not pregnant or breastfeeding. At enrollment, HIV-seronegative partners were assigned in a 1:1:1 ratio to 1 of 3 study arms: once-daily TDF, FTC/TDF, or placebo. The study regimens were indistinguishable and investigators and participants remained unaware of the randomization assignments. HIV-seronegative participants had monthly visits for up to 36 months, including HIV testing, dispensation of study medication, and standardized assessment of sexual behavior and clinical and laboratory safety. Study medication was withheld from women who became pregnant; they were referred for antenatal care and allowed to resume study medication when no longer pregnant or breastfeeding. HIV-seropositive partners were not taking antiretroviral therapy and did not meet Kenyan or Ugandan guidelines for initiation of antiretroviral therapy at the time of study entry.[14,15] HIV primary care services were provided at the study sites or within HIV care centers within the same institution. Those who became eligible for initiation of antiretroviral therapy according to national guidelines were counseled to initiate treatment and actively linked to care at local clinics.

All participants received a comprehensive package of HIV prevention services, including HIV testing with pretest and posttest counseling, individual and couples risk-reduction counseling, screening and treatment for sexually transmitted infections, free condoms with training and counseling, and referral for voluntary medical male circumcision, and post-exposure prophylaxis according to national policies.

The study was funded by a research grant from the Bill & Melinda Gates Foundation to the University of Washington. Gilead Sciences donated the study medication but did not participate in the conduct of the trial. The study protocol detailed that if PrEP were to be effective and safe for HIV prevention that those participants randomized to the placebo arm would be offered 12 months of PrEP medication, donated by Gilead Sciences.

Independent Data and Safety Monitoring Board Review

An independent Data and Safety Monitoring Board (DSMB) met every 6 months to review trial conduct and participant safety as well as PrEP efficacy for HIV prevention according to an interim monitoring plan defined before trial initiation. At an interim review of efficacy on July 10, 2011, the DSMB recommended that the results of the study be publicly reported and the placebo arm discontinued because predetermined stopping rules were met with clear demonstration of HIV protection due to PrEP.

The primary, placebo-controlled results of the trial, using data through July 10, 2011, have subsequently been published.[4] Of 82 postrandomization HIV infections, 17 were among those assigned TDF (incidence 0.65 per 100 person-years), 13 among those assigned FTC/TDF (incidence 0.50 per 100 person-years), and 52 among those assigned placebo (incidence 1.99 per 100 person-years), indicating a 67% relative reduction in HIV incidence for TDF (95% confidence interval: 44 to 81, $P < 0.001$), compared to placebo, and 75% reduction for FTC/TDF (95% confidence interval: 55 to 87, $P < 0.001$).[5] The HIV protective effects of FTC/TDF (75%) and TDF (67%) were not significantly different from each other ($P = 0.23$), and the rate of adverse events was generally similar across the study arms. At the time of the DSMB review, median follow-up participant time was 23 months. Given these results, the DSMB felt that it would be of importance to the field to continue to gain additional information on the relative efficacy, safety, and tolerability of PrEP using TDF versus FTC/TDF. Accordingly, it was recommended that, if feasible, follow-up be continued for those participants randomized to TDF and FTC/TDF and those initially

randomized to placebo be re-randomized to TDF versus FTC/TDF and followed in parallel.

Preparation for Trial Results

Preparation for trial results began before study initiation with planning and stakeholder engagement about study aims, timelines, and potential outcomes and was continued during the trial. Stakeholder activities occurred at the local site level and nationally; international engagement related to PrEP generally was ongoing in parallel, coordinated by organizations outside of the study team, often with participation of study team members. Stakeholder inventories were developed centrally, nationally, and at each site and were updated throughout the study for use as part of a rapid communications plan. Within each study country (Kenya and Uganda), 1 in-country investigator was designated the primary contact to spearhead national stakeholder engagement efforts, including periodic updates during the study. Sites did not uniformly have a dedicated staff person for engagement activities, but rather the planning involved all cadres of site teams, including research staff, outreach teams, and community advisory board members, under the direction of the site investigator. Each site also regularly organized study participant events ("couples' events") throughout study implementation as a forum for provision of updates on study timelines and other operational aspects and to receive participant feedback on various aspects of the study. Finally, the study team prepared comprehensive plans for communication of results before each interim efficacy review by the DSMB.

RESULTS

Immediately following the July 10, 2011, DSMB meeting, the study leadership met to discuss how to implement the DSMB recommendations, specifically (1) public dissemination of the study results, including to participants and stakeholders, (2) initiation of an orderly discontinuation of the study placebo arm, and (3) implementation of a framework for re-randomizing placebo arm participants into the active PrEP arms.

Results Dissemination

During the first 24 hours after the DSMB meeting, study site investigators were informed of the DSMB recommendations and results dissemination materials were developed (available at http://depts.washington.edu/uwicrc/research/studies/PrEP.html). Embargoed release of results to national and international stakeholders (including researchers, policymakers, and advocates) and media began within 48 hours. The results were publicly released approximately 72 hours after the DSMB meeting.

Before public release of the study results, embargoed release of results and dissemination materials was conducted in phases, initially beginning with all lead investigators at each site, followed by other PrEP investigators, ethical regulatory agencies, and key local, national and international stakeholders. Subsequent to public release of results and presentation at a major international HIV conference,[16] dissemination was done through individual and group teleconferences and in-person briefings, workshops, and organized meetings. More than 50 media interviews and organized meetings were conducted and over 100 site-level results dissemination meetings were completed during the 10 days following release of study results, including meetings and/or workshops with health care providers, Ministry of Health officials, community advisory groups, HIV serodiscordant couples support groups, development partners, research scientists, and program leaders in HIV/AIDS.

Discontinuation of the Study's Placebo Arm

Coincident with public release of study findings, participants were notified of the results at each study site through a number of mechanisms, including telephonic contact, daily talks for those participants with study clinic appointments that day, SMS requests to visit study clinics, and organized couples events.

On the day of public release of the trial's results, the study sponsor (University of Washington) sent each research site a listing of study ID numbers of those participants who had been randomized to the trial's placebo arm. Placebo arm participants were discontinued from the study over the course of approximately 6 weeks, primarily at the next scheduled monthly visit. This was done to permit orderly discontinuation of the placebo arm (one third of the total number of study participants, which for the largest sites amounted to over 200 couples) while being able to continue with regular study visits for participants who had initially been randomized to the trial's active PrEP arms. For some sites, tracking all placebo arm participants meant traversing catchment areas of over a 150-km radius, in some cases including boat travel to participants residing on islands on Lake Victoria. By 6 weeks after the DSMB meeting, 95% of placebo arm participants had completed a product discontinuation visit (n = 1417), with the remainder lost to follow-up (Table 1).

Re-randomization to Active PrEP

Immediately following the release of trial results, there were in-country efforts with local regulatory authorities to discuss the need for ensuring timely access to a proven effective product for placebo arm participants. Within 2 weeks of the public release of results, a protocol modification, including new informed consent documents, was developed and submitted to regulatory authorities for review to allow for the re-randomization of placebo arm participants into the active PrEP arms (Fig. 1). By 3 months, all sites had completed regulatory review, which involved 17 ethical review approvals and 9 drug regulatory authority approvals, and initiated re-randomization of placebo arm participants to either the TDF or the FTC/TDF arm.

Overall, of 1584 (621 female, 963 male) participants initially randomized to the placebo arm in the study, 1502 (585 female, 917 male) were alive and had not seroconverted to HIV (Fig. 2). Of these participants, 84 (5.6%; 74 female, 10 male) were deemed ineligible to receive active PrEP,

TABLE 1. Timelines

Activity	Date
DSMB meeting and communication of decision to lead study investigators	July 10, 2011
Study site investigators informed	July 11, 2011
Study site staff informed	July 12, 2011
Confidential communication of results in person and by teleconference to key national and international stakeholders	July 12, 2011
Release of embargoed media materials, media interviews	July 12, 2011
Public release of results	July 13, 2011
Listing of study ID numbers of those participants who had been randomized to the placebo arm provided to each study site	July 13, 2011
Results dissemination to study participants, through one-on-one discussions, phone calls, and group events	July 13, 2011 (initiated)
Discontinuation of study product for placebo arm participants, done at next scheduled monthly study visit	July 14, 2011 (initiated)
Public presentation of study results at an international scientific meeting	July 18, 2011
Completion of a protocol addendum to permit re-randomization of placebo participants to 1 of the 2 active PrEP arms	July 28, 2011
First study site obtained all regulatory approvals to implement the protocol addendum and initiate provision of active PrEP to placebo arm participants	October 5, 2011

primarily due to pregnancy and breastfeeding (which were exclusion criteria for PrEP provision in the study protocol), with 7 (0.5%; 1 female, 6 male) determined to be ineligible due to clinical safety reasons or investigator decision. Thus, 1418 participants (511 female, 907 male) were clinically eligible to receive PrEP. Of these, 1264 (89.1%; 475 female, 789 male) agreed to receive PrEP and continue in the study; they were re-randomized to 1 of the 2 active PrEP arms. Both study staff and participants were blinded to the random allocation within the 2 active arms. One hundred participants (6.7%; 27 female, 73 male) of those considered for re-randomization declined further study participation and 54 (3.6%; 9 female, 45 male) were lost to follow-up and could not be located to be offered active PrEP. Of the 100 participants who declined further participation, 62 gave no specific reason for declining, only 1 declined on the basis of potential side effects of the study medication, while the remainder declined PrEP because they had either relocated outside of the study catchment area, started new relationships, or were no longer willing to participate in the research visits.

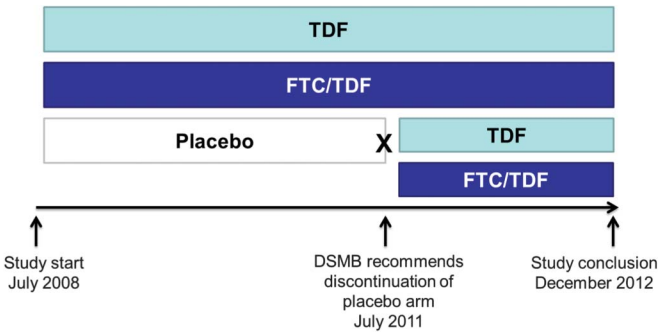

FIGURE 1. Study continuation after DSMB discontinuation of the trial's placebo arm the Partners PrEP Study initiated in July 2008. Participants were randomized in a 1:1:1 fashion to daily oral TDF, combination emtricitabine (FTC)/TDF, or placebo; participants and investigators were blinded to treatment assignment. On July 10, 2011, the trial's independent DSMB recommended discontinuation of the placebo arm due to definitive demonstration of efficacy for HIV protection of the study's active arms. After July 2011, participants originally assigned placebo were re-randomized to TDF or FTC/TDF and those originally assigned to active medication continued in their original arm. Participants and investigators remained blinded to treatment assignment (TDF versus FTC/TDF).

DISCUSSION

In the Partners PrEP Study, demonstration of HIV protection efficacy and safety at an interim DSMB review triggered a series of operational and communications activities, beginning immediately after the DSMB meeting and continuing for several months thereafter. Key aspects of the process concentrated on ethical considerations and essential GPP elements related to results dissemination to stakeholders and participants including provision of access to effective study product. Thus, our experience provides one example of the importance of study team advance planning and site preparation for trial results dissemination, including actions following a positive interim efficacy result for a biomedical HIV prevention intervention. Our study also highlights the opportunities for efficiencies in ensuring timely access to an effective product within a framework of a protocol amendment to an existing protocol.

Proactive community and stakeholder engagement regarding biomedical prevention research is essential ahead of clinical trial results. In the Partners PrEP Study, active stakeholder engagement, at the site, national, and international levels, was started before trial initiation and monitored frequently throughout the trial. The protocol team predetermined these as critical steps to ensuring researchers adhered to core elements in the conduct of HIV prevention clinical trials. When trial results became available, the study team benefited from a strong foundation of community linkages cultivated throughout the study implementation period for dissemination of the study results. Given the importance of the trial's results for HIV prevention researchers, stakeholders, and communities, findings were released quickly, including public dissemination within 72 hours and presentation of the findings at an international HIV scientific conference 8 days after the DSMB meeting.[16]

Trial participants learned of results coincident with public release of information—a decision reflecting the short timeline for release of results, limited time between embargoed release of results to national and international stakeholders ahead of a media release, and challenges in contacting >4700 couples, some of whom lived in rural locations often

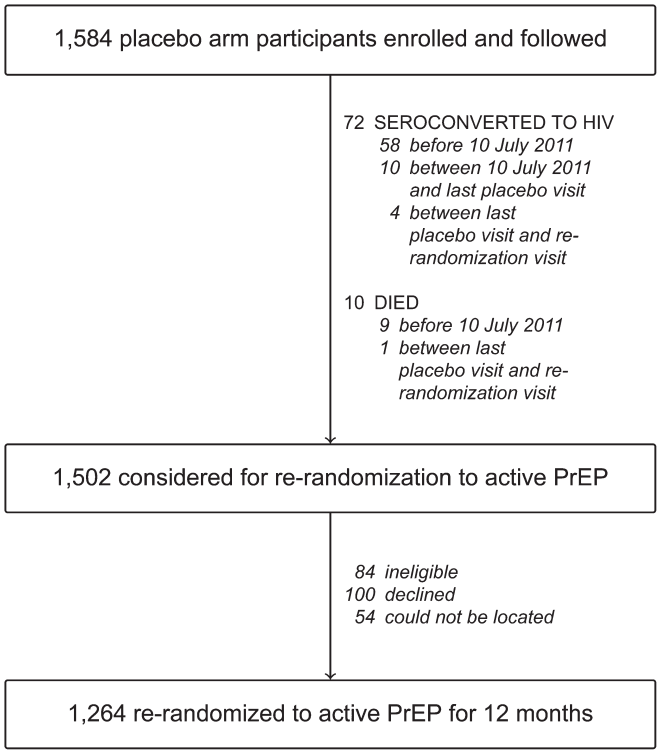

FIGURE 2. Disposition of participants initially randomized to the trial's placebo arm. For the HIV uninfected partners initially randomized to placebo, an offer of re-randomization to active PrEP (TDF versus FTC/TDF) and continued follow-up for 12 months was made. The eligibility criteria required for re-randomization reflected safety considerations laid out in the original trial protocol, including normal renal function and being not pregnant or breastfeeding.

more than 2 hours of travel time from study sites and many of whom did not have phones.

A core principle of HIV prevention trials is that those who participated in research and their communities should be the first to benefit from products demonstrated to be safe and effective for HIV prevention. Study participants are a high priority for access to effective new strategies, through follow-on or open-label studies or other mechanisms. The timing of availability of novel biomedical interventions may depend on product manufacturing timelines, regulatory approvals, and development of normative guidance. There is no global consensus around what advance planning for post-trial access should entail—plans finalized before study initiation versus when a study is underway, access within the trial protocol versus as a separate protocol or document, with up-front funding commitments versus with goals to be reactive to positive results. It is possible that a multiple approaches could achieve similar successful ends. Engagement of researchers, normative agencies, and funders is needed to dialogue on possible mechanisms through which post-trial access can be implemented and the possible duration of post-trial access that should be expected as part of a research study.

In case of the Partners PrEP Study, although the trial protocol detailed that 12 months of active PrEP would be provided to placebo participants if the trial demonstrated safety and efficacy of PrEP for HIV prevention, the specific mechanism was finalized and implemented at the time results became known. Through focused efforts, the study team was able to provide participants access to an effective product within 3 months, which involved a protocol modification to provide a regulatory and research framework for monitoring safety and efficacy during follow-up of participants while on active product. Participants enrolled into the active arms of the trial continued to receive medication and were blinded to their assignments. The implementation of the protocol modification was facilitated by several factors: an open or on-going protocol that could be modified, re-randomization to the same study arms already active in the trial (bypassing the need for new product manufacturing and importation), and the fact that TDF and FTC/TDF were already licensed for treatment in Kenya and Uganda and thus had a foundation of use experience.

In the period between the placebo-controlled results of the trial becoming known and re-randomization of placebo recipients to active PrEP, 14 participants (0.9% of those assigned to placebo in the trial) acquired HIV despite on-going individual and couple HIV risk reduction counseling. This further highlights a need for HIV prevention trials to preplan for timely access to novel biomedical HIV prevention interventions. In case of the Partners PrEP Study, products were already licensed (for HIV treatment) in the trial countries, which facilitated post-trial access. For novel biomedical prevention products, regulatory or manufacturing timelines could delay access to effective prevention strategies. Therefore, where a specific protocol for post-trial access is the modality used, one strategy might be to plan for

regulatory approvals while the main trial is ongoing, to lessen the duration between end of the study and initiation of post-trial access.

Randomization of placebo arm participants to 12 months of either TDF or FTC/TDF PrEP permitted additional data collection to determine the relative safety and efficacy of 1 versus 2 medications as PrEP; such randomization was done within the context of statistically equivalent efficacy results for TDF compared with FTC/TDF and thus equipoise regarding the 2 PrEP drugs. In addition, trial participants initially assigned to the study active arms continued their regular monthly visits without interruption after the July 2011 DSMB meeting and thus had ongoing access to effective PrEP within the context of the study protocol. Of note, some (6.7%) participants declined to receive active PrEP when offered.

Ensuring access to effective biomedical prevention products in the immediate post-trial period to trial participants after a trial demonstrates efficacy and safety for HIV prevention is only a first step in achieving widespread benefits of biomedical prevention interventions. In the Partners PrEP Study, a 12-month post-trial access period was designed as a potential bridge period from trial end to translation of study findings into policy. The study investigators and sponsor had ongoing discussions with in-country policymakers, advocates, and program leaders before, during, and after the trial results to consider in-country mechanisms for access to PrEP for participants and communities beyond the 12-month post-trial access period.

Lessons learned from the implementation of voluntary medical male circumcision following demonstration of its effectiveness for HIV prevention[17–19] indicate that translating new research into policy and widespread practice takes time and timelines may differ by location. Therefore, the period for ensuring access to these effective products remains a subject of debate in current review of GPP guidelines, reflecting lack of certainty as to when specific HIV prevention country policies would be changed to incorporate new scientific findings and resource availability. For future prevention trials, discussions about steps and realistic timelines for implementation planning, if efficacy is demonstrated, should be an important and ongoing part of policymaker engagement. Although PrEP trials were on-going, WHO and UNAIDS, in collaboration with research donors, held a series of scientific and regional consultative meetings in anticipation of trial results.[20] In July 2012, with data from the Partners PrEP Study as a part of the submission package, the US Food and Drug Administration approved a label indication for FTC/TDF as PrEP for HIV prevention.[21] Normative guidance for PrEP use and research priorities from the US Centers for Disease Control and Prevention and the WHO were released in 2012.[22–24] Demonstration projects, providing PrEP to at-risk populations, are being initiated in a variety of settings, including at Partners PrEP Study sites. In addition, discussions are ongoing in multiple countries regarding how to integrate PrEP into national prevention programs and how to monitor PrEP outcomes during implementation.[25] Given the high efficacy, tolerability, and safety of PrEP in adherent populations, countries, government (eg, PEPFAR) and non-government donors, normative agencies, scientists, and other key players should continue to engage regarding access to this effective biomedical intervention.

With multiple novel biomedical interventions in early and late phase testing, including tenofovir gel, the dapivirine vaginal ring, and other PrEP and vaccine strategies, it is anticipated that trials will demonstrate safety and efficacy of additional products for HIV prevention. Learning from experience and anticipating future issues will optimize approaches for results dissemination and post-results access to effective products, particularly for novel products requiring licensure and production scale-up. Advance preparations should continue among researchers, communities, funders, and other stakeholders. The experience of the Partners PrEP Study provides 1 model for results dissemination and provision of access to a novel biomedical prevention intervention. The finding that 89% of eligible placebo participants agreed to be re-randomized to active PrEP, despite having taken part in the trial for a median of 23 months at the time of the DSMB review, testifies to the commitment to research among study communities and to the potential acceptability or desire for PrEP as an HIV prevention strategy.

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APPENDIX. MEMBERS OF THE PARTNERS PREP STUDY TEAM

Partners PrEP Study Team: *University of Washington Coordinating Center*, Seattle, USA: Connie Celum (principal investigator, protocol co-chair), Jared M. Baeten (medical director, protocol co-chair), Deborah Donnell (protocol statistician), Robert W. Coombs, Jairam R. Lingappa, M. Juliana McElrath. *Study sites and site principal investigators*: Eldoret, Kenya (Moi University, Indiana University): Kenneth H. Fife, Edwin Were; Kabwohe, Uganda (Kabwohe Clinical Research Center): Elioda Tumwesigye; Jinja, Uganda (Makerere University, University of Washington): Patrick Ndase, Elly Katabira; Kampala, Uganda (Makerere University): Elly Katabira, Allan Ronald; Kisumu, Kenya (Kenya Medical Research Institute, University of California San Francisco): Elizabeth Bukusi, Craig R. Cohen; Mbale, Uganda (The AIDS Support Organization, Centers for Disease Control and Prevention-Uganda): Jonathan Wangisi, James D. Campbell, Jordan W. Tappero; Nairobi, Kenya (University of Nairobi, University of Washington): James Kiarie, Carey Farquhar, Grace John-Stewart; Thika, Kenya (University of Nairobi, University of Washington): Nelly R. Mugo; Tororo, Uganda (Centers for Disease Control and Prevention-Uganda, The AIDS Support Organization): James D. Campbell, Jordan W. Tappero, Jonathan Wangisi. Data management was provided by DF/Net Research, Inc. (Seattle, USA) and site laboratory oversight was provided by Contract Laboratory Services of the Wits Health Consortium (University of the Witwatersrand, Johannesburg, South Africa).