Published in final edited form as:

Int J Gynaecol Obstet. 2014 November ; 127(2): 221–224. doi:10.1016/j.ijgo.2014.07.012.

Ethical issues for late-stage trials of multipurpose prevention technologies for HIV and pregnancy

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Abstract

Multipurpose prevention technologies (MPTs) designed to simultaneously prevent pregnancy and HIV could provide urgently needed tools to address unmet sexual and reproductive health needs of women worldwide. Late-stage clinical trials will be complex given the need to demonstrate efficacy for HIV and contraceptive indications simultaneously from a single product. Currently, HIV and pregnancy prevention trials have distinctive design features that will need to be reconciled in MPT trials. This article identifies several ethical issues uniquely associated with this research that will benefit from future deliberation and guidance to ensure that this globally important research can proceed efficiently and expeditiously.

Keywords

Ethics; HIV prevention; Multipurpose prevention technologies; Pregnancy prevention

1. Introduction

A coordinated effort is underway to advance the research and development of new multipurpose prevention technologies (MPTs) [1]. MPTs are products that can provide simultaneous protection from two or more reproductive health risks, including pregnancy and sexually transmitted infections (STIs), including HIV [2]. Several MPT products designed to prevent HIV and pregnancy are currently in the early stages of product development, including three vaginal rings [3]. Similarly, work is ongoing to evaluate a single-sized cervical barrier device, the SILCS diaphragm (Kessel medintim GmbH,

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Conflict of interest: With USAID support through the HealthTech Program at PATH, Jessica Cohen has been involved in the research and development of MPT products; with the same support, Jessica Cohen also serves on the Network of Experts of the Initiative for Multipurpose Prevention Technologies (IMPT) and previously co-chaired the IMPT communication committee. Anna Mastroianni serves as a Trustee of the Population Council, New York, USA—a nonprofit organization whose research includes development of MPTs.

Frankfurt, Germany), as a delivery method for tenofovir gel for the dual prevention of pregnancy and HIV [4].

A product that must simultaneously demonstrate efficacy for prevention of both HIV and pregnancy will raise distinctive ethical issues as it moves into later-stage clinical trials, particularly Phase 2b/3 trials to evaluate clinical efficacy. Perhaps most significantly, approaches to HIV prevention efficacy trials and contraceptive efficacy trials diverge in their approach to participants' contraceptive use during the trials. Specifically, pregnancy is a contraindication in most HIV prevention trials because of the unknown risks for a woman and her fetus, and as such, contraceptive use is an eligibility requirement in most HIV prevention trials. In contrast, pregnancy is the primary outcome of interest in contraceptive efficacy trials and therefore eligibility does not include use of contraception. Women are instead asked to use the investigational contraceptive during the clinical trial to determine its efficacy.

Over the last 13 years, clinical trials of HIV prevention methods, such as microbicides and vaccines, have benefited from rich debate about the ethical conduct of this research, resulting in the promulgation of international guidelines [5-7]. The literature, including from regulatory agencies, reveals no specific ethical guidelines for contraceptive research. Existing guidelines on contraceptive development, such as the European Medicines Agency's "Guidelines on clinical investigations of steroid contraceptives in women" [8] provide guidance on trial design but do not make specific reference to ethical issues that may arise in the design and conduct of contraceptive trials. These guidance documents will serve as important foundations for future late-stage HIV/pregnancy MPT trials. However, based on the diverging trial design elements inherent in late-stage HIV/pregnancy prevention trials, these MPT trials will raise new questions. The present article seeks to highlight some of the distinctive ethical considerations that will likely result from these trials.

Just as work is currently underway to identify the regulatory challenges and pathways for MPT development to prompt discussion of possible solutions before products enter the regulatory approval process [9], the present article is intended to serve as a starting point for necessary dialogue around a number of ethical issues likely to arise in the design and implementation of late-stage MPT trials for HIV/pregnancy prevention products ("HIV/pregnancy MPTs"). Raising those issues now will allow concentrated discussions among researchers, ethicists, advocates, communities, and other key stakeholders involved in such trials. Appropriate recommendations can then be developed to support the design and conduct of those trials to anticipate and address ethical challenges and ensure that the trials can proceed as expeditiously as possible.

2. Late-stage clinical trials of HIV and pregnancy MPTs

We begin with the following assumption about HIV/pregnancy MPTs entering late-stage clinical trials: all of the scientific and regulatory requirements will have been met for preclinical and early clinical trials of each component of the MPT product (i.e. for

pregnancy and HIV prevention components, respectively) as well as for the combined HIV/pregnancy product.

As highlighted above, one significant difference between late-stage HIV prevention trials and contraceptive trials lies in the use of contraception among study participants. This specific distinction—and its need to be reconciled for HIV/pregnancy MPT trials—raises several significant ethical questions related to trial design that will require further examination. As discussed below, these include ethical issues related to selection of study populations, risk minimization, prevention standards, and provision of ancillary treatment and care to study participants during and after the trial.

3. Study populations

At the outset, one concern arises in the selection of the appropriate study populations. Late-stage HIV prevention trials are conducted in communities with high HIV incidence to demonstrate whether the investigational product significantly reduces the risk of HIV infection when coupled with other risk-reduction methods (e.g. condom use, STI screening and treatment, and others). In contrast, contraceptive efficacy studies are frequently conducted among populations that are at low risk of HIV and STIs (e.g. monogamous sexual relationships) to minimize the risk of STI infection while focusing on the primary outcome of pregnancy. Approaches to both types of studies are grounded in ethical concerns for the protection of the study participants. Since HIV/pregnancy MPTs will need to establish efficacy in preventing both HIV and pregnancy, these efficacy studies will need to be conducted in populations not only with high HIV incidence but also among women who are not using contraception but wish to prevent pregnancy.

In many regions of the world with high HIV incidence, such as Sub-Saharan Africa where many HIV prevention trials are currently conducted, long-acting methods of contraception (such as injectables and implants) are a preferred method of family planning [10]. The eligibility criteria concerns noted above would deem women using such methods ineligible to participate in HIV/pregnancy MPT trials. This raises a series of important questions: whether women will choose to drop their effective form of contraception in order to be eligible for study participation and to receive the ancillary benefits that the trial may offer (such as health care and access to HIV treatment if needed); whether screening procedures can accurately identify women using long-acting methods to appropriately identify and exclude them; and how women would be counselled if they want to avoid pregnancy and yet are interested in participating in these trials—and, related to this, whether counselling would depend on the contraceptive evidence of the specific HIV/pregnancy MPT as determined in Phase 2 trials. These issues highlight both the importance of extensive community outreach and education about the nature of research and the distinctions between effective, proven forms of contraception and investigational HIV/contraceptive methods being evaluated in such trials. It also points to the need for appropriate screening methods to accurately determine contraceptive status and fertility intentions among prospective participants. Much work has gone into understanding predictors of pregnancy within microbicide trials [11]. These lessons can benefit future HIV/pregnancy prevention trials by helping to ensure the

right questions are asked and appropriate eligibility criteria for selecting participants are identified.

4. Minimizing risks to research participants

In the case of late-stage trials for HIV/pregnancy MPTs, the primary known risks to women include becoming pregnant and/or contracting HIV while participating in the trial. While these risks are not new to HIV or pregnancy prevention trials independently, trials for combination products may be unique in that women are necessarily vulnerable to both of these significant risks as part of their study participation. As such, the trials will need to consider appropriate measures to minimize risks so that the potential benefits of the research outweigh the risks to individual participants. These are the factors that research ethics committees must take into account in determining that risks are reasonable in light of potential benefits.

There are several potential approaches to minimize risk that may be worthy of consideration. In the field of HIV prevention research, testing of new prevention modalities has always been accompanied by existing methods of risk reduction, such as condom provision and counselling. However, while condoms provide a significant risk reduction measure in the context of HIV prevention trials, it is our understanding that they are not routinely provided to women in contraceptive trials. The integration of condom provision and counselling into HIV/pregnancy MPT trials will thus require discussion. If provided for the purpose of HIV risk reduction, condom use could be recorded and factored into the efficacy analyses for both HIV prevention (as currently done in microbicide trials), as well as for pregnancy prevention (as is currently done in contraceptive trials).

Risks to women can be minimized further by testing for both pregnancy and HIV on a frequent enough basis to promptly detect either event and discontinuing the study product should either event occur. There are multiple rationales for this approach. First, if a woman contracts HIV during the trial and is exposed to a hormone/antiretroviral (ARV) combination product (assuming the ARV is also used for HIV treatment), this raises concerns about future resistance to this same ARV if needed for future HIV treatment. The microbicide field has been particularly attentive to the importance of evaluating a variety of ARV-based drugs for HIV prevention to address concerns over resistance to first-line treatment regimens [12,13]. The MPT field will also benefit from attention to measures to address drug resistance, as many ARV-based microbicide products are being paired with hormones or other pregnancy prevention modalities in MPT development [3]. Unknown risk to the pregnant women and her fetus exists from the investigational HIV/pregnancy prevention product (and thus the contraindication of pregnancy within HIV prevention trials). Even with regular HIV and pregnancy testing within trials, there is a possibility that some women would be exposed to the MPT before their pregnancy and/or seroconversion is detected.

Risk minimization considerations point to the importance of establishing observational study registries for women who become pregnant within late-stage HIV/pregnancy MPT trials. From an ethical standpoint, women should be offered the option of enrolling in these

registries to enable regular monitoring and follow-up during the pregnancy to ensure that safety concerns are promptly identified and addressed. Such is the case, for example, in the ASPIRE trial (Phase 3 microbicide trial of dapivirine ring) where this type of registry is collecting data on outcomes of pregnancies that unintentionally occur during the trial [14].

It is also likely that both pregnant and HIV-positive women will use future HIV/pregnancy MPTs once these products are introduced commercially, whether it is for only one of the established indications (e.g. pregnant women using the MPT for its HIV prevention indication), or whether it is product use without knowing if they are pregnant or HIV positive. This possibility raises other significant questions about the appropriate types of safety studies, as well as when and how they should be conducted to further address risk minimization concerns.

Notably, in the microbicide arena, while trials have regularly discontinued the study product among women who become pregnant, increasingly it is recommended that rigorous research of microbicide products be carried forward in pregnant women, allowing for eventual approval for use in pregnant women [15-17]. The Microbicide Trials Network (MTN) has initiated such research, including a Phase 1 study assessing the pharmacokinetics and placental transfer of tenofovir 1% gel among healthy pregnant women at term; the MTN is currently conducting the first expanded safety study of tenofovir 1% gel during pregnancy and lactation [18]. Research on the safety of interventions during pregnancy and lactation is an important, ethically grounded advance in this area of clinical trials and in this case is taking place concurrent to the Phase 3 trial of tenofovir 1% gel. These trials can serve as a reference for future HIV/pregnancy MPT trials.

The ability to minimize risks also depends on a sound understanding of the actual risks associated with the combination product. Those risks are not always clear, even after extensive preclinical or clinical testing, as is true for single-indication HIV prevention or contraceptive methods, much less multi-indication HIV/pregnancy prevention products. This is particularly relevant for questions about potential drug-drug interactions between the HIV and pregnancy prevention product components (e.g. hormonal contraceptives and ARV-based drugs) [19] as well as for the potential association between certain forms of hormonal contraceptives (e.g. depot medroxyprogesterone acetate, DMPA) and HIV risk [20, 21]. How to approach these and many other safety questions in an ethically appropriate manner should be decided through concerted discussion among researchers, regulatory bodies, scientists, communities, and other key stakeholders engaged in HIV and pregnancy prevention research, including those currently investigating possible linkages between hormonal contraceptives and HIV risk [22].

5. Standards of prevention

There is already broad consensus that provision of concrete and appropriate benefits to trial participants and their communities is a critical component of the ethical conduct of HIV prevention research in resource-limited settings [7,23,24]. In addition to the potential benefits that can accrue from the experimental product itself, other types of benefit are recommended. The latter are sometimes referred to as “indirect” or “ancillary” benefits

[6,25]. In this light, standards of prevention for HIV prevention trials have evolved from recommending more limited prevention packages focused on HIV prevention modalities in early vaccine trials [5,6] to more comprehensive prevention packages that also include family planning, pregnancy, and childbirth services that have been implemented in later microbicide trials [7]. Within the context of HIV/pregnancy MPT trials and the populations in which these trials will likely occur, there is a similarly strong ethical rationale for provision of this broad comprehensive prevention package to trial participants. Additionally, with the US Food and Drug Administration approval of emtricitabine/tenofovir disoproxil fumarate (TDF/FTC) in 2012 and the potential for tenofovir 1% gel to be validated and approved in the near future, stakeholders involved in HIV/pregnancy MPT trials will need to determine whether and how to factor these and other new HIV modalities into their prevention packages and trial design. Although current ethical guidance states that new HIV prevention methods should be added to the prevention package “as they are scientifically validated or as they are approved by relevant authorities” [7], this guidance leaves open how to operationalize this recommendation within trials. To address this gap, efforts have been made to bring together researchers, ethicists, advocates, and policymakers to build consensus and develop tools that can be used for decision-making with regard to when to include new HIV modalities in future HIV prevention trials [26,27]. The resulting guidance will provide a critical foundation for these questions as they relate also to HIV/pregnancy MPT trials.

Once prevention packages are made available to trial participants, an ethics question arises regarding post-trial sustainability. In many places where trials are conducted, elements of the prevention package may not be readily available in the community. However, the infrastructure needed to implement the prevention modalities may be established for the MPT trial as a first step and later expanded not only for the trial participants themselves but also for the wider community. Capacity building is widely acknowledged as a necessary accompaniment to research conducted in low- and middle-income countries [6,7]. This paves the way for ongoing provision of prevention modalities to trial participants and expansion in the wider community.

6. Ancillary care and treatment

The most recent ethical guidelines for HIV biomedical research have highlighted the obligation of study sponsors to ensure access to internationally recognized optimal care and treatment regimens, including ARVs for participants who seroconvert in trials, provision of prevention of mother-to-child HIV transmission services, as well as reproductive health care for pregnancy and childbirth (among other services) [7]. This guidance draws on the ethical principles of beneficence and justice, ensuring both that the welfare of participants is actively promoted and that all participants—regardless of their setting—are treated equitably with respect to access to care and treatment [7].

One standard objection to the level of care and treatment recommended in these guidelines is that they call for a higher level in the conduct of HIV prevention research than is routinely available to the majority of the population. However, in recent years, there have been important advances in how research sponsors and partnering national governments have

responded to provision and scale-up of HIV treatment and care within HIV prevention trials. In a review of microbicide trials sites, it was found that sites that partnered with, or located trial sites within existing government care facilities were able to provide the widest range of HIV services [28]. In one microbicide trial site in Benin for example, strong partnerships between the study sponsor and government enabled access to complete HIV care and antiretroviral therapy (ART) at the trial site, both for women who seroconverted during the trial, as well as those who screened out as HIV positive. The same services were provided for women and men in the community who were not participating in the trial but who were HIV positive. Service provision in this context was possible as the study clinic was integrated into an existing STI clinic that was also one of the national AIDS care centers [28]. Such experiences from the microbicide arena can again serve as important models for future HIV/pregnancy MPT trials.

Another objection sometimes raised is that provision of ancillary care and treatment—such as providing ART to participants who become infected during a trial—can constitute an undue inducement to participate in the research. This objection has little merit since women entering the trial are uninfected at the time of enrolment. Moreover, the hope of being protected against HIV and pregnancy can be a likely motivation for women to enroll in MPT research. If such an expectation could also count as an undue inducement, it would lead to the conclusion that these and other prevention trials could not ethically be conducted.

It could be argued that HIV/pregnancy MPT trials have an even greater obligation to provide comprehensive services given that as a prerequisite for enrollment, women in these trials are simultaneously at risk for both pregnancy and HIV. Based on this, HIV/pregnancy MPT trials should also offer women a range of pregnancy and childbirth services, including access to services for termination of pregnancy [28]. While this approach may necessitate conducting these trials in settings where pregnancy termination is safe, legal, and available—thereby limiting the locations where these trials could occur—this trade-off may be vital to ensuring that the welfare of women who become pregnant during the trial is adequately protected [7,27].

As noted above, ethical guidelines for HIV prevention research have cited the obligation of study sponsors to ensure access to internationally recognized optimal care and treatment regimens for participants who seroconvert in HIV prevention trials. In the case of HIV/pregnancy MPT trials, these guidelines oblige sponsors to provide similar comprehensive care and treatment, including ARVs, to women who seroconvert during these trials or who seroconvert *and* become pregnant. The question about study obligations for women who are found to be HIV positive at study screening is ongoing, and to date microbicide trials have provided a wide range of care and treatment options [28]. This question will also be relevant for HIV/pregnancy MPT trials. In addition to the inputs from researchers, advocates, regulators, and others involved in these trial designs, these essential decisions will require the involvement of key national stakeholders where the trials will take place to determine whether and how long-term care and treatment options can be provided to trial participants, given that their provision may be required long after the trial has ended.

Continuing provision of care and treatment for those who still need it after the completion of MPT trials poses the same question of sustain-ability as arises for prevention modalities. Here again, the capacity building that should occur during the trial is a first step in expanding care and treatment to the wider community. Practical guidance already exists in a how-to manual prepared as part of the Partnering for Care Project undertaken by the HIV Prevention Trials Network (HPTN) and FHI 360 [29]. Efforts such as this demonstrate the feasibility of sustaining benefits to participants after their participation in the trial has ended.

7. Conclusion

HIV/pregnancy MPT trials will raise new, distinctive ethical questions relevant to trial design that warrant further attention and consideration. While the research and development of HIV/pregnancy MPTs continue to advance, there should be a concerted, coordinated effort to discuss the issues raised here and other relevant ethical issues pertaining to these trials such that guidance can be developed in time to support future Phase 2b and Phase 3 trials of these products. This will contribute not only to the expeditious conduct of future research of HIV/pregnancy MPTs—which is critical for bringing new, needed prevention options to women around the world—but also to ensuring that the highest levels of safety and well-being are afforded to the women and communities who participate in this research.

Acknowledgments

Jessica Cohen's work was supported by the United States Agency for International Development (USAID) under the terms of the HealthTech Cooperative Agreement #AID-OAA-A-11-00051. The contents are the responsibility of PATH and other authors, and do not necessarily reflect the views of USAID or the United States Government. Anna Mastroianni's work was supported by the National Institutes of Health (NIH Grant no. 1 R56 AI108368-01).

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