- **Maintain investment in community engagement.** Clinical trials are invaluable to advancing the search for an AIDS vaccine. And clinical trials of the complexity anticipated in the future cannot happen without robust, well-funded stakeholder engagement. Yet various aspects of stakeholder engagement are being scaled back. The US NIAID has cut funding for its engagement on prevention research with US community-based organizations—a decision that is penny-wise (no new trials are planned in the US) but pound foolish (stakeholder engagement cannot be switched on and off—it depends on sustained investment).

Hormonal contraceptives and HIV risk: Invest in a complex trial

Over the past year, AVAC has intensified its work in the area of hormonal contraception and HIV risk. We see this issue as fundamental to effective HIV prevention for women. It is one where action must be taken, even in the midst of uncertainty. As the figure on page 29 shows, there are mixed data concerning the relationship between injectable progestogen-only hormonal contraceptives like Depo-Provera and HIV risk. Some studies suggest that this method increases women's risk of acquiring HIV, others do not.

The two main issues in this arena are: how to proceed in the context of uncertainty and whether to attempt to conduct a randomized controlled trial that might eliminate some of this uncertainty. In terms of what to do next, there are immediate steps, such as moving to increase method mix—the range of family planning options that women can choose from. At present, roughly 60 percent of women in sub-Saharan Africa use injectable contraceptives. This option is discrete and long-acting. It is selected and, given available options, preferred by many women. Many family planning programs in sub-Saharan Africa offer women few other choices—perhaps the contraceptive pill, which requires daily use, and condoms. In the context of limited choices, it is hard to know which options women actually prefer.

Another next step must be providing practical information to policy makers and service providers about how to operationalize the 2012 WHO technical guidance note on hormonal contraceptives,[2] which included new language on progestogen-only contraceptives specifying that women who are at high risk of HIV should be strongly urged to use condoms when using this method. Nearly two years after the guidance note was issued, there has been less-than-satisfying progress in this area. WHO had initially committed to developing a communications strategy; the work is being finalized in partnership with Johns Hopkins University, and a strategy is expected in 2014. Unfortunately, there has been scant involvement of civil society in this latest process even though many women's groups involved in a 2012 consultation on the topic had clear recommendations and expertise that should have been incorporated.

These steps won't address the underlying question about whether specific hormonal contraceptives increase HIV risk. Here, the major question is whether to attempt a randomized controlled trial that would seek to answer the question of how various methods, including Depo-Provera, impact HIV risk. WHO, FHI 360, Wits

[2] World Health Organization. "Hormonal Contraception and HIV: Technical Statement." *http://whqlibdoc.who.int/hq/2012/WHO_RHR_12.08_eng.pdf.* Accessed November 27, 2013.

Reproductive Health & HIV institute (WRHI), University of Washington (UW), Statistical Center for HIV/AIDS Research & Prevention (SCHARP), Eastern Cape Department of Health/University of Witwatersrand/University of Fort Hare, International Centre for Reproductive Health/University of Nairobi, Kenya Medical Research Institute (KEMRI), and University of Zimbabwe are collaborating on the trial. The Bill & Melinda Gates Foundation (BMGF) has committed US$30 million—about half of what the trial, as it is currently designed, is expected to cost. Unless full funds are committed, the trial design may be scaled back or it may not happen at all.

The proposed trial, known as Evidence for Contraceptive Options and HIV Outcomes, or ECHO, would randomize women to receive one of four effective long-acting contraceptives: Depo-Provera (a long-acting progestogen-only injectable), NET-EN (another injectable), Jadelle (an implant), or a copper intrauterine device (IUD). HIV incidence will be compared across all four arms. This design would gather information on each strategy. The oral contraceptive pill, which also contains synthetic hormones, isn't being evaluated; it is not long-acting and is less feasible for many women. The copper IUD is the only method among the four that does not contain any synthetic hormones. (Hormones alter women's genital tracts—regulating the menstrual cycle and the immune environment and altering the thickness and other aspects of the vaginal wall and cervix. If a link exists between any of the hormonal contraceptive options and HIV risk, it is likely related one of these interactions, which don't occur with non-hormonal methods like the copper IUD, the diaphragm or condoms.)

ECHO could provide answers as to whether use of any of these methods increase women's risk for HIV. This is important. The absence of data on other hormonal contraceptive methods does not mean that they have no impact on HIV risk. Technologies like NET-EN and Jadelle have not been widely used, so there's been less opportunity to collect the kind of observational data that exists for Depo-Provera. Without a trial like ECHO, there will continue to be open questions about these methods, too.

There are pros and cons to moving ahead with ECHO. On the one hand, the trial is the best hope of getting a clear answer about how different methods impact HIV risk. Without the trial, there will always be an open question about Depo-Provera—and about the hormonal methods that might become more widely used.

On the other hand, there is the argument that resources required to fund the trial would be better spent on expanding method mix. South Africa has already taken steps to move away from Depo and increase the use of other methods with a revised contraception policy that emphasizes an increase in other methods such as implants and the IUD.[3]

However, South Africa is one of only a handful of countries in sub-Saharan Africa that has the resources to implement an expanded method mix independent of donor policy, and it is not clear that funders or national policy makers will shift away from Depo in the absence of more concrete data. Nor is there information about how many of these methods affect HIV risk.

[3] Department of Health, Republic of South Africa. National Contraception and Fertility Planning Policy and Service Delivery Guidelines. *http://www.doh.gov.za/docs/policy/2013/contraception_fertility_planning.pdf, 2012.* (Accessed November 27, 2013).

Valid questions exist about the trial, many of which have been raised by African civil society advocates closely tracking the issue. Would women accept being randomized? Would they remain on the method for the full 12-month duration that trial planners say would be needed to get a clear answer? Would some or all of the methods be available to women once the trial was concluded, even if they had not previously been part of the country's contraceptive package?

Advocates have also raised questions about acting on the outcomes. Widespread introduction of the copper IUD, for example, would entail implementation challenges similar to those seen with voluntary medical male circumcision; both involve staff training, a simple medical procedure and a range of supplies that are not routinely on hand in most resource-poor settings.

The reality is that, unless additional resources are forthcoming, these questions are moot. The trial will not proceed, or it might be scaled back to a two-arm design comparing Depo to a copper IUD. In AVAC's view, the trial design should not be decided by finances. A four-arm trial will provide valuable information; a two-arm trial won't provide necessary information about other hormonal methods. Seeking multiple donors is ideal, but having other stakeholders demonstrate support for a research concept by chipping in shouldn't be a prerequisite for every trial, and probably shouldn't be for this one. If the trial budget isn't met by outside sources, the BMGF should strongly consider paying for it in its entirety. The design should incorporate clear stopping rules—so that if women participants discontinue or switch methods at rates that make the trial unfeasible, it can be stopped without delay.

At AVAC, we think this four-arm trial should move forward. The information that it stands to provide could shape global family planning programs in ways that expand women's options, addressing both family planning and HIV prevention needs. It is important to try to gather information that can be used to ensure that women have access to the best and safest family planning methods. If Depo-Provera does not increase risk, it should remain an option for those who like it, and if Depo-Provera does increase risk a move to other methods could reduce women's HIV risk in high-incidence settings in sub-Saharan Africa.

It may turn out that it is not feasible because women choose not to enroll and/or to remain on the options to which they are randomized. But the trial can be designed so that this becomes apparent sooner rather than later. We also recognize that there isn't consensus among civil society on the issue—and that more women's groups need to weigh in. For this reason, it is also essential that there be extensive, meaningful stakeholder engagement about this trial and the broader constellation of issues related to hormonal contraception and HIV. The ECHO trial, method mix expansion, and a clear communications strategy on the WHO technical guidance need to be discussed in a single conversation, and addressed in a single agenda.

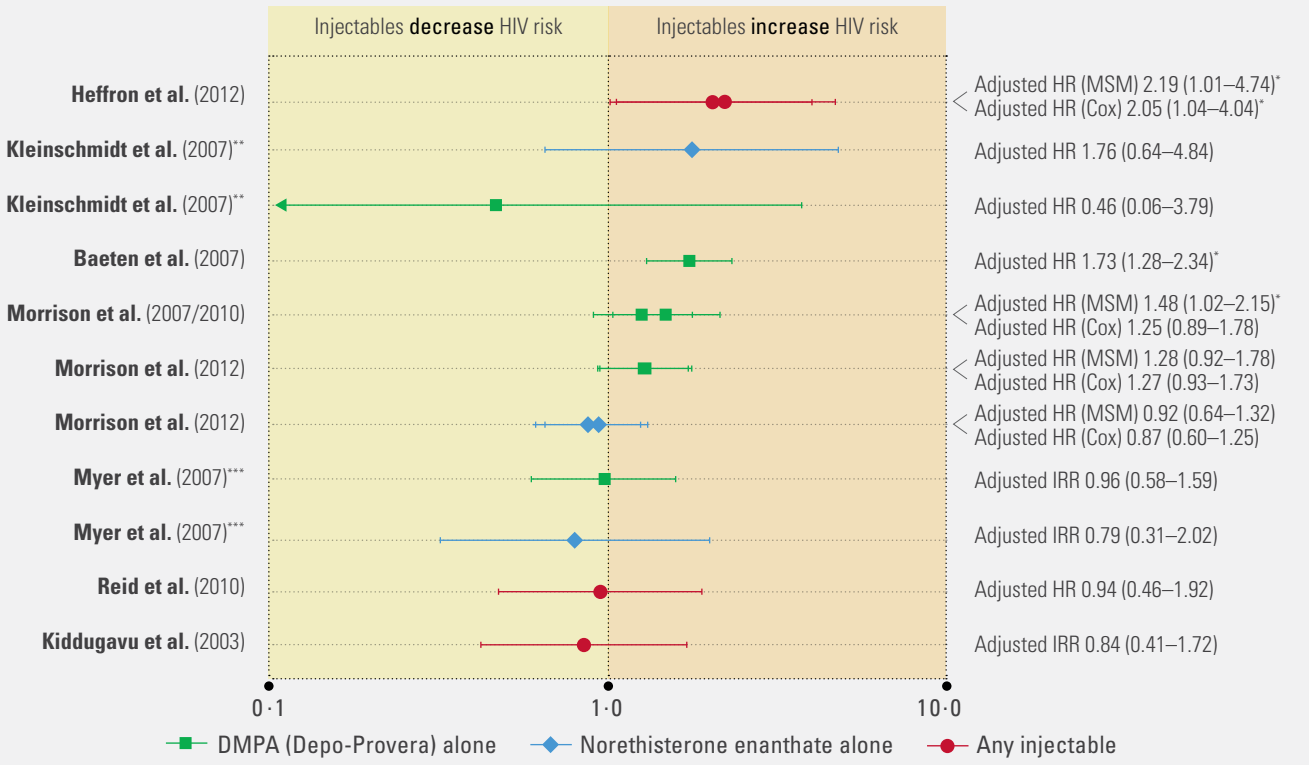
ECHO will have much in common—sites, countries, communities—with research on female-initiated methods. If the trial moves forward, it will be essential to conduct and mine the research described in first section of the Report. This includes exploring women's views of research, trust or lack thereof with respect to specific trials and research in general, and expectations and concerns about preserving fertility versus accessing state-of-the-art gynecological care.

Key next steps include the following:

- **New or existing donors should commit resources for the four-arm trial.**
- **The ECHO team should develop a formal relationship with a women's civil society steering committee** or task force that is pan-African and independent of site-specific community advisory mechanisms.
- **The ECHO team should use Good Participatory Practice (GPP) guidelines to structure stakeholder engagement** designed to determine whether the trial should happen and what its should design should be. GPP should be implemented throughout the trial if it moves forward.
- **Funders, researchers and advocates need to "connect the dots" among the ECHO trial, the uncertainty about hormonal contraceptives and HIV risk, and Family Planning 2020 (FP2020) initiative.** FP2020 is a multiyear, multimillion dollar initiative to expand access to family planning worldwide. FP2020 is focused on expansion of long-acting methods like Depo-Provera that are discrete and sought out by many women. FP2020 hasn't explicitly addressed the issue of hormonal contraceptives and HIV risk. Harmonized messaging on how FP2020, HIV prevention, the ECHO and uncertainty about Depo-Provera and other methods fit together is essential.

Use of Injectable Contraceptives and HIV acquisition: The data to date

This graphic summarizes the results of studies that gathered information on the relationship between injectable hormonal contraceptives and HIV risk. Different studies have drawn different conclusions. This is the reason for current uncertainty. None of these studies was designed to specifically evaluate this interaction. Discussions about a trial that would directly address the question are underway.



Source: CB Polis and KM Curtis. "Use of hormonal contraceptives and HIV acquisition in women: a systematic review of the epidemiological evidence." The Lancet (2013) *http://dx.doi.org/10.1016/S1473-3099(13)70155-5*