The number of women living with HIV/AIDS is increasing worldwide, and there is an urgent public health need to develop new user-initiated HIV prevention methods, including microbicides. Although funding for microbicide development has increased since 2000, financial support is provided predominantly by governmental agencies and private foundations. Many donors, including the US Agency for International Development (USAID) and the US National Institutes of Health (NIH), have policies that restrict how research funds may be used. Among these are the now-rescinded Mexico City Policy, elements of the US Foreign Assistance Act, and restrictions on non-study-related care. The effect of these restrictions on the design and conduct of clinical research is poorly understood. As part of a recent mapping exercise conducted by the Global Campaign for Microbicides, we reviewed the impact of donor restrictions on seven HIV prevention trials. We found considerable confusion within the HIV prevention field as to whether and how Mexico City and other policies affect the use of research funds. We also found that these donor-imposed policies limited the level of care provided to trial participants and the types of capacity building projects undertaken.

Introduction

An estimated 33.2 million people were living with HIV/AIDS by the end of 2007, with 12 HIV-positive women for every 10 HIV-positive men (UNAIDS, UNFPA, et al., 2004; UNAIDS and WHO, 2007a, 2007b). The disproportionate impact of HIV on women is due to a variety of biological and socioeconomic factors that make current HIV prevention tools—condoms, mutual monogamy and male circumcision—inaccessible to many (Pettifor et al., 2004; UNAIDS, UNFPA, et al., 2004; Wawer, 2008). Thus, there is a desperate need to develop new user-controlled tools to enable women and other at-risk individuals to protect themselves. Among the most promising are microbicides—substances that could be used vaginally or rectally to reduce sexual transmission of HIV.

No safe and effective microbicide is currently available on the market. Several candidate products, developed primarily for vaginal use, have been through human safety and effectiveness testing and several new antiretroviral-based products have entered human testing (AMD, 2009). Recently, a Phase 2B clinical trial of a topically applied tenofovir-based gel demonstrated effectiveness in protecting women against sexual transmission of HIV, but additional safety and effectiveness
studies will be required before the microbicide can be made widely available (Karim et al., 2010).

Funding to support microbicide development and testing comes primarily from public and philanthropic sources. In 2007, public donors like the US Agency for International Development (USAID), the US National Institutes of Health (NIH), the European Commission and various European governments accounted for 90% of the total US$226.5 million investment. Philanthropic organizations like the Bill & Melinda Gates Foundation accounted for 8%. Only 2% of the total investment in 2007 came from pharmaceutical companies and other commercial entities (HIV Vaccines and Microbicides Resource Tracking Working Group, 2008).

Before entering human trials, candidate microbicides undergo an expansive series of preclinical laboratory and animal studies (Bains, 2004). Clinical testing is even more extensive and occurs in a phased fashion (Barton and Emanuel, 2005). Late-stage effectiveness trials of candidate vaginal microbicides are particularly time-consuming, enrolling 3,000 to more than 10,000 women at high-risk for sexual acquisition of HIV (Weber et al., 2005). Such trials often occur at multiple sites in communities in sub-Saharan Africa where the underlying rate of HIV infection exceeds 2 per cent per year. Given the costs of mounting clinical trials in these communities, many of which lack well-developed healthcare and research infrastructures, a single Phase 3 trial of a candidate microbicide can cost over US$50 million.

To fund such expensive trials, research networks obtain financing and resources from multiple donors, including philanthropic organizations, national governments and international agencies. Each donor organization, however, has differing interests, legal mandates and policies that influence the design and conduct of clinical trials.

In this article, we examine the impact of donor-imposed requirements and restrictions on the design and execution of clinical HIV prevention trials. Previous discussions of this and related topics have, for the most part, taken place in academic settings without consideration of the real-world context in which the trials occur. Despite ongoing debate around what is now termed ‘standard of prevention and access to care’ (UNAIDS and WHO, 2007), information on how individual trial networks and research sites address these questions is limited (Macklin, 2008). Here, we examine evidence taken directly from interviews of researchers grappling with the needs of participants and their communities.

Methodology

To collect evidence from the field and inform discussions regarding the ethical design of future HIV prevention trials, the Global Campaign for Microbicides (GCM) began an exercise in 2006 to map the standards of prevention and access to care in seven then-ongoing Phase 2B and 3 microbicide and cervical barrier trials: CONRAD’s trial of 6% cellulose sulfate gel, Family Health International’s (FHI’s) trials of 6% cellulose sulfate gel and 1% SAVVY® (C31G) gel, the HIV Prevention Trial Network’s (HPTN’s) trial of 0.5% PRO2000/5 gel and BufferGel, the Microbicide Development Programme’s (MDP’s) trial of 0.5% and 2% PRO2000/5 gel, the Population Council’s trial of Carraguard® gel and the Global Women’s Health Imperative-University of California San Francisco trial of the Ortho All-Flex® Arcing Spring latex diaphragm & Replens® lubricant gel (the MIRA trial) (Heise et al., 2009). The majority of these studies were funded by US sponsors, primarily USAID and NIH, so the primary focus of this article is thus on US regulations and/or donor policies. However, given that most large Phase 2B and 3 trials of new HIV prevention tools are funded by multiple donors, and almost always include a US-based sponsor like USAID or NIH, it is important even for non-American researchers to understand the impact of US regulations and donor policies on the design and conduct of clinical trials.

The mapping exercise was conducted in three phases. First, a desk review of key documents was conducted. The documents included all study protocols, all site-specific and study-wide standard operating procedures (SOPs), all training manuals for staff, all trial and donor policy and guidance documents and all applicable national and international laws and regulations. Second, interviews of key international staff and study sponsors were conducted by phone. Key informants included at least one principal investigator from each of the key sponsors of these seven clinical trials, as well as experts in clinical trial ethics and national and international regulators and policymakers. Finally, visits to trial sites in four African countries were performed. These sites included: a CONRAD trial site in Cotonou, Benin, the HPTN and MIRA sites in Harare, Zimbabwe, two MDP sites in Mtubatuba, South Africa and Mwanza, Tanzania and two Population Council trial sites in Gugulethu and Soshangue, South Africa. These sites were chosen to provide a comparative sample of different sites and study populations across...
Eastern, Western and Southern Africa: newly established sites versus long-standing research collaborations, urbanized settings versus rural outposts and sites enrolling higher risk women like sex workers versus sites recruiting lower risk women from primary health clinics. Site visits included reviews of all site-level study protocols and operating procedures, reviews of other site-level study documents like consent forms and training manuals, interviews of local study investigators and staff (including study clinicians, research coordinators and participant recruiters), and visits to study clinical facilities and local care and support facilities that serve the trial communities and to which study participants are referred for additional care.

For the purposes of collecting data, a structured review and interview guide was developed that looked at nine different content domains, including a domain that examined the role and expectations of donors and policymakers in the design and conduct of the research trials. A copy of this structured review and interview guide is available upon request. For this analysis, we focused in particular on two questions: do donors have policies related to standard of prevention or access to care in the context of HIV prevention research? And, to what extent do donor-imposed requirements or restrictions affect prevention, treatment and care-related decisions at trial sites?

Results and Discussion

Donor Expectations for Prevention and Access to Treatment and Care

In our review of policy and guidance documents, we found few donor policies that clearly established a minimum standard of prevention and/or access to care for HIV trial participants. These policies generally were limited to discussions about access to anti-retroviral treatment (ART) and did not address other care-related concerns. The British Department for International Development (DFID) and the Medical Research Council (MRC), for example, expect HIV prevention trials to occur in countries where the public health infrastructure exists to provide ART and HIV-related care to trial participants (MRC, 2008). The French Agence Nationale de Recherche sur le Sida et le Hépatites Virales (ANRS) has a similar expectation, and will only fund HIV prevention trials conducted in communities where public ART programs are available (Bazin, 2004). Sponsored studies are not required to pay for treatment or care, however; trial participants identified as HIV infected at screening or during the study are referred to existing local clinics.

The largest public funder of microbicide research, the NIH, has no policies that establish a minimum level of prevention and care for HIV prevention trial participants. In 2005, the NIH did release a guidance document that requires that treatment studies in developing countries ‘address the provision of antiretroviral treatment to trial participants after their completion of the trial’ (NIH, 2005: n.p.), but this document does not establish a minimum standard of post-trial access nor does it address HIV prevention research. In fact, the NIH maintains that its authority to ‘encourage and support research’ (General Provisions Respecting National Research Institutes, 42 USC § 284) does not extend to mandating or paying for continued antiretroviral treatment following the completion of a clinical trial (NIH 2005, n.p.). Most NIH-funded trials simply refer trial participants to externally-funded treatment clinics for post-trial care (Shah et al., 2009).

Some donors do have requirements for ensuring post-trial access to effective products. To obtain funding from the Bill & Melinda Gates Foundation, grantees must submit a ‘global access strategy’ that includes a discussion of intellectual property (IP) rights. Some Gates-funded contracts also grant ‘march-in’ rights, allowing the Foundation to insist that sponsors grant IP licenses to an alternative public or private sector entities if the original sponsor is unable or unwilling to develop the product for public distribution. Similarly, USAID-funded researchers are expected to make ‘reasonable efforts’ to ensure continued availability of effective products in trial communities, including negotiating with potential manufacturers to obtain affordable pricing (USAID, 2009a). To date, neither of these donors has found it necessarily to exercise their ‘march-in’ rights but it may be necessary in the future.

Donor Policies that Restrict Access to Prevention or Access to Treatment and Care

Although we found few donor policies that established clear standards of prevention or access to treatment and care for trial participants, we found numerous examples where general policies or uncertainty about donor expectations influenced decisions about what care to provide trial participants, including restrictions on: (i) family planning activities; (ii) HIV/AIDS prevention activities; (iii) provision of non-study-related care; and (iv) construction of new facilities in foreign countries.
Restrictions on US-Funded Family Planning Activities

We encountered confusion among trial staff about what sites could provide with respect to counseling on pregnancy options, including information or referral for termination. Two general US policies touched on this matter: the Mexico City Policy and the US Foreign Assistance Act. At the time the mapping exercise was conducted, the Mexico City Policy (also known as the Global Gag Rule) was still in effect. This controversial policy—first implemented by President Reagan in 1984—required non-governmental organizations receiving US federal funds to ‘neither perform nor actively promote abortion as a method of family planning in other nations’, regardless of who funded the work (USAID, 2001; Cranem and Dusenberry, 2004). Although rescinded by President Obama in 2009, it is important to understand the impact of this policy on the design and conduct of HIV prevention trials as it may be re-instituted with the eventual election of a conservative administration in the US. For example, although the Global Gag Rule was rescinded in 1993 by then President Clinton, it was reinstated by President Bush shortly after he took office in 2001.

There are a few exceptions to the Global Gag Rule. A Presidential memorandum specifically excluded from the Mexico City Policy, for example, ‘[all] foreign assistance furnished pursuant to the United States Leadership against HIV/AIDS, Tuberculosis, and Malaria Act of 2003 [also known as the President’s Emergency Plan for AIDS Relief, or PEPFAR]’ (Bush, 2003: n.p.; Population Action International, 2004). The still-enforced Helms Amendment to the US Foreign Assistance Act prohibits the use of US foreign assistance funds for abortions or abortion-related services (Foreign Assistance Act of 1961; Development Law and Policy Program of the Center for Population and Family Health 1989). These provisions apply to all entities, foreign or domestic, that receive foreign assistance funding. A later amendment sponsored by Senator Leahy, however, clarifies that US regulations (including the Helms Amendment) ‘shall not be construed to prohibit provision of counseling on all pregnancy options, consistent with local law’ (Foreign Assistance Act of 1961 (P.L. 87–195), as amended: Section 104(f)).

For studies funded by the US government, which included all of the trials we examined except the MDP sites, these policies led to confusion among study counselors and clinicians as to their ability provide information about pregnancy options or referral for termination services in settings where abortion is legal. Although local culture and beliefs contributed to researcher discomfort of discussing abortion—highlighting the need for more objective and client-centered counseling—discussions of pregnancy and termination services were constrained by perceived donor restrictions. Uncertainty over which donor restrictions may or may not apply meant that researchers at most sites reacted cautiously. Even in South Africa, where abortion is legal, US-funded researchers were reluctant to broach the subject of termination of pregnancy. Study staff who counseled trial participants did not provide ‘options counseling’, as required by South African law (Constitution of the Republic of South Africa, 1996; Strode, personal communication), but instead referred women to local family planning clinics or gynecologists if they expressed interest in termination.

Although the Global Gag Rule is no longer US policy, not all site-level researchers in countries like South Africa may be aware that its provisions are now unenforceable. Furthermore, it is possible that a subsequent US presidential administration may re-enact the policy, leading to further confusion among site-level researchers about if and when they can provide information to study participants about pregnancy options or termination services.

Restrictions on Sexual and Reproductive Health Counseling

The Leadership against HIV/AIDS, Tuberculosis and Malaria Act of 2003, which created the original regulatory framework under which PEPFAR operates, and the US Foreign Assistance Act also include language that influences how research sites provide sexual and reproductive health counseling and services (Foreign Assistance Act of 1961; United States Leadership Against HIV/AIDS, Tuberculosis, and Malaria Act of 2003). The original 2003 authorization act did not provide funds for research, but did it require that 20% of annually available PEPFAR funds be spent on HIV prevention activities. Of those PEPFAR-provided prevention funds, at least 33% had to be spent on abstinence programs. This created a perceived expectation that abstinence and condom use could not be presented as equal choices in any US-funded prevention activity, including HIV prevention trials, regardless of the source of funding. Because of this, HIV prevention trial staff felt obliged to counsel study participants that abstinence was the only completely effective way to prevent HIV infection, despite the requirement that women must be sexually active to participate in these trials. According to
USAID, one of the key agencies responsible for implementing PEPFAR, the original 2003 authorization also required that ‘information provided about the use of condoms by projects shall be medically accurate and shall include the public health benefits and failure rates of such use’ (USAID, 2005: n.p.). This requirement was interpreted by USAID as mandating the use of explicit language when describing the effectiveness of condoms, such as ‘consistent use of condoms among sexually active discordant couples reduces likelihood of HIV infection by 80 to 90 percent. Inconsistent condom users may face the same risks of HIV infection as non-users’.

Although the 2008 re-authorization of PEPFAR removed the requirement that at least 33% PEPFAR-provided prevention funds had to be spent on abstinence programs, it did require that all ‘activities promoting abstinence, delay of sexual debut, monogamy, fidelity, and partner reduction [be] implemented and funded in a meaningful and equitable way in the strategy for each host country’ (United States Global Leadership Against HIV/AIDS, Tuberculosis, and Malaria Reauthorization Act of 2008). This continued emphasis on abstinence, monogamy and sexual fidelity in the PEPFAR authorization language is likely perpetuate the belief among site-level researchers and staff that American donors favor abstinence over condom promotion in US-funded HIV prevention activities.

None of the seven research studies that we examined were directly funded by PEPFAR or formally subject to the restrictions described above, but we did find that some site-level researchers felt pressured to revise their condom promotion and counseling messages. For example, investigators at one site were asked by a US-based Institutional Review Board (IRB) to re-phrase their condom counseling messages in ‘medically accurate terms’, a direct reference to PEPFAR language about condom effectiveness and failure rates. In another study, a US-based donor requested that local researchers explicitly inform participants of the failure rate of condoms. These site-level investigators were unwilling to talk to study participants about condom failure rates, however, and instead amended the consent document to note that, ‘condoms are effective when used accurately and consistently’ (Heise et al., 2009: 36).

Restrictions on the Provision of Non-study-related Care

Researchers conducting trials in resource-poor countries frequently work in places where existing public health clinics are overburdened, underfunded or non-existent. Many microbicide researchers thus are called upon to provide ancillary care—that is, ‘care which is not required to make a study scientifically valid, to ensure a trial’s safety, or to redress research injuries’ (Belsky and Richardson, 2004: 1495). Provision of non-study-related care is a way of improving participant retention and there are few compelling reasons why researchers should not provide additional medical and social services to study participants if possible (Richardson and Belsky, 2004; Hawkins, 2008).

Key donors like the NIH, however, have policies that restrict or prevent the use of donor funds to provide non-study-related care in the research setting. Policymakers have interpreted the NIH’s authorizing legislation as prohibiting use of federal funds to purchase drugs or supply care that is not required for scientific validity or participant safety. The NIH will neither pay for ART for individuals who seroconvert during a trial nor allow NIH-funded investigators to budget for ancillary care. Such restrictions, coupled with concerns about overburdening clinical research staff, prevented most of the trials examined here from offering ancillary care services openly. The study protocols and site-level documents we examined were either silent on this issue or explicitly stated that such care would not be provided, even though some degree of non-study-related care was available informally or ‘under the table’ at most US-funded sites. However, not all donors prevent or restrict the use of research funds to provide non-study related. The British MRC, for example, does not limit funding for ancillary care.

Restrictions on Capacity-Building Activities

Finally, because many trials occur in communities that lack well-developed healthcare and research infrastructures, researchers must establish state-of-the-art laboratory facilities and train local staff in research procedures. For the most part, these capacity-building activities have a positive impact on trial communities and many international guidance documents highlight the need to improve local research institutions and public health programs (CIOMS, 2002). However, such improvements are achieved despite restrictions that often prevent the use of donor funds for construction and other capital improvements. NIH-sponsored trials, for example, are limited to using federal funds for the ‘renovation or alternation’ of existing facilities only; with the exception of NIH-funded research facilities construction projects, no new facilities can be built (Grants For Research Projects, 42 CFR § 52; NIH, 2003). Similarly,
while USAID does not ban outright the use of federal research funds for construction of new facilities, such activities are usually funded through separate construction contracts. Research programs, like those examined as part of this mapping exercise, generally must apply for an exemption—reviewed and approved on a case-by-case basis by USAID headquarters in Washington, DC—to use USAID funds for construction or renovation. Given the lack of suitable healthcare and laboratory facilities in the developing world, such requirements or restrictions can pose a major barrier to capacity building in many of the rural or periurban communities in which microbicide trials take place.

NIH-supported trials must also abide by the Buy American Act (41 USC § 10a–10d), a general policy that requires clinic equipment and laboratory reagents be purchased from US vendors. Such equipment may be donated to local healthcare facilities or research organizations once the trial ends, but the restrictions of the Buy American Act make post-trial maintenance of donated equipment hard to sustain as acquisition of American-made parts or reagents is often difficult and prohibitively expensive.

Conclusion

In this analysis of donor policies—most often established or promulgated by large US public donors—and their impact on the design and conduct of late-stage microbicide effectiveness trials, we found but a few binding policies that establish clear standards of care for trial participants. Both the Bill & Melinda Gates Foundation and USAID, for example, require researchers to develop plans for ensuring that study participants and communities have access to effective products once the trial is over. This is a laudable goal, and we would recommend that other donor establish similar policies or requirements.

Most of the donor policies we examined, however, did not place obligations upon researchers to improve local access to treatment and care services. Rather, many of these policies were likely to have the opposite effect and affect trial-related care adversely. For example, uncertainty about restrictions on US-funded family planning activities and abortion counseling, as well as perceived restrictions on HIV prevention activities, lead some trial sites to limit counseling on pregnancy options or resulted in pressure on researchers to revise their condom promotion and counseling messages. Similarly, restrictions on the use of US federal funds for provision of ancillary care or capacity-building projects prevented some researchers from ratcheting up local standards of healthcare in a manner that was sustainable even after the study ended. More research on the long-term impact of these restrictions on local trial communities is needed, but our findings suggest that donors need to issue guidance clarifying how and to what extent various policies (both research-related policies such as the NIH restriction on providing ancillary care or access to treatment and general US policies like the Buy American Act) apply to clinical trial settings. Donors should be encouraged to develop and implement clear and consistent funding policies that are clear and understandable, and that openly encourage (rather than dissuade) all researchers to provide a range of services that ratchet up local standards of healthcare.

In addition, donors and other regulators should consider amending those policies that interfere with provision of care or investment in long-term capacity-building projects at clinical trial sites. Policymaking is often depicted as a series of iterative phases—policy formulation, policy implementation and policy modification—with many of the policies and regulations reviewed here having been modified or rescinded after years of on-going public debate. Many of the family planning policies that had the largest impact on the design and conduct of the seven HIV prevention trials that we examined date back to the early 1990s or sooner, and they have been repeatedly updated and amended as changes in technology or the political and socioeconomic climate have occurred. The Mexico City Policy, for instance, was rescinded by the Obama Administration shortly after our initial review and analysis was completed. The data presented here, however, identify several other policies or regulations that should also be discarded or amended. We would recommend, for example, that donors make funding available that can be used for the provision of non-trial-related services (including the provision of ancillary care) as a way both to increasing participant recruitment and retention and to improve standards of healthcare in the community. Indeed, all donors should carefully examine and reconsider policies that place unnecessary or non-objective restrictions on the design and conduct of clinical research trials in the developing world.

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Notes

1. The NIH and USAID are just two of the US federal agencies that sponsor microbicide development and research. The efforts of these and other federal agencies are coordinated through the US Government Strategic Plan for Microbicide Development. To prevent duplication of effort, each federal agency provides support for different aspects of the testing process. With respect to clinical microbicide trials, for example, the NIH primarily provides funding for the biological and physiological studies necessary to demonstrate microbicide safety and effectiveness. USAID, in contrast, primarily provides resources for such activities as identifying potential trial sites, and establishing and maintaining the research infrastructure necessary to conduct trials in the community (USAID, 2009b).

2. The other federal agency responsible for PEPFAR implementation is the US Centers for Disease Control and Prevention (CDC). Although the CDC is involved in microbicides research (primarily Phase 1 trials of safety and acceptability), it did not provide funding for any of the Phase 2B or 3 trials examined here.

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