Ethical Challenges in Efficacy Trials of Vaginal Microbicides for HIV Prevention

Isabelle de Zoysa, MD, MSc, Christopher J. Elias, MD, MPH, and Margaret E. Bentley, PhD

ABSTRACT

This paper discusses some of the ethical challenges raised by advanced clinical trials designed to assess the safety and efficacy of vaginal microbicides in protecting women from HIV infection. The ethical principles that guide clinical research involving human subjects require that all participants in such trials be provided available measures known to reduce the risk of HIV infection. However, this will reduce the ability of the study to assess the protective effect of the test microbicide. In addition, providing extensive services to trial participants may be construed as an undue inducement if the study is being conducted among vulnerable groups such as sex workers or women from disadvantaged communities. Suggestions are provided to resolve this dilemma in the planning and implementation of HIV prevention services for trial participants. (*Am J Public Health*. 1998; 88:571–575)

Introduction

A critical need in stemming the spread of the HIV/AIDS pandemic is to expand the range of methods that women can use for the prevention of all sexually transmitted infections,[1,2] including vaginal microbicides.[3,4] A number of products have reached the stage of advanced clinical trials to assess their safety and efficacy in protecting women from HIV infection.[2] A major challenge is to design microbicide trials that are "both scientifically rigorous and ethically defensible."[3]

This paper discusses an issue that looms large in the design of such trials: the provision of HIV prevention services to participants. Discussion first centers on why such services are required and why they should focus on the promotion of condom use. The ethical and practical dilemmas raised by this requirement are then described. Finally, implications for the design and planning of microbicide efficacy trials are explored.

The Ethical Imperatives

The most rigorous and reliable approach to measuring the efficacy of a new product, such as a microbicide, and obtaining approval for its widespread distribution is a randomized controlled trial (although for various reasons, including ethical difficulties, other designs may sometimes be more appropriate[5,6]). Such trials should include sufficient participants to have adequate statistical power to measure the benefits and any adverse effects of the experimental product. Sample size depends on the expected incidence of HIV infection in the trial participants, on the predicted reduction in incidence related to microbicide use, and on other factors such as the retention and compliance of trial participants.[4] Trials of this kind are often conducted in developing countries, among women who are at particularly high risk of heterosexually transmitted HIV infection (e.g., sex workers, clients of sexually transmitted disease clinics, and partners of HIV-infected men).

Biomedical research involving human subjects is guided by a number of basic ethical principles that are considered to be universally valid.[7] According to the principles of beneficence and nonmaleficence, investigators have an obligation to maximize benefits and to minimize risks for individuals who agree to participate in a study. This means that they have a duty to protect the health and well-being of study participants by providing them necessary health services. In clinical research, all study participants should be assured of the "most appropriate currently established" interventions to deal with the problem at hand.[8] Investigators must also be vigilant to ensure that individuals avoid all possible harm that might arise from their participation in the research. In microbicide efficacy trials, there is therefore an ethical mandate to provide services known to reduce the risk of HIV infection and accepted as the standard of care.

At present, male latex condoms are widely available and generally considered to be the most effective method, apart from sexual abstinence, of preventing the heterosexual transmission of HIV.[9] It is therefore generally recommended that, at the very least, all participants in a microbicide trial be given free supplies of condoms and be urged to use both the vaginal product and a condom during each act of intercourse.[10] (The issue of female condoms has not yet been raised in the context of microbicide trials. Nonetheless, they would need to be offered along with the male condom in areas where they have been introduced and are available.) Statistical techniques are use to measure the protective effect of microbicides over and above the protection provided by the use of condoms alone.

The Investigator's Dilemma

These ethical imperatives place investigators in a bind. The problem is that the provision of HIV prevention services to both the control and the experimental groups should reduce the incidence of HIV infection. In addition, high levels of condom use will result in a small proportion of sex acts that are protected by the microbicide alone (only these sex acts can contribute to efficacy). This will blunt the ability of the study to assess the protective effect of the microbicide. Investigators thus have a disincentive to

Isabelle de Zoysa and Margaret E. Bentley are with the Department of International Health, Johns Hopkins University School of Public Hygiene, Baltimore, Md. Christopher J. Elias is with the Population Council, Bangkok, Thailand.

provide services that will significantly increase condom use and reduce HIV infections among trial participants.

A complicating factor is that participants are often sought among sex workers or women from disadvantaged communities, who are usually poor, are often exploited by employers or other community members, and have restricted access to health and social services, particularly in developing countries. Investigators are ethically bound to protect vulnerable subjects, and they need to pay particular attention to providing benefits in exchange for participation and to reducing heightened risks and burdens.[11] The difficulty is that, on the one hand, providing extensive services to such populations may be an undue inducement to participate in the trial.[6,7] On the other hand, conducting research among them without attending to their basic health care and social needs would only increase their exploitation.

The dilemma, then, is that of striking the right balance between the need to protect the rights and health of women at risk of HIV and the need to meet demands of validity and efficiency[6] in the testing of microbicides. The available evidence regarding the efficacy of existing candidate products is inconclusive,[2,6,12,13] and there has been a call for further research. Basic rules must, of course, be observed to protect research participants. We must be careful, however, that efficacy trials do not become impractical, or else promising candidate microbicides will remain untested and unavailable, thus delaying for women access to these products that they so urgently need.

At this time, there is no argument with the ethical requirement to provide all trial participants prevention and health services, "within reasonable limits,"[11] to ensure that they derive benefits from their participation and are not exposed to undue coercion. The questions posed are as follows: What is a competent and acceptable package of services that should be offered to trial participants? and How should this package be developed? Some suggestions are offered for addressing these questions.

Implications for the Provision of Services to Trial Participants

What Condom Promotion Services Should Be Considered?

Studies of the impact of interventions to promote condom use among women at risk of HIV infection, although scant,[14] indicate that condom use can be increased under specific circumstances. In particular, interventions among women exposed to extreme risks of HIV infection, such as sex workers, have resulted in an increased proportion of commercial and casual sexual encounters in which condoms are used.[15–19] Essential elements of condom promotion efforts include ready access to condoms and education and training in HIV risk reduction strategies.[14,20,21] Training in social and sexual communication and assertiveness skills to deal with difficult situations and persist with condom use seems to be critical, particularly for disadvantaged women.[14,20,21,23] In addition, it may be useful to include opportunities for collective problem solving and peer support, which can change peer norms about condom use, and to specify workable condom negotiation strategies.[14,20–23]

All in all, studies indicate that interventions incorporating these elements can result in consistent condom use rates up to 60%. These rates, however, are often much lower despite intensive and sustained intervention efforts. Repeatedly, male resistance to condom use emerges as a major constraint that interventions targeted at women cannot break through. Furthermore, considerable heterogeneity in condom use is found among different types of sexual partnerships. In stable relationships, unprotected sex tends to be the norm.[24] Some interventions have successfully reached beyond individual women to their male partners, with high levels of consistent condom use recorded in couples in which both partners have been exposed to HIV counseling and testing[25,26] (in particular, HIV-discordant couples[27–29]). These interventions, however, are not universally applicable.[14] Ultimately, it is likely that widespread and sustained HIV risk reduction will be realized only if male involvement is ensured and if the environmental, political, and structural barriers to behavior change are addressed[22,30,31] through community mobilization, legal action, and social change.[32–34]

Contextual interventions need further evaluation and may not be feasible or appropriate in the context of a randomized, controlled trial of a microbicide. On the other hand, an intervention that combines the promotion and distribution of condoms, the provision of tailored AIDS education, and training in social and sexual assertiveness skills, aimed at individual women or groups of women who participate in the trial, is eminently practical.

What Other HIV Prevention Services Should Be Provided?

Provision of clinical services for sexually transmitted infections has a powerful impact on HIV transmission, even in the absence of any significant behavioral change,[35] and should therefore also be required in microbicide efficacy trials. In fact, many trials will include the incidence of sexually transmitted infections as a major outcome and will, as a result, involve regular monitoring of the presence of these infections. Because of their impact on HIV transmission, there is a strong case for offering treatments of sexually transmitted infections and attendant counseling services not just as part of monitoring activities but on demand as well, as an additional service to the trial participants.

Optimal management of sexually transmitted infections also includes partner management.[36] Thus, any woman who is found to have a sexually transmitted infection should be counseled about partner management, and the required drugs and counseling services should be provided to partners whom she refers for treatment. Other approaches to partner management, such as contact tracing, may be recommended at the study site and may have to be considered as well.

What About the Care and Support of Persons Living with HIV/AIDS?

HIV testing will usually be provided prior to enrollment in the trial, since HIV-seronegative women must be identified and followed up to ascertain the incidence of HIV infection. It has been pointed out that inclusion of HIV-infected individuals may be necessary to preserve the confidentiality of HIV test results.[10] It may also be helpful in that these women would contribute information about the safety of the product and its efficacy against sexually transmitted infections other than HIV.[10] More women will seroconvert after entry into the trial. All trial participants with HIV infection should be referred to services for essential medical care and social and psychological support. This raises a problem when appropriate services of this kind are not available and the social environment discriminates against persons living with HIV/AIDS.

Who Should Have Access to These Services?

Elias and Heise[3] have argued that essential services such as condoms, HIV education, and reproductive health care should also be made available to women who choose not to participate in the trial so that women will not feel under pressure to gain access to these scarce resources. One approach might be to make some services (such as condom distribution and clinical

services for sexually transmitted infections) available on a communitywide basis. The pooling of resources and the economies of scale might reduce costs.

Who Should Conduct the HIV Prevention Activities?

A common approach is to have the research staff conduct condom promotion and other intervention activities while carrying out other work required by the trial protocol, such as medical examinations or interviews to collect information on condom and microbicide use. However, the investigators and staff directly involved in the trial have a potential conflict of interest, because the trial requires HIV seroconversions (at least in the control group), which would be reduced with an effective background intervention. This moral hazard must be resolved and seen to be so by the broader community of interested parties.

The primary HIV prevention services should ideally be provided by staff who are independent of those evaluating efficacy. One approach is for the study organizers to strengthen existing public or private sector HIV prevention and care services and/or to contract with a nongovernmental organization serving the community. This offers opportunities for enhancing community involvement in the project and for developing local capacity for future intervention activities.

How Long Should the Intervention Be Continued?

Sustained and repeated interventions are likely to lead to increased condom use and greater risk reduction.[14,18] A difficult issue concerns the duration of the intervention. Services provided to study participants are often withdrawn on completion of the research, sometimes leaving them in a worse situation than before (if, for example, they have learned to rely on condoms for protection but condoms suddenly become unavailable or unaffordable). Particularly if the trial has been conducted among poor or vulnerable populations, investigators and funding agencies should consider their moral responsibilities to preserve some benefits for the participants in the longer term. This provides another argument for working with local service organizations, which may be able to take on responsibility for continuing intervention activities after the trial has been completed.

In addition, the ethical principle of justice mandates that research participants not be exposed to a disproportionate share of the research risks without an equal share of the benefits.[7,11,37] Thus, if the microbicide is demonstrated to be effective, the population in which it was tested should have first priority to receive the product after safety and efficacy have been established. This raises many issues related to plans for product approval, distribution, and cost reduction in the country where the trial is conducted, and these issues need thorough discussion before the trial is initiated.[3]

How Does One Decide What Needs to Be Done?

On the basis of the preceding, one could identify some "standard care" HIV prevention services that would incorporate distribution of free condom supplies, provision of tailored AIDS education, training in social and sexual communication and assertiveness skills, and clinical services for sexually transmitted infections. The trial organizers should ensure that these supplies and services are provided to all of the trial participants without exception. One could also identify other services that should be provided, somehow or another, to the trial participants, such as HIV care and support services. At the very least, the trial organizers should liaise with an adequate, accessible, and reliable source for these services to which the trial participants (and, if desired, their partners) could be referred.

While these general guidelines should apply in all cases, the precise configuration and intensity of services to be provided in the context of a particular microbicide efficacy trial is a question of judgment. Those involved in planning the trial must strike a balance between its ethical and scientific demands. The investigators cannot compromise their ethical obligation to provide trial participants with established interventions to reduce the risk of HIV. Cost and expediency alone are not sufficient justification for inadequate or insincere efforts in this regard. However, the investigators will need to remind themselves that offering the trial participants access to extensive services that are not otherwise available to them may be coercive in itself, especially among vulnerable populations (unless these services are offered to the entire community from which the trial participants are drawn, and for a prolonged period of time).

It is not feasible, nor is it appropriate, for scientists who are planning a trial at a particular site to attempt to address these thorny issues on their own. Some steps should be taken to facilitate a rational and transparent decision-making process. First, the investigators should seek guidance from persons who have long experience in the community and detailed knowledge about its resources, interests, and concerns. They should also consult with the prospective subjects of the research and their representatives or advocates.[6] The key role that this kind of community consultation can play in the planning, implementation, and interpretation of intervention studies in the era of HIV/AIDS has been repeatedly emphasized[6,38] and will be particularly valuable in solving the dilemmas posed by microbicide trials.

Community representatives, when engaged in a genuine partnership, can help define a reasonable and acceptable package of services for the women who participate in the trial (including services to offer in difficult situations, such as unintended pregnancy in an HIV-infected woman) and will recognize the need to keep the costs of this package down. This is important to minimize the inducement effect, to avoid raising expectations that cannot later be met, and to encourage the development of services that can be sustained after the trial is over. Beyond this, as pointed out by Melton et al.,[38] "the involvement of the community of interest in the design of the research and the interpretation of results is likely to increase the richness of the research questions, the validity of methods, the meaningfulness of interpretations, and the speed and scope of dissemination of results."

Second, the ethical review process for the trial should include laypersons who can represent the perspectives and values of the community. As stated by the Council for International Organizations of Medical Sciences,[8] "this is consistent with respect for the culture, the dignity and self-reliance of the community, and the aim of achieving community members' full understanding of the study." The involvement of a local or national committee in reviewing the scientific and ethical aspects of a trial is highly desirable, even if it is not required in the case of externally initiated and sponsored studies. Finally, exploratory research using qualitative methods may be very useful in clarifying the needs of the community, in formulating recruitment strategies and informed consent procedures, and in developing interventions in preparation for a field trial.[39,40]

Possible Consequences for Measurement of Efficacy

Studies of the impact of HIV prevention programs directed at women indicate that substantial increases in condom use can be

achieved but that this is a challenge. For many reasons, including the fact that women do not control the use of condoms, it is apparent that correct and consistent condom use is observed only among a minority of individuals. Thus, women who are exposed to extreme risks (e.g., sex workers and partners of seropositive men) may continue to suffer high HIV incidence rates, even if they receive, on an individual basis, high-quality and intensive condom promotion services. For example, incidence rates of 3 to 5 per 100 person-years have been documented, after a focused and intensive intervention, among sex workers in India[16] and Zaire[18] and among women attending antenatal and child health clinics in Rwanda.[25] In completed microbicide efficacy trials in which trial participants received condoms and repeated HIV education, HIV incidence rates of up to 7 and 9 per 100 person-years have been found among sex workers in Cameroon[13] and among individuals in serodiscordant couples in Zambia,[41] respectively.

The assumption that microbicide use presents fewer constraints to women than condom use is borne out by intervention studies in which the use of microbicides (or other female-controlled methods) is higher than that of condoms when both products are promoted together.[41-44] Therefore, trials in populations with high HIV incidence rates in which the incidence rate is measurable after the introduction of additional interventions will still be able to determine the efficacy of microbicide use if the incremental protection afforded by the use of the product is large enough and a sufficient proportion of sex acts are protected by the microbicide alone. Clearly, however, the more successful the interventions are in increasing condom use rates and reducing baseline HIV incidence rates, the more difficult it becomes to measure the incremental reduction in HIV incidence that can be attributed to microbicide use and the larger the required sample size.[3] Sample sizes remain large even in situations of high HIV incidence, and it is likely that the greatest chance for success lies in the conduct of multicenter, multisite studies.[3]

Conclusions

Efficacy trials of microbicides raise a number of ethical and practical issues, many of which are common to controlled trials of other HIV preventive interventions and are being raised with respect to ongoing drug trials among HIV-infected pregnant women[45-47] and planned HIV vaccine trials.[48] This paper has discussed considerations related to the selection and implementation of HIV prevention services for participants in microbicide efficacy trials. The conclusion is that it should be possible to meet the scientific standards of trials that can answer the urgent questions posed regarding the safety and efficacy of candidate microbicides and, at the same time, to fulfill the ethical obligations of such trials (although the basic conditions may be difficult to achieve in very vulnerable populations and/or in very disadvantaged settings). However, the path ahead is narrow and troublesome, and finding the way will require "building a new consensus"[6] through the concerted dialogue and action of scientists, activists, and community members. □

Acknowledgments

An earlier version of this paper was prepared for the Symposium on Practical and Ethical Dilemmas in the Clinical Testing of Microbicides, Airlie, Va, April 27–30, 1997, convened by the Women's Health Advocates on Microbicides (WHAM) and the Population Council.

We are grateful for the helpful advice and encouragement received from Mary Bassett, Lori Heise, Carel Ijsselmuiden, Elizabeth McGrory, and Susan Wood, and for the valuable comments and suggestions provided by 3 anonymous reviewers.

References

1. Stein ZA. HIV prevention: the need for methods women can use. *Am J Public Health*. 1990;80:460–462.
2. Elias CJ, Coggins C. Female-controlled methods to prevent sexual transmission of HIV. *AIDS*. 1996;10(suppl 3):S43–S51.
3. Elias CJ, Heise LL. Challenges for the development of female-controlled vaginal microbicides. *AIDS*. 1994;8:1–9.
4. Stone AB, Hitchcock PJ. Vaginal microbicides for preventing the sexual transmission of HIV. *AIDS*. 1994;8(suppl 1):S285–S293.
5. Finkelstein MO, Levin B, Robbins H. Clinical and prophylactic trials with assured new treatment for those at greater risk, I: a design proposal. *Am J Public Health*. 1996;86:691–695.
6. Levine C, Dubler NN, Levine RJ. Building a new consensus: ethical principles and policies for clincial research on HIV/AIDS. *IRB: A Review of Human Subjects Research*. 1991;13:1–17.
7. *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva, Switzerland: Council for International Organizations of Medical Sciences; 1993.
8. *International Guidelines for Ethical Review of Epidemiological Studies*. Geneva, Switzerland: Council for International Organizations of Medical Sciences; 1991.
9. Centers for Disease Control. Update: Barrier protection against HIV infection and other sexually transmitted diseases. *MMWR Morb Mortal Wkly Rep*. 1993;42:589–591.
10. International Working Group on Vaginal Microbicides. Recommendations for the development of vaginal microbicides. *AIDS*. 1996;10:UNAIDS1–UNAIDS6.
11. Gostin L. Ethical principles for the conduct of human subject research: population-based research and ethics. *Law Med Health Care*. 1991;19:191–200.
12. Cates W, Stewart FH, Trussell J. Commentary: the quest for women's prophylactic methods—hopes vs science. *Am J Public Health*. 1992;82:1479–1482.
13. Rowe PM. Nonoxynol-9 fails to protect against HIV-1. *Lancet*. 1997;349:1074. Comment.
14. Choi K-H, Coates TJ. Prevention of HIV infection. *AIDS*. 1994;8:1371–1389.
15. Asamoah-Adu A, Weir S, Pappoe M, Kanlisi N, Neequaye A, Lamptey P. Evaluation of a targeted AIDS prevention intervention to increase condom use among prostitutes in Ghana. *AIDS*. 1994;8:239–246.
16. Bhave G, Lindan CP, Hudes ES, et al. Impact of an intervention on HIV, sexually transmitted diseases, and condom use among commercial sex workers in Bombay, India. *AIDS*. 1995;9(suppl 1):S21–S30.
17. Fox LJ, Bailey PE, Clarke-Martinez KL, Coello M, Ordonez FN, Barahona F. Condom use among high-risk women in Honduras: evaluation of an AIDS prevention program. *AIDS Educ Prev*. 1993;5:1–10.
18. Laga M, Alary M, Nzila N, et al. Condom promotion, sexually transmitted diseases treatment, and delclining incidence of HIV-1 infection in female Zairian sex workers. *Lancet*. 1994;344:246–248.
19. Williams E, Lamson N, Efem S, Weir S, Lamptey P. Implementation of an AIDS prevention program among prostitutes in the Cross River State of Nigeria. *AIDS*. 1992;6:229–230. Letter.
20. DiClemente RJ, Wingood GM. A randomized controlled trial of an HIV sexual risk–reduction intervention for young African-American women. *JAMA*. 1995;274:1271–1276.
21. Kelly JA, Murphy DA, Washington CD, et al. The effects of HIV/AIDS intervention groups for high-risk women in urban clinics. *Am J Public Health*. 1994;84:1918–1922.
22. Heise LL, Elias C. Transforming AIDS prevention to meet women's needs: a focus on developing countries. *Soc Sci Med*. 1995;40:931–943.
23. Gupta GR, Weiss E. Women's lives and sex: implications for AIDS prevention. *Cult Med Psychiatry*. 1993;17:399–412.
24. de Zoysa I, Sweat MD, Denison JA. Faithful but fearful: reducing HIV transmission in stable relationships. *AIDS*. 1996;10(suppl A):S197–S203.
25. Allen S, Serufilira A, Bogaerts J, et al. Confidential HIV testing and condom promotion in Africa: impact on HIV and gonorrhea rates. *JAMA*. 1992;268:3338–3343.
26. King R, Allen S, Serufilira A, Karita E, Van de Perre P. Voluntary confidential HIV testing for couples in Kigali, Rwanda. *AIDS*. 1993;7:1393–1394. Letter.
27. Allen S, Tice J, Van de Perre P, et al. Effect of serotesting with counselling on condom use and seroconversion among HIV discordant couples in Africa. *BMJ*. 1992;304:1605–1609.

28. Kamenga M, Ryder RW, Jingu M, et al. Evidence of marked sexual behavior change associated with low HIV-1 seroconversion in 149 married couples with discordant HIV-1 serostatus: experience at an HIV counselling center in Zaire. *AIDS*. 1991;5:61–67.
29. Padian NS, O'Brien TR, Chang YC, Glass S, Francis DP. Prevention of heterosexual transmission of human immunodeficiency virus through couple counselling. *J AIDS*. 1993;6: 1043–1048.
30. Sweat MD, Denison JA. Reducing HIV incidence in developing countries with structural and environmental interventions. *AIDS*. 1995;9(suppl A):S251–S257.
31. Tawil O, Verster A, O'Reilly KR. Enabling approaches for HIV/AIDS prevention: can we modify the environment and minimize the risk? *AIDS*. 1995;9:1299–1306.
32. Parker RG. Empowerment, community mobilization and social change in the face of HIV/AIDS. *AIDS*. 1996;10(suppl 3):S27–S31.
33. Rojanapithayakorn W, Hanenberg R. The 100% condom program in Thailand. *AIDS*. 1996;10:1–7.
34. Visrutaratna S, Lindan CP, Sirhorachai A, Mandel JS. "Superstar" and "model brothel": developing and evaluating a condom promotion program for sex establishments in Chiang Mai, Thailand. *AIDS*. 1995;9(suppl 1):S69–S75.
35. Grosskurth H, Mosha F, Todd J, et al. Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. *Lancet*. 1995;346: 530–536.
36. Toomey KE, Latif AS, Steen RC. Partner management. In: Dallabetta G, Laga M, Lamptey P, eds. *Control of Sexually Transmitted Diseases: A Handbook for the Design and Management of Programs*. Arlington, Va: AIDSCAP/Family Health International; 1996.
37. Barry M. Ethical considerations of human investigation in developing countries: the AIDS dilemma. *N Engl J Med*. 1988;319:1083–1086.
38. Melton GB, Levine RJ, Koocher GP, Rosenthal R, Thompson WC. Community consultation in socially sensitive research: lessons from clinical trials of treatments for AIDS. *Am Psychol*. 1988;43:573–581.
39. Gittlesohn J. Qualitative research in field trials. In: Smith P, Morrow R, eds. *Field Trials for Health Interventions in Developing Countries*. 2nd ed. London, England: Macmillan; 1996:204–229.
40. Grinstead OA. Social and behavioral issues in phase III HIV preventive vaccine trials. *AIDS*. 1995;9(suppl A):S245–S250.
41. Hira SK, Feldblum PJ, Kamanga J, Mukelabai G, Weir SS, Thomas JC. Condom and nonoxynol-9 use and the incidence of HIV infection in serodiscordant couples in Zambia. *Int J STD AIDS*. 1997;8:243–250.
42. Farr G, Castro LAA, Disantostefano R, Claassen E, Olguin F. Use of spermicide and impact of prophylactic condom use among sex workers in Santa Fe de Bogota, Colombia. *Sex Transm Dis*. 1996;23:206–212.
43. Gollub E, French P, Latka M, et al. The women's safer sex hierarchy: initial responses to counseling on women's methods of STD/HIV prevention at an STD clinic. In: 11th International Conference on AIDS, July 1996; Vancouver, British Columbia, Canada. Abstract MoD583.
44. Zekeng L, Feldblum PJ, Oliver RM, Kaptue L. Barrier contraceptive use and HIV infection among high-risk women in Cameroon. *AIDS*. 1993;7:725–731.
45. Angell M. The ethics of clinical research in the Third World. *N Engl J Med*. 1997;337: 847–849.
46. Lurie P, Wolfe SM. Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. *N Engl J Med*. 1997;337: 853–856.
47. Varmus H, Satcher D. Ethical complexities of conducting research in developing countries. *N Engl J Med*. 1997;337:1003–1005.
48. Lurie P, Bishaw M, Chesney MA, et al. Ethical, behavioral, and social aspects of HIV vaccine trials in developing countries. *JAMA*. 1994;271:295–301.

Erratum

In: Hart CL, Smith GD, Blane D. Inequalities in mortality by social class measured at 3 stages of the lifecourse. *Am J Public Health*. 1998;88:471–474.

The postal code in the address given for reprints and correspondence was incorrect. The correct code is G12 8RZ.