

*Editorials***INVESTIGATORS' RESPONSIBILITIES  
FOR HUMAN SUBJECTS  
IN DEVELOPING COUNTRIES**

**M**OST people agree that investigators assume some responsibility for their human subjects, but how much? And does it matter where the research is carried out? These issues are raised by the report by Quinn et al. elsewhere in this issue of the *Journal*<sup>1</sup> and by an earlier paper in the *Lancet*<sup>2</sup> concerning another phase of the same project.

The project was carried out in 10 clusters of rural villages in Uganda to delineate the risk factors associated with heterosexual transmission of the human immunodeficiency virus type 1 (HIV-1). Villagers (including pregnant women) were surveyed on five occasions at 10-month intervals. The first goal of the project was to determine whether sexually transmitted diseases such as syphilis and gonorrhea increase the risk of HIV infection. To study that question, the investigators gave residents of 5 of the 10 clusters intermittent antibiotic treatment to reduce the prevalence of sexually transmitted diseases. At each survey, villagers were asked about their sexual practices and medical histories, and blood and other body fluids were taken for testing for HIV-1 and sexually transmitted diseases. As reported in the *Lancet* paper,<sup>2</sup> antibiotic treatment reduced the prevalence of other sexually transmitted diseases, but not the incidence of HIV-1. The current report focuses on the relation between viral load and heterosexual transmission of HIV-1 in couples discordant for HIV-1 status at base line. Not surprisingly, an increasing viral load in the initially HIV-1-positive partner was associated with a greater risk of transmission. In addition, circumcision was found to be protective in male partners. The scientific and clinical implications of these findings are discussed elsewhere in this issue of the *Journal*.<sup>3</sup>

It is important to be clear about what this study meant for the participants. It meant that for up to 30 months, several hundred people with HIV infection were observed but not treated. It was also left up to the seropositive partner in couples discordant for HIV-1 to decide whether the seronegative partner would be informed, even though both were regularly seen by the investigators. In addition, many people who were found to have other sexually transmitted diseases were left to seek their own treatment. For example, those who lived in the five village clusters given mass antibiotics also received immediate intramuscular penicillin G benzathine if they had a positive serologic test for syphilis, but in the other five clusters, such people were simply referred to free government

clinics. Such a study could not have been performed in the United States, where it would be expected that patients with HIV and other sexually transmitted diseases would be treated. In addition, in most states it would be expected that caregivers would see that seronegative partners were informed of their special risk.<sup>4</sup>

Whether research conducted in developing countries should be held to different standards from those applied in the developed countries is a subject of intense debate.<sup>5-11</sup> Many believe that investigators do not need to provide better care for human subjects than is generally available in the community from which the subjects are drawn. Thus, it is argued, since Ugandans in rural villages generally cannot obtain antiretroviral treatment, they need not be treated for HIV within research studies, even though the investigators could easily provide the drugs. As Quinn et al. say, "Antiretroviral drugs are not available in rural Uganda. Consequently, the HIV-1 RNA levels were not influenced by the use of antiretroviral drugs."<sup>1</sup> As for informing seronegative partners of their risk, Quinn et al. make it clear that they advised seropositive partners to inform their partners (they also provided free condoms), but they did not ascertain whether the seropositive partners actually did so. They cite the policy of the Ugandan government to explain why they themselves did not inform the seronegative partners.

The ethical standards, then, were indeed different from those that would govern research in developed countries. In this regard, the study of Quinn et al. is hardly unique. Many studies in developing countries now use a similar rationale for observing subjects for outcomes that could be prevented. That was true, for example, of the well-publicized trials comparing zidovudine with placebo for the prevention of the transmission of HIV from pregnant women to their infants.<sup>5,7</sup> Despite the fact that such studies would not be permitted in developed countries, they have generally been approved by the relevant ethics-review bodies, in both the host country and the sponsoring country, and efforts are under way to revise international codes of ethics to bring them into line with this practice.<sup>9,10</sup>

Many people believe that the different standards are justified not only by the local economic conditions, but by the special relevance of the studies to the regions in which they are conducted. Thus, the research on HIV in sub-Saharan Africa can be justified by the extraordinary devastation caused by the epidemic there. I agree that research should be relevant to the population from which the subjects are drawn. Unfortunately, that may seldom be the case in developing countries. For example, Quinn et al. found that the risk of heterosexual transmission correlated with viral load, but how will that information be used in Uganda? The very condition that justified doing the study in Uganda in the first place — the lack of availability of antiretroviral treatment — will greatly limit the rel-

evance of the results there. As is so often the case, the results will probably find their greatest application in the developed world.

Given the inevitable concerns about the study by Quinn et al., why was it accepted for publication in the *Journal*? For me, the decision was admittedly a very difficult one. The study had been approved by the AIDS Research Subcommittee of the Uganda National Council for Science and Technology, the human-subjects review boards of Columbia University and Johns Hopkins University, and the Office for Protection from Research Risk of the National Institutes of Health. The subjects were said to have given oral informed consent (although interviews with subjects of similar studies have indicated that it is very difficult for them to understand that they may not receive effective treatment within the study<sup>12</sup>). After its submission to the *Journal*, the paper was approved not only by the outside peer reviewers, but also by the relevant editors on the *Journal's* staff. When the paper crossed my desk for final approval, I asked two prominent ethicists who are familiar with research on HIV in developing countries to review it. One thought the study was not ethical; the other thought it was. In the face of these divergent opinions and the favorable views of the other editors and reviewers, I decided to approve publication.

I hope that publication of this paper will once again focus attention on the vexing ethical issues raised by this sort of study. The questions discussed below, in particular, need much more attention.

Codes of ethics governing research on human subjects require that investigators put the welfare of their subjects above the interests of science and of society,<sup>13</sup> but what does that mean in practical terms? Does it mean only that investigators will not harm their subjects in the course of the research? Or does it mean that investigators undertake a broader responsibility for their subjects' welfare that includes trying to treat illnesses that afflict them, even those under study? If the requirement is simply not to do harm through the research, how can investigators make that limited responsibility clear to their subjects and still ensure their cooperation? Most people, after all, naturally look on doctors primarily as healers, not research scientists.

Does it matter whether the illness studied is difficult or expensive to treat? Treating HIV infection in rural Uganda would indeed be both difficult and expensive, and at best, the treatment would only stave off AIDS for the duration of the study, not prevent it altogether. Treating syphilis, on the other hand, is relatively simple and inexpensive. In the study by Quinn et al., should all the other sexually transmitted diseases have been treated by the investigators, but not HIV-1 infection? If the expense of antiretroviral therapy justifies not offering it to subjects in certain parts of the world, should that expense be accepted as immutable?

Or should we look more closely at the pricing decisions of the manufacturers of drugs protected by patents and the possibility of competition from generic drugs in developing countries?<sup>14</sup>

The argument that certain subjects are no worse off than if they were not in the study implies that ethical standards governing research should vary with the political and economic conditions of the region. Should they? The answer will depend to some extent on how one sees the limits of the investigators' responsibility. If investigators are responsible for the subjects they enlist in their studies, and only those subjects, then the conditions of the surrounding community are irrelevant. They must do their best for their subjects, regardless. If, however, it is within the purview of investigators to consider the entire population, then perhaps it is inequitable to give research subjects better treatment than their neighbors would receive outside the study.

I believe, as I have argued elsewhere,<sup>6,15</sup> that our ethical standards should not depend on where the research is performed. I also believe that investigators assume broad responsibility for the welfare of the subjects they enroll in their studies — a responsibility analogous to that of clinicians. That would mean treating illnesses, even if they are not directly caused by the research. Furthermore, I believe that the nature of investigators' responsibility for the welfare of their subjects should not be influenced by the political and economic conditions of the region. It would follow that those conditions should not be used to justify a lower standard of care for some subjects. In practical terms, any other position could lead to the exploitation of people in developing countries in order to conduct research that could not be performed in the sponsoring countries.

I acknowledge, however, that all of these questions are debatable, and that there may be few answers that apply to every situation. What is important is that the issues be explored honestly, not defensively, and that the answers reflect moral reasoning, rather than simply expediency.

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## ANTIHYPERTENSIVE THERAPY AND THE RISK OF TYPE 2 DIABETES MELLITUS

**A**LTHOUGH thiazide diuretics and beta-blockers are often used as first-line therapy in patients with hypertension, including those with diabetes mellitus,<sup>1</sup> the possibility that these drugs may promote glucose intolerance remains a concern.<sup>2-10</sup> Short-term metabolic studies, as well as epidemiologic studies and clinical trials, suggested a causal link between the use of thiazide diuretics and the subsequent development of type 2 diabetes.<sup>3-10</sup> However, those studies were compromised by small numbers of patients, relatively short follow-up periods, changing definitions of new-onset diabetes, lack of adequate comparison groups, selection criteria that lessened the extent to which the results could be generalized, and study designs that precluded comparisons among several classes of antihypertensive drugs. In a study reported by Gress et al.<sup>11</sup> in this issue of the *Journal*, these limitations have been overcome.

The authors conducted a large, prospective, cohort study that included 12,550 adults who did not have diabetes and that was designed to examine the independent relation between the use of antihypertensive medications and the risk of the subsequent development of type 2 diabetes.<sup>11</sup> After appropriate adjustment for potential confounders, patients with hypertension who were taking thiazide diuretics, angiotensin-converting-enzyme (ACE) inhibitors, or calcium-channel antagonists were found not to be at greater risk for subsequent diabetes than patients who were not receiving any antihypertensive therapy. However, hypertensive patients who were taking beta-blockers had a 28 percent higher risk of diabe-

tes than those taking no medication.<sup>11</sup> Weight gain was not the cause of the excess risk of diabetes in patients treated with beta-blockers, since their weight gain was identical to that of participants taking no medication. Finally, in this important study, development of type 2 diabetes was almost 2.5 times as likely in patients with hypertension as in their normotensive counterparts, as has previously been noted.<sup>2</sup>

Potential mechanisms by which beta-blockers may contribute to the development of diabetes include weight gain,<sup>12</sup> attenuation of the beta-receptor-mediated release of insulin from pancreatic beta cells,<sup>13</sup> and decreased blood flow through the microcirculation in skeletal-muscle tissue, leading to decreased insulin sensitivity.<sup>14</sup> However, in the current study, the use of beta-blockers was not associated with weight gain or with hyperinsulinemia. Thus, factors not studied, such as changes in the level of aerobic exercise or subtle changes in the cellular actions of insulin, may have contributed to the diabetogenic effects of beta-blockers. Despite the potentially adverse metabolic effects of beta-blockers, they have proved to have significant long-term protective effects against cardiovascular disease in hypertensive patients,<sup>1</sup> including those with diabetes mellitus.<sup>12</sup>

In the current report, diuretics, ACE inhibitors, and calcium-channel antagonists had no significant effect on the development of diabetes.<sup>11</sup> Previously it was reported that among obese, elderly patients, those who required treatment with diuretics and beta-blockers were at greater risk for type 2 diabetes mellitus than those who had normal blood pressure.<sup>5</sup> In agreement with the current report, several other trials did not find that thiazide diuretics have diabetogenic effects. These include the trial of the European Working Party on High Blood Pressure in the Elderly,<sup>3</sup> which used a combination of triamterene and hydrochlorothiazide; the Treatment of Mild Hypertension study,<sup>9</sup> which used chlorthalidone; and the Systolic Hypertension in the Elderly Program,<sup>10</sup> which used chlorthalidone and atenolol as needed. The differences between the results of these trials and those of earlier studies may be related to the use of larger doses of medications (e.g., 50 to 200 mg of hydrochlorothiazide) in the earlier studies.<sup>2</sup> Unfortunately, Gress and colleagues do not report the doses or dose ranges of thiazide diuretics and beta-blockers used in their study.<sup>11</sup> Such information would be useful in clarifying this issue.

In general, calcium-channel antagonists have not been found to have any deleterious metabolic effects, such as glucose intolerance.<sup>2</sup> However, data from both short-term<sup>13</sup> and long-term studies indicate that ACE inhibitors may actually improve insulin sensitivity and decrease the risk of type 2 diabetes.<sup>15</sup> Indeed, in the recent Heart Outcomes Prevention Evaluation trial, there was a 30 percent decrease in the rate of development of diabetes in a cohort of patients with cardio-

vascular risk factors who were treated with ramipril, an ACE inhibitor. ACE inhibitors may exert these salutatory effects by improving blood flow through the microcirculation to skeletal-muscle tissue or by improving insulin action in mediating glucose transport at the cellular level.<sup>2</sup> The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure states that ACE inhibitors are appropriate as initial agents for lowering blood pressure in patients with type 2 diabetes because of beneficial effects on metabolism as well as their documented association with decreases in mortality from cardiovascular or renal disease.<sup>1</sup> However, in clinical trials both beta-blockers and diuretics have also been associated with decreases in morbidity and mortality from cardiovascular causes.<sup>12</sup>

Prospective studies are needed to determine whether the use of ACE inhibitors in conjunction with beta-blockers would abrogate the adverse effects of beta-blockers with respect to glucose intolerance. Until such studies are conducted, beta-blockers will continue to have an important therapeutic role in patients with hypertension who have known coronary artery disease and in hypertensive patients who have diabetes, a population in which the prevalence of underlying coronary disease is high.

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## PREVENTING SEXUAL TRANSMISSION OF HIV — NEW IDEAS FROM SUB-SAHARAN AFRICA

WHEN human immunodeficiency virus type 1 (HIV-1) was identified as the cause of AIDS more than 15 years ago, it seemed possible that an end to the epidemic would follow. However, the control of communicable diseases requires far more than the identification of causative pathogens. It also requires an understanding of the ways in which a pathogen is spread; an understanding of the biologic, behavioral, and social requirements for transmission; the development of both biologic and behavioral approaches to prevention; the mobilization of social and political forces; and money. Perhaps no disease has highlighted the importance of these requirements more than HIV-1 infection, and the continuing pandemic can be viewed in terms of the limitations in these opportunities for control.

The spread of any microbial pathogen among humans depends on the infectiousness of the host (determined by the concentration of the pathogen and its potential for transmission) and the susceptibility of those exposed (determined by hereditary and acquired resistance to infection). In this issue of the *Journal*, Quinn and his colleagues demonstrate that the blood viral burden determines the efficiency of its sexual transmission.<sup>1</sup>

Quinn et al. enrolled 15,127 persons in rural Uganda in a randomized, controlled trial designed to determine whether intermittent antibiotic treatment to reduce the prevalence of other sexually transmitted diseases would also reduce the rate of transmission of HIV-1. For reasons yet to be completely defined, this approach was not successful.<sup>2</sup> Quinn et al. were subsequently able to identify 415 couples in the study population in which one partner was initially HIV-1-positive and the other HIV-1-negative. Despite the provision of counseling and condoms as part of the

study, 90 of the initially HIV-1–negative partners (21.7 percent) seroconverted during a follow-up period of up to 30 months. The rate of transmission from female to male partners did not differ significantly from the rate of transmission from male to female partners.

Using blood samples collected during the study, Quinn et al. showed that the HIV-1–positive subjects with the highest serum HIV-1 RNA levels were the most likely to infect their sexual partners: 36.7 percent of the instances of transmission occurred among couples in which the seropositive partners had serum HIV-1 RNA levels of 50,000 or more copies per milliliter. Conversely, none of the 51 HIV-1–positive subjects with serum HIV-1 RNA levels of less than 1500 copies per milliliter transmitted the virus to their sexual partners. Because the study subjects were not receiving antiretroviral therapy, the concentration of HIV-1 RNA in blood represents a balance between viral replication and host factors limiting replication.

Other factors associated with the transmission of the virus in these couples included genital discharge or dysuria and the presence of more advanced disease in the HIV-1–infected partner. Circumcision appeared to prevent infection among the men. These results support hypotheses concerning risk factors for transmission put forward by other investigators using different methods.<sup>3–5</sup>

Programs aimed at preventing HIV-1 infection have focused primarily on uninfected people in high-risk populations. Results from this study in Uganda suggest that it may be equally important to identify HIV-1–infected persons in order to try to reduce their infectiousness. When HIV-1 infection was first recognized, the associated stigma limited the number of people who sought to determine their infection status. Today, advances in treatment offer HIV-1–infected persons compelling reasons to seek testing. Opportunistic infections associated with seropositivity for HIV-1 can be prevented through the use of well-established, inexpensive regimens that are widely available. Effective antiretroviral therapy is available in developed countries and may become available in some developing countries as well.

Antiretroviral therapy reduces the viral burden in both blood and genital secretions.<sup>6</sup> It would therefore be reasonable to assume that antiretroviral therapy would reduce the sexual transmission of HIV-1. But the results from the Ugandan study do not prove this point. HIV-1 can still be cultured from the genital secretions of some patients who are receiving antiretroviral therapy and who have undetectable levels of HIV-1 RNA in blood,<sup>7</sup> a finding that means that one cannot reassure patients that they are not contagious. Indeed, if the use of such therapy increased the likelihood that HIV-1–infected patients would practice unsafe sex in the mistaken belief they were unable to transmit the virus, it could offset the benefit of viral

suppression.<sup>8</sup> Furthermore, antiretroviral therapy is currently too expensive and the treatment regimen is too complex for routine use in developing countries. However, there are other ways to reduce the viral burden, such as treatment of some systemic infections<sup>9</sup> or genital tract infections.<sup>10</sup> As research addresses these issues, those who provide care for people with HIV-1 infection must be provided with the best behavioral and biologic approaches to prevention that are available for patients in a given community. The development of a spectrum of interventions to reduce the infectiousness of HIV-1 deserves the same attention afforded strategies designed to reduce susceptibility to infection with the virus (e.g., vaccines, topical microbicides, and safe sex).

Quinn et al. found that none of the 50 HIV-1–negative male partners who had been circumcised became infected despite exposure to their HIV-1–positive partners.<sup>1</sup> This observation is consistent with the results of many other studies.<sup>5,11</sup> The protection afforded by circumcision most likely reflects changes in cutaneous barriers after the procedure that reduce the prevalence of inflammation and genital ulcers and the access of HIV-1 to receptive cells. Countries where HIV-1 infection is endemic or epidemic might well consider promoting circumcision for its public health benefits. However, the promotion or institution of a procedure that has profound cultural implications, risks of complications, and benefits that are realized only decades later represents a formidable public health and political challenge.

Although the forces fueling the HIV-1 epidemic in sub-Saharan Africa have not been fully defined, the magnitude of this epidemic has been ascribed primarily to high-risk sexual behavior.<sup>12</sup> Yet in a recent cross-sectional study of several thousand subjects who were 15 to 49 years of age, Buve<sup>11</sup> found no differences in sexual behavior between people living in parts of Africa where the prevalence of HIV-1 was high (20 to 30 percent) and those who lived in parts where the prevalence was much lower (3 to 8 percent).

Biologic factors also have a major role. The viral subtype dominant in parts of Africa (clade C) has unique properties that favor sexual transmission.<sup>13</sup> The plasma HIV-1 RNA levels in seropositive people in sub-Saharan Africa may be higher than those in HIV-1–infected people with the same stage of disease who live in more developed countries.<sup>14</sup> Furthermore, people in sub-Saharan Africa often lack host factors that can reduce the risk of infection. Mutations in the gene for chemokine receptor 5, which confer resistance to HIV-1 infection, are rare among Africans.<sup>15</sup> Men in most of Africa are uncircumcised,<sup>1,5,11</sup> and conditions such as bacterial vaginosis<sup>16</sup> that cause changes in vaginal flora that favor the acquisition of HIV-1 are common among women in Africa. Finally, the high prevalence of classic inflammatory or ulcerative sexually transmitted diseases in the same areas where

HIV-1 infection is prevalent probably increases both the infectiousness of the virus (as demonstrated by Quinn et al.) and susceptibility to the infection.<sup>3</sup>

It is unlikely that any single strategy of prevention, whether directed at those who are infected or those who are susceptible, will end the pandemic. Accordingly, the field of “prevention sciences” has evolved to bring together unlikely and sometimes unwilling partners from diverse disciplines so that political, social, behavioral, and biologic interventions can be better utilized. Working with remarkable diligence in a remote part of sub-Saharan Africa, Quinn and his colleagues have collected data that provide critical new insights into the biologic requirements for the sexual transmission of HIV-1. Tragically, results such as these could be obtained only in places with a very high incidence and prevalence of the virus and few practical or affordable means of preventing transmission. The challenge now is to use these results to develop prevention strategies that can benefit everyone, especially those who participated in this research.

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