SCIENCE AND SOCIETY

Ethics of clinical research in the developing world

Jack Killen, Christine Grady, Gregory K. Folkers and Anthony S. Fauci

Many commentators believe that all clinical-trial participants must receive a level of care equivalent to the world's best. Using HIV/AIDS research as an example, we show how this 'Uniform Care Requirement' can undermine biomedical research aimed at improving global health, and then we point towards a more rational and balanced approach to ethical assessment.

Initiatives to extend the benefits of state-of-the-art care for HIV-infected people living in the developing world have begun in earnest. Biomedical research must be a key component of these efforts. Clearly, such research must conform to robust ethical standards intended to protect individuals and societies from harm and exploitation. However, because it must target specific medical and social problems of the developing world, studies carried out in resource-poor countries might differ substantially from those in the developed countries that are most likely to sponsor the research. These differences will raise the difficult ethical issue of a conflict with the well-meaning and commonly held view that all clinical-trial subjects must receive care that is equivalent to that which would be received in the developed world. We challenge the validity of this 'Uniform Care Requirement' as a minimal ethical standard. Using a case study drawn from HIV/AIDS research, we show that, in focusing on only the level of care provided to participants, the Uniform Care Requirement could ignore other ethical principles that are equally important in clinical research. We go on to examine certain elements of a more comprehensive ethical framework that considers the compelling need to protect individuals, maintain vigilance for exploitation and answer questions that are relevant to the particular, 'real-world' problems of poor countries.

HIV/AIDS in the developing world

The HIV/AIDS pandemic is a rapidly expanding global health disaster that is heavily concentrated in the developing world[1] (FIG. 1). The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that more than 60 million people worldwide have been infected with HIV; more than 20 million of these individuals have died, and 5 million were newly infected in the year 2001 (REF. 2). Of those infected in 2001, 95% lived in developing countries, of whom nearly 70% lived in sub-Saharan Africa. In 16 African countries, more than 10% of adults 15–49 years of age are infected with HIV. The trajectory of the pandemic in other regions of the world — particularly Eastern Europe, the Caribbean, China and India — is also of great concern[2]. Besides the toll on human lives, HIV/AIDS threatens the economic viability and political stability of many countries[1–3].

In resource-rich countries, state-of-the-art treatment with highly active antiretroviral therapy (HAART) has resulted in dramatic improvements in the quality and duration of life of HIV-infected individuals, and notable reductions in HIV-related hospitalizations and mortality[1,4]. Little, if any, of this benefit has been realized in the developing world, however, because regimens of HAART are both expensive and logistically difficult to administer[1,5] (TABLE 1). Drug prices alone

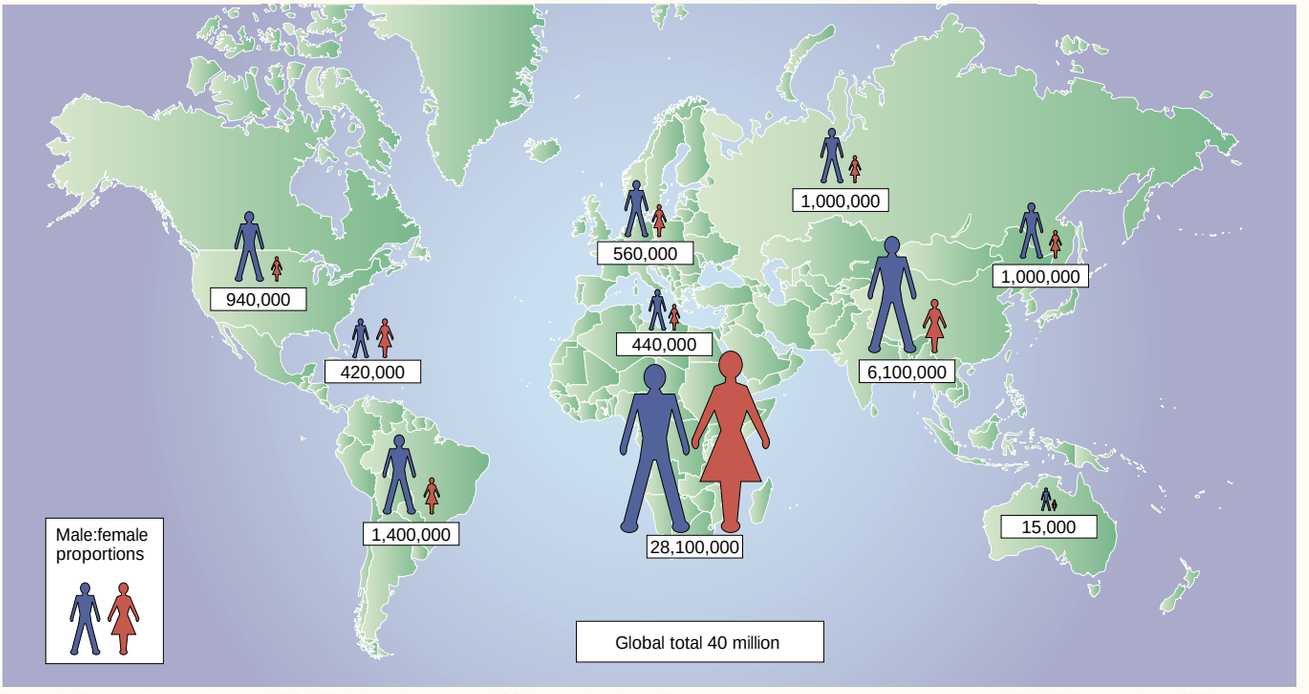

Figure 1 | **The global burden of HIV/AIDS.** As of the end of 2001, an estimated 40 million people worldwide were living with HIV/AIDS, more than 95% of whom live in developing countries where access to antiretroviral therapy is generally beyond the reach of all but a privileged few. An estimated 5 million new HIV infections and 3 million HIV/AIDS-related deaths occurred worldwide during 2001. Data are from REF. 2.

vastly exceed the health-designated resources of most countries with the highest levels of HIV seroprevalence (TABLE 2), and routine use of viral load and CD4+ T-cell counts to monitor disease progress is unrealistic and unaffordable in the frequently remote and widely dispersed, understaffed and poorly equipped health-care systems of most developing countries[5,6]. So, because most HIV-infected individuals live in resource-poor nations, HAART has so far reached only a small fraction of HIV-infected people, and most efforts to combat HIV/AIDS in the developing world have focused on prevention rather than treatment[1,6].

Fortunately, this situation is beginning to change. Growing frustration over this disparity between resource-rich and resource-poor countries dominated the most recent International AIDS conference held in Durban, South Africa, in July 2000 (REFS 7,8) (FIG. 2). Many scientists, public-health officials and activists have concluded that there is a compelling social and moral imperative for action, and have challenged conventional dogma and assumptions concerning the feasibility and priority of treating individuals with HIV/AIDS in the developing world[6,9,10]. There is also increasing recognition that the acceptability and effectiveness of HIV-screening and -prevention programmes depend on the availability of treatment[1]. At the same time, there have been marked declines in drug prices, resulting from competitive market forces generated by manufacturers of generic antiretrovirals, as well as from activist and political pressure[5,6,11]. Perhaps most significantly, the past year has witnessed the galvanization of world leaders and important global organizations, culminating in a special session of the United Nations General Assembly in June 2001, and a series of international meetings and workshops to organize and implement programmes of HIV/AIDS care, including antiretroviral therapy in the developing world[12].

Developing world research agenda

Biomedical and health-systems research aimed at informing health policy and improving prevention, diagnosis, treatment and delivery of care must be a key component of the emerging effort to bring HIV/AIDS treatment to the developing world. To be relevant, this research must be responsive to the biological, epidemiological, sociological and political factors that affect the course of the epidemic in developing countries. Unfortunately, these factors include severe global inequity in the distribution of health and health resources. In this context, there are two frequently identified HIV treatment-related research priorities (among many).

First, effective, safe and inexpensive anti retroviral therapy: drug regimens must be identified that will allow the maximal number of people to receive long-term treatment, given the practical realities of the local health-care system and severely constrained health resources. Cost and feasibility, as well as safety and effectiveness, are paramount considerations.

Second, alternative, reliable and realistic approaches to laboratory testing: most clinicians delivering HIV care in the developing world will not, for the foreseeable future, have regular access to state-of-the-art laboratories (for example, for viral-load testing and CD4+ T-cell determinations). Instead, they will need patient management algorithms based on feasible laboratory tests and clinical parameters to monitor the course and progress of their patients.

Hypothetical case study. The following clinical trial concept illustrates these two priorities. It is hypothetical, but representative of several study concepts that are being considered at present in some developing countries, and will serve as a focal point for subsequent discussion. We have called the study: Early Versus Delayed Initiation of Antiretroviral Therapy.

The government, biomedical researchers, and health-care providers of a country in sub-Saharan Africa are committed to the implementation of a programme of antiretroviral therapy. They have identified a relatively inexpensive HAART regimen based on generic drugs, as well as the resources to provide it to some, but not all, of the country's HIV-infected population. To maximize the number of people who could ultimately be treated, they seek to determine whether delaying initiation of therapy until symptoms appear would result in a clinical benefit that

Table 1 | Costs of anti-HIV drugs and laboratory tests

Antiretroviral regimens*			
A	***Cost per year (US $)‡***	***B***	***Cost per year (US $)‡***
Efavirenz	5,180	Didanosine + Lamivudine	7,208
Indinavir	6,280	Stavudine + Didanosine	7,156
Nelfinavir	8,862	Stavudine + Lamivudine	7,441
Ritonavir + Indinavir	7,248	Zidovudine + Didanosine	7,822
Ritonavir + Lopinavir	8,442	Zidovudine + Lamivudine	7,892
Ritonvair + Saquinavir	8,045		
Tests§			
CD4+ T-cell count	60–150 per test (performed two to four times per year)		
HIV RNA level	100–150 per test (performed three to four times per year)		
Range of costs (total, drugs and tests)	~$13,000–18,000 per year		

*Antiviral regimens consist of one course of therapy from list A in combination with one from list B. Antiretroviral regimens are from the 'strongly recommended' category for initial treatment of established HIV infection from the HHS/Kaiser *Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents*[13].
‡Average wholesale cost in the United States. Data from REF. 28.
§Average costs of tests in the United States are from REF. 14.

Table 2 | Countries with highest estimated adult HIV seroprevalence rates*

Country	**Adult HIV seroprevalence rate (%)‡**	**Per-capita public expenditure on health (US $)§**
Botswana	35.80	85
Swaziland	25.25	37
Zimbabwe	25.06	33
Lesotho	23.57	21
Zambia	19.95	12
South Africa	19.94	120
Namibia	19.54	79
Malawi	15.96	6
Kenya	13.95	8
Central African Republic	13.84	3
United States	0.61	1,817

*Individuals aged 15–49 years, 2000 estimates.
‡Data from the Joint United Nations Programme on HIV/AIDS, http://www.unaids.org.
§Data from REF. 29. US $, 1998.
Data for the United States are provided for comparison.

Figure 2 | **March for treatment access.** Protests such as this, before the opening ceremonies of the 13th International AIDS Conference in Durban, South Africa, in July 2000, helped catalyse a broad-based movement to reduce the cost of antiretroviral drugs in poor countries, thereby making the treatment of HIV disease in the developing world more feasible. Photograph by Greg McNeal, African American AIDS Policy and Training Institute.

is comparable to that achieved by beginning therapy earlier in asymptomatic individuals. This latter approach, which is standard practice in many developed nations, entails initiating HAART in asymptomatic HIV-infected individuals who have specified levels of $CD4^+$ T-cell count and/or plasma viraemia[13,14]. It also requires serial measurements of these laboratory parameters be taken to monitor progress[13,14], a strategy that is neither affordable nor feasible within the context of the health-care system of the developing country in question. Therefore, the researchers, care providers and government hope to validate a promising patient-management algorithm that is based on total lymphocyte count (roughly correlated with $CD4^+$ T-cell count), and various clinical parameters for decisions regarding initiation of therapy and continuing patient management (FIG. 3).

A study to address these two objectives is proposed by a collaboration of African investigators and US investigators. They plan to identify and recruit a cohort of previously untreated, HIV-infected individuals from publicly funded health clinics. They will immediately initiate HAART treatment of individuals who are clinically symptomatic. They will randomize patients who are asymptomatic to either begin treatment when their total lymphocyte count declines to a specified threshold, or begin treatment when they become symptomatic, regardless of total lymphocyte count. Throughout the study, management decisions for all patients will be based on the investigational algorithm of total lymphocyte count and clinical parameters. More intensive $CD4^+$ T-cell and viral-load assessment will be carried out in a subset of patients to validate the new approach. Long-term clinical outcomes of the two randomized groups will be determined and compared. The study, the proposed procedures for obtaining informed consent and the plan for interim monitoring of data have all been reviewed and approved by competent and duly constituted scientific and ethical review groups, both in the host country and in the United States.

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Ethical considerations

Ethical issues involved in multinational biomedical research have been the topic of considerable debate over the past several years[15–18]. HIV/AIDS clinical trials in developing countries have propelled this debate[19–23]. The trials are certain to remain focal points of controversy, given the nature and scope of the unfolding global pandemic, the research priorities mentioned above and the fact that most HIV/AIDS research worldwide will continue to be supported by sources in wealthy nations.

One of the most contentious and persistent issues in these debates concerns the level of care provided to participants of clinical trials. Some argue that as a minimal requirement, all participants of clinical research, wherever it is conducted, should receive the level of care they would receive in a developed country[18–24]. This position, which we will refer to as the Uniform Care Requirement, is sometimes presented as a ban against studies in any other country that could not be conducted for ethical reasons in the home country of the investigator or sponsor of the trial[19,24].

A frequent argument supporting the Uniform Care Requirement posits that to permit different levels of care in different clinical trials implies an ethical double-standard, one consequence of which is opening the door to exploitation of developing-country populations by researchers from resource-rich countries[20–22]. The Uniform Care Requirement attempts, very directly, to minimize these concerns. It also attempts to provide maximal benefit to trial participants.

Unfortunately, under certain circumstances the Uniform Care Requirement can mandate methodological approaches that diminish or eliminate the possibility that a study will be relevant to the subject population and, by doing so, paradoxically increase the potential for exploitation. We will examine each of these problems in relationship to the case study described above.

Judged against the Uniform Care Requirement as a minimal standard, the case study would be deemed unethical because it does not immediately provide a standard HAART regimen to a subgroup of asymptomatic individuals with low $CD4^+$ T-cell counts and high viral loads who would receive therapy under current United States guidelines[13,14]. In addition, it does not use $CD4^+$ T-cell count and HIV viral-load criteria to guide clinical decision-making, as is standard practice in the United States and other developed nations[13,14].

To be compatible with the Uniform Care Requirement, the trial would have to be redesigned to provide treatment from the outset

Box 1 | Seven requirements for ethical research

Value
A research question designed to enhance health or provide useful knowledge addressing health problems and priorities of participants.

Validity
An appropriate and feasible design and methodological rigour.

Fair subject selection
Selection of subjects and sites based on scientific appropriateness and minimization of vulnerability and risk.

Favourable risk:benefit ratio
Maximization of benefits and minimization of risks.

Independent review
Independent evaluation of adherence to ethical guidelines in design, conduct and analysis of research.

Informed consent
Processes for providing adequate information and promoting the voluntary enrollment of subjects.

Respect for enrolled participants
Respect for, and protection of, subjects' rights throughout and at the conclusion of the study.

Source: REF. 25.

to the subset of asymptomatic individuals with low $CD4^+$ T-cell counts and high viral loads, and use state-of-the-art laboratory monitoring to guide clinical decision making. However, such modification of the protocol would make the research question unanswerable, and so substantially diminish or eliminate the relevance of this research to the health-care priorities of the developing country. As we have described, the relevant scientific questions in this setting are whether delayed initiation of therapy approximates earlier initiation, and whether a feasible patient-management algorithm is valid. Applying the Uniform Care Requirement as a minimal standard would eliminate the possibility of answering the question of early-versus-delayed initiation of therapy and produce results that could only be put into practice using state-of-the-art laboratory testing, which would be neither feasible nor sustainable in that country.

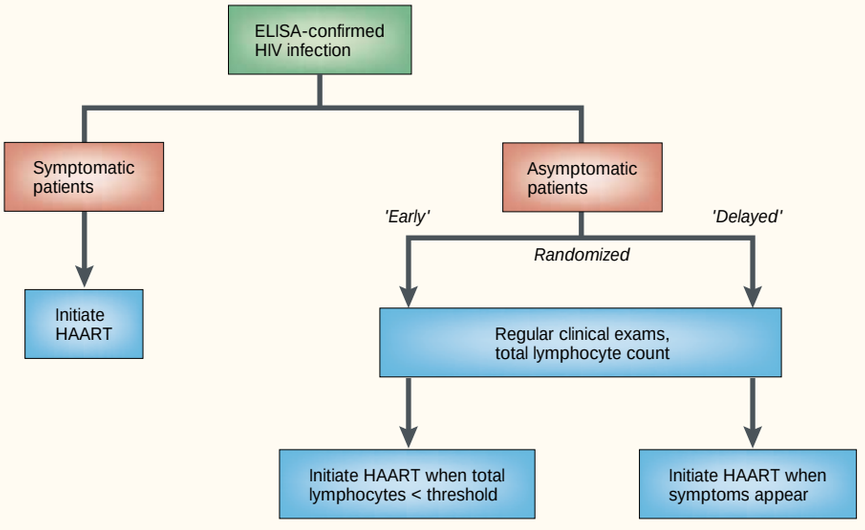

Figure 3 | **Early versus delayed initiation of antiretroviral therapy.** In a hypothetical clinical trial in a developing country, all symptomatic HIV-infected participants would be treated with highly active antiretroviral therapy (HAART). HIV-infected participants without symptoms of HIV disease would be randomized to 'early' or 'delayed' treatment groups. Initiation of HAART in the early group would begin when a patient's total lymphocyte count fell below a pre-determined threshold. In the delayed group, HAART would begin only when a patient developed symptoms of HIV diseases, regardless of total lymphocyte count.

The other scenario that is compatible with the Uniform Care Requirement would be the simultaneous performance of an identical study in the United States. However, such a study is not relevant in the United States because the specific health problem it addresses — management of HIV-infected individuals in the face of severely limited health-care resources, availability of antiretroviral drugs, and state-of-the-art diagnostic and monitoring tools — is not a major problem the United States. Moreover, a US study would probably be deemed unethical, precisely because it would not use standard and widely available laboratory monitoring, and it would randomly assign some asymptomatic people to delayed therapy when, according to standard practice guidelines, they would otherwise receive it sooner[13,14]. Finally, it is almost certain that such a study would fail in execution if it was launched in the United States, because of strong physician and patient opinions on the timing of initiation of therapy and laboratory monitoring. In short, the study should not and probably could not be conducted in the United States.

So, there are serious problems raised by the Uniform Care Requirement as a minimal ethical standard for clinical trials that are relevant to developing nations. Although the goals of its proponents are laudable, rigid application fails to consider a number of other important ethical and scientific factors, and has troubling or unacceptable consequences.

Ethical assessment

The status quo of no HIV treatment for the developing world is unacceptable from either a moral or a humanitarian perspective, and elimination of the underlying health disparities is a highly desirable but unrealistic goal for the foreseeable future. Therefore, it seems that a different approach to ethical assessment of multinational clinical research is needed.

Emanuel *et al.* recently described a framework of seven essential requirements for ethical research[25], and these are summarized in (BOX 1). This framework, built on traditional codes and widely accepted ethical principles that govern clinical research, is intended to guide investigators, ethical review committees and other interested parties. The seven requirements are to be considered and satisfied in a logical and orderly sequence so that a rational judgement about the ethics of a particular clinical study can be arrived at. The following partial analysis of the case study from the perspective of this framework is intended to further elucidate problems with

the Uniform Care Requirement, and points toward a more balanced approach to ethical analysis of international research.

Social and scientific value. The first requirement for ethical research is that the study has potential social and scientific value. In the context of international clinical research, this would include responsiveness to the health needs of the population in which it is to be carried out, a factor that is increasingly recognized as being essential to ethical research[26,27]. The case study has important potential social value in the context of a poor sub-Saharan African country struggling to find an objective basis for allocating scarce health resources. It also has notable medical and scientific value in its potential to provide objective data that would guide health-care providers through difficult, everyday problems in clinical care, including when to initiate HIV therapy and how to manage HIV-infected patients in their particular health-care context.

A crucial deficiency of the Uniform Care Requirement, as a minimal standard, is that it bypasses these considerations of context and potential social and scientific value. It seems to assume a universal set of health-research priorities and common socioeconomic conditions across nations and regions of the world. Unfortunately, this is not the reality of the world in which we live, and requirements for clinical trials based on this assumption are not valid, either in the case of HIV/AIDS or in many other health conditions that primarily afflict the developing world. In those settings, relevance to current and likely future scenarios must be a paramount consideration.

Scientific validity. The second requirement for ethical clinical research is valid scientific methodology — that is, that it stands a high probablity of yielding reliable and useful data related to the research questions it addresses. A thorough and final analysis of the scientific validity and ethics of the case study would require a review of the complete research protocol, but at the conceptual level the proposed study design directly and efficiently answers the primary study questions. Although necessary, this is not sufficient justification for the choice of methodology; one must also ask whether there are alternative methodologies that provide the same or better information with an equal or better risk–benefit ratio. Examining all other possible methodologies is beyond the scope of this discussion; however, as we have proposed, alternatives consistent with the Uniform Care Requirement impose a design that either diminishes or eliminates the social value of the study in the developing nation, or necessitate a simultaneous study of little social value and questionable ethics, to be carried out in the United States or another developed nation.

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So, perhaps the most important deficiency of the Uniform Care Requirement is that it dictates key features of study methodology and design even before the research question is framed and its value assessed. Such an approach might be workable if there were consistent valuable scientific questions across international borders, or if it were always possible to design studies to address several global priorities simultaneously and efficiently. Again, however, this is not the case with research that addresses many of the health problems in developing nations, particularly HIV/AIDS.

Fair subject selection. The Uniform Care Requirement rests, at least in part, on concerns about the unfair selection and exploitation of vulnerable populations. There is certainly an unfortunate history in medical research of exploitation of vulnerable populations that must not be ignored[15,21]. However, as the case study illustrates, at least some important research that directly addresses the needs of the developing world is not exploitative. Potentially exploitative research can — and should be — identified and prevented by careful assessment of its compliance with the requirements for social and scientific value. As described by Emanuel, *et al.*[25], ethical justification for subject selection must be determined in the context of the potential social value and scientific validity of the study, as well as an evaluation of the risks and benefits to potential subjects.

Risk–benefit ratio and independent review. Strict adherence to the Uniform Care Requirement fails to allow consideration of local perspectives on the overall risk–benefit ratio of a particular study. Instead, it can impose methodology that has important implications on ultimate community benefit without the participation of those who are most affected by the health problem to be addressed, those responsible for delivering health care to them, or the people who would be involved as participants in the study. As described by Emanuel *et al.*[25], risk and benefit must be considered in the context of potential value — a determination that, at a minimum, requires input from the subject population.

Informed consent and respect for participants. The other requirements of the framework of Emanuel *et al.*[25] would be relevant to the formal ethical assessment of the case study, and are not our objective here. Suffice it to say that they would address many elements of cultural context not directly related to the Uniform Care Issue.

Concluding remarks

The Uniform Care Requirement is based on legitimate concerns and laudable goals. However, as a minimal ethical standard it can undermine, rather than promote, research specifically targeted to health problems that primarily affect people of the developing world. Effective and sustainable treatment for HIV/AIDS and other diseases in the developing world will require studies that might not be relevant to the richest countries of the world that will be supporting them. Differences in research among developed and developing nations do not necessarily imply lower ethical standards or exploitation. An adequate ethical framework for international research must include consideration of additional factors, including local health priorities, the methodology that will best address them, and the perspectives and views of the people most directly affected by the research and its results. The arguments we have outlined here provide one approach for consideration.

Jack Killen, Christine Grady, Gregory K. Folkers and Anthony S. Fauci are at the National Institutes of Health, 9000 Rockville Pike, Bethesda, 20892 Maryland, USA.
Correspondence to J.K.
e-mail: jkillen@niaid.nih.gov.

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1. Piot, P., Bartos, M., Ghys, P. D., Walker, N. & Schwartlander, B. The global impact of HIV/AIDS. *Nature* **410**, 968–973 (2001).
2. Joint United Nations Programme on HIV/AIDS and World Health Organization. *AIDS Epidemic Update: December 2001* [online], (cited 19 Feb 02), <http://www.unaids.org/worldaidsday/2001/Epiupdate2001/Epiupdate2001_en.pdf> (2001).
3. National Intelligence Council. The global infectious disease threat and its implications for the United States [online], (cited 15 Jan 02), <http://www.cia.gov/cia/publications/nie/report/nie99-17d.html> (2000).
4. Centers for Disease Control and Prevention. HIV and AIDS cases reported through December 2000. *HIV/AIDS*

Surveillance Report **12**, 1–44 (2001).
5. Binswanger, H. P. Public health: HIV/AIDS treatment for millions. *Science* **292**, 221–223 (2001).
6. Individual members of the faculty of Harvard University. The consensus statement on antiretroviral treatment for AIDS in poor countries [online], (cited 15 Jan 02), <http://www.cid.harvard.edu/cidinthenews/pr/consensus_aids_therapy.pdf> (2001).
7. Cohen, J. AIDS meeting. Companies, donors pledge to close gap in AIDS treatment. *Science* **289**, 368–369 (2000).
8. Opinion. Grounds for hope on AIDS in Africa. *Nature* **406**, 219 (2000).
9. Cameron, E. C. Life, health and justice in the AIDS epidemic. *GMHC Treatment Issues* **15**, 1–7 (2001).
10. Farmer, P. The major infectious diseases in the world — to treat or not to treat? *N. Engl. J. Med.* **345**, 208–210 (2001).
11. Banta, D. Worldwide interest in global access to drugs. *JAMA* **285**, 2844–2846 (2001).
12. United Nations General Assembly Special Session on AIDS. Declaration of commitment on HIV AIDS: global crisis – global action. June 27, 2001 [online], (cited 15 Jan 02), <http://www.un.org/ga/aids/coverage/> (2001).
13. Department of Health and Human Services and Henry J. Kaiser Family Foundation. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents [online], (cited 15 Feb 02), <http:// www.hivatis.org> (2002).
14. Bartlett, J. G. & Gallant, J. E. *Medical Management of HIV Infection* (Johns Hopkins University, Baltimore, 2001).
15. Stephens, J. *et al.* The Body Hunters. *Washington Post* (December 17–22, 2001).
16. Macklin, R. After Helsinki: unresolved issues in international research. *Kennedy Inst. Ethics J.* **11**, 17–36 (2001).
17. Koski, G. & Nightingale, S. L. Research involving human subjects in developing countries. *N. Engl. J. Med.* **345**, 136–138 (2001).
18. Shapiro, H. T. & Meslin, E. M. Ethical issues in the design and conduct of clinical trials in developing countries. *N. Engl. J. Med.* **345**, 139–142 (2001).
19. Lurie P., & Wolfe, S. M. Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. *N. Engl. J. Med.* **337**, 853–856 (1997).
20. Angell, M. The ethics of clinical research in the third world. *N. Engl. J. Med.* **337**, 847–849 (1997).
21. Angell, M. Ethical imperialism? Ethics in international collaborative clinical research. *N. Engl. J. Med.* **319**, 1081–1083 (1988).
22. Angell, M. Investigators' responsibilities for human subjects in developing countries. *N. Engl. J. Med.* **342**, 967–969 (2000).
23. Rothman, D. The shame of medical research. *The New York Review of Books* [online], (cited 30 Nov 00), <http://www.nybooks.com/articles/13907>.
24. Annas, G. Prominent opinion: the ethics of international research trials in the developing world. *J. Med. Ethics* **II**, 7–10 (2001).
25. Emanuel, E. J., Wendler, D. & Grady C. What makes clinical research ethical? *JAMA* **283**, 2701–2711 (2000).
26. Council for International Organizations of Medical Sciences (CIOMS). *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (CIOMS, Geneva, 1993).
27. National Bioethics Advisory Commission. *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries* [online], (cited 20 Feb 02), <http://bioethics.georgetown.edu/nbac/clinical/Voll.pdf> (2001).
28. RED BOOK™ Database Service (MICROMEDEX, Greenwood Village, Colorado, 2002).
29. World Health Organization. *World Health Report 2001* (WHO, Geneva, 2001).

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National Institute of Allergy and Infectious Diseases: http://www.niaid.nih.gov
HIV/AIDS treatment
Department of Health and Human Services and Henry J. Kaiser Family Foundation. Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents: http://www.hivatis.org/trtgdlns.html#Adult
Harvard Consensus Statement on Antiretroviral Treatment for AIDS in Poor Countries: http://www.cid.harvard.edu/cidinthenews/pr/consensus_aids_therapy.pdf
Medical Management of HIV Infection by John G. Bartlett, M.D. and Joel E. Gallant, M.D., M.P.H.: http://hopkins-aids.edu/publications/book/book_toc.html
Bioethics resources
Council for International Organizations of Medical Sciences: http://www.cioms.ch/
National Institutes of Health: Bioethics Resources on the Web: http://www.nih.gov/sigs/bioethics/
National Reference Center for Bioethics Literature: http://www.georgetown.edu/research/nrcbl/
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Access to this interactive links box is free online.

ERRATUM

CHEMOKINE RECEPTORS: MULTIFACETED THERAPEUTIC TARGETS

Amanda E. I. Proudfoot

Nature Rev. Immunology **2**, 106–115 (2002).

Reference 7 was incorrectly cited. The correct citation is:
Schwarz, M. K. and Wells, T. N. Interfering with chemokine networks — the hope for new therapeutics. *Curr. Opin. Chem. Biol.* 3, 407–417 (1999).

The online version of this Review has been corrected.