Clinical Trials in Sub-Saharan Africa and Established Standards of Care

A Systematic Review of HIV, Tuberculosis, and Malaria Trials

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Context The minimum standard of care required for participants in clinical trials conducted in resource-poor settings is a matter of controversy; international documents offer contradictory guidance.

Objective To determine whether recently published trials conducted in sub-Saharan Africa met standards of care consistent with best current clinical standards for human immunodeficiency virus (HIV) treatment, tuberculosis treatment, and malaria prevention.

Data Sources Trials published during or after January 1998 that were indexed at the time of the MEDLINE and Cochrane Controlled Trials Register Search (November 20, 2003).

Study Selection All randomized clinical trials that were conducted in sub-Saharan Africa in 3 clinical domains: HIV disease, tuberculosis treatment, and malaria prophylaxis.

Data Extraction To establish criteria for best current standards of care, evidence from the literature and published guidelines accepted for well-resourced settings were analyzed; the actual care offered in the trial was then compared with these standards.

Data Synthesis A total of 128 eligible articles described data from 73 different randomized clinical trials. Only 12 trials (16%) provided care that met guidelines to both intervention and control patients. Only 1 of the 34 trials that enrolled patients with HIV disease provided antiretroviral treatment that conformed to guidelines. Conversely, all tuberculosis treatment trials (n=13, including 3 for HIV-infected patients) provided tuberculosis therapy that conformed to guidelines. Twenty-one (72%) of 29 malaria prophylaxis trials tested interventions that met guidelines, but only 3 (10%) used any active prophylactic intervention in the control group. Of the 59 trials (81%) that reported on the process of ethical review, all were reviewed by a host African institution and 64% were additionally reviewed by an institution in a developed country.

Conclusions Rates of adherence to established clinical guidelines of care in randomized clinical trials of HIV treatment, tuberculosis treatment, and malaria prophylaxis varied considerably between disease categories. In determining clinical standards for trials in sub-Saharan Africa, researchers and ethics committees appear to take the local level of care into account.

JAMA. 2004;292:237-242 www.jama.com

FOLLOWING THE 1994 ACTG 076 trial,[1] which demonstrated that an intensive course of zidovudine therapy substantially reduced the risk of transmission of the human immunodeficiency virus (HIV) from pregnant mothers to their infants, a series of trials was conducted in developing countries to test less intensive zidovudine regimens that might be affordable and feasible in that context.[2,3] These trials stimulated intense debate since they appeared to violate guidelines articulated in the Declaration of Helsinki—specifically, the requirement that research participants receive the "best proven" therapeutic method,[4] and especially because control patients did not receive any active treatment. Based in part on the Declaration of Helsinki, some proposed that any research that uses a standard of care that would be considered inferior to the standard used in resource-rich countries and would therefore be unethical in those settings, ought also to be unethical in resource-poor settings.[5,6]

However, others argued that aiming for standards available only in the wealthiest countries might have perverse consequences, since for conditions for which the "best standard" is not locally accessible, the requirement would potentially prohibit the testing of interventions most relevant to resource-poor settings.[7,8] Some have

For editorial comment see p 269.

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endorsed alternative guidelines that take into account the level of care that might ordinarily be available outside the trial in determining the required standard of care for participants in clinical trials, calling for the "best attainable and sustainable" treatment.[9,10] Various international guidelines continue to offer conflicting guidance on this issue.[11-15]

Despite the intensity of the debate, and despite its importance for international research, we are unaware of any systematic review of recent clinical trials in resource-poor countries to determine what standards are generally applied in various diseases and what ethical guidelines for such research are likely to be met. We performed a systematic review of all recent trials conducted in sub-Saharan Africa in 3 clinical areas with global public health importance—HIV treatment, tuberculosis treatment, and malaria prevention.

METHODS

Study Eligibility Criteria

We retrieved all original articles reporting results on randomized clinical trials conducted in sub-Saharan Africa published during or after January 1998 and indexed at the time of the literature search (November 20, 2003) that investigated one of the following disease areas: HIV treatment, tuberculosis treatment, and malaria prevention. We selected these discrete areas because there are proven effective interventions for each, they represent a high burden of disease in sub-Saharan Africa,[16] and, based on a prior systematic review,[17] we expected to find a sufficient number of trials to support a meaningful analysis.

We excluded trials of malaria treatment, since guidelines vary considerably from region to region, making standards across trials difficult to establish. Similarly, we excluded prevention trials for HIV and tuberculosis unless they specifically enrolled patients with active disease for which treatment guidelines might apply. For example, we included trials of HIV prevention if before-and-after HIV testing was part of the experimental protocol and if more than 10% of enrolled patients were HIV-positive at baseline. We excluded nonrandomized and pseudo-randomized controlled trials but included trials using cluster randomization schemes. Trials enrolling nonlocal populations (such as tourists), trials in northern Africa, and trials not in humans were also excluded. Multinational trials were included if some patients had been recruited in sub-Saharan Africa. Meeting abstracts, books, and other reports (eg, meeting symposia or articles in tabloid-type publications) were also excluded. Otherwise, eligible trials were included if publication was identified in the period 1998 through 2003 regardless of whether an earlier report(s) had also been published before 1998.

Identification of Trials

Our search strategy was similar to that used in a previously published systematic review.[17] Briefly, this included a sequential search of MEDLINE and the Cochrane Controlled Trials Register. Terms reflecting randomized clinical trials were conjugated with "Africa," "sub-Saharan Africa," and specific country names. We then crossed this set of citations with HIV, tuberculosis, and malaria. We screened and evaluated all abstracts derived from these searches. For all studies that could not be excluded on the basis of the abstract, we retrieved the full articles.

Database

From each article, we extracted the following information: author, journal, year of publication, the start and end dates for recruitment, unit of randomization (individual or cluster), sample size, disease(s) targeted, age distribution, type of intervention in each study arm, and country or countries of recruitment.

We also extracted, where possible, the funding source(s) for the trial, the institutional affiliation (and its location) of the first author, whether the ethical review was described in the article and, if described, whether ethical approval was obtained from an institution in the country in which it was performed (the host country), an institution in a non-African sponsoring or collaborating country, or both.

Establishing Standards of Care

Our primary objective was to determine whether recently published trials conducted in sub-Saharan Africa met standards of care consistent with "best current" standards for specific items (defined below), where "best current" is assumed to refer to a universal, optimal standard that is not constrained by the potentially limited availability of specific interventions in different settings.

For each clinical domain, we established criteria for best current standards for these items of care, based on published evidence or widely accepted guidelines as described below. We aimed to use standards of care that were established by 1996 (allowing for 2 years before the first published trial that we analyzed), since the level of care provided in a trial cannot be considered "substandard" if the standard was established subsequent to its conduct. Since care for HIV was evolving at this time, the care standard we used depended on the dates during which the trial was conducted.

Trials were then classified as providing care that either "met guidelines" or "did not meet guidelines." We used the term "met guidelines" in a narrow sense, referring only to the specific criteria we established in this study, recognizing that trials that met our criteria might still have failed to provide adequate care in other respects. The clinical standards used and their sources are summarized in TABLE 1 and discussed in more detail below. For all trials, classification was performed by consensus between 2 investigators (D.M.K. and D.M.M.).

HIV Treatment

The standard of care in trials that enrolled patients who were known to be HIV-infected were evaluated according to guidelines published by the US National Institute of Allergy and Infectious Diseases and the International AIDS Society-USA.[18-21] To meet our criteria for the best current standard, trials

enrolling patients after 1997 were required to provide patients with advanced HIV disease (either symptomatic disease or asymptomatic disease with a CD4 cell count <350/μL) with highly active antiretroviral therapy (HAART) consisting of at least 3 antiretroviral drugs, including 1 protease inhibitor or 1 nonnucleoside reverse transcriptase inhibitor.[20,21] For trials concluded before this time, but after 1995, the best current standard for patients with advanced disease required at least 2 antiretroviral drugs.[19] For any trials concluded before this time (if any), provision of at least a single antiretroviral agent would be considered to meet criteria.[18] Trials that excluded patients with advanced disease were classified as meeting guidelines, regardless of the provision of antiretroviral therapy.

As the International AIDS Society-USA recommendations indicate that antiretroviral therapy should not be withheld because of pregnancy,[20,21] these standards were applied also to trials enrolling HIV-infected pregnant women, such as mother-to-child transmission (MTCT) trials. We also did a subanalysis of these trials examining whether antiretroviral therapy was given for MTCT prophylaxis in intervention and control patients.

Tuberculosis Treatment

The standards of care in trials testing treatment strategies against tuberculosis were classified as meeting guidelines if enrollees were provided with 4 drugs for 2 months followed by at least 2 drugs for at least 4 additional months, daily or thrice weekly, according to established treatment guidelines.[22]

Malaria Prophylaxis

In 1995, a 10-trial meta-analysis showed that insecticide-treated bednets reduced the incidence of febrile parasetemia by 24% compared with untreated bednets and by 50% compared with no nets.[23] By 1996, there was substantial evidence that insecticide-treated bednets reduced both morbidity and child mortality in endemic areas.[24-29] However, formal guidelines on the implementation of insecticide-treated bednets were not developed until 2000,[30] and several chemoprophylactic regimens (particularly doxycycline and mefloquine) had also been shown to be effective.[31-34] Therefore, we classified trials that used insecticide-treated bednets (or another such insecticide-treated barrier method) or any chemoprophylactic regimen with known antimalarial properties as meeting guidelines.

RESULTS

Our search strategy identified 128 original articles presenting data from 73 separate trials. These trials are described briefly in TABLE 2. (A list of all trials included in this study is available from the authors). Among all trials, only 12 (16%) provided therapy to both treatment and control patients that might be said to be consistent with our prespecified definition of "best current" standards.

HIV Trials

There were 34 trials that studied different aspects of HIV disease in sub-Saharan Africa included in this analysis. The focus of these trials varied, including HIV treatment (n=4), MTCT prophylaxis (n=13), treatment or prophylaxis of opportunistic infections (including tuberculosis) (n=13), diarrhea/wasting (n=1), and prevention

Table 1. Reference Standard of Care in Target Areas

Disease	Standard Therapy	Source
Malaria prevention	Any active therapy (insecticide-treated barrier or chemoprophylaxis with an established antimalarial)	WHO and published clinical trials[23-31]
HIV treatment	Treatment with 3 antiretroviral drugs, including 1 protease inhibitor or 1 nonnucleoside reverse transcriptase inhibitor for patients with symptoms or with a CD4 cell count <350 cells/μL*	NIAID and International AIDS Society-USA guidelines[18-21]
Tuberculosis treatment	4 Drugs for 2 months followed by ≥2 drugs for 4 months, daily, or 3 times weekly	WHO[22]

Abbreviations: HIV, human immunodeficiency virus; NIAID, National Institute of Allergy and Infectious Diseases; WHO, World Health Organization.
*Less intensive antiretroviral regimens were used as the standards for trials concluded prior to 1997, consistent with guidelines, as discussed in the text.

Table 2. Results of Systematic Review

Type of Trial	Total No. of Trials	No. of Trials Providing Care That Met Guidelines/Total No. of Trials (%)		Trials Reporting Ethical Review		
		Control Group	Intervention Group	Overall No./ Total No. of Trials (%)	No. of Reviewing Institutions/ Overall No. (%) Host*	Sponsoring†
Total	73	14/73 (19)	32/73 (44)	59/73 (81)	59/59 (100)	38/59 (64)
HIV	34	1/34 (3)	1/34 (3)	29/34 (85)	29/29 (100)	21/29 (72)
Tuberculosis	13	13/13 (100)	13/13 (100)	8/13 (62)	8/8 (100)	2/8 (25)
Malaria	29	3/29 (10)	21/29 (72)	25/29 (86)	25/25 (100)	18/25 (72)

Abbreviation: HIV, human immunodeficiency virus.
*Host (African) country ethical review.
†Sponsoring (non-African) country ethical review.

strategies, such as the treatment of sexually transmitted diseases (n=6). These prevention trials typically enrolled patients with a very high baseline HIV prevalence rate (median seroprevalence at baseline, 100%; range, 10%-100%). Four trials assessed HIV treatment, but 3 of these were MTCT trials classified additionally as treatment trials because they compared immunological outcomes in the mothers in the different treatment groups, for example, those receiving or not receiving vitamin supplementation. The remaining treatment trial was the industry-sponsored, multinational Canada, Australia, Europe, and South Africa (CAESAR) Trial, which included patients from Canada, Australia, Europe, and South Africa and tested whether lamivudine (with or without loviride) in addition to zidovudine-based antiretroviral regimens improved outcomes.[35,36] This was the only trial that met "best current" treatment guidelines, according to our standards. Indeed, it was the only trial that offered any form of antiretroviral treatment (apart from the short courses provided as prophylaxis in the MTCT trials).

Among the 13 MTCT trials, 5 trials gave some form of antiretroviral prophylaxis to all patients in the trial, both in the intervention and control groups, although the control groups even in these trials did not necessarily receive a proven effective regimen. In another 3 trials, only the intervention group received antiretroviral prophylactic therapy. Finally, there were 5 trials that did not provide antiretroviral therapy within the protocol; these included trials testing vitamin therapies, cesarean delivery, and breast vs formula feeding.

Tuberculosis Trials

There were 13 tuberculosis treatment trials conducted in sub-Saharan Africa that were included in this review, including 3 in patients with HIV disease also included in the HIV trials discussed above. All trials met treatment guidelines for tuberculosis therapy. In the 3 trials testing tuberculosis regimens in patients with HIV disease, standard tuberculosis therapy was given, but antiretroviral therapy was not included in the protocol.

Malaria Trials

There were 29 trials that tested different strategies for malaria prophylaxis in endemic areas of sub-Saharan Africa. Of these, all but 3 trials tested the intervention against placebo or no therapy. Twenty of the 29 trials tested therapies based on interventions known to be active (insecticide-treated bednets or barriers [n=6], chemoprophylactic regimens [n=13], both [n=1]) against placebo, and thus "standards of care" were classified as meeting guidelines for the intervention group only. An additional trial tested 2 forms of chemoprophylaxis against one another; this was the only trial that was classified as providing prophylaxis that met guidelines in both intervention and control patients. Two trials used insecticide-treated bednets as controls (testing case management and indoor residual spraying). The remaining 6 trials tested unproven therapies against placebo, including vaccines (n=3), indoor residual insecticide spraying (n=1), zinc supplementation (n=1), and teaching syndromic presumptive treatment to parents (n=1) without providing or recommending either bednets or chemoprophylaxis.

Ethical Review

Fifty-nine trials (81%) reported institutional review board or "ethics committee" approval of their study in at least 1 of their published reports. Of these, all had approval from institutions within the host (African) country; 64% additionally had approval from institutions in non-African sponsoring countries. Trials with both local and nonlocal review were more likely to offer care that did not conform to clinical guidelines on the specified items than trials with local review only. Of the 38 trials that reported ethics review both locally and in a sponsoring non-African country, only 1 trial (3%) provided care that met guidelines (the CAESAR study). Of the 21 trials that reported African-only ethics review, 7 (33%) provided care that met guidelines ($P<.001$).

Funding Sources

Of 65 trials that reported funding sources, 42 (65%) received at least some funding from a western governmental agency (such as the US National Institutes of Health, the US Centers for Disease Control and Prevention, or the UK Medical Research Council); 26% (n=17) received funding from an international body (such as a United Nations agency or the World Health Organization); 22% (n=14) received funding from local governmental sources; 18% (n=12) received funding from the pharmaceutical industry; and 17% (n=11) received funding from private foundations (such as the Wellcome Trust). There was no independent association between funding sources and conformity with guidelines.

COMMENT

Our systematic review of recent trials conducted in sub-Saharan Africa found that adherence to "best current" standard of care guidelines was largely dependent on disease category. In general, patients with HIV disease enrolled in trials received care that did not conform to clinical guidelines; neither control nor intervention groups received "best current" antiretroviral therapy, even when they had symptomatic or advanced disease. In contrast, for tuberculosis treatment, all patients, in both the control and intervention groups, appeared to be treated with antituberculosis drugs according to clinical guidelines. Finally, in studies testing interventions for malaria prevention, patients in control groups were generally not provided with any active prophylaxis, although the tested interventions in the experimental arm were typically variations of proven effective preventive measures.

A likely explanation for these findings is that investigators who design and conduct these studies, and the ethics committees who review and approve them, consider trial design in the context of the local level of care rather than

the international standard of care. At the time these studies were conducted, HAART was not available to most persons in sub-Saharan Africa, and malaria prevention methods were not widely used. In contrast, the available standard of care for the treatment of tuberculosis was the same as that available in wealthy countries. It is unlikely that researchers conducting tuberculosis trials adhere to more stringent ethical standards than those conducting HIV or malaria prophylaxis trials. Indeed, even within the same trial, patients with both tuberculosis and HIV consistently received adequate tuberculosis therapy but not antiretroviral therapy.

We also found that trials in which ethical review was conducted only locally, and not also at a sponsoring (non-African) institution, were more likely to use clinical standards that conformed to guidelines. However, this may be a result of the overrepresentation of tuberculosis trials in the subset of trials that were reviewed only locally. Other explanations may include the fact that tuberculosis trials are simpler and less expensive to conduct and therefore less likely to require international collaboration, and that trials using therapies that do not conform to clinical guidelines may be more likely to be reviewed by both local and non-African sponsoring institutions as an extra precaution.

Despite the intuitive appeal that standards of care should be the same for clinical trials everywhere, many researchers appear to recognize the need for trial design to be sensitive to local levels of care, if the trials are to be relevant to the population from which patients are drawn.[37] It has been pointed out that it is not realistic to expect clinical care in sub-Saharan Africa, where approximately 50% of the population live on less than a dollar a day, to have care that is similar to well-resourced countries.[38] Comparing the effects of new interventions intended for resource-poor settings against the "best current method" from well-resourced settings may be of little value if that method is ordinarily unavailable. That is, using a universal standard of care would proscribe a whole category of research of potential import to resource-poor settings, namely the study of inexpensive "intermediate" interventions that might be effective and feasible, even if considerably less effective than the best standard.[39,40] For example, single-dose nevirapine is clearly effective for the prevention of vertical transmission of HIV,[41] but the rate of vertical transmission with this regimen ranges from 10% to 20%,[41-43] while with HAART, this rate approaches 1%.[44] Testing nevirapine against this standard would have served only to demonstrate its inferiority, not its efficacy. For this reason, comparison to "the best attainable and sustainable" standard has received considerable support as an alternative.

There are several limitations to our study. We examined only 3 clinical domains. Although these diseases account for a very high burden of illness in sub-Saharan Africa, the findings may not extrapolate to clinical trials in other diseases. Additionally, our review included only published randomized clinical trials. Unpublished clinical trials and, importantly, many cohort studies might otherwise be relevant. It should be noted, however, that the requirement for best standard of care in the Declaration of Helsinki does not seem to apply to cohort studies at all, since it only specifies the level of care that a control group should receive. Also, some might disagree with our specific definitions of standard of care for the 3 diseases included. However, we aimed at selecting standards of care that in principle are beyond controversy. Another limitation is that we did not examine comparative trials conducted in populations living in well-resourced countries in North America and Europe to compare the rate of compliance with clinical guidelines.

Finally, some might argue that examining what is actually done should be of little relevance to establishing research ethics guidelines, since normative conclusions cannot be drawn from a descriptive study; the ethical review, approval, and publication of the included studies does not imply that they were de facto ethically justified. However, when considering guidelines for the ethical conduct of clinical trials, it should be of some import to policy makers that, among studies selected in this review, only 16% of the trials conducted in resource-poor settings provided therapy that could be considered consistent with the best current standard of care, even when the Declaration of Helsinki required that standard.

Author Contributions: Dr Kent had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Kent, Mwamburi, Bennish, Ioannidis.
Acquisition of data: Kent, Mwamburi, Kupelnick, Ioannidis.
Analysis and interpretation of data: Kent, Mwamburi, Bennish, Ioannidis.
Drafting of the manuscript: Kent.
Critical revision of the manuscript for important intellectual content: Kent, Mwamburi, Bennish, Kupelnick, Ioannidis.
Statistical expertise: Mwamburi.
Obtained funding: Kent, Bennish.
Administrative, technical, or material support: Kent, Bennish, Kupelnick.
Supervision: Ioannidis.
Funding/Support: Dr Kent is a Pfizer Scholar in Clinical Epidemiology and is supported by Career Development Award K23 NS44929-01 from the National Institute for Neurological Disorders and Stroke. Dr Mwamburi is supported by training grant 1D43 TW01083-01 for Medical Informatics for African Nationals from the Fogarty International Center of the National Institutes of Health. Dr Bennish is supported by mid-career grant K24 AI/HDO1671-01 from the National Institute of Allergy and Infectious Diseases of the US National Institutes of Health and by grant 62925 from the Wellcome Trust.
Role of the Sponsor: Pfizer, the National Institute for Neurological Disorders and Stroke, Fogarty International Center of the National Institutes of Health, National Institute of Allergy and Infectious Diseases, and Wellcome Trust had no role in the design and conduct of the study, in the collection, analysis, and interpretation of the data, and in the preparation, review, or approval of the manuscript.

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