

## Randomised controlled trials in Africa of HIV and AIDS: descriptive study and spatial distribution

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### Abstract

**Objectives** To identify and describe randomised controlled trials on HIV and AIDS conducted in Africa and to map their spatial distribution using exact geographic coordinates.

**Design** Construction and analysis of a database of trials conducted wholly or partly in Africa and reported before 2004.

**Data sources** CENTRAL, Medline, Embase, and LILACS.

**Results** Our comprehensive search yielded 284 distinct records that were potentially eligible for inclusion in the database. Of these, 150 articles reported on 77 eligible trials published or reported from 1987 to 2003. Seven trials were identified exclusively from the CENTRAL database. Trials were conducted in 18 of 48 countries in sub-Saharan Africa. None were conducted in north Africa. Only 19 had a principal investigator located in an African country. Forty two trials assessed prevention and 35 assessed treatment. Most studies were funded by government agencies outside Africa (n = 43), with the pharmaceutical industry providing partial support to 16 of these. The pharmaceutical industry provided full or partial support to a further 18 trials. Only 43 trials reported conducting a power calculation for determining sample size. There was no mention of ethical approval or informed consent in 19 and 17 trials, respectively.

**Conclusion** The relatively small number of HIV/AIDS trials conducted in Africa is not commensurate with the burden of disease. Geographical mapping as an adjunct to prospective trial registration is a useful tool for researchers and decision makers to track existing and future trials.

### Introduction

The randomised controlled trial is the best study design to determine whether an intervention is effective.<sup>1</sup> Wherever possible, decisions to use particular interventions should be based on evidence from well conducted randomised trials. Over two million Africans died from AIDS in 2003, and women and children are disproportionately represented in this figure.<sup>2</sup> People with HIV and AIDS, clinicians, policy makers, health activists, and many other key players require information on the most effective forms of prevention and treatment relevant to their setting. Researchers and funders of research also require knowledge of current trials to better address gaps and disparities in research.<sup>3,4</sup>

We have assembled a database of African-based trials of prevention and treatment interventions for HIV and AIDS as part of a larger study to compare the methods of these trials with those conducted elsewhere. We have described all African trials reported before the end of 2003.

### Methods

We identified all records pertaining to HIV or AIDS in PubMed (see [bmj.com](http://bmj.com)) and added a sensitive filter to identify all possible reports of relevant randomised trials.<sup>5</sup> We searched the Central Register of Controlled Trials (CENTRAL) (issue 2, 2004); the National Library of Medicine Medline database (via PubMed on 16 August 2004); Embase via OVID (on 4 September 2004); and Latin American and Caribbean Health Sciences Literature (LILACS) (on 4 December 2004).

Searching these databases in the second half of 2004 allowed us to capture all reports up to 2003 by avoiding the delay between reporting and indexing in the database. The search was not limited by language. We included LILACS to increase our yield of trials from Portuguese speaking Africa and Embase to improve coverage of journals in European languages other than English.

One of us (NS) read each abstract to determine eligibility (table 1). Two experienced hand searchers screened all the retrieved abstracts for controlled trials, regardless of location. One of us (MC) checked the sample they identified for any African randomised controlled trials as a quality control measure. We obtained full articles of all potentially eligible trials and those about which we were uncertain. NS read these articles, determined final eligibility, and extracted data using a standardised form developed specifically for this project (table 2). The data were entered on a specifically designed MSAccess database.

### Analysis

Data are presented as numbers and simple frequencies calculated in MS Excel. Descriptive statistics and qualitative information are presented when appropriate.

### Mapping

For trial location, we recorded the geographic coordinates of each trial and used geographic mapping software (MapInfo) to plot the position of each trial.

### Results

#### Search results

We retrieved 440 records from CENTRAL, 47 from LILACS, 7734 from PubMed, and 4594 from Embase. We identified 284 discrete potentially eligible records from all the searches and obtained the full articles. The reliability of rating between NS and MC was >91%. After reading each article, NS identified 150



The search terms and the full list of references for included trials can be found on [bmj.com](http://bmj.com)

**Table 1** Eligibility criteria for randomised controlled trials included in database

	Inclusion criteria	Exclusion criteria
Intervention	Efficacy or effectiveness of HIV/AIDS specific intervention, including pilot studies	Safety and acceptability trials
	Efficacy or effectiveness of non-HIV/AIDS specific intervention, but with subgroup of at least 5% (n>10) HIV positive participants	Trials assessing behavioural interventions without measuring HIV incidence
Location	Conducted wholly in Africa, or partly if multinational trial	Trials conducted on Africans living outside continent
Participants	Infected with HIV-1, HIV-2 or dually infected, or in case of prevention trials, HIV negative, but at risk of HIV	
Trial date	Reported before 2004 (if preliminary data only, authors contacted)	

**Table 2** Data extraction items for each trial

Item	Details recorded
Reference	Publication citation; source database(s)
Intervention	Prevention; treatment
Location	Single or multicentre; city; region; country; geographic coordinates; details of other countries if multinational trial
Principal investigator	Name; affiliation; qualifications; country of residency
Funder	African; non-African; government agency; non-government agency; inter-government agency; pharmaceutical
Ethical approval	African committee; non-African committee; method of informed consent
Methods	Sample size; power calculation

articles dealing with a total of 77 randomised controlled trials (figure 1) (see [bmj.com](http://bmj.com) for full list of trials and articles).

**Article details**

Sixty eight of the 77 trials were reported in articles retrieved by the PubMed search, either exclusively (three) or in combination with the CENTRAL and Embase searches. We retrieved seven trials exclusively from CENTRAL and two exclusively from Embase. No eligible articles were retrieved from LILACS.

We identified 71 of the 77 trials from full journal articles. Three of the trials were reported only in conference proceedings, and three were identified from news articles retrieved in the searches with additional information being

obtained directly from the original authors (three of these trials are unpublished). A large proportion of the 150 articles were published in the journals *Lancet* (n=28) and *AIDS* (n=28). Twelve articles appeared in the *Journal of Acquired Immune Deficiency Syndrome*, and five articles each in the *Journal of Infectious Diseases*, *Clinical Infectious Diseases*, and the *New England Journal of Medicine*. The rest were published in 50 other journals and indexed news bulletins. Four of these were from the French journals of *Santé*, *Revue des Maladies Respiratoires*, *Annales de la Société Belge de Médecine Tropicale*, and *Pathologie et Biologie*. Thirty trials had been published in more than one article, with one trial of micronutrient supplementation to prevent mother-to-child transmission being published in nine different articles.<sup>6</sup>

**Principal investigators**

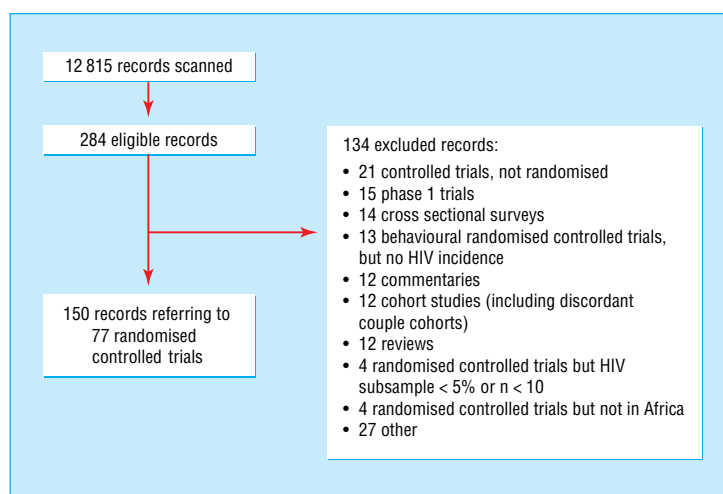
Not every trial clearly reported the identity of the principal investigator. When we were uncertain, we classified the first author of the main trial report as the principal investigator. The principal investigator was based in the United States for 23 trials and in the United Kingdom for eight trials. Other principal investigators based outside Africa were from Australia (1), Belgium (3), Canada (3), Denmark (1), France (4), Ireland (3), Germany (2), Sweden (1), Switzerland (1), and the Netherlands (4). The principal investigators based within Africa were from Côte d'Ivoire (4), Kenya (2), Malawi (2), South Africa (4), Zambia (3), and Zimbabwe (4). We could not identify the location of the principal investigator for two trials.

**Trial characteristics**

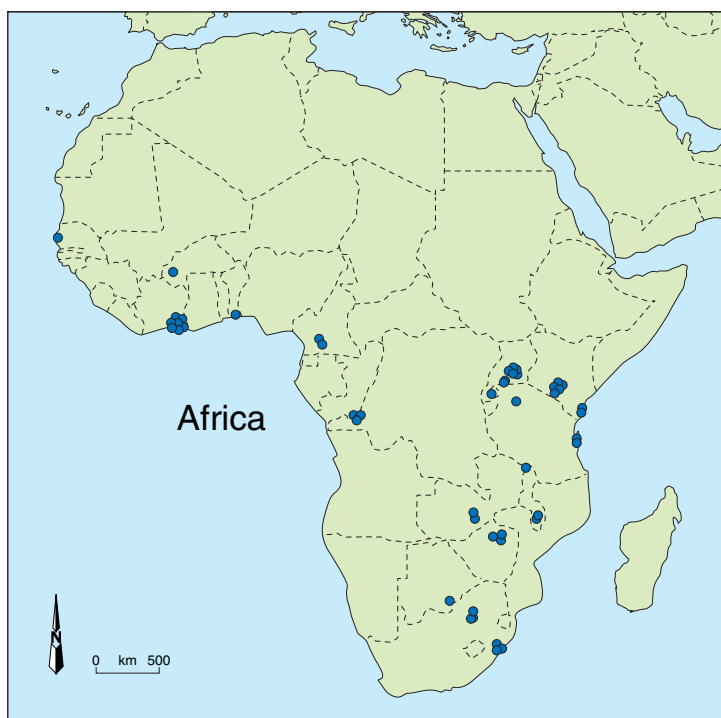
Forty two trials assessed prevention interventions and 35 were treatment trials.

For prevention, we categorised interventions to reduce transmission from mother to child (13); drugs for preventing opportunistic infections (12); microbicides (5); behavioural interventions (5); drugs for preventing HIV transmission (such as treatment of sexually transmitted infection) (4); and other prevention measures (such as nutritional supplements) (3). We did not find any completed trials of vaccine efficacy.

Treatment trials included drug treatment of HIV and AIDS (7); drug treatment of opportunistic infections (12); drug treatment of other infections in people with HIV and AIDS (11); and other treatments (such as nutritional supplementation) (5). None of the trials assessed behavioural treatments for HIV and AIDS.



**Fig 1** Inclusion of trials in database



**Fig 2** Randomised controlled trials of prevention of HIV and AIDS, 1987-2003. Circles indicate site of trial based on geographic coordinates. N=42 (some trials have more than one country location)

The earliest trial started in 1987 and assessed the preventive efficacy of a microbicide, nonoxinol 9 gel, among 138 women in Nairobi, Kenya.<sup>7</sup> Two other studies, both conducted in what was then Zaire (now the Democratic Republic of Congo), began before 1990.<sup>8,9</sup> Start dates were uncertain for 15 trials, and the 59 remaining trials began during the 1990s or early 2000s.

#### Location and mapping

Figures 2 and 3 show the location of the trials categorised according to prevention or treatment. Trials have been conducted in 18 of the 48 countries of sub-Saharan Africa with no trials in north Africa. Forty two trials were single centre studies and 25 were multicentre trials done within a single African



**Fig 3** Randomised controlled trials of treatment of HIV and AIDS, 1987-2003. Circles indicate site of trial based on geographic coordinates. N=33 (coordinates were not available for two trials)

country. Nine trials were multinational multicentre trials, five of which took place in more than one African country. The four other trials were conducted across continents.

### Sample size and quality of methods

Sample size ranged from 16 participants in a nutritional supplement trial conducted in a rural area of Uganda<sup>10</sup> to 39 836 participants in a trial assessing a pneumococcal conjugate vaccine in HIV positive and HIV negative children in Soweto, South Africa.<sup>11</sup> In 43 trials authors reported conducting an a priori power calculation, but this was unclear or not reported in the other trials.

Sixty eight trials compared two interventions or strategies, five included three comparison groups, two included four, one included five, and one had six. All, apart from one crossover trial, used a parallel randomised design. Simple randomisation was reported in 33 trials and simple stratified randomisation in one trial. Forty three reported using blocked or blocked stratified randomisation. Most trials (73) were randomised at the individual level. Four were cluster trials, three of which were large prevention trials (with more than 12 000 participants) assessing the effectiveness of both pharmaceutical and behavioural treatment for sexually transmitted infections on preventing HIV transmission.<sup>12-14</sup> Cluster correlation coefficients were used in the analyses of all three trials. A smaller prevention trial of peer education in 2219 factory workers in Zimbabwe was also cluster randomised but did not report using a cluster correlation coefficient in its analysis.<sup>15</sup> Thirteen trials reporting on mother to child transmission were all randomised at the individual level.

### Funding and ethics

We could not identify the primary funder for every trial—for example, when trials were funded by more than one source. Government agencies outside of Africa provided funding to 43 trials (table 3). The pharmaceutical industry provided full or partial funding, or provided drugs and placebo treatments, to 34 trials. Sixteen of the trials that were funded by governments outside Africa also received funding from the pharmaceutical industry. Twenty three trials received funding from international non-government and inter-government agencies such as the World Health Organization and UNAIDS. African government agencies and African non-government agencies provided funding to five trials. Funding was not reported for four treatment trials and one prevention trial.

Fifty eight trials reported receiving ethical approval from an approving authority, with 39 trials receiving approval from both local African and non-African institutions. Nineteen trials did not report on ethical approval; of which 13 were treatment trials and 10 were trials of drugs. Informed consent was obtained in writing in 34 trials, orally in 7 trials, and by unspecified methods in 19 trials. Consent was not reported in the 17 other trials.

## Discussion

This is the first comprehensive attempt to identify and describe all randomised controlled trials on HIV and AIDS conducted in Africa up to 2003. It is innovative in displaying the extent and scope of the trials graphically by linking the data directly to geographic coordinates. This provides an immediate and accessible overview of the current status of trial evidence.

### Strengths and weaknesses

A major strength of our study is the extremely broad search and the lack of language restrictions. We contacted authors for additional information for the small number of trials that were

**Table 3** Details of non-African government agencies providing trial funding

Country and government agency	No of trials funded/agency*
Australia:	
AUSAid	1
Australian National Council of AIDS	1
National Centre in HIV Epidemiology and Clinical Research	1
Austria:	
International Atomic Energy Agency	1
Belgium:	
Belgian Administration for Development and Cooperation	2
National Fonds voor Wetenschappelijk Onderzoek	1
Canada:	
Medical Research Council	3
Ontario HIV Treatment Network	1
Canadian Infectious Diseases	1
Denmark:	
Danish International Development Assistance	1
France:	
French agency of research on AIDS (ANRS)	4
Ministry of Cooperation	3
Germany:	
Centre for International Migration and Development	1
Japan:	
Ministry of Education, Science and Culture	1
Netherlands:	
Royal Netherlands Embassy of Zambia	1
Dutch Ministry of Welfare, Health and Sport	1
Sweden:	
Swedish International Development Cooperation Agency	1
Swedish Heart and Lung Foundation	1
Swedish Research Council	1
United Kingdom:	
British Council	1
Medical Research Council	4
Overseas Development Fund	2
Department of International Development	3
United States:	
National Institutes of Health (NIH):	
Fogarty International Center	7
HIV Network for Prevention Trials	1
National Institute of Allergy and Infectious Diseases	3
National Institute of Child Health and Human Development	3
World AIDS Foundation	1
NIH grant to Family Health International	1
Veterans' Affairs Research Service	
Center for Diseases Control and Prevention, Atlanta	4
US Agency for International Development	5
Armed Forces Institute of Pathology	1
Europe:	
European Commission	3

\*Numbers are not exclusive as some agencies cofund the same trial.

described only in news articles and expect that contacting the authors of every trial would yield additional information.<sup>16</sup> A thorough search of conference proceedings might also be useful. Although recent research has shown that conference abstracts might not accurately summarise subsequent full reports,<sup>17</sup> the fact that about half the research reported at conferences does not get published in full might make such abstracts a useful source of additional trials.<sup>18</sup>

### The 10/90 disequilibrium

A remarkable finding from our study is how few HIV/AIDS trials have been conducted on the African continent over the past two decades. It highlights the gulf between the global burden of disease and research on intervention, the so called 10/90



disequilibrium,<sup>19-21</sup> and confirms previous findings that HIV/AIDS trials are under-represented in sub-Saharan research.<sup>22</sup> Most of the trials were funded by government agencies outside Africa, followed by pharmaceutical companies and international non-government and inter-government organisations. This may reflect a lack of economic ability, political will, or research capacity to conduct intervention research in African countries. Commercial funding is a source of potential bias in trials and may influence results.<sup>23-24</sup> Although we are not aware of any evidence to link non-commercial agency sponsorship to biased results, research funded by such organisations may be driven by priorities different from those of the country where the trial is done.<sup>25-26</sup>

Few principal investigators were based in African countries, although it is possible that a proportion of principal investigators were of African origin and working abroad.<sup>27</sup> Despite this uncertainty, it suggests that publication of trial results continues to be driven by researchers external to the continent. It is difficult to predict how this impacts on African collaborating researchers, but it does suggest that transfer of skills and knowledge to local researchers must remain a fundamental aim of any trial conducted in Africa.<sup>25</sup>

### Ethical issues

Nineteen of the 77 trials did not report on whether ethical approval had been obtained. Although this may simply reflect inadequate reporting, it is also possible that ethical approval may not have been obtained. In a survey of 203 researchers living in developing countries, Hyder and colleagues found that 44% of respondents reported that their studies did not undergo any review (technical, scientific, or ethical) in the country where the study was done.<sup>28</sup> They argued that ethical review in both the host and the donor country should be standard in collaborative research. Only half of the HIV/AIDS trials in Africa met this standard.

### Conclusions

A major challenge for a database such as that created in this study is keeping up to date so as to provide useful information for patients, carers, clinicians, researchers, and policy makers. To facilitate this, we endorse prospective trial registration, which will make key trial information accessible to the public at no charge.<sup>29-30</sup> In addition, we recommend that those responsible for trial registers should consider including geographic coordinates for the trial to allow graphical display of geographic data.

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Contributors: NS had the original idea to compare trial quality of HIV/AIDS trials in different locations. NS developed the study design under the supervision of MC and JV, conducted the data collection and analysis, wrote the first draft of the paper, and is guarantor. MC monitored and checked data collection. All authors contributed to the interpretation of results and edited the manuscript for important scientific content.

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## What is already known on this topic

People living in sub-Saharan Africa carry the heaviest burden of HIV and AIDS, with an estimated 25 million individuals infected with HIV

Randomised trials and systematic reviews of these provide the most reliable way to assess the relative effects of different interventions for both prevention and treatment

## What this study adds

In the past 20 years, of the many randomised controlled trials on HIV and AIDS only 77 (42 prevention, 35 treatment) have been conducted on the African continent and few principal investigators were based in African countries

Most of the 77 trials were funded by government agencies or non-governmental organisations outside Africa and by pharmaceutical companies

Mapping trials with geographic coordinates is a useful tool for researchers and decision makers to keep track of existing and future trials

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