AIDS in Africa IV

HIV/AIDS treatment and HIV vaccines for Africa

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Increased support from the global HIV/AIDS community is driving advances in HIV treatment and vaccine development in the developing world. Care of patients with AIDS includes many biomedical, nutritional, psychosocial, and behavioural interventions. In resource-poor settings, antiretroviral drugs should be given with use of standardised treatment regimens and streamlined algorithms for monitoring use. A safe and effective HIV vaccine will supplement prevention efforts to protect uninfected people against infection, or might possibly be able to modify the course of HIV infection. Advances have been made in understanding the immune response and immunisation to HIV, and new ideas for candidate vaccines have been developed, including several based on HIV-1 strains prevalent in Africa. HIV vaccine efficacy trials are needed in Africa to determine whether these advances can be translated into clinical and public health benefits. In this review, we discuss the prospects for use of treatment and vaccines in resource-poor settings.

HIV/AIDS workers want to improve access to care and support for people living with HIV/AIDS in developing countries,[1-4] and to develop an effective preventive vaccine for uninfected people at risk.[5] The challenges in turning these visions into practice include securing and mobilising funds and technical assistance from the international community, allocating scant national resources between competing health priorities, and developing or enhancing local systems of care. The demand for drugs in the developing world results from their proven benefit,[6,7] and is amplified by price reductions from pharmaceutical manufacturers and development of generic versions.[4,8] Effective preventive medical interventions, such as vaccines and microbicides, could supplement prevention efforts—including behaviour change, condom use, and management of sexually transmitted infections—to protect uninfected people. In this review, we discuss the prospects for use of treatment and vaccines for HIV disease. We refer to HIV to include HIV-1 and HIV-2, in general, but have delineated the type in the text where necessary.

HIV treatment

The case for treatment

Treatment of HIV-infected people with antiretroviral drugs and drugs for prevention and treatment of opportunistic infections benefits individuals, communities, and nations. Furthermore, effective HIV care and support can enhance prevention efforts by reducing stigma, increasing rates of uptake of HIV testing, and possibly reducing transmission.[1,9,10] However, since the capacity to provide high-level care and adequate diagnostic and monitoring facilities varies greatly between and within countries, approaches to care should be manageable within and adaptable to local conditions.[11-14] Public, private, and business sector efforts are needed to meet these challenges. Most people in need of care are reliant on the public sector, but are the least able in society to advocate for and access care beyond very basic services. Caring for these millions of people will require enhancement of governmental and non-governmental programmes, attention to political, community, and health-care infrastructures, and cultural matters (panel 1). Because of the magnitude of the epidemic in many countries, the absolute numbers of people who could be managed in the private sector, with or without support from outside sponsors, is substantial.[14] Price reductions have increasingly made antiretroviral drugs attainable for people seeking care in the private sector. Standards of care could be improved with use of models including training, assistance, and incentives for private practitioners to manage large numbers of patients. Finally, the business sector could enhance the productivity of their companies, and improve people's lives, by providing care to HIV-infected employees and their families.

Who should be treated?

In public sector programmes, antiretroviral drugs should be used equitably and judiciously to ensure that patients with similar needs have an equal chance to receive treatment within reasonable bounds of capacity and geographical limitations, and that patients with symptomatic disease are treated first.[15-17] Providers would only have sufficient information to treat asymptomatic people if CD4+ cell count testing were available to stage a patient's illness. However, CD4+ cell count enumeration is unavailable in many less-developed countries, and techniques are needed that are simpler and less expensive than flow cytometry. The first asymptomatic patients to receive treatment should be those with a CD4+ cell count

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Search strategy and selection criteria

The authors identified recent appropriate citations. No specific search strategy was used.

Panel 1: Considerations for the successful introduction of antiretroviral therapy into a community

1. Acceptance of treatment by political and community leaders
2. Education and sensitisation of community
3. Training of health-care and community workers
4. Enhancement of health-care infrastructure to enable monitoring for effect and toxicity
5. Judicious and equitable patient selection process
6. Secure and sustainable system for acquisition and distribution of drugs
7. Design of the programme adapted to local conditions
8. Culturally appropriate methods to ensure adherence and provide support to patients
9. Preventive therapy for opportunistic infections
10. Continuing assessment of knowledge, attitudes, and behaviours

less than $2{\cdot}0\times10^8$ cells/L and, if resources allow, those with $2{\cdot}0–3{\cdot}5\times10^8$ cells/L.[17] Delaying treatment for asymptomatic patients with more than $3{\cdot}5\times10^8$ cells/L would be acceptable in most circumstances. If CD4+ cell counts cannot be obtained, treatment should be started in patients with early symptomatic disease (WHO stage 2 or 3) at a total lymphocyte count of less than $1{\cdot}0–1{\cdot}2\times10^8$ cells/L.[17]

Individual versus standardised approaches

Scientific evidence and expert opinion can be used to direct a rational approach to antiretroviral drugs.[15–17] In developed countries, antiretroviral therapy is usually given to patients by a doctor with whom they have a one-to-one relationship. Standardised regimens of antiretroviral treatment as part of AIDS programmes, in which many patients would be treated under the direction of fairly few physicians, are being proposed for resource-poor settings,[12,17,18] and have some potential advantages (panel 2). A reliable network of physicians, mid-level health-care providers, and community health workers would be needed to implement such strategies. A strategy for the introduction and order in which antiretroviral drugs are given to patients who have not previously received treatment could be agreed by most health-care providers for a first and second-line regimen and, if enough drugs were available, perhaps a third-line. HIV-1, group M, non-B subtype isolates obtained from antiretroviral-naive patients are generally as sensitive to antiretroviral drugs as subtype B viruses, both in vitro[19–27] and in vivo,[28–30] indicating that similar antiretroviral regimens are acceptable for these subtypes. However, HIV-2 and HIV-1 group O viruses might not be sensitive to non-nucleoside reverse transcriptase inhibitors (NNRTIs),[31,32] which health-care workers need to consider when designing regimens in areas where these viruses circulate.

Panel 2: Potential advantages of a standardised approach to antiretroviral treatment

1. Simplified training and education of providers and patients
2. Drug regimens consistent with international standards, but based on local availability
3. Short list of products to manage
4. Streamlined monitoring for toxicity
5. Predictable patterns of development of resistance
6. Rational sequence of drug combinations
7. Aid support of drug adherence

First-line regimens should be able to suppress viral replication and improve the immunological status of most patients for at least 1 year.[33] Some patients will not adhere to, or not tolerate, the initial regimen, and in others it will fail to work. However, a standardised second-line regimen should have a high chance of a successful response, with or without extensive laboratory monitoring of the effects in individual patients. However, if two regimens fail, designing a third is more difficult with a standardised than an individual approach. Furthermore, toxicity and resistance to individual drug components could be higher in a standardised than an individual system of treatment if patients were kept on a regimen too long because of restricted options for switching. Since there are few facilities in African countries to measure real-time serial viral load, CD4+ cell count, and resistance to drugs in vitro, assessment and implementation of simpler laboratory techniques are needed to provide clinicians with readily available biomedical markers of drug effect.

Toxicity

Monitoring adverse effects to antiretroviral drugs presents challenges for which there are few data from resource-poor settings. Side-effects seen in patients in developed countries might be worse in patients who have poor nutritional status and high levels of exposure to pathogens in less-developed countries.[34] Some effects, such as headache from zidovudine, nausea from many antiretroviral drugs, confusion or vivid dreams from efavirenz, and pruritus or mild rash from nevirapine, are frequent when treatment is started, yet are usually transient and manageable. Self-limiting toxic effects have to be differentiated from more severe manifestations; thus, education of providers, patients, and caregivers is critical. Other toxic effects, such as peripheral neuropathy or lipodystrophy, can worsen progressively with time but can be identified at early stages. However, side-effects such as anaemia and hepatotoxicity might not be detected early if clinical criteria only are used. In many settings, haemoglobin concentration can be measured but not tests for liver function. Most worrying are rare toxic effects, such as severe rashes with desquamation or damage to the mucosa, hypersensitivity reactions, pancreatitis, and lactic acidosis, which can progress rapidly and be life threatening. These effects would generally not be detected with laboratory monitoring, and, furthermore, need high standards of medical attention that might not be available in some settings.

Assessment of suspected drug reactions is simplified if the probable side-effects of a standardised regimen are known. Where available, laboratory tests for toxic effects should be incorporated into care programmes. If tests are unavailable, clinical definitions of adverse effects should be developed, and health-care workers trained to recognise clinical signs and symptoms. Short-to-medium term side-effects should be the focus at the beginning of programmes, with attention given to long-term effects later. Since death is the inevitable outcome of advanced AIDS, an individual is more likely to benefit from treatment than undergo life-threatening toxic effects, even without laboratory monitoring.

Resistance

Disorganised use of antiretroviral drugs could lead to widespread development of resistance, limiting future treatment options for individuals and populations,[12] which lends further support to standardisation of treatment. In developed countries, zidovudine was first used in 1987, followed by an era of sequential monotherapy with

nucleoside reverse transcriptase inhibitors (NRTIs) from 1990 to 1995, and dual NNRTI drugs by 1996. Since 1997, treatment has consisted of highly active antiretroviral therapy (HAART) that includes an NNRTI, a protease inhibitor or, more recently, three NRTIs if one is abacavir.[15] With hindsight, the serial introduction of drugs and treatment strategies provided an optimum environment for emergence of resistance to antiretroviral drugs in the USA.[35] Even in patients treated only with protease inhibitor-based HAART, substantial resistance can be detected.[36] Despite this development, morbidity and mortality in North America and Europe have fallen substantially,[6,7] and many patients derive immunological benefit even after resistance has developed.[36,37]

Whether use of nevirapine to prevent mother-to-child transmission of HIV will negatively affect or be affected by widespread use of antiretroviral regimens that include an NNRTI is unknown. For resistance to affect a nevirapine-based programme, either the women in the programme would have had to have developed resistance from previous long-term treatment or have acquired a resistant virus from partners who had been receiving such treatment—both situations are currently very rare. Alternatively, in programmes to prevent mother-to-child transmission, some women and their children who received one dose of nevirapine developed mutations associated with resistance that faded over time.[38,39] Whether this short-term resistance will have substantial detrimental effects on subsequent responses to antiretroviral drugs in these mothers or their children is unknown. However, we should move forward with proven interventions and treatment to prevent mother-to-child transmission of HIV, using the best and most practical available options, which might include an NNRTI.

Opportunistic infections

Many of the most important causes of HIV-related disease in Africa could be prevented—in particular, tuberculosis and bacterial infections.[40] Many people present to health services dying from opportunistic infections that could have been prevented. A 6-month course of isoniazid for people with latent tuberculosis infection is recommended by WHO/UNAIDS—provided that it does not detract from treatment of active tuberculosis.[41,42] Practical difficulties include exclusion of active tuberculosis before starting prophylaxis, and sustaining adherence to treatment. Although the best length of time for treatment of latent tuberculosis infection has not been established, for those at highest risk, lifelong treatment, though unproven, might be a logical approach. Additionally, continued preventive therapy for tuberculosis after treatment of active disease might be useful in areas where risk of new infection is high. Regimens containing rifampicin might give longer protection against latent tuberculosis infection than a 6-month course of isoniazid,[43,44] but there are concerns about the development of rifampicin resistance and subsequent spread of rifampicin-resistant tuberculosis. Additionally, rifampicin should not be used with many antiretroviral drugs since it can alter the way they are metabolised.[45] Antiretroviral regimens should be designed to complement tuberculosis programmes, either by use of drugs that can be coadministered with rifampicin, or by delaying antiretroviral treatment until after the rifampicin component of the tuberculosis regimen has been completed.

Co-trimoxazole has reduced morbidity and mortality in Côte d'Ivoire by lowering the frequency of bacterial diseases and diarrhoea.[46,47] Whether it will be equally effective in eastern and southern Africa where the prevalence of resistance to co-trimoxazole in non-typhoid *Salmonella* spp is much higher is less clear. Preventive treatment with co-trimoxazole seems to have the most benefit at advanced stages[46,48] of HIV disease, though it also has an effect in early disease, in part because of prevention of malaria.[47] These benefits should be balanced against the potential for resistance from widespread use of co-trimoxazole, especially with respect to malaria control.[49] Furthermore, there are also justifiable concerns about the possible effect on programmes for the integrated management of childhood illness, in which co-trimoxazole is a key agent. Cryptococcal disease is also a major cause of morbidity and mortality in many African and Asian countries. Antifungal treatment has long been unaffordable in these regions. However, fluconazole has become cheaper, and interest has increased in the use of this and other antifungal drugs for prophylaxis, but their effectiveness needs to be confirmed by studies.

A 23-valent pneumococcal polysaccharide vaccine was ineffective in HIV-infected adults in Uganda,[50] perhaps because of poor response in patients with advanced AIDS. Although they are not currently recommended in Africa, newer conjugate vaccines might be more effective than the 23-valent type, although they protect against a narrower range of pneumococcal serotypes.

Knowledge, attitudes, and beliefs

Medical care in many resource-poor settings is often episodic, focusing on management of acute medical conditions. Provision of drugs for chronic disease requires an understanding of the underlying disease and the benefits, limitations, and risks of treatment. Development of culturally appropriate training and education materials will aid proper understanding and use of drugs. Enlisting and gaining the support of key community members, traditional healers, religious leaders, and local medical providers can help to develop a supportive environment and dispel misconceptions about treatment. Adherence to antiretroviral regimens is critically important, since non-adherence can lead to development of viral resistance, transmission of resistant virus, and disease progression.[51,52] Strategies to improve adherence can be related to patients, regimens, direct observation of treatment, and clinician or health-teams. In resource-poor settings, these approaches could include enlisting family members as medication companions, and home visits by community health workers trained to enhance drug adherence.

Availability of treatment might increase risk-taking behaviour in some people.[53] Research on modification of behaviour with prevention messages should include analysis of whether perception of risk for transmitting or acquiring HIV infection is altered by the availability of treatment programmes. Thus, the limitations of treatment must be widely understood so that people do not think that there is a cure or a magic bullet to prevent infection.

HIV vaccines

The case for preventive HIV vaccines for Africa

Although there had been more than 45 million cumulative HIV infections in Africa by the end of 2001, there have been only two small, phase I, preventive HIV vaccine trials in the continent most severely affected by the epidemic. HIV vaccines need to be developed for testing in Africa, and these candidates put through clinical trials leading to large-scale phase III efficacy trials in the continent. Such trials could establish whether candidate vaccines could protect people from HIV infection, or disease, or both, and perhaps also reduce the infec-

tiousness of vaccinated people who do become infected. We do not know the immunological factors that would protect people from HIV infection, or disease, or both, and there is no ideal animal model for testing preventive HIV vaccines; thus, only phase III trials undertaken in many people at risk of infection would prove the effectiveness of a candidate vaccine. Preventive HIV vaccines are designed for use in HIV-uninfected people; they might provide protection from HIV infection

AP Photo/Jean-Marc Boujou

Vaccine trial launch, Kenyatta Hospital

(sterilising immunity) or might modify the course of HIV infection, resulting in less-severe disease or a delay in progression to AIDS. In the past year, renewed optimism has surrounded the possibility of development of a safe and effective HIV vaccine that could blunt the effects of the epidemic.[54,55] This optimism is based on advances in understanding the human immune response to HIV infection and HIV immunisation; data from trials in monkeys showing that immunisation with DNA vaccines, with or without booster immunisation, can control immunodeficiency virus infection;[56-58] and development of new ideas for candidate vaccines, including several based on HIV-1 strains prevalent in Africa.

The remarkable genetic diversity of HIV-1 strains in Africa seems a major hurdle to development of a broadly protective vaccine.[59] Although all known HIV-1 subtypes and an array of intersubtype recombinant viruses, often in complex mosaic forms, are found throughout the continent,[60] the major HIV-1 subtypes accounting for most infections in Africa are subtype C in southern Africa, subtypes A and D in eastern Africa, and circulating recombinant form 02_AG (CRF02_AG) in west-central Africa. However, the relevance of the defined genetic HIV-1 subtypes to HIV vaccine-induced protective immunity is unknown. Results of research have increased understanding of cross-subtype immune responses. Some cytotoxic T lymphocyte epitopes are conserved across HIV-1 subtypes,[60] offering hope that a broadly protective HIV vaccine can be developed.

International HIV vaccine trials

During the past 15 years, most HIV vaccine development and assessment has taken place in developed, western countries. Early candidate HIV vaccines were based on the HIV-1 subtype B strains prevalent in western nations, and most human clinical trials were done in the USA and Europe. Globally, there have been more than 80 phase I and phase II trials,[61] and only one product—a bivalent, recombinant gp120 vaccine (AIDSVAX, VaxGen; Brisbane, CA, USA)—has reached large-scale phase III efficacy testing in North America, the Netherlands, and Thailand. Subunit rgp120 products, such as the AIDSVAX products, are the first generation of HIV vaccines. These vaccines were designed to induce HIV-specific antibodies intended to prevent HIV infection, similar to the mode of protection of hepatitis B virus vaccines.[62] Efficacy results from the AIDSVAX B/B trial in 5109 high-risk homosexual men and 309 women at heterosexual risk in North America and the Netherlands will be available in early 2003;[63] results from the Thai AIDSVAX B/E trial in 2545 injection drug users in Bangkok should be available in late 2003.[64]

Canarypox vector vaccines (ALVAC, Aventis Pasteur; Marcy l'Etoile, France), designed to induce cellular immunity (cytotoxic T lymphocytes), are among the second generation of HIV vaccines. Phase II trials of canarypox vaccines, with and without rgp120 boosts, were done in 2001 in Thailand[65] and the USA[66] to provide safety and immunogenicity data on which to base decisions of whether or not to proceed to phase III efficacy trials. An efficacy trial sponsored by the US Walter Reed Army Institute of Research is scheduled to take place in Thailand in late 2002 and receive funding from the US National Institutes of Health (NIH) from the start of the fiscal year 2003.[67] However, disappointing cytotoxic T lymphocyte data from the US phase II trial led to an announcement by the NIH that the efficacy trial in North America, Latin America, and the Caribbean had been cancelled.[67] In Africa, the first HIV vaccine trial assessed ALVAC vCP205, a canarypox construct based on HIV-1 subtype B, in a phase I, placebo-controlled trial in 40 HIV-seronegative people in Kampala, Uganda, where HIV-1 subtypes A and D predominate.[68,69] This trial was designed to assess cross-subtype cytotoxic T lymphocyte responses, and was successfully undertaken by a group that included Ugandan, French, and American scientists. However, an overall low rate of cytotoxic T lymphocyte activity was identified,[68] and ALVAC vCP205 did not advance further.

Candidates from the next generation of HIV vaccines will probably be the first to move forward to phase III efficacy trials in Africa. The first HIV vaccine trial in Africa of a product based on HIV strains from that continent began in Nairobi, Kenya, in 2001 (figure).[70] A collaborative group including Oxford University, UK; the University of Nairobi, Kenya; the Kenyan AIDS Vaccine initiative (KAVI); and the International AIDS Vaccine Initiative (IAVI) developed DNA and modified vaccinia Ankara vaccines on the basis of the *gag* gene of HIV-1 subtype A and multiple cytotoxic T lymphocyte epitopes, including some identified in studies of exposed, uninfected Kenyan female sex workers.[71-74] The phase I trial of the DNA vaccine, which included 18 people, began in Nairobi in early 2001, after an initial phase I trial of this vaccine in England, UK, in 2000. The phase I trials

Panel 3: **Factors that support HIV vaccine development and assessment**

1. High-level political and institutional support for HIV prevention research and HIV vaccine trials
2. A clear national plan to guide HIV vaccine development and assessment
3. A clearly delineated process for scientific and ethical review of proposals and study protocols
4. Human research participants' protections in place
5. Well established HIV surveillance and epidemiology research
6. Community involvement in HIV research and HIV vaccine trials
7. Informed and engaged media
8. Supportive environment for prevention and intervention research
9. Openness to interinstitutional and international collaborations
10. Development of capacity in research, clinical trials, data management, and laboratory facilities

of the modified vaccinia Ankara vaccine began in England in 2001, and in Nairobi in early 2002. Later trials are planned to assess DNA priming with boosting with modified vaccinia Ankara.[70]

Lessons learned

Three small-scale phase I trials in Uganda and Kenya were very important in showing that such trials could be successfully undertaken in Africa, and have served to identify issues that need to be addressed in planning future trials in the continent. The investigators in Uganda encountered social, political, legal, and ethical obstacles that had to be surmounted to complete the trial.[69] The clinical trial experience in Kampala provides several lessons on how to address public misunderstanding and fear, the need for ethical guidelines and regulatory control mechanisms, and the importance of involving communities and media in preparations for such trials. UNAIDS has used these experiences to develop an information booklet, *A Media Handbook for HIV Vaccine Trials in Africa*,[75] and a guidance document entitled *Ethical Considerations for HIV Preventive Vaccine Research*.[76] These publications are examples of the work of the WHO-UNAIDS HIV Vaccine Initiative in supporting international efforts to do HIV vaccine research and clinical trials.[77]

The experience in Thailand offers several lessons for moving forward with HIV vaccine trials. Faced with a rapidly expanding HIV epidemic in the early 1990s, Thailand actively embraced HIV vaccine development and assessment. At the end of 2001, in addition to a phase III trial in Bangkok, there had been seven phase I/II HIV vaccine trials in Thailand—more than in all the rest of the developing world.[5] Moreover, three vaccine companies (Chiron, VaxGen, and Aventis Pasteur) produced candidate vaccines based on the predominant HIV-1 subtype (CRF01_AE or subtype E) in Thailand. Important lessons can be learned from this work in Thailand about the path leading to such trials,[64] and support of national HIV vaccine development and assessment (panel 3).

HIV vaccine candidates being developed for Africa

An increasing number of HIV vaccines are being developed for Africa.[78] The table shows a summary of potential candidate vaccines under development or in assessment that are based on non-subtype B HIV-1 strains prevalent in Africa. Because there are many HIV-1 subtypes, circulating recombinant forms, and intersubtype recombinant strains in the continent, and since the distribution of these subtypes will probably change over time,[60] an ideal HIV vaccine will be one that can protect against genetically diverse HIV-1 strains. Polyvalent HIV-1 vaccines might be developed and assessed in Africa. As the products shown in the table proceed through preclinical testing and early human clinical trials, the need for vaccine trial capacity in Africa will increase. Preparations should be made now to develop sites for phase I, II, and III clinical trials.[79]

Preparing for HIV vaccine trials in Africa

In anticipation of new vaccine candidates, preparations for HIV vaccine trials are being made in several African nations: the HIV Vaccine Trials Network (HVTN, sponsored by the US NIH) supports institutions and investigators in South Africa, Botswana, and Malawi;[80] the US Centers for Disease Control and Prevention (CDC) is strengthening field research sites in Côte d'Ivoire and Kenya; the US Military HIV Research Program is developing epidemiological, clinical, and infrastructure capacity in Uganda, Kenya, Tanzania, and Cameroon;[65] the International AIDS Vaccine Initiative (IAVI) is supporting preparations for trials in Kenya, Uganda, Nigeria, and South Africa;[70] the British Medical Research Council is supporting epidemiological capacity building in Uganda; the French Agence Nationale de Recherche sur le SIDA (ANRS) is working with collaborators in Senegal and Côte d'Ivoire to prepare for trials; and national programmes have been initiated in Kenya (Kenyan AIDS Vaccine Initiative) and South Africa (South African AIDS Vaccine Initiative).

Vaccine construct type	HIV-1 subtype					
	A	CRF02_AG	C	D	CRF01_AE	G
Subunit protein (various)	X		X	X	X	
DNA (various)	X	X	X	X	X	
Canarypox (ALVAC) virus vector (Aventis Pasteur)	X				X	
NYVAC (Aventis Pasteur)			X			
Modified vaccinia Ankara (MVA) virus vector (various)	X	X	X	X	X	
Sindbis virus vector (Chiron)			X			
Venezualan equine encephalitis replicon particles (Alpha Vax)			X			
Salmonella vector (Institute of Human Virology)		X	X			X
Adeno-associated virus vector (Targeted Genetics)	X		X			
Adenovirus vector (Merck; NIH Vaccine Research Center)	X		X			

X=type of construct used for that HIV-1 subtype. Blank squares=type of construct not used for that HIV-1 subtype. Data from references 61 and 78.

Preventive HIV vaccine constructs based on non-subtype B HIV-1 strains prevalent in Africa currently in development, assessment, or both, by HIV-1 envelope subtype

The African AIDS Vaccine Programme (AAVP) was formed in 2000, with support from the WHO-UNAIDS HIV Vaccine Initiative, and in June, 2000, issued *The Nairobi Declaration: an African appeal for an AIDS vaccine*.[77] AAVP, representing a broad, multidisciplinary group of African public health officials and scientists, seeks "to advocate and support a coordinated effort to contribute to the global HIV vaccine development goals, ensuring that appropriate and affordable vaccines are developed for Africa in the shortest possible time".[77] These multinational efforts highlight the need for unprecedented international cooperation and collaboration in preparing for and undertaking large, phase III HIV vaccine trials in Africa. Development of a safe and broadly effective HIV vaccine will probably require a series of HIV vaccines trials done in parallel and in sequence.

Conclusion

The burden of HIV-related disease in Africa demands that enhanced efforts be made to treat large numbers of infected people with antiretroviral drugs while work proceeds to develop effective preventive vaccines. Treatment programmes should move forward, despite concerns that scarce resources could be used in other ways. Standardised approaches to treatment could aid implementation, but we need to identify ways to increase access to care and to develop simplified monitoring schemes for positive and negative treatment effects. As vaccine development proceeds, it will be important to anticipate and plan for large-scale access to any HIV vaccine effective in phase III trials.[81] Effective planning on how to obtain and distribute HIV vaccines will hopefully help to avoid the situation faced with antiretroviral therapy, in which the drugs were initially widely used in only developed countries. Integrated and parallel efforts for treatment and prevention are warranted to address the monumental problem of HIV in Africa.

Contributors

P J Weidle and T D Mastro led the review. All authors participated in the writing and review of the manuscript.

Conflict of interest statement

None declared.

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