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CENTENNIAL REVIEW

Human immunodeficiency virus (HIV) in developing countries

N. FRENCH[*], P. KALEEBU[†], E. PISANI[‡] and J. A. G. WHITWORTH[§]

[*]*Wellcome Trust/LEPRA Karonga Prevention Study, P.O. Box 46, Chilumba, Malawi*
[†]*Medical Research Council/Uganda Virus Research Institute Unit on AIDS, P.O. Box 49, Entebbe, Uganda*
[‡]*London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, U.K.*
[§]*Wellcome Trust, Euston Road, London NW1 2BE, U.K.*

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The human immunodeficiency virus (HIV) is causing the most destructive epidemic of recent times, having been responsible for the deaths of more than 25 million people since it was first recognised in 1981. This global epidemic remains out of control, with reported figures for 2005 of 40 million people infected with HIV. During 2005 there were 4.9 million new infections, showing that transmission is not being prevented, and there were 3.1 million deaths from the acquired immunodeficiency syndrome (AIDS), reflecting the lack of a definitive cure and the limited access to suppressive antiretroviral treatment in the developing countries that are most severely affected. The current state of the epidemic and the response to date are here reviewed. Present and future opportunities for prevention, treatment and surveillance are discussed, with particular reference to progress towards an HIV vaccine, the expansion of the provision of highly active antiretroviral therapy, and the need to focus control programmes on HIV as an infectious disease, rather than as a development issue.

CURRENT EPIDEMIOLOGICAL SITUATION

The human immunodeficiency virus (HIV) epidemic is not evenly spread across the world and, in fact, there appear to a multitude of different epidemics playing out in different populations according to a variety of different circumstances. These are detailed on an annual basis by the Joint United Nations Programme on HIV/AIDS (UNAIDS; Anon., 2005*a*).

Sub-Saharan Africa is the region hardest hit by the epidemic, being home to about two-thirds of all those infected with HIV, despite containing only about 12% of the global population. The main mode of transmission in Africa is by heterosexual contact, and infections in many populations have spread from high-risk groups into the general population. Southern Africa is the current epicentre of the epidemic, with prevalences of adult infection exceeding 20% in Botswana, Lesotho, Namibia, South Africa, Swaziland and Zimbabwe. The epidemic in this region is expanding rapidly. In South Africa, for example, the reported prevalence of HIV infection rose from $<1\%$ in 1990 to almost 25% a decade later. In contrast, the prevalences in East Africa now appear to have at least stabilized, and there is evidence that they have fallen substantially in Uganda and, more recently, in Kenya (Shelton *et al.*, 2006). Prevalences in West Africa have generally remained much lower than those seen in the south and east of the continent.

There is worrying evidence of fast-growing epidemics in Eastern Europe and

Reprint requests to: J. A. G. Whitworth.
E-mail: j.whitworth@wellcome.ac.uk; fax: +44 (0)20 7611 7288.

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in Central and East Asia. The populations in many Asian countries are vast, so even small proportions engaging in high-risk activities can translate into large numbers of people infected. The pattern of the HIV epidemic across Asia is highly varied, however, with stabilization in some areas but expansion in others. Even within a single country, India, diverse epidemics appear to be occurring at the same time (Kumar *et al.*, 2006). Overall, injecting-drug use is the strongest driver of the epidemic in Asia. Most users are also sexually active, however, and the intersection of drug injection and sex has jump-started a significant HIV epidemic in several Asian countries. In the Russian Federation, Ukraine, China, Indonesia, Pakistan and Vietnam, there is evidence that HIV is spreading rapidly through populations of drug injectors and men and women who buy and sell sex. Drug injection and anal sex in prison account for a disproportionate fraction of new infections in many countries.

A small number of Caribbean nations and one or two in the western Pacific have recorded prevalences of HIV infection among adults that are similar to those seen in sub-Saharan Africa, with the majority of infections being transmitted through heterosexual intercourse, often associated with commercial sex. In Latin America, HIV prevalence is highest among men who have sex with men (MSM) and commercial sex workers (CSW), although in some countries in this region, such as Argentina, drug injection also contributes significantly to new HIV infections.

The HIV epidemic has been described as the single greatest threat to security and development in the world today (Anon., 2001). After several decades of progress thanks to increased sanitation, improved living conditions, expansion of primary health care and immunizations, infant mortality is now rising again in several countries in sub-Saharan Africa as the result of HIV infections and reduced care following parental deaths. Life-expectancy at birth has fallen by more than 15 years in some African countries, with the greatest burden of mortality falling on young adults, who typically are the most productive part of the work force. As a result, it has been calculated that national gross domestic product falls 1% a year in countries where HIV prevalence has reached 8% (Anon., 2005*b*).

RESPONSE TO THE EPIDEMIC

Despite these appalling figures, there are suggestions that some progress is being made to combat the epidemic in some places. Decreases in the incidence of new infections have been seen in certain populations, for example, among MSM in Western countries throughout the 1980s and early 1990s, among CSW in Cambodia and Thailand, and in injecting drug users (IDU) in Spain and Brazil. Equally there have been falls in incidence among young people in Uganda dating back to the early 1990s (Mbulaiteye *et al.*, 2002), and now there is some evidence of similar trends emerging from Kenya, Zimbabwe and urban Haiti (Anon., 2005*a*; Shelton *et al.*, 2006). These declines, which seem at least partially attributable to changes leading to less risky sexual behaviour, provide some glimmers of hope. In Uganda, however, there are worrying signs that the earlier reported declines are not being sustained (Wawer *et al.*, 2003).

Behavioural change leading to safer sex, in particular the three components of the 'ABC' approach (Abstinence, Be faithful, use Condoms), has been the mainstay of prevention campaigns for many years. Although there has been fierce and polarized debate about the relative merits of these three components, there is general agreement that all three are important and have a part to play (Parkhurst, 2002; Shelton *et al.*, 2004). Abstinence, or at least delaying first sex, has a role in preventing infections in adolescents in the early years of their sexual maturity, but it is unclear if abstinence has

any long-term effect on the overall incidence of infection. In theory, delaying first sex may allow girls to mature to the point where they are able to negotiate safer sex more easily, and may shorten the length of the critical premarital period of a young individual's sexual career. Being faithful, through mutual monogamy and the elimination or reduction in the number of casual partners, has been suggested to be a major component in the reduction of HIV prevalence in some settings, perhaps through the reduction in the number of concurrent sexual partnerships. The results from the more rigorous studies of this topic are, however, by no means consistent (Mbulaiteye *et al.*, 2002; Wawer *et al.*, 2003; Gregson *et al.*, 2006). There are also suggestions that, in some circumstances, young people are becoming more likely to chose sexual partners of their own age, thereby reducing age mixing and the chance of choosing an infected partner (Gregson *et al.*, 2002). The use of condoms has probably been a major factor in reducing the levels of HIV infection in some areas, and the results of some studies in Uganda indicate that this, together with mortality of HIV-infected individuals, has been a major driver in reducing HIV prevalence (Wawer *et al.*, 2003). The results of other research, however, have indicated that, whereas condoms may have reduced epidemic levels in some countries where the major driver is commercial sex, their promotion is unlikely to have much impact in generalised epidemics where the majority of transmissions are occurring within married couples, who rarely use condoms (Allen *et al.*, 2003).

Sexually transmitted infections (STI), especially ulcerative conditions, have been shown to facilitate the transmission and acquisition of HIV (Wasserheit, 1992). Health services providing syndromic diagnosis and treatment for STI have therefore been widely promoted for the prevention of HIV transmission, and have been shown to be effective in reducing HIV incidence in some circumstances (Grosskurth *et al.*, 1995). The effectiveness of this intervention seems to depend on the stage of the epidemic and the aetiological pattern of the STI present in the area (Orroth *et al.*, 2003). The link between high-risk sexual behaviour, STI and HIV is much stronger in expanding HIV epidemics than in more mature, generalised epidemics, where the risk is more diffusely distributed into the lower-risk population. Treating STI to reduce the infectiousness of, and susceptibility to HIV may be particularly effective where both HIV and STI are concentrated among sex workers and their clients (Fleming and Wasserheit, 1999). As the syndromic treatment of STI is mostly targeted at curable bacterial infections, it will be much less effective in settings where most STI are viral, such as those caused by herpes simplex virus type-2 (HSV2).

As recently as 3 years ago, it could have been argued that the practice of HIV medicine in most developing countries was a sub-speciality of palliative care. Limitations in the supply of drugs meant that there was minimal effective care for serious co-infections and limited palliation available at the best of times. The natural history of HIV disease in Africa meant that 50% of individuals would be suffering from AIDS within 8–9 years of infection (Morgan and Whitworth, 2001), and life-expectancy following an AIDS diagnosis would be measured in months (Morgan *et al.*, 1997; French *et al.*, 1999; Morgan and Whitworth, 2001). The provision of daily co-trimoxazole therapy was beginning to find favour, offering modest but measurable improvements in survival (Anglaret *et al.*, 1999; Wiktor *et al.*, 1999; Grimwade and Gilks, 2001), but no other intervention based on prophylaxis against opportunistic infections had been shown to confer survival benefit (Whalen *et al.*, 1997; French *et al.*, 2000; Grant *et al.*, 2001; Quigley *et al.*, 2001).With the introduction of potent multi-drug therapy for HIV care in the developed world in 1996 (Collier *et al.*, 1996), it was clear that antiretroviral agents

had to be made available in the poor countries with high HIV burden, if significant alterations in survival and quality of life were to be achieved in such areas. In 2003, the survival prospects for an HIV-positive patient in a developing country began to improve, as a consequence of increasing political pressure from multiple sources, the establishment of the Global Fund for AIDS, Tuberculosis and Malaria (GFATM), and the subsequent development of the World Health Organization's '3 by 5' initiative. Access to cheap or free antiretroviral therapy (ART) is increasing throughout the developing world and, whilst universal and equitable access to such therapy is still some way off, a new and more optimistic phase of the HIV pandemic has begun. This phase, however, brings with it many new challenges, mixed in with the old challenge of inadequate systems of secondary health care, particularly for the management of chronic disease.

Whilst all efforts to prevent HIV transmission and treat those infected should be applauded, it is clear that the response to the epidemic and the range of available interventions need to be greatly expanded. Opportunities for the future are outlined in the next sections of this review.

PREVENTION OF HIV TRANSMISSION

Compared with the treatment of existing cases of the disease, the prevention of infection is a much more effective means of controlling an epidemic. For many years the primary response to the HIV epidemic focused on the prevention of infection by encouraging changes in sexual behaviour and treating STI. This approach has only been supplanted in the past few years, with the massive expansion of ART provision shifting the balance of the response from prevention towards care. Recently, there has been a recognition that prevention has been relatively neglected and again needs more attention (Anon., 2005*b*).

It is generally agreed that prevention activities need to focus not simply on the risk behaviours that are the immediate causes of HIV infection but also on the social, cultural and economic factors that encourage risk behaviour or prevent people from acting to protect themselves and their partners from infection. Changing the social and cultural landscape — the mechanisms that subordinate women to men, that undermine earning power, that promote discrimination against same-sex partners, that favour research for diseases of the rich — requires political leadership and national and international co-operation, and these have been in short supply in all but a handful of countries (Anon., 2005*a*). Sadly, with over 3 million people dying of AIDS each year, we cannot afford to wait for the world to become fair and equitable. We need to focus on AIDS as an infectious disease that is eminently preventable, relatively incurable, and ultimately fatal. The existing prevention efforts need to be expanded and refined while new, appropriately focused methods for prevention are developed.

Voluntary Counselling and Testing

There is a pressing need to ensure that prevention and treatment activities are better linked and co-ordinated. Voluntary HIV counselling and testing (VCT), for example is widely seen as a major access point to individuals for both HIV prevention and treatment. There is increasing evidence from Kenya, Brazil and Uganda that expanded access to ART leads to greater participation in VCT (WHO, 2005*a*), by reducing stigma and discrimination, and also by giving those who attend VCT hope that something can be done for them if they should be found to be seropositive. There is still some doubt, however, about whether increased access to ART will also lead to complacency in the population and an increase in unsafe sexual behaviour (Stolte *et al.*, 2002).

The provision of VCT needs to re-orientated, to make it more effective. In generalised epidemics, being faithful to one partner may not be enough to prevent infection if that partner acquires HIV outside the relationship. It is essential that serodiscordant partnerships are identified, through VCT, so that individuals know not only their own serostatus but also that of their partner. At present, it is estimated that only one in every 10 Africans has been tested for HIV and knows his or her own serostatus, let alone that of their partner (Anon., 2005*b*). It is clear that VCT services need to be scaled-up, targeted at those at high-risk, made more accessible, and made free-of-charge (to improve coverage), and that couple counselling, to identify serodiscordant couples, needs to be promoted.

Appropriate Prevention Services for Those Who Need Them

The effective control of HIV depends on the provision of services to the people who need them most, in situations where uninfected people are most likely to be having unprotected sex or to be sharing needles with infected people. The best choice of services will depend on the setting but might include the provision of needle-exchange programmes for IDU and prisoners, or the provision of condoms for CSW and their clients, and MSM, including prisoners. Female-controlled methods of prevention may be particularly important in situations — including marriage — where men are likely to be infected but unwilling to use condoms to protect their partners. Female condoms have been shown to be effective and should be widely distributed and promoted.

Future Prevention Methods: Microbicides

Vaginal microbicides that a woman could use to prevent infection are also being developed. These are chemical agents placed within the vagina in order to prevent infection with HIV and, potentially, other sexually transmitted micro-organisms. The development of microbicides requires some understanding of the basic science of viral entry and replication, since most of these products are aimed at prevention of infection at the mucosal surface or blockage of early viral replication.

The 'first-generation' microbicides were substances, such as nonoxynol-9 (N9), that appeared capable of blocking viral entry by disrupting the lipid bilayer of the HIV envelope. Unfortunately, when N9 was investigated in clinical trials, not only was it found to have no significant efficacy against HIV infection but it also caused local vaginal toxicity (Kreiss *et al.*, 1992; Roddy *et al.*, 1998; Van Damme *et al.*, 2002).

The hope is that 'second-generation' microbicides, such as PRO 2000 (polynaphthalene sulfonate) and other sulphated polymers, carageenan (derived from seaweed) and cellulose sulphate (Ushercell), will stop HIV binding to the various receptors that the virus uses to enter host cells. These substances have been demonstrated to have low local toxicity and are now entering Phase-III trials in developing countries (Weber *et al.*, 2005), so their effectiveness as microbicides will be determined in the next few years.

The 'third-generation' microbicides are topical antiviral agents, including non-nucleoside reverse-transcriptase inhibitors (NNRTI) such as UC781 and TMC120, that are being developed as vaginal gels. Phase-II trials of some of these compounds have started in some developing countries. A buffer gel that helps to reduce the vaginal pH, creating an environment that is possibly less conducive to HIV infection and other STI, is also being investigated.

Other Prevention Measures

Male circumcision has recently been shown to be a promising intervention. This had been indicated by the results of

observational studies and is likely to be due to the high density of target cells for HIV in the foreskin. In one trial in South Africa, recently circumcised men were found to have a 60% lower chance of contracting HIV than the uncircumcised (Auvert *et al.*, 2005). Two other trials are now in progress. If these confirm the earlier results, public-health authorities will need to address the cultural and logistic challenges of providing minor surgical facilities for circumcision that are accessible to the population at risk.

Apart from horizontal transmission between adults through sexual and parenteral routes, another major mode of transmission is vertically from an HIV-infected mother to her baby. Without any intervention, vertical transmission occurs in about one-third of cases. Such transmission is largely preventable, however, through the provision of antiretroviral drugs to the mother and child, the avoidance of breast feeding, and the use of elective Caesarian section. These interventions are, however, proving difficult to implement in developing countries, particularly those in sub-Saharan Africa. In such areas, safe obstetric surgery is accessible to only a small proportion of the population, and in most cases, for cultural, financial and practical reasons, there is little alternative to breast feeding. In these circumstances, the best advice is probably to encourage women to breast feed exclusively for 3–4 months and then to wean abruptly onto weaning foods. This allows babies to gain a major benefit from breast milk while minimising the potential for HIV transmission (WHO, 2002, 2004). Even though very simple regimens, such as a single oral dose of nevirapine to the mother during labour and a single dose to the infant within 72 h of birth, have been demonstrated to be effective in reducing mother–child transmission of HIV (Guay *et al.*, 1999), coverage is still only about 5% in sub-Saharan Africa, although it varies widely across the region. The main barriers to implementation are inadequate health services, the mothers' general lack of knowledge of their HIV status, stigma, discrimination, and lack of access to services (WHO, 2005*b*).

The use of post-exposure prophylaxis after needle-stick injuries, to prevent systemic infection very soon after transmission has occurred, has led to the concept of providing pre-exposure prophylaxis to high-risk groups, to prevent transmission occurring. Several trials of pre-exposure prophylaxis have been launched among IDU and CSW in developing countries, using the antiretroviral drug tenofovir, either alone or in combination. Some of these trials have been halted because of political pressure stemming from (possibly unwarranted) concerns about the ethical conduct of the studies. In particular, these concerns relate to the standard of care provided for study participants, especially over whether ART would be made available for life to any participant who happened to seroconvert (Mills *et al.*, 2005).

As described earlier, the syndromic treatment of STI is widely promoted as a means of reducing HIV transmission. The emerging role of HSV2 has been much discussed because infection with this virus is incurable and manifests with episodic ulceration. It is potentially amenable to suppressive therapy, although treatment for this infection is rarely included in any guidelines for syndromic management. HSV2 has been shown to be strongly associated with HIV in sub-Saharan Africa, where it has been implicated in up to 60% of transmissions in women (Wald and Link, 2002; Freeman *et al.*, 2006). The guidelines for the syndromic management of STI are therefore being updated to include consideration of suppressive treatment for HSV2 in some circumstances. Trials are underway to determine whether suppressive therapy with acyclovir or related antiviral drugs can reduce HIV transmission by minimising the clinical manifestations of HSV2. If these studies show benefit, then the next logical step will be the development of an HSV2 vaccine, which could have a major effect on the HIV epidemic.

Many believe that the only long-term solution to the HIV epidemic is the development of an effective HIV vaccine, but this poses formidable problems. These are described in the next section of this review.

VACCINE DEVELOPMENT

Virology

Since the isolation in 1983 and 1986, respectively, of HIV-1 and the much less pathogenic HIV-2, there has been a tremendous effort to study the virology and immunology of HIV in an endeavour to find better interventions and treatment. It was quickly discovered that both types of HIV are single-stranded RNA retroviruses characterised by their ability to make DNA using the enzyme reverse transcriptase. It is believed that HIV was introduced into human populations from non-human primates (Keele *et al.*, 2006). HIV-1 is genetically close to the simian immunodeficiency virus (SIV) in chimpanzees (SIVcpz) and HIV-2 to SIV in sooty mangabeys (SIVsm). It seems likely that SIVcpz was introduced into humans in the early part of the 20th Century, through meat preparation or primate bites. HIV-1 may have crossed into the human population on three separate occasions, leading to the three major groupings known as the M (main or major) group and the less common and geographically confined N (new) and O (outlier) groups (Hahn *et al.*, 2000).

There are nine recognised subtypes within HIV-1 group M, of which the most common are subtypes A and C, followed by B. There are also two common circulating recombination forms (CRF01-AE and CRF02-AG). The greatest diversity of HIV-1 is found in Central Africa. Co-infection and unique recombination forms, demonstrating co-infection or dual infection, are increasingly recognised in East Africa, where three major subtypes, A, C and D, co-circulate (Dowling *et al.*, 2002; Hoelscher *et al.*, 2002; Yirrell *et al.*, 2002). The biological relevance of these different genetic subtypes in terms of disease progression, vaccine development and transmission remains uncertain (Peeters *et al.*, 2003). Currently, most commercially available tests are able to detect infection in all individuals infected with any of the group-M HIV-1 subtypes, with some of the newer tests including antigens to detect HIV-2 and HIV-1 group-O viruses.

A key early breakthrough in research on HIV was the discovery that the CD4 molecule was the major receptor for viral entry (Dalgleish *et al.*, 1984; Klatzmann *et al.*, 1984). Several other cellular proteins, including the chemokine receptors CXCR4 and CCR5, were later discovered to be the co-receptors for viral entry (Cocchi *et al.*, 1995; Alkhatib *et al.*, 1996; Feng *et al.*, 1996). Entry, however, involves other mechanisms after attachment, including fusion of the virion and the target cell — a process that involves the V3 envelope region on glycoproteins gp120 and gp41. Entry and integration into host DNA are followed by viral replication, in which several host and viral factors, including the HIV accessory proteins nef, Vpr, Vpu and Vif, play a role.

Immunology

Most of the clinical features of HIV infection can be ascribed to the profound immune deficit that develops in infected individuals. HIV disease is characterised by a progressive loss in the numbers and function of CD4 T lymphocytes. There are also functional defects in other cells, such as B lymphocytes, monocytes, macrophages, dendritic cells (DC) and natural killer (NK) cells. Another important factor contributing to decreased immune function is the immune suppression that results from the generalised immune activation associated with a poorly controlled HIV infection.

It has recently been reported that the greatest damage to the human immune system occurs at the time of acute or primary infection. At this stage, which

typically lasts for <3 months post-infection, many gut-associated lymphocytes are destroyed (Guadalupe *et al.*, 2003; Mehandru *et al.*, 2004) and some of this damage is irreversible.

In the past few years, there have been many studies of the adaptive mechanisms (i.e. the specific immune responses mediated by T and B lymphocytes) and the innate mechanisms (i.e. the non-specific immune responses) behind the protective immune responses to HIV-1. A few weeks after HIV-1 infection, antibodies that can neutralize the virus begin to appear. Typically, however, these HIV-1-specific neutralizing-antibody responses are only transiently effective within an individual. It is puzzling why these antibodies become less effective and fail to eradicate the virus. Some of the possible reasons include viral mutation, glycosylation of the viral envelope, and conformational folding, leading to the masking of important antigenic regions. CD8 cytotoxic T lymphocytes (CTL) were first implicated in suppressing HIV replication in 1994, in studies demonstrating that the reduction in viraemia seen during acute infection was temporally associated with the appearance of HIV-specific CD8+ T cells (Borrow *et al.*, 1994; Koup *et al.*, 1994). These cells kill virus-infected cells, thus limiting the production of new virions, and secrete a variety of soluble factors that contribute further to the suppression of viral replication. In spite of this, HIV persists and there is disease progression to AIDS in the presence of HIV-specific CTL activity. The failure of CTL to control HIV infection may result from the accumulation of viral mutations, leading to viral escape and the down-regulation of class-I molecules of the major histocompatibility complex (MHC). CD8 T cells are also dependent on the help of CD4 T cells, and T helper cells become impaired early in HIV-1 infection (Pitcher *et al.*, 1999; Rosenberg *et al.*, 2000).

The innate immune system is composed of many different recognition and effector components, including NK cells, Toll-like receptors, defensins, the complement system, phagocytic cells, and DC. Other soluble mediators involved in innate immunity — including CC (cysteine–cysteine) chemokines such as RANTES ('regulated upon activation, normal-T-cell expressed and secreted') and the macrophage-inhibitory proteins (MIP) 1α and 1β produced by activated macrophages, DC, NK and γδT cells — play a role in the inhibition of viral entry, by blocking CCR5 co-receptors (Levy *et al.*, 2003). Since HIV is primarily a mucosal infection, there has been much interest in understanding the mucosal immune response. Both innate and adaptive immune responses in the mucosa have been shown to have some anti-HIV activities, including chemokines and secretory IgA antibodies to HIV (Lehner and Anton, 2002).

Individuals differ in their susceptibility to HIV-1 infections as well as in their rate of disease progression once infected. Individuals homozygous for the CCR5Δ32 deletion are almost completely protected from HIV-1 infection (Dean *et al.*, 1996; Liu *et al.*, 1996; Samson *et al.*, 1996). The CCR2-64I allele and genotype have been associated with delayed progression to AIDS in African women (Anzala *et al.*, 1998). Some human-leucocyte antigen (HLA) alleles, such as HLA B57 and B 27, have also been associated with slow disease progression (Kaslow *et al.*, 1996; Migueles *et al.*, 2000). Other polymorphic human genes reported to have an impact on HIV-1 infection include TRIM5α and APOBEC3G (Xu *et al.*, 2004; Speelmon *et al.*, 2006).

Prophylactic Vaccines

Based on an increasing understanding of the virology, immunology and genetics of HIV, there has been progress in HIV vaccine development. In 2005, 13 new trials of preventive AIDS vaccine candidates began in nine countries around the world (Anon., 2006). Many of these trials involve

a prime–boost approach, in which two candidate vaccines are administered, separately, to try to improve the immune responses induced. In the early trials most candidate vaccines were designed to induce neutralizing antibodies. One such vaccine candidate reached Phase-III trials but unfortunately did not prevent infection (Flynn *et al.*, 2005). Most of the vaccine candidates that are currently being investigated are aimed at stimulating T-cell responses. A Phase-III trial of a canarypox-vectored vaccine (vCP1521) boosted by AIDSVAX® B/E gp120, which aims to induce both antibodies and T cells, is currently underway among 16,000 volunteers in Thailand (Karnasuta *et al.*, 2005). Despite their often good safety profiles in early studies, most vaccine candidates have not progressed to Phase III because they have not been found sufficiently immunogenic.

One approach to vaccine development is to use live vector vaccines. In this approach, harmless viruses or bacteria are engineered to ferry foreign genes, such as those of HIV, into human cells. One of the most promising vaccine candidates uses a weakened adenovirus vector. Other vectors used include canarypox, modified vaccinia virus Ankara, and adeno-associated virus. The major issue that could make these vectored vaccines less potent in developing countries is the high levels of pre-existing immunity to related natural infections in the population, which may reduce the immune response to such vaccines. There are now attempts to use viruses from non-human primates as vectors, to overcome this hurdle.

In any attempts to find a safe and effective vaccine, the ultimate goal has to be clear. Sterilizing immunity is an ideal but, perhaps for now, an unrealistic goal. A more realistic aim might be to reduce viral load and therefore reduce transmission and disease progression. The rationale for this approach is supported by the results of studies on discordant couples, which have shown that there is a threshold of viraemia (about 1700 vRNA copies/ml plasma) below which transmission of HIV is extremely unlikely (Gray *et al.*, 2001). The challenges facing vaccine developers include a lack of detailed knowledge on the protective immune response and the induction of mucosal immunity, poor immunogenicity in humans, the lack of a good animal model, viral diversity, and the ability of HIV to mutate and so escape immune pressure.

It is unclear whether any vaccine will protect against all the diverse viral subtypes, although some vaccines tested have induced cross-subtype immune responses (Ferrari *et al.*, 1997; Cao *et al.*, 2003). The incorporation of the more conserved gag and pol regions of the viral genome in vaccines, or the use of multi-subtype vaccines, is therefore being considered.

There are also financial challenges, since most of the vaccine research is funded by public money, such as that from the United States' National Institutes of Health. In general, private industry has shown little interest in the development of an HIV vaccine, largely because of the uncertainty of ever succeeding in producing an effective vaccine and making a profit from the venture.

The researchers who conducted the initial vaccine trials in developing countries faced additional challenges, including the limited regulatory and scientific capacity to review protocols and the low enrolment of women (Mugerwa *et al.*, 2002; Mugyenyi, 2002; Mugisha *et al.*, 2006). There will be even more challenges as larger efficacy trials are planned. Such trials will require large populations or cohorts that are well characterised in terms of the prevalence and incidence of infection at baseline and during follow-up. Cohort development will require the upgrading of infrastructure, medical-treatment and data-management capabilities, regulatory frameworks and laboratory support, and the involvement of the target communities. All of these improvements will have to be accompanied by the highest-attainable levels of non-vaccine prevention, including the provision to trial

participants and communities of condoms and mutually-agreed levels of medical care or referral. This will not be simple or inexpensive. The international community is trying to come together to address some of these challenges, in order to accelerate vaccine development. The Global HIV Vaccine Enterprise was recently created for this purpose (Klausner *et al.*, 2003).

TREATMENT AND CARE

Prophylaxis of Opportunistic Infections

The natural history of HIV infection is dominated by a relatively small number of clinical syndromes resulting from opportunistic infections with specific aetiological agents. These vary in different parts of the world. In Africa, the pathogens responsible for the commonest opportunistic infections are *Mycobacterium tuberculosis*, *Streptococcus pneumonia*, *Cryptococcus neoformans*, non-typhoidal *Salmonella*, *Plasmodium falciparum* and human herpes virus-8 (Grant *et al.*, 1997; French *et al.*, 1999, 2001, 2002; Corbett *et al.*, 2002; Anglaret *et al.*, 2003; Van Ousterhout *et al.*, 2005). The infections with *M. tuberculosis* and *St. pneumoniae* are particularly notable as they occur at all stages of HIV infection, are caused by pathogens that are themselves highly virulent, and, in HIV-positives, are associated with high mortality. Furthermore, although successful ART almost eliminates the clinical manifestations of infection with *C. neoformans* or non-typhoidal *Salmonella*, it fails to bring down the risk posed by *M. tuberculosis* or *St. pneumonia* infection to that seen in the HIV-negative members of the same population (Girardi *et al.*, 2005; Heffernan *et al.*, 2005; Lawn *et al.*, 2005*a*). In addition, there is the theoretical potential for ART to increase the transmission of *M. tuberculosis* in the community, by increasing the pool of infectious cases. Effective prophylaxis for these infections remains necessary but the best way of achieving this remains unclear. Co-trimoxazole is the only prophylaxis currently recommended for co-infections (WHO, 2006*a*) but (unlike the situation in the developed world, where co-trimoxazole is primarily used for preventing *Pneumocystis jirovecii* pneumonia) this drug's mode of action in sub-Saharan Africa, and elsewhere in the developing world, is unclear (Watera *et al.*, 2006). Consequently, there is no available evidence to define when co-trimoxazole prophylaxis should be stopped in a developing country. Although this gap in our knowledge was of little consequence a few years ago, it urgently needs to be filled now that ART is increasingly available.

Antiretroviral Therapy

As discussed earlier, a major recent response to the epidemic has been improved access to ART globally, especially through the World Health Organization's '3 by 5' initiative (WHO, 2005*b*). The price of first-line treatment has fallen by 37%–53% over the past 5 years while the number of people in developing countries on ART has tripled in the past 2 years, to an estimated 1.3 million. Access has expanded in every region. In sub-Saharan Africa, for example, the number of people on ART has increased 8-fold, with the number of operational treatment sites increasing to >5000. The use of ART in this region probably prevented a quarter of a million deaths in 2005, and the effects of improved access to treatment will become greater over time (WHO, 2006*b*). There is still much to be done, however — only one in every 10 Africans and one in every seven Asians who need ART are being treated. The best coverage has been achieved in Latin American and the Caribbean, where roughly two-thirds of those who require treatment have access.

Early Mortality and Immune Reconstitution

Dramatic changes in disease experience and survival are achievable for individuals started on ART. Survival data from most

reported treatment cohorts and from the available national-programme statistics indicate that 85%–95% of those starting treatment will be alive 1 year later (Seyler *et al.*, 2003; Coetzee *et al.*, 2004). These figures do not take account of the deaths that occur between HIV diagnosis, treatment registration and the commencement of therapy (Lawn *et al.*, 2005*b*). It should be possible to decrease pre-treatment fatalities by speeding up the process of registration, with biological rather than programmatic factors then mainly dictating outcome. Individuals who start ART but do not survive the first year are most likely to die within the first 3 months of treatment. A nadiral CD4 count is a strong predictor of early death (Coetzee *et al.*, 2004; P. Munderi, unpubl. obs.). At the simplest level, these early deaths reflect the natural history of untreated disease, during a phase when the beneficial effects of ART treatment, viral suppression and immune recovery are evolving but not yet fully established. It remains unclear what roles co-infections and immune-reconstitution disease play in this early mortality. Strategies such as targeted short-term prophylaxis or presumptive therapy are now being assessed as adjuvants to ART.

Delivery of Antiretroviral Therapy

The supply of ART to millions of people is perhaps the single most ambitious health undertaking ever to take place. The endeavour is remarkable for several reasons, not only for the scale of the procurement and supply of medicines themselves but also that ART is being introduced into healthcare systems that have often been unable to deliver chronic health care for conditions such as hypertension, diabetes or heart failure. The supply of drugs will need to be sustained and increased to accommodate the rising percentage of the population in need of therapy. The level at which this figure plateaus will depend on the survival benefits achieved with therapy and the underlying changes in transmission of HIV within communities (Gray *et al.*, 2003). If adequate access is to be achieved, much of the drug delivery will have to take place outside hospitals, at health centres and smaller health clinics, and be managed by care providers with minimal training. The World Health Organization (WHO) has already established standardized guidelines for practitioners faced with the decisions of when to start ART, provide a substitute regimen because of toxicity, switch treatment because of drug failure, and/or stop ART and move to end-of-life care (Kim and Gilks, 2005). In developing countries it is yet to be established how much decentralization of care can take place, what changes will need to be made to the developed-country model of delivery, and what compromises will have to made.

Monitoring of Therapy

Laboratory capacity in developing countries, particularly in Africa, is at present unable to support the wide-spread use of laboratory investigations in the management of HIV disease (Zachariah *et al.*, 2006). Significant developments in technology are needed if CD4 counting and the measurement of viral load are to become available outside a few clinics. Current recommendations for starting ART are based on either clinical criteria (conditions defined by the WHO as stage 4 or stage 3) or on CD4 counts ($<$200 cells/μl or, in some cases, $<$350 cells/μl). Without CD4 counting the timing of the initiation of ART is problematic, with at least 20% of individuals who would qualify for therapy on the basis of their CD4 counts failing to qualify for ART on the basis of clinical staging (French *et al.*, 1999; Kassa *et al.*, 1999; Diomande *et al.*, 2003; Zachariah *et al.*, 2006). Conversely, many individuals who qualify for ART because they have pulmonary tuberculosis or bacterial pneumonia (stage-3-defining illnesses) may start treatment prematurely and divert resources from the most needy (Gilks *et al.*, 1996; Morris *et al.*, 2003; Zachariah *et al.*, 2006).

Once therapy has been initiated, subsequent monitoring to detect treatment failure raises further issues. When limitations in the supply of second-line therapy make altering treatment difficult, there may be no great benefit in detecting those who have failed first-line therapy. In the context of ART programmes in developing countries, it remains unclear whether, and to what extent, the addition of laboratory parameters to the current clinical decision-making process will alter the overall individual and programmatic outcomes.

Drug Resistance

What is predictable is that there will be an increase in drug-resistant HIV in individuals and consequently an increase in transmission of such viral strains within communities. Although primary drug resistance in Africa is at present uncommon, increasing numbers of individuals on ART will increase the absolute numbers of individuals carrying drug-resistant strains, as has already been seen in the developed world (Weidle *et al.*, 2002; Richard *et al.*, 2004). The inability to identify these individuals reliably, by laboratory testing or through clinical monitoring, will increase the opportunity for virus transmission. The speed at which drug resistance develops and its impact on ART programmes will need to be carefully monitored (Diaz *et al.*, 2005*b*), although its impact has been predicted to be small (Blower *et al.*, 2005). A particular area of concern is the consequences of basing programmes for the prevention of mother–child transmission on nevirapine monotherapy, and the long-term therapeutic outcomes for the mothers and children. Few data are available on the genetic mechanisms of drug resistance in HIV of subtypes other than B. Recently Kantor *et al.* (2005) concluded, however, that global surveillance and genotypic assessment of drug resistance should focus primarily on the known, subtype-B, drug-resistance mutations, since there are only minor differences with other subtypes.

Pharmacology of ART

Antiretrovirals are an unusually complex set of drugs to be delivered, with minimal medical expertise, to such large numbers of individuals. Some side-effects, such as debilitating peripheral neuropathy with stavudine, occur commonly, whereas others, such as nevirapine-associated toxic epidermal necrolysis and hepatitis, may be less common but potentially fatal. The long-term, metabolic, adverse consequences of ART observed in the developed world are yet to be seen as problems in this early phase of roll-out in developing countries. It is unclear what types of adverse effects will be seen in the developing world, how frequently any will occur, and how they can be managed adequately in a minimal-skills model of delivery. The results of pharmacological studies carried out in Caucasian populations may not accurately reflect the pharmacokinetics and dynamics of the drugs in African and Asian populations under different nutritional and environmental conditions. Fortunately, although most ART drugs have been developed using studies based on the subtype-B virus that is common in North America and Western Europe, they appear to be just as active against non-B viruses.

The pharmacology of these agents is complicated, and the cheaper combination therapies used in developing countries (mainly stavudine–lamivudine–nevirapine) lack 'forgiveness' if compliance is not near-perfect. When ART is discontinued during an intercurrent illness, for instance, there will be periods of monotherapy with the drugs that have longer half-lives, with a consequent increased risk of the development of resistance. The picture is further complicated by complex drug interactions, most importantly those between rifampicin, a mainstay of anti-tuberculosis treatment, and nevirapine and the protease inhibitors. A further cause for concern is the potential for interaction between lumefantrine, a constituent of Coartem (an antimalarial drug being promoted by the WHO for

Africa) and the protease inhibitors (Khoo *et al.*, 2005). Given the frequent overlap of HIV disease, tuberculosis and malaria, much more detailed information on these interactions and their clinical implications is urgently required.

Future Prospects for ART

The situation for HIV-infected individuals in developing countries has improved significantly in the past few years. For those involved in the delivery of care in resource-limited settings, the challenges are not only sustaining what has already been achieved but also continuing to extend the provision of care even more widely and equitably and formulating an efficient model of care that takes account of the problems faced in such settings. If successful, this may provide a framework for dealing with other chronic health problems in developing countries.

Many developing countries are still falling far short of targets for distributing ART, but there are exceptions, such as Uganda, Thailand, Botswana and Brazil, where distribution has been relatively successful. There remain tensions over how best to operationalize the expanded delivery of ART. These stem from differing views of the extent to which programmes should give priority to enrollment, by seeking to increase the numbers of patients on ART, or to adherence, by establishing systems to ensure that once on ART, patients can adhere to therapy (Bass, 2005).

There are serious questions to be addressed about the sustainability of these ambitious plans, especially as the number of patients on ART is likely to increase substantially over time, as life-expectancy rises and levels of mortality fall (Van Damme *et al.*, 2006). Will fragile health systems and personnel with limited training be able to cope? So far, the provision of ART has been funded through external sources, particularly the (United States') President's Emergency Fund for AIDS Relief (PEPFAR), the GFATM and the World Bank. Long-term donor commitment cannot, however, be taken for granted.

One of the paradoxes of improving treatment for any incurable, infectious disease is that, as life-expectancy increases, so does the number of people who are able to pass on the infection. Although ART certainly reduces infectiousness, prevention services will have to be expanded as treatment coverage increases and HIV prevalence rises.

IMPROVED UNDERSTANDING OF HIV WORLDWIDE

The recent increased global commitment to combating the HIV epidemic is a huge experiment and it is unclear how successful the greatly increased expenditure will be in preventing morbidity and mortality. To allow effectiveness to be evaluated, there is a need to develop robust monitoring frameworks and methods. Knowledge of the distribution of the virus and the behaviours that spread it has greatly increased in recent years, not least because of a concerted effort to improve systems of HIV surveillance around the world.

'Second-generation' Surveillance

From tracking the (greatly under-reported) numbers of AIDS cases that, because of the natural history of HIV infection, reflected patterns in the incidence of HIV infection a decade earlier, the world has progressed through simple sentinel surveillance for HIV in pregnant women attending antenatal clinics to more appropriate, 'second-generation' surveillance systems. These aim to track infections in the sub-populations most likely to be affected by HIV, as well as the behaviours that spread them (WHO, 2000). In countries with generalised epidemics, such as those in sub-Saharan Africa, routine surveillance is still mostly based on women attending antenatal clinics. By comparing the results

of such surveillance with those of national household surveys (Boerma *et al.*, 2003), it has been found that the data from the antenatal clinics tend to under-estimate the HIV prevalence in the general population, although there are biases inherent in both antenatal-clinic and household-survey surveillance. The routine sentinel surveillance of the STI that share a common route of transmission with HIV but often indicate more recent risk is also recommended, but rarely implemented.

Recent reviews of surveillance systems in developing countries concluded that HIV surveillance has improved from the nadir that followed the dismantling of the WHO's Global Programme on AIDS in the mid 1990s (Garcia-Calleja *et al.*, 2004). Although they remain feeble in much of the world, behavioural-surveillance systems — a critical component of second-generation surveillance — are growing ever stronger in Asia and also improving in some Latin American countries (Anon., 2004).

Towards 'Third-generation' Surveillance

Since the start of the 21st Century, gaps have appeared in even the best second-generation systems of surveillance. To understand where HIV prevention and care are most needed, it is necessary to know not just the proportion of each group that is infected or at risk, but the absolute numbers (Anon., 2002, 2005*c*). Several countries, including giants such as China, Indonesia and the Russian Federation, have now incorporated systematic estimates of the size of the sub-populations most at risk for HIV into their routine surveillance activities.

The tracking of HIV prevalence has always been a substitute for the tracking of new infections, and, as therapy complicates the already complex relationship between infection, behaviour and survival time, it is proving to be an increasingly poor substitute (Diaz *et al.*, 2005*a*). New technologies are being developed to increase the feasibility of tracking incident infections in routine surveillance (Janssen *et al.*, 1998; Parekh *et al.*, 2002) but, until these technologies are ready for wide-spread use, it is essential that data on risk behaviour, treatment and antiretroviral resistance are routinely collected (Diaz *et al.*, 2005*b*), to help interpret the changes seen in HIV prevalence.

USING SURVEILLANCE TO IMPROVE HIV PREVENTION

Given that the distribution of HIV and the behaviours that spread it have been elucidated and the technologies that prevent the spread of HIV — largely condoms and clean needles — are simple and affordable, it is shocking that an estimated 4.9 million people became newly infected with this eminently preventable virus in 2005.

Generalising Risk: the 'Vulnerability' Paradigm

AIDS burst into the world's consciousness, in the early 1980s, as a disease of gay men, drug injectors and prostitutes. The stigma associated with these behaviours caused many governments to ignore or deny the epidemic, allowing it to gain ground when it might most easily have been curtailed. At the other end of the spectrum, many activists rightly sought to avoid blaming people for risky behaviours that were, in some cases, forced on them by circumstance. Risk behaviours were often the products of poverty, gender inequality, compromised human rights and other broad social factors; in consequence, everyone was equally 'vulnerable' to HIV infection (Bayer, 1991; De Cock *et al.*, 2002). With HIV increasingly presented as a universal development problem, there was little incentive to use surveillance data to pinpoint the behaviours associated with, and the sub-populations at, greater risk of acquiring or passing on HIV. This was true even in countries outside of sub-Saharan Africa,

where HIV continues to be transmitted very largely through drug injection, sex between men, and commercial sex — behaviours practised by a small minority of the population who might benefit greatly from specialised prevention services.

Back to Public-health Principles

In the mid 2000s, the failure of the 'everyone is at risk' approach prompted calls for HIV to be treated not as a problem of development or human rights but as an infectious disease (De Cock *et al.*, 2003; Pisani *et al.*, 2003; Frieden *et al.*, 2005). This required a recognition that, whereas poverty and other factors may affect behaviour, the spread of HIV between adults is ultimately determined by three factors:

- the likelihood that an infected individual will have sex or inject drugs with an uninfected individual;
- the likelihood that the resulting discordant contact will be unprotected; and
- the likelihood that a new infection will occur if an unprotected discordant act of sex or injection does take place.

To be effective, HIV prevention efforts will have to change at least one of these three factors, and do so on a significant scale. The targeted reduction of demand for drugs and sex with high-risk partners (e.g. intergenerational sex in sub-Saharan Africa, and commercial partners globally) will affect the first. Increased condom use and use of sterile needles will affect the second. Reduced STI prevalence and viral load will affect the third. Achieving these goals should therefore be the main priorities in prevention efforts.

It has been argued that countering the spread of HIV is most easily achieved by increasing HIV testing, so that HIV-infected individuals can be provided with prevention services (Janssen *et al.*, 2001; De Cock *et al.*, 2006). This will certainly be important, particularly in generalised epidemics. A high proportion of HIV transmission, however, appears to take place shortly after infection, when the viral load is high (Wawer *et al.*, 2003; Pilcher *et al.*, 2004), and even expanded testing facilities are unlikely to identify these early infections. Where the risk of exposure to HIV is clearly concentrated in a definable sub-population, prevention services should be provided for most members of that sub-population, whether or not the sero-status of those members is known.

As access to life-prolonging therapy increases the number of people living with HIV, opportunities for sex and injection between infected and uninfected people will increase and so will the need for effective prevention. More effective HIV prevention will depend, in the first place, on using HIV- and behavioural-surveillance and HIV-testing data to identify the situations in which infected people are exchanging body fluids with uninfected people. This type of analysis is not currently required by the GFATM or other major funders of prevention efforts, and is rarely performed by governments when they consider their own distribution of prevention resources. The result is that many prevention programmes are targeted at numerically large populations such as 'young people', whose sexual contacts — in almost every country outside sub-Saharan Africa and in many in that continent as well — are likely to be entirely between uninfected people. Few funders currently require treatment programmes to be linked to active and appropriate programmes of prevention, although treatment provides an obvious entry point for many prevention services (Mukherjee *et al.*, 2003).

CONCLUSIONS

The stakes are rising in the HIV epidemic. Prevention and treatment activities are being expanded, with a current annual global expenditure of some U.S.$8300 million, mainly from PEPFAR, GFATM and the World Bank. The epidemic remains

uncontrolled, however, with increasing numbers of new cases and the total number of people currently living with HIV infection reaching 40 million for the first time. Although there is an increasing number of options for prevention and treatment, it is clear that much more needs to be done.

The synergies between prevention, treatment and care need to be exploited. It is likely that successful treatment programmes will create more effective environments for HIV prevention, and that intensified HIV prevention is required to make programmes of HIV treatment more affordable and sustainable. Mathematical modelling indicates that a comprehensive approach to prevention and treatment could avert at least 55% of new infections in sub-Saharan Africa (Stover *et al.*, 2002; Salomon *et al.*, 2005). Testing and treatment services can be used to refer people to appropriate prevention services, and even to track use of those services. Drug injectors should be referred to methadone-maintenance and sterile-needle programmes, whereas those infected or exposed sexually should be provided with STI-screening and -treatment services and regular supplies of condoms and lubricant. Equally, people presenting for prevention services — especially those associated with a high risk of exposure to HIV, such as STI treatment or drug detoxification — should be provided with counselling and HIV-testing services, and with access to prophylaxis and treatment for opportunistic infections and to ART, as necessary. The stigma associated with HIV has made people wary of contact tracing — a standard tool in the control of other infectious diseases. Increased access to ART, however, puts the referral (for HIV testing and prevention) of the sexual and injecting partners of those in treatment back on the agenda.

Analyses have been conducted on the cost-effectiveness of these various prevention and treatment strategies in sub-Saharan Africa and South–east Asia (Hogan *et al.*, 2005). In these areas, it appears that the best value is to be had from mass media campaigns, education and treatment for STI in CSW, treatment of STI in the general population, VCT, prevention of mother–child transmission, school-based education, and ART. The cost-effectiveness of these interventions ranges according to circumstances, however, from <U.S.$50 to U.S.$5000 per disability-adjusted life-year.

It is essential that ambitious, yet achievable, targets for controlling HIV are developed. Given the shortage of some 1 million professional healthworkers in sub-Saharan Africa alone, it is necessary for countries to develop a public-health approach to decentralize ART services and to delegate care from medical doctors to trained healthworkers. Major inroads into the HIV epidemic could be made by intensifying prevention programmes and integrating these with treatment expansion. This will require additional funds, estimated at an extra U.S.$6000 million annually, and long-term donor commitments. This is a pivotal period in the history of the HIV epidemic and future generations will judge us all on our response. One wonders if there will be another chapter on HIV written in 2106, to mark the bicentenary of the *Annals of Tropical Medicine and Parasitology*.

REFERENCES

Alkhatib, G., Combadiere, C., Broder, C. C., Feng, Y., Kennedy, P. E., Murphy, P. M. & Berger, E. A. (1996). CC CKR5: a RANTES, MIP-1 alpha, MIP-1 beta receptor as a fusion cofactor for macrophage-tropic HIV-1. *Science*, **272**, 1955–1958.

Allen, S., Meinzen-Derr, J., Kautzman, M., Zulu, I., Trask, S., Fideli, U., Musonda, R., Kasolo, F., Gao, F. & Haworth, A. (2003). Sexual behaviour of HIV discordant couples after HIV counselling and testing. *AIDS*, **17**, 733–740.

Anglaret, X., Chêne, G., Attia, A., Toure, S., Lafont, S., Combe, P., Manlan, K., N'Dri-Yoman, T. & Salamon, R (1999). Early chemoprophylaxis with trimethoprim–sulphamethoxazole for HIV-1-infected adults in Abidjan, Côte d'Ivoire: a randomised trial. Cotrimo-CI Study Group. *Lancet*, **353**, 1463–1468.

Anglaret, X., Messou, E., Ouassa, T., Toure, S., Dakoury-Dogbo, N., Combe, P., Mahassadi, A., Seyler, C., N'Dri-Yoman, T., Salamon, R. & ANRS 1203 Study Group (2003). Pattern of bacterial diseases in a cohort of HIV-1 infected adults receiving cotrimoxazole prophylaxis in Abidjan, Côte d'Ivoire. *AIDS*, **17**, 575–584.

Anon. (2001). *Declaration of Commitment on HIV/AIDS: Global Crisis — Global Action*. New York, NY: United Nations.

Anon. (2002). *Estimating the Size of Populations at Risk for HIV: Issues and Methods, a Joint UNAIDS/IMPACT/FHI Workshop: Report and Conclusions*. Research Triangle Park, NC: Family Health International.

Anon. (2004). *AIDS in Asia: Face the Facts*. Bangkok: Monitoring the AIDS Pandemic (MAP).

Anon. (2005*a*). *AIDS Epidemic Update*. Geneva: Joint United Nations Programme on HIV/AIDS.

Anon. (2005*b*). *Intensifying HIV Prevention*. Geneva: Joint United Nations Programme on HIV/AIDS.

Anon. (2005*c*). *Guidelines on Estimating the Size of Populations at Risk for and Infected with HIV*. Jakarta: Directorate General of Communicable Disease Control and Environmental Health.

Anon. (2006). 2005: year in review. *Vax*, **4**, unnumbered.

Anzala, O. A., Ball, T. B., Rostron, T., O'Brien, S. J., Plummer, F. A., Rowland-Jones, S. L. & University of Nairobi Collaboration for HIV Research (1998). CCR2-641 allele and genotype association with delayed AIDS progression in African women. *Lancet*, **351**, 1632–1633.

Auvert, B., Taljaard, D., Lagarde, E., Sobngwi-Tambekou, J., Sitta, R. & Puren, A. (2005). Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 trial. *PLoS Medicine*, **2**, e298.

Bass, E. (2005). The two sides of PEPFAR in Uganda. *Lancet*, **365**, 2077–2078.

Bayer, R. (1991). Public health policy and the AIDS epidemic. An end to HIV exceptionalism? *New England Journal of Medicine*, **324**, 1500–1504.

Blower, S., Bodine, E., Kahn, J. & McFarland, W. (2005). The antiretroviral rollout and drug-resistant HIV in Africa: insights from empirical data and theoretical models. *AIDS*, **19**, 1–14.

Boerma, J. T., Ghys, P. & Walker, N. (2003). HIV estimates from national population-based surveys as a new gold standard. *Lancet*, **362**, 1929–1931.

Borrow, P., Lewicki, H., Hahn, B. H., Shaw, G. M. & Oldstone, M. B. (1994). Virus-specific CD8+ cytotoxic T-lymphocyte activity associated with control of viremia in primary human immunodeficiency virus type 1 infection. *Journal of Virology*, **68**, 6103–6110.

Cao, H., Kaleebu, P., Hom, D., Flores, J., Agrawal, D., Jones, N., Serwanga, J., Okello, M., Walker, C., Sheppard, H., El-Habib, R., Klein, M., Mbidde, E., Mugyenyi, P., Walker, B., Ellner, J., Mugerwa, R. & The HIV Network for Prevention Trials (2003). Immunogenicity of a recombinant human immunodeficiency virus (HIV) canarypox vaccine in HIV-seronegative Ugandan volunteers: results of the HIV Network for Prevention Trials 007 Vaccine Study. *Journal of Infectious Diseases*, **187**, 887–895.

Cocchi, F., de Vico, A. L., Garzino-Demo, A., Arya, S. K., Gallo, R. C. & Lusso, P. (1995). Identification of RANTES, MIP-1 alpha, and MIP-1 beta as the major HIV suppressive factors produced by CD4+ T cells. *Science*, **270**, 1811–1815.

Coetzee, D., Hildebrand, K., Boulle, A., Maartens, G., Louis, F., Labatala, V., Reuter, H., Ntwana, N. & Goemaere, E. (2004). Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa. *AIDS*, **18**, 887–895.

Collier, A. C., Coombs, R. W., Schoenfeld, D. A., Bassett, R. L., Timpone, J., Baruch, A., Jones, M., Facey, K., Whitacre, C., McAuliffe, V. J., Friedman, H. M., Merigan, T. C., Reichman, R. C., Hooper, C. & Corey, L. (1996). Treatment of human immunodeficiency virus infection with saquinavir, zidovudine, and zalcitabine. AIDS Clinical Trials Group. *New England Journal of Medicine*, **334**, 1011–1017.

Corbett, E. L., Churchyard, G. J., Charalambos, S., Samb, B., Moloi, V., Clayton, T. C., Grant, A. D., Murray, J., Hayes, R. J. & De Cock, K. M. (2002). Morbidity and mortality in South African gold miners: impact of untreated disease due to human immunodeficiency virus. *Clinical Infectious Diseases*, **34**, 1251–1258.

Dalgleish, A. G., Beverly, P. C. L., Clapham, P. R., Crawford, D. H., Greaves, M. F. & Weiss, R. (1984). CD4(T4) antigen is an essential component of the receptor for AIDS retrovirus. *Nature*, **312**, 763–767.

De Cock, K. M., Mbori-Ngacha, D. & Marum, E. (2002). Shadow on the continent: public health and HIV/AIDS in Africa in the 21st Century. *Lancet*, **360**, 67–72.

De Cock, K. M., Marum, E. & Mbori-Ngacha, D. (2003). A serostatus-based approach to HIV/AIDS prevention and care in Africa. *Lancet*, **362**, 1847–1849.

De Cock, K. M., Bunnell, R. & Mermin, J. (2006). Unfinished business — expanding HIV testing in developing countries. *New England Journal of Medicine*, **354**, 440–442.

Dean, M., Carrington, M., Winkler, C., Huttley, G. A., Smith, M. W., Allikmets, R., Goedert, J. J., Buchbinder, S. P., Vittinghoff, E., Gomperts, E., Donfield, S., Vlahov, D., Kaslow, R., Saah, A., Rinaldo, C., Detels, R. & O'Brien, S. J. (1996). Genetic restriction of HIV-1 infection and progression to AIDS by a common deletion allele of the chemokine receptor 5 structural gene. *Science*, **273**, 1856–1962.

Diaz, T., De Cock, K., Brown, T., Ghys, P. D. & Boerma, J. T. (2005*a*). New strategies for HIV surveillance in resource-constrained settings: an overview. *AIDS*, **19** (Suppl. 2), S1–S8.

Diaz, T., Loth, G., Whitworth, J. & Sutherland, D. (2005*b*). Surveillance methods to monitor the impact of HIV therapy programmes in resource-constrained countries. *AIDS*, **19** (Suppl. 2), S31–S37.

Diomande, F. V., Bissagnene, E., Nkengasong, J. N., Maurice, C., Monga, B., Laga, M. & Nolan, M. L. (2003). The most efficient use of resources to identify those in need of antiretroviral treatment in Africa: empirical data from Côte d'Ivoire's Drug Access Initiative. *AIDS*, **17** (Suppl. 3), S87–S93.

Dowling, W. E., Kim, B., Mason, C. J., Wasunna, K. M., Alam, U., Elson, L., Birx, D. L., Robb, M. L., McCutchan, F. E. & Carr, J. K. (2002). Forty-one near full-length HIV-1 sequences from Kenya reveal an epidemic of subtype A and A-containing recombinants. *AIDS*, **16**, 1809–1820.

Feng, Y., Brider, C. C., Kennedy, P. E. & Berger, E. A. (1996). HIV-1 entry cofactor: functional cDNA cloning of a seven-transmembrane, G protein-coupled receptor. *Science*, **272**, 872–877.

Ferrari, G., Humphrey, W., McElrath, M. J., Excler, J. L., Duliege, A. M., Clements, M. L., Corey, L. C., Bolognesi, D. P. & Weinhold, K. J. (1997). Clade B-based HIV-1 vaccines elicit cross-clade cytotoxic T lymphocyte reactivities in uninfected volunteers. *Proceedings of the National Academy of Sciences of the United States of America*, **94**, 1396–1401.

Fleming, D. T. & Wasserheit, J. N. (1999). From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sexually Transmitted Infections*, **75**, 3–17.

Flynn, N. M., Forthal, D. N., Harro, C. D., Judson, F. N., Mayer, K. H. & Para, MF; The rgp120 HIV Vaccine Study Group (2005). Placebo-controlled phase 3 trial of a recombinant glycoprotein 120 vaccine to prevent HIV-1 infection. *Journal of Infectious Diseases*, **191**, 654–665.

Freeman, E. E., Weiss, H. A., Glynn, J. R., Cross, P. L., Whitworth, J. A. & Hayes, R. J. (2006). Herpes simplex virus 2 infection increases HIV acquisition in men and women: systematic review and meta-analysis of longitudinal studies. *AIDS*, **20**, 73–83.

French, N., Mujugira, A., Nakiyingi, J., Mulder, D., Janoff, E. N. & Gilks, C. F. (1999). Immunologic and clinical stages in HIV-1-infected Ugandan adults are comparable and provide no evidence of rapid progression but poor survival with advanced disease. *Journal of Acquired Immune Deficiency Syndromes*, **22**, 509–516.

French, N., Nakiyingi, J., Carpenter, L. M., Lugada, E., Watera, C., Moi, K., Moore, M., Antvelink, D., Mulder, D., Janoff, E. N., Whitworth, J. & Gilks, C. F. (2000). 23-valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: double-blind, randomised and placebo controlled trial. *Lancet*, **355**, 2106–2111.

French, N., Nakiyingi, J., Lugada, E., Watera, C., Whitworth, J. A. G. & Gilks, C. F. (2001). Increasing rates of malarial fever with deteriorating immune status in HIV-1-infected Ugandan adults. *AIDS*, **15**, 899–906.

French, N., Gray, K., Watera, C., Nakiyingi, J., Lugada, E., Moore, M., Lalloo, D., Whitworth, J. A. G. & Gilks, C. F. (2002). Cryptococcal infection in a cohort of HIV-1-infected Ugandan adults. *AIDS*, **16**, 1031–1038.

Frieden, T. R., Das-Douglas, M., Kellerman, S. E. & Henning, K. J. (2005). Applying public health principles to the HIV epidemic. *New England Journal of Medicine*, **353**, 2397–2402.

Garcia-Calleja, J. M., Zaniewski, E., Ghys, P. D., Stanecki, K. & Walker, N. (2004). A global analysis of trends in the quality of HIV sero-surveillance. *Sexually Transmitted Infections*, **80** (Suppl. 1), I25–I30.

Gilks, C. F., Ojoo, S. A., Ojoo, J. C., Brindle, R. J., Paul, J., Batchelor, B. I., Kimari, J. N., Newnham, R., Bwayo, J., Plummer, F. A. & Warrell, D. A. (1996). Invasive pneumococcal disease in a cohort of predominantly HIV-1 infected female sex-workers in Nairobi, Kenya. *Lancet*, **347**, 718–723.

Girardi, E., Sabin, C. A., d'Arminio Monforte, A., Hogg, B., Phillips, A. N., Gill, M. J., Dabis, F., Reiss, P., Kirk, O., Bernasconi, E., Grabar, S., Justice, A., Staszewski, S., Fatkenheuer, G. & Sterne, J. A. (2005). Incidence of tuberculosis among HIV-infected patients receiving highly active antiretroviral therapy in Europe and North America. *Clinical Infectious Diseases*, **41**, 1772–1782.

Grant, A. D., Djomand, G. & De Cock, K. M. (1997). Natural history and spectrum of disease in adults with HIV/AIDS in Africa. *AIDS*, **11**, s43–s54.

Grant, A. D., Kaplan, J. E. & De Cock, K. M. (2001). Preventing opportunistic infections among human immunodeficiency virus-infected adults in African countries. *American Journal of Tropical Medicine and Hygiene*, **65**, 810–821.

Gray, R. H., Wawer, M. J., Brookmeyer, R., Sewankambo, N. K., Serwadda, D., Wabwire-Mangen, F., Lutalo, T., Li, X., van Cott, T. & Quinn, T. C. (2001). Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1 discordant couples in Rakai, Uganda. *Lancet*, **357**, 1149.

Gray, R. H., Li, X., Wawer, M. J., Gange, S. J., Serwadda, D., Sewankambo, N. K., Moore, R., Wabwire-Mangen, F., Lutalo, T. & Quinn, T. C. (2003). Stochastic simulation of the impact of antiretroviral therapy and HIV vaccines on HIV transmission; Rakai, Uganda. *AIDS*, **17**, 1941–1951.

Gregson, S., Nyamukapa, C. A., Garnett, G. P., Mason, P. R., Zhuwau, T., Carael, M., Chandiwana, S. K. & Anderson, R. M. (2002). Sexual mixing patterns and sex-differentials in teenage exposure to HIV infection in rural Zimbabwe. *Lancet*, **359**, 1896–1903.

Gregson, S., Garnett, G. P., Nyamukapa, C. A., Hallett, T. B., Lewis, J. J., Mason, P. R., Chandiwana, S. K. & Anderson, R. M. (2006). HIV decline associated with behavior change in eastern Zimbabwe. *Science*, **311**, 620–621.

Grimwade, K. & Gilks, C. (2001). Cotrimoxazole prophylaxis in adults infected with HIV in low-income countries. *Current Opinion in Infectious Diseases*, **14**, 507–512.

Grosskurth, H., Mosha, F., Todd, J., Mwijarubi, E., Klokke, A., Senkoro, K., Mayaud, P., Changalucha, J., Nicholl, A., Ka-Gina, G., Newell, J., Mugeye, K., Mabey, D. & Hayes, R. (1995). Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. *Lancet*, **346**, 530–536.

Guadalupe, M., Reay, E., Sankaran, S., Prindiville, T., Flamm, J., McNeil, A. & Dandekar, S. (2003). Severe CD4 T cells depletion in the gut lymphoid tissue during primary human immunodeficiency virus type 1 infection and substantial delay in restoration following highly active antiretroviral therapy. *Journal of Virology*, **77**, 11,708–11,717.

Guay, L. A., Musoke, P., Fleming, T., Bagenda, D., Allen, M., Nakabiito, C., Sherman, J., Bakaki, P., Ducar, C., Deseyve, M., Emel, L., Mirochnick, M., Fowler, M. G., Mofenson, L., Miotti, P., Dransfield, K., Bray, D., Mmiro, F. & Jackson, J. B. (1999). Intrapartum and neonatal single-dose nevirapine compared to zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet*, **354**, 795–802.

Hahn, B. H., Shaw, G. M., De Cock, K. M. & Sharp, P. M. (2000). AIDS as a zoonosis: scientific and public health implications. *Science*, **287**, 607–614.

Heffernan, R. T., Barrett, N. L., Gallagher, K. M., Hadler, J. L., Harrison, L. H., Reingold, A. L., Khoshnood, K., Holford, T. R. & Schuchat, A. (2005). Declining incidence of invasive *Streptococcus pneumoniae* infections among persons with AIDS in an era of highly active antiretroviral therapy, 1995–2000. *Journal of Infectious Diseases*, **191**, 2038–2045.

Hoelscher, M., Dowling, W. E., Sanders-Buell, E., Carr, J. K., Harris, M. E., Thomschke, A., Robb, M. L., Birx, D. L. & McCutchan, F. E. (2002). Detection of HIV-1 subtypes, recombinants, and dual infections in East Africa by a multi-region hybridization assay. *AIDS*, **16**, 2055–2064.

Hogan, D. R., Baltussen, R., Hayashi, C., Lauer, J. A. & Salomon, J. A. (2005). Cost effectiveness analysis of strategies to combat HIV/AIDS in developing countries. *Lancet*, **331**, 1431–1435.

Janssen, R. S., Satten, G. A., Stramer, S. L., Rawal, B. D., O'Brien, T. R., Weiblen, B. J., Hecht, F. M., Jack, N., Cleghorn, F. R., Kahn, J. O., Chesney, M. A. & Busch, M. P. (1998). New testing strategy to detect early HIV-1 infection for use in incidence estimates and for clinical and prevention purposes. *Journal of the American Medical Association*, **280**, 42–48.

Janssen, R. S., Holtgrave, D. R., Valdiserri, R. O., Shepherd, M., Gayle, H. D. & De Cock, K. M. (2001). The serostatus approach to fighting the HIV epidemic: prevention strategies for infected individuals. *American Journal of Public Health*, **91**, 1019–1024.

Kantor, R., Katzenstein, D. A., Efron, B., Carvalho, A. P., Wynhoven, B., Cane, P., Clarke, J., Sirivichayakul, S., Soares, M. A., Snoeck, J., Pillay, C., Rudich, H., Rodrigues, R., Holguin, A., Ariyoshi, K., Bouzas, M. B., Cahn, P., Sugiura, W., Soriano, V., Brigido, L. F., Grossman, Z., Morris, L., Vandamme, A. M., Tanuri, A., Phanuphak, P., Weber, J. N., Pillay, D., Harrigan, P. R., Camacho, R., Schapiro, J. M. & Shafer, R. W. (2005). Impact of HIV-1 subtype and antiretroviral therapy on protease and reverse transcriptase genotype: results of a global collaboration. *PLoS Medicine*, **2**, e112.

Karnasuta, C., Paris, R. M., Cox, J. H., Nitayaphan, S., Pitisuttithum, P., Thongcharoen, P., Brown, A. E., Gurunathan, S., Tartaglia, J., Heyward, W. L., McNeil, J. G., Birx, D. L., de Souza, M. S. & TAVEG Thai AIDS Vaccine Evaluation Group, Thailand (2005). Antibody-dependent cell-mediated cytotoxic responses in participants enrolled in a phase I/II ALVAC-HIV/AIDSVAX B/E prime–boost HIV-1 vaccine trial in Thailand. *Vaccine*, **23**, 2522–2529.

Kaslow, R. A., Carrington, M., Apple, R., Park, L., Munoz, A., Saah, A. J., Goedert, J. J., Winkler, C., O'Brien, S. J., Rinaldo, C., Detels, R., Blattner, W., Phair, J., Erlich, H. & Mann, D. L. (1996). Influence of combinations of human major histocompatibility complex genes on the course of HIV-1 infection. *Nature Medicine*, **2**, 405–411

Kassa, E., Rinke de Wit, T. F., Hailu, E., Girma, M., Messele, T., Mariam, H. G., Yohannes, S., Jurriaans, S., Yeneneh, H., Coutinho, R. A. & Fontanet, A. L. (1999). Evaluation of the World Health Organization staging system for HIV infection and disease in Ethiopia: association between clinical stages and laboratory markers. *AIDS*, **13**, 381–389.

Keele, B. F., van Heuverswyn, F., Li, Y., Bailes, E., Takehisa. J., Santiago, M. L., Bibollet-Ruche, F., Chen, Y., Wain, L. V., Liegeois, F., Loul, S., Mpoudi Ngole, E., Bienvenue, Y., Delaporte, E., Brookfield, J. F. Y., Sharp, P. M., Shaw, G. M., Peeters, M. & Hahn, B. H. (2006). Chimpanzee

reservoirs of pandemic and nonpandemic HIV-1. *Science*, in press.

Khoo, S., Back, D. & Winstanley, P. (2005). The potential for interactions between antimalarial and antiretroviral drugs. *AIDS*, **19**, 995–1005.

Kim, J. Y. & Gilks, C. (2005). Scaling up treatment — why we can't wait. *New England Journal of Medicine*, **352**, 2392–2394.

Klatzmann, D., Campagne, E., Chamaret, S., Gurest, J., Guetard, D., Hercend, T., Gluckman, J. C. & Montagnier, L. T. (1984). Lymphocyte T4 behaves as the receptor for human retrovirus LAV. *Nature*, **312**, 767–771.

Klausner, R. D., Fauci, A. S., Corey, L., Nabel, G. J., Gayle, H., Berkley, S., Haynes, B. F., Baltimore, D., Collins, C., Douglas, R. G., Esparza, J., Francis, D. P., Ganguly, N. K., Gerberding, J. L., Johnston, M. I., Kazatchkine, M. D., McMichael, A. J., Makgoba, M. W., Pantaleo, G., Piot, P., Shao, Y., Tramont, E., Varmus, H. & Wasserheit, J. N. (2003). The need for a global HIV/AIDS vaccine enterprise. *Science*, **300**, 2036–2039.

Koup, R. A., Safrit, J. T., Cao, Y., Andrews, C. A., McLeod, G., Borkowsky, W., Farthing, C. & Ho, D. D. (1994). Temporal association of cellular immune responses with the initial control of viremia in primary human immunodeficiency virus type 1 syndrome. *Journal of Virology*, **68**, 4650–4655.

Kreiss, J., Ngugi, E., Holmes, K., Ndinya-Achola, J., Waiyaki, P., Roberts, P. L., Ruminjo, I., Sajabi, R., Kimata, J., Fleming, T. R., Anzala, A., Holton, D. & Plummer, F. (1992). Efficacy of nonoxynol 9 contraceptive sponge use in preventing heterosexual acquisition of HIV in Nairobi prostitutes. *Journal of the American Medical Association*, **268**, 477–482.

Kumar, R., Jha, P., Arora, P., Mony, P., Bhatia, P., Millson, P., Dhingra, D., Bhattacharya, M., Remis, R. S. & Nagelkerke, N., for the International Studies of HIV/AIDS (ISHA) Investigators (2006). Trends in HIV-1 in young adults in south India from 2000 to 2004: a prevalence study. *Lancet*, **367**, 1164–1172.

Lawn, S. D., Badri, M. & Wood, R. (2005*a*). Tuberculosis among HIV-infected patients receiving HAART: long term incidence and risk factors in a South African cohort. *AIDS*, **19**, 2109–2116.

Lawn, S. D., Myer, L., Orrell, C., Bekker, L. G. & Wood, R. (2005*b*). Early mortality among adults accessing a community-based antiretroviral service in South Africa: implications for programme design. *AIDS*, **19**, 2141–2148.

Lehner, T. & Anton, P. A. (2002). Mucosal immunity and vaccination against HIV. *AIDS*, **16** (Suppl. 4), S125–S132.

Levy, J. A., Scott, I. & Mackewicz, C. (2003). Protection from HIV/AIDS: the importance of innate immunity. *Clinical Immunology*, **108**, 167–174.

Liu, R., Paxton, W. A., Choe, S., Ceradini, D., Martin, S. R., Horuk, R., MacDonald, M. E., Stuhlmann, H., Koup, R. A. & Landau, N. R. (1996). Homozygous defect in HIV-1 coreceptor accounts for resistance of some multiply-exposed individuals to HIV-1 infection. *Cell*, **86**, 367–377.

Mbulaiteye, S. M., Mahe, C., Whitworth, J. A. G., Ruberwantari, A., Nakiyingi, J. S., Ojwiya, A. & Kamali, A. (2002). Declining HIV-1 incidence and associated prevalence over 10-years in a rural population in south–west Uganda: a cohort study. *Lancet*, **360**, 41–46.

Mehandru, S., Poles, M. A., Tenner-Racz, K., Horowitz, A., Hurley, A., Hogan, C., Boden, D., Racz, P. & Markowitz, M. (2004). Primary HIV-1 infection is associated with preferential depletion of CD4 T lymphocytes from effector sites in the gastrointestinal tract. *Journal of Experimental Medicine*, **200**, 761–770.

Migueles, S. A., Sabbaghian, M. S., Shupert, W. L., Bettinotti, M. P., Marincola, F. M., Martino, L., Hallahan, C. W., Selig, S. M., Schwartz, D., Sullivan, J. & Connors, M. (2000). HLA B*5701 is highly associated with restriction of virus replication in a subgroup of HIV-1infected long term nonprogressors. *Proceedings of the National Academy of Sciences of the United States of America*, **97**, 2709–2714.

Mills, E., Rachlis, B., Wu, P., Wong, W., Wilson, K. & Singh, S. (2005). Media reporting of tenofovir trials in Cambodia and Cameroon. *BMC International Health and Human Rights*, **5**, 6.

Morgan, D. & Whitworth, J. (2001). The natural history of HIV-1 infection in Africa. *Nature Medicine*, **7**, 143–145.

Morgan, D., Maude, G. H., Malamba, S. S., Okongo, M. J., Wagner, H. U., Mulder, D. W. & Whitworth, J. A. (1997). HIV-1 disease progression and AIDS-defining disorders in rural Uganda. *Lancet*, **350**, 245–250.

Morris, L., Martin, D. J., Bredell, H., Nyoka, S. N., Sacks, L., Pendle, S., Page-Shipp, L., Karp, C. L., Sterling, T. R., Quinn, T. C. & Chaisson, R. E. (2003). Human immunodeficiency virus-1 RNA levels and CD4 lymphocyte counts, during treatment for active tuberculosis, in South African patients. *Journal of Infectious Diseases*, **187**, 1967–1971.

Mugerwa, R. D., Kaleebu, P., Mugyenyi, P., Katongole-Mbidde, E., Hom, D. L., Byaruhanga, R., Salata, R. A., Ellner, J. J. & The HIV-1 Vaccine Trial Group (2002). First trial of the HIV-1 vaccine in Africa: Ugandan experience. *British Medical Journal*, **324**, 226–229.

Mugisha, E., Nakwagala, F., Konde, C., Johnson, B., Nanvubya, A., Birungi, J., Muluubya, A., Kiwanuka, P., Nielsen, L., Schmidt, C., Fast, P., Thiry, G. & Kaleebu, P. (2006). Community based volunteer recruitment and community involvement: experiences and lessons learnt from the second HIV

vaccine trial in Uganda. *Journal of Acquired Immune Deficiency Syndromes*, in press.

Mugyenyi, P. N. (2002). HIV vaccines: the Uganda experience. *Vaccine*, **20**, 1905–1908.

Mukherjee, J. S., Farmer, P. E., Niyizonkiza, D., McCorkle, L., Vanderwarker, C., Teixeira, P. & Kim, J. Y. (2003). Tackling HIV in resource poor countries. *British Medical Journal*, **327**, 1104–1106.

Orroth, K. K., Korenromp, E. L., White, R. G., Gayvole, A., Gray, R. H., Muhangi, L., Sewankambo, N. K., Quigley, M., Wawer, M. J., Whitworth, J. A. G., Grosskurth, H., Habbema, J. D. F. & Hayes, R. J. (2003). Higher risk behaviour and rates of sexually transmitted diseases in Mwanza compared to Uganda may help explain HIV prevention trial outcomes. *AIDS*, **17**, 2653– 2660.

Parekh, B. S., Kennedy, M. S., Dobbs, T., Pau, C. P., Byers, R., Green, T., Hu, D. J., Vanichseni, S., Young, N. L., Choopanya, K., Mastro, T. D. & McDougal, J. S. (2002). Quantitative detection of increasing HIV type 1 antibodies after seroconversion: a simple assay for detecting recent HIV infection and estimating incidence. *AIDS Research and Human Retroviruses*, **18**, 295–307.

Parkhurst, J. O. (2002). The Ugandan success story? Evidence and claims of HIV-1 prevention. *Lancet*, **360**, 78–80.

Peeters, M., Toure-Kane, C. & Nkengasong, J. N. (2003). Genetic diversity of HIV in Africa: impact on diagnosis, treatment, vaccine development and trials. *AIDS*, **17**, 2547–2560.

Pilcher, C. D., Tien, H. C., Eron Jr, J. J., Vernazza, P. L., Leu, S. Y., Stewart, P. W., Goh, L. E. & Cohen, M. S., for the Quest Study and the Duke–UNC–Emory Acute HIV Consortium (2004). Brief but efficient: acute HIV infection and the sexual transmission of HIV. *Journal of Infectious Diseases*, **189**, 1785–1792.

Pisani, E., Garnett, G. P., Grassly, N. C., Brown, T., Stover, J., Hankins, C., Walker, N. & Ghys, P. D. (2003). Back to basics in HIV prevention: focus on exposure. *British Medical Journal*, **326**, 1384–1387.

Pitcher, C. J., Quittner, C., Peterson, D. M., Connors, M., Koup, R. A., Maino, V. C. & Picker, L. J. (1999). HIV-1 specific CD4+ T cells are detectable in most individuals with active HIV-1 infection, but decline with prolonged viral suppression. *Nature Medicine*, **5**, 518–525.

Quigley, M. A., Mwinga, A., Hosp, M., Lisse, I., Fuchs, D., Porter, J. D. H. & Godfrey-Faussett, P. (2001). Long-term effect of preventive therapy for tuberculosis in a cohort of HIV-infected Zambian adults. *AIDS*, **15**, 215–22.

Richard, N., Juntilla, M., Abraha, A., Demers, K., Paxinos, E., Galovich, J., Petropoulos, C., Whalen, C. C., Kyeyune, F., Atwine, D., Kityo, C., Mugyenyi, P. & Arts, E. J. (2004). High prevalence of antiretroviral resistance in treated Ugandans infected with non-subtype B human immunodeficiency virus type 1. *AIDS Research and Human Retroviruses*, **20**, 355–364.

Roddy, R. E., Zekeng, L., Ryan, K. A., Tamoufe, U., Weir, S. S. & Wong, E. L. (1998). A controlled trial of nonoxynol 9 film to reduce male-to-female transmission of sexually transmitted diseases. *New England Journal of Medicine*, **339**, 504–510.

Rosenberg, E. S., Altfeld, M., Poon, S. H., Phillips, M. N., Wilkes, B. M., Eldridge, R. L., Robbins, G. K., D'Aquila, R. T., Goulder, P. J. & Walker, B. D. (2000). Immune control of HIV-1 after early treatment of acute infection. *Nature*, **407**, 523–526.

Salomon, J. A., Hogan, D. R., Stover, J., Stanecki, K. A., Walker, N., Ghys, P. D. & Schwartlander, B. (2005). Integrating HIV prevention and treatment: from slogans to impact. *PLoS Medicine*, **2**, e16.

Samson, M., Libert, F., Doranz, B. J., Rucker, J., Liesnard, C., Farber, C. M., Saragosti, S., Lapoumeroulie, C., Cognaux, J., Forceille, C., Muyldermans, G., Verhofstede, C., Burtonboy, G., Georges, M., Imai, T., Rana, S., Yi, Y., Smyth, R. J., Collman, R. G., Doms, R. W., Vassart, G. & Parmentier, M. (1996). Resistance to HIV-1 infection in Caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. *Nature*, **382**, 722–725.

Seyler, C., Anglaret, X., Dakoury-Dogbo, N., Messou, E., Toure, S., Danel, C., Diakite, N., Daudie, A., Inwoley, A., Maurice, C., Tonwe-Gold, B., Rouet, F., N'Dri-Yoman, T. & Salamon, R. (2003). Medium-term survival, morbidity and immunovirological evolution in HIV-infected adults receiving antiretroviral therapy, Abidjan, Côte d'Ivoire. *Antiviral Therapy*, **8**, 385–393.

Shelton, J. D., Halperin, D. T., Nantulya, V., Potts, M. & Gayle, H. D. (2004). Partner reduction is crucial for balanced 'ABC' approach to HIV prevention. *British Medical Journal*, **328**, 891–894.

Shelton, J. D., Halperin, D. T. & Wilson, D. (2006). Has global HIV incidence peaked? *Lancet*, **367**, 1120–1121.

Speelmon, E. C. D., Livingston-Rosanoff, D., Li, S. S., Vu, Q., Bui, J., Geraghty, D. E., Zhao, L. P. & McElrath, M. J. (2006). Genetic association of the antiviral restriction factor TRIM5alpha with human immunodeficiency virus type 1 infection. *Journal of Virology*, **80**, 2463–2471.

Stolte, I. G., Dukers, N. H. T. M, de Wit, J. B. F., Fennema, H. & Coutinho, R. A. (2002). A summary report from Amsterdam: increase in sexually transmitted diseases and risky sexual behaviour among homosexual men in relation to the introduction of new anti-HIV drugs. *Eurosurveillance*, **7**, 19–22.

Stover, J., Walker, N., Garnett, G. P., Salomon, J. A., Staneki, K. A., Ghys, P. D., Grassly, N. C., Anderson, R. M. & Schwartlander, B. (2002). Can

we reverse the HIV/AIDS pandemic with an expanded response? *Lancet*, **360**, 73–77.

Van Damme, L., Ramjee, G., Alary, M., Vuylsteke, B., Chandeying, V., Rees, H., Sirivongrangson, P., Mukenge-Tshibaka, L., Ettiegne-Traore, V., Uaheowitchai, C., Karim, S. S., Masse, B., Perriens, J. & Laga, M., on behalf of the COL-1492 Study Group (2002). Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: a randomized controlled trial. *Lancet*, **360**, 971–977.

Van Damme, W., Kober, K. & Laga, M. (2006). The real challenges for scaling up ART in sub-Saharan Africa. *AIDS*, **20**, 653–656.

Van Oosterhout, J. J., Laufer, M. K., Graham, S. M., Thumba, F., Perez, M. A., Chimbiya, N., Wilson, L., Chagomerana, M., Molyneux, M. E., Zijlstra, E. E., Taylor, T. E. & Plowe, C. V. (2005). A community-based study of the incidence of trimethoprim–sulfamethoxazole-preventable infections in Malawian adults living with HIV. *Journal of Acquired Immune Deficiency Syndromes*, **39**, 626–631.

Wald, A. & Link, K. (2002). Risk of human immunodeficiency virus infection in herpes simplex virus type 2-seropositive persons: a meta-analysis. *Journal of Infectious Diseases*, **185**, 45–52.

Wasserheit, J. N. (1992). Interrelationships between human immunodeficiency virus infection and other sexually transmitted diseases. *Sexually Transmitted Diseases*, **19**, 61–77.

Watera, C., Whitworth, J. A. G., Muwonge, R., Todd, J., Nakiyingi, J., Brink, A., Miiro, G., Antvelink, L., Kamali, A., French, N. & Mermin, J. (2006). Feasibility and effectiveness of cotrimoxazole prophylaxis for HIV-1-infected adults attending an HIV/AIDS clinic in Uganda. *Journal of Acquired Immune Deficiency Syndromes*, in press.

Wawer, M. J., Serwadda, D., Li, X., Quinn, T. C., Sewankambo, N. K., Kiwanuka, N., Kigozi, G. & Gray, R. H. (2003). HIV-1 transmission per coital act, by stage of HIV Infection in the HIV+ index partner, in discordant couples, Rakai, Uganda. In *10th Conference on Retroviruses and Opportunistic Infections*, abstract 40 (www.retroconference.org/2003/cd/Abstract/40.htm). Alexandria, VA: Foundation for Retrovirology and Human Health.

Weber, J., Desai, K. & Darbyshire, J., on behalf of the Microbicide Development Programme. (2005). The development of vaginal microbicides for prevention of HIV transmission. *PloS Medicine*, **2**, e142.

Weidle, P. J., Malamba, S., Mwebaze, R., Sozi, C., Rukundo, G., Downing, R., Hanson, D., Ochola, D., Mugyenyi, P., Mermin, J., Samb, B. & Lackritz, E. (2002). Assessment of a pilot antiretroviral drug therapy programme in Uganda: patients' response, survival, and drug resistance. *Lancet*, **360**, 34–40.

Whalen, C. C., Johnson, J. L., Okwera, A., Hom, D. L., Huebner, R., Mugyenyi, P., Mugerwa, R. D. & Ellner, J. J. (1997). A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. Uganda–Case Western Reserve University Research Collaboration. *New England Journal of Medicine*, **337**, 801–808.

Wiktor, S. Z., Sassan-Morokro, M., Grant, A. D., Abouya, L., Karon, J. M., Maurice, C., Djomand, G., Ackah, A., Domoua, K., Kadio, A., Yapi, A., Combe, P., Tossou, O., Roels, T. H., Lackritz, E. M., Coulibaly, D., De Cock, K. M., Coulibaly, I. M. & Greenberg, A. E. (1999). Efficacy of trimethoprim–sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1-infected patients with tuberculosis in Abidjan, Côte d'Ivoire: a randomised controlled trial. *Lancet*, **353**, 1469–1475.

World Health Organization (2000). *Guidelines for Second Generation HIV Surveillance*. Document WHO/CDS/EDC/2000.05. Geneva: WHO.

World Health Organization (2002). *Prevention of HIV in Infants and Young Children. Review of Evidence and WHO's Activities*. Document WHO/HIV/2002.08. Geneva: WHO.

World Health Organization (2004). *Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants. Guidelines on Care, Treatment and Support for Women Living with HIV/AIDS and their Children in Resource-constrained Settings*. Geneva: WHO.

World Health Organization (2005*a*). *'3 by 5' Progress Report, June 2005*. Geneva: WHO.

World Health Organization (2005b). *Progress on Global Access to HIV Antiretroviral Therapy: an Update on '3 by 5'*. Geneva: WHO.

World Health Organization (2006*a*). *WHO Expert Consultation on Cotrimoxazole Prophylaxis in HIV Infection*. Technical Report Series. Geneva: WHO.

World Health Organization (2006b). *Global Access to HIV Therapy Tripled in past Two Years, but Significant Challenges Remain*. Geneva: WHO.

Xu, H., Svarovskaia, E. S., Barr, R., Zhang, Y., Khan, M. A., Strebel, K. & Pathak, V. K. (2004). A single amino acid substitution in human APOBEC3G antiretroviral enzyme confers resistance to HIV-1 virion infectivity factor-induced depletion. *Proceedings of the National Academy of Sciences of the United States of America*, **101**, 5652–5657.

Yirrell, D., Kaleebu, P., Mogan, D., Watera, C., Magambo, B., Lyagoba, F. & Whitworth, J. (2002). Inter- and intra-genic intersubtype HIV-1 recombination in rural and semi-urban Uganda. *AIDS*, **16**, 279–286.

Zachariah, R., Teck, R., Ascurra, O., Humblet, P. & Harries, A. D. (2006). Targeting CD4 testing to a clinical subgroup of patients could limit unnecessary CD4 measurements, premature antiretroviral treatment and costs in Thyolo district, Malawi. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **100**, 24–31.