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News and Commentary

HIV/AIDS in 2004: the epidemiologist's point of view

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Although more than two decades has passed since the first clinical description of the acquired immunodeficiency syndrome (AIDS) and the identification of its causative agent, the human immunodeficiency virus (HIV), the number of people living with this infection continues to rise. Today there is no part of the world that has not been affected by the HIV/AIDS epidemic. The extent of the infection throughout the world, however, varies greatly. The worst of the epidemic is now centred in developing countries, especially sub-Saharan Africa, accounting for around three-quarters of the overall HIV-related deaths, and two-thirds of all people living with HIV/AIDS. In addition, the incidence of new infections is growing in other areas such as Eastern Europe and parts of Asia. The dynamics of the pandemic also varies in the different parts of the world, and to date, only in sub-Saharan Africa has a pattern of spread to the general population been recorded.[1]

From the latter part of the last decade, the use of new and potent combination antiretroviral therapy (often referred to as highly active antiretroviral therapy – HAART) has had a major impact on epidemics occurring in industrialized countries. Several clinical trials have demonstrated the efficacy of HAART in reducing viral replication and reconstituting immunity, leading to longer periods of symptom-free disease and survival after AIDS diagnosis, and to changes in the natural history of HIV-associated illnesses.[2,3] Observational studies confirmed these results at the population level, reporting decreased HIV-related deaths and AIDS-defining opportunistic infection over time.[4,5] However, if the incidence of HIV infections remains stable in developed countries, due to the decrease in HIV/AIDS mortality because of HAART, the future impact of HAART will be to actually increase the prevalence of HIV infection in the population.

HAART impact on the incidence of HIV infection is less clear, but some possible effects have been suggested. In fact, HAART may decrease HIV transmission by diminishing HIV RNA shedding in biological fluids, such as semen and cervicovaginal secretions.[6,7] On the other hand, the prolonged survival of HIV-infected subjects, by determining an increase in the prevalence of potential sources of infection, can increase the incidence of HIV infection in susceptible populations. In addition, possibly related to the decreased concern of HIV transmission from HAART-treated people, a rebound in unsafe sexual behaviours has been reported in some population groups.[8,9] Lastly, the widespread use of HAART has increased the chances of acquiring drug-resistant viral strains.[10] All these factors could counterbalance the effective role of HAART in diminishing HIV spread at the population level.

The impact of HAART remains confined to the richest parts of the world, and the vast majority of people in need of this therapy do not have access to it. However, experience gained in countries such as Brazil show that antiretroviral therapy can also be successfully introduced in resource-constrained countries and there are some success stories in prevention from less-developed countries. An example is the marked decline of HIV incidence recorded in Uganda following interventions aimed at increasing condom use, promoting delayed initiation of sexual activity, reducing multiple sexual partnerships, treating sexually transmitted diseases, and providing HIV voluntary counselling and testing services.[11]

The aim of this paper is to briefly review the evolving global picture of the HIV/AIDS epidemic, to describe some of the factors affecting the impact of HAART at the population level, and to outline the future challenges for the control of the HIV epidemic.

A global view of the HIV/AIDS epidemic

As of 2003, an estimated 35. 9–44.3 million people were living with HIV/AIDS worldwide and over 20 million people had already died due to HIV/AIDS; therefore, to date over 60 million people have been infected. During 2004, 4.9 million new HIV infections and 3.1 million deaths due to HIV/AIDS were estimated to have occurred[1] (Table 1).

In Western Europe and in North America, trends of the epidemic appears to be similar. For example, in the US the number of AIDS cases reported each year decreased steadily from 1994 to 1998. From 1999 to 2001, the AIDS incidence levelled off while a small increase in the number of new AIDS diagnoses was recorded in 2002.[12] This downtrend is believed to reflect primarily, at least since 1996, the effect of HAART in decreasing the probability of an HIV-infected individual progressing to AIDS, rather than a continuing decrease in HIV incidence. In fact, following a decrease recorded in the second part of the 1980s, the trend of newly acquired HIV infections is estimated to have been rather stable in the last decade, with approximately 40 000 new infections occurring each year.[13] A similar discrepancy between trends in incidence of newly diagnosed AIDS cases and newly diagnosed HIV infection has been recorded in Western Europe.[14] In fact, while the number of AIDS cases decreased from 1994 to 1999 and remained quite stable thereafter, data on newly diagnosed HIV infections, available

Table 1 Global estimates of the HIV/AIDS epidemic at the end of 2004

Region	People living with HIV	Prevalence of HIV among adults[a] (%)	New HIV infections in 2004	Deaths due to AIDS in 2004
Sub-Saharan Africa	25.4 million	7.4	3.1 million	2.3 million
South and South-East Asia	7.1 million	0.6	890 000	490 000
Latin America	1.7 million	0.6	240 000	95 000
Eastern Europe and Central Asia	1.4 million	0.8	210 000	60 000
East Asia	1.1 million	0.1	290 000	51 000
North America	1.0 million	0.6	44 000	16 000
Western and Central Europe	610 000	0.3	21 000	6500
North Africa and Middle East	540 000	0.3	92 000	28 000
Carribean	440 000	2.3	53 000	36 000
Oceania	35 000	0.2	5000	700
Total	*39.4 million*	*1.1*	*4.9 million*	*3.1 million*

[a]15–49 years of age. Data from Joint United Nations Programme on HIV/AIDS and World Health Organization.[1]

for 12 European countries, showed an increase between 1997 and 2002, with a 28% rise in 2002 compared to the previous year. In regard to this, the number of newly diagnosed HIV infection decreased in intravenous drug users, while a sharp increase was recorded among people infected through heterosexual contacts (122% between 1995 and 2002). Interestingly, this increase appears to be due mostly to people immigrating from sub-Saharan Africa.

Eastern Europe, only marginally involved in the epidemic a few years ago, has recently experienced the largest growth. In a 5-year period, from 1996 to 2001, the number of HIV infections diagnosed each year increased 10- fold going from 8110 to 99 449.[15] Intravenous drug use is presently driving the epidemic in Eastern Europe, while the number of sexually acquired HIV infection is still relatively low. The potential does exist, however, for an increase in sexual spread of the infection, as exemplified by the syphilis epidemic that occurred in the former Soviet Union during the 1990s.[16] Moreover, the expansion of prostitution and the high prevalence of drug use and sexually transmitted diseases among these people suggest that sex workers may play an important role in the future spread of HIV infection, as already seen in some Asian countries such as Thailand. The spread of HIV in the former Soviet Bloc took place at a time when the political system, and consequently the health system, was collapsing and this made prevention of new infections, as well as care of those already affected, extremely difficult in this area. In addition, it has been estimated that the epidemic will cost 1% of the Gross Domestic Product in terms of loss productivity, and that 1–3% of the Gross Domestic Product will be needed to for care for HIV-infected individuals.[17]

Sub-Saharan Africa is suffering the worst devastation from the epidemic in comparison to the rest of the world. Heterosexual sex is the major transmission route, together with a persistent level of mother-to-child transmission.[1] However, in recent years, it has been difficult to precisely estimate the trend of infection due to changes in data sources and estimation methods over time.[18] Recently, an analysis of subregional differences and time trends of HIV prevalence has been performed using homogeneous data collected from antenatal clinics during 1997–2003.[19] This analysis showed that HIV spread is still increasing in Southern Africa, where prevalence among pregnant women is above 23%, while it appears to have stabilized at around 4–5% in Central and Western Africa. Only in some Eastern African countries, notably in Uganda, are there signs of a decline in HIV prevalence.

On the Asian continent, which includes the world's most populous countries, the epidemic started late compared to other parts of the World and the first AIDS cases were recorded in India and the South-Eastern countries during the mid-1980s. Presently, this region accounts for the second highest cumulative number of people living with HIV/AIDS, but the spread of infection is extremely diverse in the different countries.[1,20] In the countries that were involved earlier in the epidemics, such as Cambodia, Thailand, and some states of India, prevalence is now above 1%. The epidemic is growing at a considerable pace in countries such as China and Indonesia, while other countries such as Bangladesh, Laos, and the Philippines are still only marginally affected. A common pattern of spread, driven mainly by injecting drug users and sex workers, has been recorded in many Asian country, although the role of sexual transmission between men has been increasingly recognized.[21] As described at the beginning of the 1990s for Thailand,[22] HIV spread often began among injecting drug users and then among sex workers and their clients.[20] These individuals, in turn, infect their female partners and thus the epidemics can make inroads into the general population. Surveillance data show that high HIV prevalence rates, up to 60%, has been recorded among sex workers at different points in time in many Asian countries such as Thailand, Cambodia, and Indonesia. Fast growing prevalence rates have also been recorded in the same countries among injecting drug users. However, in no Asian country has the high prevalence levels, comparable to those in sub-Saharan Africa, been reached in the general population.[20] In addition, only in sub-Saharan Africa does the HIV epidemic have a 'generalized' transmission pattern, characterized by the wide spread of the epidemic among the adult population and a predominance of heterosexually transmitted infections. In Southern and South Eastern Asia, as well as in other parts of the world, although the number of infected people continues to increase, the pattern of HIV transmission remains 'concentrated' among population

groups characterized by high-risk behaviours. The reason for this differences in spread pattern, generalized *versus* concentrated, is only partially understood and is probably due to various factors.[20] Differences in biological factors favouring sexual transmission of the virus may exist, including the different prevalence of male circumcision, while to date there is no evidence that HIV strains circulating in the different parts of the world may differ in their sexual transmission rate.

The societal response to AIDS also plays a very important role. For example in Thailand and Cambodia, which were hit hard by the epidemics in the 1980s, important prevention campaigns focused mainly on sex workers and their clients, and these interventions may have limited further spread of the infection.

Finally, relevant differences in patterns of sexual behaviour may exist in different populations. In this context, emphasis has recently been placed on concurrent partnerships.[23] Available data suggest that men and women in sub-Saharan African countries do not have any greater number of sexual partner in their lifetime than in other parts of the world; however, men and women in Africa often have more than one partner at a time (concurrent partnerships) for prolonged periods of time.[24] Mathematical modelling suggests that concurrent partnerships may determine a much more rapid HIV spread compared to serial monogamy or casual sexual contacts.[25] In fact, a person who has a concurrent partnership is more likely to have sexual contacts with an uninfected person soon after acquiring the infection and it is during this period that HIV viral load, and thus infectivity, is usually very high.

Impact of HAART at a population level

The effects of HAART on morbidity and mortality

When zidovudine was first introduced into the treatment of HIV/AIDS patients, improved morbidity and mortality were reported in people with advanced disease. [26,27] However, later studies on zidovudine monotherapy did not show any clear long-term benefits in terms of reducing mortality.[28] The standard of care shifted from monotherapy to sequential therapy with nucleoside reverse transcriptase inhibitors (NRTI), later followed by combined NRTI therapy, after large clinical trials showed a marked decrease in morbidity and mortality rates in comparison to zidovudine monotherapy.[29,30] The highest increase in survival rates for HIV-infected individuals was seen by using triple combination therapy, also called HAART, that included protease inhibitors.[2]

Observational studies confirmed these results at the population level, showing a decreased risk of AIDS-defining opportunistic infections and death soon after the introduction of HAART.[3–5,31–33] In addition, time to AIDS and death after seroconversion has continued to improve in recent years most likely as a result of an increasing uptake of HAART and of the availability of a growing number of antiretrovirals.[34] However, reducing morbidity and mortality without reducing the rates of new infections should result in an increased prevalence of HIV infection. In fact, an increase in the number of people estimated to be living with HIV/AIDS has been reported in the US since the end of 1997[14] and similar data has been reported for Western Europe.[16]

Data from cohort studies and surveillance systems clearly show that from 1996, a decreasing trend in incidence can be observed for nearly all opportunistic infections among HIV-infected people in industrialized countries. For example, among people enrolled in the Adult and Adolescent Spectrum of Disease (ASD) Project in the US, the incidence of *Pneumocystis jirovecii* (formerly *Pneumocystis carinii*) pneumonia declined by 21.5% per year between 1996 and 1998; in the same period, the incidence of *Mycobacterim avium complex* disease decreased by 39.9% per year and that of candida esophagitis by 16.7% per year.[35]

The impact of HAART at the population level on the incidence of HIV-associated opportunistic infections may determine effects that go beyond the population of those infected with HIV as exemplified by the case of tuberculosis. Tuberculosis is the only HIV-associated respiratory infection that can readily be transmitted to non-HIV-infected people. In regards to this, one of the factors contributing to the resurgence of tuberculosis in several parts of the world is HIV infection. This is due both to the high risk of a HIV-infected individual developing active tuberculosis and to the increased risk of non-HIV-infected person contracting tuberculosis from them.[36] In the US, the number of tuberculosis cases increased between 1985 and 1990, and 28 000 reported cases of tuberculosis were in excess to what was expected from historical trends.[37] It was estimated that at least 30% of the excess cases reported could be directly attributed to the HIV epidemic.[38] From 1992 onward, however, the number of reported cases has decrease and, in 1999, a 34% decrease in the incidence of tuberculosis was observed compared to 1992. However, the decrease in HIV-associated tuberculosis was even greater. In fact, the proportion of tuberculosis cases with HIV infection between 1993–1994 and 1998 decreased from 15 to 10% among people of all ages and from 29 to 20% among those aged 15–44 years.[39] This downward trend appears to reflect in part the intensification of control measures, including those specifically targeted at HIV-infected people.[40,41] In addition, the widespread use of HAART appears to have also significantly contributed to the decline of HIV-associated tuberculosis. For example, in San Francisco, tuberculosis interventions have intensified since 1991.[42] The overall tuberculosis incidence rate dropped from 46.0 to 29.8 per 100 000 population between 1991 and 1997, and an even larger reduction was observed among HIV-infected people (from 491.8 to 65.6). Interestingly, although the tuberculosis incidence decreased by 5–15% per year between 1991 and 1996, a 80% decrease was recorded in HIV-infected individuals (from 295.1 to 65.6 per 100 000) between 1996 and 1997 when HAART became available. This observation is confirmed in studies in which data on antiretroviral use in individual patients were analysed. In the US, among HIV-infected people enrolled in the ASD project, a greater than two-fold decrease in the overall incidence of tuberculosis was observed from 1992 to 1997, and the risk of tuberculosis was reduced by 80% in people on HAART and by 40% in people on other antiretroviral therapies, compared to those who received no antiretrovirals.[43] Similar results are reported in a cohort study from Italy in which patients who took

dual combination therapy had an 80% reduction in the risk of tuberculosis, while those on triple combination therapy had a 91% reduction in the risk of tuberculosis compared to patients who did not receive combination therapy.[44]

Tuberculosis is the most common HIV-associated opportunistic infection in many less-developed countries, especially in sub-Saharan Africa, and observational studies suggest that when HAART is used in these countries, the effects on tuberculosis incidence is of the same order of magnitude as those of the industrialized world.[45,46] Based on these observations it has been suggested that many of the excess cases of tuberculosis due to HIV infection could be averted by implementing antiretroviral therapy. By using model simulations, it has been shown that HAART use in developing countries would indeed lead to a reduction in the incidence of HIV-associated tuberculosis.[47] However to obtain a 50% reduction, it would be necessary to start therapy earlier than presently recommended (at CD4 cells count above 500/mmc), and to achieve a high coverage of therapy with high adherence. Currently, this is an unrealistic goal for developing countries and thus it is more likely that in the future a progressive scaling up of HAART use will improve cure rate and survival of patients with HIV-associated tuberculosis rather than have a direct role in prevention.

HAART and infectiousness

High viral levels of HIV in the source are clearly correlated with the probability of HIV transmission, regardless of the transmission route. Since HAART may reduce plasma concentrations of HIV to undetectable levels, it has been hypothesized that it may have a significant effect in reducing the infectiousness of HIV-infected people and, consequently, in reducing the spread of the epidemic.

The effect of HAART use on the spread of HIV has been clearly demonstrated for vertical transmission. The level of HIV viral load in the plasma is clearly correlated with the probability of viral transmission to children. In one study among women not receiving antiretrovirals, no vertical transmission was found among women with a viral load less than 1000 copies/ml rate, vertical transmission was 20% for women with a viral load of 1000 to 10 000 copies/ml, and increased up to 60% for a viral load level above 100 000 copies/ml.[48] In 1994, it was shown that the rate of mother-to-child transmission could be reduced by two-thirds by means of a complex regimen of zidovudine, given both to HIV-infected women during pregnancy and delivery, and to the newborn for a few weeks.[49] Since these results were reported, an increasing number of pregnant women in industrialized countries have received antiretroviral treatments. More recently, these treatments were based on antiretroviral combinations,[50] together with the adoption of other proven prophylactic interventions that reduce vertical transmission, such as the avoidance of breastfeeding and elective caesarean section. This resulted in a dramatic reduction of the vertical transmission rates at the population level. For example, a European study reported a decline of the HIV vertical transmission rate from 15.5% in 1994 to 2.6% after 1998. At the same time, the use of antiretroviral treatment during pregnancy increased, including both the full regimen of zidovudine given to the mother and the newborn (from 28% in 1995 to 89% by 1999) and the use of triple therapy started in pregnancy (from $<1\%$ in 1997 to 44% in 1999).[51] Similarly in the US, data from the Women and Infants Transmission Study showed a decrease in the vertical transmission rate from 19.5% prior to 1994 to 7% among women receiving zidovudine since 1994. Moreover, no cases of transmission were recorded among 70 women who received a combination regimen that included protease inhibitors.[52] In a more recent study in New York City, it has been shown that the overall transmission rate decreased from 11% in 1997 to 3.7% in 2000 and a 2.4% transmission rate was observed among women taking combination antiretroviral therapy.[53] Thus, mainly as a result of the increasing use of antiretroviral during pregnancy, the incidence of vertically acquired paediatric AIDS has dramatically decreased in industrialized countries as exemplified by the 90% decrease recorded in the US between 1992 and 2002.[14]

Sexual transmission of HIV presently accounts for the vast majority of new HIV infections worldwide.[1] However, the actual impact at the population level of HAART on the transmission of HIV through sexual contacts, even in industrialize countries, is still unclear. Available data does suggest, however, a clear link between plasma viral load and the infectiousness by sexual transmission. For example, in a study conducted in Uganda among untreated HIV-infected individuals, HIV viral load was the major determinant of the risk of sexual transmission, and the rate of viral transmission to sexual partners ranged from zero for individuals with viral load >400 copies/ml to 2.2 per 100 person-year for a level of 400–3500 copies/ml up to 23.0 person-year when viral load was above 50 000 copies/ml.[54] Moreover, although evidence exists for viral compartmentalization, with different HIV-1 variants detected in plasma and in the genital secretions,[55] a positive correlation between plasma virus load and virus shedding in genital secretions has been shown. Indeed, several studies have suggested that decreased viral levels in genital secretions paralleled that recorded in the peripheral blood after HAART treatment.[5,32,54,56] On the other hand, replication competent virus was detected in seminal cells of subjects with undetectable levels of HIV RNA in blood plasma. Also, HIV-1 DNA was commonly detected in the anorectal mucosa of homosexual men receiving HAART who had HIV plasma viremia <50 copies/ml.[57,58] Therefore, although decreased levels of HIV infectiousness with the use of potent antiretroviral therapy is the general rule, a certain level of infectiousness may remains, despite a good virological response to HAART.

Studies on the effects of antiretroviral therapy on the sexual transmission of HIV-1 at the population level are more difficult to accomplish compared to those on vertical transmission, mainly due to the difficulty of conducting population studies.[59] In an observational study among HIV serodiscordant couples conducted when zidovudine therapy came into clinical use, treated men had a 50% reduction in the risk of transmitting HIV.[60] No similar data regarding HAART-treated people are available, although a case report indicated an increased risk of HIV transmission following HAART discontinuation,[61] and a model simulation based on data gathered from homosexual men during 1994–1999 from San Francisco suggest a 60%

reduction of infectivity through sexual contacts after the widespread use of HAART.[62]

Population data are somehow contradictory. Data for Taiwan suggest, for example, that since HAART was made available, the transmission rate has been reduced by approximately 50%, while the incidence of others sexually transmitted diseases has remained stable.[63] In contrast, no decreasing trends in incidence have been recorded in industrialized countries in the last decade and there are reports suggesting that in some areas of North America or Western Europe, the incidence of HIV infection may have increased among men who have sex with men, which interestingly has paralleled an increase in risky sexual behaviours.[64–66]

Results from mathematical model simulations may help in comprehending to what extent HAART, by reducing HIV viral load in individual patients, affects the epidemic spread of the virus and which other factors may counteract the effect of therapy. In a model based on the epidemic among gay men in San Francisco, antiretroviral treatment provided to 50–90% of people living with HIV could substantially reduce not only AIDS death but also the incidence of new infections over a 10 year period.[67] However, this latter effect may be abrogated or even reverted by an increase in risky behaviours. In fact, although HAART may decrease the probability that an individual on treatment may transmit HIV during a single unprotected sexual intercourse, if this individual increases the number of unprotected intercourses and/or the number of new sexual partners, the chances of infecting other people while on treatment may remain the same or even increase compared to before treatment. Thus, the model predicts that a mere 10% increase in prevalence of risk behaviours could be enough to abrogate any beneficial effect of HAART at the epidemic level. This aspect has been analysed in greater detail in another model simulation based on the San Francisco epidemic.[68] A key parameter describing the epidemic dynamics of an infectious disease is the basic reproduction rate (R_0), which is the number of new infections that one infected person generates during his lifetime. This model predicts that R_0 would go below 1, implying a possibility of eradicating the epidemic over a 30-year period, only if a high uptake of therapy would be accompanied by a reduction in risky sexual behaviours. If risky sexual behaviours would remain stable or increase, then R_0 would be around 1 or 1.15, respectively. Although these figure would be lower than that estimated for the early 1990s, this would imply a stable or still increasing trend in the epidemic.

Unfortunately, empirical data suggest that an increase in risky sexual behaviours may have actually occurred in some population groups in industrialized countries when HAART came into widespread use. This has also been suggested indirectly by the increase in incidence of sexually transmitted disease recorded, in particular among men who have sex with men from different areas of the world.[69–71] as well as by the results of several behavioural surveys.[8,9,72,73] One hypothesis put forward to explain this increase relates to the difficulty in maintaining safe sexual behaviour (the so-called 'safe sex fatigue'). On the hand, it is possible that availability of HAART itself may be an important determinant of this trend, since HIV-infected people on HAART may feel they are not likely to transmit HIV and uninfected people may perceive the disease as less severe and are less afraid of getting it. A recent meta-analysis reviewed the evidence available on the association between HAART and sexual behaviour.[74] This analysis found no evidence that HIV-infected people receiving HAART have increased risky sexual behaviours compared to untreated people, even when an undetectable viral load is achieved. However, HIV-infected or uninfected people who believed that receiving HAART or having an undetectable viral load makes HIV transmission less likely showed an increased prevalence of risky behaviours. Similarly, an increase in risky behaviours has been documented among those who are less concerned about getting the infection because of the availability of an effective antiretroviral treatment.

Thus taken together, available evidence suggest that HAART-treated individuals may be less likely to transmit the virus via the sexual route, although it is unlikely that HAART *per se* will be sufficient to decrease HIV incidence and to lead to the eradication of the epidemic.

Antiretroviral-resistant HIV: a novel epidemic

The emergence and spread of antiretroviral-resistant HIV strains is another potential threat to the effectiveness of HAART at the individual as well as the population level.[75–77]

HIV isolates resistant to zidovudine were identified shortly after this antiretroviral compound was licensed for clinical use,[78,79] and it was shown that these strains can be transmitted through sexual contact,[80] from mother to child[81] and following exposure to infected blood.[82] However, it was not until HAART came into widespread clinical use that resistance to antiretrovirals emerged as a relevant public health problem.

Resistance to antiretrovirals is usually defined 'acquired' when it develops in a treated individual who was infected with a drug-sensitive strain or 'transmitted' (also called primary) when it is detected in an antiretroviral naïve patient. Blower *et al*.[83] developed an elegant model to analyse the epidemiological evolution of viral resistance to antiretrovirals and the relative importance of transmitted *versus* acquired resistance. They identified four key factors that may affect the proportion of new HIV infections that are caused by antiretroviral-resistant strains. (1) The proportion of HIV-infected people receiving antiretrovirals therapy; as this proportion increases, the probability for acquiring a resistance variant/strain from a treated person will also increase. (2) The rate at which patients on antiretroviral treatment develop drug resistance; this rate is dependent upon intrinsic potency and tolerability of antiretroviral drugs in use and upon adherence to treatment, and as it increases it will in turn increase the overall prevalence of resistant infections. (3) The relative fitness of the resistant strains, that is, transmissibility of a resistant strain compared to drug-sensitive strains which depends on two factors: the intrinsic replicative capacity of the resistant strain and the degree to which the treatment could decrease viral load. (4) The transmissibility of drug-sensitive strains from patients on treatment, which is dependent upon the effect of the therapy on viral load. In addition to that, as mentioned above for the overall epidemic, the prevalence of risky behaviours among treated patients is of great

importance. Using this model, Blower *et al*. predicted that the proportion of new infections due to resistant strains among gay men in San Francisco would increase from 0.25% in 1996 to 15.6% in 2005, and acquired resistance would be the major factor involved. Although model parameters values were uncertain, the prediction proved to be quite accurate and a number of surveys have suggested that the incidence of transmitted drug resistance may actually be on the rise in the industrialized world. One study analysed drug resistance among recently infected antiretroviral naïve people in San Francisco from 1996 to 2001.[84] The prevalence of mutations associated with resistance to nucleoside reverse transcriptase inhibitors (NRTI) decreased from 25 to 7% between 1996–1997 and 1998–1999 but returned above 20% in 2000–2001. Genotypic resistance to non-nucleoside reverse transcriptase inhibitors (NNRTI) was not detected in 1996–1997 but its prevalence increased to 13% in 2000–2001. Resistance to protease inhibitors increased progressively from 2.5% in 1996–1997 to 7.7% in 2000–2001. In contrast, mutations affecting sensitivity to all three classes of antiretrovirals remained rare and was detected only in one case (1.2%) observed in 2000–2001. This study illustrates several important points in the epidemic dynamics of transmitted drug resistance. First, the variation in the proportion of new infections due to resistant viruses over time may reflect the trend for patients on nonsuppressive regimens to harbour resistant viruses. For example, prior to combination therapy there may have been a high prevalence of NRTI-resistant strains among treated patients with virologic failure. With the implementation of more potent regimes, the prevalence of patients with detectable viral load harbouring these resistant viruses decreased with a concomitant decreases in the transmission rate. The re-emergence of NRTI-resistant strains transmission in more recent years may reflect an increasing proportion of virologic failure in patients extensively treated with HAART. Second, the trend in prevalence of NRTI resistance may be indicative of how rapidly transmitted resistance may spread after new antiretrovirals are introduced into clinical practice. Finally, the very low level of transmission of resistance viruses, contrasting the relative frequency that resistance occurs in patients, may reflect an impaired replicative capacity of mutated strains and consequently the decreased probability of their transmission.[85] Similar results are reported from studies conducted in North America and Western Europe.[86–88]

Other studies however, although confirming the alarming prevalence of transmitted resistance, provide different information on recent trends, being that in some regions transmitted resistance has stabilized in recent years.[89–91] This discrepancy may have a number of explanations including the different proportions of chronically infected patients on therapy, the different proportions of those on therapy with undetectable viral load, the different proportions of new infections acquired from infected individuals who may not have been exposed to antiretrovirals, such as immigrants from developing countries, and an increasing mortality of people infected with resistant strains.

In addition, differences in epidemiological design of the studies and in methods for detecting and criteria for interpreting resistance make it very difficult to draw general conclusion. However, it is clear that drug resistance is here to stay and, as suggested by data from South America, it will probably spread beyond industrialized country as the use of HAART increases in other parts of the world.[92]

Future challenges of prevention

A discussion on the status of research for an AIDS vaccine is beyond the scope of this paper. However, when considering future trends of the epidemic and strategies to control it, it should be kept in mind that a vaccine capable of preventing HIV infection does not appear to be at hand. Presently, more than 30 candidates vaccine are being tested in a number of small-scale human trials (IAVI. Ongoing Trials of Preventive HIV Vaccines www.iavireport.org/specials/OngoingTrialsofPreventiveHIVVaccines.pdf; accessed on October 20, 2004). However, two phase III trials that were concluded in 2003 showed no efficacy of the candidates vaccine tested[93,94] and currently only one large-scale phase III trial designed to test the efficacy of a candidate vaccine in preventing the new establishment of infection is underway. The development of an effective vaccine will require an enormous economic, political, and social effort and important scientific questions on the biological mechanisms underlying a protective immune response to HIV are still unanswered.[95,96]

Currently, new vaccine strategies are aimed at eliciting a HIV-specific cellular CD8 immune response in uninfected people. It is unlikely that such a vaccine will prevent infection; however, a vaccinated individual, upon contact with the virus, should be able to rapidly mount a T-cell response that could limit the initial spread of the virus and better control viral replication. The reduction of viral load in infected individuals could then be expected to reduce both the probability of progression to clinically overt disease and the transmission of virus to other individuals.[96,97] However, similar to HAART, it is unlikely that such an 'imperfect' vaccine will lead to eradication of infection, especially in communities with high prevalence of infection,[98] and its overall epidemiological impact may not necessarily be beneficial. In fact, a disease-modifying vaccine that prolongs survival of those living with HIV also increases the time period during which an infected person may transmit the virus to other people. Model simulations suggest that to be effective at the epidemic level such a vaccine should affect the viral load such that it reduces the per-partnership probability of transmission to at least 75%. In addition, if the prevalence of risk behaviours increases coincidentally with the use of the vaccine, again this may abrogate any positive effects of the vaccine on the spread of the infection.[99]

Even if the wider use of HAART and in the future disease-modifying vaccines control the epidemic, it is prevention targeted at modifying risky behaviours which will be the cornerstone of strategies aimed at curbing HIV spread. The availability of HAART, rather than being an alternative to behaviour modifying efforts, should be regarded as an opportunity for expanding HIV prevention.[13,100] Increasing access to antiretroviral therapy may increase the willingness to undergo HIV testing, as suggested by data from Brazil where the number of people seeking HIV voluntary testing and

counselling increased in 1999–2003 and paralleled the increase in the number of patients receiving antiretroviral therapy.[100] Moreover, availability of effective therapy may reduce the stigma associated with a disease that, until recently, was regarded as incurable. The use of HAART may bring millions of people into specialized health care settings, providing the opportunity to deliver and reinforce prevention messages.

The challenges for the future will be to integrate HIV prevention messages into patient care, to increase the awareness of HIV-infected individuals to preventative measures. A recent study suggest that quite often HIV-infected people do not receive messages on safe sex in the context of clinical care and than HIV prevention counselling is significantly less common than counselling on adherence to antiretroviral therapy or on nutrition.[101] On the other hand, it has been shown that health care providers can be trained to deliver during medical visits brief safe-sex counselling that may be effective in reducing HIV transmission behaviours in people with HIV.[102] Integration of prevention into medical care for HIV thus appears feasible, and should be pursued in industrialized and developing countries alike. In particular, when implementing HAART programmes in a country where resources are constrained, it should be kept in mind that no funding programme can keep the pace with the increasing medical needs and costs of people living with HIV, unless the incidence of new infections are reduced by increasing prevention efforts. Finally, as the availability of HAART increases, prevention efforts for uninfected people who are at risk must also be enhanced. In this context, it will be important for people to understand the potential benefit and limitations of currently available therapy. Every effort should be made to avoid erroneous beliefs and misconceptions about HAART that may favour and increase risky sexual behaviours which could ultimately overwhelm any benefit of HAART on the course of the epidemic.

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