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HIV epidemiology and the effects of antiviral therapy on long-term consequences

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Abstract

Twenty-seven years have now elapsed since the first description of AIDS in homosexual men in San Francisco, USA. Since those early reports in 1981, millions of people have died from this disease and millions are living with HIV infection worldwide. The rate of new cases of HIV infection has stabilized in some parts of the developed world, but in other areas of the world, especially in Africa, south-east Asia and eastern Europe, the number of newly infected individuals continues to rise alarmingly. Despite international commitment, there is still much to be done to improve access to antiretroviral drugs in areas of greatest need, especially sub-Saharan Africa. The availability of antiretroviral drugs is a key factor in limiting the pandemic and prolonging the lives of those infected, but a more universal, targeted approach, incorporating prevention, early diagnosis, counselling and treatment, will only succeed in stemming the spread of the virus. In the face of the apparent inability to control the increasing rate of new infections there are some positive signs in the battle against HIV/AIDS. In developed countries, the introduction of antiretroviral drugs has resulted in a significant reduction in AIDS-related mortality and improved survival. As access to antiretroviral drugs in the developing world improves, it is hoped that these trends will begin to be reflected worldwide. As HIV/AIDS shifts from a fatal to a chronic disease, however, a new range of health complications and threats to mortality are beginning to arise.

Keywords

AIDS; epidemiology; HIV; mortality

Introduction

Despite greater knowledge and awareness, the HIV/AIDS pandemic continues unabated throughout all areas of the world and has accounted for the deaths of 2.0 million people in 2007. In the same year, 2.7 million people became newly infected, primarily through sexual transmission or intravenous drug use, although mother-to-infant transmission and blood transfusion remain a problem in some areas. This equates to one new infection every 10 s or 7400 new infections every day. Of these 2.7 million new infections, 1.9 million occurred in sub-Saharan Africa. According to the most recent statistics from the Joint United Nations Program on HIV/AIDS (UNAIDS), approximately 33 million people are living with HIV, 67%

of whom live in sub-Saharan Africa [1]. The next geographical area of concern is south and south-east Asia, with 5.0 million infected people. In addition to these known areas of high incidence, we are also seeing rapid rises in the incidence of HIV infection in eastern Europe and other populous areas of Asia, highlighting these areas as the next areas at great risk.

HIV in sub-Saharan Africa

Sub-Saharan Africa is home to just over 10% of the world's population but more than 65% of all people living with HIV worldwide reside here. In 2007, approximately 22 million people in the region were living with HIV and there were approximately 1.9 million new infections; 1.3 million people died last year as a result of AIDS. The prevalence of HIV/AIDS in the region is almost 6%. Epidemiological trends for HIV infection differ in Africa compared with other areas of the world. Currently, in contrast to the developed world where HIV-infected men outnumber infected women, in some cases by 2 : 1, more African women than men are infected with HIV, an expression of the often highly unequal social and socioeconomic status of women and men in most of the region [1]. Three-quarters of all women living with HIV are in sub-Saharan Africa; women comprise approximately 11.2 million (51%) of infected adults in this region. The HIV/AIDS epidemic has reversed trends in improving life expectancy throughout much of Africa. For example, until the mid-1980s, life expectancy in Botswana, South Africa, Swaziland, Namibia and Zimbabwe was increasing; however, the HIV/AIDS epidemic has had a profound effect in terms of reducing life expectancy by approximately 15 years in many of these areas (Fig. 1) [1].

It is important to remember that HIV does not come alone: it is an immunosuppressive disease, and its prevalence means that the incidence of other endemic diseases around the world is also increasing. Between 1990 and 2005, the density of new cases of active tuberculosis in Africa dramatically increased, and in 2001 tuberculosis was the most common cause of morbidity and mortality in patients with HIV infection in sub-Saharan Africa [2]. A similar trend is being identified in many countries throughout the world. Hand in hand with this increased incidence has come an additional complication, with the development of multidrug-resistant strains of the tubercle bacillus against which the drugs commonly used to treat the disease are ineffective. Extremely drug-resistant (XDR) tuberculosis is resistant to both first-line and many second-line antituberculosis drugs, occurs almost exclusively in HIV-infected patients and is associated with an accelerated fatality rate [3]. Drug-resistant forms of tuberculosis pose a major threat to populations around the world and a challenge to tuberculosis-control activities everywhere. A recent outbreak of XDR tuberculosis in Kwazulu-Natal in South Africa was characterized by alarmingly high mortality rates. Of 53 cases of confirmed XDR tuberculosis, 44 had been tested for HIV and all were positive; 52 of these 53 patients died, on average within 25 days, including those being treated with antiretroviral drugs [4]. Given the underlying HIV epidemic, drug-resistant tuberculosis could have a severe impact on mortality in Africa and the World Health Organization (WHO) have issued a call for urgent preventive action.

HIV in Asia and Oceania

The prevalence rates of HIV/AIDS in south and south-east Asia are much lower than in Africa, approximately 0.6%, but given that half of the world's population – almost four billion people – lives in this area of the world, a relatively small prevalence rate still equates to a substantial HIV-infected population. It is estimated that almost 5 million people in this region are living with HIV; a large pool of infected individuals potentially to transmit the virus to other individuals, leading to 380 000 new infections in 2007 [1]. Whereas transmission in Africa is primarily through sexual contact, in Asia it is primarily through intravenous drug use, although transmission between men who have sex with men (MSM) and heterosexual transmission are also important sources of new infections [1]. This area of the world is becoming a major cause

for concern because of the lack of recognition of the problem for many public health officials and delayed implementation of effective control programs.

HIV in western and eastern Europe

In 2007, approximately 137 000 newly diagnosed cases of HIV infection were reported from Europe; the largest number of HIV cases (over 110 000) was reported from eastern Europe, over twice that of western Europe and over 10 times that of central Europe [5]. Data show that higher rates of HIV infection are now being seen in Russia and the Ukraine, where the epidemic was quiescent until the fall of the Berlin wall [5]. Once that occurred, movement of illicit populations and drugs into other countries brought a subsequent rise in rates of HIV. Although MSM were the initial group exposed to HIV in these countries, they have been replaced by intravenous drug users as the main driver of the epidemic in eastern Europe. There has been an increase in the number of new cases of sexual transmission reported among heterosexuals, often as a result of unprotected sex with intravenous drug users, and it is expected that the pattern in eastern Europe may begin to mimic that seen in the United States and western Europe.

The effects of retroviral drugs

Increased survival

The United States had a burgeoning AIDS epidemic and a rate of AIDS-related mortality that was escalating until the mid 1990s. The introduction of antiretroviral drugs and HAART, including protease inhibitors, brought a sharp decline in fatalities, improvements in survival (Fig. 2) and a sharp drop in the reporting of AIDS cases [6]. Therefore, although HIV continues to be transmitted virtually unabated in the United States, its fatal consequences are diminishing. In most of the developed world, HAART has had a positive impact on AIDS survival, with an increase in the number of HIV-infected patients on HAART being reflected by declines in deaths and the development of AIDS. In the first years of the HIV/AIDS epidemic, the median survival rate was approximately 12 months from time of diagnosis of AIDS. In the era of HAART, median survival had increased to 60 months by 1995, and initial estimates suggest that by 2006 approximately 85–90% of patients will survive beyond 6 years after the diagnosis of AIDS [7]. Although somewhat mixed, access to treatment has increased considerably in some sub-Saharan African countries, and the beneficial effects of such increases are starting to be translated into declining numbers of AIDS cases and HIV/AIDS-related deaths as seen in the United States. Botswana, for example, has one of the highest incidences of HIV infection in the world, but a successful roll-out of antiretroviral therapy nationwide has led to the beginnings of a decline in AIDS-related mortality (Fig. 3) [8]. Overall, the HIV/AIDS epidemic has reversed decades of gradual gains in life expectancy in Africa and in parts of sub-Saharan Africa, life expectancy is now 15–30 years lower than three decades ago [9].

Decreased mother-to-child transmission

The use of antiretroviral drugs has blocked mother-to-child transmission (MTCT) effectively enough to have almost eradicated this form of transmission in the developed world. With no treatment, transmission rates in Europe and the United States were 15–30% and this was reduced to approximately 1–2% with the advent of HAART [10]. In the developing world, where antiretroviral drugs are not widely available, MTCT remains a major cause of HIV transmission. There was an inexcusable delay in getting these drugs into developing areas of the world, but when eventually trialed in these populations it was shown that short-course antiretroviral drugs (zidovudine and lamivudine) in late pregnancy and during and after birth, or single-dose nevirapine given to mothers in labor and their baby immediately after birth, could significantly reduce MTCT rates. This effect was seen even in breastfeeding populations, essential in areas where clean drinking water is unavailable and breast feeding must be encouraged [11].

International response to the HIV/AIDS pandemic

Since the United Nations Declaration of Commitment on HIV/AIDS in 2001, pledges and commitments for total annual resources available for HIV care rose from US\$1.6 billion to US\$8.2 billion in 2005, and the number of people receiving antiretroviral drugs increased fivefold worldwide and up to eightfold in southern Africa [1]. Despite this apparent commitment, the pandemic is outpacing the global response; in 2005 there were more AIDS deaths and new HIV infections worldwide than ever before [11]. Under the original '3 by 5' goal set by the WHO and UNAIDS in 2001, three million people were meant to be on the antiretroviral drug treatment they needed by 2005; that target was not met, and only 1.3 million people were receiving treatment by the end of 2005, with an estimated 2 million receiving antiretroviral drugs by 2006. Only approximately one in five people in low and middle-income countries receive the antiretroviral drugs they need. Approximately one in six of the 4.7 million people in need of antiretroviral drugs in sub-Saharan Africa were receiving them in 2005; however, access is uneven between countries, with coverage reaching or exceeding 50% only in Botswana, Namibia and Uganda [1]. In some areas only 11% of HIV-positive pregnant women received antiretroviral drug treatment that would help prevent MTCT, and only 15% of children in need of treatment had access to it [12]. Despite measurable successes in some countries, universal access remains a distant prospect in other countries.

Issues around antiretroviral drug roll-out in low-income countries

Mortality rates in HIV-infected patients from low-income settings in Africa, south America and Asia have been shown to fall substantially within the first few months of HAART, approaching those seen in western Europe and north America after approximately 4–6 months of treatment, and the provision of free treatment in low-income settings is associated with lower mortality [13]. Patients in low-income countries in this study had increased mortality rates in the first few months of therapy compared with those from developed countries [13]. This difference could be explained partly by the fact that patients from low-income countries tended to have lower CD4 cell counts and more advanced disease at diagnosis than those from high-income countries. Many HIV/AIDS patients in resource-poor countries also have other underlying co-morbidities, such as tuberculosis and invasive bacterial and fungal infections, which, given the limited access to therapies for such infections in low-income countries, may also contribute to this initial high mortality.

Despite concerns, evidence suggests that favorable levels of adherence can be achieved in sub-Saharan African settings, at least in the initial stages when the patient is experiencing major improvements in their health and wellbeing [14]. Adherence is essential for successful viral suppression and to reduce the risk of viral resistance. Adherence with full viral suppression is an important predictor of survival, and treatment interruptions are an important predictor of drug resistance [15]. Failure to suppress virus replication completely has been shown to result in the development of resistance to some antiretroviral drugs, especially protease inhibitors, even at relatively high levels of adherence [16,17]. In industrialized countries, regular measurement of the viral load is routinely used to monitor therapy and to evaluate adherence. Unless monitoring of viral load is adopted alongside the introduction of antiretroviral drugs in developing countries, the risks of drug resistance arising and being transmitted are greatly increased; unfortunately, the necessary laboratory infrastructure for such monitoring is not currently available in most countries of sub-Saharan Africa [18].

Slowing the pandemic

Overall, improved access to treatment seems to be having some effect in reducing HIV transmission. Effectively slowing the pace of the HIV/AIDS pandemic is, however, a complex issue; we can keep people alive longer and hope that we can make them less infectious through

treatment, but treatment alone cannot stop transmission and other strategies are needed. One recently recommended measure is male circumcision. Recent trials in Uganda [19], Kenya [20] and South Africa [21] demonstrated 55–60% reductions in the risk of HIV acquisition in men who had been circumcised, highly statistically significant findings. In response to these findings, the WHO and the UNAIDS Secretariat convened an international expert consultation to determine whether male circumcision should be recommended for the prevention of HIV infection. Experts attending the consultation recommended that male circumcision should be recognized as an additional important intervention to reduce the risk of heterosexually-acquired HIV infection in men as part of a comprehensive HIV prevention package throughout the world.

HIV/AIDS: the shift from a fatal to a chronic disease

Although decreasing the mortality associated with HIV/AIDS may seem a distant prospect in many areas of the world, real progress is being made in others. Between 1987 and 1994, for example, HIV/AIDS was a major cause of death in the United States, with the death rate increasing every year to become the leading cause of death in young adults. With the advent of antiretroviral drugs, and especially the introduction of protease inhibitors in the mid-1990s, mortality began to decrease significantly (Fig. 4) [22]. This trend is evident in other developed countries and, as already discussed, we are also beginning to see similar trends in some of the resource-poor countries who are best managing the epidemic. The decreases in AIDS-related mortality are an encouraging sign that HIV-infected individuals are living better and longer lives, although it is important to bear in mind that the improvement in clinical management and patient survival must be matched by reductions in the incidence of new HIV infections if the pandemic is to be contained.

As management improves, people with HIV/AIDS will be living longer and, therefore, will become increasingly susceptible to the chronic diseases we are now beginning to recognize as long-term sequelae of this disease. A recent US HIV outpatient study has shown that, although the death rate from AIDS-related causes fell significantly between 1996 and 2004, the proportion of deaths from non-AIDS-related diseases increased [23]. This increase was especially prominent in non-AIDS malignancies, hepatic disease and cardiovascular and pulmonary disease. As mortality from HIV/AIDS continues to improve, these long-term consequences of infection will become of increasing significance and will require comprehensive management strategies.

In conclusion, the HIV/AIDS pandemic continues unabated throughout the world, with successes in some areas being outweighed by the acceleration of spread in others, including eastern Europe. Only a more universal, targeted approach, incorporating both prevention and treatment, will succeed in limiting that spread. We will need innovative methods for early diagnosis coupled with counselling in order to initiate treatment strategies as early as possible. We will also need to emphasize novel methods of prevention, including male circumcision, microbicides and pre-exposure prophylaxis, if we are to have any effect on limiting the spread of this disease. Although a vaccine is not likely to be available in the near future, there have been promising breakthroughs in research on vaccines that reduce viral load, decreasing chances of transmission. As a preventive HIV vaccine is probably still at least a decade away, we are going to rely on treatment as well as prevention modalities to try to slow this pandemic and to manage the effects of a disease which still, despite our efforts, leaves millions dead throughout the world every year.

We now have treatment options, which, at least in those patients who have access to them, are essentially converting a disease that was historically fatal in a relatively short time period into a chronic living disease. The consequences of this paradigm shift in outcome is that people

living with HIV are now at greater risk of developing previously unrecognized long-term complications, some of which are discussed in detail in this supplement.

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Fig. 1. Impact of HIV on life expectancy in Africa

■ Botswana; ▲ South Africa; ○ Swaziland; □ Zambia; ● Zimbabwe. Reproduced with kind permission of UNAIDS [1].

Fig. 2. Cumulative proportion of patients surviving by months after the first diagnosis of an AIDS-defining opportunist infection 1997–2004 [6].

Fig. 3. Decline in registered AIDS-related mortality in age groups with implementation of antiretroviral therapy in Botswana
 ■ On antiretroviral treatment; + 0–4 years; ● 5–24 years; ◆ 25–54 years; ▲ 55+ years. ART, Antiretroviral therapy [8].

Fig. 4. Estimated number of AIDS patients and deaths among adults and adolescents with AIDS (United States and dependent areas) 1985–2005.^a

▲ AIDS; ◆ deaths. ^aData have been adjusted for reporting delays [22].