HIV and AIDS in relation to other pandemics

Among the viruses plaguing humans, HIV is a recent acquisition. Its outstanding success as an infection poses immense scientific challenges to human health and raises the question “What comes next?”

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In Darwinian terms, the recent emergence of human immunodeficiency virus type 1 (HIV-1) is an outstanding success. HIV has readily exploited various niches provided by our lifestyle in the developed world, including air travel, narcotic dependence and steamy, promiscuous bath houses (Shilts, 1987). However, it is wreaking the most havoc among the world's poorest and most underprivileged communities, in which life expectancy has dropped by 20 years on average. The death toll from HIV/AIDS worldwide is equivalent to three World Trade Centre attacks every day (Table 1). Great advances have been made in our understanding of the molecular biology of the virus, and these have been rapidly translated into saving lives through screening and therapy, but HIV's spread among humans seems set to continue unless we can develop a truly efficacious vaccine. With no end to the pandemic in sight, the societal and medical impact of AIDS is profound, and could affect human health and development in further surprising and unfortunate ways. HIV/AIDS presents a frightening although fascinating *danse macabre* of sex, drugs and death.

We are a *nouveau riche* species as regards infectious disease

When comparing HIV/AIDS with other new epidemics of infectious diseases, we can see that they usually catch us off-guard. Our only hope is that they are self-limiting, such as the outbreaks of Ebola in Africa, Nipah in Malaysia, H5N1 influenza in Hong Kong, variant Creutzfeldt-Jakob (vCJD) disease in the UK and Legionnaire's disease in the USA. Four of these five examples are zoonoses, crossing from animals to humans as a result of changes in human ecology such as deforestation and food technology; the fifth, Legionnaire's disease, was helped by our creation of large artificial lungs, cooling

Table 1 | UNAIDS estimates of infections with HIV and deaths due to AIDS in December 2002

Group	Subgroup	No. of people (in millions)
Total deaths from AIDS, 1982–2002		25.0
Number of people living with HIV/AIDS	Global	42.0
	Africa	29.4
	Adults	38.6
	Women	19.2
	Children	3.4
People newly infected with HIV in 2002		5.3
AIDS deaths in 2002		3.2
Children orphaned by AIDS		14.8

units and jacuzzis, which provide an ideal environment for the propagation of a microbe that likes warm, humid, aerated conditions. HIV, with its long, infectious, but inapparent, period of incubation, is not self-limiting and is now out of control. It also started as a zoonosis from primates, but became adept at transmission through sexual activity and needle-injecting drug use, as well as from mother to child.

The emergence of so many new diseases in the past 25 years indicates how short-sighted it was for the US Surgeon General to declare soon after the eradication of smallpox in 1977 that infectious diseases had been conquered. Moreover, old ones have a habit of bouncing back, as can be seen from multidrug-resistant bacteria, the resurgence of tuberculosis, and the recurrence of typhus in places of war, such as Bosnia. In his 1546 treatise on syphilis, *De Contagione*, written more than 300 years before the germ theory of disease, Girolamo Fracastoro prophesied: “There will come yet other new and unusual ailments in the course of time. And this disease will pass away, but later it will be born again and be seen by our descendants.”

Overall, we can consider today's collection of human infectious diseases in three ways, as listed for viruses in Table 2 (McMichael, 2001; Weiss, 2001b). We have ‘family heirlooms’ that co-evolved with the human host ever since we diverged from apes and earlier. These are represented mainly by persistent infections, often passed vertically, and they tend to be seriously pathogenic only when the health of the host is already compromised. Then there are the temporary exhibits, or zoonoses, in which the human is a dead-end host. But some of these infections do take off to become new acquisitions that are adapted to maintenance in a human reservoir. Smallpox and measles are probably less than 13,000 years old, and cholera first appeared only in 1817. The 1918–1919 influenza pandemic started as a new zoonosis from birds, like the H5N1 influenza in Hong Kong in 1996. Thus, we are a *nouveau riche* species as regards infectious disease. Indeed, the emergence

Table 2 | ‘Family heirlooms’ and new acquisitions among human viruses

‘Family heirlooms’ that have co-evolved with humans

α -, β - and γ -herpesviruses
Retroviruses, such as endogenous genomes and human T-cell leukaemia virus
Papilloma and polyoma viruses, such as HPV-18, BK
Hepatitis B virus

Temporary exhibits — zoonoses with self-limiting outbreaks

Rabies, from dogs and bats
Ebola, reservoir not known
Lassa and Hanta, from rodents
Nipah, from fruitbats via pigs

‘New’ acquisitions permanently established in human populations

Smallpox (eradicated as a natural infection, 1977)
Measles, from ruminants
Influenza, from birds and pigs
HIV, from primates

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of AIDS followed by vCJD has alerted us to the risk of emerging zoonoses, enabling us to look ahead critically at technologies such as xenotransplantation (Weiss, 2000). What stops the temporary exhibits from adapting to onward transmission is not clear; in today's global village, the next Ebola outbreak could easily go the way of pandemic influenza or HIV/AIDS (Garrett, 1995). Severe acute respiratory syndrome (SARS) is jet-setting across the world as I write.

In 1836, aboard the *Beagle*, Charles Darwin noted that "Wherever the European has trod, death seems to pursue the aboriginal". Just as zoonoses can attack a wholly naive human population, infections can be exported from an endemic area to a previously unexposed one. Cortez could not have conquered the Aztecs without the helping hand of smallpox and measles, which decimated native American populations (McNeill, 1976) and thus encouraged the slave trade as a means of providing labour for the new plantations. Opening trade routes had a role in spreading many infections. The Central Asian silk route brought plague to Europe in 1347 (Zeigler, 1970); the Spaniards shipped measles, smallpox, malaria and yellow fever to the Americas; Captains Cook and Vancouver calamitously delivered measles to several Polynesian island populations; and the truck routes from Zaire, through Tanzania and Uganda, to Kenya in the early 1980s did the same for HIV/AIDS (Serwadda *et al.*, 1985).

AIDS was first recognized as a disease in May 1981, and the causative HIV virus was first isolated just two years later (Barré-Sinoussi *et al.*, 1983). Sero-epidemiological surveys in 1984 indicated that about 20% of gay men attending clinics and 34% of haemophiliacs were already HIV positive. 'Slim' disease in Uganda and the aggressive Kaposi's sarcoma in Zambia were found to be manifestations of AIDS, as 10% of young adults were already HIV positive in sub-Saharan Africa (Serwadda *et al.*, 1985). It became clear that AIDS was not merely a curiosity among gay men in the developed world, but would become a worldwide problem.

We now know that there are two types of HIV virus, HIV-1 and HIV-2, that crossed into humans from quite distinct primate species (Hahn *et al.*, 2000). HIV-1 is closely related to SIVcpz of chimpanzees. It is classed phylogenetically into three groups—M, N and O—which differ from each other in genetic sequence as much as each does from SIVcpz, indicating that each group represents a separate chimpanzee-to-human transfer. HIV-2, in contrast, resembles SIVsm of the sooty mangabey monkey, with at least six separate transfers of this virus to humans. Whereas HIV-1 groups N and O remain localized in Gabon and Cameroon, close to their former reservoir species, and HIV-2 is present mainly in West Africa (with some spread to Europe and India), HIV-1 group M has given rise to the worldwide pandemic, diverging into various clades or subtypes, known as A–K. It is not yet clear what has made HIV-1 M fitter for pandemic spread. Furthermore, recombinant forms of HIV-1 are becoming increasingly evident in regions where more than one group or subtype circulates. HIV-1/HIV-2 recombinants have not yet been recorded, but now that both are prevalent in West Africa, novel hybrid viruses might emerge.

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It seems strange that so many primate-to-human lentivirus transfers have occurred in recent history. The only one for which we have a reasonably accurate starting time is the pandemic strain, HIV-1 group M. The first known positive human sample dates from 1959 in Kinshasa, Zaire, but from detailed phylogenetic studies of extant strains, a date for the species jump can be estimated as 1931 ± 12 years (Korber *et al.*, 2000). The widespread use of non-sterile injecting equipment in Africa in the second half of the twentieth century might have helped HIV-1 to establish a reservoir before its sexual transmission became common (Drucker *et al.*, 2001). Thus, from a point of origin about 70 years ago, HIV-1 M currently infects 42 million people, not counting the 25 million who have already died from AIDS (Table 1). HIV is spreading rapidly in Eastern Europe and Asia, where its incidence could outstrip that in Africa within a decade.

Fig. 1 | The scale of HIV variation. Sequence divergence of envelope glycoproteins of HIV (gp120 V2-C5) compared with that of influenza A H3 (HA1). The length of the spokes indicates the degree of divergence, with the scale shown. HIV variation in a single person six years after infection (nine genomes analysed) is similar to that of worldwide influenza A (96 genomes) in a single year. The greatest amount of variation is in the Democratic Republic of Congo, where HIV first developed and has diversified into subtypes A–K (except for subtype B, which is prevalent in the West, and E, which is prevalent in Thailand). CRF01, circulating recombinant form. (Adapted from Korber *et al.*, 2001.)

Fig. 2 | The HIV replication cycle. (Reproduced with permission from Weiss, 2001a.)

To control AIDS, one must reduce the incidence of HIV transmission. Although it is fashionable to blame poverty for disease, it was a vaccine rather than the alleviation of poverty that eradicated smallpox. Our most important challenge for AIDS is therefore to develop a safe but efficacious vaccine. Various immunogens have been developed, ranging from whole, killed virus particles to recombinant viral proteins, alongside DNA vaccines and vectors expressing HIV proteins. Priming with one, for example HIV DNA, and boosting with another, for example recombinant vaccinia containing the same DNA constructs, is one promising approach (McMichael & Rowland-Jones, 2001), but there is little evidence so far that any of the immunogens will give lasting protection against heterologous natural strains of HIV. Whereas some commentators view the problem of an HIV/AIDS vaccine principally as a global lack of will and coordination (Cohen, 2001), I see it more as a scientific impasse. To quote Samuel Beckett: "Ever tried. Ever failed. No matter. Try again. Fail again. Fail better." One of the problems facing vaccine development is the extreme genetic and antigenic variability of HIV-1. We think of influenza as a highly variable virus, yet the HIV population present in a single individual six years after infection

can be as great as the global variation for an influenza outbreak (Fig. 1). The best vaccine against SIV is a live attenuated one that gives broad protection (Shibata *et al.*, 1997), although it is not appropriate for human use. Even a partly effective vaccine that prevented, say, 50% of infections or exposures would be valuable in slowing down the pandemic.

Despite the failure to produce an efficacious HIV vaccine, much has been accomplished in the prevention of AIDS. Early in the AIDS epidemic, before HIV had been identified, epidemiologists already knew that the causative agent was transmitted sexually and parentally, and clinical immunologists had characterized the syndrome as one resulting from a specific loss of T-helper, CD4-positive lymphocytes. Within two years of the discovery of HIV-1, laboratory experiments had been developed into robust, mass-produced kits to allow the serological screening of all blood donations in developed countries for HIV-specific antibodies. This success in making blood and blood products safe again is a superb example of rapid translational research for the benefit of public health.

The development of therapeutics to control HIV load and progression to AIDS is another genuine success story, which was achieved through rational drug design based on the known molecular biology of

the viral replication cycle. Current drugs in clinical use target two virus-specific enzymes (Richman, 2001): the reverse transcriptase (RT) that is active in an early step of infection, and the protease that is required for the maturation of progeny virus particles. The HIV life cycle presents opportunities for blocking other steps in replication (Fig. 2). New drugs entering phase I/II clinical trials include those targeted to the gp41 transmembrane glycoprotein, to block fusion of the viral envelope with the cell membrane, and inhibitors of integrase, to prevent the insertion of a provirus into the chromosomal DNA of the newly infected cell. However, in the 1980s it became apparent from early trials with the RT chain-terminator, azidothymidine (zidovudine), that HIV quickly develops drug resistance through mutation, and most infections soon become resistant to treatment. Combination therapy with three or four drugs directed at RT and viral protease have proved to be effective in reducing viral load on a longer-term basis. Highly active anti-retroviral therapy (HAART) has had a remarkable effect in reducing AIDS mortality, but only among those fortunate enough to have access to the drugs (Fig. 3); and even sustained HAART is insufficient to eliminate HIV and 'cure' the infected person. Within a few weeks of stopping HAART, the virus load rebounds to previous levels. Therapy is therefore likely to require lifelong use, which is good news for pharmaceutical companies but not for patients or for the economics of health provision. It is not yet known whether those who respond well to HAART will eventually develop multiple resistance to the drugs; we have probably gained a time window rather than an indefinitely successful way of containing the disease.

Changing human behaviour to reduce the rate of transmission seems as daunting as developing a vaccine. Health education can have a role, as seen in Uganda, where fewer sexual partners and the use of condoms are encouraged. Clean-needle exchange centres for injecting drug users were

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Fig. 3 | For whom the bell tolls. (A) Annual AIDS deaths in sub-Saharan Africa (population 640 million) compared with those in USA (population 273 million). (B) Deaths in the USA in more detail, showing the five leading causes of death in men and women 25–44 years old. Over the course of ten years, AIDS came to be the leading cause of death in this generally healthy age group. The sharp decline in mortality followed the introduction of highly active anti-retroviral therapy, although the prevalence of HIV infection has not decreased. (Data obtained from UNAIDS and the US Centers for Disease Control and Prevention.)

Fig. 4 | Cancers linked to AIDS. Standardized rates of four cancer types in 1973–1990 among men aged 25–44 years who have never married. This population-based open cohort of 83,000 was estimated to include 2% HIV-positive men in 1977, rising to 24% in 1985. The increase in viral cancers is notable, whereas colo-rectal cancer incidence remained stable. Relative risks for cancer in 1990 compared with the overall age-matched US male population are about 600:1 for Kaposi's sarcoma (KS), 37 for non-Hodgkin's lymphoma (NHL), 1.0 for colo-rectal carcinoma and 9.9 for anal carcinoma. Kaposi's sarcoma is now the most frequent malignancy seen in sub-Saharan Africa, where the infection rate of Kaposi's sarcoma herpesvirus is about 44% in contrast with 2.3% in the USA (Boshoff & Weiss, 2002; Rabkin & Yellin, 1994).

pioneered in The Netherlands. Preventing mother-to-child transmission by non-nucleoside RT inhibitors can cut vertical transmission by more than 50%.

Given the enormous social and economic impact of AIDS, it is not surprising that myths leading to denial about or blame for HIV/AIDS continue to flourish, ranging from divine retribution to conspiracy theories. Some websites hold that HIV does not exist, or if it does, it is a harmless passenger in the human body. When those in government espouse such ideas and are attracted to the notion that anti-retroviral drugs do more harm than good, their people suffer. This emphasizes the importance of the Durban Declaration (2000) in reiterating the causality between HIV and AIDS. Blame for unleashing AIDS has been placed on the USA, from deliberately releasing it as a recombinant virus to the unwitting contamination of live attenuated polio vaccine during trials in Africa in the late 1950s. This desire to hold to account some human agency for what is a natural calamity is reminiscent of the slaughter of Jews in Rhineland in 1348 in the face of the plague (Zeigler, 1970; Watts, 1997), and the sixteenth-century myths about syphilis, then a new disease. Other myths clutch at hope, such as the widespread view of men in parts of Southern Africa that sex with a virgin will cleanse them of HIV, leading to increasing childhood rape.

HIV induces immune deficiency, wasting and dementia, and most AIDS deaths result from opportunistic infections that are secondary to the immunocompromised state. Foremost among these is tuberculosis. Whereas HIV in an AIDS patient can only be transmitted sexually or parenterally, his or her high load of tuberculosis is a danger to all close contacts, as well as being a breeding ground for drug-resistant strains. Similarly, the underlying cause of the cancers suffered by AIDS patients is persistent virus infections that usually elicit milder diseases in immunocompetent individuals. Kaposi's sarcoma and many of the B-cell non-Hodgkin's lymphomas are caused by γ -herpesviruses, whereas cervical and anal cancer is caused by human papilloma virus types 16 and 18 and related strains (Boshoff & Weiss, 2002). The incidence of these 'opportunistic neoplasms' is greatly increased in AIDS patients (Fig. 4).

The HIV pandemic is still at an early stage of its global burden. Faced with an explosion of HIV among rural blood donors and recipients, China has taken measures to curtail non-sterile collection, but the transmission of HIV in South and South East Asia, especially by prostitutes, remains a grave threat to public health. In the urban poverty of the favelas in Brazil and the shanty towns of Africa and India, HIV finds fertile ground. Inadequate provision or poor adherence to anti-retroviral drugs is a sure recipe for the emergence of multidrug resistance. One can speculate about the future impact of HIV/AIDS in various models. Will society change towards a more puritanical outlook, or will the band play on (Shilts, 1987) in a millennial, apocalyptic fever? Will the sheer numbers of immunocompromised people scupper health programmes, such as the measles and polio eradication campaigns as HIV-positive individuals become persistent spreaders of otherwise acute infections? Will sporadic opportunistic infections not previously known to be transmitted from human to human evolve into new pathogens? About ten free-living species of *Mycobacterium* such as *M. avium intracellulare*, *M. fortuitum* or *M. kansasii* occasionally colonize AIDS patients. Could one of them emerge as a new scourge of humans like *M. tuberculosis* by using this unprecedentedly large immunocompromised population as an aid to parasitism (Weiss, 2001a)?

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