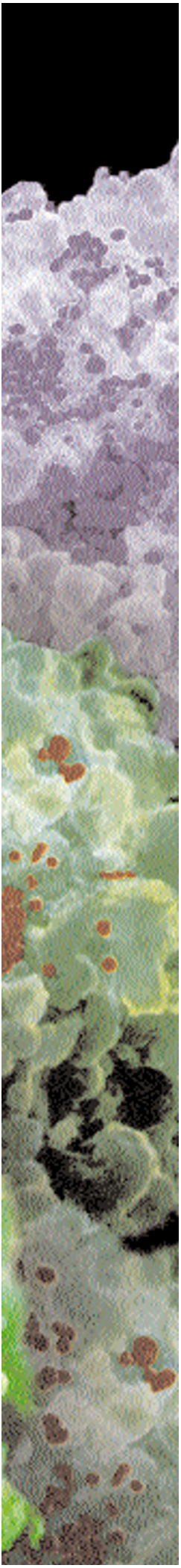

Gulliver's travels in HIVland

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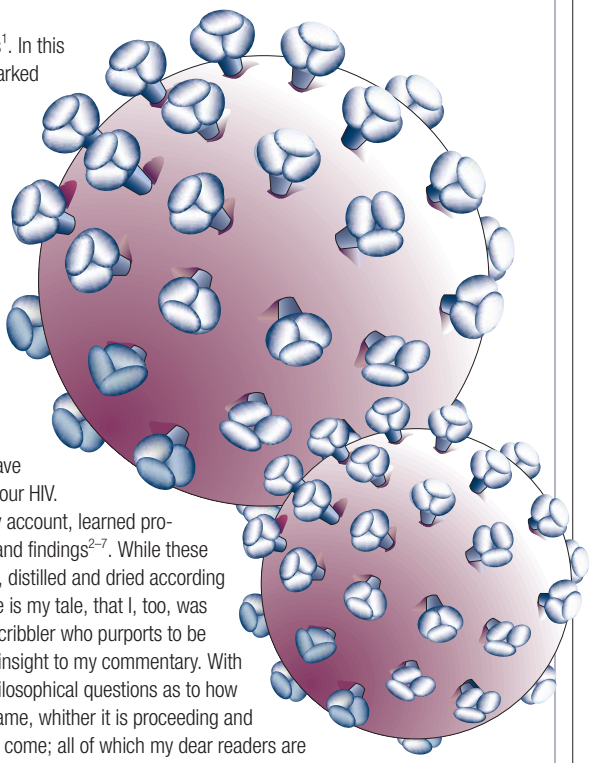
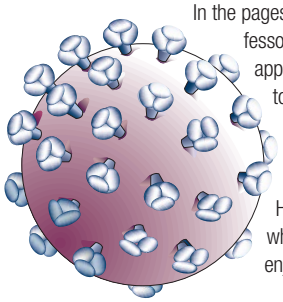
The emergence of HIV and AIDS is narrated here through the eyes of the legendary Irish traveller Gulliver, observing the replication, cross-species origin, evolution, diversity and transmission of HIV. Ethical problems of vaccine trials, the social impact of AIDS, and prospects for its prevention, including the development of topical virucidal lotions, are discussed. The existence of a growing proportion of HIV-infected, immunocompromised children and adults may significantly affect current immunization programmes and the evolution of opportunistic infections.

I, Lemuel Gulliver, have observed wondrous phenomena in many lands[1]. In this my latest account, I shall endeavour to convince you that we are embarked upon a doleful new adventure that is only now beginning to unfold[2]. My story concerns a creature even smaller than the Lilliputians, indeed so minute as to be invisible, named — after quarrelsome debate among a band of pundits in 1986 — the human immunodeficiency virus (HIV). This virus invades the body and slowly corrupts its defences[3,4], so that without intervention by apothecary's powders[5], or a modification of Mr Jenner's vaccine[4,6], the infected subject will eventually perish, on account of invasion by other microbes, and a general wasting of the body, or the mind[7], a collation of afflictions called AIDS[8].



According to the esteemed comptrollers of estimates in Geneva[2], during the first year of the third millennium, this fourth horseman of the apocalypse has caused the demise of some six million people. Since the pestilence first came to notice exactly 20 years ago[9], some 23 million have been slain by it, and 37 million women, men and children currently harbour HIV.



In the pages of this journal, following hard on my account, learned professors of HIVland survey the latest facts and findings[2–7]. While these appendices contain scientific knowledge, distilled and dried according to usual academic practice, so strange is my tale, that I, too, was implored by my editor to engage a scribbler who purports to be an expert on these matters, to add insight to my commentary. With his help, I shall confine myself to philosophical questions as to how HIV procreates in cells, whence HIV came, whither it is proceeding and what HIVland may resemble in years to come; all of which my dear readers are enjoined to view as idle speculation, unsure prediction or wild conjecture.

How HIV commandeers host cells

Like all viruses, HIV is a parasite that replicates within living cells of the host (Fig. 1). HIV has nine genes and belongs to the lentivirus genus of retroviruses. It carries two RNA copies of its genome within virus particles. Viral reverse transcriptase converts them to one DNA copy within the infected cell (a form of meiosis involving genome recombination), which enables HIV to be integrated into the host DNA and to use the cell's genetic machinery to make new virus. Reverse transcriptase was the first target of antiviral drugs in clinical use[5], the second being the protease enzyme that cleaves precursor proteins into components of the viral core during particle assembly. Other promising targets for anti-HIV drug development include the interaction with cell-surface receptors and integration of the viral DNA into host chromosomal DNA.

HIV infects cells mainly of the immune system[8]. T-helper lymphocytes express the CD4 antigen to which HIV attaches. Chemokine receptors serve as co-receptors that guide the viral envelope glycoproteins into a conformation permitting membrane fusion and entry into the cell. Although many co-receptors have been defined in culture, only CCR5 and CXCR4 seem to be used *in vivo*, by HIV strains having an 'R5' or an 'X4' tropism, respectively[10]. Besides $CD4^+$ lymphocytes, macrophages and dendritic cells also harbour HIV. Macrophages are an important reservoir of infection, including the microglia in the brain[7]. Dendritic cells bind HIV through DC-SIGN receptors and carry it from mucosal ports of entry to the lymph nodes where they activate lymphocyte infection[11]. High levels of virus replication and cell destruction and turnover occur at all stages of infection[3,5], although it takes years before the $CD4^+$ cell count falls below the threshold for symptomatic immunodeficiency to become manifest.

Once upon a time, in the early twentieth century, there was a virus — the simian immunodeficiency virus or SIV_{CPZ} — that lived in harmony with its host, the chimpanzee. This host resembled the yahoo, described in my voyage to the houyhnhnms[1], save it was hairier, and of a milder disposition. One night, SIV_{CPZ} had a premonition that over the course of the next 100 years its gentle host would so diminish in numbers as to be in grave danger of extinction. Being wholly reliant on the chimpanzee for its own procreation, SIV_{CPZ} would not survive unless it found a new home.

Now, there was a legend so fanciful one durst not repeat it for fear of ridicule; yet it be so strong in folk memory that one plucks the courage to declare it. Namely, a distant cousin to SIV, yellow fever virus (YFV), had boarded a six-legged, two-winged little monster called *Aedes* that supped on the blood of the hairy ape, then drank from the yahoo, thus transmitting YFV. These newly infected naked apes were captured by cruel kinsmen from the north and were bound and shackled to sailing vessels that crossed the great ocean westerly for 40 days and nights, to disembark upon a new shore. Ever-helpful *Aedes* assisted YFV to escape and colonize numerous New World monkeys and yahoos, and thrive among them. Each summer, YFV made forays to the north, slaying thousands in Memphis, Philadelphia and even New Amsterdam until finally, 101 years ago, Colonel Walter Reed and Dr Carlos Finlay demonstrated the role of *Aedes* and brought the advancing enemy to a halt.

To its alarm, SIV_{CPZ} found it was unable to emulate YFV because *Aedes*, and her sisters *Culex* and *Anopheles*, declined to transmit it. No one is entirely sure how the virus managed to cross into its human host to become HIV-1. Indeed, its possible routes of cross-species transmission have recently been keenly disputed at the Academy of Lagado[12] (described in my voyage to Laputa[1]) and contamination of oral polio vaccine no longer seems plausible[13,14]. But cross the species 'barrier' it did. Likewise, SIV_{SM} of sooty mangabey monkeys found its way to humans as HIV-2.

Adaptation and spread

The cross-species transfer of HIV-1 and HIV-2 from chimpanzees and mangabeys into humans resulted in a change of virulence, as the natural simian hosts do not develop AIDS. Yet the pathogenesis of primate immunodeficiency viruses seem oddly uncoupled from their transmission dynamics. For example, asymptomatic sooty mangabeys carry viral loads as high as the macaques and humans that succumb to AIDS from infection by essentially the same virus[15]. This change of virulence may therefore be determined more by the host response to infection than by properties of the virus. One possible explanation is that HIV infection activates the human immune system, providing a larger pool of cells permissive for ongoing infection and for apoptosis (programmed cell death)[16]. The eventual depletion of $CD4^+$ T-lymphocytes[3] finally tips the balance of power between virus and the immune system in favour of the virus. If we understood better how the host controls SIV infection in mangabeys and chimpanzees, we might find ways to effect HIV control in humans.

HIV-2 seems to be less pathogenic than HIV-1 and to cause disease more slowly[17]. But this observation may mask a bimodal spectrum of virulence in which some individuals carrying HIV-2 progress to AIDS at a similar rate to those with HIV-1, whereas a higher proportion are long-term non-progressors. It is also noteworthy that among the HIV-2-infected people who do develop AIDS, brain disease is more common[18].

HIV-1 and -2 probably encountered many hurdles in adapting to their new host. Some expeditions to humankind may have petered out altogether; others like HIV-1 group N and O remained geographically close to the point of cross-species transfer. But HIV-1 group M was more adventurous, taking every opportunity to transmit its progeny by exploring the highways and intimate byways of its host's behaviour — crossing sexually from man to woman, woman to man and man to man, crossing vertically from mother to child, and horizontally through hollow needles.

HIV diversity

Needles especially may have unwittingly aided the early dispersion of HIV, owing to the widespread re-using of needles and syringes in Africa in the mid-twentieth century[19]. Once HIV became established in its new host, overland trucks, overseas troops and airlines enabled a far more rapid and widespread dispersion than mosquitoes could have effected. HIV-1 group M diversified into distinct subtypes or clades, A–H, with subtype B colonizing the Americas, subtype C moving south to the Cape and north to the Horn of Africa, and subtype E east to Thailand. This outward radiation of HIV-1 group M genomes can be plotted as a starburst[20], but when the clades crossed paths, HIV-1 recombined, so that some genomes have a highly complex genealogy[21,22]. Even recombinants between groups M and O have been recorded[23,24].

My fable related how the precursor to HIV-1 escaped extinction in an ever dwindling host population, currently estimated to be less than 150,000 chimpanzees, separated into isolated troupes. HIV can now sample a new horde of almost six billion, among whom it currently resides in 37 million, or approximately 1 in 162 humans. And by weakening the host's immune system, HIV opened the door to numerous other microbes — the opportunistic infections by viruses, bacteria, fungi and animal parasites.

Now, I shall surely be admonished by some high authority if I would have you believe that a simple virus were capable of premeditated purpose, which has no place in HIV's affairs. Rather HIV has followed the precepts postulated by Charles Darwin and Alfred Russel Wallace, whereby the fittest shall survive and multiply, passing on their fitness traits. Neither is HIV capable of altruistic behaviour towards unrelated microbes, according to the precepts of Bill Hamilton[25]. So the term 'opportunistic infection' aptly describes the exploitation of the expanding ecological niche provided by HIV.

Is HIV evolving in the sense of changing its phenotype, mode of replication, virulence and transmission[22,26]? Or, is it merely expanding, with genetic diversity representing more noise than biological signal? The answer is both, for the basic molecular biology of replication remains constant (Fig.1) while the explosion of HIV into the new terrain of the human body and the human population has allowed an unprecedented degree of genetic diversity, upon which natural selection can then play. HIV selection occurs rapidly in response to antiretroviral drugs[5] and immune attack[4], compounding the problem of vaccine development[6]. It occurs when the virus adapts to use new co-receptors for entry to the host cell, but an identical mutation can both alter cell tropism and lead to escape from neutralization[27]. So it is a moot point as to which is exerting the selective pressure.

There is much we do not yet understand about HIV variation. Is there selection of variants for different compartments such as the lymph nodes and brain, or do the differences reflect stochastic founder effects? Do the envelope variants that emerge in late-stage infection, with a tendency to switch from R5 to X4 phenotype, really exacerbate progression to AIDS, or are they opportunistic variants that cannot emerge until CD4 T-cell counts fall below a threshold level? Why have X4 viruses not emerged in subtype C[28]? Why is the R5 phenotype usually reset at transmission? One explanation is that only R5 viruses can bind to or infect dendritic cells such as Langerhans cells in the mucosa[11], yet R5 viruses are also selected following parenteral transmission. Are some subtypes more virulent than others? Could HIV-1 eventually become attenuated[22]?

HIV is an ideal organism for functional genomics modelling; HIV is a ready-made experiment in maximal mutagenesis while maintaining function and replicative fitness. This has already been exemplified for HIV-1 reverse transcriptase and protease, for which

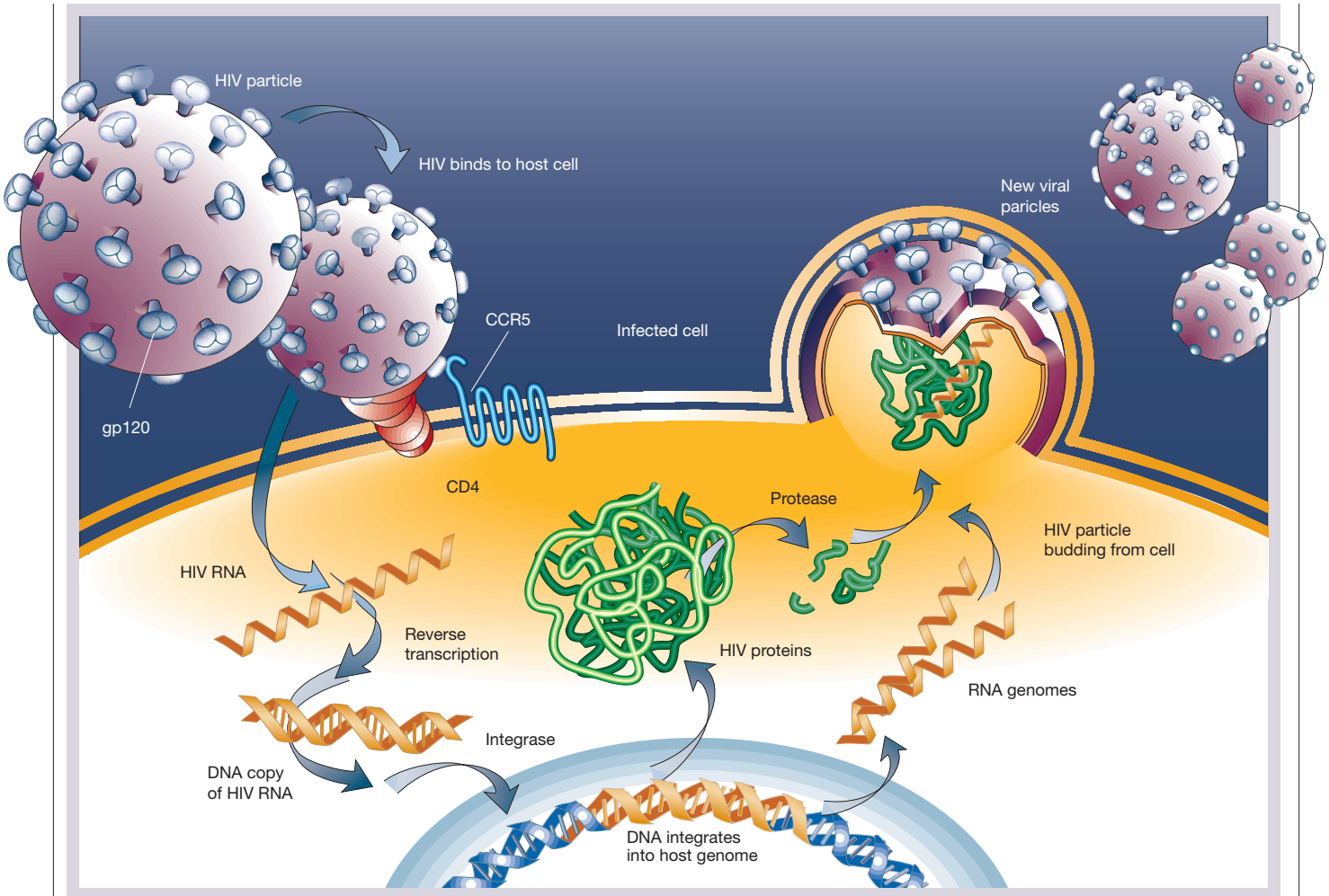


Figure 1 The human immunodeficiency virus. Replication cycle of HIV showing multiple steps available for attack by antiretroviral drugs.

there exist crystal structures, resistant variants to numerous drugs, a vast sequence database and relative fitness data. The degree of genomic diversity that HIV generates in a single infected individual can be greater than the worldwide diversity of influenza A virus during an epidemic[29]. Where, then, can HIV take us, with millions of infected people each possessing such viral diversity?

How conservative is the HIV phenotype and what new tricks might HIV learn? One nightmare scenario for us would be if HIV were to change its mode of transmission. If *Yersinia pestis* can switch from flea-borne bubonic plague to the air-borne pulmonary form of the disease, could HIV also sample new transmission dynamics — adding saliva, aerosol or arthropod vectors to the sex and blood it already enjoys? Forget the mosquitoes beloved of yellow fever, but consider ticks and biting bugs. Can we be sure that it is beyond the ingenuity of HIV to travel aboard the mouthparts (analogous to dirty needles) during interrupted feeding of common bugs such as the cone-nosed *Rhodnius* in Brazil, or the bed-bug *Cimex* in Russia? After all, horseflies or clegs transmit the lentivirus, causing equine infectious anaemia[30]. Identifying a new route of transmission may be overlooked unless surveillance methods are designed to detect it. Sentinel cases might be children with HIV-negative parents.

Prevention and intervention

Uneven as the landscape is, HIVland looks set to extend its borders to grasp tens of millions more infected people[31]. There are, however, some means of slowing its expansion, and some badly affected communities have managed to reduce the rate of HIV transmission through health education[2]. Restraint on the number of sexual partners, treatment of common sexually transmitted infections (which increase susceptibility to HIV) with antibiotics and antivirals, promoting condom use, and clean needle-exchange programmes all help to curb HIV transmission.

The identification of protective factors of HIV transmission does not necessarily make prevention easy. For instance, it is now clear that circumcised men in Africa have a significantly lower probability of acquiring HIV infection[32]. These epidemiological findings make

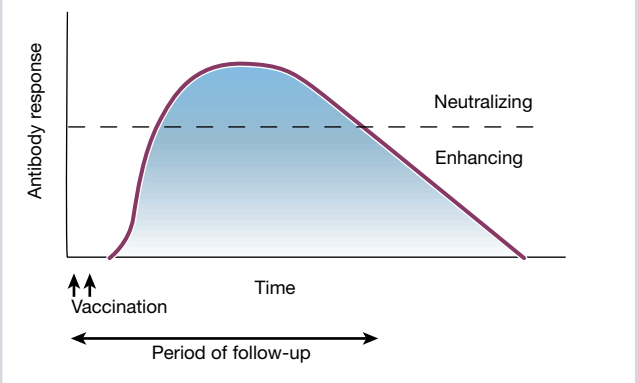


Figure 2 Scheme showing how a humoral immune response to gp120 vaccine may switch from providing protection to enhancing the risk of infection, perhaps after the surveillance period has ended.

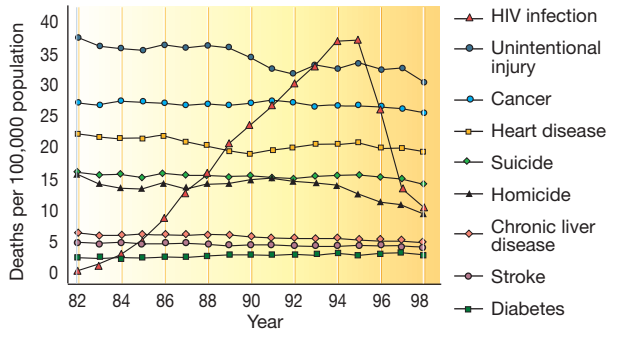


Figure 3 Trends in annual rates of leading causes of death among adults aged 25–44 years in USA over the period 1982–1998. The data from 1998 are preliminary. (Source: Centers for Disease Control and Prevention.)

biological sense, given the high density of Langerhans cells in the prepuce[33]. Although some communities that did not previously practise circumcision are beginning to do so, promulgating such an intervention as public-health policy is fraught with problems. Not only is circumcision a sensitive cultural issue, but a false sense of security might be counterproductive. Although circumcision reduces the chances of HIV infection in men by approximately 60%, it might lead to a rise in HIV transmission through higher-risk sex if men considered themselves to be completely protected. Condoms would be more effective if only men everywhere could be persuaded to adopt them, and to adhere to their use regularly[34].

The Cinderella of HIV research is the development of topical microbicides or virucides. Compared with the research funding available to her big sisters, antiretroviral drugs and vaccines, virucides need to attract more support for research and development[34]. If virucides can be incorporated successfully into vaginal gels, foams and suppositories, they would enable women to provide a means to improving sexual health for both sexes. Whereas the spermicide nonoxynol-9 is too inflammatory, certain sulphated polysaccharides show promise for formulation as anti-HIV molecules for topical application[35]. Virucides could be our best hope for preventing HIV infection until we can deliver a safe, efficacious, affordable vaccine.

Although HIV elicits strong immune responses, these ultimately fail to control infection[4]. Nabel[6] catalogues the obstacles confronting an effective HIV vaccine, while pointing to some promising leads. Cohen[36] has documented the lack of coordination of HIV vaccine research and development. Even a vaccine with <50% efficacy could have a significant impact in reducing HIV transmission[37]. Yet a dilemma exists between purists who wish to see scientific proof of efficacy, and pragmatists who believe that the evidence will come only from conducting human trials[36].

The pressure to conduct clinical trials of candidate vaccines is intense. An immunogen based on the gp120 envelope antigen has progressed to phase III clinical trials, after approval by international and local ethical committees, despite no evidence of efficacy, on the lilliputian logic that if it is available it must be used. Gp120 stimulates a humoral response, including weak neutralization of the HIV strain from which it is derived. This type of vaccine might conceivably be worse than useless, as it might elicit antibodies that enhance infection by targeting macrophages and dendritic cells via complement and Fc receptors[8]. The trial design is unlikely to reveal any increased risk because the enhancement may occur after the period of follow-up among high-risk vaccinees has ended (Fig. 2); and by targeting people illicitly injecting drugs there is likely to be significant loss to follow-up by those at greatest risk. When this writer ventured to raise these points at an AIDS vaccine conference last May, he was politely but firmly rebuked by an envoy from one of the worst afflicted countries in Asia on the grounds that 'something must be done' for his people, a view that won overwhelming applause from the participants. One remains concerned that the heart overrules the head, although we earnestly hope that these fears will prove to be unfounded.

To most readers of *Nature*, AIDS research has followed a steady progress of science successfully translated into medical practice. AIDS was first noted[9] in 1981. Within two years HIV was identified, and by late 1985, serological screening was in place to prevent further infection through blood transfusion and blood products. By 1986, the first antiretroviral drug, zidovudine, was in clinical trial, culminating in the success of combination chemotherapy[5] based on rational drug design, which has led to a 60% reduction of AIDS mortality in the United States (Fig. 3). Our knowledge of HIV and of cell biology is immense, although vaccine development has been much slower than forecast.

Among the people most affected by HIV, Western gay men seized the opportunity to convert stigma and fear into empowerment to set the agenda for research and public health, often knowing more about their condition than their doctors. But for the 90% of HIV-infected people in developing countries there has been little or no access to these scientific advances. There is currently a North–South dispute between protecting the patents of the pharmaceutical companies and demanding access to cheaper generic drugs as a human right. But even generic drugs are beyond the health budgets of the worst affected nations. Besides, if 20% of the US population were HIV-infected, its health management and insurance systems would collapse.

Culture and belief in HIVland

Sometimes the drugs are shunned even when offered at no cost. After HIV swept across southern Africa in the 1990s, some leaders blamed poverty rather than HIV for AIDS, finding scapegoats to attack, just as when the Black Death came to Europe in 1347[38,39]. One leant his ear to siren voices singing that HIV was harmless and that AIDS was not transmissible, so encouraging the misconception that AIDS in Africa is a distinct disease, contrary to all the evidence[40,41].

HIV will not drive humans to extinction, for even rabbits survived the 99% mortality of myxomatosis. But HIV has already reduced life expectancy[2] and will destabilize society by selectively removing its young adults.

> Who, therefore, can foretell what changes in belief[42] we may witness in the coming years, as the nature and extent of HIV's destruction finally becomes apparent. Did not the sixth-century Justinian plague presage the rise in ascetic religions — Christianity in Europe, Islam in the Near East and Buddhism in the Far East? Did not the Pope in Avignon first encourage, then try to suppress, the Flagellants[39] who rose up in 1348 to counter the Black Death that culled saints and sinners alike? Did not smallpox introduced by the Spanish 'centaurs' help to convince the demoralized Aztecs that Christ was more powerful than Quetzalcóatl? Did not the pandemic of greatpox[43] (syphilis) that cut a swathe across Europe and Asia from 1495–1530 influence the Reformation? Did its devastation not help to persuade the Tokugawa Shogunate in Japan to quarantine their islands from the outside world for nigh on 300 years? Although Bynum[44] has cautioned Nature's readers not to swallow too facile an interpretation of past pestilence in the light of AIDS today, it would be surprising if the HIV pandemic did not effect major changes in our mores. So will the band play on[45], or will the pendulum swing away from our contemporary society, as the religious right press AIDS to their cause of just deserts, and 'ecofascists' bless HIV for curbing human population growth?

Effect of HIV on infectious disease

The impact of HIV/AIDS on other infectious diseases will be enormous. First, opportunistic infections, which seldom cause serious disease in immunocompetent people, are frequently the sentinels of

AIDS[9]. Over 100 opportunistic infections by viruses, bacteria, fungi and protozoa have been associated with AIDS. Disease by known pathogens such as tuberculosis also becomes exacerbated in AIDS. Antibiotic resistance to bacteria is more frequently found, and HIV-infected adults may regain susceptibility to childhood infections such as *Streptococcus pneumoniae*[46]. Thus the HIV-infected population can spread virulent strains of pathogens such as tuberculosis to others who are not necessarily at risk of HIV itself.

Second, HIV infection affects public-health immunization programmes. For instance, multivalent pneumococcal vaccine is ineffective in HIV-infected Africans[47]. Live 'attenuated' vaccines such as vaccinia, measles and oral polioviruses may become dangerous pathogens in the immunosuppressed person[48–50]. Moreover, HIV can convert acute infections into long-persistent ones[50], as cell-mediated immune responses are crucial for clearance of virus infections like enteroviruses, measles, mumps and influenza. The World Health Organization needs to give further thought to the power of HIV to scupper its disease-eradication programmes[49]. With 1.5 million HIV-infected children in Africa, can we really eradicate polio within the next few years?

Third, AIDS could conceivably generate new types of epidemics. When the proportion of immunodeficient individuals in a population remains very low, the chance of direct transmission of opportunistic infections from one to another is even smaller. But HIV-infected people can act as incubators of microbes that previously relied on animal reservoirs: for example, the *Mycobacterium avium* complex, canine *Toxoplasma*, alphaviruses of birds, enteric infections of farm animals, and numerous other microbes not normally transmissible between humans.

With the AIDS pandemic, such microbes now have a new host population in which to play darwinian selection. Where 10% or more of a community are HIV-infected, direct transmission between immunodeficient individuals becomes plausible. Microbes that are poorly adapted for human infection could become well adjusted, first to the immunodeficient host and eventually to immunocompetent humans, provided they learn the tricks of human-to-human transmission. These could include free-living microbes from the environment[51,52], including non-tuberculous *Mycobacteria*, *Legionnella*, *Pseudomonas*, *Fusarium* and other fungi, as well as microbes and parasites from animal sources.

Free-living bacteria, fungi and protozoa now have 37 million and rising immunocompromised people in which to learn to become human parasites. The bacteria could acquire antibiotic resistance or adaptive, pathogenic genes from the plasmids, phages and mobile pathogenicity islands[53] of their human-adapted relatives, and yet escape the vaccines now in use. Moreover, animal infections could gain a firm foothold in the human population, particularly fast-evolving RNA viruses. The vast number of susceptible humans is a novel, unique window of opportunity for microbes originating from animals, the soil or water to evolve into human pathogens. This issue of the potential community impact of a massive immunodeficient reservoir therefore demands analysis by those who model infectious disease dynamics and evolution. Long after HIV itself is controlled (we hope) by immunization, new diseases may roam former HIVland. □

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