Tuberculosis, HIV and the developing world

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ABSTRACT – This article reviews the immunology, genetics, epidemiology and treatment of two of the most important infectious diseases in the world, HIV and tuberculosis (TB). The pandemic of TB has been greatly magnified by the advent of the HIV epidemic. In the developing world, probably 50% of HIV seropositive individuals are co-infected with TB. The TB epidemic has expanded both because of increased susceptibility of patients to new tuberculous infection and also because of the greater chance of a primary complex leading to disseminated disease. The evidence that TB has had any effect on the HIV epidemic is less clear in the developed world with effective antiretroviral therapy. In resource-poor countries, many HIV infected individuals die prematurely of TB. Both organisms infect immunologically competent cells, and the control of infection in both has a large genetic component. The complex immunological response and process of cytokine release has a marked impact on both control of disease and the pathological effects of infection. Treatment of TB was associated with the development of resistance until the need for combination chemotherapy was recognised. It was then realised that one of the major factors making treatment of TB difficult was poor long-term adherence. Exactly the same sequence of events in terms of our understanding of the treatment of HIV infection has occurred more recently. These two infections undoubtedly present the most serious challenge to public health across the world, and are likely to be controlled only by a global mobilisation of resources not seen since the end of the last European war.

Tuberculosis (TB) and AIDS, the most important infectious causes of death in the world, share many similarities and contrasts in demography, transmission and pathogenesis. The huge research interest in HIV has meant that more is known about this virus, its dynamics and pathogenesis than any other. In contrast, although TB has been a scourge to humanity for thousands of years, much less is known about the basic pathogenetic mechanisms which cause the disease.

Epidemiology

TB has been recognised for centuries, with active disease present in Egyptian mummies. In contrast, HIV 1 probably arose from an animal vector (chimpanzees) in Africa some time between 1930 and 1950. HIV flourishes in the context of poverty, ignorance and lack of female autonomy, particularly with regard to their sexual partners. Sixteen million people have already died of AIDS, 35 million are living with HIV, and over 15,000 die daily. Perhaps the most poignant moment of Nelson Mandela's speech closing the recent World AIDS Conference in Durban was the statement that half the teenagers living in South Africa could expect to die of HIV infection.

An almost equally large epidemic of TB has resurfaced in the developing world. About one-third of the world's population has been exposed to infection, and the annual rates of disease and death are 8–12 million and approximately three million, respectively. The incidence of TB declined in the UK, USA and most of the developed world during most of the 20th century. An initial fall preceding the development of effective chemotherapy was associated with improved socio-economic circumstances. However, in the last 20 years the incidence of TB in the UK and USA has either stabilised or risen, in large measure due to co-incident HIV infections (Figs 1, 2, 3). For

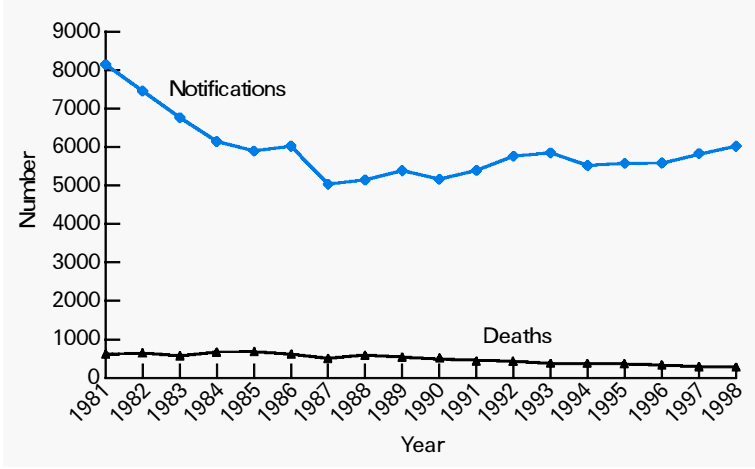


Fig 1. Tuberculosis: notifications and deaths, England and Wales 1981–1998 (*Source*: Office for National Statistics and Public Health Laboratory Service, Communicable Diseases Surveillance Centre).

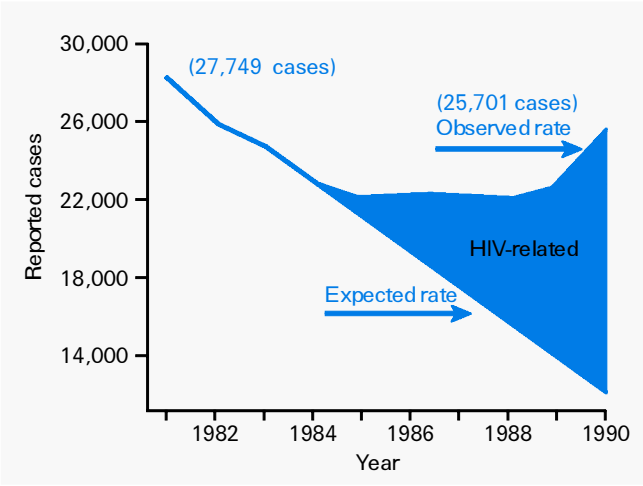


Fig 2. Tuberculosis notification rates in USA (NY State).

example, in the North Thames Region, which has the highest prevalence of HIV in the UK, 35 cases (average age 50 years) of TB were notified in 1980 compared with 215 in 1998, mainly amongst young single men (average age 25).

Worldwide, half of all individuals infected with HIV are also infected with TB. One-third of all HIV deaths are attributable to TB, and the lifetime risk of an HIV positive person developing TB is 50% compared with 5–10% for an uninfected individual. In an individual previously infected with TB (Mantoux positive), the lifetime risk of reactivation is 5–7%, in contrast to an annual 10% risk in patients co-infected with HIV. The main reason for the strong association between the two diseases has been considered to be the high rate of reactivation. However, since TB and HIV flourish in similar poor socio-economic circumstances, it is likely that another important cause is recent infection, with the development of active disease as a result of immunosuppression. In Africa, TB tends to occur in HIV infected individuals with high CD4 counts, and is likely to be a reflection of progressive primary disease. In contrast, in the USA, the median CD4 count at presentation with TB is low (<200 cells/mm^3) and even lower for disseminated disease (<100 cells/mm^3), probably reflecting the reactivation of quiescent primary infection in severely immunosuppressed patients.

TB in an HIV positive individual is associated with falls in the CD4 count and rises in the viral load. These changes are not specific to TB – any infection causing activation of HIV via cellular mechanisms, including Nκβ and changes in the cytokine milieu which favour HIV replication, will produce similar effects. There is no epidemiological evidence that TB worsens the prognosis of HIV (Table 1). Similarly, TB prevention in the form of chemoprophylaxis may not improve the overall mortality of HIV. Nevertheless, control measures directed against TB would have a marked benefit on the health of the HIV population worldwide.

Table 1. Tuberculosis and risk of death with HIV.

EUROPE (EUROSIDA)	– risk of death	RH	1.2	Tuberculosis
		RH	1.6	Pneumocystis pneumonia
		RH	3.4	Mycobacterium avium intracellulare
		RH	4.2	Cytomegalovirus

Tuberculosis prophylaxis has no effect on mortality.
RH = relative hazard.

Cellular entry of HIV and tuberculosis

Viruses gain entry to cells via specific cell surface receptors. HIV is no exception, with entry possible only into cells with a CD4+ cell surface receptor (CD4+ T helper (Th) cells and macrophages). It was appreciated at an early stage of the HIV epidemic that the process of cellular entry also required a second receptor, but it has only recently been identified as a chemokine receptor. These receptors are responsive to chemo-attractant cytokines and are composed of two families of seven-domain transmembrane proteins. Two of these receptors, CCR5 and CXCR4, are particularly important for entry into macrophages and lymphocytes, respectively. A large deletion of the CCR5 receptor (Δ32) is a rare balanced polymorphism in Caucasians. Those homozygous for this deletion are relatively protected from acquiring HIV following exposure, and heterozygous individuals have slow progression rates.

Mycobacterium tuberculosis is phagocytosed by macrophages as the first step in cellular entry. A number of receptors are involved, including the complement, surfactant and scavenging receptors. In addition, *M. tuberculosis* has an important high

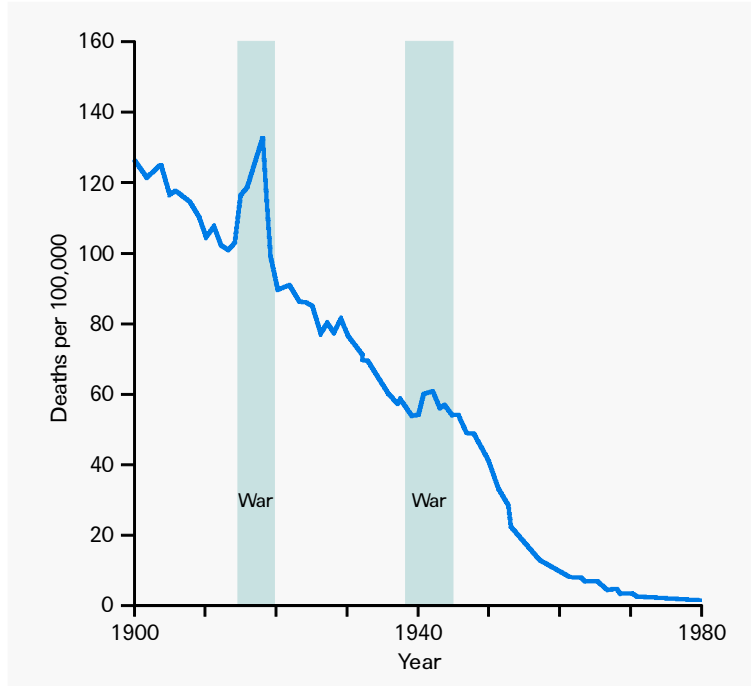


Fig 3. Death rates (per 100,000) for respiratory tuberculosis in England and Wales, 1900–1980.

molecular weight surface protein, lipoarabinomannan (LAM), which interacts with a mannose receptor. Receptor interactions may be responsible for the increased virulence of particular mycobacteria. Those which use CR2 to gain entry to macrophages may avoid the respiratory oxidative burst associated with enhanced killing of the infecting organisms. Downregulation of LAM by some bacteria may also avoid chemo-attraction of CD4 lymphocytes.

Immunity to HIV and tuberculosis

Immunity to HIV

There are few data about innate immunity to HIV other than the CCR5 deletion already mentioned. There is limited evidence that those individuals exposed to HIV but not infected (eg haemophiliacs) have higher levels of the natural ligands of CCR5, RANTES and macrophage inflammatory protein 1α and 1β.

A small number of commercial sex workers constantly exposed to HIV but not infected have high levels of lymphoproliferative responses (LPR) to HIV-specific antigens but no other evidence of HIV infection. This is not likely to be innate immunity but rather a specific immune response. If these commercial sex workers reduce their activity, such LPR responses wane and they are at high risk of HIV seroconversion if they subsequently resume prostitution.

In contrast to TB, the immune response to HIV is usually ineffective and disease progresses in 95% of patients. Seventy-five percent of individuals exposed to HIV develop a seroconversion illness a few weeks later, associated with very high levels of replication of HIV and massive HIV plasma viral loads. Within a few weeks, the viral load in the plasma has fallen considerably, the timing being related to the development of HIV-specific cellular responses. In contrast, neutralising antibodies to HIV are found only later (Fig 4). Tetramer staining techniques have demonstrated that 1–2% of the CD8+ positive cell population responds to specific HIV epitopes at this time.

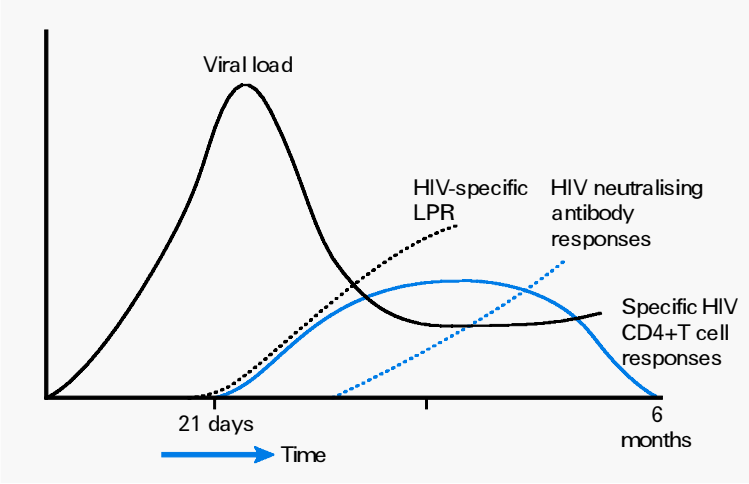


Fig 4. The course of HIV viraemia and related immunological events (LPR = lymphoproliferative response).

Perhaps the best evidence for the importance of the cellular immune system in the initial control of HIV comes from a primate model of infection with a retrovirus, simian immunodeficiency virus (SIV), which produces a disease similar to AIDS in macaques. If monkeys are depleted of CD8+ T cells prior to infection with SIV, the normal fall in viral load does not occur and death follows rapidly. Recent experiments in the same model have indicated that there are specific CD8+ T cell responses to SIV epitopes, which produce selective pressure encouraging SIV mutations.

A similar selective pressure has been shown in humans with HIV. Although a CD8+ response is sufficient to eradicate acute viral infections in animals, long-term control of chronic infections like lymphochoriomeningitic virus in mice also requires CD4+ Th cell responses. A specific CD4+ Th response occurs in most HIV infected individuals shortly after seroconversion, but this disappears within six months and may be one reason for progressive infection in the majority of patients. This loss of response may be due to cellular activation, with subsequent death of those HIV infected CD4 helper cell clones with specificity to HIV. Alternatively, CD4+ Th cells with specificity to HIV epitopes persist, but are unable to respond to antigenic stimulation.

In the overwhelming majority of individuals infected with HIV, progressive destruction of the immune system occurs over the years following seroconversion. First, a number of minor opportunistic infections occur, primarily involving the skin and mucous membranes; these are followed by deep-seated opportunistic infections causing high mortality. During this period, LPR to recall antigens, then to allo-antigens and finally to mitogens, diminish usually in parallel with a falling CD4 count. The CD8+ and CD4 repertoire responses can be measured by amplifying the V beta region of the T cell receptor using polymerase chain reaction technology. Perturbations of this repertoire in CD8+ cells, indicating both deletions and engagement with antigen, occur at all disease stages. The repertoire of the CD4+ T cells also becomes progressively more abnormal as the count falls. CD4+ helper cells elaborate two types of cytokine response, one which predominantly stimulates the cell-mediated immune responses (Th1) and the other humoral immunity (Th2). This is a simplistic view of a highly complex regulatory process, although useful conceptually. Th1 responses predominate early in HIV infection, while later CD4 helper cells elaborate mainly Th2 type cytokines. It is at present unclear whether this is important pathogenetically or occurs as a result of the type of antigen presented to the T cells.

Long-term non-progressors. In 5% of patients with HIV infection, progressive disease does not occur over prolonged periods of time (long-term non-progressors). These individuals maintain a strong lymphoproliferative response to viral and recall antigens and, perhaps most importantly, to HIV-specific epitopes. In addition, the CD4+ helper response to HIV antigens is maintained. The CD4 count remains high in such

individuals and they elaborate Th1 type cytokines. The HIV viral load is low, but a wide diversity of quasi species is present. The implication of these findings is that a strong lymphoproliferative response directed against HIV-specific epitopes, amplified by a CD4 helper response, keeps HIV viral replication in check and successive mutations of the virus are controlled by the immune system. An alternative explanation would be that these individuals have contracted a less virulent viral strain which, although producing many quasi species, remains relatively less damaging to the immune system. This seems to be true of only a small proportion of long-term non-progressors who have a deletion in *NEF*, one of the regulatory genes of HIV.

Much of this specific immune response against HIV is genetically determined. The specific major histocompatibility complex (MHC) alleles of an individual determine the precise epitopes of a foreign antigen which can be presented to CD4+ and CD8+ T cells. Perhaps not surprisingly, certain ancestral haplotypes are associated with slow progression rates. In addition to deletions in the CCR5 receptor already mentioned, it has been suggested that other chemokine receptor polymorphisms (eg CCR2), and genetic variance in the natural ligands of these receptors (eg RANTES for CCR5 and stromal derived factor I for CXCR4) may influence progression rates of HIV infection. More than 60% of long-term non-progression can already be explained by genetic factors, and this is likely to increase as more genetic variations influencing progression rates are uncovered.

This is also likely to be true of TB, but studies of these factors are as yet at an early stage. In one intriguing observation, proliferative responses induced by tuberculin in a group of individuals infected, but without progressive disease (Mantoux positive), were much higher than in those individuals who developed active TB. Even after successful treatment, such responses remained lower one year later. It is obviously possible that these poorer responses were genetically driven.

Immunity to tuberculosis

Immunity to TB is radically different from that to HIV, the majority of patients recovering from infection without treatment, vaccination with BCG having some protective effect, and re-infection being relatively rare following initial exposure (although whether this is also true of HIV is unknown). Responses to TB include:

- complete eradication of infection
- control of infection within a primary complex, usually associated with a positive Mantoux test
- progressive disease.

There are some similarities between HIV and TB immunity. In particular, TB also replicates in an immunocompetent cell (the macrophage), which is itself important for the eradication of infection. Thus, downregulation of normal immune function may be one reason for progressive TB infection in some patients, in particular those with HIV disease.

M. tuberculosis may be killed by macrophages following ingestion via a variety of mechanisms, including generation of reactive oxygen intermediates, reactive nitrogen intermediates (nitric oxide (NO)) and phagocytic lysozyme fusion. Evasion of these mechanisms may be important for mycobacterial virulence, and genetic defects in these mechanisms may lead to disease. Mice with a genetically induced defective respiratory oxidative burst or defects in NO production are highly susceptible to tuberculous infection.

Macrophages secrete a variety of cytokines which may be important in the control of TB, including interleukin (IL)-8, a chemo-attractant, and tumour necrosis factor (TNF)α. Genetically manipulated mice which do not produce TNFα are exquisitely sensitive to tuberculous infection. TNFα has an ambiguous role: it is important in the formation of the granuloma which has a central role in the protection against TB, but is also probably pivotal in producing caseating necrosis typical of progressive disease. The ease with which macrophages kill tuberculous organisms is enhanced by cytokines released by other immunologically competent cells like CD4+ Th cells which produce interferon (IFN)γ. The balance of evidence indicates that this also has an important role in controlling the infection. In contrast, some cytokines may enhance the risk of infection progressing: thus, tissue growth factor (TGF)β, produced by macrophages, and IL-10 may reduce activation of macrophages. The release of TGFβ appears to be increased in those with progressive disease.

Granuloma. The granuloma created following TB infection consists of macrophages and epithelioid cells embedded in an extracellular matrix of proteins with adherence and chemoattractant properties. These cells are surrounded by T lymphocytes. The assembly of a granuloma is created by a delicate balance between the secretion of a variety of stimulating and inhibitory cytokines. There is little doubt that CD4 helper cells are crucial in the control of TB, both by activating macrophages and by attracting other immunocompetent cells to the site of infection. CD4+ Th cells may be attracted to the site of infection by LAM present on the mycobacterial cell surface. In addition to activation of macrophages, CD4Th cells may cause them to die by apoptosis using a Fas ligand mechanism. A predominant Th1

Key Points

The HIV epidemic has been associated with an enormous increase in the pandemic of tuberculosis (TB)

In a minority of patients with HIV, a particular genetic constitution allows long-term control of infection. This is likely to be true of TB

***Mycobacterium* tuberculosis is an organism that grows in macrophages. The induced cellular and cytokine responses are responsible not only for disease control or progression but also for the pathogenesis of the infection**

Successful treatment of HIV and TB infection requires long term adherence to multi drug regimens in order to avoid drug resistance

response appears to be associated with protection from TB, while a Th2 response is associated with disease progression. It has been suggested that IL-12 may be important in determining this phenotypic response of the CD4 helper cells.

Most viral infections are controlled by CD8+ cytotoxic response following intracellular antigen presentation on the cell surface in conjunction with Class I antigen. The more important responses in TB are likely to be CD4+ helper cell responses presented on macrophages in conjunction with Class II antigen, but CD8+ cells may also have a role. Thus, some mycobacterial antigens may act as superantigens, and mycobacteria may also infect some cell types expressing Class I antigen. Knock-out mice which lack part of the MHC Class I antigen (β_2-microglobulin) are extremely sensitive to tuberculous infection.

There are many areas in which concomitant HIV infection may tip the balance in tuberculous infection towards progressive disease. Individuals with both infections have reduced lymphoproliferative responses and less production of IFNγ and IL-2 *in vitro* when stimulated with tuberculous antigen in comparison to patients infected only with TB. Thus, Th1 type cytokines are reduced. However, there is little evidence for an enhanced Th2 response as IL-4 production appears to be the same in co-infected and tuberculous-only individuals. Results for the production of IL-10 are more controversial, some studies showing increased stimulation while others do not. The production of IFNγ in patients co-infected with HIV and TB can undoubtedly be enhanced *in vitro* by the addition of antibodies to IL-10, indicating the potential importance of this cytokine in inhibiting the 'beneficial' Th1 type response.

There are a number of histological differences between TB in patients in whom it is the sole infection and in those co-infected with HIV which have a bearing on the likely immunological responses. In early HIV disease, hyper-reactive granulomas are seen with thin-walled macrophages and increased amounts of caseation, and many acid-fast bacilli are likely to be present. In contrast, in late disease, in which there is profound anergy, there are few CD4+ helper cells in poorly formed granulomas with much suppurative necrosis and no giant cells.

Prevention

Both TB and HIV are rooted in poverty and their long-term control requires improvement in social circumstances. Specific educational attempts are crucially important in those developing countries where the HIV epidemic is in its infancy. Mathematical modelling has shown that targeting high-risk groups in this setting has a profound effect on the epidemic. In contrast, in countries where the epidemic is already mature, intervention has to be directed to the whole population and be sustained in order to have any impact. While public figures have been criticised recently for failing to recognise the central role that HIV has in producing the AIDS epidemic, it is probably more realistic to set this in the context of the importance of poverty and the need for mobilisation of major resources, rather than simply a requirement for cheap drugs to combat the infection. For example, although drugs are highly effective in reducing the rates of maternal transmission of HIV, this benefit is largely lost by 24 months in a breast-feeding population. Formula feeding, in the context of poverty and a lack of secure water supplies, may increase the mortality from other causes although it will reduce HIV transmission. Thus, a simplistic solution which merely provides more drugs to prevent mother to child transmission is likely to have only limited benefit.

Treatment

The treatment of TB and HIV also offers fascinating parallels and contrasts, for example, the

- need for combination therapy
- emergence of resistance
- importance of adherence
- ability to eradicate infection.

Tuberculosis

In most cases, TB should be an entirely treatable condition. Work on TB initiated by the Medical Research Council (MRC) shortly after the second world war showed remarkable responses to single drug therapy, but a high relapse rate due to the development of resistance (Table 2). The concept of dual or triple therapy to prevent resistance was developed, and in a series of landmark studies the MRC developed many of the standard regimens now used for treatment of TB.

HIV

With the advent of highly active antiretroviral therapy (HAART), the prognosis of HIV infection has also been markedly improved (Fig 5), although the ultimate effect on mortality is unknown. Treatment of HIV is lifelong. Early hopes that eradication would occur if complete cessation of viral replication could be achieved for several years have been dashed by the discovery of a small compartment of cells containing 'latent' virus, or virus replicating outside present drug control. This ensures that replication rapidly resumes following cessation of therapy.

Table 2. Anti-tuberculosis chemotherapy (from Ref 1).

	One vs two drugs		
Total no. of patients	54	59	53
Results at 6 months	**S (%)**	**P (%)**	**SP (%)**
Died	9	3	2
Culture-negative	19	8	33
S resistant*	67	–	10

* those with positive cultures.
P = placebo; S = streptomycin.

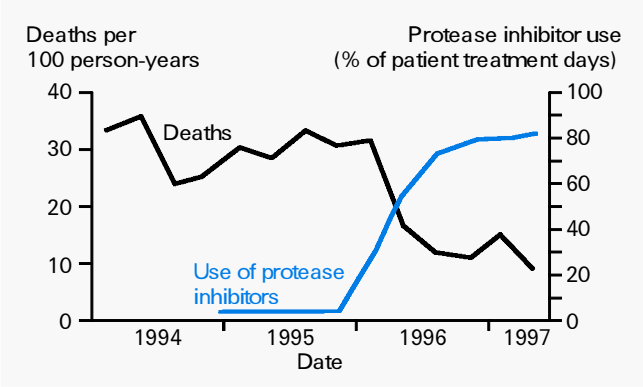


Fig 5. Impact of protease inhibitor-based highly active antiretroviral therapy: mortality in HIV-infected subjects with more than 100 CD4 cells/mm^3 (from Ref 2).

Single drug therapy for HIV yielded only transient improvements as the initial drugs were not potent and resistance also rapidly developed. In the setting of HIV, where the replication and spontaneous mutation rates are both very high, such resistance often develops as a result of selection of strains from the pre-existing pool of quasi species rather than *de novo* generation of resistance (thought to be the most important mechanism with TB). The MRC, in conjunction with the French AIDS agency (ARNS), was again responsible for one of the pivotal combination studies of the treatment of HIV infection (DELTA). In this study, the addition of *two* nucleoside analogues which inhibited the reverse transcriptase enzyme of HIV was associated with a 30% reduction in mortality over a two-year follow-up (Fig 6) and also with a delay in the development of resistance to one component of the regimen.

There was also a major advance in the treatment of HIV following the development of potent drugs inhibiting the viral protease enzymes. These drugs, in combination with a reverse transcriptase inhibitor (nucleoside analogues), cause a profound and long-term suppression of viral replication, associated with a marked reduction in the short-term risk of death and recurrence of AIDS events.

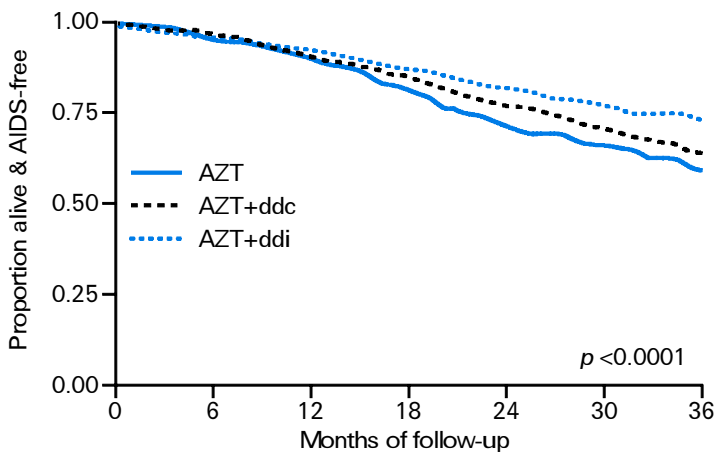
Table 3, which enumerates the reasons for failure of tuberculous treatment, could be reproduced from a modern textbook of HIV disease. The factors involved in increased mortality from HIV infection are:

- late treatment once an AIDS diagnosis has been established
- poor adherence
- not using potent regimens.

Adherence is difficult to study, and was largely ignored by HIV physicians in the early part of the epidemic. Retrospectively, many of the early regimens were intolerable, with a high pill burden, complex food and timing requirements, and unpleasant short-term toxicities. The drug companies are now making valiant efforts to correct these problems with the next generation of drugs. It is likely that the equivalent or better results that can now be obtained in the treatment of HIV disease, using two nucleosides and a non-nucleoside reverse transcriptase inhibitor instead of a proteinase inhibitor, are achieved as a result of better adherence to these regimens with less short-term toxicity and once daily dosing. The property of 'forgiveness' which allows some latitude in the timing of the dose probably also contributes to their success.

The developing world

Treatment of TB in the developing world has shown the crucial importance of adherence to treatment. Many infected individuals are migrants with poor financial circumstances, and they tend to stop treatment when they feel better. Together with the availability of many drugs over-the-counter, this has led to an increasing prevalence of resistance to drug treatment. This is



Number at risk							
AZT	620	578	536	457	333	227	100
AZT+ddc	615	583	538	474	359	234	108
AZT+ddi	627	583	547	486	381	271	120

Fig 6. Progression to AIDS/death: Delta 1 study (AZT = 3'-azido-2',3'-dideoxythymidine (zidovudine); ddC = 2',3'-dideoxycitidine (zalcitabine); ddI = 2',3'-dideoxyinosine (didanosine)).

Table 3. Reasons for failure of chemotherapy.

- Prescribing inadequate regimens
- Irregularity in taking drugs
- Stopping taking drugs
- Drug toxicity
- Drug-resistant infection at start

also a major worry for the current HIV treatments because transmission of drug-resistant viruses has already been demonstrated. Fortunately, the prevalence of such resistance is low at present in most western societies.

On the positive side, TB treatment, once considered very expensive, is now affordable in all countries of the world. Although there was initial criticism of researchers working on TB in resource-poor countries, ultimately affordable regimens of considerable benefit have been developed. It is hoped that similar developments can occur with HIV treatment. Examples of ways in which new regimens can be made affordable include pulse or interrupted therapy and the use of drug interactions to allow lower dosages of some components of the regimen. Some anti-HIV drugs are relatively inexpensive to manufacture. If intellectual property right laws were to be suspended, it would be possible for generic manufacturing companies to produce drugs which would reach a far greater proportion of individuals with HIV in the world. However, TB is an example of where, if the profit motive is removed, new drug development tends to cease. Thus, a delicate balance needs to be struck between persuading pharmaceutical companies to supply drugs cheaply to the developing world and continuing to provide sufficient incentive to produce new compounds.

Control programmes for HIV and TB have similar requirements for which there are no simplistic solutions. TB and HIV are likely to be controlled only if global awareness of the problems can be heightened and resources mobilised to an extent not seen since the second world war.

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