HIV and AIDS

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HIV and AIDS comprise one of the greatest threats to the public health this century, especially in the developing world. This paper examines the medical and scientific background to HIV-related disease, describes current treatments, including the prospects for an effective HIV vaccine, and looks at current research.

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Summary

1. Infection with the **H**uman **I**mmunodeficiency **V**irus (HIV) causes gradual destruction of the immune system, the final stage of which is called **A**cquired **I**mmune **D**eficiency **S**yndrome or **AIDS**. AIDS only began to be characterised clinically in the early 1980s (the virus responsible, HIV, was discovered in 1985), and yet by the end of 1994 the estimated number of those infected with HIV world-wide is estimated at over 19 million. The vast majority of these, and the majority of AIDS cases, are concentrated in the resource-poor countries of the developing world, where the geographical expansion of infection continues almost unabated. HIV/AIDS affect primarily sexually active adults and thus a relatively young age group. It therefore has profound health, social, economic and political consequences, especially in those areas of the world where economies are fragile.

2. The HIV virus which causes AIDS infects and destroys mainly cells of the immune system, leading to its eventual total collapse. Death usually ensues from overwhelming infection or from widespread tumours. The length of time from infection with HIV to progression to AIDS is highly variable. It is becoming increasingly apparent that some will remain well for years.

3. Many advances have been made in the treatment of HIV/AIDS, especially in the treatment of the unusual infections which accompany AIDS. However, it now seems that the first generation of drugs targeted specifically at the virus itself such as AZT, may not be as universally useful as was hoped. New drugs are being developed but HIV's ability to develop resistance is a persistent problem. Combining drug therapies is increasingly being seen as the way forward but this has the problems of increased side-effects and greatly increased cost.

4. While HIV/AIDS remains incurable, prevention is the best strategy. Human behaviour is difficult and slow to change and subject to cultural pressures. A vaccine would be the most desired option but research so far has been disappointing. The decision of the USA not to go ahead with widespread clinical trials of two vaccines (both based on components of HIV's outer coat) on the grounds of their dubious efficacy has left other nations with a dilemma. The WHO has since permitted trials of these same vaccines in developing countries should their governments wish it. Trials of one of the vaccines began in Thailand early in 1995, though some scientific and ethical concerns remain.

5. It is possible that novel and innovative therapies, for example finding ways of boosting the immune system or using the techniques of gene therapy may be fruitful areas of future research. Reports of individuals who seem to have acquired natural immunity to HIV offer some hope for the development of new therapies and vaccines.

6.All interventions are costly and the key problem world-wide will be that of the accessibility and affordability of treatments.

CONTENTS

I. Introduction

Despite a massive, one might say almost unprecedented, world-wide investment in education, counselling, research, and behavioural intervention campaigns to slow the spread of the *human immunodeficiency virus* which causes *acquired immune deficiency syndrome* (AIDS), HIV infection continues to spread almost uncontrolled especially in the developing world. It has major effects on public health and leaves other social, political, and economic consequences in its wake. The World Health Organisation (WHO) estimates that by 2000 at least 40 million persons will be HIV-infected with more than 10 million deaths attributable to AIDS.[1]

II. Patterns of Infection

A. Global Distribution of HIV/AIDS

The global pattern of spread of HIV/AIDS is markedly uneven. At the end of 1994 the World Health Organisation (WHO) Global Programme on AIDS (GPA) estimated that of the 19.5 million HIV-infected individuals, roughly 80% live in developing countries. Africa, which has suffered the longest-running epidemic has hitherto borne the heaviest burden of disease: with less than 10% of the world's population, sub-Saharan Africa accounts for more than two-thirds of the estimated cases of AIDS world-wide and over 90% of cases in women and children. In Uganda in 1994 life expectancy dropped to 37 years, the lowest in the world, with a further projected fall to 31.5 years by 2010.[2] 2.5 million new HIV infections occurred world wide in 1994.[3]

Recently the most marked geographical expansion has been into South and South-east Asia. Total HIV infections there increased to 3 million in 1994 from 2 million the previous year representing the greatest proportionate increase by region[4] and constituting a grave public health concern.

Michael Merson, former director of the WHO GPA has said:

> "Asia's epidemic may ultimately dwarf all others in scope and impact."[5]

Latin America has seen roughly 2 million infections, North America over 1 million, and Western Europe 500 000 with lesser numbers in Australasia, Eastern Europe and East Asia and the Pacific. As a recent editorial in the *British Medical Journal* pointed out:

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[1] The next steps towards a global AIDS vaccine *Science* Vol 266 25 November 1994 p 1335
[2] What's happening to AIDS? *BMJ* 10 December 1994 pp 1523-4
[3] ibid
[4] *Global AIDS news- the newsletter of the WHO global programme on AIDS* 1995 No 1 p 5
[5] AIDS: the third wave *Lancet* January 22 1994 pp 186-7

> "In contrast to the relative stability of AIDS in industrialised countries, the epidemic is expanding rapidly in resource-poor areas. Like so many other infectious diseases including those that are sexually transmitted, AIDS is emerging as a disease of poverty, both globally and within individual societies."[6]

A *Lancet* editorial has split the way HIV has spread into three patterns of infection. In pattern 1 countries (USA, Canada, Western Europe, Australasia, North Africa and parts of South America) HIV has spread mainly among gay and bisexual men and injecting drug users. Those who have acquired infection heterosexually comprise a small (albeit rising) proportion of cases. In pattern II areas, (the reminder of Africa and South America) most people have acquired HIV heterosexually, with approximately equal numbers of men and women. A third pattern is beginning to emerge in South and South-eastern Asia, especially in countries like Thailand, where three groups, injecting drug users, female commercial sex workers, and young heterosexual men have successively borne the brunt of infection. In Thailand, the prevalence of HIV infection among men with sexually transmitted diseases (STDs) rose from 0% in 1989 to 6% by 1992. Of Thai army conscripts from the north of the country, 15.3% were found to be HIV infected. It is of interest that the same commentator reports that *95% of the annual global HIV/AIDS budget is spent in Pattern 1 countries*.[7]

HIV disease and AIDS leads to increased susceptibility to other infectious diseases, the most important of which in a public health sense is **tuberculosis** (TB). TB is now the chief cause of death of those with AIDS in Africa. Heightened concern at the emergence of new drug-resistant strains which do not respond to conventional drug treatment prompted the WHO to declare TB a global emergency in 1993. Global efforts to combat TB had previously slackened off in the belief that it had been brought under control by the development of effective drug regimes and by vaccination programmes.[8]

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[6] What's happening to AIDS? *British Medical Journal* 10 December 1994 pp 1523-4
[7] AIDS: the third wave *Lancet* January 22 1994
[8] WHO calls for action against TB *Science* Vol 267 24 March 1995

B. HIV/AIDS in the UK

1. Health of the Nation

The *Health of the Nation* describes HIV/AIDS:

> "...perhaps the greatest new threat to public health this century."[9]

and in combination with the related field of sexual health identified it as one of 5 Key Areas. Central objectives in the Government's policy included a reduction in the incidence of HIV infection and other sexually transmitted diseases (STDs), strengthening monitoring and surveillance, provision of effective services for diagnosis and treatment of HIV and STDs in general[10]. The strategy was based on 5 points:

a) prevention through public awareness campaigns and community based initiatives, education in schools and colleges, improved infection control procedures, improved prevention and better treatments for injecting drug misusers

b) monitoring surveillance and research

c) treatment, care and support

d) social, legal and ethical issues

e) international co-operation[11]

2. HIV/AIDS surveillance in the UK

UK surveillance of HIV infection and AIDS is implemented through:

a) the voluntary confidential reporting systems operated by the Public Health Laboratory Service (PHLS) AIDS Centre at the Communicable Disease Surveillance Centre

b) unlinked anonymous HIV surveys also implemented by the PHLS AIDS Centre.

At the time of writing the most recent PHLS figures show that in the last quarter (October-December) of 1994 there were 442 reports of new cases of AIDS in the UK bringing the cumulative total to 10 304. The cumulative total of recognised HIV infections is 23 104[12].

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[9] *The Health of the Nation* Cm 1986 Department of Health 1992 p 17 see also p 92
[10] ibid p 94
[11] ibid p 97-8
[12] *Quarterly AIDS and HIV figures* PHLS 27th January 1995

It is estimated that on average, people newly diagnosed with AIDS were infected with HIV 10 years previously and that numbers of AIDS cases do not give a picture of the current pattern of HIV infection.

The UK has one of the lowest AIDS prevalence rates in Europe (i.e the number of AIDS cases existing per million population at any one time) especially when compared to France, Italy and Spain. The reasons for these differences are likely to be complex[13].

3. Future projections

The most recent projections for the spread of HIV/AIDS in this country were made in 1993, using data obtained up until the end of June 1992. They show an expected yearly rise in the number of new cases of AIDS until 1997 (again because of the long average length of time which it takes for an HIV infected person to progress to AIDS, reported numbers of AIDS cases reflect levels and patterns of HIV infection some years ago). These projections also suggest that although AIDS incidence among homosexual men may plateau in 1994 with a slow decline to 1997, new AIDS cases in those infected through heterosexual intercourse will continue to rise. The report also suggested that there had been a peak in *new* HIV infections among injecting drug users in 1985, followed by a subsequent fall.[14]

However, the Government has stressed the need for continued monitoring and surveillance:

> "...the long term uncertainty about the course of the disease argues strongly for continued vigilance and the need to avoid any sense of complacency. The position of some of our European neighbours shows clearly what could happen here if the momentum of our prevention effort is lost."[15]

More recently the Government announced plans to allocate £230 million on HIV/AIDS services in the year 1995/6 of which £49 million will be spent on prevention. In addition local authorities received £12.9 million in AIDS Support Grant in 1994/5 (at the time of writing next year's grant has yet to be announced.)

Over the next three years the UK expects to commit £2 million to support third World HIV/ AIDS measures.[16]

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[13] *On the state of the Public Health 1993- the annual report of the Chief Medical Officer* Department of Health 1994 pp 143-4

[14] *The incidence and prevalence of AIDS and other severe HIV disease in England and Wales for 1992-7: projections using data to the end of June 1992* Communicable Disease Report CDR Supplement 1 PHLS 1993

[15] *Latest AIDS predictions vindicate Government's approach* Department of Health Press Release H93/798 14th June 1993

[16] *NHS to spend £230 million on HIV/AIDS next year* Department of Health Press Release 94\554 30 November 1994

III. HIV/AIDS- Scientific and Medical

A brief word about viruses

Viruses are simple infectious particles consisting of the instructions (in the form of DNA or sometimes RNA) for making yet more virus particles, surrounded by a protective envelope. Inside the envelope are more proteins which regulate the activity of the virus. Viruses enter the cells of the organisms that they infect (the host) and use the resources of the cells to make new virus particles which are released and go on to infect more cells.

Viruses can cause disease in plants and animals including humans and are a broad and heterogenous category of organisms, ranging from the relatively innocuous *adenovirus* which causes the common cold to those which cause measles and mumps, to the virulent and much publicised Ebola virus which is rapidly fatal.

Unlike bacteria and other classes of infectious organism viruses cannot reproduce themselves outside living cells. They need to infect to survive.

A. The Human Immunodeficiency Virus (HIV)

1. General

The HIV virus which causes AIDS was identified only 10 years ago and its host (the organism which it infects) is humankind. Other members of the family of viruses to which it belongs cause infections in a broad spectrum of animal species including sheep, goats, cats, cows, horses, and some apes.

In the early 1980s it became apparent that certain sub-groups of the US population were displaying a previously undescribed combination of symptoms which suggested that they were suffering from serious deficiencies in their immune systems. The term **acquired immune deficiency syndrome** or **AIDS** is simply a description of this. Deaths were dying from infections normally innocuous in healthy people (*opportunistic infections*), and from unusual tumours (it is becoming increasingly widely recognised that the immune system has a part to play in the defences against some tumours such as some skin cancers). Initially, most of the patients were homosexual men and it was suggested that recreational drugs or recurrent sexually transmitted infections were responsible for this new condition. (This theory has some adherents today, most notably the American cell biologist Peter Duesberg who does not believe that HIV infection is the cause of AIDS- "the Duesberg hypothesis"[17]).

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[17] AIDS and the "innocent" virus *New Scientist* 28 April 1988 pp 34-5 and Duesberg and the new view of HIV *Nature* 19 January 1995 p 189

2. Two types- HIV-1 and HIV-2

At roughly the same time in the early 1980s in the USA and at the Pasteur Institute in Paris, two separate groups of researchers identified the virus which is now known as HIV. When a new form of the HIV virus was identified in West Africa in the mid 1980s the original type was renamed **HIV-1** and the new sub-type termed **HIV-2**.[18]

AIDS is caused primarily by the HIV-1 virus with only some cases resulting from HIV-2 infection.[19] HIV-2 is slightly different to HIV-1 in that although it infects people in the same way and makes them vulnerable to the same opportunistic infections, progression to AIDS seems to be slower. So far most HIV-2 infection has been localised in West Africa. HIV-2 seems generally to be a slightly "weaker" form of HIV-1 and generally much less aggressive: it is estimated to have a 5-to 9-fold lower probability of transmission per sexual act than HIV-1 and studies in Africa have shown that transmission from mother to child during pregnancy is rare. Genetic studies have shown that HIV-2 is more closely related to an immunodeficiency virus of macaques (simian immunodeficiency virus or SIV_{mac}) than it is to HIV-1.[20]

3. Structure of HIV

The HIV-1 virus is in some ways a typical virus. Its outermost shell or **envelope** is made of protein surrounded by a fatty membrane in which are embedded spikes of HIV's two major envelope proteins **gp 120** (which has formed the basis of the first generation of AIDS vaccines- see section **VI. C**) and **gp 41**. Inside this envelope lies another concentric protein shell. The innermost part of the virus, the **core** has two major components:

a) the genetic material of the virus embodied in two strands of **RNA** (related to DNA) from which new copies of the virus are made, and

b) other proteins called **enzymes** which are vital in various ways for the successful formation and maturation of new infectious viral particles or **virions**. HIV has three main enzymes. They are important not only for an understanding of how the virus works but also because blocking or altering the function of one or more of them has been and will be used in the future as an approach to developing anti-HIV drugs. *Reverse transcriptase* (blocked by **AZT**- see section **IV.C**) aids the process by which HIV genetic material is converted into a form into which it can be inserted into that of the infected person: *integrase* assists that process of integration and *protease* is involved in final maturation and assembly of a new virions which can then go on to infect other cells.

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[18] *HIV and AIDS* KE Nye and JM Parkin 1994 pp 1-2
[19] *Microbiology* 2nd edition LM Prescott, JP Harley and DA Klein 1993 p 723
[20] Learning about HIV-2 *Lancet* November 19 1994 pp 1380-1

4. Infection.

The main cell which HIV infects and destroys is a white blood cell important in the immune system called the **CD4+** cell (sometimes referred to as the CD4+ T- helper lymphocyte). The virus attaches itself via one of its gp 120 spikes to the outer membrane of this cell. This causes in change in the structural arrangement of gp 120 and gp 41 which in turn leads to the fusion or melting together of the membranes of virus and cell and leading to the *virus being taken into the cell*. Once inside HIV-DNA is produced from HIV-RNA with the help of the enzyme *reverse transcriptase*. This viral DNA is then incorporated into the genetic material of the host cell genome (assisted by HIV *integrase*) and the host CD4+ cell is basically turned into a "factory" for the production of the components of new HIV particles. These components are then assembled to form complete HIV virus particles at the outer layer of the infected cell, pass *out* through the cell membrane and then are free to infect other cells.

5. The origin of the HIV virus

If the HIV virus is new then where has it come from? Two theories are that either the virus "jumped" from another species (most likely another primate) to infect humans a few decades ago or that it has been present in humans for much longer but in a relatively isolated population. There are some related viruses such simian immunodeficiency viruses (SIV) which infect certain types of monkey. Some are genetically similar to HIV-2. It is possible that all these viruses share a common, possibly benign, ancestor.

6. The first human case?

The first known cases of AIDS in humans have been traced back to the 1950s. Until recently the very first case of AIDS documented in the medical literature was thought to be that of a patient at Manchester Royal Infirmary in 1959. He died of an unusual combination of illnesses, a pneumonia caused by *Pneumocystis carinii* (PCP) and *cytomegalovirus*, as well as *herpes* infection around his mouth and anus (these illnesses are all prominent feature of AIDS). The case was felt to be an unusual one and was written up in the *Lancet* in 1960. When AIDS began to be defined as a clinical entity, the possibility that this man had AIDS was raised. DNA analysis of tissue samples confirmed the presence of genetic material of parts of the HIV-1 virus in some of his tissues. It was subsequently concluded that this man represented the first case of AIDS documented in the medical literature. Some inconsistencies remained: it was unclear as to how he might have acquired the infection as he was said to be a heterosexual who did not use intravenous drugs. His National Service (he was in the Royal Navy) was performed exclusively in England apart form a brief voyage to Gibraltar in 1957.

Recently, re-analysis of the tissue samples from the same patient by researchers in the USA failed to find any evidence of HIV-1 in tissue that was supposed to come from him. Furthermore the second batch of material sent to the USA seemed to come from a different

patient. The tissue samples are now being tested by independent Home Office scientists.[21] The outcome of the analysis is awaited.

7. Transmission of the HIV virus

There are three main ways in which HIV can be transmitted from person to person: through penetrative sexual intercourse, through contact with infected blood or tissue products (such as the sharing of needles by injecting drug users or through transfusion with HIV-positive blood or blood products such as occurred with those haemophiliacs who were infected with contaminated Factor VIII) and from mother to baby, in the womb, at birth or possibly through breast feeding.

Though HIV has been identified in most body fluids such as saliva, sweat and tears, these contain only a low concentration of virus and it seems that infections cannot occur by this route.[22]

B. What happens when a person becomes infected with HIV?

1. General

HIV causes disease and leads to AIDS by destruction of the immune system of the infected person.

Most viruses produce their impact in a matter of days or weeks: influenza virus leads to 'flu usually within 1-5 days after exposure, chicken pox may appear after up to three weeks' contact with an infected person. HIV is different in that except for a generally mild illness which may be no more than fever, sore throat and a rash which up to 70% of people experience a few weeks after initial infection with the virus, most HIV-infected people have no symptoms for the first five or so (some would say longer) years. They may look healthy and feel well, although they can transmit the virus to other people. Once infected the vast majority seem to be infected for life.

2. Testing for HIV

After a person is infected with HIV the immune system produces *antibodies* (these are produced in response to most diseases and help to fight off infection: the generation of antibodies is the basis of immunisation). The virus itself is difficult to test for in the blood stream so generally it is the *anti-HIV antibody* which is tested for and which forms the basis of the most widely used test for HIV infection. An HIV-positive person (someone who is

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[21] Researchers in US dispute first case of AIDS *British Medical Journal* 15 April 1995 p 957
[22] *AIDS: Images of the Epidemic WHO* 1994 p12

seropositive for HIV) is someone whose blood is infected with HIV and who has anti-HIV antibodies present in their blood. **Children** form a notable exception: all infants born to HIV-positive mothers are HIV-antibody positive at birth because of the transfer of the mother's HIV-antibodies across the placenta during pregnancy. These maternal antibodies usually disappear from 10 months but may persist up to 18 months of age. The persistence of antibodies beyond this age is generally taken as being indicative of HIV infection. Thus there is a quite lengthy period in which, especially in the absence of other illnesses indicative of HIV-related disease, the HIV status of the baby or toddler may be in doubt (see section **III. D**).[23]

Antibodies to HIV usually take two to three months to appear in the bloodstream of an infected individual. This "window" period following initial infection is a time in which the infected person will test negative on standard antibody blood tests, but is still infectious. Usually when an antibody is produced in response to an infection it helps to kill or inactivate the virus or other infectious organism and thus bring the disease to an end. However, the anti-HIV antibodies are unable to inactivate the virus in the usual way. The virus then goes on to infect and destroy key cells in the immune system causing eventual breakdown of the immune defences leaving the individual open to a variety of infections and tumours most of which the immune system would normally be expected to deal with.[24]

3. Monitoring HIV infection

i. CD4+ count

Disease progression may be monitored by the symptoms and illnesses which infected individuals suffer and by the individual's **CD4+ count**. The CD4+ cell (its full name is the CD4+ T helper lymphocyte) is a type of white blood cell important in controlling and co-ordinating the immune response vital in fighting off infection. CD4+ cells are the main target of HIV.

Healthy people with healthy immune systems usually have more 950 CD4+ cells in each microlitre of blood. (It is worth noting that some people seem never to have more than 500 and yet remain healthy). The number of CD4+ cells falls progressively over the course of HIV infection and people with full-blown AIDS usually have a count of less than 200. In the USA a CD4+ count of less than 200 in an infected person is a definition of AIDS.[25] The CD4+ count is the most useful "signpost" as to how HIV diseases is progressing.

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[23] ABC of AIDS Ed. M Adler 1991 p62
[24] *AIDS: Images of the Epidemic* World Health Organisation 1994 p 5
[25] *AIDS: Images of an epidemic* pp6-7

ii. p 24 antigen

A protein made by HIV called *p24 antigen* can also be used as a marker of disease activity as its presence is associated with progression of disease. Anti-HIV agents which show clinical efficacy lead to a decline in p 24 levels. However, up to 50% of those with AIDS are p24 antigen negative and the rate may even be higher in some African groups. This limits its clinical use as a diagnostic marker[26].

C. HIV and its progression to AIDS

1. Background

i. Opportunistic infections

AIDS is the end point, the final result, of HIV infection. As its name implies it describes a state in which the immune system of the individual is so weakened, that death ensues from overwhelming infection with normally innocuous organisms or from characteristic tumours. Such **opportunistic infections** are diseases caused by organisms which are too "weak" to produce diseases in normal healthy individuals or conditions caused by disease-causing (pathogenic) organisms which are unusually severe. Opportunistic infections can thus be seen as an expression of the weakness of the immune system in AIDS and HIV infections. As the disease progresses and the immune system weakens, different organisms can break through the immune defences to cause disease.[27]

ii. Progression to AIDS

The length of time between infection with HIV and the appearance of AIDS is variable and may be anything from a few years to twenty or more. The reason for this variation is unknown. Theories range from differences in the "aggressiveness" (**virulence**) of the various strains of the virus, to differences in individual genetic make-up determining the efficiency of the immune response. An individual able to mount an efficient immune response may experience a slower progression to AIDS. Another theory is that the presence of other infectious diseases may accelerate the progression: it is known that HIV is more likely to be transmitted through sexual intercourse in presence of other sexually transmitted diseases. Disease progression is especially rapid in infants and young children: around 80% become seriously ill or die before their fifth birthday. [28] Most HIV-infected people suffer intermittent bouts of illness which increase in severity as their immune systems collapse. Different disease-causing organisms break through the immune system at different stages as the CD4+ count falls

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[26] HIV and AIDS p 74
[27] *HIV and AIDS* p 44
[28] *AIDS images of an epidemic* p 6

Both the infections suffered and the CD4+ count are used to give some indication of the state of the illness, and are used to classify the stages of the illness. The CD4+ count is the most useful and the most widely used marker (surrogate marker) of HIV-related disease. Patients with counts of less than 200 have a high rate of progression to AIDS over a short period of time and benefit from prophylactic treatment against some major opportunistic infections such as *Pneumocystis carinii* pneumonia (PCP), and possibly with the drug AZT. There are some who develop major opportunistic infections despite maintained CD4+ counts and those who run low CD4+s and yet remain healthy[29]. These discrepancies may be explained as the result of the test measuring the *numbers* of cells involved and not how well the CD4+ cells are functioning.

2. Clinical stages of HIV infection

The case definition system for AIDS in use in the UK is the European AIDS Surveillance case definition (introduced in July 1993), which revised the previous case definition used by the US Centers for Disease Control (CDC).

The course of HIV infection can be divided into several stages only the last of which is called AIDS.

In the earliest stage an individual may be symptom free. Next, he or she may notice swollen lymph nodes (felt as "swollen glands" or lumps) in the neck, armpits and groin but may otherwise feel well. This is known as **persistent generalised lymphadenopathy (PGL)**.

As HIV infection progresses and as the CD4+ count falls, individuals develop minor illnesses. Such illnesses are symptoms of **AIDS related complex (ARC)**. Though not life-threatening, they are a sign that HIV disease is progressing and therefore may presage full-blown AIDS. Patients may pass from any of the clinical stages to AIDS, but to date individuals have not shown regression of HIV-related disease back to a clinically and immunologically stable state.[30]

There are a number of symptoms which are **AIDS-defining**. An individual who is HIV-positive and who has one or more AIDS defining conditions is said to have AIDS. The list covers several tumours, one of the commonest of which is *Kaposi's sarcoma*, opportunistic infections, a common example of which in the West is PCP, wasting and HIV-related disease of the nervous system.

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[29] *On the state of the public health* 1993 Department of Health 1994 p 141
[30] *HIV and AIDS* p 43

3. Survival time to death

Much recent work points to the survival times from the diagnosis or infection with HIV being much longer than was previously thought.

Several recent studies have shown that a proportion of those who are infected with HIV-1 remain well and symptom free up to or more than 10 years after the initial diagnosis. Studies of homosexual and bisexual men have found that about half remain free of AIDS 10 years after initially becoming infected, and one of these studies, the San Francisco City Clinic study, has shown that 8% of men infected for between 10 and 15 years remain clinically well with only minor abnormalities of the immune system and blood.[31] Epidemiologists from the Royal Free Hospital in Hampstead studying progression to AIDS in a large cohort of HIV positive haemophiliac men have suggested that:

> "...a substantial proportion of participants in this cohort will probably be free of AIDS 20 and 25 years after initial HIV-1 infection."[32]

Why some should remain well for so long is not known but is likely to depend on many factors affecting the *relationship* between the virus and the infected person. Some HIV strains may be more "aggressive" than others: individuals' immune systems may react to the virus in different ways, proving more or less efficient at preventing the virus reproducing itself and making more virus. It is known that *genetic* differences may also play a part: differences in the genetics of the immune system can also influence the progression to AIDS. Those with high levels of circulating virus (this is controlled largely by the host, reflecting an inability of the host immune response to clear the virus in some way) both initially and as the infection wears on seem to progress more rapidly to AIDS.

An editorial in the *British Medical Journal* put it:

> "But are these factors modifiable? Can they be manipulated to change the outcome for people who seem prognostically at greater risk of progression?"...the natural course of HIV-1 infection is now being elucidated in these smaller cohorts of long-term survivors. A complex web of viral characteristics and host factors that determine the immunological response to HIV-1 infection will probably determine who remains free of symptoms. Unravelling this immunological puzzle may well be the crucial element in the development of an effective vaccine against HIV-1 and our control of other chronic viral infections."[33]

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[31] Long term survival in HIV-1 infection *British Medical Journal* t July 1994 pp 283-4
[32] *BMJ* t July 1994 p283
[33] ibid

D. HIV Infection in children

World-wide, the majority of HIV infection is transmitted by sexual intercourse. It thus follows that as the epidemic continues more and more women and more and more children will become infected. It is something of a truism in medicine that children do not behave as miniature adults and this is certainly true of HIV-related disease. Diagnosis cannot be made in the same way, and the fact that a child's neurological and immune systems are in the process of development means that the presentation of disease in infants and children is quite different from that in adults. CD4+ counts are only a poor predictor of prognosis: PCP carries a 90% mortality in the first year of life (whereas in adults this figure is only 10%) and Kaposi sarcoma, a common tumour in HIV-positive adults, is rare.

Babies born infected with HIV can become ill very rapidly after birth. The diagnosis of HIV-positivity is not as straightforward as that in the adult.

All infants born to HIV-positive mothers will be HIV-antibody positive and thus test positive on the standard HIV test. This is because when the child is in the womb the mother's antibodies pass through the placenta and reach the its blood stream. *The child may not be infected but still appear HIV-antibody positive on standard testing due to the presence of maternal antibody.*

Furthermore, in the first few months of life there is little difference between the amount of antibody in infants carrying the virus and in those not carrying the virus. During the second year of life the child clears this maternal antibody from the blood and uninfected children become HIV-antibody negative (in infected children HIV-positivity will persist).

These difficulties in diagnosing HIV infection in babies and infants leads to many dilemmas in management, in terms of whether a child whose HIV status is not known should be fully vaccinated against common childhood diseases, should they receive treatment to prevent against PCP in case they are HIV-positive, should they be treated with anti-HIV drugs such as AZT. There is also grave emotional distress for the parents who may have to wait for months to be sure of the HIV-status of their child.[34]

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[34] HIV and AIDS pp 61-63

IV. Treatment of HIV-related disease- Drug therapies

Optimism for new therapies waxes and wanes rapidly. Much of the current outlook is gloomy. Although there have been advances in the treatment of the opportunistic infections characteristic of AIDS, the first major drug directed at HIV itself, AZT, which has been a mainstay of treatment may not be as effective as was hoped. Other promising drugs in development include blockers of the HIV *protease* enzyme (see section **IV. B**) but the ability of HIV to develop **resistance** is likely to be a continuing problem with the use of all drugs.

A. Treatment of opportunistic infections

During the last decade, the average life expectancy of those with AIDS in the developed world has increased from six months to more than three years. Most of this progress has not been due to progress in the treatment of the virus itself, but due to advances in the management of the opportunistic infections associated with it, such as *Pneumocystis carinii* pneumonia (PCP), infection with a tuberculosis-like organism called *Mycobacterium avium* complex (MAC), a viral infection *cytomegalovirus* (CMV) which causes permanent blindness and tuberculosis itself.

B. Treatment of wasting

Wasting disease (**cachexia**) is another serious problem for AIDS patients, with the body mass falling below a level capable of sustaining life. Preliminary studies have shown that a genetically engineered form of human growth hormone previously used to treat undersized children could be an effective treatment for this facet of AIDS.[35]

C. Antiretroviral drugs (i.e. drugs directed at HIV itself) e.g. AZT

The ultimate goal for any anti-HIV therapy would be the complete eradication of the HIV virus from the body. Whether this is likely to be achieved or not is in doubt as the virus integrates itself into the host (in this case the human) genetic material, and therefore to eradicate the virus, all the infected cells in the body would have to be removed. This is theoretically possible in tissues which have a rapid turnover time and renew themselves quickly, such as some blood cells but not within the central nervous system (CNS- i.e the brain and spinal cord) where cells cannot be replaced. A more realistic aim is a therapy which can act directly against the virus, suppressing it to such an extent that it fails either to damage the infected person or to infect new cells. The disease process would theoretically be halted and progression to AIDS delayed.

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[35] Trials raise hope of breakthrough drug *Financial Times* August 12th 1994

1. AZT

Zidovudine (also known as Retrovir but most commonly known as **AZT**) is the most widely used antiviral drug and is often given from the diagnosis of HIV infection in the belief that it may delay the progression to AIDS and thus improve survival. It does not eradicate the virus from the body and so is not a cure[36]. For that past 8 years it has been a mainstay of HIV treatment.

AZT is a "pro-drug" and is converted into the active form inside the body. It works by blocking the function of the enzyme *reverse transcriptase*, a protein inside the HIV virus essential in the process of transcribing DNA from the viral RNA (see section **III. A**). In the presence of AZT, the viral genetic material is unable to convert from RNA to DNA, and thus unable to integrate into the genetic material of the cell. No new HIV particles can be formed.

There are two problems with the clinical use of AZT quite independent of whether it works or not. **Side effects** with AZT are common. Within 1 to 2 weeks there may be headache and nausea, followed at 4 - 6 weeks by suppression of the bone marrow leading to anaemia. Late side-effects are gastrointestinal disturbances and muscle disease. The other major limitation of AZT is the ability of HIV to acquire **resistance** to the effect of the drug. Resistant strains of HIV are commonly found after 6 months or more of AZT treatment. Resistance is acquired as a result of **mutations** in the HIV RNA which allow it to evade AZT's mechanism of action.

Clinically, AZT has been found to improve survival and reduce infection rate in patients with AIDS and with advanced ARC, prolonging survival of those with AIDS by roughly 10-12 months[37]. Following this success further trials took place in individuals with earlier stages of infection with the rationale that it might be possible to prevent the development of HIV-related disease.

> "The history of the investigation of zidovudine illustrated the importance of conducting appropriate placebo-controlled trials. Because the pressure to find a cure for the disease was so great many of the anti-retroviral studies which followed were either not placebo-controlled, used "surrogate" endpoints...or used rather "soft" clinical endpoints. Such trials suggested that zidovudine may prevent disease progression when used at an asymptomatic phase of HIV infection. These trials generally used small numbers of patients and/or had only a short follow-up time. However, a long term placebo controlled European study.....has put these results into question."[38]

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[36] *British National Formulary* March 1995 p 256
[37] *HIV and AIDS* p 67
[38] *HIV and AIDS* pp 69-70

The study mentioned above is the **Concorde** study[39] which published its findings in April 1994. It investigated the effect of *early (i.e. from the time of enrolment in the trial)* versus *deferred* (until the onset of ARC, AIDS or in situations of persistently low CD4+ count if the clinician thought it was indicated) AZT treatment.

1749 HIV infected individuals from centres in the UK, Ireland and France were randomly allocated to AZT 250mg four times a day or placebo. They were followed up over a period of three years. The outcomes of patients who were treated with AZT from enrolment were compared with those whose AZT treatment was only started when they had ARC or AIDS. After three years of follow up there was no statistically significant difference in clinical outcome between the two therapeutic policies, probabilities of death and progression to ARC or AIDS being similar in both groups[40]. The results of this trial, which differ from those of other smaller trials have been controversial and caused confusion amongst health professional and patients alike.[41] James Lipsky wrote in the *Lancet*:

> "Overall Concorde does not provide compelling evidence that zidovudine is of great use in non-pregnant symptom free adults with HIV infection."

However, another commentator has written on Concorde:

> "This does not mean that anti-retroviral drugs are of no use in early infection, but that improved regimes will have to be developed."[42]

It *is* known that AZT can protect babies born to HIV-positive mothers. A US trial, conducted by the AIDS clinical trial group (ACTG) found that the number of babies infected was reduced by two-thirds in HIV- positive mothers who were given AZT while they were pregnant,[43] the rate of transmission from mother to child being 25% among offspring of women taking a placebo, and only 8% among children of women taking AZT.[44] One commentator has written:

> "AZT...certainly has a role in the treatment of patients with HIV-1 infection, especially in reducing transmission of virus from HIV-1 seropositive mothers to their newborn, and in treating patients with advanced disease. But the first results of the Concorde study are a reminder that AZT has limited value when given to patients who do not have advanced disease....."[45]

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[39] "*Concorde: MRC/ANRS randomised double blind controlled trial of immediate and deferred zidovudine in symptom free HIV infection*." Concorde Co-ordinating Committee *Lancet* April 9th 1994
[40] "Concorde lands." James Lipsky *Lancet* April 9th 1994
[41] Zidovudine for mother, fetus and child: hope or poison? *Lancet* July 23rd 1994
[42] *HIV and AIDS* p 70
[43] *Hard slog ahead as AIDS loses high profile*. New Scientist 20th August 1994
[44] Women as women with HIV Richard Horton *Lancet* March 4 1995 pp 531-2
[45] AIDS: time to turn to basic science Bernard N. Fields *Science* 12 May 1994

AZT may also still be useful in **combination** with other dugs, such as 3TC[46]. Two multicentre North American trials have shown that combining AZT with 3TC yielded better results than with either alone. However none of the AZT/3TC trials has so far evaluated whether the combination reduced the incidence of AIDS-related infections and prolongs the lives of HIV infected people. Studies to date have analyzed the response of surrogate markers (such as the CD4+ count) which act as "signposts" to whether the treatment has an effect[47].

2. Protease inhibitors

Other new drugs in development are the *protease inhibitors*. These act by blocking the function of HIV *protease* responsible for final maturation of the HIV virus.

At the 10th International AIDS Conference in Yokohama Japan in 1994 a scientist from one of the pharmaceutical companies developing a protease inhibitor at present known only by its number L 735524, asserted that this drug could almost eliminate the virus from the blood within two weeks. However, as HIV acquired resistance its levels begin to build up again usually by about four weeks. Resistance may build up less quickly if protease inhibitors are used in combination with other drugs (basically the chance of the virus mutating to a form where it is resistant to two drugs is much less than the chance of its mutating to a form which is resistant to a single drug: the chance of the virus evading three treatments at the same time is even less). [48]

Roche the Swiss pharmaceutical giant, is holding a lottery for AIDS patients in the US this summer. The 2 280 "winners" will receive a supply of the experimental protease inhibitor, **saquinavir**. The drug was designed largely by computer modelling using the known structure of HIV protease. There are several clinical trials both in North America and internationally underway. The lottery, which lies somewhere between a clinical trial and full availability has been agreed between the company, the US Food and Drug Administration (FDA) and the AIDS lobby. Other pharmaceutical companies also have protease inhibitors in development.

Until the clinical trails are completed and the results published and subject to peer review, it is difficult to say what the effects of the protease inhibitors will be and in which patients they prove most effective. However, it has been reported that it is hoped that as a class they are as effective as the first generation of *reverse transcriptase* inhibitors with fewer of the toxic side effects. However, they also seem to share the problem with AZT that the fast mutating HIV virus can evolve resistance to them relatively quickly.[49]

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[46] Optimism on new AIDS therapy Clive Cookson *Financial Times* 21st November 1994
[47] AIDS mood upbeat for a change *Science* Vol 267 17 February 1995 pp 959-960
[48] Triple therapy offers high cost hope *Financial Times* August 11th 1994
[49] Speed is of the essence *Financial Times* June 27th 1995 p 16

V. Treatment-New Therapies

It is possible that entirely new and innovative modes of therapy will have to be developed for the treatment of HIV/AIDS.

A. Gene therapy

(see *Library Research Paper 93/66 Gene Therapy*). Briefly gene therapy is based on the principle that transfer of a healthy or therapeutic gene into a target cell can essentially rectify a disease. This novel approach may be widened in application in order to help those with HIV/AIDS. Genes which are similar to those of the virus but not identical could transferred to CD4+ cells thus disrupting HIV's ability to reproduce itself. Genes could also theoretically be transferred to CD4+ cells to boost the immune system in some other way. Viagene, a Californian biotechnology company has developed a system to deliver viral genes to healthy cells in HIV-positive patients, in an effort to boost the immune response to the virus.[50]

B. Cytokines

Cytokines are chemicals made in the body which regulate the numbers and function of cells in the immune system. **Interleukin-2 (IL-2)** is one such chemical which activates CD4+ cells, stimulating them to divide and increase in numbers as they circulate in the blood.

Recent work has shown that IL- 2 may be able to delay the onset of AIDS by bolstering the immune system. Researchers at the US National Institutes of Health in Bethesda, Maryland have treated a few people with AIDS with IL-2. In most of the patients the CD4+ count increased by more than 50% in the 12 months after treatment began. This study (like the AZT/3TC combination trials cited above) measured the effects of IL-2 only by markers and thus it is impossible at this early stage to say whether IL-2 has any lasting benefit other than a relatively short-term one or whether it has any significant clinical effects. IL-2 was especially effective in those with only moderate immunodeficiency to start with and in those with lower levels of the virus. Side effects of IL-2 are unpleasant and include severe flu-like symptoms, malfunction of the kidney and liver, rashes, nausea and diarrhoea. The authors conclude:

> "Interleukin-2 clearly merits further evaluation as a treatment for patients with HIV infection...the potential benefit of interleukin-2 will have to be weighed against its potential side effects."[51]

If a clinical benefit is to be expected it will probably only occur in those with CD4+ counts greater than 200.

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[50] *Financial Times* U=June 27th 1995

[51] Increases in CD4+ T lymphocytes with intermittent courses of IL-2 in patients with Human immunodeficiency virus infection - A preliminary study Joseph Kovacs et al *New England Journal of Medicine* 1995; 332: 567-75

V . Prevention- changing behaviour

As AIDS remains so far incurable and as once a person is infected with HIV they seem to remain so for life, it would seem a sensible strategy to place the emphasis in HIV/AIDS management on preventing infection spread.

Prevention is already being attempted by attempting to *change people's behaviour* for example by public education programmes promoting safe sex and safe injecting behaviour, but human behaviour is complex and often resistant to change. At the 10th international AIDS conference in 1994 a European study of heterosexual couples with one infected partner found that half of them regularly did not use a condom.

Behavioural scientists bemoan the fact that although vast sums have been expended understanding the virus and developing therapeutics, the area of behavioural science has been relatively neglected even though behaviour change has been demonstrated to be a potentially effective means of slowing the spread of the virus. It is known that HIV is spread unevenly among populations and groups. This is apparent both globally and on a much smaller scale. For example in Honduras in 1992 there were 13.4 cases of AIDS reported per 100 000 population whereas in the same year in neighbouring Guatemala 0.96 cases were reported per 100 000 population. In the UK, Glasgow and Edinburgh have quite different rates of disease among especially vulnerable groups. The difference may even be observed between neighbourhoods, as demonstrated between contiguous and non-contiguous areas of San Francisco.

The likeliest explanations for these differences are not differences in the inherent biological susceptibility of populations to HIV and AIDS but to differing patterns of behaviour, to the length of time from the introduction of HIV into the community, to the prevalence of other sexually transmitted disease and in access to information and services.[52].

A recent editorial in the *Lancet* pointed out that Governments and health officials devote considerable resources to blood screening programmes and pay less attention to STD prevention strategies such as condom distribution.

> "In other cases, great public concern has focused on HIV transmission through non-existent means (e.g. mosquitoes) or extremely low risk settings (e.g. from infected health care workers) while thousands of new HIV infections occur through unprotected intercourse."[53]

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[52] *Risking everything? risk behaviour, risk change and AIDS* Peter Aggleton et al Science Vol 265 15 July 1994
[53] Preventing HIV- have we lost our way? *Lancet* May 28 1994

VI. Immunisation

As specific drugs targeted against the virus have not proved as effective as was hoped, the pressure for an effective **vaccine** has increased. Another important advantage a vaccine could have is **cost:** the costs of new drug therapies are largely out of the reach of developing countries.[54]

A. What is vaccination?

There are numerous vaccines available for many types of bacterial (whooping cough, typhoid) and viral (mumps, measles and rubella) illnesses and they are used world wide. A vaccine is essentially a weakened preparation derived from an infectious organism which challenges the body's immune system to produce *antibodies.* A vaccine is insufficient to produce the disease but sufficient to produce an immune response. Should an individual be exposed to the organism at a later date it is hoped that the individual has ready pool of cells which will be ready to manufacture antibodies which can then eliminate the infectious organism and prevent infection from developing.

B. The ideal vaccine

Peter Lamptey director of the AIDS control and Prevention project pointed out at the IXth international AIDS conference in Berlin:

> "The ideal HIV vaccine has to be safe, orally administered, single dose, stable, inexpensive, confer permanent life-long immunity and be effective against all HIV "strains". This is obviously an unrealistic expectation, at least in the next 10 to 20 years."[55]

C. Vaccine research

The development of an effective HIV vaccine is proving much more difficult than was thought. There are several different reasons for this:

a) *strains of HIV may differ markedly*: a vaccine effective against one strain may not prove so against another

b) *HIV reproduces and mutates very quickly*: in a similar way in which it develops resistance to drugs, HIV may thus make a vaccine become "outdated" in a very short period of time (this is similar to the case with influenza virus: the outer coating of the

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[54] Triple therapy offers high cost hope *Financial Times* August 11th 1994
[55] Risking everything? Risk behaviour, behaviour change and AIDS *Science* 15 July 1994 pp 341-2

virus changes itself from year to year and thus this year's virus may not be recognised by last year's vaccine: this necessitates the reformulation of the influenza vaccine annually.)

c)*HIV spreads directly from cell to cell*. Thus the virus is protected from antibodies which are present in the body fluids (such as blood) which bathe the cells.

1. the first generation of vaccines

Despite these problems the search for a vaccine has been eager and the first generation of vaccines have used the gp 120 part of the outer protein shell of HIV (see section **III.A**) to generate an immune response to HIV. Overall, the results of vaccine research have been disappointing so far. Antibodies prepared in volunteers against one specific strain of HIV efficiently neutralised the original virus but failed to neutralise viruses isolated from several other AIDS patients.[56] Another alternative would be to base a vaccine on whole live particles of HIV which had been weakened in some way (rubella and polio vaccines are both "live" vaccines) although whether the public would ever countenance this is in doubt.[57]

2.The debate over HIV vaccine trials

The two vaccines at the most advanced research stage are both recombinant (genetically engineered) forms of the HIV's envelope protein gp 120 and are made by Genentech (a US company) and Biocine (a joint venture between Chiron and Ciba Geigy).[58] Both vaccines have been tested for safety in human subjects but their ability to protect against HIV has not.[59] The usual next step for such vaccines would be phase III trials i.e. more widespread trials of efficacy in communities where HIV infection is occurring.

However, in June 1994 the US National Institute for Allergy and Infectious Diseases (UNIAID) rejected phase III clinical trials of these vaccines in the USA. It has been reported that many members of the advisory panel felt that the vaccines were unlikely to be sufficiently effective to make the large scale trial worthwhile. Essentially, the vaccine's potential to protect people did not look sufficiently convincing to justify a costly and politically sensitive trial when the US had a relatively small HIV epidemic. The US decision seems to have been strongly influenced by AIDS activists who have doubted the value of the trials.[60]

Since then a WHO advisory committee has approved phase III trials for these same vaccines in developing countries should their governments wish it. Brazil, Thailand and Uganda will go ahead with large scale trials. So why are the developing counties different? Why should

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[56] Vaccine against AIDS? *Lancet* February 26th 1994 p 493
[57] An attenuated vaccine for AIDS John Beale *Lancet* May 27th 1995
[58] The HIV vaccine paradox *Science* Vol 264 20 May 1994
[59] Will Third World gamble on HIV vaccines? *New Scientist* 8th October 1994
[60] AIDS epidemic forces third World to test vaccines *New Scientist* 22nd October 1994 p 10

a vaccine rejected for full testing in its country of origin because of doubts about its efficacy be suitable for clinical trials in developing countries? Does the balance of risk versus benefit alter with need?

A high prevalence of HIV infection in certain areas may be the basis for arguing that even a vaccine of low efficacy may hold some public health benefit in those areas. Representatives from the developing counties involved told the WHO at the advisory committee meeting in Geneva in October 1994 that they had different needs from the US, arguing that HIV is spreading so rapidly in their populations that they cannot afford to wait indefinitely to find out whether the vaccines work or not[61].

The major concerns are that such vaccines simply will not work or that the degree of protection that they afford will be so slight as to be insignificant on a population basis. Other worries are that the genetically engineered fragments of HIV used to engender an immune response in the vaccines *(immunogens)* may actually *enhance disease progression* and infectiousness in recipients who had become infected and that they could also increase the rate of HIV transmission by engendering a false sense of security and encouraging high risk sexual behaviour.[62]

Some at the meeting believed that the only way to determine the true efficacy of a vaccine is to run an efficacy trial and that failure is an acceptable outcome. Others disagreed and felt that both the chances and consequences of failure were sufficiently great that a phase III trial of the recombinant gp 120 candidate vaccines is unwarranted. It is true that no-one knows with any certainty how effective these vaccines are likely to be. Estimates as to how effective the vaccines would be ranged from 0 to 50%. Could a vaccine with an efficacy of 30-50% save many lives over a 5-year period in a community where the prevalence of HIV infection is high and transmission rates are high?

Another important issue discussed remains the **cost**, a central issue in all mass immunisation programmes. Little is known about the eventual cost of any HIV vaccine and the issue will become increasingly important, especially in developing counties if efficacy is low or the duration of protection short, meaning that additional booster doses would be required.

The WHO committee finally recommended :

> a) that any decision to go ahead with any trial of any product must be made by the government of the country hosting the trial and that phase I/II safety trials (trials to determine the *safety* only or otherwise of a vaccine or other medicinal product) in that country should precede a phase III trial.

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[61] AIDS Epidemic forces Third World to test vaccines *New Scientist* 22 October 1994 p 10
[62] Approaches to AIDS vaccines *Lancet* November 19 1994 p 1425

> b) the particular HIV-1 subtype(s) circulating in the proposed trial population should be a consideration: e.g. a vaccine based on a subtype B envelope should not be tested in an African Country where sub-types A and C predominate.
>
> c) counselling of the trial population as to the potential risk of vaccination and to the necessity of following safe sexual practices should be mandatory (this provision of information might alone have a significant effect).[63]

John Moore of the Aaron Diamond AIDS Research Centre in New York wrote in *Nature* of the WHO decision:

> "...some may interpret the WHO decision as the result of pressure by biotechnology and pharmaceutical companies who wish to experiment with products deemed unsatisfactory for use in Western counties. But this would not be a fair reaction to the WHO decision...There remain many scientific uncertainties but the committee's decision was informed and objective."[64]

The WHO decision does have major implication for the companies involved. Had the decision to be made to suspend trials as happened in the USA:

> "... the companies were expected to abandon AIDS vaccine research entirely. Genentech has spent more than $100 million on AIDS vaccines so far and has 300 000 doses of its vaccines in cold storage."[65]

Since the decision of the Thai government to begin phase II trials of the Genentech gp 120 vaccine from the beginning of 1995, there have been further concerns raised concerning the appropriateness of the subtypes of the vaccines in relation to the population in which they are to be used (the second WHO recommendation).

There have now been identified 5 common and 4 rarer subtypes of HIV-1 labelled A to H and O, based on difference in their genetic sequence. Both the Genentech and Biocine vaccines are based on HIV-1 subtype B the main North American strain. This is also the more common strain in Thailand and Brazil, though not in Africa. In Thailand subtype B seemed to be concentrated in drug users in and around Bangkok, while subtype E was found mainly in those who had acquired their infection heterosexually. It would therefore have seemed sensible to conduct the trial on uninfected drug users. However, recently subtype E has become increasingly common in drug users too. A recent study from Bangkok found that 50% of drug users in Bangkok with HIV were infected with subtype B and the other half with E. A vaccine designed around subtype B may not protect against subtype E and thus the vaccine could be inappropriate for at leas half the people in the trial. Furthermore even for

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[63] The WHO and why of HIV vaccine trials *Nature* Vol 372 24 November 1994 pp 313-4
[64] ibid
[65] AIDS epidemic forces Third World to test vaccines *New Scientist* 22 October 1994 p 10

those infected with sub-type B, it is now known that some of the HIV-1 subtype Bs seen in North America are markedly different from those circulating in Thailand.[66]

Others may argue that no one really knows whether differences in subtype will affect the immune response and affect the vaccine's ability to protect.

3. Cost

Even if the trials do go ahead and even if the vaccines offer even a degree of protection against infection with HIV the problem remains as to who will pay. The WHO is expected to ask for public funds to help support the vaccine companies. The problem with AIDS vaccines highlights the wider tension between the social need for them and the private sector's concerns about investing in them.[67]

D. Can some people acquire immunity naturally?

There have been two significant recent reports. A small population of prostitutes in Nairobi seem to be protected from infection remaining seronegative for HIV and disease-free despite repeated exposure to HIV.[68] Similarly three Gambian prostitutes have been reported as showing signs that they have been exposed to the virus but have cleared it from their bodies.[69] Recently there has been reported the case of a child who was identified as being infected with HIV shortly after birth, but whose infection subsequently cleared and who remains free of detectable disease and infection 5 years later.[70] All these cases raise the possibility that at least some people may be able to eliminate the virus from their systems and acquire some natural immunity to infection, a finding that may be useful in developing new treatments in he future. With the first generation of vaccines based on g 120 looking so unpromising, there is hope that studying how these people have remained disease-free might form the basis for the development of a second generation of vaccines or other treatment initiatives.

E. Cost of Treatment

As an editorial in the *Lancet* put it:

> "AIDS is a calamity. To comprehend this stark fact it is enough to realise that even when efficient drugs and vaccines become available the insurmountable problems will be those of accessibility and affordability..."[71]

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[66] Will the strain show in Bangkok? *New Scientist* 7th January 1995
[67] ibid
[68] Vaccine against AIDS *Financial Times* 28th January 1995
[69] Small steps in AIDS *Financial Times* 28th January 1995
[70] *Clearance of HIV infection in a perinatally infected infant* Bryson YA et al New England Journal of Medicine March 30 1995 pp 833-8
[71] Vaccine against AIDS? *Lancet* February 26th 1994 pp 493-4

A fundamental problem with all forms of therapy for HIV and AIDS is the extraordinary rapidity and ease with which the virus can change itself (mutate) and thus develop resistance to drug therapies (or theoretically vaccinations). Possible solutions to this either require a stream of new and effective drugs, or the use of several drugs in *combination* such as has already been used in TB. The problem with both these strategies is **cost**.

Treatment with AZT costs roughly £1600 a year, compared with a per capita health expenditure of some developing African countries of $5 to $10. Combining drugs will increase costs even further. Thus it is likely that such therapies are already out of reach of a substantial population infected with the virus. In parts of Africa even condoms, clinics for the treatment of sexually transmitted disease, education and counselling are unlikely to be affordable.[72] What good is the news that AZT can decrease by two-thirds the perinatal spread of HIV from mother to fetus, if most women in the developing world where 90% of the world's infected women and children are placed, cannot afford it? A vaccine is often seen as the cheapest option, but should one ever be developed, who will pay for it?

HIV/AIDS opens up many wider questions about poverty and inequality, education and access to health care.

VI. Recent steps in research

A. The dynamics of HIV infection

The HIV virus had been thought to be relatively dormant during the phase of infection when the person is clinically well, having to be triggered by some (unknown) event into a more aggressive form to lead to the immune destruction which leads to ARC and AIDS. However work published early in 1995 has indicated that this may not be the case.

Rather than being quiescent, the virus may be reproducing itself as fast as possible from the outset and destroying the infected person's immune cells, including CD4+s, at a rapid rate. Although the amount of virus in the blood of someone carrying HIV remains roughly *constant* over, for example, a month, the researchers found that in someone carrying this hid a much more complex picture. Their research suggested than in a HIV-+ person virus particles are being produced at the rate of roughly 1 billion a day with 2 billion of the infected person's immune cells, including CD4+s, being destroyed every 24 hours. Thus someone infected with HIV must be losing and replacing at least *2 billion* CD4+ cells every day. Were these cells not being replaced then a mere 15 days would wipe them out totally. The net result initially is that the CD4+ count remains static and the patient well. Indeed the fact that HIV+ persons may remain well for so long is actually a function of the massive reserve capacity of the immune system.

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[72] Triple therapy offer high cost hope. *Financial Times* August 11th 1994

Why in time the virus essentially wins the contest is in doubt. Possibly the strain of producing billions of new CD4+ cells every day finally exhausts the immune system. Another hypothesis rests on HIV's rapid rate of reproduction. It has been estimated that an HIV + person can carry up to 1 million genetically distinct variants of the virus. Perhaps this variability in time comes to mean that as the immune system destroys the virus the remaining virus becomes more and more variable, more difficult for the immune system to recognise as HIV and harder for it to hunt it down and destroy. (This has been likened to the battle in Greek mythology between Hercules and the multiheaded Hydra. Each time Hercules cut off one of Hydra's heads two more grew back in its place). The immune system would then be gradually overrun by virus it had no means to destroy.

If this new picture of HIV infection is correct, then delaying treatment with an effective drug until AIDS has set in is incorrect. A more sensible response would be to begin treatment with a drug that can limit the proliferation of the virus as soon as possible after infection (when a drug is found which does this job well enough to delay the progression from HIV to AIDS) and to which the virus is unable to develop rapid resistance. This may also mean that drugs become more difficult to develop as the more rapid rate of reproduction will imply that HIV can develop resistance to therapeutic agents even more rapidly than was thought. [73]

B. Other recent work

There have been several other interesting pieces of research published recently:

1. *Nef* protein

Nef is a regulatory protein made by the HIV virus. Several researches are now coming up with work which shows that *Nef* may be a critical factor in paving the way for the virus to cause disease.[74]

2. Can infection with the milder variant HIV-2 protect against infection with HIV-1?

Work with prostitutes in Senegal has found that women infected with HIV-2 were three times more likely to avoid infection with HIV-1. 805 Commercial sex workers (CSWs) were followed up over a nine year period. 10% of infected women became HIV-1 positive but only 7 out of 187 who had HIV-2 also became infected with HIV-1. Whether this is actually

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[73] HIV's war of attrition *New Scientist* 13 May 1995
[74] AIDS mood upbeat- for a change *Science* Vol 267 17 February 1995 pp 959-60

protection remains to be seen. HIV -2 of course also causes AIDS but over a much longer time period.[75]

3. Boosting other parts of the immune system

Another way forward might be the development of other ways of boosting the immune response, causing the production of cells which may kill the HIV virus *directly* rather then by the production of antibodies. An ideal treatment would be one that would eliminate the virus from the body: but one that could significantly decrease the viral load in the blood would be wonderful in that it could delay the progression to AIDS.

> "There is growing awareness among AIDS scientists that cell-mediated immunity the crucial defence against HIV and that perhaps something can be done to improve it."[76]

4. The cause of Kaposi's Sarcoma

Recent work suggests that it may be caused by a previously undiscovered virus apparently linked to the herpes virus family.

VII. Future Research- where does it go from now?.

There have been vast sums of money and time invested in research and development on HIV and AIDS. There is continuous ongoing debate about where the money should be spent in future. There have been several calls in the scientific press arguing that too much emphasis was being placed on developing treatments for AIDS and not enough on basic research, arguing that a safe and effective treatment would be much more likely to emerge if the latter were in place.[77] Lacking a basic understanding of how the virus works, scientists have yet to discover a drug or vaccine that can outwit it. A recent commentator, calling for a re-examination of AIDS research priorities has written summing up progress in the last ten years of HIV research:

> "Much has been achieved. We have attained some understanding of the pathogenesis of the disease. A class of useful anti-retroviral drugs, the reverse transcriptase inhibitors, has been introduced. The likelihood of transmission of HIV infection from a pregnant woman to her child can be markedly diminished by treatment with one of these agents zidovudine. Treatments for opportunistic infections have made impressive inroads and have prolonged and improved the lives of people living with AIDS.

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[75] AIDS study raises hope of vaccine *Times* 16 June 1995 p 8
[76] Vaccine against AIDS? *Lancet* February 26th 1994
[77] AIDS mood upbeat- for a change *Science* Vol 267 17th February 1995

> "Nonetheless these achievements have not provided us with the robust therapies that had been hoped for nor is a highly effective preventive vaccine in sight. Our ability to alter risk-taking behaviours is still very limited. We do not understand major aspects of the virus's interaction with the infected individual and the nature of the host response to the virus is far from clear. A turning point has now been reached. Simple continuation of the policies of the past is likely to bring us only slow fitful progress."[78]

There is a feeling among some scientists that the limited progress made thus far is due to an inadequate knowledge base which in turn may be due to the pressure and desperation to find therapeutic and preventive measures, rather than developing an understanding of the dynamics of the infection and its progression. 15 years is a short time in which to discover a disease and find an effective cure, let alone for a virus as inaccessible as HIV. There have been calls in the USA and in this country for a more "back-to-basics " approach in AIDS research with more emphasis on basic science in particular the basic mechanisms underlying how the virus causes the disease and its progression. Another US commentator likewise calling for more basic AIDS research in 1994, points out that the speed with which HIV was identified as the cause of AIDS came from a commitment to basic research into viruses and the ways in which they cause cancer in the late 1960s and 1970s:

> "A treatment or preventive strategy for the disease is as likely to come from fundamental discoveries in fields other than AIDS research as from those targeted for AIDS.
>
> "Paradoxically, by targeting too narrowly, we may slow down progress in combating AIDS. We must not compromise research in other areas of basic science at the expense of these directed programmes. This would risk eliminating the research project that holds the ultimate answers to a critical piece of the puzzle. We must give serendipity (and reasoned scientific redirection) a chance to join the war on AIDS."[79]

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[78] Reexamining AIDS research priorities William E Paul *Science* Vol 267 3 February 1995 pp 633-636
[79] AIDS: Time to turn to basic science Bernard N Fields *Nature* Vol 369 12 May 1994

Glossary

ACTG- AIDS Clinical Trial Group

AIDS- Acquired Immune Deficiency Syndrome

AIDS-related-complex- minor illnesses which may presage AIDS

Antibodies-a substance made by cells of the immune system designed to neutralise an infectious agent

ARC- see **AIDS-related-complex**-

Azidothymidine- see **AZT**

AZT- also called azidothymidine, zidovudine, Retrovir. Anti-HIV drug.

CD4+ cell- strictly the **CD4+ T helper lymphocyte**- blood cell important in controlling and co-ordinating the immune response to infection, and especially important in HIV. The CD4+ cell is the prime target for HIV. Numbers dwindle as infection progresses. Numbers used as a marker to monitor HIV infection

Cytomegalovirus-virus. Causes unnoticed or insignificant disease in healthy adults but may be more serious in those with deficient immune systems e.g. transplant recipients or those with AIDS. Common cause of blindness in AIDS.

DNA- deoxyribonucleic acid. The genetic material of most living things, including humans.

Duesberg hypothesis- theory propounded by Peter Duesberg, a biologist who believes that HIV does not cause AIDS

Epidemiology-the study of disease as it affects populations (rather than individuals)

Envelope- outermost shell of a virus

Gene therapy- a process in which diseases are cured or ameliorated by replacing defective genes in a target cell or tissue. Currently in development.

gp 120- a protein which is a major component of the outer coat of HIV. Used as the basis for many of the first generation of experimental HIV vaccines.

GPA- the World Health Organisation Global Programme on AIDS- shortly to be supersede by the United Programme on AIDS (see UNAIDS).
HIV- the Human Immunodeficiency Virus-the virus which causes AIDS. HIV-1 is the more common and virulent form. HIV-2 remains largely localised to West Africa

Incidence- a measure of how common a condition is in a population- the number of new cases which appear over a given period. Usually expressed a x number of cases per 100 000 population per year (also see **Prevalence**)

Immune system-a collection of cells, proteins and organs distributed throughout the body which aim to prevent infection from potentially harmful infectious organisms such as bacteria, viruses and fungi. Also plays a role in the control of cancer, and in the phenomena of allergy, hypersensitivity, and transplant rejection. Stimulated by vaccination.

Immunosuppression- the state where the activity of one' s immune system is reduced. This may be desirable in some cases e.g. where disease is causes by over activity of parts of the immune system or in transplantation, where immunosuppression is induced to prevent rejection. May also accompany a wide variety of diseases and poor general health, especially marked in leukaemia and AIDS. If severe such as in leukaemia and AIDS, lead to overwhelming and life threatening infection, often with organisms which normally cause little or insignificant disease in humans.

Kaposi's Sarcoma (KS)-condition characterised by aggressive malignant skin tumours. Prominent feature of AIDS. In HIV negative persons, KS is rare and develops slowly. Newly thought to be caused by infection with a herpes-like virus**.**

Opportunistic infection- infection causes by organisms which are not usually harmful to humans, or infections caused by common disease-causing organisms but in an unusually severe way. Common in AIDS.

Pathogenic- disease-causing

Persistent Generalised Lymphadenopathy- see PGL

PGL- Persistent Generalised Lymphadenopathy- clinical stage of HIV related disease in which swollen lymph nodes (which are parts of the immune system) can be felt in the neck, armpits or groins.

PCP- *Pneumocystis carinii* pneumonia (see **Pneumocystis carinii**). A major cause of death in AIDS.

PHLS-Public Health Laboratory Service

Prevalence- one of the two major measures used to indicate how common a disease is in a population. The total number of cases of a condition in existence at any one time in a population. Usually expressed as the number of cases per million population. (see also **Incidence)**

Pneumocystis carinii- a simple infectious parasite. Causes opportunistic infections chiefly pneumoniae, in those with damaged immune systems usually those with AIDS or leukaemia.
Prophylaxis- a treatment or intervention designed to prevent disease occurring e.g. antimalarial tablets are given before travel to a malaria-endemic area with the aim of preventing the development of the disease.

Recombinant DNA - Nowadays, any DNA which has been artificially manipulated in the lab. Formerly, a piece of novel DNA made in the lab by cutting and joining together two sequences of DNA. If a recombinant DNA makes a protein or hormone, that protein or hormone is said to have been made by recombinant DNA technology, or alternatively by genetic engineering.

Resistance- a process by which an infectious organism in this case HIV becomes refractory to the effects of a drug or vaccine. A major problem with all HIV directed interventions.

Retrovirus- family of viruses of which HIV is a member

Reverse transcriptase-protein vital for the production of new HIV particles. Blocked by AZT

Retrovir- see **AZT**

RNA- ribonucleic acid. The genetic material of some viruses including HIV. Also an intermediate form of genetic material in a wide range of living organisms including humans.

Seronegative-the state of testing negative for a condition in this case HIV infection

Seropositive- the state of testing positive for a condition in this case HIV infection

STD- Sexually Transmitted Disease

UNAIDS- the United Programme on AIDS. due to replace the WHO Global Programme on AIDS by the end of 1995. UNAIDS is co-sponsored by the United Nations Childrens' Fund (UNICEF), the United Nations Educational Cultural and Scientific Organisation (UNESCO), the United Nations Population Fund (UNFPA) the World Bank and the WHO.

Virion- a single viral particle

Virus- a simple infectious organism consisting of genetic material surrounded by a protective envelope. In Man cause diseases ranging from the common cold to AIDS.

WHO-World Health Organisation

Zidovudine- see AZT

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