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AIDS: SCIENCE AT A CROSSROADS : The science of AIDS and its impact on the developing world

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Introduction

In 1995, AIDS research stands at a crossroads. Over the past 10 years, much of the research on AIDS has centred on trying to find a cure or a vaccine, with very limited results. While more has been learnt about AIDS in a short time than about almost any other disease, many of the basic questions about the development of AIDS and the behaviour of HIV, the virus which leads to AIDS, remain unanswered.

And the few treatments available for people with AIDS are expensive and beyond the budgets of developing countries - which account for nine-tenths of the worlds' cases of HIV.

This briefing looks at the main scientific issues the epidemic has raised so far and the challenges ahead. It reviews the basic information about HIV and AIDS and the available treatments for the disease, setting out what is known and what is still uncertain. And it analyses some of the controversies surrounding HIV.

Since 1981, when AIDS was first identified, research has moved fast but not fast enough to satisfy anyone. A scattering of antiviral drugs exist that slow down HIV's replication, but none can prevent

the eventual onset of AIDS or death. Vaccines are now on trial, but even the most optimistic scientists suspect that these will at best offer only partial protection against infection. It is also unlikely a successful vaccine will be available in the next 10 years. Meanwhile, people continue to become infected at the rate of several thousand each day.

Some scientists now believe that it is now time to re-emphasise basic research, to try and answer some of the enigmas posed by HIV. For instance, how does HIV attack the immune system, the body's first line of defence against infection? Why do some people with HIV stay healthy for many years, while others develop AIDS quickly and die? Until we hold the answers to these questions, it may prove impossible to find an effective cure for the disease, or a successful vaccine.

For the short to medium term, the outlook is difficult. Few scientists believe it is realistic to expect to find an outright cure for AIDS. But many hope it will become possible to devise therapies that will dramatically slow down the disease process and buy many years of healthy life. Even that more modest goal, however, is still a long way off. Moreover, even if new therapies and vaccines are designed, will they be affordable and available for developing countries?

Beyond the biomedical problems, there are complex behavioural and social difficulties. Even though there are technically simple means such as condoms to stop the virus from spreading, those means are not available or acceptable to many. Poverty and cultural constraints continue to deprive people of control over their own lives and the power to protect themselves. It is not enough, for example, to advise people to use condoms when many women have no say in their partners' behaviour and when childbearing defines a woman's identity and status.

WATCH OUT FOR

Accurate terminology

Do not confuse HIV and AIDS. HIV, the human immunodeficiency virus, is the virus which leads to AIDS, the acquired immune deficiency syndrome. The vast majority of people who are infected with HIV (also known as HIV positive) do not have AIDS and may show no symptoms of disease, although most of them will develop AIDS over a period of time. Terms such as "AIDS-infected" should be avoided - it is unclear whether this means someone infected with HIV or ill with AIDS.

Treat with scepticism any claims to have found a cure or vaccine for AIDS

In many countries, physicians, traditional healers or alternative therapists have claimed to have found a cure or vaccine for AIDS. None of these claims has ever been proved, although some treatments have proved effective in relieving some of the symptoms associated with AIDS, such as diarrhoea or thrush.

If you hear of a healer or doctor in your area claiming to have found a cure for AIDS, try not to report it uncritically. Reporting such claims can give false hopes to infected or ill people, and encourage unscrupulous practitioners who stand to make money from these claims. Ask local AIDS support organisations, national or regional AIDS control authorities and respected medical or scientific sources for advice, comment and criticism to include in your articles if you report the claims.

Even minor scientific advances can be magnified by inaccurate, or ill-informed reporting. For example, claims that a new compound "destroys HIV in the test tube" is not sufficient to proclaim it as a potential cure - bleach destroys HIV in a test tube, but it is not usable as a treatment for people with HIV or AIDS.

If vaccine trials are being carried out in your country:

What benefits will your country gain from participation? Are participants voluntary? Are they fully informed and do they fully understand the nature of the research? Are participants also given information on how to avoid HIV infection, for instance by using condoms? Is the strain (or subtype) of HIV the vaccine is designed for the most common in your country? If a successful vaccine is developed, has anything been done to ensure that your country can afford it? Contact your National AIDS Control Programme for information.

A Panos briefing on HIV vaccine trials is available from Panos London (see below for details)

TB and STDs - HIV's dangerous associates

Is investment directed at tuberculosis (TB) prevention programmes in your country? What about the prevention of sexually transmitted diseases (STDs), which increase the risk of contracting HIV?

If AIDS is not considered to be a problem in your country, is any information available on the prevalence of other STDs within the country? HIV is primarily sexually transmitted - if other STDs are present, the conditions which favour the spread of HIV are already there.

Key Facts

- HIV spreads from person to person through unprotected sexual intercourse, vaginal or anal, through sharing of contaminated needles or other transfusion equipment, in infected blood, and from mother to child before and during birth and through breastfeeding.
- An estimated 19.5 million people have been infected with HIV since the beginning of the pandemic.
- Nine-tenths of the world's cases of HIV and AIDS are in developing countries.
- It is unlikely that a successful vaccine against HIV will be available in the next 10 years.
- There is no cure for HIV or AIDS. The few clinically-tested treatments which are available to help treat people with AIDS are beyond the health budgets of developing countries.
- The direct medical cost of treating AIDS is estimated at US$ 32,000 per capita in the United States. In Zambia, it is about US$ 374.
- In the North, political commitment to tackling AIDS may be faltering. The next few years will be critical in determining whether AIDS remains high on the world's agenda or whether it is forgotten.
- HIV infection dramatically increases the chances of developing tuberculosis disease, from 10% in a lifetime to 8% per year.
- Sexually transmitted diseases (STDs) enhance the efficiency with which HIV spreads from person to person, partly by increasing inflammation and bleeding in the genital area.
- According to a 1990 WHO estimate, there are at least 250 million new cases of STDs worldwide each year. In the developing world, STDs are among the leading causes of disease burden.

1. THE CHANGING PICTURE

1995: Time to go back to basics

AIDS research is at a crossroads. More has been learnt in a short time about AIDS than about almost any other disease. Yet the unanswered questions are among the most important. For example, why do some people with HIV remain healthy for many years while others rapidly develop disease? Why are effective drugs so elusive? Does the immune system put up an effective defence against the virus at any stage before it is destroyed and, if it does, can it be strengthened? So far, research has focused mainly on trying to find a cure for AIDS, and a vaccine against HIV. Now, scientists are concentrating again on the basic unanswered questions.

In May last year, the late Dr Bernie Fields, a leading molecular US biologist at Harvard Medical School in Boston, wrote in the journal Nature that it was time to rethink the strategy to concentrate more on basic science, such as learning how the disease damages the immune system, and less on the narrow pursuit of vaccines and therapies. "The focus on drugs and vaccines made sense a decade ago, but it is time to acknowledge that our best hunches have not paid off and are not likely to do so," he argued.

In the past 12 months, a number of AIDS research organisations have been rethinking their approach. Speaking at the Tenth International Conference on AIDS in Yokohama, Japan, in August 1994, Dr William Paul, an immunologist and the new director of the US government's giant Office of AIDS Research (OAR), said he believed scientists were "at a turning point in the history of the disease".

He believed that "the current inadequacy of treatments for HIV infection and the absence of a vaccine to protect the uninfected are largely due to the wide gaps in our understanding of the [underlying disease process] .... If we do not provide innovative scientists with the resources and opportunities to attack the basic unsolved problems related to AIDS and HIV, we may find that a decade from now, we are no further along in our struggle."

The OAR has overhauled the US National Institutes of Health's entire AIDS research programme - whose budget is US$ 1.3 billion - to devote more resources to basic science and fewer to clinical trials.

This return to basic research is leading some teams of researchers to examine in detail what happens when the virus infects people. For example, Dr David Ho and his colleagues at the Aaron Diamond AIDS Research Center in New York, US, have shown in research published by the scientific journal Nature in January this year, that, even when people have no symptoms of disease, the virus in their body is rapidly reproducing itself in large numbers. Each new virus particle stimulates the production of certain vital defence cells known as CD4 T cells. The researchers believe that this creates a rapid turnover of defence cells which then become catastrophically depleted, making the person vulnerable to other infections.

Another example is the renewed interest in an important group of defence cells known as dendritic cells. In separate studies, researchers have analysed the effects of the virus on these cells. Dendritic cells act as "agents of introduction" in the immune system, bringing foreign proteins that enter the body, such as proteins from infectious agents, to meet the other defence cells and stimulating them to respond. As the first line of defence, these cells may be vital in protecting the body from infection. But some researchers have suggested that HIV destroys the normal function of dendritic cells, leading to a domino-like collapse of the rest of the immune system.

Funding under threat

While research into AIDS has reached a turning point, efforts to control and prevent the disease are also facing a crisis - this time for political and economic reasons. In the North, political commitment to tackling AIDS may be faltering. This is despite evidence that preventing HIV infection is among the most cost-effective ways to protect the health of populations (1) and despite the urgency of the problem.

Funds from the rich countries to support AIDS control and prevention programmes in developing countries climbed steeply through the 1980s but began to fall in the early 1990s (2). By 1994, efforts to prevent infection, such as condom promotion, blood screening and education programmes, were estimated to cost US$ 1.5 billion a year worldwide. But only 13% of that sum was spent in developing countries, according to a report by the Rockefeller Foundation (3).

At a world summit on AIDS in December 1994, organised by the French government, the World Health Organization (WHO) and UNESCO, only two countries committed themselves firmly to give new money to support developing countries - France and the UK. In the US, the new Republican-led Congress has again expressed impatience and frustration with the UN system and has

stressed its commitment to solving domestic problems rather than international ones. The next few years will be critical in determining whether AIDS remains high on the world's agenda or whether it is forgotten.

Brief history of an epidemic

AIDS was first identified in 1981 when US doctors found a number of homosexual men suffering rare and debilitating diseases which only affect people whose immune system is severely weakened. By 1982, US health officials had labelled the cluster of conditions the acquired immune deficiency syndrome, AIDS. The virus which causes AIDS was identified in 1983 by a French team led by Dr Luc Montagnier and in 1984 by a team led by Dr Robert Gallo at the US National Cancer Institute. It was later named HIV, the human immunodeficiency virus.

Through the early and mid-1980s, research moved rapidly, producing tests to detect antibodies to the virus and establishing the routes by which the virus spread and the extent of the pandemic. HIV was found in Africa, the Americas, Europe, Oceania and Asia. WHO set up its Global Programme on AIDS (GPA) and mobilised governments to start control programmes and prevention activities. By 1987, the first drug against HIV, zidovudine (AZT) had been licensed.

Since 1981, some 4.5 million people have developed AIDS, according to WHO estimates - and this is just the beginning of a wave of AIDS cases that will follow as people who are already infected with HIV become sick.

By the beginning of the 1990s, it was clear that the developing countries were bearing the overwhelming burden of HIV infection and AIDS. Today, WHO estimates that some 90% of HIV infections are taking place within the developing world. Already, more than 11 million of the estimated 18 million infected adults in the world since the beginning of the pandemic are in sub-Saharan Africa. But Africa's epidemic could be outpaced by the explosive spread of the virus in Asia, the most populous continent. There, at least 3 million people are estimated to have been infected already, but the number could reach 10 million within just five years, says WHO, out of a global projected total of 40 million. HIV is already estimated to be the single greatest cause of lost years of healthy life in young adult men in the developing world (1).

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2. HIV: A COMPLEX VIRUS

What is HIV?

Of all life forms, HIV belongs to one of the most adaptable and successful, viruses. Viruses are extremely simple, often having only a handful of genes wrapped in a protein coat, but they hijack the machinery of their hosts' cells so that the cells make multiple copies of the viruses. Having replicated in this way, the viruses can go on to infect other cells. This creates a problem for researchers: any antiviral drug which interferes with the reproduction of the virus is also likely to interfere with the normal cell functions, and to cause side-effects in the patient.

Another problem is that HIV is very variable. As the virus reproduces itself in the body of an infected person, it can change rapidly - and can confuse the immune system with its many different variants. Within one individual, a baffling array of different variants may be present after just a few months. Within and between populations, meanwhile, the variation is even greater: different strains, or subtypes, of the virus are circulating, each of which may look quite

different to the immune system. Scientists do not yet know whether a vaccine based on one subtype of HIV will protect against another.

HIV belongs to the group of viruses known as retroviruses. Most life forms have their genetic material stored by the molecule known as DNA (deoxyribonucleic acid) the so-called "blueprint of life". Retroviruses, as well as some viruses, have their genetic material in the form of a different, related molecule known as RNA (ribonucleic acid). But the retroviruses - unlike RNA-based viruses such as measles, influenza or polio - have to convert the RNA into DNA before they can operate inside their hosts cells. They do this with the help of an enzyme (or biological catalyst) called reverse transcriptase.

HIV infects several types of cell in the human immune system - the white blood cells known as "T-helper" or CD4 cells that are involved in orchestrating the immune response, and macrophages, the all-purpose "guzzler" cells that scavenge foreign material. HIV also infects cells in the brain.

How does the virus spread?

HIV is present in detectable amounts in blood, seminal fluid, vaginal and cervical secretions, and breast milk. It has also been detected occasionally in saliva, but there is no evidence that anyone has become infected through kissing alone.

The virus spreads from person to person through unprotected sexual intercourse, vaginal or anal, through sharing of contaminated needles or other transfusion equipment, in infected blood, and from mother to child before and during birth and through breastfeeding. HIV is not spread by normal household contact such as the sharing of eating utensils, bathrooms and toilets, or by coughs or sneezes. Despite persistent fears to the contrary, there is no evidence that mosquitoes, bedbugs or other biting insects can spread HIV.

The 'latent' phase is anything but

In recent years, several teams of researchers have learnt that from the earliest stages of infection, the virus "hides" in the lymph nodes, where it is in close contact with a stream of incoming and outgoing T cells. Gradually, it destroys the immune system.

The greatest public attention to HIV research has focused on work led by Dr Anthony Fauci at the US National Institute of Allergy and Infectious Diseases but others in France, Britain, the Netherlands and Australia had also reached similar conclusions. Together, their findings suggest that there is no real "latent" stage of infection: even while a person appears to be completely healthy, the virus is destroying the architecture of the immune system. Late in the disease process, virus spills out into the bloodstream.

The most recent studies, using the latest techniques of molecular biology, show that there is much more virus present in the body than earlier measurements had indicated. HIV reproduces itself rapidly and the CD4 cells that are mobilised to respond to it fight a losing battle to rebuild their forces.

This period of asymptomatic infection (when a person is infected, and can transmit the virus, but has no external symptoms of illness), can last several years - on average, according to US research, most people who are infected with HIV will develop symptoms within 12 years. This delay may be much shorter in people who are subjected to many other infections and whose

nutrition is poor, although there are few studies. Most of the world's estimated 19.5 million people who are infected with HIV are unaware of their condition.

AIDS is a collection of symptoms that develop when the HIV positive person's immune system can no longer defend itself against all the bacteria, viruses and parasites in the environment. It can include weight loss, diarrhoea, tuberculosis and opportunistic infections with a wide range of other organisms, such as Cryptosporidium, a parasite that causes diarrhoea, cytomegalovirus, a virus that interacts with HIV and causes eye problems for infected people, Kaposi's sarcoma, a tumour primarily affecting the skin, and Pneumocystis carinii, which causes pneumonia. Once a person develops AIDS, they may live for two years or more if they have good treatment, or a year otherwise.

Resisting illness and infection

A small proportion of HIV positive people - perhaps 5% - appear to remain free of any damage to their immune system or symptoms for 15 years or more. The reason for this resistance to illness is unclear - it appears that some of these "long-term survivors" have very efficient immune mechanisms; others seem to be infected with particularly weak strains of HIV.

A small minority of people seem to be able to resist infection with HIV. Teams of researchers have studied people who are exposed to the virus regularly, and appear to be uninfected - for example, a group of gay men in the US practising unprotected anal sex with multiple partners and groups of prostitutes in Kenya and the Gambia who regularly accept clients who refuse condoms. No one knows why the virus has not been detected among these studied groups: it could be that their immune systems are extraordinarily efficient, or that they were exposed to an unusually weak virus which triggered their defences. It is also possible that these people are infected, but that tests have so far failed to detect their infection. The common finding so far is that these lucky few have very strong T cell responses to the virus, suggesting that this is an important component of defence.

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3. HIV'S GLOBAL SPREAD

HIV spreads essentially through sexual intercourse. People who have little access to information and limited control over their circumstances are particularly at risk, especially when their sexual behaviour is dictated by economic necessity. People who have other untreated sexually transmitted diseases, which increase the likelihood of HIV transmission during sex, are also at greater risk. The virus has therefore prospered in poor communities, mainly in the developing world, but also in the rich world's deprived inner cities. Low levels of literacy and poor health care contribute to the problem.

Increasingly, as HIV spreads, it brings with it another devastating disease - tuberculosis. One-third of the world's population is estimated to be infected with the TB bacterium but only one in 10 will ever develop the disease under normal conditions. However, it appears that HIV infection dramatically increases the chances of developing TB disease, from 10% in a lifetime to 8% per year. As a result, active TB is on the increase in many parts of the world. WHO has declared TB a global health emergency and predicts it will kill 30 million people in the coming decade - some of whom will also be infected with HIV. Currently, an estimated 5.6 million people in the world are dually infected with TB and HIV, according to WHO.

Who is affected?

Worldwide, at least 80% of infections are among heterosexuals. In the industrialised countries, the majority of affected people are gay men and injecting drug users, but heterosexuals are now the fastest-growing group at risk in these countries too. In the developing world women are becoming infected as fast or faster than men. WHO estimates that in Africa, overall, six women now become infected for every four men.

The extent of homosexual activity and infection in many developing countries is unknown but likely to contribute to some degree to the total number of infections. There is evidence that men have sex with men all over the world. Often, they will not define themselves as homosexual or bisexual. Prejudice and legislation against homosexual activity in many countries hampers both the collection of information on men who have sex with men, and the existence of effective prevention directed at them. As a result, in many countries, no data exists on HIV infection and transmission through this route.

But generalised statistics belie the complexity of the global pandemic. It is in fact a string of separate and highly varied epidemics, each influenced by local factors. For example, in Thailand, it appears that one strain (or subtype) of HIV has been predominant among injecting drug users in Bangkok while a very different strain has been circulating among heterosexuals in the north of the country. There is now an overlap between the two mini-epidemics: clearly, injecting drug users also have sex.

On the other side of the world, in Edinburgh, Scotland, a short period of needle-sharing among drug users in the early 1980s appears to have caused an explosive epidemic of HIV whose impact is still being felt a decade later. In neighbouring Glasgow, the rate of infection among drug users is dramatically lower. The importance of unforeseen local factors in all these mini-epidemics demonstrates the dangers of becoming complacent about the spread of HIV and the patterns of infection around the world.

STDs: a major factor of risk

Even given the complexity of the different mini-epidemics, it is difficult at first to understand why the broad patterns of infection in the industrialised world and the developing countries appear to be so different. Why do so many more heterosexuals have HIV in Africa, Asia, Latin America and the Caribbean than in North America, Australasia and Europe?

One answer is that in developing countries, rates of infection with other sexually transmitted diseases (STDs) such as gonorrhoea, chlamydia, syphilis and chancroid are much higher than in the industrialised countries, and many of these STDs help to fuel HIV's spread. According to a WHO estimate in 1990, there are some 250 million new cases of STDs worldwide every year and, whereas STDs have largely declined in the industrialised world since the 1970s, in developing countries they are among the leading causes of disease burden (1). Estimates of the prevalence of gonorrhoea in pregnant women in developing countries range from 3 to 15%.

Numerous studies have found that STDs help the spread of HIV, partly by increasing inflammation and bleeding in the genital areas and therefore increasing the numbers of cells that can harbour HIV. The effect is to enhance dramatically the efficiency with which HIV spreads from one sexual partner to another. In a population where the rate of partner change is very low and where other STDs are rare, the chance of becoming infected with HIV by a single sex act may be - very roughly - as low as 1 per 1,000. But in groups where the prevalence of STDs is high, such as commercial sex workers, the chance of becoming infected appears to be much higher (2).

Women, once again, are at greatest risk. With most genital infections, it is much easier for a man to infect a woman than for a woman to infect a man. In communities where medical care is difficult to obtain, STDs go neglected, often for months or years. Most STDs are simply and cheaply treated once they have been diagnosed, but women in particular may have no symptoms.

A second answer to the question of why the developing world is so disproportionately affected is that women's social and economic dependence on men makes them particularly vulnerable. Many women are in unequal sexual relationships where they cannot protect themselves. In many communities, they are not expected to discuss sex with men, still less demand safer sex. Women who have no income and no rights to property cannot leave men who may coerce them into sex, and may be forced into commercial sex work to support themselves. Young women are at the greatest risk of all. More than half of all infections in women happen before the age of 24, according to WHO.

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4. DESPERATELY SEEKING ANSWERS: HIV'S MYTHS AND MYSTERIES

More than virtually any other disease, AIDS has generated myths and far-fetched theories about its origin, its causes and even its very existence. These are probably linked to fear and denial prompted by a virus which is fatal, infectious, incurable and sexually transmitted - and can infect people for years before they show any signs of illness.

Where did HIV come from (and where is it going)?

HIV is not - despite persistent beliefs - an alien from outer space or an agent of biological warfare. It has close relatives in the animal kingdom. Immunodeficiency viruses are known to infect cats, cattle, and monkeys, for example. The closest relatives of HIV are found in monkeys, and many scientists believe that at some point in recent history, immunodeficiency viruses entered the human population from other primates.

This is not an outlandish idea: many viruses and bacteria "jump" species. For example, influenza viruses are thought to originate in domestic fowl and spread to pigs before they are transmitted to humans. Many virologists have argued that a forerunner of HIV could have "jumped" species from monkeys to humans if blood from a monkey was splashed into a cut or a mucous membrane, such as the eye. In communities where monkey meat is eaten and where monkeys are often kept as pets, this scenario is plausible. Strains of the HIV-related simian immunodeficiency virus (SIV) have been found in macaques, mangabeys, mandrills and vervets. A number of scientists such as Dr Gerald Myers of the Los Alamos National Laboratory HIV Database in New Mexico, US, have discussed the origins of the virus but have not been able to do more than speculate.

There are in fact two distinct human immunodeficiency viruses: HIV-1, which is widespread around the world; and HIV-2, a less virulent form which has been mainly confined to West Africa with a few cases of infection elsewhere. HIV-2 is genetically similar to certain strains of SIV found in captive macaques. HIV-1, however, is genetically distant from SIV and HIV-2. HIV-1's closest relatives have been found in a very small number of chimpanzees from central and West African countries, but the samples of virus from these animals are still being analysed. It seems probable that HIV-1 and HIV-2 "jumped" species separately and have separate ancestors.

But no one knows exactly when either virus first entered the human population. Until recently, scientists believed that they had found the earliest clear, documented case of HIV infection in a British sailor who died in 1959 of a wasting disease and whose stored tissues were reported to be infected with HIV. However, this case is now in serious doubt. Whatever the outcome, there is no evidence of widespread HIV infection before the mid to late 1970s, anywhere in the world.

The most plausible theory is that HIV entered the human population sometime in the past - maybe as recently as the 1970s but certainly within the last 100 years - and then remained isolated in a small or remote group who may not have been severely affected by it. Wherever the virus originated, its explosive spread began only in the 1970s when urbanisation, cheap travel and major international conflict increased the potential for people from different communities to have sex with each other.

There have been claims of an isolated case of HIV infection in 1959 in Kinshasa (then Leopoldville), Zaire. But contrary to popular opinion, there is no evidence of widespread HIV infection in Zaire or anywhere else in sub-Saharan Africa before the mid to late 1970s. Successive testing of stored tissues and blood samples from the 1950s and 1960s has failed to find any HIV infection (4). Claims by Western journalists that AIDS is just a new name for an old disease long prevalent in sub-Saharan Africa have irritated doctors and others in Africa who recognised it as something new and different (5).

Each time the virus makes copies of itself within the cells of an infected person, it makes errors in its genetic material. Over time, therefore, it changes its genetic makeup significantly and develops different variants (see page 3). By 1995, researchers had identified eight broad genetic strains (or subtypes) of HIV-1 around the world, labelled A to H, all of which belong to a group the researchers call "M".

In North America, a strain of HIV called subtype B is prevalent but in other populations, including those of the former Soviet Union, much of sub-Saharan Africa and Brazil, several subtypes coexist (6). There is also a different group known as the "O" group, genetically very different and identified so far only in Gabon, Cameroon and France.

Polio vaccine exonerated

There are many popular alternative theories of the origin of AIDS, including some that are less outlandish than the germ-warfare or space-alien theories. None, however, is supported by evidence. One that seemed plausible at first glance was the suggestion that a monkey virus and forerunner of HIV contaminated the first batches of a polio vaccine that was tested in the Congo and Zaire in the late 1950s. Monkey kidney cells were used to culture the poliovirus used in the vaccine.

However, this theory was effectively discounted by a committee of experts, chaired by Dr David Ho of the Aaron Diamond AIDS Research Center in New York in 1992. There are several reasons why the vaccine is highly unlikely to be responsible. First, HIV is unlikely to have survived in the kidney cells used to grow the vaccine. Second, the vaccine was given by mouth and HIV rarely survives in the gut. Thirdly, the geography and the epidemiology are wrong: if HIV's forerunner had been transmitted first to humans in the Congo on this scale, researchers would have expected to see an epidemic there first. As has been shown above, there is no evidence of such an epidemic during the 1960s.

In years to come, HIV will presumably continue to mutate. It is possible that either more virulent or less virulent strains could emerge. What seems most certain is that the situation will become even more diverse and complex than it is today.

Is AIDS a myth?

For the past eight years or so, a small but vocal minority in the AIDS research community - and a group of supporting journalists - has argued that HIV is not the cause of AIDS. Led by Dr Peter Duesberg, a virologist at the University of California, Berkeley, the dissidents argue that HIV is just a harmless passenger virus that happens to be found in all the people who get AIDS.

The factors that cause the disease are not HIV at all, they argue, but lifestyle factors, such as use of recreational drugs or having many sexual partners. They claim AIDS can even be caused by the antiviral drugs used to combat HIV, such as AZT. Duesberg and others, such as Dr Robert Root-Bernstein, argue that the evidence linking HIV with AIDS is unconvincing. They believe that AIDS in Africa scarcely exists or has been grossly exaggerated; and they believe that current testing methods are not valid.

Duesberg is a respected virologist and a member of the National Academy of Sciences in the US. A small number of scientists support him, but the overwhelming majority say he is selective with data and ignores the published literature. Nevertheless, his views have been publicised and enthusiastically promoted by some sections of the media, such as the Sunday Times in the UK.

The gaps in scientific knowledge about HIV are considerable. There is a need for challenges to the established research community, but the questions that have yet to be answered are not those that Duesberg is asking. Unfortunately, many scientists have preferred to ignore Duesberg rather than take issue with him. This has two damaging effects: it allows him to gain status with the media for being a stifled dissenter; and it diverts public and scientific attention from the real, more demanding unanswered questions about HIV.

The main points made by the "AIDS dissidents" are the following:

- HIV has not been shown to meet the classical requirements, known as Koch's postulates, that must be met if a microbe is to be identified as the direct cause of a disease. Robert Koch, a German microbiologist, discovered the bacillus that causes TB, Mycobacterium tuberculosis, in 1882. His work was central in establishing the theory that germs cause disease. To prove that a microbe causes disease, Koch said, it must be isolated from a sick animal, given to a healthy one and seen to cause the same symptoms; then it must be isolated again.

However, Koch's postulates are in practice difficult to meet with a number of infectious diseases - including, ironically, tuberculosis. In the case of HIV, however, there may now be a near-perfect case, resulting from a disastrous laboratory accident in the US in which three workers were accidentally infected with purified, cloned HIV. In 1993, William Blattner of the National Cancer Institute reported that the three all had falling CD4 counts and one had developed Pneumocystis carinii pneumonia. None of the individuals had other risk factors for infection (7).

- Drugs, alcohol, a buildup of stresses on the immune system from contaminated blood products, and too many sexual partners, can all be blamed for destroying the immune system and causing AIDS. But lifestyle appears to be less important than Duesberg believes. Data from several sources suggest that haemophiliac men and gay men infected with HIV tend to develop AIDS at roughly the same rate (8). For

the vast majority of people affected by HIV in the developing world, the "lifestyle" factors that Duesberg blames are irrelevant. For most, recreational drugs are not available. Alcohol abuse is a growing problem among men, but not among women, who are at least as severely affected by HIV as shown above. Few would doubt, however, that malnutrition may accelerate the course of AIDS, as it appears to do in other diseases such as TB.

- ✍ AIDS is just a name for old diseases in Africa, such as malaria, TB or malnutrition. HIV is innocent, the dissenters argue. But a study by Ugandan and British-funded researchers, published in The Lancet in 1993 (and reported in 1992 at the IXth International Conference on AIDS in Berlin, Germany) showed that people in rural southwest Uganda who were infected with HIV were 60 times more likely to die in young adulthood than people in the same community who were HIV negative, even after potentially confounding factors had been considered.
- ✍ AIDS is not linked to HIV, and is not sexually transmitted. The epidemiology of HIV clearly runs against this claim. Within populations, where HIV is found, AIDS is found too. And if the disease were not the result of a sexually transmitted agent, it would not show the pattern of distribution within societies that it does show: it is concentrated largely among sexually active younger adults and, where the virus is prevalent, it is commonest among those who have unprotected sex with large numbers of partners. Claims that the virus is "harmless" are cruel and dangerous, and insulting to those who have been infected.
- ✍ AIDS is linked to AZT and its side effects. Most people with AIDS have never been within a mile of AZT. The drug is economically beyond the reach of most people in developing countries. Within the industrialised countries, where AZT has been available to most people with AIDS, controlled trials have shown that the drug has significant side effects, but there has never been any evidence from these trials that it "causes" any of the symptoms of AIDS.

Are HIV tests reliable?

Some dissenters also argue that the existing tests for detecting antibodies to HIV are unreliable. Tests that are relatively affordable and used worldwide are designed to detect the antibodies that the immune system makes to respond to HIV, and not to detect the virus itself. Tests to detect the virus require expensive technology and sophisticated laboratories, and are generally not available in most developing countries.

In the early years of AIDS, some highly-publicised studies found unconvincingly high rates of HIV infection in certain communities in Africa, using the simple antibody test for the virus, known as an enzyme-linked immunosorbent assay (ELISA). The figures quoted were sometimes as high as 60%. It turned out that some of these tests were invalid because of reactions between some of the reagents in the test and antibodies to malaria parasites in people's blood. Later generations of tests have had no such problem.

A more sophisticated test, the so-called Western Blot, has also now come under criticism, most recently in 1993 in the journal Bio/Technology by researchers at the University of Western Australia. Western Blot tests consist of bands on a gel that show the presence of antibodies to viral proteins. In trained hands, these tests produce results as accurate as for any other infectious disease. Poorly interpreted, they too could be misleading, however. For example, a Western Blot from an uninfected person may show a single band corresponding to an HIV protein, but in the absence of all the rest, it does not constitute a positive result. Careless or poorly-trained laboratory workers may be reporting occasional false positive results.

But since most people in Africa have no access to laboratory tests for HIV, and many people become ill and die without having been diagnosed, because of the lack of healthcare facilities and medical personnel, the official figures are likely to be underestimates, not overestimates as the dissidents argue.

More importantly, WHO's figures are based on extrapolations from figures for known centres of excellence. Tests carried out in the centres of excellence in sub-Saharan Africa, such as the Uganda Virus Research Institute in Entebbe, are checked from time to time by participating laboratories in the West and their results are as accurate as any industrialised country's (9).

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5. VACCINES: WHERE ARE WE NOW?

HIV - a challenge to vaccine designers

The search for a vaccine or vaccines against HIV has proved much more difficult than expected. Vaccines aim to protect people from infection with a particular microbe by stimulating their immune system to make a protective response against it. They do so by presenting the immune system with a "dummy" microbe - either a killed one, or a part of one, or a live but weakened one. But with HIV, there are some fundamental problems.

- First, the virus is highly variable, not just between the different subtypes (see page 3) but also within subtypes and even within infected individuals, each of whom may harbour a "swarm" of diverging variants. A vaccine based on one subtype may or may not provoke an immune response that "recognises" different ones.
- Equally difficult for the vaccine designer, HIV can enter the body hidden inside an infected cell. This puts it effectively out of reach of the immune system. No one knows for sure whether the specific immune response raised by cells in the mucous membranes in sexual organs is crucial for protection, but the question is an important one because most people become infected through the mucous membranes of the genital tract during sexual intercourse, not through the bloodstream during blood transfusion or injection with an infected needle.
- The immune response to infection consists of two broad arms: antibodies, which attach themselves to the virus and block it out of cells; and T cells, which kill infected cells. Most scientists believe that both arms of the system will be needed to protect against HIV. But so far, despite intensive effort, no researchers have been able to pinpoint exactly which parts of the immune response to HIV matter in protecting people from infection. Until they do, some scientists argue, it will be difficult to design a vaccine that works. Others, such as Ronald Desrosiers of Harvard University, disagree: they argue that the history of vaccines has been built on testing vaccines that may not be understood at all, but which have been found through empirical research to work (8).
- Another problem is the lack of a good "animal model". Scientists usually study an infection and the effect of an experimental vaccine in animals, such as mice and monkeys, that can be infected and develop similar or comparable symptoms to humans. The animal can be vaccinated and deliberately exposed to infection to find out whether the vaccine works. In the case of HIV, however, the best model is the macaque, infected with the simian immunodeficiency virus (SIV). Chimpanzees can be infected with HIV-1, but because they are an intelligent, endangered and protected species, in short supply and prohibitively expensive, scientists are reluctant to use them.

Who will foot the bill?

And, as if the scientific difficulties were not great enough there is another, equally pressing economic problem. In the 1980s, pharmaceutical and biotechnology companies were enthusiastic about developing HIV vaccines. Even so, estimates in a report by the Rockefeller Foundation (3) suggest that the total private sector expenditure on HIV vaccine research in 1993 was around US$ 25 million. The public sector, overwhelmingly the US government, spent US$ 135 million. Now that it is clear that the vast majority of infections are in the developing world, where few people or governments can afford to buy vaccines at market price, the motivation for the private sector is reduced - particularly since the US announced that it had postponed any large-scale domestic field trials of HIV vaccines.

Vaccine trials also pose a number of essential ethical questions. For instance, according to ethical guidelines on vaccine testing, participants to a trial must be volunteers; they must also be able to understand the nature of the research involved and any possible risks and effects associated with it. Because many of the issues linked to HIV vaccines are very complex, this is difficult to establish. For ethical reasons, people who participate in vaccine trials must also be counselled on how to avoid infection and to protect themselves. This may in turn reduce the number of people who become infected, and make it more difficult for researchers to judge how well the vaccine works, but it would be unethical not to counsel people in this way. Another problem is that participating in a vaccine trial might make people feel that they are protected - and encourage them to practise behaviour which increases their HIV risk.

Nevertheless, concerned scientists in both the public and private sectors are now working to establish a new global initiative to accelerate the development of vaccines that the world can afford. The Rockefeller Foundation report suggests that the initiative would require collaboration between the public and private sectors and could be modelled on a number of different existing mechanisms such as the International Task Force on Hepatitis B Immunization or the Children's Vaccine Initiative. It should also focus on developing vaccines based on subtypes of the virus that are found worldwide, such as A, E, C and D, and not on subtype B, which has dominated the epidemic in the US but which will become increasingly less important in the global picture.

How researchers are tackling the issue

So far, more than a dozen candidate vaccines have been tested in small groups of people, mainly in the US and Europe, to establish whether they are safe and to find out what sort of immune response they provoke - two essential steps which have to be completed before a vaccine can be tested for its capacity to prevent infection. Most of these vaccines are based on genetically engineered forms of HIV's protein coat gp120. All but one have been based exclusively on subtype B.

Two vaccines made by US companies have been tested in large-scale safety trials. So far, however, there have been no trials to test whether the vaccine can actually protect people from infection, but trials are due to begin next year on these vaccines. To establish whether a vaccine can protect people from infection, researchers will have to vaccinate a large number of people at high risk of infection, half with vaccine and half with a "dummy" vaccine or placebo, and then compare the numbers that become infected in each group. If the group that received the real vaccine has significantly fewer infections than the placebo group, the vaccine will be judged to have given some protection.

In the meantime, the effects of these vaccines have been measured in laboratory studies where blood samples from vaccinated people are mixed with virus to see whether the vaccine stimulates

antibodies and T cells and whether these can combat the virus. Overall, most of these vaccines stimulate antibodies against the virus and a few stimulate T cells, but in no case does the response last for long or at any great strength. It is not clear how much protection these vaccines would offer.

An important development in the 1990s has been the discovery by Dr Ronald Desrosiers, at Harvard University, of a very different approach based on a live, but genetically altered virus. Desrosiers found that a vaccine based on a live form of SIV can protect macaques from infection with the wild virus. The altered form of SIV used in the vaccine had had certain pieces of genetic material removed and failed to cause disease in the monkeys.

However, there are major safety concerns. No one knows whether a live but weakened and "disarmed" virus could regain its strength and its weaponry, through gene mutation or through recombining with the natural virus. Other researchers have found that deleted pieces of genetic material in SIV can "rebuild" themselves, raising the possibility, however remote, that the vaccine virus could revert to normal and cause disease. Elsewhere, researchers discovered that infant macaques born to the vaccinated animals developed disease.

Taken together, these concerns are likely to make authorities such as the US Food and Drug Administration highly nervous of even considering authorising tests in people. Nevertheless, scientists argue that where the risk of HIV infection is very high, the relative risk of complications from the vaccine may be a risk worth taking. Following a meeting at WHO in Geneva in October 1994, Dr Edward Mbidde, head of Uganda's National AIDS Committee, said the Western nations "had not seen the epidemic" and that its pace and scale in his country demanded action.

A WHO expert committee argued in June 1993 that a highly effective vaccine with a risk of serious adverse reaction of 1 in 100,000 might be preferable to the risk of infection in some communities, or preferable to the risk that a less effective vaccine might fail. In some populations, such as users of certain STD clinics, or young adults in high-incidence districts, something like 1 in 25 is becoming infected each year.

Vaccine trials: not for the faint-hearted

Back in 1991, a number of countries with high levels of HIV infection declared their intention to prepare for field trials of HIV vaccines. WHO selected four to whom it would give support in assessing the protocols for trials and helping to develop the infrastructure and train personnel. They were: Brazil, Rwanda, Thailand and Uganda. WHO said that trials would be undertaken only with the authority of the sovereign state and only after the candidate vaccine had been field-tested first in its country of origin.

Since then, much has changed. In 1994, the US decided to postpone indefinitely its own, domestic large-scale trials of the two most extensively developed HIV vaccines, leaving the developing countries on their own. The reason given for postponing the trials in the US was that there was insufficient evidence that these vaccines would protect people to justify large, costly trials now. However, US health officials stressed that other countries with higher incidences of HIV might take a different view.

At the October 1994 WHO meeting, an expert group representing scientists, public health officials, activists and the private sector from Thailand, Brazil and Uganda and from the North concluded that trials could go ahead elsewhere provided the sovereign state authorised them. The expert group said that the pace of the epidemic in these countries meant that even a modest protective effect might be better than nothing.

The first trials are now beginning in Bangkok, Thailand - aimed initially at confirming the safety and immunogenicity of the vaccine. Tests of whether the vaccine actually protects will begin about a year from now. However, the trials are beset even now with controversy. The pattern of subtypes in Thailand is changing rapidly and some scientists argue that the Genentech vaccine to be used in the trial - which is based on subtype B - is inappropriate in a population where both subtypes B and subtype E are prevalent, but where subtype E is gaining the upper hand. Others defend the trial, saying that until it is done no one will know whether a vaccine based on one subtype will protect against infection with another.

The question is important, not just for Bangkok, but for others in different countries and continents. At present there is virtually no effort going into developing vaccines based on subtypes prevalent in Africa, such as A and D. Uganda is unlikely to start a trial until an appropriate vaccine has been developed, or until there is evidence that a B-based vaccine could protect against other subtypes. Rwanda's AIDS research programme has been destroyed in the violent conflicts of 1994. Meanwhile Zaire, which had planned vaccine trials not directly with WHO, but with the US government, has also lost its AIDS research programme because of civil unrest.

The real prospects for a global HIV vaccine are limited at present. First of all, it is unlikely that a successful vaccine will be available in the next 10 years. And, apart from all the scientific problems, there has been little practical focus on the needs of the developing world. There is no estimate at present of how much a vaccine might cost, but it would almost certainly be too expensive for developing countries without some subsidy or other incentive from the public sector that would allow the private sector to recoup research costs. A number of such schemes have been discussed by the pharmaceutical companies and the international health organisations. So far no clear agreements have been reached.

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6. DRUG TREATMENTS: WHAT'S IN THE CUPBOARD?

There is no cure for AIDS, but a number of treatments have been developed to help deal with the various opportunistic infections which people with HIV and AIDS may contract, and to try and delay the onset of AIDS.

Orthodox therapies

The existing treatments for HIV infection and the symptoms of AIDS have benefited patients in the rich world but have scarcely touched the developing countries. Mainly because of good treatments for opportunistic infections such as cytomegalovirus or Pneumocystis carinii, people in the North can now expect to live for about two years after AIDS has been diagnosed - twice as long as in the early 1980s.

In the South, the available data suggest the survival is much shorter. Doctors in the South are frustrated by the lack of basic antibiotics and antifungals they need to treat these opportunistic infections. But with total annual health budgets per capita of as little as US$ 13.5 on average in sub-Saharan Africa, even these cheap drugs are out of reach. The antiviral drugs that attack HIV itself, such as zidovudine (AZT) are out of the question: one day's supply for someone with AIDS costs about US$ 15.

So far, approaches to the direct treatment of HIV have focused on either attacking the virus, by designing antiviral drugs or boosting the immune system against it. In addition, there is a wide range of drugs to treat opportunistic infections such as tuberculosis.

The earliest type of antivirals are known as nucleoside analogues: they include zidovudine (AZT), ddI, ddC, 3TC, stavudine and FLT. All these drugs work in the same way: they mimic the protein building blocks (nucleosides) in a cell and stop the virus from assembling its genetic material. When HIV replicates, it has to turn its genetic material from RNA into DNA, which it does with the help of its enzyme reverse transcriptase. The enzyme builds up the chain of building blocks in DNA by assembling nucleosides from the cell. The "false" nucleosides generated by the drug join into the chain and stop further real nucleosides from being added, like a broken bead in a necklace.

Trials of AZT show that it can benefit people with AIDS for a limited period by slowing down the process of disease. However, its benefits are short-lived; people who start taking it when they have HIV infection but no symptoms will tend to develop AIDS as soon as they would have done if they had not taken the drug. Unfortunately, the drug can also have significant side effects including anaemia and muscle wasting. Nevertheless, a study from the US National Institute of Allergy and Infectious Diseases showed in early 1994 that the drug could cut by two-thirds the number of infections passed from mothers to their unborn children. Encouraging though this is, most pregnant women with HIV in the world have no hope of obtaining AZT. And the long-term effects of the drug, if any, on a foetus are unknown.

Other antivirals include protease inhibitors, which work by inhibiting protease, an essential viral enzyme enabling HIV to reassemble new copies of itself, by chopping up large proteins into smaller ones. Saquinavir, one of several protease inhibitors on trial, has produced some encouraging results on its own and in combination with other antivirals (10).

The main problem with antivirals of all types is that HIV rapidly develops resistance to them. Researchers hope that combinations of different antivirals will help to lengthen healthy life and reduce the opportunities for drug-resistant strains to emerge. However, there are few data as yet to either support or destroy their hopes.

Rather than attack the virus directly, some treatments are designed to reinforce defences against it by boosting the immune system. They include so-called therapeutic vaccines, in which an already infected person receives an injection of genetically engineered envelope protein. The aim of a therapeutic vaccine is to trigger a new immune response in the infected person, in the hope that it might strengthen the natural immune response against the virus. Despite bullish early claims, the effects of these therapeutic vaccines is unclear.

Another approach is to give HIV-infected people infusions of purified human "messenger chemicals", or cytokines, which may modify their immune response to the virus.

Alternative therapies

A serious handicap faced by AIDS educators throughout the world is the growth of claims made by alternative or traditional healers that they have found a cure for AIDS. None of these claims has ever been substantiated.

Given the paucity of good conventional therapies it is not surprising that a large number of people with HIV have tried various alternative and complementary medicines and therapies. These range from vitamin supplements and other simple dietary measures to crystal therapies

and astrology. The lack of research on most of these makes it difficult to present clear conclusions. Nevertheless, many individuals say they have been helped by such therapies. As with all medicines, herbal medicines may have toxic side effects and in addition, herbal medicines may contain toxic impurities. Because the alternative medicine industry is less closely regulated than the conventional pharmaceuticals industry, patients are obliged to check their practitioners' credentials as closely as possible (11), (2).

While there is evidence that some alternative therapies can provide relief from some AIDS-associated symptoms and infections, claims that alternative or traditional treatments can cure AIDS must be treated with extreme caution and scepticism. So far, none of the claimed "AIDS cures" has ever been proved to work, and some practitioners have exploited the fears and weaknesses of their patients unscrupulously.

However, particularly in developing countries where conventional modern medicine requires expensive imported drugs to treat HIV- and AIDS-related symptoms, traditional herbal remedies can offer a much cheaper alternative. In many parts of the developing world, traditional healers are the first port of call for many ill people - a survey carried out a few years ago by the Zimbabwe Traditional Healers' Association found that 80% of Zimbabweans consult a traditional healer at some point, and 30-40% of all patients go to a traditional healer first.

Since the 1980s, pharmaceutical companies have been investigating plants used by traditional societies as potential sources for new drugs and treatments. According to The Lancet, fewer than 10% of the world's estimated quarter of a million flowering plant species have been scientifically examined for their medicinal potential (12).

The following alternative therapies have been used to treat patients with AIDS:

- Homeopathy: some homeopaths claim success in treating specific symptoms of AIDS, such as night sweats or weight loss. Some have also treated emotional symptoms linked with the disease such as shock, depression and anxiety. Evidence is hard to obtain, however, since homeopathy is difficult to test using the randomised controlled trials that are favoured by conventional modern medicine. This is because homeopathic treatments are tailored to individuals, whereas clinical trials depend on giving large numbers of people the same treatment.

- Special diets: some, such as anti-candida (a fungal infection commonly know as thrush, which many people with AIDS are prone to) diets, are designed to reduce the risk of opportunistic infections in immunocompromised people. Others, such as macrobiotic diets, are part of a strategy to increase the individual's wellbeing, health and boost the immune system.

- Physical therapies such as osteopathy, hydrotherapy, chiropractic manipulation and massage can be used together with alternative or conventional medicine.

- Chinese herbal medicine: In marked contrast to other alternatives to Western medicine, traditional Chinese medicine has been at least partly researched. Chinese tradition considers that microbes cause disease in the body only when its life force is depleted. Most Chinese remedies tested against HIV appear to increase the resistance of the cells of the immune system rather than attack the virus itself. Some increase antibody levels, many are reported to increase T cell levels. More than 30 products have been tested in animals and in healthy human volunteers.

The most important Chinese herb in HIV disease, and the most extensively studied, is astralagus. It increases the production of antibodies in healthy humans and stimulates several factors in the immune system in mice. Many Chinese herbalists have prescribed it as part of an immune-stimulating compound for HIV-positive people.

Other important Chinese herbs used to treat HIV include: Andrographis paniculata - which is used to treat TB, and inhibits HIV in the test tube; Hypericum performatum (in synthetic form, hypericin), which is used to treat Hepatitis B virus infection in China and inhibits HIV in the test tube; and Viola yeodensitis, which inhibits, but does not kill, HIV. Doctors in San Francisco are currently testing a Chinese herbal formula in people with HIV. A short-term collaborative study in Tanzania between Chinese practitioners and Tanzanian doctors suggested that symptoms were relieved in most of a small number of cases. However, long-term health was not reported (11).

- Other herbal treatments: In many developing countries where traditional medicine is still practised, traditional herbalists have tried various approaches to treat AIDS or associated illnesses. In Zimbabwe, after a spate of spurious AIDS cure claims by traditional healers, limited trials were carried out by the Blair Research Laboratory on herbal cures from traditional healers. These trials showed that some herbal preparations can be effective in alleviating some of the symptoms linked with AIDS, such as diarrhoea and weight loss. However, none of the compounds tested could cure AIDS or rid the body of HIV.

A study conducted in Kigali, Rwanda (before the recent conflict) and in Kampala, Uganda, found that most women were using both traditional healers and modern medicine to treat AIDS and other diseases. The study also found that traditional healers were usually interested in collaborating with modern medical practitioners, and that all the healers questioned knew the symptoms of AIDS and the routes of transmission of HIV (13). There is also evidence that in many countries, traditional healers can sometimes help people with HIV or AIDS by providing psychological support and counselling.

- Acupuncture, another Chinese traditional therapy, can benefit people with AIDS, both in long-term programmes and in hospices for those receiving terminal care.

The cost of AIDS treatments

AIDS is expensive. The direct medical cost of treating the disease has been assessed in a number of different countries (14). In the developing countries, on average, it is roughly equal to per capita GNP. In the rich countries, it often exceeds per capita GNP. For example in the US, in 1991, the cost of treating each AIDS patients was estimated at US$ 32,000 a year - or 161% of GNP per capita. In Zambia, the cost was US$ 374, or 96% of GNP. And in Zaire, the cost varied dramatically between US$ 132 and US$ 1,585 - which translates into anything between 78% and a staggering 932% of GNP (2).

In much of sub-Saharan Africa, care provided at home in a person's village may be extremely cheap while hospital care in a major city will be 50 times as expensive - and this is without antivirals.

The World Bank reported in 1993 that even in Tanzania, where the government pays a large share of health costs, affected households had spent on average a crippling US$ 60 - equivalent to a year's rural income - on treatment and funerals (1). In Thailand, a small study in Bangkok in 1990 found that the total direct cost of diagnostics and drug treatments was just over US$ 1,300. Some 80% of that was for drugs; AZT alone accounted for two-thirds of the total drug costs (2).

But in most developing countries, AZT is not even an option. In Malawi in 1994, the estimated cost of treating AIDS patients without any expensive antivirals, but just routine drugs such as aspirin, was estimated to be US$ 20 million. This was expected to more than treble by 1998.

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CONTACTS

The World Health Organization (WHO)

Global Programme on AIDS, 20 Ave.
Appia, CH-1211,
Geneva 27, Switzerland.
Tel: 41 22 791 2111

The Global AIDS Policy Coalition

5th floor, 8 Story St,
Cambridge, MA 02138,
USA.
Tel: 1 617 496 4370

This briefing was written by Phyllida Brown and edited by Laurence Zavriew, Panos.
