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Is it possible that AIDS and HIV could be treated as easily as diabetes? New wonder drugs are raising hopes but, says Philip Watson, prevention is still the best cure

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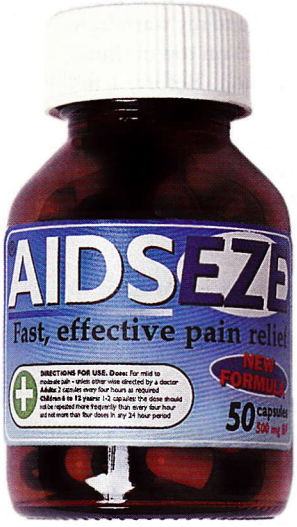


LAST YEAR, 32-YEAR-OLD Mark Pawsey ran the London Marathon for the first time. There is, perhaps, nothing exceptional about this, even for someone who has been HIV-positive for twelve years. But the famous race was to inadvertently become a turning point in his life.

For someone who had always been fit and active – he ran and worked-out regularly – it seemed to take him longer than usual to recover. His energy levels began to drop. He caught cold after cold, and contracted any flu bug that was around. He badly injured his shoulder simply lifting a weight in the gym, and strained his groin jogging. Warts started to appear. And, at the end of the year, he caught shigella: a bacterial infection that causes fever, stomach pains and bloody diarrhoea.

His CD4 count – a measure of white blood cells in the body and an indicator of immune system health – had fallen to its lowest level ever: 140. CD4 counts vary widely from person to person, but in a healthy individual it is usually well above 600. Another indicator called a viral load test, a new

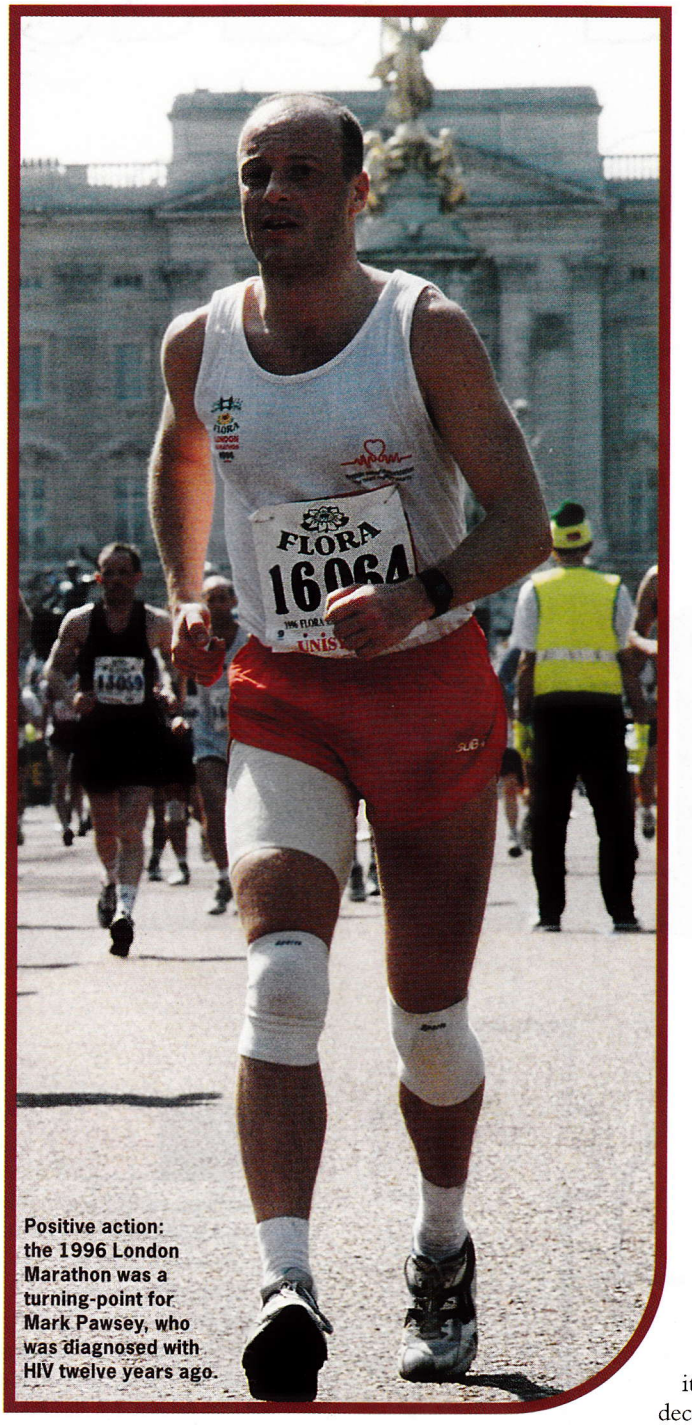
PHOTOGRAPH: GARRY HUNTER

measure which counts the number of HIV particles in a sample of blood, also gave cause for alarm.

"I was feeling very, very low and seemed to be in a downward spiral," remembers Pawsey. "I'd never been really ill or, like some, suffered life-threatening illnesses, but it was one thing after another – the little problems that bring you down. I kept trying to get on top of things, but I just couldn't seem to. I'd lost my motivation in life."

He was so depressed that he that he considered giving up his stage manager's job at a London theatre. Then, last March, his doctor advised him to start a course of anti-HIV treatments. Pawsey had resisted such drugs in the past, largely because he associated taking pills with serious illness. Eventually, he agreed to try a course of two drugs: AZT, the first anti-HIV drug to be licensed and widely used; and 3TC, a new drug first approved for use in the UK in August, 1996.

The side effects were severe. Already taking drugs to ward off the opportunistic infections that HIV patients are prone to, as well as anti-inflammatory drugs for his shoulder, and vitamins to maintain his general health, Pawsey found that the extra dosage caused nausea and even hallucinations. He also developed a condition called peripheral neuropathy – a sensation of tingling pins and needles in the hands.



Positive action: the 1996 London Marathon was a turning-point for Mark Pawsey, who was diagnosed with HIV twelve years ago.

After a month, Pawsey switched to a triple-drug therapy by adding an experimental new inhibitor called nevirapine. A licensed drug in the US, but only recently available in this country as part of an "expanded access" scheme – in which the patient becomes part of a clinical trial – nevirapine has been shown in early studies to have significant benefits if combined with two other drugs like AZT and 3TC.

For the first two weeks, Pawsey again felt discomfort and nausea. But after a month, his CD4 count had risen to 240, which took him out of the high-risk bracket. In a viral load test, his HIV count had fallen to undetectable levels.

"I can't tell you the difference the treatment has made," he says. "I've got my energy back for swimming, running and gym work, and I'm going clubbing again. My shoulder and groin have recovered and my warts have cleared up. I feel on top of things now: it's amazing. Before, I felt that the illness was controlling me, but now I feel I'm controlling it. Taking these drugs is the best thing to happen to me since I became ill twelve years ago."

Mark Pawsey is not alone in his evangelical advocacy of the new anti-HIV drugs. The subject of a flurry of press reports – almost rivalling the tabloid "Shirley Valentine" tales of the HIV-positive Cypriot and the Essex housewife – the new combination or "cocktail" therapies have had many claims made on their behalf. There have been stories about "significant advances", "dazzling discoveries" and "miracle breakthroughs".

In the States, claims for the new drugs have not been limited to the tabloids. One advert, for capsules called Crixivan, ran across three pages in the September issue of men's magazine *Details*, under the headline "In the battle against HIV, there's a change in outlook". Crixivan is a protease inhibitor, and its makers claim that it "significantly decreases viral lode, and increases CD4 levels, in many patients".

In a study published last May by Dr David Ho, of New York's Rockefeller University, it was even suggested that treatment with a particular combination of three drugs – AZT, nelfinavir and lamivudine – could eradicate all known HIV infection from a patient after just three years.

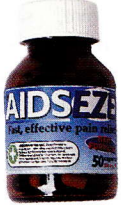
Ho, one of the world's leading AIDS researchers, is said to have since revised this estimate, and is now quoting a timescale nearer

five years than three. Many AIDS experts have also pointed out that the three-year period is nothing more than a mathematical equation, dependent on many variables that are, as yet, clinically untested. Still, an impression has been created that medical science may be getting close to a late twentieth-century Holy Grail: the cure for AIDS.

"There have been enormous developments in drug therapy over the last three years, and compared with just a year ago, people who were very, very sick are now very, very well," says Dr Mark Nelson, a consultant physician at the Chelsea and Westminster Hospital in London, one of Europe's largest centres for HIV treatment and research. "But while I am optimistic that we will eventually find a cure, we are still a long way from finding it."

Nelson argues that Dr Ho's work in the US was conducted on an unrepresentative group: newly-infected patients. "David Ho's research is based on getting people very early and the majority of HIV patients don't present themselves like that. We are now seeing more and more patients taking the triple-drug combination Ho is using, failing to see any improvement, and the virus remaining."

Still, many who work in the AIDS field are profoundly encouraged by the number and success rate of new drugs. "The way I usually describe the situation is that we haven't come to the end of the journey, but we've seen some useful signposts," says Lisa Power, health advocacy manager of AIDS charity the Terrence Higgins Trust. "Three or four years ago, we were in despair about treatments – there seemed to be no breakthroughs. Now, HIV research has really picked up steam and the train is just roaring through."



"Before, I felt that the illness was controlling me; now I feel I'm controlling it. These drugs are the best thing to happen to me"

Not only has there been progress in the efficacy of anti-HIV drugs, but medical science has seen dramatic improvements in the treatment of the infections that can affect a damaged immune system. Illnesses such as PCP – a type of pneumonia that was a common cause of death in the early years of the AIDS epidemic – and Kaposi's sarcoma, a form of cancer, are now easily preventable or treatable with drugs.

There has even been some testing of drugs that strengthen and rebuild parts of the immune system. In trials, an experimental and unlicensed drug called interleukin-2 has been shown to substantially increase patients' CD4 counts, thereby improving the body's ability to fight HIV, and possibly other infections.

New research published in August has also suggested that many people may be naturally resistant, or even immune, to the disease. US scientists have found that the presence of genetic mutations can lead to a dramatic slowing-down of the onset of AIDS or, for a tiny amount of people, actually confer complete immunity. These findings open up the possibility of "gene therapy": a futuristic treatment where these protective mutant genes are introduced into the patient's body.

As a result of these advances, the death rate of British AIDS patients has fallen by up to 40 per cent, and the number of people who develop full-blown AIDS has dropped by 30 per cent. The rate of PCP diagnosis, the most common AIDS indicator disease, has also fallen. Hospital wards have closed and, in the US, some hospices are no longer needed. Some HIV-positive people have even been able to obtain life insurance.

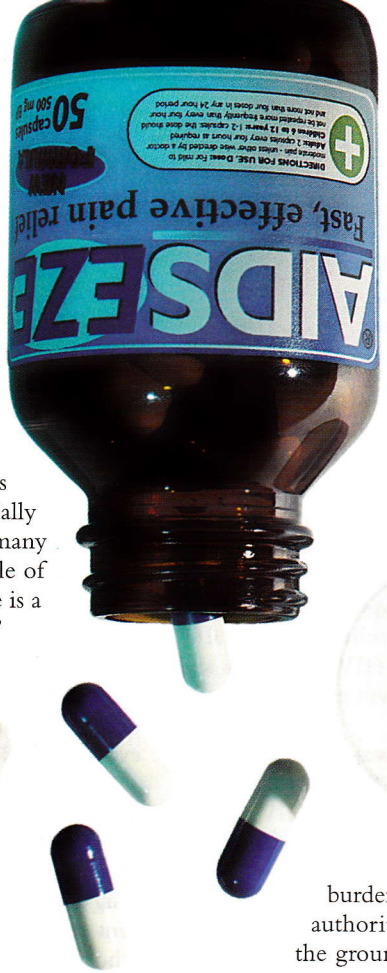
"This is the most significant period in AIDS research we have ever lived through," says Keith Alcorn, editor of the *National AIDS Manual*, the "bible" of AIDS information and treatments. "The improvements really have been enormous. Someone taking a triple-drug treatment today has, over a two- or three-year period, an 80 per cent reduced risk of disease progression compared to someone who, just two years ago, was taking one drug such as AZT."

Lisa Power says she can see a time when HIV can be managed and treated in a similar way to other viruses and illnesses, such as tuberculosis and diabetes. In TB treatment, a large combination of drugs is taken over a relatively long period, usually nine to eighteen months, from the time the disease is suspected or diagnosed. Because TB, like HIV, can become resistant to drugs, the combination is fine-tuned as the treatment continues. Once the TB has been reduced to an undetectable level for a significant period, the patient can come off the drugs. Diabetes is also a chronic condition, but it is a manageable illness if the correct drugs are taken.

In truth, AIDS research teams are a long way from developing HIV therapies as advanced as these. It is now generally accepted in the scientific community that HIV plays a central role in the development of AIDS, but researchers still do not understand exactly what that role is, and how much other factors – such as age, the presence of other viruses and the method of infection – may contribute. The human immune system is immensely complex and there are many different ways that a virus such as HIV can affect it.

HIV is also a particularly difficult virus to control and suppress. As a retrovirus – one that copies its genetic material onto that of the patient's own cells – it infects patients for the rest of their lives. It replicates and mutates very often and quickly, which makes it very resistant to treatment. And HIV has an extraordinarily wide distribution in the body. Not only can it infect the central nervous system, it can also spread to areas including the epididymis (the tiny

PHOTOGRAPH: GARRY HUNTER



tubes in the testicles), bone marrow and lymphoid tissues, and such "sanctuary sites" as the brain, where drugs can not penetrate.

"HIV is actually a very un-clever virus and is very poor at reproducing, and this makes it especially difficult to treat," says Dr Nelson. "It makes as many mistakes as it can every day throughout the whole of its genes, and every time it makes a mistake there is a chance that the virus has become more resistant."

"There has never been a viral disease that has been totally eliminated from the body, so the chances of that happening with HIV are pretty slim," explains the *National AIDS Manual*'s Keith Alcorn. "At the moment these new drug treatments are really, really speculative."

As remarkable as some of the new combination therapies undoubtedly are, there are also disadvantages. First is the extremely confusing array of drugs available and (because of their often experimental nature) the risks they entail. While the Terrence Higgins Trust has been active in this area, producing a range of leaflets to explain the new treatments, there are differing scientific opinions about when to start drug therapies, and in what combination.

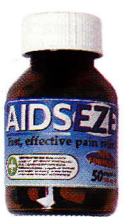
HIV research is in a very dynamic and volatile state, and clinical trials are also changing our understanding of treatments almost monthly. It has recently been discovered, for example, that some of the group of drugs called protease inhibitors can cause permanent damage to the immune system if the treatment is not immediately effective. This was not known when HIV patients first started taking the drugs. People living with HIV are often forced to take a calculated risk with highly toxic drugs that require strict adherence to a disruptive and life-restricting regimen. In the hope of hitting upon a combination that works, they are gambling with their lives.

"It is a very exciting time if you're a scientist, researcher or AIDS worker, but it's pretty frightening if you're actually living with the virus," says Lisa Power. "It's a real mixture of hope and despair. There's a massive amount of hope that these new drugs will lead to lasting benefits, but also constant discoveries of their limitations. People living with HIV have a lot of uncertainty in their lives to start with. Add a complete uncertainty as to the best road to take with treatments, and it's not difficult to understand why people are scared."

Another factor that has caused controversy is the cost of providing combination therapy. Taking three or more experimental drugs twice a day for a year can cost between £10,000 and £15,000; some commentators have argued this is an unacceptable and excessive burden on the National Health Service. Some health authorities have failed to supply combination therapy on the grounds of cost; patients have been referred to larger cities such as London and Manchester.

Others, including Dr Brian Gazzard, clinical director of the leading Kobler Clinic at the Chelsea and Westminster Hospital, have pointed out that – compared to other procedures such as open-heart surgery or kidney dialysis – HIV drugs are actually one of the least expensive life-saving options that medicine can offer. Savings have also been made because fewer HIV patients are now being treated.

"Treatments can be expensive, but they are very cost-effective," says Dr Nelson. "They save on the cost of preventative hospital treatment for the complications and illnesses associated with HIV, and have put many talented young men and women back to work and allowed them to contribute to society again – £15,000 sounds excessive, but it's not what you are spending, it's what you are getting back."



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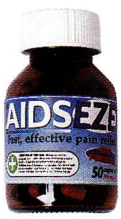
The hyperbole has also led some to believe that they no longer need to protect themselves against HIV infection. Lisa Power says there is much anecdotal evidence to suggest that people now think they don't have to worry about the risk of catching the virus as these new drugs represent some kind of "HIV morning-after pill". And because others might also mistakenly believe themselves to be no longer infectious, there is a danger that they will practice unsafe sex. This is already apparent among gay communities in the US and Australia, where studies show that the rates of sexually transmitted disease are on the increase. Over-confidence about the success of new drugs has been cited as one of the reasons.

"I have heard some people say that it doesn't matter if you get

HIV now because there is a treatment for it – this is simply not the case," warns Dr Nelson. "The most important thing is prevention, not treating something after it is broken."

If prevention through safe-sex awareness campaigns has proved to be the most successful method of controlling the spread of HIV in the west, the only truly effective way to eradicate the virus on a global scale is through vaccination. In developing countries that are unable to afford the high cost of combination drug treatments, and where incidences of the disease are higher (95 per cent of the world's 23 million people infected with HIV are in the developing world), at present, vaccinations are the only meaningful option.

But this is another area of AIDS research that has been prone to difficulties and disagreements. When the first cases of AIDS were reported in the early Eighties, it was thought that it would take no more than a few years to develop a vaccine. But after more than ten years of research, no vaccine has yet been produced.



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It was believed that HIV would be no more difficult to protect against than viruses such as polio and smallpox. But HIV's ability to mutate into many different sub-types has made it much more difficult to find a cross-resistant drug. Another stumbling block is the fact that scientists have never been able to produce a vaccine that protects against sexual transmission. The development of a vaccine that is safe, highly protective, simply administered, and globally available and affordable seems a long way off. In 1996, US government scientists estimated that the earliest any vaccine could be licensed is the year 2002.

Professor Frances Gotch, head of the department of immunology at the Chelsea and Westminster Hospital and one of the country's leading vaccine researchers, remains optimistic about developments, however. "There are many problems that face us in the future, but I do think that we will eventually find an AIDS vaccine," she says. "We've gone an awful long way and we now have a very good idea of the immune responses that we need to induce."

Professor Gotch argues that the lack of a profit incentive in developing a human AIDS vaccine is one of the main reasons for the lack of progress. "Drugs companies stand to make huge profits if they can produce anti-HIV drugs that work for people who are already infected and live in the west," she says. "Vaccine research is much, much less lucrative and fashionable. A really good vaccine only has to be given to people once, and it has to be cheap to be used worldwide."

There are also many ethical considerations surrounding the type of vaccine to be developed, and on whom it is to be tested. Vaccines have been produced that offer 100-per cent protection to monkeys, but these use live (albeit weakened) viruses. Although this has proved to be a highly successful strategy for producing vaccines against other diseases, it is highly unlikely that the world community would ever find such human experimentation acceptable, because HIV is lethal. So far, experiments have been restricted to the use of envelope proteins of HIV among certain nominated groups, such as populations in Africa and south-east Asia, where the prevalence and incidence of infection is very high, or among volunteers from high-risk groups, such as intravenous drug users, in the west.

Because there are so many different strains of HIV, places such as Uganda, in central Africa, where Professor Gotch has worked, have also objected to the potential "guinea-pigging" of their citizens.

There are concerns that the African population may be used to test an HIV vaccine that may only offer protection against a sub-type of the virus found in the west. The fears have been fuelled by recent allegations that people in South Africa have had anti-HIV combination drug treatments withdrawn after taking part in successful trials.

Professor Gotch argues that education programmes and prevention strategies are still the best cures for HIV. "Just as the best protection against snake bite is wearing Wellington boots in swamps, the best possible vaccine throughout the world is the use of a condom," she says. "Unfortunately, that doesn't necessarily mean everyone's going to wear one, or that condoms are always going to work."

As for Mark Pawsey, he is planning to run in the 1998 London Marathon next April. After sustaining an injury towards the end of that fateful 1996 race, he was disappointed by his finish time of four hours 38 minutes. He is already in training for his next attempt, and is confident that this time he will beat the four-hour mark. He puts the transformation in his approach down to his combination therapy.

"I was twenty when I was first diagnosed as having HIV, and the doctors told me I'd had my last Christmas," he says. "But they were wrong, and it took all my strength to fight back. These drugs are all about hope, and that hope fuels your enthusiasm and spirit, and you begin to think, well, life's worth living again. Ten years ago, I never thought I would make it to 30. Now I'm thinking about what I'm going to be doing when I'm 60." ■

The National AIDS Helpline is a 24-hour service that provides general information, support and advice about HIV and AIDS (tel: 0800 567123). The Terrence Higgins Trust Helpline operates from noon-10pm daily (tel: 0171 242 1010). *The* latest information about HIV drugs is available from the *National AIDS Manual* (tel: 0171 627 3200).

PHOTOGRAPH: GARRY HUNTER