

Zidovudine — a harbinger of hope for sufferers from AIDS in the 1980s

In this sixth article in a series on landmark drugs, Jenny Bryan looks at the antiviral zidovudine, which, as the first drug to be licensed for the treatment of AIDS, brought hope to sufferers, who at the time were mainly gay men, and saved them from an automatic death sentence

If ever a product deserved the much over-used description of “breakthrough”, it was zidovudine (Retrovir) — the first antiviral drug licensed for the treatment of AIDS, 21 years ago this month. At a time when a diagnosis of AIDS was an automatic death sentence, zidovudine brought hope to a community of mainly gay men who had been watching their friends succumb to the opportunistic infections associated with AIDS since it was first reported in 1981.¹

“It was the first example of a drug that worked in AIDS and so it was a tremendously important first step,” says Brian Gazzard, HIV/GUM clinical research and education director at Chelsea and Westminster Hospital, London.

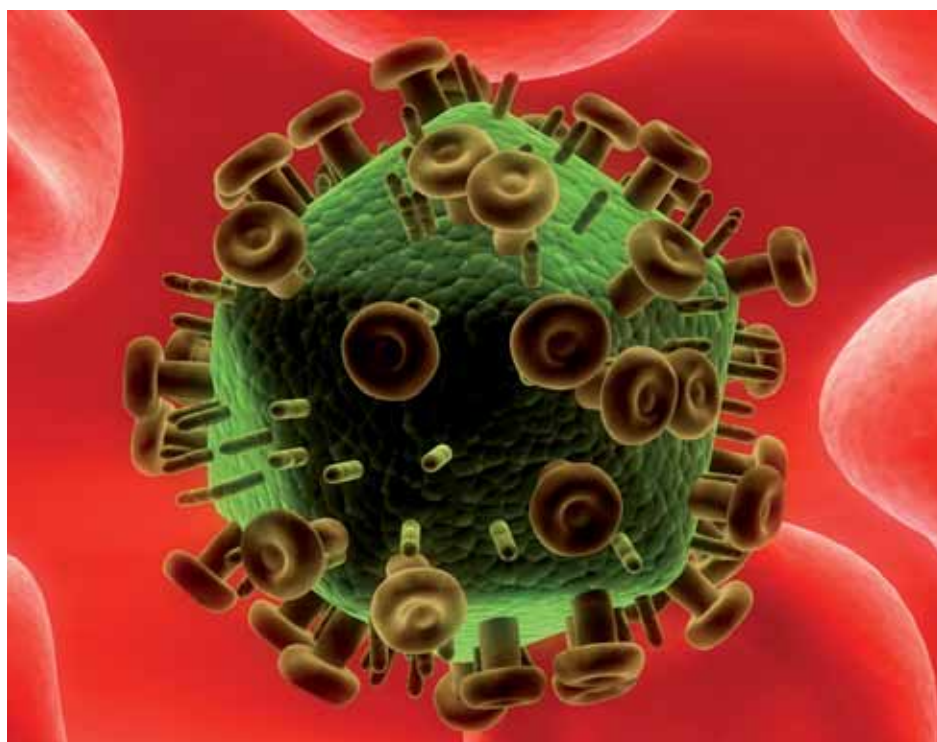
Zidovudine was not developed for AIDS. It was first synthesised in 1964 as part of a research programme at the Michigan Cancer Foundation. Without any promise as an anti-cancer drug, it was dropped until the US pharmaceutical subsidiary of the Wellcome Foundation, ultimately to become part of GlaxoSmithKline, screened it for antiviral activity late in 1984. The Wellcome scientists discovered activity against the AIDS virus and, within a few months, this was confirmed by National Cancer Institute, Food and Drug Administration and Duke University laboratories.

Zidovudine is a nucleoside reverse transcriptase inhibitor (NRTI). Retroviruses, such as HIV, use the enzyme, reverse transcriptase, to transcribe their RNA into DNA so that it can be integrated into that of the host cells it is infecting.

As a thymidine analogue, zidovudine uses the HIV reverse transcriptase to incorporate itself into the growing chain of viral DNA. But, once incorporated, zidovudine’s different chemical structure from the viral deoxynucleotide ensures that no further elongation of the viral DNA can occur. In effect, it acts as a terminator.

Toxicological and pharmacological testing of zidovudine in spring 1985 was quickly followed by the first phase I clinical study. This showed that zidovudine was well absorbed and penetrated the blood-brain barrier, which was important because of the neurological complications of AIDS.² Fifteen of the 19 patients in this first study had a significant increase in their T cell count.

A subsequent phase II, 24-week, placebo-controlled trial of 282 AIDS patients with the opportunistic infection *Pneumocystis carinii* with or without AIDS-related complex,



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HIV virus — zidovudine was a tremendously important first step in HIV treatment

(ARC), started in February 1986, was halted early, in September 1986, because of the obvious benefits of zidovudine.³ One patient in the zidovudine group died and 24 had opportunistic infections compared with 19 deaths and 45 infections in the placebo group.

Further trials were under way in Europe and the US, and Wellcome reported that it had diverted large numbers of research staff from other projects to work on zidovudine. The extra effort paid off and, within a few months, the drug had a licence in the UK for “the management of the serious manifestations of HIV infection in patients with AIDS or ARC”. It was licensed in March 1987.

“After such a dramatic reduction in mortality, zidovudine was licensed in record time, with less than six months’ experience in human beings. There was a problem with toxicity because, on the 1,200mg dose that was used initially, 50 per cent of patients needed blood transfusions, but we soon found that 600mg was just as effective,” Professor Gazzard recalls.

In 1990, zidovudine’s licence was extended to include patients with early symptomatic disease, and asymptomatic, progressive disease.

But it was not all plain sailing. As early as 1989, *The Sunday Times* raised questions about the speed with which the drug had been licensed and suggested that the side effects of the drug outweighed any benefits. In 1993, the newspaper jumped on the results of the Concorde trial, which failed to show any advantage of early treatment for asymptomatic HIV patients compared with delaying treatment until patients developed AIDS or ARC or had a low CD4 count.⁴ “The cure that failed”, blazed the headline on 4 April 1993.

“The results were misunderstood,” explains Professor Gazzard. “It wasn’t that the drug didn’t work, but that there was no additional benefit to starting treatment early before symptoms appeared. We also realised that, because of the high risk of resistance with zidovudine, starting treatment too soon would just bring forward the time when the drug was likely to become ineffective.”

While AIDS specialists unexpectedly found themselves having to defend zidovudine in response to adverse publicity about Concorde, there was no doubting the positive benefits of zidovudine for babies born to women infected with HIV when the 076 study was published the same year.⁵ In this placebo-controlled trial of nearly 500 preg-

nant HIV-infected women, zidovudine given before and during childbirth, and for six weeks afterwards, reduced the risk of maternal-infant transmission by two thirds.

By the time that Concorde and 076 were published, zidovudine had competition from two other NRTIs — didanosine or ddI (Videx) and zalcitabine or ddC (Hivid). And, in 1996, the Delta trial showed that using two NRTIs together to treat symptomatic AIDS patients and asymptomatic patients with low CD4 counts could prolong life and delay progression compared with using zidovudine alone.⁶ Subsequent use of ddC was limited by toxicity but combining ddI and zidovudine was shown to help delay resistance and opened the door to a growing range of antiretroviral combinations.

The most recent update of the British HIV Association guidelines⁷ for adults with HIV recommends treatment for those with:

- Symptomatic HIV infection or AIDS, regardless of CD4 count or viral load
- Asymptomatic patients with a CD4 count <200cells/ml, regardless of viral load
- Asymptomatic patients with a CD4 count of 201–350cells/ml, depending on viral load, rate of CD4 decline, patient's wishes and presence of hepatitis C infection

Standard treatment is now a combination of two NRTIs as the “backbone” of so-called

highly active antiretroviral therapy (HAART), together with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor, depending on the patient and the presence of drug resistance.

“People still take zidovudine and combining it with a second NRTI, lamivudine, as Combivir, gave it a new lease of life because lamivudine slows the development of resistance to zidovudine. It's a very popular combination in Africa, for example,” says Professor Gazzard.

Lipodystrophy — unsightly fat redistribution associated with some antiretroviral drugs, including zidovudine — has impacted on drug choices. But combined formulations of NRTIs and, more recently, NRTIs and NNRTIs are making treatment easier and more convenient to take. “At one time, people were having to take 18 pills a day, at set times of day, but those days are gone and even the most complicated regimens are only four or five tablets twice a day,” adds Professor Gazzard.

However, he believes that pharmaceutical companies have probably gone as far as they can with the current approaches to treatment. They have reduced the side effects of anti-HIV drugs, made them easier to take and lowered prices. But, as Professor Gazzard points out, they have not yet managed to cure AIDS: “Before 1987, we thought that HIV treatment was hopeless, but zidovudine did change all that. It didn't prove as effective as

we originally hoped, but it did show us that we could affect outcomes and slow progression of HIV.”

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