HIV treatments and highly active antiretroviral therapy

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SYNOPSIS

The treatment of HIV and AIDS has changed considerably over the last 20 years as knowledge and treatment options have increased. Highly active antiretroviral therapy is the prescription of a variety of antiretroviral medications used in combination. Potent combined regimens offer the greatest likelihood of reducing the replication of HIV, facilitating CD4 T cell expansion and delaying progression to AIDS. However, these treatments are not without complications and have substantial adverse effects.

Index words: AIDS, antiviral drugs.

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The early years of HIV

A great deal has happened since HIV/AIDS first came to the attention of the medical community in the early 1980s. The first reports were made to the Centers for Disease Control in the USA in 1981 when five young, homosexual men were diagnosed with the rare *Pneumocystis carinii* pneumonia. The risk groups for this new syndrome of immunosuppression soon extended from homosexual men to include injecting drug users, Haitians, transfusion recipients, female sexual contacts and Africans.[1] In 1982, the term 'acquired immune deficiency syndrome' (AIDS) was first used, replacing the previous acronym 'gay related immune deficiency'. The virus responsible for HIV was isolated in 1983 and serological tests to detect HIV antibodies were commercially available from March 1985.

Early treatments

In 1987, zidovudine was the first drug approved for the treatment of HIV. Zidovudine was the first of a class of antiretroviral drugs called nucleoside analogue reverse transcriptase inhibitors. Members of this drug class are nucleoside analogues and when they are phosphorylated in the cell they inhibit the HIV enzyme, reverse transcriptase. This results in premature termination of the HIV proviral DNA copy of the viral RNA chain and disrupted viral replication.

Initial excitement about zidovudine was tempered when the drug did not provide longer-term benefits and was accompanied by unwanted adverse effects, such as nausea, headaches, myopathy and anaemia. Following the approval of zidovudine, progress regarding HIV treatment was slow. Additional nucleoside analogue reverse transcriptase inhibitors were developed and were increasingly prescribed as 'dual therapy'. These drugs included didanosine (ddI), lamivudine (3TC), stavudine (d4T) and zalcitabine (ddC). Trials, such as Delta and ACTG (AIDS Clinical Trials Group) 175, compared the relative efficacy of monotherapy and dual therapy. The findings from these studies established the superiority of dual therapy over monotherapy. At the same time significant advances were made in the prophylaxis of opportunistic infections, especially *Pneumocystis carinii* pneumonia and *Mycobacterium avium* complex.

Treatment and monitoring advances

During 1995-97, several sequential developments dramatically changed HIV care. Firstly, there was a greater understanding of the dynamics and pathophysiology of HIV. It was found that throughout most of the disease HIV replicated at an astonishing rate, producing around 10 billion virions daily. The new virions infected available CD4 T cells and other immune targets, causing depletion of CD4 T cells and driving the immune system to increase T cell replication.

Following these revelations, HIV viral load testing was introduced as a new means of assessing the prognosis and response to therapy. (Previously treatment was monitored using the CD4 T cell count and other surrogate markers.) Viral load testing quantified the number of copies of HIV RNA/mL of blood. This test is currently the most accurate and reliable predictor of the rate and likelihood of HIV disease progression.[2]

The third significant development was the introduction of new and more potent antiretroviral drugs. Two new classes of antiretroviral drugs emerged—the protease inhibitors and the non-nucleoside reverse transcriptase inhibitors.

Protease inhibitors are designed to inhibit the HIV protease enzyme which is essential for the production and cleavage of mature infective virions. The first trial of these new drugs (ACTG 229) investigated saquinavir, in combination with zidovudine and zalcitabine. The success of the triple combination arm of this trial led to the accelerated approval of saquinavir.

The non-nucleoside reverse transcriptase inhibitors have a similar mode of action to the nucleoside analogue reverse transcriptase inhibitor class, but prevent HIV replication by directly binding to the reverse transcriptase enzyme. Inhibiting this enzyme prevents the synthesis of a DNA copy of the RNA strand.

HAART

From 1996, the management of HIV underwent substantial change. Drugs from three different classes could now be combined to form more effective treatment regimens. Highly active antiretroviral therapy (HAART) became the new

standard of care for controlling the HIV epidemic in the Western world. There was initial hope that HAART taken continuously for a number of years might lead to the eventual eradication of HIV from the body.

The effectiveness of this new style of treatment was rapidly apparent. Impressive results were obtained from trials of the protease inhibitors. With the use of potent combinations of medication, typically containing one protease inhibitor and at least two other drugs from one or more different classes, there were sharp and sustained declines in the incidence of AIDS defining illnesses, hospitalisations and deaths.[1] The estimated number of AIDS-related deaths in the USA fell nearly 70% from 1995 to 1999 (Fig.1). Hospitalisations and AIDS defining diagnoses fell by 60–80% during this period and the time to diagnosis of AIDS was also extended.[2] Studies in 1999 confirmed that immune reconstitution resulting from HAART was nearly complete and researchers showed that it was safe to discontinue prophylaxis for opportunistic infection when sufficient CD4 T cells had been re-established. The new combined regimens were expensive, but savings from inpatient care and quality life years regained offset treatment costs.

HAART failure

Treatment success did not come without a price and unpleasant adverse effects were relatively common with the new classes of medications. The protease inhibitors often cause gastrointestinal adverse effects such as significant nausea and diarrhoea. Drug interactions between protease inhibitors and other medications were frequent and problematic. The non-nucleoside reverse transcriptase inhibitors had the potential to cause rashes, hepatotoxicity and occasionally Stevens-Johnson syndrome. Treatment regimens with HAART were more complex than monotherapy or dual therapy and typically required numerous tablets to be taken multiple times a day with rigid dosing intervals and restrictions around food. Adherence to these schedules was difficult and needed to be sustained for treatment to be effective.

Fig. 1

This graph shows that when HAART became available in 1996, the outlook for patients with HIV improved dramatically. The number of HIV-related deaths fell as HAART usage rose from zero to almost 80% of patient days (on average, patients with HIV received HAART therapy 80% of days).

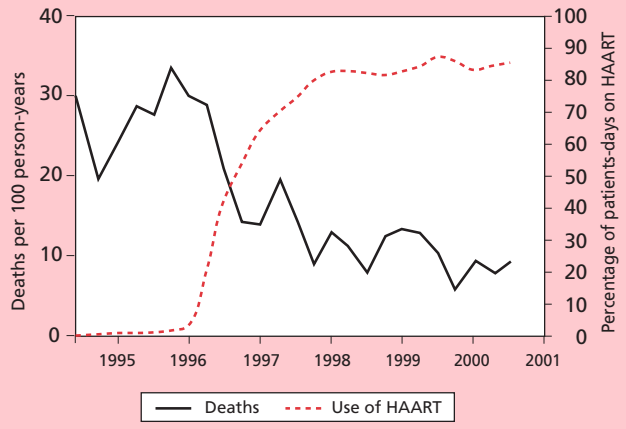

Figure reproduced from AIDS 2002;16:1617-22 with permission from Lippincott Williams & Wilkins.

Within a short period of time less favourable reports emerged that in clinical practice around half of the patients were 'failing' HAART. Treatment failure was shown by the re-emergence of virus, detectable by viral load testing, in the blood of patients who had received HAART for a year or more.[2] Failure rates were highest in those with advanced disease, those who received antiretroviral treatments before HAART was instituted, and those with less than optimal compliance with treatment.

Drug resistance developed to the new classes of antiretroviral drugs, as had already been seen with zidovudine and other nucleoside analogue reverse transcriptase inhibitors. The result of drug resistance was a loss of viral suppression leading to a rise in viral load and fall in T cell numbers, with the resultant risk of disease progression.

Treatment complications

Significant toxicity and adverse effects are associated with antiretroviral therapy. These include:

- lipodystrophy and insulin resistance
- mitochondrial toxicity, lactic acidosis and hepatic steatosis
- osteopenia
- peripheral neuropathy
- myopathy
- nephrolithiasis.

Lipodystrophy, a syndrome of fat redistribution and serum lipid/glucose abnormalities, was first reported in 1998. High concentrations of triglyceride, cholesterol and glucose are found, typically in combination with body fat changes including fat wasting in the limbs, truncal obesity and loss of facial fat. This syndrome occurred most frequently in patients taking protease inhibitors and certain nucleoside analogue reverse transcriptase inhibitors (such as stavudine). Some of the physical manifestations of the condition were obvious and stigmatising, particularly the formation of a 'buffalo fat hump' on the upper back and marked facial wasting. Concerns about the long-term impact of these changes and the potential for an elevated risk of cardiovascular disease and diabetes, further complicated decisions about treatment options.

The current state of play

HIV continues to have enormous global impact, particularly in the developing world. Around 40 million people are infected worldwide and new infections occur at a rate of 14 000 per day. Currently in Australia, approximately 22 100 people are HIV positive and to October 2002, 6184 deaths had occurred due to AIDS.[3] Eradication of HIV by continuous therapy is highly unlikely, due to the very long half-life and latency of some immune cells infected with HIV. No cure is in sight and a preventive vaccination will not be available in the near future.

New drugs within the existing classes of antiretrovirals and further classes of drugs (such as vaccines, fusion inhibitors

Table 1

Risk of developing AIDS in 6 years (%)

HIV viral load (copies/mL)	*CD4 T lymphocyte count (cells/microlitre)*		
	CD4 < 350	*CD4 350-500*	*CD4 > 500*
> 55 000	93	79	67
20–55 000	73	57	50
7–20 000	42	40	26
< 7000	19	22	15

Treatment is recommended when the risk of developing AIDS is greater than 50%.

and co-receptor antagonists) have been developed. These are variously available through trials and special access schemes. Modifications to existing drugs have sought to improve dosing schedules, with once-daily treatments and the combination of up to three drugs in a single tablet. Attention has been focused on the need to improve and maintain compliance to maximise the impact and duration of whatever treatment regimen is adopted. Consequently, there is a need to tailor treatment to suit each individual and the lifestyle they lead.

From the late 1990s to the present time, HIV treatments have come under increasing scrutiny. Long-term treatment with HAART is clearly not straightforward or without consequences. Developing alternative regimens for those in whom treatment has failed, simplifying regimens to improve compliance and managing the wide range of adverse effects is a challenge.

HIV treatment has become increasingly complex and clinicians must confront numerous issues and dilemmas, without a clear consensus on the best treatment strategy to adopt.

Awareness of the complications and adverse effects related to antiretroviral therapy has made many clinicians more cautious about advocating early treatment, in contrast to the 'hit hard and early' approach initially adopted with HAART. The current Australian, American and British guidelines for starting antiretroviral therapy are much more conservative than those released in 1997. Protease inhibitors are now used less frequently in early treatment regimens than they were when HAART first came into vogue and nearly every drug combination included at least one protease inhibitor.

Treatment of symptomatic HIV infection or AIDS extends life and most clinicians would offer therapy in these situations. However, in asymptomatic patients, current recommendations suggest that treatment does not start until the CD4 T cell count falls below 350/microlitre or the HIV load exceeds 50 000 copies/mL. These recommendations are based on the risk of developing AIDS within six years without treatment (Table 1).[4]

In just over 20 years AIDS has grown from a cluster of cases into a substantial global health problem. In the Western world, the disease has changed from being predictably fatal to a chronic manageable condition, for those in whom the drugs work well. In the world's poorest nations, however, little has changed and effective therapy is almost completely unattainable. The epidemic continues to rage out of control and the main concerns are more basic; prevention, diagnosis, access to health care and palliation.

REFERENCES

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4. Kelly M. The state of play: HIV treatment. HIV Australia 2002;1:13-5.

FURTHER READING

AIDSinfo: HIV/AIDS Medical Practice Guidelines. US Department of Health and Human Services.
http://www.aidsinfo.nih.gov/guidelines

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 71)

5. The best combination of drugs for the treatment of HIV infection is unknown.
6. HIV has not developed a resistance to protease inhibitors.

Patient support organisations

National Association of People living With HIV/AIDS (NAPWA)

and

State and Territory AIDS Councils (see page 67)

The National Association of People living With HIV/AIDS (NAPWA) is Australia's peak non-government advocacy organisation representing people living with HIV/AIDS community-based groups from each of Australia's states and territories.

Contacts

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