

## HIV medicine

THROUGHOUT THE WORLD until the mid-1990s, HIV infection was invariably fatal, with a median survival of one to two years after diagnosis of AIDS. Symptomatic HIV disease and AIDS imposed significant burdens on health-care budgets, in addition to the often immeasurable societal costs. Now, for some, the availability of more effective antiretroviral therapies has transformed the HIV/AIDS epidemic. Mortality and AIDS diagnoses have fallen precipitously since widespread introduction of these treatments.<sup>1,2</sup> Evidence to date suggests that the effectiveness of antiretroviral therapy has persisted.<sup>3</sup> Mother-to-child HIV transmission can be effectively controlled, so that in the developed world paediatric HIV infection is rare. In developed countries, antiretroviral therapy is one of the most cost-effective interventions for treatment of a chronic disease.<sup>4</sup> These unequivocal improvements are largely unprecedented for an infectious disease only 20 years old.

However, HIV/AIDS continues to represent a significant global public health crisis. The United States identified HIV/AIDS as a threat to national security, and a special session of the United Nations General Assembly was convened in 2001 to address the epidemic. In the past five years, a clear paradox has emerged. On the one hand is the challenge of sustaining the improved longevity and quality of life for people who have access to effective treatments and care. On the other is the challenge of securing equivalent outcomes in the estimated 95% of HIV-infected people who live in countries that cannot afford antiretroviral therapy. For these 34 million or so people, HIV infection remains a death sentence.

**HIV/AIDS in developed countries.** Combination antiretroviral therapy is not curative. The intent of treatment is to reduce the rate of virus replication, thus forestalling further damage to the immune system and, in most people, facilitating recovery and reducing the risk of life-threatening opportunistic infections or neoplasia. However, effective drug regimens are complex, and adherence is difficult. Ongoing virus replication increases the risk of selecting viruses that are resistant to treatment. As all 15 currently available antiretroviral drugs inhibit only one of two enzymes (HIV reverse transcriptase or protease), the selection of viruses resistant to one drug often carries the additional penalty of cross-resistance to other drugs. This limits the options available for future treatment.

Each antiretroviral therapy has well described acute and chronic toxicities. More recently, clinical observations from Australian researchers implicate these agents in development of a syndrome termed lipodystrophy.<sup>5</sup> Characteristically, patients present with abnormalities in body fat; many have insulin resistance, and some develop type 2 diabetes mellitus. The increased risk of cardiovascular disease arising from the glycaemic abnormalities may be compounded by hyperlipidaemia of an atherogenic profile. As all HIV-infected patients will need lifelong treatment with antiretroviral agents, these newly described toxicities could be a

significant impediment to continued successful clinical outcomes.

There is an urgent need for new therapies that inhibit HIV replication at new sites (such as HIV integrase and virus-cell fusion), that do not select for cross-resistance to other antiretrovirals, and that are not associated with metabolic toxicities. The potential role of immunotherapies (eg, interleukin 2 and therapeutic vaccines) warrants continued investigation, as they may be unaffected by cross-resistance to antiretrovirals and may have less long term toxicity.

**HIV/AIDS in developing countries.** The scale of the HIV/AIDS problem in the developing world is alarming. Life expectancy in some countries will be reduced, in the absence of HIV treatment, by as much as 50%. This effectively negates all gains achieved through public health programs in these countries over recent decades. Addressing the inequities of healthcare around the world will take more than biomedical solutions — not only do drugs need to be made available more cheaply, but healthcare professionals need training, education, support and resources. In addition, treatment must be seen in the context of a comprehensive prevention and care framework. We need to revisit how medical research might contribute to resolving this enormous crisis. As part of such an approach, evaluations are being planned of simplified methods for clinical monitoring of HIV disease, deferred treatment strategies and abbreviated therapy regimens.

We can be optimistic that research will deliver at least a partially effective prophylactic vaccine, but even optimistic estimates suggest this will take seven to 10 years. Every day about 15 000 people are infected with HIV, of whom 95% are in developing countries. In the seven to 10 years that a vaccine may take to develop, some 35 million people will be facing a reduced lifespan unless there is substantial change in their access to proven treatments. For the remaining 5% of HIV-infected individuals, the challenge is to develop new treatments.

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