Antiretroviral therapy has revolutionised the management of human immunodeficiency virus (HIV). Advances in research leading to the development of combination antiretroviral therapies (ARTs) have led to significant decreases in AIDS-related morbidity and increases in life expectancy for individuals with access to treatment. The goal of ‘getting to zero: zero AIDS-related deaths’ now is within reach. Globally nearly 10 million people have access to ART; however, further rollout efforts are required to reach the 34 million people living with HIV sustainably over the long term. Changing paradigms see a broader scope for ART with a push towards earlier initiation, and even pre-exposure prophylaxis, with public health goals of preventing new infections.

In Australia, collaborative research efforts, bipartisan political will and subsidised medication costs have allowed around 13 000 people to be maintained on antiretroviral therapy. Despite this, the challenges of continuous lifelong suppressive therapy remain, as currently there is no cure. Poor adherence can lead to disease progression and drug resistance, limiting future treatment options. Antiretroviral resistance in Australia appears to have been stable, but changing epidemiology and evolving viral subtypes may impact these rates. This article will reflect on the advances in antiretroviral research, rollout and resistance in our region.

Australia has benefitted from early access and rollout of ART, and now has one of the highest treatment rates in the world, with around 50–70% of those diagnosed receiving treatment, and 85–95% of those with a suppressed viral load (see Figure 1)\(^1\). Progression to AIDS has been halved, deaths have fallen by 80%, and life expectancies approaching the general population can now be expected\(^2\)–\(^4\).

Currently available ART targets five key pathways of the HIV life cycle (see Figure 2). Reverse transcriptase inhibitors prevent transcription of viral RNA to DNA, preventing viral replication. In 1987, treatment was limited to monotherapy with a nucleoside reverse transcriptase inhibitor (NRTI) until the availability of dual NRTI therapy in 1992. The release of protease inhibitors (PIs) in 1995 allowed dual class highly active antiretroviral therapy (HAART) that has transformed the management of HIV. They remain a component of one of the preferred initial treatment regimens. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are also an important part of the antiretroviral landscape, and are currently also recommended as part of the preferred first line regimens for naïve patients\(^5\).

The longevity of earlier regimens was limited by significant toxicities, leading to poor adherence and ultimately treatment failures. Newer combination therapies are utilising novel classes with unique mechanisms of action and favourable side effect profiles. The fusion inhibitors were FDA approved in 2003 and offered hope for those with drug resistant virus, but their widespread use was restricted by the need for subcutaneous injection. They act by inhibiting the viral cell membrane from fusing with host cell, preventing entry into the host CD4+ T cell (Figure 2). Development of the co-receptor antagonists, approved in 2007, was a step towards personalised medicine, with targeted therapy available to patients whose virus preferentially used the CCR5 co-receptor for host cell entry. The rollout of this class was hampered by the need for a highly specialised test (Trofile® co-receptor tropism assay), initially only available in the United States with a lengthy turnaround time. The newest
The integrase inhibitors, have impressive effects on viral kinetics, appear to be well tolerated, and are now included in the Australian guidelines as a preferred regimen for treatment of naïve patients. They act by competing with viral DNA for binding with integrase, preventing integration of virus into host cell DNA. This five class armamentarium of ART, available in high-income countries, including fixed dose combinations (FDCs) has allowed HIV to be managed as a chronic disease with a single daily pill.

The sound evidence base for the development and rollout of ART has been a result of international collaboration, pharmaceutical engagement and participation in clinical trials. Australian clinical and laboratory researchers have been involved in development of almost every antiretroviral available on the market. Much has been learnt from cohort studies, including descriptions of the natural history of HIV, however long-term randomised controlled trials (RCTs) with clinical endpoints were instrumental in providing definitive evidence for ART. As newer drugs became rapidly available, RCTs needed to yield results in a timely manner, rather than waiting for clinical endpoints. This meant that the laboratory marker of suppressed viral load was used as a surrogate endpoint allowing shorter follow up periods of up to 48 weeks. As a result, diagnostic laboratories play an important role in providing HIV viral load monitoring, now recommended as the preferred method to diagnose and confirm treatment failures. In low-income countries, with access to only three or four classes of ARVs, access to viral load monitoring is not routinely available, hence clinical and CD4 count monitoring may be used to diagnose treatment failure. In this setting, virological failure is more difficult to detect and assess, resulting in heterogeneous failure rates of up to 20%, contributing to the risk of emerging resistance on a global scale.

Subsidised treatment is available for Medicare eligible Australian citizens and permanent residents via the section 100 scheme of the highly specialised drugs program of the National Health Act 1953, however access is not universal. For approximately 450 Medicare ineligible temporary residents in care, the options include purchasing full cost ART (around $12 000/year), enrolment in clinical trials or sourcing generic ART from overseas. This is often prohibitive, and as a result less than 50% of these patients have an undetectable viral load, increasing transmission risk. Programs such as the Australian HIV observational database Temporary Residents Access Study (ATRAS) that provide compassionate access ART have increased the proportion with viral load suppression, which minimises the risk of transmission. Despite access to ART (for those Medicare eligible), there are ongoing challenges in maintaining lifelong suppressive combination therapy, including managing chronic toxicity and ensuring adherence.

Resistance can develop to every class of antiretrovirals, ultimately leading to treatment failure, cross resistance and reduced effectiveness of first line drugs. Combination triple therapy aims to increase the threshold to resistance by including a regimen of at least two classes, usually comprising a ‘backbone’ of reverse transcriptase inhibitors paired with another agent, however this dogma may be challenged in the future.

The introduction of HAART in 1996 was accompanied with a precipitous decline in the rate of RT mutations, with no increases...
in PI resistance. However, the locally predominant subtype B mainly occurs in men who have sex with men and still comprises the majority of new infections in Australia overall. Ongoing surveillance of changing subtypes and patterns of resistance, particularly in higher burden regions of Australia is imperative.

In other regions, such as Asia and Africa, the availability of resistance testing is more limited and virological failures rates due to resistance are much more varied. In the setting of failure of a first line regimen in resource limited countries, a recent Australian led study has demonstrated that a novel combination of a boosted PI and integrase inhibitor is non-inferior to the WHO recommended nucleotide and PI based regimen. While providing much needed clinical trial data for the one million people in low to middle income countries requiring second line treatment, this novel regimen currently is not cost effective in some of these countries where ART is provided through donor or publicly funded programmes.

The scope for ART is broadening to settings beyond treatment of the individual living with HIV. ART for post exposure prophylaxis, while not TGA licensed for this indication, has been available in Australia for high risk occupational and non-occupational exposures. Additionally, non-prescribed informal use for recreational or pre exposure prophylaxis has been reported in HIV negative people, sometimes during high risk behaviour.

Treatment paradigms are shifting from being solely focused on the outcomes of the individual living with HIV. ART for post exposure prophylaxis, while not TGA licensed for this indication, has been available in Australia for high risk occupational and non-occupational exposures. Additionally, non-prescribed informal use for recreational or pre exposure prophylaxis has been reported in HIV negative people, sometimes during high risk behaviour.

One consideration is revising pre-existing dose guidelines, in the form of dose optimisation studies that re-evaluate the lowest effective dose, which on a global scale can result in significant cost savings. The ENCORE1 48 week analysis demonstrated non-inferiority of 400mg dose of the NNRTI efavirenz compared to the standard 600mg dose, with significantly less associated toxicity.

Figure 2. Mechanism of action of available classes (boxed text) of antiretrovirals. Image has been reprinted with permission from Macmillan Publishers Ltd: [Nat Rev Drug Dis] (De Clercq et al.; 6(12): 1001–1018.), copyright (2007).
Studies such as these breathe extended life into currently available ARVs. This broader public health approach to treatment must be balanced with the benefits of treatment for the individual patient. Despite all the advances in antiretroviral treatment over the years, one of the most fundamental questions remains unanswered: when to start treatment? The 2013 WHO guidelines have been edging towards earlier treatment, and now recommend ART initiation at CD4 count >350 and ≤ 500 cells/mm³ regardless of clinical stage. When faced with an individual patient, the decision to start earlier must be balanced against a commitment to taking a lifelong medication. The Strategic Timing of AntiRetrovirals Trial (START) due for completion in December 2015 aims to answer this question (NCT00867048).

The development of ART has led to significant improvements for individuals living with HIV, and could lead to an AIDS free generation. On a community level, the rollout of ART has had significant impacts on transmission and rates of new infections. The current goal of 'getting to zero' requires further ART rollout efforts and healthcare support spending from a shrinking funding pool.

The following references are needed to bridge this gap.

References


Biographies

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