

HIV THERAPY

past, present and future

Since the identification of HIV in 1983 and licensing of zidovudine (AZT), the first antiretroviral agent, in 1986 we now have more than 20 agents available for HIV treatment from five drug classes. A patient starting therapy for the first time today can start on one pill once a day, a huge improvement to the complex regimens that characterised earlier stages in the history of HIV treatment. In addition, the past year has seen newly licensed drugs from both existing and new drug classes which have shifted the treatment paradigm for highly experienced individuals with high levels of drug resistance. However, the majority of HIV-infected subjects worldwide do not have access to the multitude of drugs we enjoy in the developed world; last year alone more than two million adults and children died of AIDS-related causes. This article will review recent advances in HIV treatment and discuss future challenges that the research community, pharmaceutical industry, healthcare providers and HIV-infected patients will need to address as time goes on.

HIV is a retrovirus meaning it is an RNA, rather than DNA, virus but has a unique enzyme (reverse transcriptase) enabling the transcription, in host cells, of viral RNA into DNA. HIV replication results in progressive immune decline; the resultant abnormalities are manifold but most clearly manifested as a reduction in CD4+ T-helper cells which are crucial in orchestrating the immune response. Monitoring CD4 cell numbers remains the primary way of monitoring HIV-related immune decline and deciding when to commence therapy.

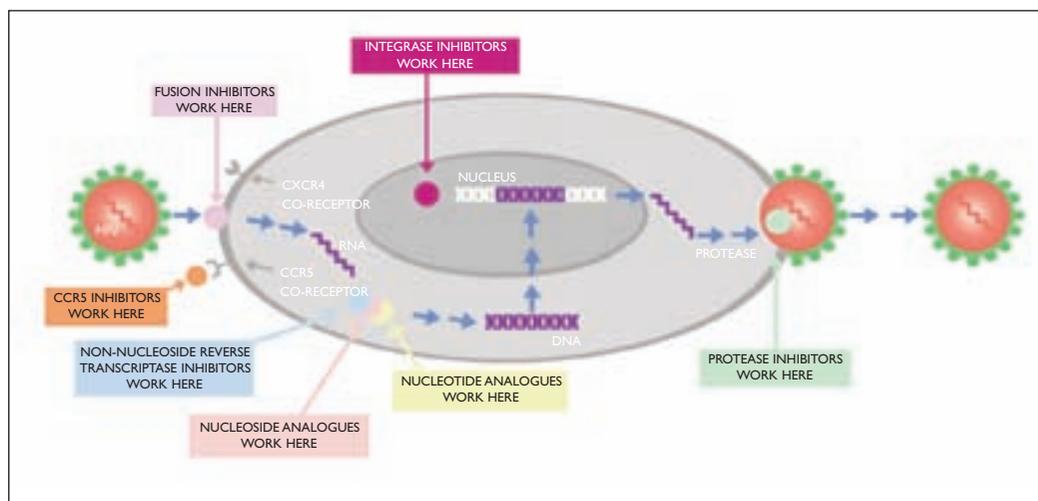
HIV entry: HIV gains entry to human cells via a cell surface molecule, the CD4 receptor, and then one of two additional surface molecules or co-receptors, CCR5 or CXCR4. Most transmitted HIV uses CCR5 receptors only but with advancing disease the proportion of CXCR4-using virus

increases. Drugs that block CXCR4 are in early stages of clinical development but maraviroc, a CCR5 blocker, was licensed at the end of last year for treatment-experienced patients. This is the first ARV that acts on a host cell, rather than a viral, target precipitating concerns regarding the long-term safety. However, some individuals naturally lack CCR5 receptors and although at increased risk of some conditions (eg West Nile virus), they are at a lower risk of others (eg rheumatoid arthritis); there do not appear to be any serious consequences of having no or reduced levels of CCR5. Initial signals from clinical trials suggested maraviroc and other CCR5 antagonists may be associated with increased malignancy rates but these have not been borne out with longer follow-up. After co-receptor binding the process of fusion between HIV and the host cell is triggered. It is at this fusion step that enfuvirtide, the first licensed entry

By Dr Laura Waters

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Figure 1
Illustration of HIV lifecycle
within target cell and drug
targets



inhibitor (2003), acts. Enfuvirtide was previously a crucial part of ‘salvage’ regimens and helped patients with high levels of drug resistance achieve viral suppression.

Reverse transcription: Once HIV gets into host cells it uses its reverse transcriptase enzyme to create a DNA copy of the viral RNA. Two groups of drugs inhibit this enzyme, nucleosides analogues (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). NRTIs were the first ARV class to be developed and remain a cornerstone for most regimens.

Integration: The next step in the HIV replication cycle is for the HIV-DNA to be integrated into the host cell genome, a step catalysed by the viral integrase enzyme. Raltegravir is a first-in-class integrase inhibitor that was licensed for treatment-experienced patients at the end of last year.

Packaging: Following integration and the production of viral components by the host cell, a number of processes take place during which viral particles are assembled and released. A key part of the packaging process is the viral protease enzyme, another important drug target. Protease inhibitors play a key role at all treatment stages.

The sites of action of current ARVs are summarised in **Figure 1**.

A potted history

The virus responsible for Acquired Immune Deficiency Syndrome (AIDS) was identified in 1983. By 1986 AZT, a nucleoside analogue (NRTI) originally developed as an anti-cancer agent, had

been licensed. However, it quickly became apparent that NRTI monotherapy resulted in only short-term immunological benefits. Dual NRTI therapy only prolonged the inevitable development of drug resistance and it was not until the advent of a second ARV class, protease inhibitors (PI), in 1995 that truly potent regimens could be created. PIs heralded the era of ‘highly active antiretroviral therapy’ or HAART and the majority of patients who could tolerate these combinations could expect to achieve virological suppression and subsequent immune recovery. The developments in ARVs were reflected in the dramatic reduction in HIV-related morbidity and mortality secondary to durable responses to treatment (**Figure 2**).

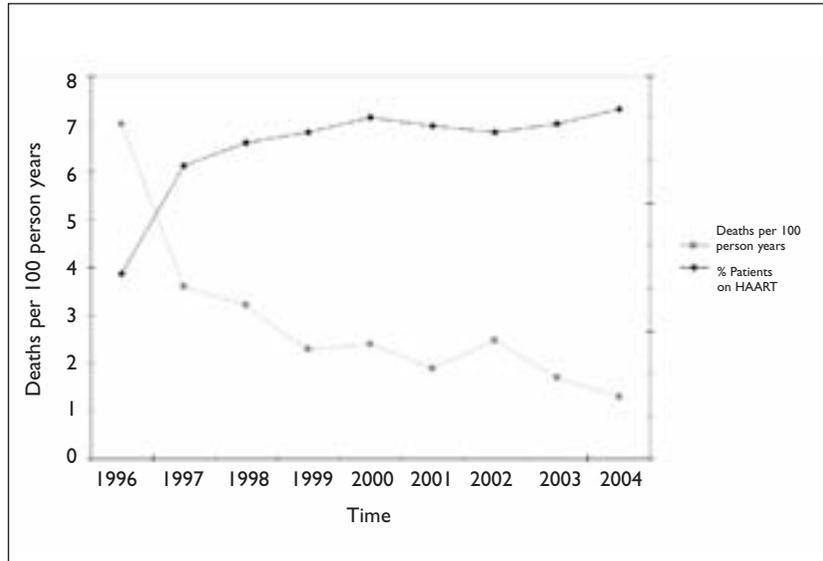
However, early PI-based regimens were associated with high pill burdens, complex dosing schedules and high levels of toxicity including severe diarrhoea, kidney stones and skin disorders. In 1998 a third ARV class became available, the non-nucleoside reverse transcriptase inhibitors (NNRTIs). NNRTIs offered simpler dosing and fewer gastrointestinal side-effects than the PI class and remain first choice for first-line therapy in the UK today. 2000 saw the advent of PI boosting; high pill numbers and frequent dosing were necessary to maintain adequate plasma concentrations of PIs. The discovery that low doses of ritonavir could be used to boost levels of other PIs via an interaction with the hepatic cytochrome p450 system revolutionised PI therapy enabling fewer pills and less frequent dosing. In addition, secondary to the higher and more stable drug levels achieved, boosted PIs are associated with very low levels of resistance, even after virological failure, which preserves treatment options. The high genetic barrier of PIs make them a good choice for poorly adherent and irregularly attending patients.

We now have more than 20 licensed agents from 5 classes available for HIV therapy:

- NRTIs
- NNRTIs
- PIs
- Entry Inhibitors
 - Fusion inhibitors
 - CCR5 antagonists
- Integrase Inhibitors

The timeline of drug development is illustrated in **Figure 3**.

Ultimately, the goal of treatment is to suppress viral replication. In practice, this means suppressing plasma virus to levels below the lower limit of detection for routine HIV-RNA assays, most commonly less than 50 copies/ml. Viral suppression subsequently enables immune recovery as measured by an increase in circulating CD4 cells. However, current agents target only activated cells meaning that HIV remains locked in latent T-cells and eradication of HIV is not currently possible. Small trials using agents that activate latent cells, such as sodium valproate, have yielded conflicting, and generally disappointing results. In addition much of the HIV-mediated immune damage occurs in the very early stages of infection; a dramatic reduction in intestinal CD4 cells is observed during



the initial weeks and reconstitution may not occur despite successful suppression of plasma viraemia.

Consensus guidelines universally recommend a combination of three drugs, two NRTIs and an NNRTI or ritonavir boosted PI (PI/r) for initial therapy for the majority of patients. The British HIV Association (BHIVA) guidelines express a clear preference for efavirenz, an NNRTI, over a PI/r. Nevirapine, the other licensed NNRTI

Figure 2
Mortality and HAART use over time (ref: Palella et al. J Acquir Immune Defic Syndr 2006;43:27-34)

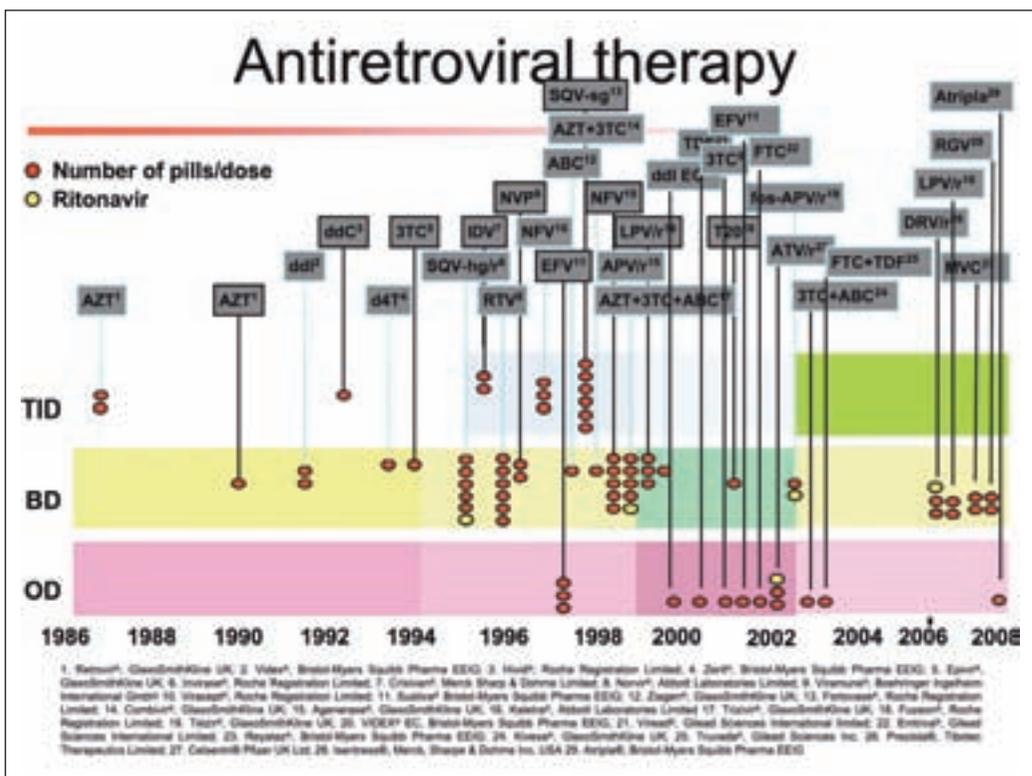


Figure 3
Timeline of ARV development

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remains an alternative to efavirenz for patients with CD4 counts that fall within its prescribing restrictions (nevirapine is associated with hepatotoxicity and cutaneous reactions that are more frequent in patients with higher CD4 cell counts).

Theoretically if patients are given a drug regimen containing three fully active drugs, and take their medication on time, every day they will maintain viral suppression for an indefinite period of time. In reality, maintaining near perfect adherence is unrealistic for most individuals and evidence shows that adherence declines over time. Adherence is clearly linked with drug tolerability and several studies have demonstrated that the main reason patients discontinue therapy or miss doses is side-effects. Although tolerability profiles have improved over the years, no agent will be side-effect free and there will always be individuals who need to switch away from agents for tolerability and toxicity reasons.

NRTIs

Fixed-dose combinations (FDC) of NRTIs have contributed greatly to improvements in ARV pill burden. Four fixed-dose combinations of NRTIs are licensed including two that are recommended by the BHIVA guidelines for first-line treatment: Truvada® (tenofovir + emtricitabine) and Kivexa® (abacavir + lamivudine). The other FDCs, Combivir and Trizivir, both contain AZT which has been associated with lipoatrophy a potentially painful and stigmatising condition. Current treatments for lipoatrophy are limited so, although AZT remains a first choice NRTI during pregnancy, it is no longer a preferred option in most guidelines. Lamivudine and emtricitabine are very similar agents with a low rate of adverse events; the main difference between boils down to tenofovir vs abacavir. The key tenofovir-related toxicities are renal and bone. Tenofovir renal toxicity is classically a proximal tubular defect – in clinical trials approximately 1% of patients experience renal dysfunction which is reversible on cessation of the drug. Tenofovir use has resulted in an increase in renal monitoring in HIV out-patient settings which has revealed mild renal abnormalities to be common, including among non-tenofovir-treated patients. In terms of bone toxicity there have been case reports of osteomalacia type events and in trials tenofovir is associated with a small, non-progressive reduction in bone mineral density. The main treatment-limiting side-effect of abacavir was hypersensitivity (HSR), affecting 5-8% of patients. The discovery that a genetic polymorphism was strongly predictive of HSR led to the introduction

of a genetic screening test (for HLA-B*5701); by withholding abacavir from subjects testing positive the rate of HSR has been dramatically reduced (no confirmed cases in a large clinical trial and around 1% in real life). The near elimination of HSR and the perceived complexity of renal monitoring led to a shift toward Kivexa for first-line treatment until two recent studies. The D:A:D Study, a large European cohort, showed an unexpected increased in heart attack risk associated with recent abacavir use (90% increase compared with other combinations); the mechanism remains uncertain but many clinics are switching their high cardiovascular risk patients away from abacavir and shifting to tenofovir for new patients. In addition a large US Study, ACTG-5202, randomised more than 1,800 patients to Truvada- or Kivexa-based therapy. An interim safety analysis revealed significantly higher rates of virological non-response on Kivexa for patients with a baseline viral load more than 100,000 copies/ml. This led to the unblinding of patients with high baseline viral loads and anecdotally has contributed to the shift away from abacavir for first-line treatment.

NNRTIs

To date two NNRTIs have been licensed, efavirenz and nevirapine. As discussed previously, nevirapine use is somewhat limited by CD4 restrictions hence efavirenz is the first choice in the BHIVA guidelines. Efavirenz is associated with a degree of CNS toxicity (bad dreams, insomnia, anxiety) in around 50% of patients; these are transient for most but can be severe or persistent for some. Pipeline NNRTIs, including the soon to be licensed drug etravirine, may provide an alternative for patients needing to switch away for CNS toxicity reasons. A major weakness of current NNRTIs is their low genetic barrier to resistance; just one mutation can lead to cross-class resistance so many clinicians will avoid NNRTIs for patients likely to have low levels of adherence. The investigational second generation NNRTIs etravirine (or TMC-125) and TMC-278 have higher barriers to resistance (three mutations are required to confer reduced susceptibility to etravirine) and select for mutations more slowly *in vitro*. In practice, like their older counterparts, all NNRTIs require support from other agents.

The 'three in one' pill

The end of 2007 saw the licensing of Atripla®, a FDC of tenofovir, emtricitabine (ie Truvada) plus efavirenz. Not only is this the first licensed combination of two classes (NRTI + NNRTI), it is the first, and hopefully not the last, collaboration

between two pharmaceutical companies: Gilead Sciences (Truvada) and Bristol-Myers Squibb (efavirenz). A decade ago the prospect of one pill once a day seemed unlikely but now, thanks to improvements in drug formulations and the joining of two pharmaceutical companies, it is a reality. Atripla is widely used in the US and increasingly used across the UK and, despite the fact that first-line therapy had already been condensed to two pills once a day, is proving very popular with patients. We are unlikely to see any further reduction in dosing for a long time but already TMC-278 has been studied as a depot injection and if other agents can be formulated in the same way this could one day be the next simplification (Figure 4).

Protease inhibitors

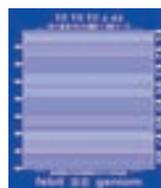
As previously discussed the introduction of PI boosting allowed simpler PI dosing schedules; unboosted PIs are generally now not recommended. Boosted PIs have a high genetic barrier to resistance meaning that, generally, several mutations are required to confer significant drug resistance. The potency of boosted PIs is such that they can be used successfully as monotherapy. Unlike other drug classes (such as NRTIs, NNRTIs and integrase inhibitors) that, if used as single agents, would result in rapid resistance development and treatment failure, PIs can adequately suppress virus without additional support. This works best in an induction-maintenance manner, ie when patients with viral suppression on a drug combination switch to monotherapy; trials so far suggest that PIs work less well if used as monotherapy initially. PI monotherapy is a useful option for poorly adherent patients or those experiencing toxicity from agents in other classes. Despite improvements in dosing, PIs tend to be associated with gastrointestinal (GI) and metabolic side-effects including hypercholesterolemia. Newer PIs such as darunavir and particularly atazanavir have better GI profiles compared to older PIs such as lopinavir/ritonavir; atazanavir also has a better lipid profile than other PIs in treatment-naïve, treatment-experienced and patients switching therapy. Whether these cholesterol differences translate to clinically meaningful benefit remains to be seen and one study showing significant lipid improvements showed minimal change in Framingham risk score when switching to atazanavir. Atazanavir is currently the only PI licensed for once daily dosing in Europe but boosted darunavir, although licensed only for twice daily use in treatment-experienced patients, is increasingly being used once daily and a recent trial supports this. The initial darunavir studies were performed



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Figure 4

Right: A typical regimen in 1996: Stavudine, lamivudine, indinavir, 10 pills, TDS
Far right: An option in 2008: Atripla, one pill once a day



in patients with extensive treatment histories and resistance and yielded previously unseen rates of viral suppression for this difficult to treat group. The resistance profile of darunavir is such that the majority of viral strains exhibiting resistance to other PIs retain darunavir susceptibility. The concern that earlier use of darunavir will 'waste' this agent has not been supported by the, admittedly limited, data we have so far. Patients using darunavir second-line remained susceptible to other PIs and a significant proportion were still sensitive to darunavir too. The fact that few patients failing boosted PIs, particularly darunavir, develop detectable mutations makes it difficult to predict the long-term impact. Research into other mechanism of resistance is ongoing and may explain why patients fail PIs with no discernible resistance to them. Tipranavir is another PI designed to treat highly resistant patients but its use is limited by high rates of GI and hepatic toxicity. Tipranavir requires boosting with higher ritonavir doses than other PIs (200mg twice a day) and although unsuitable for early lines of therapy (due to toxicity) it has a distinct resistance profile from darunavir and remains valuable for those individuals with mutation patterns that support its use.

Integrase inhibitors

Raltegravir is the only licensed agent in this class. In highly experienced patients the use of raltegravir with other active agents led to viral suppression rates of up to 90%, comparable to those seen with first-line regimens. Although currently licensed for highly experienced patients only, raltegravir has been studied as a first-line option and left to 48-week viral suppression rates almost identical to efavirenz (each with a tenofovir/lamivudine backbone). One differ-

ence was that raltegravir led to faster rates of viral suppression than efavirenz; again, the significance of this is uncertain but it has been suggested that faster suppression shortens the time that virus is replicating under drug pressure and may therefore limit the emergence of future resistance. This remains to be seen. As well as high efficacy, raltegravir has, so far, proved to be a very safe and well-tolerated agent with no excess of serious side-effects over placebo in the experienced trials and a better CNS toxicity and lipid profile than efavirenz in the treatment-naïve study. Obviously it is early days and past experience has taught us that it can take years for adverse events to manifest. Elvitegravir is an investigational integrase inhibitor that has also shown high rates of efficacy in highly treatment-experienced subjects. Unlike raltegravir it, like PIs, required ritonavir boosting. Ritonavir itself is at least partially responsible for some of the adverse events and toxicities associated with boosted PIs. In treatment experienced patients elvitegravir is likely to be used with a PI (therefore ritonavir) anyway but the need for ritonavir boosted may limit its potential use first-line.

Entry inhibitors

As previously discussed, enfuvirtide was previously a cornerstone of salvage therapy but is now rarely used. As an injectable agent it has, for now, been largely superseded by newer agents but may yet experience a renaissance as some patients inevitably experience failure on the current choices. Maraviroc shows significant benefit over placebo in treatment-experienced subjects and is licensed for this indication. In a treatment-naïve trial maraviroc + Combivir failed to prove non-inferiority to efavirenz + Combivir (using 10% confidence limits) for the below 50 copies/ml end-point. Although it

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was better tolerated, maraviroc was associated with higher numbers of virological failures than efavirenz; most efavirenz 'failures' were, in fact, discontinuations secondary to side-effects. In order to determine susceptibility to maraviroc a tropism test must be performed to see if an individual harbours any CXCR4 using virus; CCR5 blockers only work in patients with only CCR5 tropic virus. A major limitation of the initial tropism test (a phenotypic assay) was a relatively low sensitivity for CXCR4 strains; it could only reliably detect CXCR4 using virus at levels of 10% or more. An enhanced assay enables CXCR4 virus to be detected when present at proportion as low as 0.1% to 0.3% and may better identify patients for whom maraviroc is likely to be an option. At least some of the patients entered in the maraviroc first-line study may have been excluded with the more sensitive test. Vicriviroc is the next furthest along in development of the CCR5 antagonists and has similarly yielded impressive results compared to placebo in experienced populations. It also has the advantage of once daily dosing (maraviroc is twice daily).

Future challenges

A key challenge is how to achieve and maintain high levels of adherence over long periods of time. A large study comparing continued therapy with CD4-guided treatment interruption (the SMART Study) was a nail in the coffin for intermittent treatment strategies after higher rates of HIV and non-HIV-related illness and death were observed. Although carefully planned treatment interruptions can still be utilised on an individual basis, the consensus is that, once started, HIV treatment is for life. Further improvements in toxicity rates and drug forgiveness (the ability to miss doses without resistance and loss of efficacy) may build on developments to date and enable us to accept that long-term, high adherence is difficult to achieve and therefore allow us to work around it. In addition, accumulating evidence that starting therapy at higher CD4 counts than we are currently has led to a shift in guidelines to reflect this. Of course, starting earlier means a longer time on treatment.

Long-term therapy means managing long-term side-effects, the most important of which is probably cardiovascular disease (CVD). We know that HIV *per se*, PIs and possibly abacavir are associated with an increased risk of CVD compared with other agents but further work is needed to elicit why and what can be done to limit this. Studies measuring markers of cardiovascular disease (such as markers of inflammation, coagulation and endothelial function) demonstrate differences

between HIV-negative and positive subjects and ARV-treated and untreated patients. In the future, routine monitoring of cardiovascular markers and other organ systems may better define when and what treatment to start.

In general, starting therapy late is associated with worse outcomes and the fact that, at present, around one in three HIV-infected patients in the UK remain undiagnosed means improving HIV detection is crucial. Outreach services and finger-prick HIV tests that provide near instant results have gone some way to increase testing but ultimately only the destigmatisation and normalisation of HIV testing will diagnose the undiagnosed.

Conclusion

The rate of HIV drug development is almost unprecedented in terms of the progress made in such a relatively short period of time. The speed with which new agents come into, and fall out of, favour is rapid compared to many other disease areas. Because of this HIV has been transformed from an essentially terminal condition to a chronic, manageable one and individuals who have access to therapy can expect near normal life expectancy. Unfortunately, for most of the HIV-infected population worldwide this is not a reality and much work, on many levels, is required to address this.

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