

## Problems – Theoretical and Real – In the Drug Treatment of HIV-AIDS

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Human immunodeficiency virus (HIV) infection is the most important infectious disease of our time. Likewise, the availability of highly effective therapy for HIV represents one of the greatest accomplishments of drug research and development in modern times. Antiretroviral therapy (ART), usually comprising a combination of 3 drugs that act against one or more steps in the viral life cycle, has transformed HIV from a disease that was almost universally fatal as recently as the mid-1990s, into a manageable chronic disease which has a virtually normal life expectancy.

Surprisingly, this miraculous advance in HIV therapy is under-appreciated and sometimes actively downplayed. I have heard several theoretical objections raised in Singapore: firstly, that ART is not a “cure” for the disease; secondly, that the long-term efficacy is unknown; and thirdly that it is not proven to be cost-effective in Singapore. The first of these contains an element of truth because ART suppresses but does not eradicate the virus. As a consequence, therapy needs to be continued for life, but this is no different from medication (e.g., insulin) for other chronic diseases, and should not detract from the effectiveness of ART. Approaching this objection semantically, as it deserves, ART does in fact reverse permanently the HIV-induced state of acquired immunodeficiency, i.e. it does “cure” AIDS. Indeed, if started early in the course of disease, it can do even better than cure: it can *prevent* the development of AIDS.

As for the second concern, it is true that there is no long-term efficacy data beyond 15 years of ART use. However, it is now accepted beyond reasonable doubt that treatment effects will be sustained long-term. Even if we were to find that ART starts to fail in stable patients when they reach their 15<sup>th</sup> anniversary of therapy (which is biologically implausible), most would agree that those extra 15 years of good quality life are well worth having. Addressing the third objection, ART has been shown to be cost effective in rich and poor countries alike, and there is local data indicating that Singapore is no exception.<sup>1</sup>

There are, however, some real limitations of ART. Although therapy markedly improves outcome at whatever

stage of HIV disease it is started, the outcome is less good when it is started in patients who already have AIDS or are severely malnourished.<sup>2</sup> Restoration of the immune system with ART does take time – months to years – and patients starting ART late have a period where they remain vulnerable, albeit at reduced risk, to life-threatening opportunistic infections and other disease complications.<sup>3</sup> Financial constraints have meant in the past that many patients in Singapore have chosen (or have had no choice but) to delay starting ART, although this has now been mitigated in part by the availability of cheaper ART from other countries in the region. Nowadays, the principal reason that ART is started late in Singapore is that many patients wait until they have advanced disease, and develop an opportunistic infection, before they present for care and get tested for HIV.<sup>4</sup> There are many explanations for the reluctance of Singaporeans with HIV risk factors to come forward for earlier testing, but the misconception amongst individuals that there is no advantage to them of knowing their HIV status is an important contributing factor. This is one reason why the message about the effectiveness of ART needs to be presented unambiguously (and mechanisms put in place to ensure access to ART for those who test positive but cannot afford the full cost of the drugs).

More than 20 antiretroviral drugs are licensed for use in various combinations, making it possible to construct a number of ART regimens that are easy to take and are very well tolerated. The first-line therapy currently favoured in most developed countries (a combination of tenofovir, emtricitabine and efavirenz) is now available as a single pill taken just once a day. It has few side effects, apart from neuropsychiatric disturbances that usually abate after the first few days. The range of therapeutic options means that intolerable side-effects need no longer represent a major problem with ART.

One of the most commonly used first-line ART regimens in Singapore has been a combination of stavudine, lamivudine and nevirapine, which has become popular mainly because patients have managed to access this as a

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cheap generic combination from Thailand. It is taken as a single pill twice daily, and is highly effective. It is well tolerated in the short-term apart from a nevirapine-related rash (that is severe and treatment-limiting in less than 5% of patients) and hepatotoxicity (mainly in women with early disease, in whom the drug is avoided). The main problem in the long-term is the development of facial (and other peripheral) lipoatrophy, which can be stigmatising and distressing to some patients and which is closely related to the stavudine component of the regimen.<sup>5,6</sup>

Other combinations with fewer long-term side effects will become increasingly used in Singapore as the range of affordable (generic) drug options increases in surrounding countries, or local treatment becomes more financially accessible. Drug-drug interactions may sometimes present a challenge. Interactions are particularly likely to occur when patients need ART and concomitant therapy for tuberculosis, but with expert drug management a successful therapeutic outcome for both diseases is entirely feasible.

A high level of adherence to ART is absolutely critical for therapeutic success. Even a few missed doses can result in rebound of viral replication and the development of drug resistance. Although maintaining such high levels of adherence (at least 90% to 95% of doses taken on schedule) proves impossible for some patients with competing priorities in their day-to-day lives, in my experience (shared by many colleagues) the vast majority of HIV patients in Singapore are able to meet this challenge. Appropriate counselling at the start of therapy and enquiring about missed doses at each follow-up visit in order to reinforce the importance of adherence are the keys to success. I recall patients who reported that they had *never* missed a dose, even after many years of treatment. With such admirable levels of adherence, treatment is almost invariably successful.

A degree of sophisticated and expensive laboratory monitoring is used in most developed countries in conjunction with ART, such as sequencing the patient's virus prior to starting therapy to detect transmitted drug resistance and monitoring levels of HIV in the blood ("viral load") every few months during treatment, in order to detect virological rebound early. However, transmitted

drug resistance is not common in Singapore, making baseline genotyping largely unnecessary.<sup>7</sup> It is likely that HIV can be managed adequately without intensive viral load monitoring in patients who adhere well to therapy. Also, there may be little point in measuring viral load frequently to detect early rebound in patients who will choose to delay the switch to a (usually considerably more expensive) second-line regimen after failure is detected.<sup>8</sup>

In summary, the message about the benefits of ART needs to be widely and unambiguously disseminated in order to encourage those with HIV risk factors to come forward for early testing and gain access to treatment. Contemporary ART regimens are highly effective, easy to take and have few side effects. Problems with HIV treatment are more theoretical than real.

#### REFERENCES

1. Paton NI, Chapman CAT, Sangeetha S, Mandalia S, Bellamy R, Beck EJ. Cost and cost-effectiveness of antiretroviral therapy for HIV infection in Singapore. *Int J STD AIDS* 2006;17:699-705.
2. Paton NI, Sangeetha S, Earnest A, Bellamy R. The impact of malnutrition on survival and immune response in patients starting antiretroviral therapy. *HIV Med* 2006;7:323-30.
3. Zhou J, Paton NI, Ditango R for the TREAT Asia HIV Observational Database. AIDS-defining illness diagnosed within 90 days after starting highly active antiretroviral therapy among patients from the TREAT Asia HIV Observational Database. *Int J STD AIDS* 2007;18:446-52.
4. Bellamy R, Sangeetha S, Paton NI. AIDS-defining illnesses among patients with HIV in Singapore, 1985-2001: results from the Singapore HIV Observational Cohort Study (SHOCS). *BMC Infect Dis* 2004;4:47.
5. Yang Y, Wilder-Smith A, Panchalingam A, Tha NO, Paton NI. Changes in body fat measured by DEXA in patients taking different formulations of stavudine. *HIV Clin Trials* 2005;6:337-43.
6. Paton NI, Earnest A, Ng YM, Karim F, Alboulhab J. Lipodystrophy in a cohort of human immunodeficiency virus-infected Asian patients: prevalence, associated factors and psychological impact. *Clin Infect Dis* 2002;35:1244-9.
7. Hsu L-Y, Subramaniam R, Bacheler L, Paton NI. Characterisation of mutations in CRF01\_AE virus isolates from antiretroviral treatment-naïve and -experienced patients in Singapore. *J Acquir Immune Defic Syndr* 2005;38:5-13.
8. Zhou J, Paton NI, Ditango R, Chen YMA, Kamarulzaman A, Kumarasamy N, et al for the TREAT Asia HIV Observational Database. Experience with the use of a first-line regimen of stavudine, lamivudine and nevirapine among TAHOD patients. *HIV Med* 2007;8:8-16.