

Strategies to improve treatment outcome

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One of the most important strategies to improve outcome when treating HIV infection is to ensure that all the factors that might impact in a negative way on continuous adherence to combination antiretroviral therapy (cART) are identified before treatment is started. As there are several preferred and alternate combinations for antiretroviral therapy (ART)-naïve patients recommended by the Department of Health and Human Services (DHHS) guidelines,¹ greater individualisation of cART using different but equipotent regimens is now possible. Strategies to improve and maintain high levels of drug adherence are discussed in Chapter 8. Viral resistance testing is a helpful guide in making the choice of antiretroviral agents in both the ART-naïve and treatment-experienced population and is discussed further in Chapter 8. Pharmacokinetic enhancement of levels of protease inhibitors using boosting-doses of ritonavir is discussed in Chapter 5.

There are three other key strategies, which have been embraced with varying degrees of enthusiasm and success in the clinical trial and clinic setting over the last decade. These are:

- therapeutic drug monitoring
- structured treatment interruption
- immunotherapy with cytokines and therapeutic vaccination.

10.1 Therapeutic drug monitoring

In order for therapeutic drug monitoring (TDM) to be useful, the candidate drugs need to have an established therapeutic range. This needs to be measured using samples, which are easily obtained from the patient i.e. a blood sample. The therapeutic range is the range of concentrations which have been established, preferably in properly conducted trials in different populations (age, ethnicity, race, hepatic and renal function), which evoke a good clinical response with minimal drug-related toxicity. TDM in theory could be useful because there is considerable inter-patient variability in drug concentration (for the same drug at the same dose) and data for a drug-concentration anti-HIV effect. However, there is a paucity of data for drug concentration-toxicity relationships.

TDM cannot be applied to monitoring levels of nucleoside reverse transcriptase inhibitors (NRTI), as the relationship between the intracellular (active) form and plasma levels has not been established. However, for many of the non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitor (PI) there are data describing relationships between drug levels and treatment response.²⁻⁵ Despite the limitations and many unanswered questions there is consensus that these data provide a framework for further study of TDM. However, clinicians using TDM to adjust doses for toxicity or treatment of drug-related toxicity need to take extreme care that they do not over interpret results (with reference to intra-patient variability in plasma levels), and in fact predispose the patient to the

development of resistance through under-dosing. In addition, there are other options for toxicity-management including switching component drugs.

Possible scenarios for use of therapeutic drug monitoring:

- drug-drug interactions – e.g. rifampicin and PI*
- physiological changes that might effect the pharmacokinetic (PK) profile of a drug e.g. pregnancy,* paediatrics*
- pathophysiological states that might impact on drug PK e.g. abnormalities of the gut (changes in absorption and sometimes excretion), hepatic impairment (changes in metabolism and plasma protein binding), renal impairment (changes in excretion)*
- use of experimental combinations e.g. raltegravir and unboosted atazanavir
- in patients with multidrug resistant HIV in whom higher drug levels might be required to inhibit HIV*
- for concentration-related toxicities e.g. atazanavir-induced hyperbilirubinaemia*
- as a crude assessment of adherence especially in ART-naïve patients who are not responding to cART

*British HIV Association Guidelines⁶ recommend the use of TDM in all of the above clinical scenarios as they identify these situations as being ones in which drug concentrations may be more difficult to predict.

10.1.1 Limitations of therapeutic drug monitoring

There are many problems associated with the use of TDM. First, relatively few laboratories actually perform TDM and those that do may use in-house non-standardised assays without any external quality control (Section 4.2). In addition, interpretation of new antiretroviral level data may not be performed in a timely manner by experts in the field in order to guide drug dosing. Many investigators have chosen to sample the trough plasma drug level, as viral breakthrough may be more likely to occur at this point, but this method has some limitations. The trough level does not always correspond to the minimum inhibitory concentration during a dosing interval, and many factors can influence this trough level including intra- and inter-patient and laboratory variability. For drugs with relatively short half-lives, the trough level may not be an accurate reflection of drug exposure, only reflecting the previous two or three doses. Also, the ways in which these values for the minimum target concentrations have been defined may not be broadly applicable i.e. many were defined during monotherapy and not in combination therapy. Further Guidance on TDM can be found in the position paper by the Adult AIDS Clinical Trials Group Pharmacology Committee³ and at <http://www.hivpharmacology.com>.

10.1.2 Pharmacokinetic enhancement with ritonavir

The role of low doses of ritonavir to boost the levels of other PI and some other antiretroviral components (i.e. maraviroc) is described in Chapter 5. The relationship between plasma levels of boosting doses of ritonavir and levels of the primary PI (i.e. the drug being boosted) have not been fully established.

In summary, there are strong theoretical reasons why TDM should be useful in the management of HIV. At this juncture, routine use of TDM in clinical practice is not recommended because there is a lack of data from prospective studies showing that TDM improves clinical outcome. Moreover, clinicians should be strongly discouraged from decreasing doses of component antiretroviral agents for toxicity reasons as they may inadvertently promote the development of viral resistance.

10.2 Role of treatment discontinuation

cART has revolutionised the treatment of HIV, with improved clinical outcomes and reduced mortality from AIDS-related illnesses (Chapter 5). The inability of cART to eradicate HIV, however, means that treatment must be continued indefinitely, with patients remaining on therapy for long periods. Problems associated with continuous therapy include the morbidity and mortality associated with drug-related toxicity, difficulties in adhering to life long treatment and, in the developing world, cost. There have been several clinical trials of structured treatment interruption conducted over the past five years. The various scenarios in which interruptions have been explored include:

- primary HIV infection
- in treatment-experienced patients with multidrug resistant virus who are virologically failing their present combination
- in patients with CD4 cell counts above the current recommended thresholds for commencement of cART.

10.2.1 Structured treatment interruption following treatment in primary infection

At the present time there are insufficient data to recommend the use of cART in primary infection as it is unknown whether there is any long-term benefit associated with cART-use in this setting. Treatment of primary infection remains optional.¹ The SPARTAC study is a large randomised study exploring the benefits of short courses of cART compared with no treatment in primary infection.⁷ The results of this study should be helpful in further guiding the use of cART in primary infection.

10.2.2 Structured treatment interruption in treatment-experienced patients with multidrug resistant virus who are virologically failing their present combination

Partial virological suppression has been associated with clinical benefit,⁸ and therefore the current treatment guidelines do not recommend structured treatment interruption in this setting. Results of various trials of treatment interruption in this setting have yielded conflicting results. The rationale behind many of these trials was the observation that cessation of cART could be

associated with reversal of resistance mutations and restoration of wild type virus. This in turn might, in theory, lead to a better and more durable response to cART once it was recommenced.^{9,11} Patients with multidrug-resistant HIV and HIV RNA levels of more than 5000 copies/mL were randomised to a four-month structured interruption of treatment followed by a change in cART (treatment-interruption group) or to an immediate change in cART. Structured interruption of treatment was associated with significantly greater progression of disease and did not confer immunological or virological benefits or improve the overall quality of life.¹² In addition, with longer follow-up, it was found that patients with multidrug resistant HIV-1 treatment failure who underwent treatment interruption before changing cART regimens had a prolonged negative impact on CD4 cell count recovery and did not confer progression of disease or virological benefits.¹³ However, with the advent of new potent drugs in old classes and several new classes of agent it is now possible to construct a regimen that can suppress virus fully and lead to substantial immune restoration in many patients with multidrug resistant HIV. Hence, the rationale for treatment interruption in this setting becomes even less justifiable as a strategic approach.

10.2.3 Structured treatment interruption in patients with CD4 cell counts above the current recommended thresholds for commencement of cART

CD4 cell count guided treatment interruptions are not recommended. Recently, two separate, randomised clinical trials of CD4 cell count-guided treatment interruption have been reported. The first of these, the SMART study,¹⁴ is described in more detail in Chapter 5. The second, the TRIVACAN study¹⁵ which used the same CD4 cell count triggers for stopping and restarting treatment, also showed that interruption was an inferior strategy compared to continuous cART. Both studies were stopped early following the recommendations of their respective Data Safety and Monitoring Boards. Further analyses are ongoing to better understand the pathogenesis underlying these findings. In contrast, several smaller studies of treatment interruption have not shown any deleterious effects. This may have been a consequence of smaller numbers and shorter duration (i.e. underpowered to detect a clinical difference) or different design (i.e. different restart thresholds).¹⁶⁻¹⁸

Guidance on cessation of cART in the setting of vertical transmission is provided in the current DHSS guidelines from November 2008.¹

10.3 Role of immune-based therapy

10.3.1 Recombinant interleukin-2

Interleukin-2 (IL-2) is a potent stimulator of T cell proliferation and maturation and has been studied in a number of trials of people with HIV infection.¹⁹ Studies of IL-2, first using continuous intravenous infusion and more recently five-day cycles of twice a day subcutaneous dosing, have demonstrated significant increases in CD4 cell counts in the absence of sustained increases in plasma HIV RNA levels. The predominant expansion occurs in the naïve CD4 cell pool and some of these cells have a unique phenotype with persistent expression of CD25, the IL-2

receptor.²⁰ Expression of this receptor seems to be associated with longer survival of these T cells and may explain why, after an induction period with intermittent recombinant interleukin (rIL)-2, the higher CD4 cell count can be maintained with less frequent cycling (the maintenance phase).^{20, 21} Importantly, this expanded CD4 cell pool appears to be functionally normal.²⁰ While rIL-2 is associated with a number of predictable toxicities (i.e. constitutional upset), the duration is relatively short during and post completion of the five-day dosing cycle.

Importantly, none of the studies to date has been powered to determine whether this increase in CD4 cell count translates into clinical benefit, although a reduction in opportunistic infections has been reported.²² Hence, the clinical benefits of rIL-2 with cART compared with cART alone have been explored in two prospective, randomised, controlled clinical endpoint studies, SILCAAT and ESPRIT.

The patient population in SILCAAT and ESPRIT²³ are adults with HIV infection with CD4 cell counts <300 cells/ μ L and >300 cells/ μ L respectively on cART. Results from these two studies show there is no clinical benefit from the addition of rIL-2.^{24, 25}

The negative results of ESPRIT and SILCAAT are likely to impact significantly on the future of cytokine-based therapy in the setting of HIV. Moreover, it is clear, at least from the phase III rIL-2 data that CD4+ increases secondary to cytokine use cannot reliably be used as surrogate markers of clinical efficacy.

10.3.2 Therapeutic vaccination

The most promising therapeutic vaccination strategies explored over the last decade have been those aimed at generating HIV-specific T cell immune responses to help control viral replication.²⁶ Investigators and patients have been interested in therapeutic vaccination to either defer the commencement of continuous cART or use these same immune responses to control HIV virus levels following cessation of cART. An effective therapeutic vaccine could have potential utility in the developing world where access to potent, relatively toxicity-free cART is limited. The biggest barrier to moving forward with therapeutic vaccination has been the poor performance of these vaccines in controlling HIV viraemia even when T cell immune responses against HIV appeared robust.²⁶ Moreover, both the results of the STEP²⁷ and SMART¹⁴ studies have added extra questions about the role of prophylactic vaccination, first with the failure of the most promising candidate T cell vaccine in the prophylactic arena²⁷ and then with anxiety regarding treatment interruption following vaccination.

References

- 1 Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. November 3, 2008; 1-139. Available at: <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. (cited February, 2009)
- 2 Acosta EP, Gerber JG; Adult Pharmacology Committee of the AIDS Clinical Trials Group. Position paper on therapeutic drug monitoring of antiretroviral agents. *AIDS Res Hum Retroviruses* 2002;18(12):825-34.
- 3 Back D, Gatti G, Fletcher C, Garaffo R, Haubrich R, Hoetelmans R, et al. Therapeutic drug monitoring in HIV infection: current status and future directions. *AIDS* 2002;16(Suppl 1):S5-37.

- 4 Burger DM, Aarnoutse RE, Hugen PW. Pros and cons of therapeutic drug monitoring of antiretroviral agents. *Curr Opin Infect Dis* 2002;15(1):17-22.
- 5 Van Heeswijk RP. Critical issues in therapeutic drug monitoring of antiretroviral drugs. *Ther Drug Monit* 2002;24(3):323-31.
- 6 Gazzard B. British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy 2006. *HIV Medicine* 2006;7:487-503
- 7 The Short-Pulse Anti Retroviral Therapy at HIV sero Conversion (SPARTAC) study. Available at: <http://www.ctu.mrc.ac.uk/studies/spartac.asp> (cited January 2008)
- 8 Deeks SG, Hoh R, Neilands TB, Liegler T, Aweeka F, Petropoulos CJ, et al. Interruption of treatment with individual therapeutic drug classes in adults with multidrug-resistant HIV-1 infection. *J Infect Dis* 2005;192(9):1537-44.
- 9 Ruiz L, Ribera E, Bonjoch A, Romeu J, Martinez-Picado J, Paredes R, et al. Role of structured treatment interruption before a 5-drug salvage antiretroviral regimen: the Retrogene Study. *J Infect Dis* 2003;188(7):977-85.
- 10 Katlama C, Dominguez S, Gourlain K, Duvivier C, Delaugerre C, Legrand M, et al. Benefit of treatment interruption in HIV infected patients with multiple therapeutic failures: a randomized controlled trial (ANRS 097). *AIDS* 2004;18(2):217-26.
- 11 Jaafar A, Massip P, Sandres-Sauné K, Souyris C, Pasquier C, Aquilina C, et al. HIV therapy after treatment interruption in patients with multiple failure and more than 200 CD4+ T lymphocyte count. *J Med Virol* 2004;74(1):8-15.
- 12 Lawrence J, Mayers DL, Hullsiek KH, Collins G, Abrams DI, Reiser RB, et al. Structured treatment interruption in patients with multidrug-resistant human immunodeficiency virus. *N Engl J Med* 2003;349(9):837-46.
- 13 Lawrence J, Hullsiek KH, Thackeray LM, Abrams DI, Crane LR, Mayers DL, et al. Disadvantages of structured treatment interruption persist in patients with multidrug-resistant HIV-1: final results of the CPCRA 064 study. *J AIDS* 2006;43(2):169-78.
- 14 The Strategies for Management of Antiretroviral Therapy (SMART) Study Group. CD4+ count - guided interruption of antiretroviral treatment. *N Engl J Med* 2006;355:2283-96.
- 15 Danel C, Moh R, Minga A, Anzian A, Ba-Gomis O, Kanga C, Nzunetu G, et al. CD4-guided structured antiretroviral treatment interruption strategy in HIV-infected adults in West Africa (Trivacan ANRS 1269 trial): a randomised trial. *Lancet* 2006;367(9527):1981-9
- 16 Maggiolo F, Ripamonti D, Gregis G, Quinzan G, Callegaro A, Suter F. Effect of prolonged discontinuation of successful antiretroviral therapy on CD4 T cells: a controlled, prospective trial. *AIDS* 2004;18(3):439-46.
- 17 Cardiello PG, Hassink E, Ananworanich J, Srasuebku P, Samor T, Mahanontharit A, et al. A prospective, randomized trial of structured treatment interruption for patients with chronic HIV type 1 infection. *Clin Infect Dis* 2005;40(4):594-600.
- 18 Ananworanich J, Siangphoe U, Hill A, Cardiello P, Apatheerapong W, Hirschel B, et al. Highly active antiretroviral therapy (HAART) retreatment in patients on CD4-guided therapy achieved similar virologic suppression compared with patients on continuous HAART: the HIV Netherlands Australia Thailand Research Collaboration 001.4 study. *J AIDS* 2005;39(5):523-9.
- 19 Pett SL, Kelleher AD. Cytokine therapies in HIV-1 infection: present and future. *Expert Rev Anti Infect Ther* 2003;1(1):83-96.
- 20 Sereti I, Martinez-Wilson H, Metcalf JA, Baseler MW, Hallahan CW, Hahn B, et al. Long-term effects of intermittent interleukin 2 therapy in patients with HIV infection: characterization of a novel subset of CD4(+)/CD25(+) T cells. *Blood* 2002;100(6):2159-67.
- 21 Kovacs JA, Lempicki RA, Sidorov IA, Adelsberger JW, Sereti I, Sachau W, et al. Induction of prolonged survival of CD4+ T lymphocytes by intermittent IL-2 therapy in HIV-infected patients. *J Clin Invest* 2005;115(8):2139-48.

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- 22 Emery S, Capra WB, Cooper DA, Mitsuyasu RT, Kovacs JA, Vig P, et al. Pooled analysis of 3 randomized, controlled trials of interleukin-2 therapy in adult human immunodeficiency virus type 1 disease. *J Infect Dis* 2000;182:428–34.
- 23 International Network for Strategic Initiatives in Global HIV Trials (INSIGHT). Available at: <http://insight.cabr.umn.edu/> (cited August 2008)
- 24 Losso M, Abrams D, INSIGHT ESPRIT Study Group. Effect of Interleukin-2 on Clinical Outcomes in Patients with a CD4+ Cell Count of 300/mm³: Primary Results of the ESPRIT Study and INSIGHT ESPRIT Study Group. CROI 2009, Montreal, Canada, 8-11Feb2009, 90aLB
- 25 Levy Y and SILCAAT Sci Committee. Effect of Interleukin-2 on Clinical Outcomes in Patients with CD4+ Cell Count 50 to 299/mm³: Primary Results of the SILCAAT Study. CROI 2009, Montreal, Canada, 8-11Feb2009, 90bLB
- 26 Johnston MI, Fauci AS. An HIV vaccine-evolving concepts. *N Engl J Med* 2007;356(20):2073-81
- 27 Cohen J. AIDS RESEARCH: Promising AIDS Vaccine's Failure Leaves Field Reeling. *Science* 2007;318(5847):28–9