THERAPY DEVELOPMENTS IN SOUTHERN AFRICA

Immune response and structured treatment interruptions in HIV-1-infected individuals treated with antiviral therapy

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INTRODUCTION

Progress in the field of HIV treatment and the prevention of AIDS-related complications has led to a significant decline in mortality and morbidity in developed countries. Limitations of the currently available antiviral therapies include the cost of treatment, metabolic complications of treatment, and the development of viral resistance. The development of resistant viral strains is related to difficulties with compliance, recognition of ongoing viral replication despite undetectable serum viral loads, poor drug penetration into sanctuary sites, and the discovery that resting CD4 cells can provide a reservoir for HIV-1 with a predicted decay rate of approximately 60 years. The chance of achieving viral eradication with currently available treatment options appears to be very small. Therefore strategies involving sustained treatment with enhancement of HIV-specific immune control mechanisms need to be investigated.

Implementation of antiviral therapy in patients in South Africa, a region with a seroprevalence rate of up to 22%, is limited by cost, expertise of medical personnel and lack of medico-political will to fund therapy. In order to broaden access to treatment, strategies to reduce the overall drug therapy cost will advance the call for treatment interventions and require investigation.

While current guidelines for antiviral therapy are under review, mainly because of the shift in the risk benefit ratio of early continuous therapy, only limited cost benefits will be derived from initiating successful therapy later. Such delays in therapy may increase access to therapy in the initial period when patients with higher CD4 counts are delayed from initiating therapy. However, most patients will progress to the stage where they require antiviral therapy, thus the gain in initial cost reduction will be lost as disease progression occurs.

By means of this review the authors wish to stimulate a discussion in southern Africa of the relevance of antiviral therapy strategic treatment interruptions. To achieve this aim we will review the current literature of treatment-related immune reconstitution and HIV-specific immune control of HIV replication, and will propose a hypothesis of the potential benefits of structured treatment interruptions.

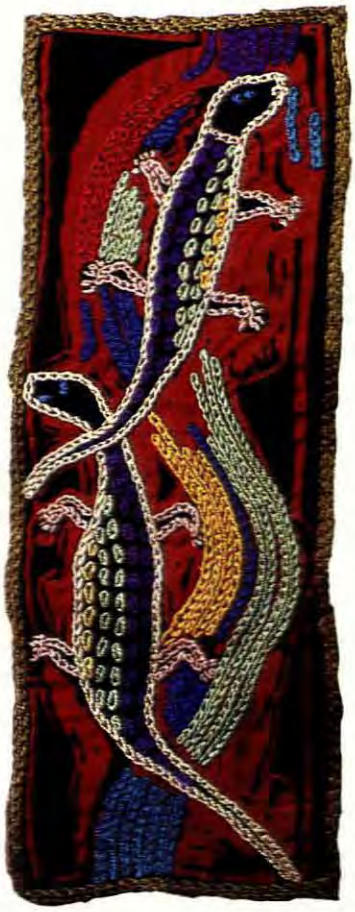
Structured treatment interruption and induction of HIV-specific immune responses by therapeutic vaccine are a potential strategy to harness the immune response to natural infection, complementing existing antiviral therapy options to control viral replication, yet reducing overall drug exposure, toxicity and cost. Continued treatment safety without the development of viral resistance requires further evaluation. To date, structured treatment interruption protocols have not demonstrated the development of resistance. Interventions to enhance HIV-1-specific immune responses provide a platform to increase the delivery of broad access to therapy, while emphasising the durability and safety of treatment of patients.

Strategies to enhance the HIV-specific immune response in persons already infected are founded on several important observations. First, there are a number of observations to document the inverse relationship between HIV viral load and HIV-specific cellular immunity.[1-5] Another set of observations has documented that viral load is a predictor of disease progression, clinical course or duration of asymptomatic disease before AIDS. There is now overwhelming evidence to show that HIV antigen-specific CD8+ cells play an important role in the control of HIV replication.

Second, extensive experience in treating patients with antiviral therapy, in particular HAART, with long periods of undetectable viral loads has been associated with diminished anti-HIV cellular immune responses. This has been demonstrated by using peptide/MHC tetramers that

track *ex-vivo* circulating numbers of antigen-specific CD8+ T cells.[6-8] These findings suggest that viral suppression and lowering the threshold of antigen load lead to a reduction in the quantitative immune response to HIV.

Third, when HAART is terminated in patients who have achieved undetectable viral loads, even for periods of years, almost all patients undergo a re-emergence of viral replication. Increased replication can result in a higher viral set-point occurring in patients who have demonstrated immune reconstitution with high CD4 counts (> 400 cells/mm^3).[9] Whether this means a loss of immune control in these individuals or a rebound of more virulent viruses, remains to be elucidated.



High-level HIV-specific immune responses are associated with low viral replication, delay in progression to AIDS in chronically infected individuals[2-5,10] and protection of high-risk exposed individuals.[11,12] HIV-1-infected long-term non-progressors maintain high CD4+ T-cell proliferation responses to p24 antigen and to recall antigens, as well as high levels of HIV-1-specific CD8 + T-cell responses in association with low viral loads.[3] However, the majority of HIV-1-infected subjects fail to suppress to an undetectable viral load in the absence of antiviral therapy and even-tually lose CD4+ T-cell-proliferative responses.[13,14] Loss of cellular immune response in the absence of therapy is associated with disease progression to AIDS.

Of importance is the observation that cytotoxic T lymphocytes (CTL) play an important role in the control of HIV infection and a decrease in the HIV-specific CTL has been observed after successful antiviral therapy, consistent with the dependence on continued viral replication to sustain HIV-specific CTL.[15]

THERAPY, IMMUNE RECONSTITUTION AND ANTIVIRAL RESPONSES

Antiretroviral therapy (ART) has many beneficial effects in chronically infected persons. Irrespective of the disease stage during which it is started, antiretroviral-mediated suppression can facilitate restoration of CD4+ T-cell proliferative responses to recall antigens and can fill CD4 and CD8 TCR Vβ repertoire gaps, among other effects.[16-27] Recovery of immune function following HAART in chronically infected subjects has renewed interest in augmenting anti-HIV-1 immune responsiveness in chronically infected persons. Increasing cell-mediated immunity against HIV-1 would be expected to delay disease progression and increase the efficacy of treatment by complementing ART-mediated suppression with immune-mediated control. Multiple strategies for boosting HIV-1-specific immune response under HAART are being explored.[28-30] It remains undetermined how effectively these antiviral responses would be maintained in light of mounting data suggesting that prolonged HAART can result in a decline in HIV-1-specific cellular immune responses.[16,15,31,32]

LIMITATIONS OF ANTIVIRAL THERAPY

While treatment is not accessible to the majority of southern African patients, the Clinician's Society has elected to maintain the international guidelines for treatment with antiviral therapy. Treatment guidelines for HIV-1 infection are centred on achieving viral suppression using HAART, based on the association between viral suppression and improved clinical outcome.[33-38] Current guidelines recommend the use of potent combinations of multiple agents with the aim of suppressing viral replication to levels below the limit of quantification of current assays. This recommendation is based, in part, on the evidence that the duration of HIV suppression is proportional to the nadir of the initial drop in plasma HIV-1 RNA, and is supported by data indicating that HIV replication is effectively, if not absolutely, stopped by achieving viral load < 20 copies/ml. The generation of resistance and rebound of resistant virus is related to the ineffective suppression of viral replication. In experiments, resting CD4+ cells from patients on combination ART for up to 1 year were studied for the presence of genotypic drug resistance indicative of ongoing viral replication. With HIV-1 RNA levels of less than 20 copies, no drug-resistant mutations were found in the patients. However, low-level replication was detected in patients with a level between 20 and 400 copies/ml.[39,40] Thus, patients who do not achieve suppression below 50 copies/ml are more likely to experience a rebound as resistant virus eventually emerges in the setting of continued viral replication. Therefore, the current goal of HAART is to sustain lifelong suppression without treatment interruption, with the hope of viral eradication if therapy is sustained. However, adverse drug effects, treatment cost, and the difficulty of maintaining optimal adherence for a prolonged duration, limit the feasibility of lifelong HAART-mediated viral suppression.[41,42] Moreover, the recent discovery of a long-lived latent reservoir of HIV-1 and a low level of viral replication in spite of undetectable plasma viraemia has raised concern about the feasibility of viral eradication with the use of antiretroviral regimens.[43,44]

In addition to difficulties with adherence leading to drug resistance, use of antiretroviral drugs can result in unintended side-effects. Short-term complications such as pancreatitis, peripheral neuropathy and cytopenias related to nucleoside reverse transcriptase inhibitors, have been described for years. In the past 2 years unexpected endocrine and metabolic complications associated with successful ART have been reported.[45-48] Different investigators have associated factors such as duration of therapy,[46] type of therapy,[47] degree of viral suppression,[49] and even demographic characteristics[50-52] with the metabolic syndrome of peripheral lipodystrophy. The apparently increasing incidence of these metabolic complications, combined with a lack of understanding of their pathophysiology and clinical implications, leaves many clinicians and patients in a quandary about treatment. Interruptions in therapy have resulted in amelioration of some of the manifestations of lipodystrophy and improved wellbeing among patients *within 2 - 4 weeks of therapy interruption.*

Both long-term and short-term side-effects of antiviral therapy may be addressed by a reduction in the total amount of drug exposure. Combined strategies of STI and therapeutic vaccine may reduce the total drug exposure by as much as 50%.

TREATMENT INTERRUPTION AND ANTIVIRAL RESPONSES

HIV-1 REBOUND DURING TREATMENT INTERRUPTION

Today many patients treated with protease inhibitor (PI), or non-nucleoside reverse transcriptase inhibitor (NNRTI)-based HAART regimens undergo transient treatment interruptions. The HIV-1 viral dynamics during the treatment interruption demonstrate a rebound of viral load similar to pre-treatment baseline value in the majority of patients. This rebound begins within 4 - 7 days of the interruption and demonstrates a similar doubling time to that described by Ho *et al.*[53] The dynamic of this viral rebound is independent of the duration of initial treatment.[54] The source of viral rebound is hypothesised to be latently infected cells as measured by integrated DNA.[55-56] Further, the source of viral rebound appears to be from low-level persistent replication. This is supported by the similarity in rebound in patients whose viral loads are between undetectable and 5 copies/ml versus 5 - 19 c/ml.[57] Higher viral load rebound is observed in patients with a baseline viral load of 20 - 50 copies/ml than in patients with viral loads of less than 5 copies/ml.[58]

On re-initiating suppressive therapy the viral dynamic or slope of the decline is similar to that of the initial treatment. Adequately suppressive therapy in a compliant patient is associated with an undetectable viral load after the re-initiation of therapy. Such a viral load rebound is not associated with the development of resistance. No mutations associated with the reverse transcriptase gene or protease gene have been detected. On reintroducing the treatment, an undetectable viral load was achieved.[58,59]

ENHANCEMENT OF HIV-1 SPECIFIC CD4 AND CD8 CELL RESPONSES DURING TREATMENT INTERRUPTION

The association between cellular immune responses against HIV-1 antigens and temporary suppression of HIV-1 replication in the absence of therapy has been recently documented in acutely infected subjects treated within 120 days of infection who had their treatment interrupted.[60,61] Importantly, an association with viral replication and increased CD8-mediated cellular immune responses following temporary drug discontinuation was observed as reported.[61] This observation, along with the observation of preserved and enhanced CD4+ T-cell responses following initiation of suppressive therapy,[13] has generated the hypothesis that periods of treatment interruption in acutely infected individuals may preserve and boost HIV-1-specific cellular immune responses in newly infected subjects.

These observations have also been demonstrated in chronically infected individuals participating in a time-limited treatment interruption. Increased HIV-1 replication results in significant increases in anti-HIV-1-specific cellular immune response.[62] During a treatment interruption the magnitude and duration of the viral replication was interpreted as an important factor for the expansion of immune-mediated responses against endogenous viral antigens. The interruption needs to be of a limited period, as HIV-1-specific immune responses appear to be lost at high levels of viral replication. As suggested by studies of early infection, re-initiating therapy may be a critical factor in preserving *de novo* boosted CD4 T-cell responses against HIV-1.13 Also, the period of treatment after re-initiation requires further evaluation, as CD4 and CD8 T-cell-specific responses may be decreased with chronic suppressive therapy.[10,32]

HIV-SPECIFIC NEUTRALISING ANTIBODIES (NAB)

Initial seroconversion is associated with the development of neutralising antibodies. Quantitations of neutralising antibodies indicate that both nonspecific and antigen-specific antibody levels are sensitive to HIV viral load. Patients receiving potent ART show a decline in the number of antibody-secreting cells (as measured by ELISPOT assays), as well as the titres of circulating antibodies.[63] The corollary is that ongoing antibody production is dependent on continual viral replication and immune system exposure. More recently it has been shown that HAART therapy has little effect on Nab titres and that intermittent therapy with HAART can in fact enhance autologous neutralisation levels.[64] This suggests that controlled exposure to HIV antigens may allow the immune system time to develop or maintain a more effective Nab response. These data support the notion of intermittent therapy with the use of a therapeutic vaccine as immunogen to enhance antibody responses. The relative contribution of Nab and cellular immunity in controlling

viral replication is not established. *In vitro* data emphasise the cellular immune response to be more efficient in controlling viral replication. Further research is required to address neutralising antibodies in the strategy for immune control of HIV replication and potentially to establish the relative contribution of each 'arm' of the immune system.

CONCLUSION

Progress in the development of treatment strategies to reduce overall treatment exposure is evident in the associated tangible excitement among patients, clinicians and researchers. The observations presented here advance the rationale for further investigation of structured treatment interruption in acute and chronically infected persons as a potential mechanism for augmenting HIV-1-specific immune responses.

Future developments in this field will need to include specific measurement of cellular immunity in relation to the magnitude and time to rebound in viral load following sequential STIs. Specifically, future research is required to enhance the understanding of STI immune changes, the impact on viral reservoir levels, and immune reconstitution including the thymic-derived lymphocyte reconstitution. Aspects of viral diversity, timing of STI and the addition of therapeutic vaccine will also require further attention. The application of STI may be diverse for patients presenting with acute HIV infection and chronic HIV infection respectively. Once the optimum application of STI has been elucidated by careful clinical phase I/II studies, the translation of these results into clinical practice will require a large international collaborative effort to design a clinical phase II study.

Of course, safety concerns must be carefully considered in relation to any treatment interruption, given our understanding of the mechanism underlying viral resistance and the potential loss of CD4 T cells. While the outlook for continued development of such strategies is good, no recommendations of changes in current treatment strategies can be made. Patients should be encouraged to follow the current best practice guidelines as far as possible and to await the outcome of further clinical studies designed to measure the clinical impact of STI. Given the current literature and the limitations of antiviral therapy we do not believe that the inherent risks of this intervention outweigh the potential benefits, and believe that further study of strategic treatment interruption is warranted.

The authors of this review wish to stimulate discussion and ethical debate in order to advance the development of research aimed at immune-based therapies in combination with antiviral therapy. Extracts of this review article have been integrated with the permission of Dr L Montaner.

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Your comments are appreciated and will assist in the development of a research strategy in structured treatment interruptions in southern Africa.

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