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# Structured Treatment Interruption in Patients Infected with HIV

## A New Approach to Therapy?

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## Abstract

Current antiretroviral regimens are limited by issues of potency, adherence, toxicity, resistance and cost. With these limitations and the realisation that eradication of HIV infection currently is not possible, there is enthusiasm for strategies that allow discontinuation of medications, such as the structured treatment interruption (STI). STI is hypothesised to have benefits in three distinct clinical scenarios: acute treated infection, chronic treated infection with controlled viraemia, and chronic treated infection without controlled viraemia (salvage therapy).

In patients with acute treated HIV infection, STI may preserve or enhance cellular immune responses to allow continued virological suppression in the absence of ongoing treatment. The Berlin patient presented with acute HIV infection prior to seroconversion and received antiretroviral therapy. After two treatment interruptions (for intercurrent infections), he permanently discontinued therapy and remained virologically suppressed for 2 years. Investigators from Massachusetts General Hospital described eight patients with acute or early HIV infection who received treatment and then underwent one or two STI. After the STIs, five of eight patients showed enhanced cellular immune responses and continued with virological suppression off treatment for a median of 2.7 years.

In patients with chronic treated infection with controlled viraemia, STI may enhance immune responses as in the case of acute infection, or may allow decreased drug exposure and toxicity. Investigators from the National Institutes of Health enrolled 18 patients with chronic HIV infection and virological suppression while taking antiretroviral regimens. With a single STI, all patients rebounded, although one (6%) ultimately continued off therapy with virological suppression. The largest study of STI is the Spanish Swiss Intermittent Treatment Trial in which 128 patients with chronic suppressed HIV infection on antiretroviral therapy underwent four cycles of STI. At 52 weeks, 17% had suppressed viral load levels of <5000 copies/ml in the absence of therapy.

In patients with chronic treated infection without controlled viraemia (salvage therapy), STI promotes a shift from resistant to wild-type (i.e. no mutations) virus. In the Hamburg cohort, the shift to wild-type virus was seen in 28 of 45 heavily treatment-experienced patients after an STI. Seventy-two percent of these patients experienced a virological response on a subsequent regimen, although many ultimately experienced virological rebound. In the San Francisco cohort, a shift to wild-type virus was seen in 15 of 17 protease inhibitor-experienced pa-

tients and six of these patients achieved virological suppression to <200 copies/ml on a new regimen.

Risks associated with STI include increases in viral load levels with the risk of loss of virological control (i.e. failure to resuppress on therapy), repopulation of viral reservoirs and antiretroviral resistance, and decreases in CD4+ cell counts with the risk of loss or dysregulation of immune function and the occurrence of clinical events. Other risks include acute retroviral syndrome and the recurrence of short-term adverse effects.

Currently, STI cannot be recommended as part of routine clinical care. Prospective studies are needed to assess the risks and benefits of this strategy in all clinical settings.

Antiretroviral treatment has led to significant decreases in HIV-related morbidity and mortality over the last several years.[1,2] However, current first-line regimens are limited by their antiretroviral potency, complexity, toxicity, potential to result in antiretroviral resistance and cross-resistance, and cost. In addition, adherence and tolerability issues may compromise the quality of life for patients. With the realisation of the limitations of current HIV treatment regimens and the fact that viral eradication is not achievable at present,[3-5] strategies for stopping medications have been considered. Among these is the structured treatment interruption (STI). The STI has been postulated to offer benefits in three distinct clinical settings: (i) acute treated HIV infection; (ii) chronic treated HIV infection with controlled viraemia; and (iii) chronic treated HIV infection without controlled viraemia (salvage therapy). The distinct hypotheses for using an STI differ for the different clinical situations. Recently, initial studies to test these hypotheses have been reported (table I).

## 1. Acute Treated HIV Infection

In HIV infection, immunity in the form of HIV-specific CD4+ cells and cytotoxic T lymphocytes (CTL) may be lost early in infected patients.[14,15] Early treatment of acute HIV infection with antiretroviral agents has been shown to preserve HIV-specific cellular responses,[16] but these may be lost with continued antiretroviral therapy.[15] One or more STI in the setting of acute treated HIV infection may preserve or stimulate immune mechanisms that allow control of the infection in the absence of therapy.

Lisziewicz and Lori first described the consequences of treatment interruption in a patient with acute treated HIV infection, the so-called 'Berlin patient'.[6] This patient first presented to medical care during acute HIV infection, before complete seroconversion. He received the HIV protease inhibitor, indinavir, the nucleoside reverse transcriptase inhibitor, didanosine, and the ribonucleotide reductase inhibitor, hydroxyurea. His baseline viral load level, confirmed at approximately 85 000 copies/ml, rapidly decreased to <500 copies/ml with treatment. After approximately 2 weeks of treatment, the patient developed epididymitis and discontinued therapy, with a documented increase in the viral load level to about 8000 copies/ml. He resumed therapy a week later and again experienced a rapid decrease in viral load level to <500 copies/ml.

Approximately 3 months later, he developed nausea and vomiting in the setting of hepatitis A infection and stopped antiretroviral therapy again. Surprisingly, his viral load level remained suppressed to <500 on two occasions while off therapy. He briefly restarted therapy, but then discontinued it permanently and had HIV RNA levels <500 copies/ml documented on multiple occasions over the subsequent 2-year period. Of note, HIV RNA was detected in lymph node tissue and replication-competent virus was recovered from resting CD4+ cells isolated from the patient, demonstrating persistence of HIV infection. His CD4+ cell count and CD4+ to CD8+ cell ratio increased to normal lev-

**Table I.** Selected studies of structured treatment interruption (STI) of antiretroviral therapy in patients with HIV infection

| Study (reference) | Study population | Major findings |
|---|---|---|
| **Acute treated HIV infection** | | |
| Lisziewicz et al.[6] | The Berlin patient | After 2 treatment interruptions, a single patient remained virologically suppressed off therapy for 2 years |
| Rosenberg et al.[7] Massachusetts General Hospital Cohort | 8 patients with symptomatic acute or early (<180 days from exposure) HIV infection | After 1-2 STI, 5 of 8 remained virologically suppressed off therapy for an average of 2.7 years |
| **Chronic treated HIV infection with controlled viraemia** | | |
| Davey et al.[8] National Institutes of Health Cohort | 18 patients with chronic infection (12 who had previously received interleukin-2); HIV RNA <500 copies/ml, CD4+ >350 cells/mm$^3$ | After a single STI, 1 of 18 (6%) remained virologically suppressed off therapy |
| Fagard et al.[9] Spanish Swiss Intermittent Treatment Trial (SSITT) | 128 patients with chronic infection; HIV RNA <50 copies/ml, CD4+ >300 cells/mm$^3$ | After 4 cycles of STI, 9 of 54 (17%) had HIV RNA <5000 copies/ml at 52 weeks |
| **Chronic treated HIV infection without controlled viraemia (salvage therapy)** | | |
| Miller et al.[10,,11] Frankfurt Cohort | 48 patients with treatment experience (94% with 3-drug class experience) and HIV RNA >500 copies/ml | After treatment interruption, 28 of 45 (62%) had shift from resistant to wild-type virus; after 24 weeks of a new regimen, HIV RNA levels reduced to <500 copies/ml in 18 of 25 (72%); 73% had subsequent viral rebound |
| Deeks et al.[12,,13] San Francisco General Hospital Cohort | 18 patients with protease inhibitor experience and HIV RNA >2500 copies/ml | After STI, 15 of 17 (88%) had shift from resistant to wild-type virus; HIV RNA levels reduced to <200 copies/ml at 24 weeks in 6 of 15 who restarted therapy (40%) |

els. In addition, he had a progressive increase of some HIV-specific CD4+ cellular responses. This patient served as the first example that several cycles of treatment interruption could lead to long-term suppression of HIV infection without antiretroviral therapy, at least in the setting of acute treated HIV infection.

In a pilot study, Ortiz and colleagues studied six patients, five of whom had received antiretroviral therapy during acute or early (<120 days after exposure) HIV infection, who underwent an STI.[17] Three of these six patients had suppressed viraemia for at least 4 to 24 months after discontinuation of therapy. Two of these patients had suppressed viral load levels and demonstrated the presence of broad HIV-specific CTL responses. The other patient had a low level of viraemia (HIV RNA <300 copies/ml) off therapy and demonstrated enhanced neutralising antibody titres and CTL responses.

Rosenberg and colleagues studied eight patients with symptomatic acute or early (<180 days after exposure) HIV infection.[7] All were started on combination antiretroviral therapy, with two nucleoside analogues and a protease inhibitor, typically within 72 hours of diagnosis (range 2 to 34 days). Patients received therapy for an average of about 20 months (range 358 to 1081 days) and then discontinued therapy. After the therapy interruption, viral load levels became detectable again after a median of 17 days (range 7 to 38 days). In three patients, viral load levels decreased again without treatment to <5000 copies/ml and two of these patients remained off therapy for 7 to 9 months. The other patient restarted therapy briefly, but ultimately discontinued again and had an HIV RNA of 280 copies/ml after 5 months off therapy. In these three patients, HIV-specific CD4+ responses were maintained and after re-exposure to virus, CTL activity was increased.

The other five patients restarted treatment when their viral load levels increased to >5000 copies/ml, and four had levels >50 000 copies/ml. All five underwent a second treatment interruption, with a subsequent rise and then fall in HIV RNA (without treatment) to <5000 copies/ml. Three of these five patients resumed therapy when HIV RNA reached 4600, 10 860, and 17 100 copies/ml, respectively, while two others remained off therapy for 5 to 6 months. HIV-specific CD4+ cell and CTL responses increased after the treatment inter-

ruptions. In total, five of the eight patients remained off therapy for an average of 2.7 years at the time of publication of the report. This report demonstrated, in a small group of patients with acute/early HIV infection, that STI could lead to long-term virological suppression in the absence of antiretroviral therapy.

### 2. Chronic Treated HIV infection with Controlled Viraemia

In a patient with chronic HIV infection taking antiretroviral therapy that results in virological suppression, STI may augment HIV-specific immune responses, as in the case of acute treated HIV infection. Alternatively, STI may simply offer the opportunity to decrease drug exposure and the associated toxicity, or simply 'provide a break' from therapy.

Davey and colleagues studied 18 patients with chronic HIV infection receiving combination antiretroviral therapy with HIV RNA <500 copies/ml and CD4+ cell counts >350/mm$^3$ for at least a year.[8] Interestingly, 12 of these patients also had taken interleukin-2 (IL-2) in a previous study and had documented low frequencies of resting, latently HIV-infected CD4+ cells. After an average of at least 2 years of virological suppression to <500 copies/ml in this cohort, antiretroviral treatment was stopped. Viral load levels increased to >50 copies/ml in all 18 patients, typically within 2 to 3 weeks. Previous IL-2 therapy did not appear to effect the rate of viral rebound. In 2 of the 18 patients, virological rebound patterns were somewhat different: in one, viral rebound was delayed by several weeks compared with the other cohort patients and in the other, the maximal level of viral rebound was only several hundred copies/ml. In patients who elected to reinstitute therapy, all HIV RNA levels were quickly resuppressed to <50 copies/ml. The single patient who appeared to have a controlled HIV RNA level off therapy demonstrated brisk proliferation to HIV p24 antigen using a lymphocyte proliferation assay.

Two other pilot studies assessed the effects of single STI in patients with chronic treated HIV infection with control of viraemia. Ruiz and colleagues studied 12 patients who had suppressed viral load levels for at least 2 years while taking antiretroviral therapy and then underwent a single STI.[18] Whereas ten patients experienced rebound of viral load levels, two did not. All of the patients resumed therapy and experienced virological resuppression. No changes in CD4+ cell counts, clinical events or viral resistance were seen in the study population. Two patients demonstrated enhancement of an HIV-specific response to p24 antigen. Papasavvas and colleagues compared five patients with virological suppression on antiretroviral treatment who underwent an STI with five control patients not taking therapy.[19] After a median of 55 days, one of five patients who interrupted treatment had an HIV RNA level <1080 copies/ml, while the other four experienced virological rebound. All patients had virological resuppression after resuming therapy and there were no changes in CD4+ cell counts. Compared with the controls who did not receive treatment, the patients who underwent STI demonstrated significant increases in HIV-specific CD4+ and CTL responses during and after interruption of therapy.

An additional two pilot studies assessed repeated STI in chronic HIV infection. Ruiz et al. randomised 26 patients taking antiretroviral therapy with at least 2 years of viral suppression to <50 copies/ml and a CD4 : CD8 ratio of >1 to either undergo STI (n = 12) or continue therapy (n = 14).[20] Of the 12 patients who underwent three STIs, ten experienced viral rebound during each of the STI, one had no viral rebound, and one had viral rebound only during the second and third cycles. For the ten patients with viral rebound, mean virus doubling time increased from the first cycle to the second and third cycles, and enhancement of HIV-specific CD8 and CD4 responses were noted. Garcia et al. studied ten patients taking antiretroviral therapy for at least 1 year with HIV RNA levels <20 copies/ml who underwent three cycles of STI.[21] All ten patients experienced virological rebound, but viral doubling times increased between the first and third STI. By the third STI, six of nine

patients had viral load levels lower than their baseline levels prior to the original initiation of therapy and demonstrated enhanced HIV-specific immune responses.

The largest study of STI in patients with chronic virological suppression is the Spanish Swiss Intermittent Treatment Trial (SSITT).[9] 128 patients were enrolled who were antiretroviral treatment naïve before starting a non-NNRTI-containing potent combination antiretroviral regimen, had not experienced virological failure on the regimen, had a documented decrease in HIV RNA to <50 copies/ml for at least 6 months and a CD4+ cell count of at least 300/mm$^3$. The design of the study was to stop treatment for 2 weeks and then resume it for 8 weeks for four cycles with a final treatment discontinuation at week 40. The study endpoints were the amplitude of the rebounds in viral load levels and the proportion of patients with HIV RNA <5000 copies/ml in the absence of therapy at week 52. Patients in whom viral load levels were not suppressed to <50 copies/ml after resuming therapy were excluded from further treatment interruptions.

Before starting therapy, the study patients had a median viral load level of 4.5 $\log_{10}$ (~32,000) copies/ml and a median CD4+ cell count of 388/mm$^3$. The median duration of antiretroviral therapy before study entry was 26 months and baseline CD4+ cell count on therapy was 727 cells/mm$^3$. In preliminary results presented at the 8$^{th}$ Conference on Retroviruses and Opportunistic Infections, 80 patients had undergone four STI cycles and 55 of them had reached 52 weeks. Virological rebound to >50 copies/ml occurred in 76% after the first cycle and 79% after the fourth cycle. There were no significant changes in rebound viral load levels or CD4+ cell counts. Twenty-four (19%) were excluded for failure to resuppress to <50 copies/ml after restarting therapy and one of these developed antiretroviral resistance mutations. High pretreatment HIV RNA levels, high virological rebound levels, and low CD4+ cell counts correlated with failure to resuppress. Nine of 54 (17%) had HIV RNA <5000 copies/ml after 12 weeks off therapy at 52 weeks and at the same time, 3 of 55 (6%) had HIV RNA <50 copies/ml. The authors associated this response with earlier initiation of therapy after diagnosis of HIV infection. This study remains ongoing and updated results are anticipated.

A different approach for STI in patients with chronic virological suppression has the goal of decreasing drug exposure and toxicity. Studies currently in progress have given 'structured intermittent therapy (SIT)' for periods of 2 months of therapy followed by a 1-month discontinuation, or 7 days of therapy followed by a 7-day discontinuation.[22,23] In the shorter cycle trial,[23] 12 patients with HIV RNA levels <500 copies/ml for at least 6 months and <50 copies/ml twice immediately before study entry and a CD4+ count of at least 300/mm$^3$ were assigned to receive stavudine, lamivudine, indinavir and ritonavir for a 7-day on and off cycle for 24 months.[23] Failure was defined as HIV RNA >500 copies/ml or a confirmed >25% decline from baseline in CD4+ cell count. In preliminary results, three patients had HIV RNA levels <50 copies/ml at 24 weeks and one at 12 weeks. A fifth patient was noncompliant with the study and resumed therapy. There was no significant change in CD4+ cell counts. Longer-term results are anticipated.

### 3. Chronic Treated HIV Infection Without Controlled Viraemia (Salvage Therapy)

There is an increasing group of patients with chronic infections who have experienced virological failure and have limited treatment options. The use of STI in this clinical setting has been associated with a shift in the most prevalent strain of virus from multiply-resistant virus to wild-type virus, and this shift has been associated with an improved response to subsequent treatment options.[10-13] In contrast to its use in patients with virological suppression, the use of an STI in the 'salvage' setting is to provoke this shift in resistance pattern.

Miller and colleagues first described this finding in a retrospective, observational study of patients followed as part of the Frankfurt Co-

hort.[10,11] Forty-eight patients were identified who had taken antiretroviral agents, but interrupted treatment for at least 2 months, with an HIV RNA level of >500 copies/ml. One of these patients had two distinct treatment interruptions, and thus contributed to a total of 49 treatment interruption episodes. Patients had taken antiretrovirals a median of 3.9 years (range 0.3 to 9.2) before treatment interruption. The median duration of treatment interruption was 121 days (range 54 to 322). The median number of previous antiretroviral agents taken was nine (range 4 to 13) and 45 patients (94%) had taken all three classes of antiretroviral drugs.

Prior to treatment interruption, the median HIV RNA level was 5.07 $\log_{10}$ (~120,000) copies/ml and median CD4+ cell count was 155 cells/mm$^3$. Matched phenotypic resistance tests were available on 45 patients. At baseline, patients demonstrated virus with resistance to a median of eight drugs (range 2 to 11). At the end of treatment interruption, the median HIV RNA level was 5.87 $\log_{10}$ (~740,000) copies/ml and CD4+ cell count was 49 cells/mm$^3$. Surprisingly, significant reduction in both phenotypic and genotypic resistance was seen, with a complete shift to wild-type virus in 28 patients. In a multivariate analysis, a shorter time of previous antiretroviral treatment and a higher CD4+ cell count were associated with a greater chance of reversion to wild-type virus after treatment interruption.

Subsequent treatment with three to eight antiretroviral drugs resulted at 8 weeks in a median reduction of viral load of 2.8 $\log_{10}$ (shift group) versus 1.0 $\log_{10}$ (no shift group) copies/ml.[11] Within 24 weeks, HIV RNA decreased to <500 copies/ml in 18 of 25 (72%) [shift group] versus 2 of 12 (17%) [no shift group]. Patients who experienced the shift to wild type virus were significantly more likely to have a virological response [relative hazard (RH) 5.22, $p = 0.006$]. In longer-term follow-up, however, virological rebound occurred after a median of 73 days in 73% (shift group) and 100% (no shift group).

Deeks and colleagues published analogous data from treatment-experienced patients in the San Francisco cohort and explored the mechanism of the shift to wild-type virus.[12,13] Patients were selected who had taken an HIV protease inhibitor for at least 12 months and had a documented viral load level of at least 2500 copies/ml in the preceding 6 months. If the patients had experienced a rise in CD4+ cell count of at least 100 cells/mm$^3$ above baseline on their previous treatment regimen, they were randomised 2 : 1 to discontinue or continue therapy. If they had a CD4+ cell count rise of <100 cells/mm$^3$ on therapy, they were enrolled in the observational portion of the study in which they discontinued therapy.

A total of 23 patients were enrolled, 11 randomised to discontinue therapy and five randomised to continue therapy. The additional seven patients were observed after discontinuing therapy. At baseline, the randomised patients had viral load levels from 4.0 to 5.1 $\log_{10}$ (10 000 to 125 000) copies/ml and CD4+ cell counts from 245 to 355 cells/mm$^3$, whereas the nonrandomised patients had viral load levels from 4.1 to 5.6 $\log_{10}$ (12 000 to 400 000) copies/ml and CD4+ cell counts from 36 to 143 cells/mm$^3$. One patient randomised to discontinue therapy continued nucleoside analogues and was excluded from further analysis. After discontinuing therapy for 12 weeks, the median HIV RNA increased by 0.84 $\log_{10}$ copies/ml and CD4+ cell count decreased 128 cells/mm$^3$ versus a median HIV RNA increase of 0.31 $\log_{10}$ copies/ml ($p < 0.001$) and CD4+ decrease of 15 cells/mm$^3$ ($p = 0.005$) in the group who continued therapy. The changes after treatment discontinuation demonstrate the residual antiretroviral effect of the regimen, even in the setting of virological failure.

Drug resistance remained stable in the five patients who continued therapy, while protease inhibitor susceptibility shifted to wild-type (i.e. no mutations) within 16 weeks in 15 of 17 patients who discontinued therapy. The shift in resistance occurred abruptly and typically occurred for all the drugs at the same time. Both the HIV RNA level increase and CD4+ cell count decrease occurred rapidly after the shift in drug susceptibility. Assays of the multiply-resistant viruses revealed a median

replicative capacity that was 20% of that of wild-type virus with a median increase in replicative capacity of 50% during the 12 weeks of treatment interruption. Thus, the STI in this clinical setting appeared to allow a virus with greater replicative capacity to emerge and provoke significant changes in viral load levels and CD4+ cell counts.

Of the 17 patients who discontinued treatment, 15 subsequently resumed therapy and at week 24 experienced a median decrease in viral load level of 1.6 $\log_{10}$ copies/ml with 6 of 15 (40%) with decreases to <200 copies/ml. At the same time, the median increase in CD4+ cell count was 77 cells/$mm^3$. Of note, patients who started a new class of drugs (a nonnucleoside reverse transcriptase inhibitor or fusion inhibitor) as part of their new regimen had a greater likelihood of virological suppression.

**Table II.** Risks of structured treatment interruptions of antiretroviral therapy in patients with HIV infection

| |
|---|
| **Virological** |
| Virological rebound |
| Loss of virological control (i.e. failure to suppress viraemia after restarting therapy) |
| Viral repopulation of tissue reservoirs |
| Antiretroviral resistance |
| **Immunological** |
| CD4+ cell decline |
| Loss or dysregulation of immune function |
| **Clinical** |
| AIDS-defining or HIV-associated events |
| Acute retroviral syndrome |
| Recurrence of acute adverse effects (e.g. rash, nausea) |
| Precipitation of a hypersensitivity reaction (e.g. with an abacavir-containing regimen) |
| Pharmacokinetic issues |
| ?Reduction in adherence |
| ?Access issues |

## 4. Risks of Structured Treatment Interruptions

The risks of STI include virological, immunological, and clinical factors (see table II). Neumann and colleagues first addressed these in a pilot study of ten patients who received combination antiretroviral therapy for 28 days, interrupted therapy for 28 days, and then resumed their therapy, to assess the consequences of the treatment interruption.[24] In this pilot study, the rate of viral load decrease was similar both initially and after resuming therapy following the STI and no resistance mutations were detected. The authors concluded that there were no deleterious effects from using this strategy.

From the virological point of view, an STI leads to virological rebound in most patients. This rebound, in turn, may lead to a loss of virological control (i.e. failure to resuppress viral load levels after resuming therapy) in patients with previous suppression. In the SSITT study, failure to resuppress viral load levels to <50 copies/ml after restarting antiretroviral therapy following an STI occurred in 19% of patients.[9] Virological rebound will also probably lead to a repopulation of tissue reservoirs.[25] Loss of virological control may also lead to antiretroviral drug resistance, particularly with the use of cycles of treatment and interruption. In the SSITT study, significant resistance mutations developed in at least one patient with previous viral suppression.[9] A mathematical model estimated that the risk of developing resistance during an STI would increase by several thousand over the risk associated with continuing antiretroviral therapy.[26] A second group used mathematical modelling and concluded that the risk of drug resistance might be low if viral load levels during the STI remained below baseline levels.[27]

STI may also lead to a decline in CD4+ cell count, with a coincident loss or dysregulation of immune function, which may precipitate clinical events. In the Frankfurt cohort, 17 AIDS-defining events occurred in 15 patients[11] and in the San Francisco cohort, seven events occurred in six patients, including three events that occurred during the STI.[13] In these heavily treatment-experienced patients with virological failure, the question of whether the STI directly led to the clinical events remains unclear. Other clinical issues include the occurrence or recurrence of the acute retroviral syndrome after discontinuing medications,[28-30]

the recurrence of acute drug-related adverse effects (e.g. rash, nausea), and the possible precipitation of a hypersensitivity reaction (e.g. with an abacavir-containing regimen). Pharmacokinetic issues also may arise in the period around an STI since the half lives of antiretroviral drugs vary, as do their effects on hepatic enzyme function. Exploration of STI as a strategy may also impact more generally on treatment adherence in the sense that stopping therapy is now perceived as a reasonable possibility. Finally, access to medications may be compromised or complicated by patients who temporarily stop their therapy.

## 5. Conclusions

Despite the proven benefits of antiretroviral therapy, issues of potency, adherence, toxicity, resistance, and the inability of therapy to eradicate HIV infection has created enthusiasm for new approaches to treatment, including STI. The use of one or more cycles of STI in acute treated infection has led to virological suppression without drug treatment in a small number of patients. This has not been seen commonly in patients with chronic treated infection, although STI may offer a strategy to decrease drug exposure and toxicity. In the salvage therapy setting, STI is associated with a shift from multiply-resistant virus to wild-type virus with an increase in replicative capacity that causes a rapid increase in viral load level and decrease in CD4+ cell count. This shift of resistance pattern may promote a higher rate of virological response on a subsequent regimen, although the durability of this response is uncertain.

Although the hypotheses and small case series of STI have led to great enthusiasm, STI cannot currently be recommended as a part of routine clinical care. It is important to verify the available preliminary findings in prospective, randomised studies to carefully assess and weigh the benefits and risks of this approach. Clinicians and patients considering STI should strongly consider a clinical trial that will allow frequent monitoring and close follow-up. In the event that a clinician and patient decide to proceed with an STI outside the setting of a clinical trial, every effort should be made to reduce risks, including maximising opportunistic infection prophylaxes and very close monitoring.

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