Treatment interruptions in HIV-infected subjects

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Despite a high antiviral efficacy, the use of highly active antiretroviral therapy (HAART) in clinical practice is often impaired by the long-term toxicity of antiretroviral treatment, the increased rate of human immunodeficiency virus-1 (HIV-1) drug resistance in treated patients and the cost of therapies, so that possible interruption of HAART has to be considered as part of the current clinical practice. However, this strategy is usually followed by a rapid viral rebound with a substantial loss of CD4 T lymphocytes because the HIV suppression with HAART does not result in reconstitution of the HIV-specific immune response. Structured treatment interruption (STI) has already been investigated in HIV-infected subjects with well-controlled viral replication (initiating treatment during primary or chronic HIV infection) and in those with multiple treatment failures. A clear benefit of STI in patients with chronic infection remains controversial and these benefits are more often observed in patients starting treatment during primary HIV infection.

Keywords: HIV, HAART, STI

Introduction

The current use of highly active antiretroviral therapy (HAART) in clinical practice has led to a significant decline of morbidity and mortality among subjects infected with the human immunodeficiency virus (HIV).1–3 and current guidelines suggest that HAART has to be continued lifelong.4 Nevertheless, the growing concern about the long-term toxicity of antiretroviral drugs, the prevalence of HIV-1 drug resistance in patients receiving therapy and the substantial cost of continuous treatment has focused the interest on its possible interruption. Further, some HIV-infected individuals refuse treatment and spontaneously interrupt the prescribed drugs for short or long periods of time. Patients discontinuing HAART usually develop rapid viral rebound and loss of CD4 T lymphocytes because the HIV suppression with HAART does not result in reconstitution of the HIV-specific immune response.5

The role of structured treatment interruption (STI) as a possible strategy in clinical practice is still controversial. STI has been investigated in subjects with well-controlled viral replication (initiating treatment during primary or chronic HIV infection) and in subjects with multiple treatment failures. In the first case, the rationale is to reduce the total exposure to therapy, in the second is to re-establish the circulation in the plasma of a virus potentially still susceptible to more antiretroviral drugs.6–9 A clear benefit of STI in patients with chronic infection remains to be established and, when present, it is more often observed in patients starting treatment during primary HIV infection.10

STI usually results in a transient viral load rebound and decreased CD4 counts that may affect the overall efficacy of treatment, so patients interrupting therapy have to be accurately monitored and therefore STI should not be done outside strictly experimental settings.

STIs in patients with chronic infection and suppressed plasma viraemia

The rationale for STI in these subjects is based on immune stimulation as a result of re-exposure to HIV during viral rebound (autologous immunization). The hypothesis forming the basis of STI for patients with primary infection is that the still preserved immunity could control the viral replication once the treatment is stopped. For patients with chronic infection, the treatment interruptions may allow the stimulation of a helper T cell and cytotoxic T lymphocyte (CTL) response. In both cases, the aim is to control, at least partially, the plasma viraemia in the absence of treatment. However, the interruption of an effective HAART regimen even after 2 years of virus suppression resulted in viral load rebound to levels similar to those pre-HAART, suggesting that HAART cannot significantly alter the intrinsic HIV-RNA peak.11,12

In patients receiving long-term treatments, the possibility of shorter exposure to antiretroviral drugs can significantly reduce the occurrence of long-term drug-related toxicities. Moreover, it has to be considered that in clinical settings a considerable proportion of subjects choose spontaneously to temporarily...
discontinue their treatment, because of toxicities or because of their desire to have a break from therapy. Therefore it is becoming extremely important to better manage the possible implications of the use of STI in the current clinical practice.

Studies in patients with primary infection

Anecdotal data on a small number of patients with primary HIV infection who were able to control plasma viraemia without antiretroviral treatment have been initially reported. A prospective study comparing 8 patients interrupting and 10 continuing treatment found that, despite an initial viral rebound, 3 out of 8 subjects interrupting treatment had HIV-RNA levels which rapidly dropped to <5000 copies/mL. The other five subjects resumed treatment and then underwent a second interruption cycle. Of these, only one required the re-initiation of treatment after 5.5 months. The others remained off treatment with HIV-RNA levels persistently <500 copies/mL; further, a significant increase of CTL response was observed in these subjects compared with baseline.10,15

Treatment interruptions in patients who started an antiretroviral treatment very soon after getting HIV infected have been associated with an increased HIV-specific cellular immunity. A partial control of viral replication has been achieved in some individuals, but in the majority of them the viral rebounds followed the expected kinetics. To date, no data have been reported on the failure to reach a complete viral suppression upon treatment re-initiation or to the emergence of drug resistances in this population. The role of specific antiretroviral-drug classes [e.g. protease inhibitors (PIs) versus non-nucleoside reverse transcriptase inhibitors] as well as the timing, frequency and duration of STI have never been assessed due to the small number of patients included in those studies.

Studies in patients with chronic infection

The number of studies in this group of patients is substantially larger. When an individual gets infected with HIV, the immune system is damaged, and such damage can progress during the chronic phase. As a consequence, the patients’ response to STI during the chronic phase of infection is expected to be variable.

In particular, the role of CD4+ cell count nadir has been correlated with the CD4+ cells decline during the treatment interruption and with the consequent higher probability of re-starting treatment.16,17

Conflicting data have been reported on the rate of clinical progression in these patients. A large cohort study considering STI longer than 12 weeks demonstrated that patients interrupting treatment are at higher risk of short-term clinical progression (defined as death or a new AIDS-event) than patients continuing treatment, even adjusting for the current CD4 at the time of interruption. This finding suggests that the CD4 depletion (and the consequent increase of viral replication) observed during STI may only partially explain the increased risk of clinical progression during STI.18 On the contrary, a previous report considering STI up to 3 months did not find any correlations between the interruption of therapy and clinical progression.19

Studies evaluating the efficacy of specific antiretroviral-drug classes in subjects re-starting treatment found that subjects re-starting treatment with PIs have a higher probability of reaching virological suppression than patients re-starting with non-nucleoside reverse transcriptase inhibitors (NNRTI), mainly due to the low rate of mutations selected.20-22 In a large international study, 600 patients on successful therapy were randomized to either continued therapy or to interrupt treatment with a scheme of one week on, 1 week off. In this study, more than 50% of patients were classified as virologically failed at the end of the week-off therapy. Further, all the patients failing an NNRTI- and most of those failing a 3-NRTI-based HAART developed mutations inducing multiple drug resistances.23

An ACTG study on patients with CD4 >350 cells/mm3 followed-up for 96 weeks showed that the most important predictor of HIV-disease progression (time to CDC category B or C event or death or CD4 <250 cells/mm3) was a lower CD4-cell nadir and that the decline of CD4 cells was faster during the first 8 weeks of interruptions.24

The STACCATO trial, which randomized subjects to continue or stop treatment, demonstrated that after treatment interruption, little evidence of treatment resistance emerged. As expected, drug-related adverse events were more frequent in patients who continued therapy, whereas minor manifestations of HIV infection were more frequent in patients with STI.25

An Italian study randomized subjects with persistent suppression of viral replication to continued HAART or to undergo an STI; their findings demonstrated that potential candidates for STI are subjects with high pre-HAART CD4-cell count, absence of archived mutations and a residual viral replication <2.5 copies/mL HIV-RNA.26

In summary, STI may be able to reconstitute the immune system in some chronically infected subjects, but this outcome is both variable and difficult to predict among individual patients. In particular, the quality of immune reconstitution during late-stage infection appears to be different from that occurring during acute infection. After treating an acute HIV infection the immune control of HIV replication during the treatment interruption can be better achieved than in the chronic infection, where HIV rebounds are usually higher.

Viral rebound and the risk of developing drug resistance are frequent findings in patients undergoing STI. In subjects with long-term viral suppression, an uncontrolled viral rebound can induce a possible acute retroviral syndrome.27 Other possible concerns are the potential recurrence of acute side effects of therapy during STI (e.g. hypersusceptibility reaction, rash, etc.) and the negative impact on adherence or on tolerance of therapy, because STI may cause patients to be less willing to take medications for long period of time.

STIs in patients with treatment failure or multi-drug resistant viruses

The rationale for treatment interruptions in heavily pre-treated subjects harbouring multi-drug resistant viruses was the observation that the virus population rapidly shifted from this variant to the wild type (or near wild type) and led to the hypothesis that after a treatment interruption the virus might be treatable again.

However, some studies showed that even if the wild-type virus can re-emerge after treatment interruption, the virological response is only transient after re-starting therapy for the re-emergence of baseline resistance patterns and also for the occurrence of additional mutations in patients failing this strategy.28
The clinical outcome of heavily pre-treated patients interrupting HAART has been evaluated in two large trials with conflicting findings. The study of Lawrence et al. randomized 270 patients with multidrug-resistant viruses and with HIV-RNA >5000 copies/mL to a 4 month structured interruption of treatment followed by a change in antiretroviral regimen (n = 138) or to an immediate change in the regimen (n = 132). Disease progression or death occurred in 22/138 in the treatment interruption group and in 12/132 in the control group, with 2.57-fold higher risk in the first group. Further, the treatment interruption group had a lower immunological and virological benefit, whereas the reported quality of life was comparable between the groups. The study of Katlama et al. randomized 68 subjects with multiple previous treatment failures and with CD4 <200 cells/mm³ and HIV-RNA >50000 copies/mL to receive a GigHAART salvage regimen for 24 either immediately or after 8 weeks of treatment interruption. A higher proportion of subjects in the treatment interruption group had virological success after 12 weeks compared with patients receiving multi-drug therapy alone (62% versus 26%, P = 0.007). Further, treatment interruption led to an increase in the number of the susceptible drugs of the multi-drug regimen. The different results of these reports can be partially explained by the different end-points considered (disease progression in the first, virological success in the second). At the moment, no data have yet showed that in heavily pre-treated subjects with very few therapeutic options, a treatment interruption can reduce the rate of disease progression and death. As a consequence, this strategy should be avoided in patients not completely responding to antiretroviral treatment and with advanced disease.

Conclusions
The use of STI is not uncommon in clinical practice. In the majority of cases they are requested by the patients or seem to be associated with long-term drug-related toxicity. In a limited subset they have been used in patients heavily pre-treated to resume wild-type virus. Further, the substantial cost of long-term antiretroviral therapy has to be taken in consideration.

However, the role of STI as a possible therapeutic approach is still controversial. Although it seems acceptable and convenient in patients starting antiretroviral treatment during primary HIV infection or in subjects with chronic infection and with high levels of CD4 cells count (and a high nadir of CD4 cells count), in other individuals its use should be strictly evaluated and controlled. In particular, it should be avoided in patients with highly advanced disease harbouring multi-drug resistant viruses, due to the higher risk of disease progression.

In conclusion, patients interrupting treatment need to be accurately monitored and the use of STI should perhaps be discouraged outside clinical trials.

Transparency declarations
None to declare.

References


