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Structured treatment interruptions (STI) in chronic suppressed HIV infection in adults (Review)

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ABSTRACT

Background
Although antiretroviral treatment (ART) has led to a decline in morbidity and mortality of HIV-infected patients in developed countries, it has also presented challenges. These challenges include increases in pill burden; adherence to treatment; development of resistance and treatment failure; development of drug toxicities; and increase in cost of HIV treatment and care. These issues stimulated interest in investigating the short-term and long-term consequences of discontinuing ART, thus providing support for research in structured treatment interruptions (STI).

Structured treatment interruptions of antiretroviral treatment involve taking supervised breaks from ART. STI are defined as one or more planned, timing pre-specified, cyclical interruptions in ART. STI are attempted in monitored clinical settings in eligible participants. STI have generated hopes of reducing drug toxicities, decreasing costs and total time on treatment in HIV-positive patients. The first STI was attempted in the case of a patient in Germany, who later permanently discontinued treatment. This successful anecdotal case report led to several trials on STI worldwide.

Objectives
The objective of this systematic review was to assess the effects of structured treatment interruptions (STI) of antiretroviral therapy (ART) in the management of chronic suppressed HIV infection, using all available high-quality studies.

Search strategy
Nine databases covering the time period from January 1996 to March 2005 were searched. Bibliographies were scanned and experts contacted in the field to identify unpublished research and ongoing trials. Two reviewers independently extracted data, and evaluated study eligibility and quality. Disagreements were resolved in consultation with a third reviewer. Data from 33 studies were included in the review.

Selection criteria
STI is a planned, timing pre-specified experimental intervention. In our review, we decided to include all available intervention trials in HIV-infected patients, with or without control groups. We reviewed evidence from 18 randomized and non-randomized controlled trials, and 15 single arm trials. Single arm trials were included because these pilot studies made significant contribution to the early development and refutation of hypotheses in STI.

Data collection and analysis
Trials included in this review varied in study participants, methodology and reported inconsistent measures of effect. Due to this heterogeneity, we did not attempt to meta-analyse them. Results were tabulated and a qualitative systematic review was done

Main results
For the purpose of this review, STI strategies were classified either as a timed-cycle STI strategy or a CD4-guided STI strategy.
In timed-cycle STI strategy, a predetermined period of fixed duration (e.g. one week, one month) off ART was attempted followed by resumption of ART, while closely monitoring changes in CD4 levels and viral load levels. Predetermined criteria for interruption and resumption were laid out in this strategy. Timed-cycle STI fell out of favor due to reports of development of resistance in many studies. Moreover, there were no significant immunological and virological benefits, and no reduction in toxicities, reported in these studies.

In CD4-guided STI strategy, ART was interrupted for variable durations guided by CD4 levels. Participants with high nadir CD4 levels qualified for this approach. A reduction in costs of ART, a reduction in mutation, and a better tolerability of this CD4-guided STI strategy was reported. However, concerns about long-term safety of this strategy on immunological, virological, and clinical outcomes were also raised.

Authors’ conclusions
Timed-cycle STI have not been proven to be safe in the short term. Although CD4-guided STI strategy has reported favorable outcomes in the short term, the long-term safety, efficacy and tolerability of this strategy has not been fully investigated. Based on the studies we reviewed, the evidence to support the use of timed-cycle STI and CD4-guided STI cycles as a standard of care in the management of chronic suppressed HIV infection is inconclusive.

SYNOPSIS
Structured treatment interruptions (STI) of antiretroviral therapy (ART) have been studied as an alternative strategy in the management of HIV-infected patients. STI involve planned, pre-specified cyclical interruptions in ART with an aim to alleviate treatment fatigue, provide possible immunological benefit, reduce drug toxicities and decrease costs of care.

This systematic review aims to synthesize the evidence for use of STI as an alternative strategy in the management of chronic suppressed HIV infection. STI is a planned, experimental intervention, and the evidence from 33 available intervention trials has been summarized. Currently, several large STI trials are underway, investigating long-term effects of STI strategies. Their results will be available in a few years. Based on the studies we reviewed, we find that there is insufficient evidence to support the use of STI as a standard of care in the management of chronic suppressed HIV infection.

BACKGROUND
The introduction of antiretroviral treatment (ART) has led to a decline in morbidity and mortality of HIV infection in the developed world. (Flepp 2001). However, long-term management with ART has presented challenges to patients and providers. These challenges include increased pill burden, adherence to medication, increase in ART toxicities, higher cost of HIV management (Hirschel B 2001, Lori 2002). Moreover, concerns about development of resistance, treatment failure and treatment fatigue have been raised by providers (Benson 2001, Blankson 2001). These concerns stimulated interest in understanding the short-term and long-term consequences of periodically discontinuing the use of antiretroviral therapy (Dybul 2002, Havlir 2002). These intermittent, supervised, periodic breaks in ART have been termed “structured treatment interruptions,” or STI (Miller 2001, Lori 2000). STI have been defined as “one or more planned, pre-specified, cyclical interruptions in ART,” monitored by CD4 T-cell counts or HIV RNA levels. They have been attempted in eligible participants in controlled clinical trial settings.

Researchers have been investigating the effects of STI for several years (Ananworanich 2005). The first success with STI was reported in 1999, in the case of a patient from Germany, in whom, on development of complications from ART, two sporadic interruptions were attempted (Lisziewicz 1999). This patient developed a strong antiviral HIV-1 specific immune response and subsequently discontinued treatment permanently. This early anecdotal successful case report lead to studies of STI in clinical settings worldwide.

Larger controlled trials investigating STI are currently underway in different parts of the world. (e.g., BASTA, SMART, ISSPART, TRIVICAN, DART, ANRS 0164; CTN 164, CTN173, CTN 167 (OPTIMA) CTN190 (SMART) ANRS 112, ANRS 100). In United States, NIAID is investigating effects of STI alone or in conjunction with immune-adjuvants (NCT00084032, NCT00100646, NCT0080106, NCT0035893, NCT0013663, NCT0001899, NCT0071890). The trial results are expected in a few years. In this context, the role of STI remains to be determined.

STI have been investigated in three distinct HIV patient populations:

i) acute HIV infection (primary HIV infection),
ii) chronic HIV infection with suppressed viremia (controlled HIV infection),

iii) chronic HIV infection with unsuppressed viremia (uncontrolled HIV infection or treatment failure or salvage therapy).

Patients in these three categories of HIV infection (primary HIV, chronic suppressed, chronic unsuppressed) differ immunologically, virologically, and clinically. Therefore, to assess the performance of STI in each category, each category was analyzed separately.

We have summarized the evidence of effects of STI in these three categories of HIV infection in three separate reviews. This is the first review in the series. Patients with chronic suppressed (controlled) HIV infection constitute the majority of patients in clinical practice in the developed world, and the evidence in this review will be of relevance to them.

Aims and objectives of STI

The aims of STI in chronic suppressed HIV infection are:

i) decrease in exposure to ART with an aim to reduce total time on treatment, and alleviate treatment fatigue;

ii) decrease in ART toxicity and adverse effects;

iii) maintenance of treatment efficacy and control of viral rebound on ART resumption;

iv) investigation of the "auto-immunization hypothesis," i.e. the repeated exposure to autologous virus during off-ART periods, with the hope of enhancement of immune response (Fagard 2003, Fischer 2003).

OBJECTIVES

The objective of our systematic review was to summarize the effects of structured treatment interruptions in adults with chronic suppressed HIV infection.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Inclusion criteria

STI are planned interventions, in monitored settings. We included randomized controlled trials, and non-randomized controlled trials that compared patients on STI with participants on continuous ART. We also included non-randomized controlled trials and single arm intervention trials, because they contributed to the early developments in the field.

Exclusion criteria

Studies investigating unplanned, unstructured treatment interruptions were excluded, (i.e. those with naturally occurring treatment interruptions, drug discontinuations due to drug safety and tolerability). Case reports, case series, editorials, reviews, expert opinions, newsletters, modelling studies, in-vitro studies, and animal studies were excluded. Non-English studies, abstracts, and letters were excluded due to lack of complete peer-reviewed information.

Types of intervention

HIV-infected adults on continuous ART

Intervention strategies:

STI strategies were classified into two major categories:

i) Timed-cycle STI

ii) CD4-guided STI

i. Timed-cycle STI:

In this strategy, a timed-cycle STI (a predetermined timed period of fixed duration off ART) has been attempted, followed by resumption of ART. Timed-cycles have been guided by CD4 or viral load (VL) levels. ART is interrupted if CD4 levels are high (>350 cells/ml) or if VL is undetectable (VL<50 copies/ml). ART is resumed when CD4 levels fall (<200 cells/ml) or VL rebounds (500-5000 copies/ml); or, if patients experience adverse effects and are unable to tolerate STI. Criteria for reintroduction of ART and STI duration have been clearly specified in these trials.

ii. CD4-guided cycle STI:

In this strategy, ART is interrupted for variable durations guided by HIV-specific CD4 levels. ART is interrupted when CD4 are high (>350 cells/ml) and resumed if CD4 drops to low levels (<200 cells/ml). Patients with high nadir CD4 400-500 cells/ml qualify for this approach.

Types of co-intervention

In some studies, co-interventions (e.g. immune adjuvants such as interleukin-1, hydroxyurea mycophenolate mofetil) were used in addition to STI.

Classification of study design

I. Randomized controlled trials

In randomized controlled trial settings, participants on STI were compared to participants on continuous ART, or alternative STI strategies were compared.

II. Non-randomized controlled trials

In non-randomized controlled trial settings, participants on STI were compared to participants on continuous ART.

III. Single arm intervention studies and uncontrolled trials

In single arm trials, effects of STI were investigated in participants, with no comparison groups.

Types of outcome measures

The following outcomes were investigated:
1. Immunological outcomes:
a. absolute and percent changes in HIV-specific CD4 cell count
b. absolute and percent changes in nadir CD4 counts
c. absolute and percent changes in HIV-specific CD8 T-cell specific response
d. relative changes in CD4:CD8 ratio

2. Virological outcomes:
a. absolute changes and log changes in HIV RNA viral load

3. Clinical outcomes:
a. occurrence of opportunistic Infections
b. progression to CDC stages A, B, C
c. occurrence of acute retroviral syndrome
d. health related quality of life outcomes

4. Drug related outcomes:
a. adverse effects and toxicities
b. resistance mutations

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: HIV/AIDS Group search strategy

Time Period
The search strategy covered the period 1st Jan 1996 to 1st March 2005.

Search string
The search for trials was performed using the Cochrane HIV/AIDS Review Group search strategy, with the help of the Cochrane HIV/AIDS Review Group in San Francisco (and South Africa).

Our MEDLINE search string is reproduced below:
(["HIV"[MESH]] OR ["Acquired Immunodeficiency Syndrome"[MESH]] OR [HIV-1 [TW]] OR [HAART [TW]] OR [AIDS [TW]] OR ["Antiretroviral Therapy, Highly Active"[MESH]])
AND (((structured treatment interruption*) OR [Structured therapeutic interruption*) OR [structured intermittent therapy]) OR [scheduled treatment interruption*) OR [drug holiday*) OR [planned interruption*) OR [treatment interruption*) OR [strategic treatment interruption*) OR [intermittent therapy] OR [intermittent treatment)))

Databases and sources
Nine databases were searched:
1) Cochrane Controlled Trials Register (CENTRAL)
2) MEDLINE
3) EMBASE
4) BIOSIS
5) Web of Science
6) AIDSLINE (via NLM Gateway)
7) ACTIS (AIDS Clinical Trials Information Service)
8) Database of Abstracts of Reviews of Effectiveness (DARE)
9) Proceedings and abstracts from AIDS conferences, global meetings (via NLM Gateway)

In addition, bibliographies of included studies and relevant review articles were searched. Experts in the field were also contacted to identify unpublished research and ongoing trials

Strategy
For the first screen, 3186 potentially relevant articles were identified and screened; 1182 duplicate citations were excluded; 1139 citations were selected for further review. From these, we excluded 951 citations and studies for a variety of reasons (e.g., they were modelling studies, animal studies, case series, case reports, reviews, opinions, news items, or editorials). The remaining 188 articles were identified as relevant. Of these, 60 articles were excluded for several reasons (e.g., they were concerned with basic sciences, or were letters). In the third screen, 128 full-text articles were retrieved. Of these, 72 were excluded for several reasons (e.g., they were non-English-language studies or abstracts). A total of 56 articles were pooled in three categories of HIV infection (acute, chronic HIV suppressed, and chronic HIV unsuppressed). The final data abstraction for this review on chronic suppressed HIV infection was done on 33 studies.

METHODS OF THE REVIEW

Study eligibility
In the first screen, two reviewers independently screened titles and abstracts and evaluated study eligibility. Reviewers were not blinded to the names of the authors, journals, and other publication details. Articles identified as relevant in the first screen were evaluated in greater detail in the second screen using full text reports. Trials meeting inclusion criteria were considered eligible for inclusion.

Qualitative review
Trials investigated different STI strategies in diverse patient populations worldwide with varying eligibility criteria. Reported outcomes varied across trials. Outcome reporting was inconsistent, with no reporting of measures of effect. Therefore, it was considered inappropriate to combine them together in a meta-analysis. Trial results were tabulated and the evidence was summarized qualitatively.

Data abstraction:
Data were abstracted independently by two reviewers (NPP, JPT), using a standardized data extraction form. Disagreements were resolved by consensus after consultation with a third reviewer (JL). The two reviewers also independently assessed the methodological quality of all the included trials. The inter-rater reliability was high (kappa=0.8)

Extracted data included information on study design, clinical setting, country, patient population, type of trial, eligibility criteria

Structured treatment interruptions (STI) in chronic suppressed HIV infection in adults (Review)

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of participants, sample size for STI and control groups, STI strategy, duration and cycles, outcomes, and assessment of quality.

**DESCRIPTION OF STUDIES**


**Classification of studies**
Studies were classified according to STI strategies, and further classified by study designs.

**A. Timed-cycle STI**

**A. Category 1: Randomized controlled trials**
Studies in which pre-defined cycles of STI of fixed duration were attempted in clinical trial setting in which eligible participants were randomly assigned to an STI arm and a continuous ART arm. N=14 trials.

**A. Category 2: Non-randomized controlled trials**
Studies in which pre-defined cycles of STI of fixed duration were attempted in eligible participants, with control groups were assembled at baseline, but the intervention was non-randomized. N=7 trials.

**A. Category 3: Single arm/uncontrolled trials**
Early uncontrolled pilot studies in which STI of fixed durations were attempted in eligible participants with no comparison groups. This group also included the largest single arm intervention study with before-and-after comparisons, the Swiss-Spanish Intermittent Treatment Trial. N=14 trials.

**B. CD4-guided STI:**

**B. Category 1: Randomized controlled trials**
Studies in which eligible participants were randomly assigned to a CD4-guided STI cycle arm and a continuous ART arm. CD4-guided STI were also referred to as "pulse therapy" and the goal was "to maintain CD4 above a particular level, using cycles of varying duration." N=4 trials.

**B. Category 2: Non-randomized controlled trials**
In a single study, a cohort of participants was assembled at baseline and STI of variable duration were attempted, guided by HIV-specific CD4 levels (Boschi 2004). N= 1 trial.

**B. Category 3: Single arm/uncontrolled trials**
In a single study, a cohort of participants was assembled at baseline, and variable cycles of STI were attempted in eligible study participants with chronic HIV infection (Tarwater 2003). N=1 trial.

**A. Timed-cycle STI:**

**A. Category 1: Randomized controlled trials (refer to table of comparisons)**
Seven trials were identified in this category. Study sample sizes varied from 12 to 53. Timed-cycle STI of one week to two months durations were attempted. Varying ART regimens for variable durations (6 months to 3 years) were used. Eligibility criteria varied across trials. (e.g. most commonly, age>18 years, CD4 nadir >400, VL<50 cop/ml, no history of opportunistic infections or AIDS defining illness, no history of drug resistance) at baseline. Varying durations of follow up were reported.

**A. Category 2: Non-randomized controlled trials (refer to table of comparisons)**
Six trials were identified in this category. Study sample sizes ranged from 8-45 participants. Timed-cycle STI of two weeks to three months were attempted. Varying ART regimens for variable durations (exceeding 6 months) were used. Eligibility criteria varied across trials (e.g. undetectable VL at baseline, CD4>350 cells/ml); varying durations of follow up (1 month to 2 months) were reported.

**A. Category 3: Single arm/uncontrolled trials (refer to table of comparisons)**
Fourteen trials were identified in this category. These early controlled trials were pilot studies with small study sample sizes ranging from 9-20. Timed-cycle STI of varying durations (1-2 months) were attempted. Varying ART durations (6 months to one year) and varying ART regimens were used. Eligibility criteria varied across trials. The largest trial in this category was the Swiss-Spanish Intermittent Treatment Trial (SSITT), with a sample size of 133, in which timed-cycle STI of “two weeks on and eight weeks off” were attempted. These pilot studies were seminal in generating evidence in the field, but were limited by the absence of comparison groups. The study findings were later replicated in large randomized controlled trials.

**B. CD4-guided STI:**

**B. Category 1: Randomized controlled trials (refer to table of comparisons)**
Four studies reporting on two trials, were identified in this category. Study sample sizes varied from 26 to 150. STI durations were guided by nadir CD4 levels (CD4<400). ART durations varied from 6 months to 4.6 years. Various ART regimens were used (2NRTI + PI, 2NRTI, SQV+RTV, PI+NNRTI+NRTI) were used. Eligibility criteria varied across trials.

**B. Category 2: Non-randomized controlled trials (refer to table of comparisons)**
In this category, a cohort of participants was assembled at baseline. There was only one trial in this category with a sample...
size of 71. Two to four cycles of STI of variable durations were attempted. STI were guided by nadir CD4 (i.e. ART stopped when CD4>500, reintroduced when CD4<300); ART duration exceeded 36 months. Variable ART regimens were used. Eligibility criteria included both treatment naïve and treatment experienced participants. The total follow up duration was 28 months.

B. Category 3: Single arm/uncontrolled trials (refer table of comparisons)
The single trial in this category (Tarwater 2003) had a sample size of 105. Variable STI durations were attempted; median duration of STI was 114 weeks. ART duration at baseline exceeded 6 months. The objective of the study was to determine best predictors of STI pulse therapy in which “cycles of therapy followed by prolonged interruption” were studied.

METHODOLOGICAL QUALITY

The methodological quality of the trials was assessed using two methods:
1. Jadad’s scale, a validated quality assessment instrument
2. Cochrane method for adequacy of concealment of allocation.

We also referred to the Cochrane Handbook for assessing study quality.

On the Jadad scale, each study was critically appraised for the following criteria and a Jadad score was assigned. Each criterion was assigned a score of 1 on a total of 5 points.

The Jadad scale comprises the following criteria:
I. Was the study randomized? (1 point)
   a. If so, was allocation concealed? (1 point)
II. Was the study double-blinded? (1 point)
   a. If so, were outcome assessors blinded? (1 point)
III. Was there a complete description of withdrawals and dropouts? (1 point)

Concealment of treatment allocation was assessed using the standard Cochrane criteria. Studies were graded based on the following criteria:

Grade A adequate: Centralized, sequentially numbered sealed envelopes, on site computer system allocation, pre-numbered or coded.
Grade B unclear: If methods were not adequately described
Grade C inadequate: If sequences such as consecutive series of patients, case record numbers, date of birth, date of admission were used
Grade D not used/not reported: If methods were not reported

RESULTS

We summarized results across trials and have provided individual study results. For more details on individual studies, please refer to the tables.

A Timed-cycle STI

A. I. Category 1: Randomized Controlled Trials:

Results in summary across trials

In the timed STI cycle studies we reviewed, there was a pattern of decline in HIV-specific CD4 T-cells in five studies (Alexander 2003, Dybul 2003, Florence 2004, Plana 2004, Ruiz 2000). There was no evidence of significant immunological or virological benefit in four studies (Alexander 2003, Florence 2004, Papasavvas 2004, Plana 2004). Reports of resistance mutations were noticed in two studies (Dybul 2001, Papasavvas 2004). There were no improvements in metabolic parameters, nor were there adverse effects in one study (Dybul 2003). Only one study that used a co-intervention in addition to STI, i.e. containment of viral rebound and maintenance of stable CD4 during STI, reported different results (Garcia 2003).

Results of individual studies: (refer to table of comparisons)

Dybul 2003 attempted a timed-cycle STI in 52 participants. STI cycles of 4 weeks off and 8 weeks on ART were attempted. Eligibility criteria of participants were CD4>300 cells/ml, VL<500 copies/ml. ART duration exceeded six months. As a result of the study, an increase in VL >50 copies/ml was reported in 26% participants in the STI arm and 9% of participants in the control arm. There were no differences between the groups in HIV-specific immune responses (CD4 T-cell counts and CD8 T-cell counts) with no reports of auto-immunization benefit. Reports of resistance were present in 3 of 5 STI (60%) participants. In terms of changes in metabolic parameters, significant differences (p=0.04) in total cholesterol and triglyceride levels reported between groups at week 40, were lost at week 48, thus there were no reductions in adverse effects of ART.

Garcia 2003 attempted a timed-cycle STI in 20 participants. Participants were randomized to a control (continuous ART arm) and an intervention (ART plus hydroxyurea arm) for 24 weeks followed by 5 timed STI cycles. Eligibility criteria of participants were CD4 >500 copies/ml, VL>10,000 copies/ml, and ART duration greater than 52 weeks. As a result of the interventions, VL<5000 copies/ml was reported in 8/9 participants in the intervention arm, and 4 of 10 participants in the control arm. The intervention arm reported a better control of viral load with a lower virological set-point. The authors attributed this result to the cytostatic effect of hydroxyurea on CD4 T cells.

Ruiz 2000 reported results of a timed-cycle STI in 26 participants. Twelve participants were randomized to an intervention arm of...
three cycles of STI with use of an interleukin co-intervention; continuous ART was administered in the control arm. Eligibility criteria of participants were HIV-1 asymptomatic adults >2 years, two years of viral suppression with ART, HIV-1 RNA <50 copies/ml for 24 months, and CD4/CD8 ratio >1 for duration greater than six months. In the intervention arm, there were reports of HIV-1 RNA rebound in all three STI cycles. No significant change in CD4 and CD8 T cell counts or in memory and naive subpopulations were seen. The authors suggested use of immune-based therapies for restoring HIV specific immune response.

Alexander 2003 reported results from a timed-cycle STI trial with 12 participants. Three cycles of STI (2 cycles of 1 month, followed by a 3-month final interruption) were attempted. Eligibility criteria of participants were CD4>400, VL<50 and duration of HIV 12 years. Pre-ART HIV RNA-level predicted HIV RNA-level during STI. Four of eight participants (50%) maintained stable CD4 T cell counts during STI. In three participants, rash, myalgia and respiratory symptoms were reported. Duration of STI affected CD4 cells. The authors suggested avoidance of STI in patients with high viral loads and high virological setpoints. The study results were limited by small sample size.

Papasavvas 2004 investigated timed STI cycles of 2 weeks, 4 and 6 weeks (phase I) followed by a one long STI cycle (phase II) in a sample of 42 participants and compared to continuous ART group with a single interruption. Follow up of 81 weeks was reported. Eligibility criteria were CD4>400, CD4 nadir>100 and age>18 years. Primary outcome was defined as time to viral rebound (>5000 copies/ml) at 4 weeks. There was no significant difference between the two groups with respect to time to viral rebound during the open ended TI of 4 weeks [1-8] weeks, and STI group 5 [4-8] weeks. (p=0.36). Secondary outcomes were defined as study-defined safety criteria, viral resistance, therapy failure and retention of immune constitution. There were no differences in secondary outcomes noted between groups. There was no evidence of postulated virological benefit or immune reconstitution, nor was there any reduction in adverse effects of ART. STI failed to confer a clinically significant virological benefit.

Plana 2004 reported follow up data on 45 participants recruited from two trials, the Swiss-Spanish Intermittent Treatment Trial and a pilot study by Garcia et al. In these trials, STI of “one week on and one week off” were attempted. In the pilot STI trial, a total of five cycles of STI were attempted. At baseline, participants had VL<20 copies/ml for 32 weeks, HAART duration for one year. In patients with nadir CD4>400, increased HIV-1 specific immune response seen; significant decrease in CD4 T cell percentage (p<0.001); and an increase in response to CD8 T cell between day 0 and week 52 (p<0.0001) was reported. VL set point during final STI was lower, positively correlated to baseline VL before HAART (p<0.0001). STI did not control viral replication, possibly because boosted cytotoxic cell responses lacked durable, strong and sustained helper T cell response. To reset VL set point, alternative approaches to augment helper T cell response need investigation. Reduction of viral set point after STI was not understood. HIV-1 specific cellular immune responses can be augmented following cycles of therapy interruption in very early stage HIV-1 chronically infected individual.

Florence 2004 reported long term clinical follow up data for 2 years on 26 of 60 participants of STI trials, who stayed off therapy after STI in 60 participants. Timed-cycle STI of varying durations (2 weeks to 4 months) were attempted. Eligibility criteria of participants were asymptomatic chronic HIV infection, pre STI viral load<20 copies/ml, nadir CD4 >500. Two of four trials used co-interventions hydroxyurea and mycophenolic mofetil in addition to STI. At the end of 2 years, in 11/26 participants, the plasma viral load without ART was significantly lower than pre HAART plasma VL and CD4 cell counts remained stable in all patients. Plasma VL remained lower than the viral set point. 43% patients did not resume therapy long term, and 42% patients had a lower virological setpoint. 18% patients with CD4 >500 were able to maintain a lower pVL for a long time after a period of STI. The authors concluded that STI could benefit a minority of patient population.

A.II. Category 2: Non-randomized controlled trials:

Results in summary across trials:

In this category, timed-cycle STI of 1-2 months were attempted in eight controlled trials in small samples of patients (n=9-20). As a result of STI, a pattern of a decrease in HIV-specific CD4 T-cell counts and viral rebound was noticed across five studies (Garcia 2001, Molto 2004, Montes 2005, Ortiz 2001, Ruiz 2000). An increase in CD8 T-cell immune response was reported in one study (Ruiz 2000). In one study, there were no significant changes in metabolic parameters (serum hepatic transaminase, lipid levels as a result of STI (Dybul 2001). An increase in interleukin-16 was reported in one study (Montes 2005). Reports of development of drug resistance mutations were seen in one study (Molto 2004). However, two studies used STI in addition to hydroxyurea, and reported different results (Foli 2002). No significant changes in HIV specific immune response (i.e. CD4 and CD8 T-cell counts) were reported as a result of STI; this difference was attributed to hydroxyurea.

Results of individual studies (refer to table of comparisons):

Ortiz GM 2001 attempted three cycles of STI of onemonth and three months duration in 12 participants. Eligibility criteria were CD4 counts>400 cells/ml for six months, VL<400 copies/ml for three months, and normal renal, hepatic, and hematopoietic function. In STI participants, a decrease in HIV specific CD4 T-cell counts (p=0.001), an increase in HIV specific CD8 T-cell response (p=0.003), a rebound in VL (viral load) (p=0.34) was noticed. In control participants, stable CD4 cell counts, no increase in CD8 T cell counts and VL were reported. There was no clear benefit accrued to STI in this study.
Lori 2002 and Foli 2002 attempted one timed-cycle STI of 8 weeks duration, in 9 participants, the PANDA cohort (treated with hydroxyurea and didanosine), and compared them to a control group (n=7) on continuous ART. Eligibility criteria were CD4 counts of 250-500 cells/microlitre, on hydroxyurea/didanosine, and similar VL and CD4 at baseline. In Lori 2002, STI participants (the PANDA trial) reported a significant control of viral rebound (p<0.002), with a median increase in CD4 cells from 444 cells/mm³ to 512 cells/mm³. In comparison, four of seven control participants failed to control VL, with a decrease in CD4 T-cell count. This trial suggested that HIV could be controlled during STI, and that hydroxyurea and didanosine could prove valuable additions to therapy.

Foli 2002 also reported on the PANDA cohort. STI participants contained viral rebound during STI, with no significant changes in CD4 counts from a median of 444 cells/mm³ to a median of 512 cells/mm³ at week 8 (p=0.31). In the comparison group, reports of significant decrease in CD4 counts from 428 cells/mm³ to 340 cells/mm³ (p=0.02) were seen. A linear correlation between viral load at baseline and at the end of STI was noted. In comparison, control patients on continuous ART experienced a significant drop in CD4 counts from 428 cells/mm³ to 340 cells/mm³ (p=0.02). At week 40, differences between the STI and the control group were not significant (p=0.14). Foli suggested that the potential of STI to enhance immune response differed from patient to patient, and that hydroxyurea aided in control of virus.

Montes 2005 reported results of 3 cycles of timed-cycle STI (4 weeks off and 8 weeks on) in 45 participants. STI participants (n=15) were compared to age and sex matched controls (n=20). As a result of three cycles of STI, CD4 count decreased from 769 to 637, CD8 count decreased from 1415 to 1270, and VL was undetectable at all three cycles. There were no reports of AIDS-defining illnesses. There was a reported increase in serum levels of IL-16 cytokine level after each interruption. STI failed to modify immunological parameters.

Molto 2004 attempted timed-cycle STI of “2 weeks off and 4 weeks on” in 15 participants and compared them to 30 age- and sex-matched controls (n=20). As a result of three cycles of STI, CD4 count decreased from 637 to 545 copies/ml. During STI, median drop in CD4 counts was 23.5% in 4 weeks, and 33% in 8 weeks. CD4 nadir in STI group was 340, and CD4 nadir in control group was 560. There were no differences in viral load seen in patients who resumed treatment by week 48. No patients developed AIDS-defining events. CD4 nadir emerged as a predictor of treatment re-initiation.

Tuldra 2001 reported results of a controlled trial in 24 participants. Four STI cycle of 30 days duration were attempted in 12 participants and compared to 12 controls. The reported quality of life and perceived health status was better in STI participants than control participants (p=0.02) and health status decreased on treatment resumption. Effort to follow medication was greater at first resumption of therapy and feeling of freedom from duty of medication intake reported in 70% participants. There were no differences with respect to CD4 and VL on reintroduction of ART. There were no differences between CD4 and VL between the two groups. A greater effort was needed to resume therapy in participants on STI.

### A.III. Category 3: Single arm/uncontrolled trials (refer to table of comparisons)

#### Results in summary across trials

To summarize, there were fifteen single arm trials of small sample sizes in this category. A pattern of decline in CD4 as a result of STI was reported in four studies (D’Offizi 2002, Fagard 2003, Garcia 2001, Martini 2002). Two studies reported no change in mean CD4 cell counts (Dybul 2001, Ruiz 2000); one study reported an increase in memory CD4 T-cell subset (p=0.03) (Garcia 1999). A pattern of viral rebound was reported by seven studies (Fischer 2003; Garcia 1999, Garcia 2001, Martini 2002, Oxenius 2002, Oxenius 2002a, Ruiz 2001). No significant change in VL during STI was reported in two studies (Dybul 2001, Fagard 2003). Risk of evolution of resistance in STI was reported in two studies (Hance 2001, Martinez-Picado 2002). Concern of emergence of mutant variants during viral replication was reported in one study (Metzner 2003). A transient improvement in metabolic parameters during STI was reported in two studies (Dybul 2001, Hatano 2000).

#### Swiss-Spanish Intermittent Treatment Trial

The largest study in this category was the Swiss-Spanish Intermittent Treatment Trial (SSITT), which recruited 133 patients. Eligibility criteria were baseline median CD4 count of 740/microlitre, and an undetectable viral load. Four fixed cycle STI cycles of “2 weeks off and 8 weeks on” were attempted. This trial generated and refuted a major hypothesis in the field.

The SSITT was reported in five studies (Fagard 2003, Fischer 2003, Metzner 2003, Oxenius 2002, Oxenius 2002a). Fagard 2003 opined that results of the SSITT trial did not favor the “auto-immunization hypothesis,” so additional immune adjuvants to enhance immune response were needed. Oxenius 2002 reported in their study that STI were unsuccessful in lowering the virological setpoint, nor did they bring about a change in equilibrium between HIV-specific immunity and viral levels. The hypothesis of contribution of cytotoxic lymphocytes in controlling viral replication during STI was rejected by them. Fischer 2003 suggested an increased risk of development of resistance in timed-cycle STI. Factors such as pro-viral DNA, cell associated HIV RNA, pretreatment plasma VL predicted viral replication in STI.A small sub group of patients with slower viral rebound could qualify as candidates for STI. Metzner 2003 reported that variants of HIV-1 virus carrying drug resistant mutations could emerge during periods of HIV-1 replication. Resistance mutations L90M and M184V were detected during periods of viral replication.

#### B. CD4-guided STI
B. I Category I: Randomized controlled trials: (refer to table)

Four trials reported on the novel CD4-guided STI strategy. The first randomized controlled trial to compare alternative STI strategies was the multicentric STACCATO trial (Ananworanich 2003). This trial had three arms, a “one week on and one week off” (WOWO) STI arm, a CD4-guided STI arm and a continuous ART arm. It was reported by three studies (Ananworanich 2003, Cardiello 2005, Nuesch 2005).

Ananworanich 2003 reported results in different arms. The eligibility criteria of participants were CD4>350 copies/ml and VL<50 copies/ml. In timed-cycle “one week on and one week off” STI arm, virological failure (VL>500 copies/ml) was reported in 53% patients, leading to premature termination of this arm. In comparison to the continuous ART arm, virologic failure was reported in two patients. In the CD4-guided arm, there were no virologic failures. The success of this arm set the trend for future exploration of CD4-guided STI cycles.

Cardiello 2005 reported on clinical outcomes in 71 patients from the STACCATO trial. At the end of STI, the median CD4 in the WOWO arm was 582, in the control arm it was 547, and in the control arm it was 637. The VL (log copies/ml) in the WOWO arm was 1.70, in the CD4 arm it was 1.96 and in the control arm it was 1.69. Undetectable viral load was achieved in 72% of participants in the WOWO arm, 45% of participants in the CD4 arm, and 100% of participants in control arm. Grade 3 and Grade 4 events were reported in 46% of participants in the WOWO arm, 65% of participants in the CD4 arm and 44% of participants in the control arm. Treatment failure was reported in 31% participants in the WOWO arm. Comparing time on therapy in the three arms: on continuous ART it was 100%; in the CD4-guided arm it was 87%; and the fixed cycle arm it was 96%. In the CD4-guided arm, participants did very well, although savings in ART and long-term outcomes need to be investigated.

Nuesch 2005 reported follow up on this trial at 108 weeks. Resistance tests were conducted in 20 of 23 HIV-infected Thai patients. There were reports of one major mutation (T215Y) in the CD4 arm. There were no reports of virological failure at 48 weeks. At 108 weeks, there were reports of one virological failure in the STI arm and one virological failure in the continuous arm. CD4-guided STI appear to be safe in this patient population. Mutations in CD4-guided arm decreased from 36% pre STI, to 6% after STI.

Maggiolo 2004 reported on the BASTA study that investigated CD4-guided STI in a sample of 69 patients. Eligibility criteria of participants were age >18 years, CD4>800, VL<50 copies/ml. At baseline, VL was undetectable and CD4 was 1077 copies/ml. Intention to treat analysis was conducted in this study. Follow up duration was reported at 64 weeks. The primary endpoint was defined as the proportion of subjects maintaining a CD4 cell count >400. The secondary endpoint was defined as the dynamic and predictive variables of CD4 cell loss. In the STI group, participants with a CD4 cell count <400 were not statistically different from those in the control group. There were no differences in metabolic parameters between STI and control groups. Two patients developed adverse events. In a multivariate model, the parameter significantly associated with the possibility to stay off therapy and prolong STI was CD4 cell count (B=1.749, p=0.001). The main predictor of decline in CD4 was nadir CD4 (p<0.001). Greater viral rebound and greater cell loss were reported in the low nadir CD4 group. CD4-guided STI were considered safe in patients with fully controlled virus. Overall, pulse therapy seems to be an alternative strategy for a wide variety of chronic-HIV-infected individuals responding to HAART.

B. II Category II: Non-randomized controlled trials: (refer to table)

Boschi 2004 reported results of CD4-guided STI of variable durations in 71 patients. During follow-up of 28.3 months, 49 patients restarted therapy and 22 remained off therapy. The first interruption median duration was 15 months. The overall reduction of time off therapy was 71%. The variable significantly associated with duration of the first interruption were age HR 1.05 (1.02-1.09), stage of disease HR 5.20 (2.14-12.91) and nadir CD4. Those with low nadir CD4 (<200) reported HR 16.48 (6.2-43.7) and those with nadir CD4 200-349 reported HR 2.58 (1.36-4.8) compared to baseline nadir CD4 (>349). In a multivariate model, nadir CD4 count emerged as a strong predictor of duration of interruption. Nadir CD4 also determined the total time off therapy. Thirty-five percent (35%) had nadir CD4<200, 63% had CD4 200-349, and 81% had CD4>349. Complete virologic suppression was achieved when therapy was reintroduced. The duration of first interruption and the reduction of time on therapy significantly correlated with nadir CD4 cell count. Patients rapidly regained CD4 counts on treatment resumption. If monitored carefully, treatment interruptions guided by CD4 cell were clinically safe in patients with high CD4 cell counts.

B. III Category III: Single arm intervention study (refer to table)

Tarwater 2003 reported results of CD4-guided TI of variable durations in this single arm trial. Compared to patients with CD4>500 cells/mm3, those with a baseline CD4 cell count of <200 were 4.4 times more likely to resume therapy, and those with CD4 counts between 200-350 cells/mm3 were 3 times more likely to resume therapy. The decrease in CD4 count was 159 in those who resumed therapy compared to 80 in those who did not. Viral load was 64,500 in those who resumed therapy compared to 20,000 in those who did not. The best predictor of TI duration was pre treatment CD4 cell count. Participants with low virological set points and high CD4 cell count were able to discontinue therapy. Patients with greatest increase in CD4 post ART experienced the most rapid decline in CD4 cells.

Quality assessment of trials:
Quality assessment of Category 1: Randomized controlled trials:
Of 11 randomized controlled trials in this category, a majority were judged to be of moderate quality (3/5) on Jadad’s scale. Only one trial (Papasavvas 2004) scored high on quality (4/5). A majority of the studies (>90%) were unclear in reporting of concealment of treatment allocation. An intention to treat analyses, power and sample size calculations were clearly reported in two trials (Maggiolo 2004, Papasavvas 2004).

Due to doubts about nature and safety of the intervention, blinding was not attempted in the trials. However, withdrawals and dropouts were clearly reported in all the trials. The longest follow-up durations (one and two years) were reported in two studies (Florence 2004; Plana 2004). Primary outcomes were clearly reported in two trials (Maggiolo 2004, Papasavvas 2004). Effect measures were clearly reported in one trial (Maggiolo 2004). There was the possibility of detection bias and performance bias in these trials.

Quality assessment of Category 2: Non-randomized controlled trials:
Of seven controlled trials in this category, a majority were judged to be of moderate to poor quality (2/5 to 1/5) on Jadad’s scale. All the trials were non-randomized and blinding was not attempted. Although there was a clear reporting of withdrawals and dropouts, the reported follow up was of short duration but varied considerably across trials (8 weeks-64 weeks). Due to small sample sizes (12-45), there was limited power to detect differences between groups. Although these trials were non-randomized, only one trial (Boschi 2004) reported measures of effect. There is possibility of selection, detection, and performance bias in these trials.

Quality assessment of Category 3: Single arm uncontrolled trials:
Of 16 single arm/uncontrolled trials in this category, the majority were of poor quality (1/5) on Jadad’s scale. All the trials were non-randomized, open, and outcome assessors were unblended; there is a possibility of detection bias. A majority of trials were of small sample size, except for the largest trial with a sample of 133. The follow up duration was variable across trials. These trials were non-randomized, and measures of effect were not reported. There was possible selection, detection, performance and attrition bias in these trials.

**DISCUSSION**

A) Methodological limitations of studies

**Sample size:** Many trials were of small sample size (<100), thus the power of the studies to detect differences was limited. There was a high likelihood of making the type II error with small sample sizes. Moreover, there were no clear descriptions of a priori criteria for expecting a difference between groups, and explanations of calculations of power and sample size were unclear in the majority (>90%) of trials. There was the possibility of erroneous conclusions based on power and sample size alone.

**Allocation concealment:** In the majority of trials (>98%), concealment of treatment allocation was inadequate and unclear, raising the possibility of performance bias.

**Follow up:** In some studies, follow up of one and two years have been reported (Florence 2004, Nuesch 2005, Plana 2004), but in the majority of studies, the follow up durations were less than 6 months. There is insufficient evidence to help assess the long-term safety of STI.

**Intervention designs:** STI is an experimental intervention, and should be recognized as such in the studies.

**Eligibility criteria:** Patient populations and eligibility criteria varied across trials.

**Lack of standardization of outcome:** A lack of standardization of outcomes was evident across trials. Lack of definition of primary and secondary endpoints was also evident. Commonly reported outcomes were immunological (CD4, CD8, subset of CD4 cells, CD4:CD8 ratios) and virological (VL, HIV RNA level). Changes in means of outcomes (reported as significant/non-significant with *p* values) made it difficult to compare across studies. Measures of effect were reported in two trials. Due to inconsistencies in reporting of outcomes, it was difficult to compare the effect of intervention and interpret evidence across trials.

**Outcome reporting bias:** In studies where primary and secondary outcomes are not clearly stated, there is the possibility of outcome reporting bias.

**Inclusion of uncontrolled trials:** Our objective was to synthesize evidence on STI for all outcomes reported by all trials in the field. We included non-randomized trials that were early pilot studies in the field on STI. The largest single arm trial, Swiss-Spanish Intermittent Treatment Trial, refuted the “auto-immunization hypothesis.” This was a major development in the field of STI. The results of this trial were replicated later by randomized controlled trials in the field.

**Bias (selection, detection, attrition, performance bias):** In RCT, trials were open due to doubts about nature and safety of intervention, outcome assessors were unblinded to the intervention, thus there is possibility of detection bias. Allocation concealment was inadequately reported in a majority (>95%) of the trials, thus there is a possibility of performance bias. In two trials, co-interventions, such as hydroxyurea, and interleukins, were used in addition to STI. It was difficult to separate the effect of STI from that due to the co-intervention.

**Inconsistent measures of effect:** Due to reporting of different outcomes by different trials, and lack of standardization in reporting outcomes, a consistent measure of the intervention could not be evaluated across trials. Hazard ratios (HR) were reported in...
two studies (Boschi 2004, Tarwater 2003). HR were estimated for progression to AIDS-defining illness stratified over levels of CD4 in one study. In another study, HR were reported for likelihood of resuming treatment stratified over levels of CD4.

Varying durations of follow up: A majority of the trials (>90%) reported follow up less than six months. One trial reported on CD4-guided STI at 108 weeks (Nuesch 2005), and the results indicated better performance of this trial. The other two fixed cycle STI trials reported follow up for one and two years (Florence 2004, Plana 2004). Due to varying durations of follow up, long term safety and efficacy of this strategy could not be assessed.

Semantics in STI: Semantics in STI are a matter of concern. A variety of terms, such as “on and off cycling,” “strategic treatment interruptions,” “planned treatment interruptions,” “supervised treatment interruptions,” “sequential treatment interruptions,” “cyclical therapy,” “structured intermittent therapy,” “supervised intermittent therapy,” and “pulse therapy” were all used to describe STI.

Definition of STI: Although the concept, and hypothesis for STI was clearly stated, the consensus on the definition of STI was clearly lacking in a majority of studies.

B) Applicability: risks/benefits of STI
STI strategies present several challenges.

Viral rebound: During timed-cycle STI, there is a risk of significant viral rebound, a concern of reseeding viral reservoirs and a risk of transmission of virus (Garcia 1999, Ortiz 2001). STI also run the risk of development of resistance and emergence of viral mutations during periods of viral replication. (Deeks 2003, Martínez-Picado 2002, Martini 2002). Factors such as use of ART with greater bioavailability and long intracellular half-lives, presence of suboptimal therapy in the past and adherence to ART also played a role in evolution of resistance (Dybul 2003). In CD4-guided STI so far, the viral suppression is achieved after resumption of treatment. (Ananworanich 2003; Boschi 2004; Cardiello 2005; Tarwater 2003).

CD4 cells: There is a risk of loss of peripheral CD4 T cells during periods off therapy. Nadir CD4 cell appeared to play an important role as major predictor of STI especially in CD4-guided STI strategies (Boschi 2004, Tarwater 2003). Although a pattern of decline in CD4 in timed-cycle STI was noticed, pulse therapy (Tarwater 2003) and CD4-guided STI (Boschi 2004) produced no significant immunological impairment.

ART regimens: type, duration, cycling of drugs: A major challenge in STI is to interrupt ART regimes without jeopardizing efficacy of the treatment and impairing immune response. It is important to maintain an optimum drug level during STI. The durations of ART regimens both pre-STI and post-STI are also important in determining response to an STI. Varying ART regimens have been considered. Identification of safe regimens to interrupt is a challenging domain for research. It is also important to take into account the patient’s immunological and virological profile, ART history (tolerance, safety and compliance), and presence or absence of resistance mutations before attempting STI. Drugs with long half-life and grater bioavailability have the potential for resistance (Deeks 2002; Deeks 2003; Dybul 2003).

Opportunistic infections (OI): The risk of recurrence of OI is always a concern in STI. In some studies, reports of acute retroviral syndrome, cases of oral candidiasis, pneumocystis carinii pneumonia, thrombocytopenia, were reported during STI (Alexander 2003; Martini 2002; Montes 2005). In CD4-guided STI strategies, there were no reports of AIDS-defining illness (Boschi 2004)

ART toxicities: It was thought that STI would lead to reduction in ART toxicities. Two studies investigating timed-cycle STI, however, demonstrated no reduction in metabolic parameters, though follow-up durations were limited to less than one year (Dybul 2003; Hatano 2000).

Quality of life: It is hoped that STI will provide improvement in quality of life in the long term. Patients found improvement in their quality of life during STI, but faced difficulty in reinitiating treatment after STI (Tuldra 2001).

Factors determining response to STI: To summarize, the factors hypothesized to play a role in determining success of timed-cycle STI were the baseline immunological and virological profile of participants, resistance mutations and suboptimal therapy, and past ART regimens. Predictors such as pro-viral DNA levels, viral levels in reservoirs, rate of drop in CD4 during STI, and the rate of virological control during STI determined response to an STI. (Fagard 2003, Fischer 2003, Oxenius 2002a). In CD4-guided STI cycles, nadir CD4 emerged as an important predictor of STI (Boschi 2004, Maggiolo 2004, Tarwater 2003).

C) Evolution of research in STI:

Early pilot studies: The early research in single arm trials explored the “auto-vaccination hypothesis,” i.e., that repeated exposure to autologous virus would stimulate immune response. However, this hypothesis was refuted by the results of largest single arm intervention study, the Swiss-Spanish Intermittent Treatment Trial (Fagard 2003, Fischer 2003, Oxenius 2002a). The data were corroborated by small uncontrolled trials and several controlled trials in the field.

Timed-cycle STI: Later, in the setting of randomized controlled trials, various timed-cycle strategies of varying durations were attempted in eligible participants. In all timed-cycle STI trials, a pattern was evident. There was no enhancement of immune benefit, nor was there a significant virological benefit due to STI. This led investigators to lose hope of enhancing immune response. There was a gain in CD8 T-cell- specific response in some studies, but it failed to sustain itself in the long term. In some trials, concerns about development of resistance were raised. There was no reduction in metabolic parameters in the long term, leading us to reject the notion of reduction of antiretroviral drug toxicities.
CD4-guided STI: In one randomized trial, two STI strategies, a timed-cycle “one week on and one week off” STI and a CD4-guided STI, were attempted (Ananworanich 2003). Reports of development of resistance in the timed-cycle STI, and favorable outcomes in the CD4-guided STI cycle arm, set a trend towards investigation of CD4-guided STI trials (Boschi 2004, Cardiello 2005; Maggiolo 2004; Tarwater 2003). In these trials, where variable STI durations were attempted, they monitored CD4 levels. Patients with high nadir CD4 (>400-500) qualified for this approach. Although a greater tolerability of this approach was reported in terms of the risk of clinical disease progression, concerns were raised about extent of immunological impairment due to long periods off treatment, and sustainability of this approach over longer durations of time. Moreover, hypothesized reductions in ART side effects and toxicities were not adequately investigated. A reduction in costs of ART and mutations however, was demonstrated by two trials (Cardiello 2005; Nuesch 2005). Trials are currently underway investigating long-term effects of this approach (e.g. SMART, BASTA). Results of these trials are expected in a few years.

D) Limitations of the review:
We used a comprehensive search strategy to identify studies. We attempted to contact authors for additional information regarding trials. We were unable to include non-English-language studies, abstracts, letters, and unpublished data, due to a lack of peer-reviewed material. Given the rapid evolution of research in this field, there is a possibility of having missed a few studies.

AUTHORS’ CONCLUSIONS

Implications for practice
Based on our review, there is insufficient evidence to support the use of timed-cycle and CD4-guided STI cycles in patients with chronic suppressed HIV infection. Further research is warranted to comment on the efficacy of STI over long periods of time. Timed-cycle STI provided no clear evidence of immunological and virologic benefit. Development of resistance, and no reduction in ART toxicities were reported. In comparison, CD4 cycle STI strategy reported favorable outcomes (no immunological impairment, reduction in exposure to ART, reduction in mutations) in the short term, but the long term effects of this strategy have not yet been completely investigated.

STI in practice require careful monitoring of clinical, virological, immunological and drug related outcomes. Several STI trials worldwide are currently underway to compare the long-term outcomes of timed-cycle and CD4-guided STI strategies. Some trials have incorporated therapeutic vaccines and immune-adjuvants, in addition to STI, to potentiate immune response. However, until the results of ongoing trials become available, STI should not be attempted by patients themselves, outside of controlled clinical trial settings.

Implications for research
There is a need for development of a standard methodology of reporting trials. In addition, a standardized reporting of important primary and secondary endpoints, with measures of effect should be emphasized. This will aid in assessment of comparisons across studies and assessment of efficacy of the intervention. Investigation of important secondary outcomes such as development of resistance, adverse effects of drugs, reduction in metabolic parameters, effect on quality of life, and reduction in costs will help assess overall efficacy of STI interventions. A long-term follow up with monitoring of immunological and virological parameters will help assess the safety of this strategy.

POTENTIAL CONFLICT OF INTEREST
None.

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We acknowledge Gail Kennedy and Tara Horvath from the Cochrane HIV/AIDS review group, San Francisco for their constant support and encouragement. We acknowledge Dr. Madhukar Pai and Dr. Haynes Sheppard for providing useful comments, suggestions and discussions on the topic. We also acknowledge Dr. Mark Dybul, Dr. Christine Katlama, Dr. Annette Oxenius, Dr. Lidia Ruiz for responding to our questions and requests for clarification.

SOURCES OF SUPPORT

External sources of support
• No sources of support supplied

Internal sources of support
• No sources of support supplied
References to studies included in this review

Alexander 2003 [published data only]


Ananworanich 2003 [published data only]


Boschi 2004 [published data only]


Cardiello 2005 [published data only]


D’Offizi 2002 [published data only]


Dybul 2001 [published data only]


Dybul 2003 [published data only]


Fagard 2003 [published data only]


Fischer 2003 [published data only]


Florence 2004 [published data only]


Foli 2002 [published data only]


Garcia 1999 [published data only]


Garcia 2001 [published data only]


Garcia 2003 [published data only]


Hance 2001 [published data only]


Hatano 2000 [published data only]


Lori 2002 [published data only]


Maggiolo 2004 [published data only]


Martinez-Picado 2002 [published data only]


Martini 2002 [published data only]


Metzner 2003 [published data only]


Molto 2004 {published data only}

Montes 2005 {published data only}

Nuesch 2005 {published data only}

Ortiz 2001 {published data only}

Oxenius 2002 {published data only}

Oxenius 2002a {published data only}

Papasavvas 2004 {published data only}

Plana 2004 {published data only}

Ruiz 2000 {published data only}

Ruiz 2001 {published data only}

Tarwater 2003 {published data only}

Tuldra 2001 {published data only}

References to studies excluded from this review
Alfeld 2002

Ananworanich 2003a

Benson 2001

Chen 2002

Deeks 2001

Deeks 2003

Delaugerre 2001

Devereux 1999

Fagard 2005

Frost 2002
Frost SD, Martinez-Picado J, Ruiz L, Cloet B, Brown AJ. Viral dynamics during structured treatment interruptions of chronic human

Garcia 2002


Halfon 2003


Haslett 2000


Izopet 2004


Jaafar 2004


Katlama 2004


Lawrence 2003


Lori 2000


Miller 2000


Neumann 1999


Ortiz 1999


Poulton 2003


Prado 2000


Rosenberg 2000


Ruiz 2003


Schweighardt 2002


Taffe 2002


Tebas 2002


Tremblay 2003


Verhofstede 1999


Yerly 2004


Youle 2000


References to ongoing studies

1. ISSPART. Ongoing study Starting date of trial not provided. Contact author for more information.

2. SMART. Ongoing study Starting date of trial not provided. Contact author for more information.

3. BASTA study. Ongoing study Starting date of trial not provided. Contact author for more information.

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Ananworanich 2005


Benson 2001


Blankson 2001


Bonhoeffer 2000


Chen 2002


Deeks 2002


Dorman 2000


Dybul 2002


Dybul 2003a


Flepp 2001


Gulick 2002


Hatano 2000a


Havlir 2002


Hirschel B 2001


Idemoyer 2003

Idemoyer V. The concept of structured treatment interruptions in the management of patients with human immunodeficiency virus (HIV) disease: where are we currently?. *HIV Clin Trials* 2003;4(2):79–83.

Jadad 1996


Lisziewicz 1999


Lisziewicz 2002


Lori 2002


Lori 2000a


Lori 2001


Lori 2002


Lori 2002a

Miller 2001

Miller 2003

Montaner 2005

Oxenius 2003

Parienti 2002

Yerly 2003

*Indicates the major publication for the study

**TABLES**

### Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Alexander 2003</th>
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<td>Methods</td>
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<td>HIV +ve12 years</td>
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<td>Interventions</td>
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<td>STI 2 cycles of 1 month each and one final of 3 month.</td>
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<td>Median ART interruption: 2.7 years</td>
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<tr>
<td>Outcomes</td>
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<tr>
<td>CD4 T cells: Stable CD4 T cell percentage in 4/8 patients. Decline in CD4 T cell percentage in 4/8 patients. CD4 levels fluctuated with central memory CD4 cells and naïve CD4 T cell subsets. VL: PreHAART viral RNA predicts HIV-RNA levels during STI. A/E: Rash, fatigue and myalgia, respiratory symptoms and lymphadenopathy.</td>
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</table>
### Characteristics of included studies (Continued)

**Notes**
- STI to be avoided in patients with high viral setpoints, decline in CD4 T cell decline rapid. Pre-HAART viral set point and CD4 T cell response predict plasma viral level during STI.
- Duration of STI determines effect on CD4 T cells.

<table>
<thead>
<tr>
<th>Study</th>
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<td></td>
<td>FUP: STI WOWO: 27.8 weeks</td>
</tr>
<tr>
<td></td>
<td>STI CD4 guided: 24.9 weeks</td>
</tr>
<tr>
<td></td>
<td>Control ART: 24.1 weeks</td>
</tr>
<tr>
<td></td>
<td>w/o d/o: reported</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Participants</th>
<th>Three Intervention arms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. STI Week on and week off (WOWO); N=36</td>
</tr>
<tr>
<td></td>
<td>2. STI CD4 guided arm; N=39,</td>
</tr>
<tr>
<td></td>
<td>3. Control arm: Continuous ART; N=37</td>
</tr>
<tr>
<td></td>
<td>EC:-</td>
</tr>
<tr>
<td></td>
<td>N=600 patients randomized</td>
</tr>
<tr>
<td></td>
<td>1.CD4&gt;350</td>
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<tr>
<td></td>
<td>2.VL&lt;50cop/ml</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Arm 1 STI 1 wk on/off arm1</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Arm 2 CD4 guided STI</td>
</tr>
<tr>
<td></td>
<td>Arm 3 Continuous tmt ART: triple therapy</td>
</tr>
<tr>
<td></td>
<td>3TC +d4T +SQV/RTV ART resume if CD4&lt;350; Weeks 96-108 all three groups received ART.</td>
</tr>
</tbody>
</table>

| Outcomes       | STI WOWO Arm 1: Virological failure (VL>500 copies/ml) reported in 19/36 patients, trial arm terminated. Efavirenz based regimens considered better than others. CD4 guided arm2: no failures reported. Continuous treatment Arm 3: 2 failures (chi square p<0.001) compared to WOWO arm. Resistance: 184V mutations in 2 patients, 103N mutations in one patient on EFV, 181C mutation in one on NVP. |

| Notes          | WOWO arm: high failure rate, terminated. Failure due to different ARV regimens. |

| Allocation concealment | B |

### Study

**Study**

**Boschi 2004**

<table>
<thead>
<tr>
<th>Methods</th>
<th>NRCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=71 patients;</td>
<td>Non randomized</td>
</tr>
<tr>
<td>Open</td>
<td></td>
</tr>
</tbody>
</table>
Characteristics of included studies (Continued)

Follow up: 2105.4 months

FUP 38-64 weeks
w/o and d/o: reported

Participants
N=71
EC:
CD4>500
Age>18 years;
On ART;
VL: undetectable during last follow up, stable ART.
Baseline median CD4 at first STI 790 (657-1041)
Nadir CD4 median 352(294-445)
PreHAART VL: 4.95(4.40-5.26);
Males 51%, median age 39 years;
Tmt naive: 43/71
Tmt exp: 28/71

Interventions
STI: variable durations; first TI median duration 15 months;
Protocol: Discontinue ART if CD4 >500, restart therapy if CD4 drops <200; On ART resumption, patients eligible for an STI if CD4>500 or signs of toxicity developed.
ART duration pre STI: 36 months;
ART regimen: PI + NNRTI;
ART resumption: patients choice, pregnancy, CD4<200;
Median first TI duration: 15 months.
Primary end point: 1. Safety of STI (defined as lack of AIDS defining event, absence of virological failure).
Secondary end point: 1. CD4 2. Immunological response 3. Any parameter correlated with TI duration 4. duration of TI 5, reduction of ART exposure;

Outcomes
Factors significant with duration of First TI: 1. Age HR 1.05(1.02-1.09) 2. Nadir CD4: Nadir CD4 200-349 reported HR 2.58 (1.36-4.82); Nadir CD4 <200 reported HR 16.48(6.2-43.7) (reference group nadir CD4>349) ; 3. stage of disease: HR 5.20 (2.14-12.91) p<0.0001
In a multivariate model, Nadir CD4 significantly predicted the duration of TI.
Of 71 patients, 49 restarted ART, 22 remained off ART.
24 interrupted ART twice, 9 patients interrupted ART thrice, 6 patients interrupted ART four times.
No AIDS Defining illness reported.
Nadir CD4 Nadir time off tmt
<200 35%
200-349 63%
>349 82%

Notes
If monitored, CD4 guided treatment interruptions were safe in patients with high nadir CD4, no reduction in efficacy of therapy.

Allocation concealment D

Study Cardiello 2005

Methods RCT
N =71
Randomized
STACCATO
Open
FUP=48 wks
w/o d/o: reported

Participants STI 3 arms
Characteristics of included studies (Continued)

1. Week on and week off (WOWO) N=26
2. CD4 guided arm N=23
3. Continuous therapy arm N=25

EC-
1. CD4>350
2. VL<50cop/mlb

Interventions
Arm 1 STI 1 wk on/off
Arm 2 CD4 guided STI
Restart treatment if CD4 drops<350, on treatment failure, switch to continuous tmt
Arm 3 Continuous tmt
ART 2 NRTI + 1 PI for 1-2yr

Outcomes
End of STI CD4 >350
Median CD4:
WOWO arm : 582
CD4 arm: 547
Control arm: 637
VL(log cop/ml):
WOWO arm: 1.70
CD4 arm:1.96
Control arm: 1.69
Undetectable VL:-
WOWO arm:-72%
CD4 arm:-45%
Control:-100%
Grade ¾ event:
WOWO arm:46%
CD4 arm-65%
Control arm-44%
Treatment failure
WOWO:31% patients
Time off treatment:-
WOWO arm:96%;
CD4 arm: 87%;
Control: 100%
ART use:-WOWO arm: ART use 69.8%
CD4 arm: ART use 41%;

Notes
Arm 1: WOWO arm: STI mutations reported due to prior suboptimal therapy. STI successful in maintaining
CD4 >350 cells, but virological failure reported;
Arm2: CD4 cell guided arm: Clinical outcomes comparable to continuous therapy arm; decrease in CD4
reported;
Larger trials with longer follow up needed;

Allocation concealment B

Study D’Offizi 2002
Methods Uncontrolled
N=26
Non randomized
open trial;
w/o d/o: reported
Characteristics of included studies (Continued)

Participants
EC: Asymptomatic chronic HIV infection, ART for 2 yrs, stable CD4 T cell counts >500 for 12 months, undetectable HIV RNA <50 copies/ml.

Interventions
STI: 1 cycle of 1 month.

Outcomes
STI response into two groups. Group A - rapid viral rebound < 1 month, Group B - delayed / no rebound (in 4 months)
Group A patients: significant decrease in CD4 and CD8 subset. ART resumption restored plasma viremia and CD8 to baseline.
Group B showed no significant CD4 or CD8 T cell modulation.

Notes
In chronic infections, the immune system is progressively damaged. Adjuvant therapy, could help restore cytotoxic T lymphocyte effector function.

Allocation concealment
D

Study
Dybul 2001

Methods
Uncontrolled
N=10
Open
Non randomized
FUP= 52 wks

Participants
STI n=10
EC: VL <500 copies/ml for 6 months;
Enrolment criteria: VL undetectable, CD4>300 cell/mm3;

Interventions
STI: 1 week on and off
ART duration: 22 months,
Regime: D4T+3TC+IDV+RTV,

Outcomes
VL: No difference in mean proviral DNA of 474 +/-88 and 404 +/-115 copies/mm3; no sig change in VL CD4; No significant change in mean CD4T cells count;
Toxicity: Decrease in serum cholesterol (p=0.001) LDL cholesterol of 22% during 24 weeks of SIT
Short cycle SIT maintained suppression of HIV in peripheral blood and lymphoid tissue, preserved CD4T cell count for 32-68 weeks. No detectable increase in cellular activation or HIV specific CD8 CD4 immune response noted.

Notes
Short cycle SIT could decrease costs, toxicity, useful where cost is a concern and accessibility is limited.
Investigation of long term effect of ART on antiviral resistance needed.

Allocation concealment
D

Study
Dybul 2003

Methods
RCT
N= 52
Randomized,
Open
FUP= incomplete;
w/o and d/o: reported;

Participants
STI N=26; Control N=26;
EC=CD4>300 * 6 months, 3 drug ART * >6 months, VL<500 copies/ml >6 months,
Exclusion criteria: No drug resistance, No oral candida, Not on Abacavir, Nevirapine, VL <50ml during screening for enrolment.

Interventions
STI 4 week duration followed by 8 weeks on ART;
trial prematurely terminated due to development of resistance in STI arm; ART regime not specified.
### Characteristics of included studies (Continued)

**Outcomes**
- CD4: No difference in CD4 or CD8 cell counts between groups;
- VL: VL >50 copies/ml seen in 26% STI long cycle patients intermittent ART, and 9% controls;
- Resistance: 3/5 STI patients
- Metabolic: Significant differences in total cholesterol and triglyceride levels seen (p=0.04) at week 40, differences were lost at week 48.

**Notes**
- No enhancement of immunologic parameters, no significant autoimmunization; No significant reduction in of serum lipid levels at wk 48; no decrease in ART toxicities, larger studies with longer follow up needed

**Allocation concealment** B

### Study: Fagard 2003

**Methods**
- Uncontrolled
- N=133
- SSITT
- Non randomized,
- Open,
- FUP= 96 weeks,
- w/o d/o reported

**Participants**
- EC: Chronic HIV infection, CD4 740 /microlitre, VL<50copies/ml for 21 months; Enrolment Criteria: VL<50copies/ml, CD4>300 micro/litre; pre-STI ART duration 21months(6-43),
- Duration of HIV infection median 26months(8.5-44.5months), treatment indefinitely suspended 40 weeks after study

**Interventions**
- STI 4 cycles of 2 weeks duration, and 8 weeks on ART

**Outcomes**
- For all STIs, no significant difference noted in patients with a detectable rebound (p=.7)nor height of viral rebound(p=.25). After suspension of ART at week 40, VL rebound >200 copies/ml in 86%, at week 46, in 97%. Subjects. On stopping treatment, in the first 12 weeks, median CD4 counts decreased from 792 to 615 /microlitre, and stabilised later. Median CD8Tcell increased from 343 to 1930, no OI were observed. CD4 decreased from 792/microlitre to 615/microlitre at week 52 (P<0.001), 2 patients reported resistance 1/133 184 V mutation RT gene, ARV syndrome.
- Of 133 patients,
  - at week 40, 90 were followed,
  - at week 52, 79 remained and of them, 23 had viral load <5000copies/ml (responders), 56 had viral load>5000 copies/ml (nonresponders);
- at week 96,13 had viral load >5000 copies/ml, 10 had viral load <5000 copies/ml.
- 82 patients restarted treatment after SSITT, 3-6 months post STI,
- 68 patients had VL<200 c/ml, 12 pts VL>200c/ml, 1 pt received salvage therapy.

**Notes**
- Results did not favor the auto vaccination hypothesis. STI could not attain goal of low or undetectable viremia without ART.

**Allocation concealment** D

### Study: Fischer 2003

**Methods**
- Uncontrolled
- N= 14,
- SSITT
- Non randomized
- Open,
- FUP unclear ,
- w/o and d/o: reported

**Participants**
- EC: Chronic HIV infection, pre-STI ART duration > 6months, undetectable VL 11-32 months, CD4 range 347-1269, At Enrolment: VL<50copies/ml, CD4>300 micro/litre;
Characteristics of included studies (Continued)

Interventions
STI 4 cycles of 2 weeks duration, and 8 weeks on ART;

Outcomes
During the first cycle, VL >50 cop/ml in five patients at day 4, eight patients had VL>100 cop/ml at day 8, 12 patients >100 copies/ml at day 14, Viral rebound occurs in 8 days of STI reflecting activation of reservoirs, and upregulation of residual viral capacity. M184V variants were detected. Mean time to viral rebound is 2.3 days. Viral replication is induced during the 1 week STI, increases risk of emergence of drug resistance during the long term cycling. Levels of proviral DNA, pretreatment plasma VL, cell associated HIV RNA, may predict the time point and magnitude of viral rebound.

Notes
Larger clinical trials required to assess drug regimens, immunomodulatory substances.
A group of patients with slower rebound kinetics can be identified.

Allocation concealment
D

Study Florence 2004

Methods
Follow up study on STI
4 STI protocols followed;
RCT;
N=60
Open,
w/o and d/o=unclear
fup=reported;

Participants
STI N=26
Control N=18
EC:-
Asymptomatic chronic HIV infection,
Pre STI ;VL<20 copies/ml; Nadir CD4 >500
Baseline: Median CD4 718; Median VL 4.12 log;
Co-intervention: Hydroxyurea and Mycophenolic mofetil.

Interventions
STI: variable (2 wks to 4 months);
Median ART duration:746 (55-941)days;
ART regimens:-PI+2NRTI; PI+1NNRTI +1NRTI

Outcomes
Median CD4 814 (677-951), Plasma VL <20 cop/ml; Off HAART: 822 days(642-1022)
No adverse effects, No Opportunistic infections:no Aids defining illness;
VL: 18% patients has VL 0.5 log lower than baseline. Median pVL during the first, second, third year after interruption of HAART were 2.58 cop/ml, 3.10 cop/ml, 3.59 cop/ml. The pVL set point was defined as the mean of last three pVL measurements.
CD4: Remained stable during the period, median Cd4 794 (1yr), 851(2 yr), 838(3yr).
Plasma VL remained lower than the pVL set point before initiation of any antiretroviral therapy. No predictor of virological response identified in a logistic model. 43% patients did not resume therapy long term, 42% patients had a lower virological setpoint. Of them, 18% patients with CD4 >500 were able to maintain a lower pVL for a long time after a period of STI.

Notes
Long term, STI strategies may not be beneficial to a majority but a small minority of patients with high CD4 T cell could tolerate STI. Treatment with hydroxyurea exerted partial control of viral replication.

Allocation concealment
D

Study Foli 2002

Methods
NRCT
N=16
Non randomized
Open
FUP= 6 wks
### Characteristics of included studies (Continued)

<table>
<thead>
<tr>
<th>Characteristics</th>
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</thead>
<tbody>
<tr>
<td>Participants</td>
</tr>
<tr>
<td>STI N= 9; Control N= 7</td>
</tr>
<tr>
<td>EC: Median viremia= 337 HIVRNA copies/ml, STI and control groups similar in CD4 and VL</td>
</tr>
<tr>
<td>Interventions</td>
</tr>
<tr>
<td>STI 1 cycle of 8 week; ART resumed if VL&gt;10,000 copies/ml, CD4 count decreased below 200 cells/mm3, PANDA cohort; ART Didanosine and Hydroxyurea</td>
</tr>
<tr>
<td>Outcomes</td>
</tr>
<tr>
<td>PANDA's contained viral rebound during STI, CD4 counts in PANDA's did not change significantly (p=0.31) from a median of 444 cells/mm3 to a median of 512 cells/mm3 at week 8. In continuous treatment patients, CD4 counts decreased significantly from 428 cells/mm3 to 340 cells/mm3, (p=0.02). In both groups, a linear correlation between viral load at baseline, and at the end of STI was found. STI could reconstitute the immune response damaged in chronic infection, but this outcome is questionable for any given patient. A substantial control of HIV replication was achieved compared to HAART treated patients.</td>
</tr>
<tr>
<td>Notes</td>
</tr>
<tr>
<td>PANDA's maintain a low but detectable level of HIV for several years exposing immune system to therapeutic amounts, of autologous antigen to induce T cell immunity. Hydroxyurea is cytostatic could be a valuable tool to be used in the setting of STI.</td>
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<td>Allocation concealment</td>
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</table>

#### Study: Garcia 1999

| Methods |
| Uncontrolled |
| N=8; non randomized |
| Open |
| FUP: unclear, w/o d/o reported |
| Participants |
| EC: Chronic HIV-1 infection, ART for 1 year, CD4 >500 cells/mm3, VL >10,000 copies/ml |
| Interventions |
| STI 1 cycle of 31 days |
| Outcomes |
| VL: Viral rebound detected in all patients; CD8 T cells: no change. Naïve CD45RA Cd4 & CD8 T cells decreased from 49% to 39% p=.04, Memory CD45RO and CD8 T cells increased from 33% to 42% (p=0.005) On ART resumption: VL fell below 20 copies/ml, CD4 cells increased to 44% |
| Notes |
| VL rebound similar to that observed after treatment discontinuation, results from low level persistent viral replication, no resistance detected. Two patterns of response, one in VL >5 cop/ml and other in VL <5cop/ml were noted. It is critical to develop strategies, that could potentiate HIV specific immune response. There were no difference in these parameters wrt to age, gender, Hepatitis C, duration of HIV- infection |
| Allocation concealment |
| D |

#### Study: Garcia 2001

| Methods |
| Uncontrolled |
| N=10 |
| Non randomized |
| Open |
| FUP= 6months, w/o and d/o unclear |
| Participants |
| STI N=10 |
| EC: CD4 >500 copies/ml, VL>10,000 copies/ml, in 2 occasions separated by 1-3 months, |
| Interventions |
| STI total duration 12 weeks, average duration STI 4 weeks |
**Characteristics of included studies (Continued)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Participant Details</th>
<th>Intervention Details</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Garcia 2003</strong></td>
<td>N=20; randomized, open FUP 48 weeks, w/o d/o unclear</td>
<td>STI 5 cycles of STI. Hydroxyurea discontinued in 1st, 2nd, 3rd cycles and given in 4th and 5th cycles. If VL exceeded 200 copies/ml, ART was resumed. Co-intervention: Hydroxyurea</td>
<td>VL ≤ 5000 copies/ml seen in 8/9 patients in HU gp and 4/10 patients in HAART groups; Increase in neutralizing activity and magnitude of CTL response, from baseline. Trend towards higher response in responder patients (p=0.01)</td>
<td>Safe approach in terms of virological response. Recovery of immune parameters 6 months of resuming therapy. Clinical trials should proceed with caution until long term safety is clear.</td>
</tr>
<tr>
<td><strong>Hance 2001</strong></td>
<td>N=12; non randomized open FUP= unclear w/o and d/o= reported</td>
<td>STI 1 cycle of 3 months, ART duration not reported, ART regime RTV + SQV + IDV + NFV</td>
<td>V82A, L90M mutations noted, strains expressed better fitness under drug free conditions. Resistant strains decreased in most patients, apparent conversion to wild type virus observed,</td>
<td>Replacement of resistant plasma quasi species by wild type genomes occurs during STI. 3 month duration is short for washout of resistant virus. Sequential accumulation of mutations in protease gene leads to progressive decline in viral fitness. Future studies needed to identify mechanisms by which replication in resistant viruses is impaired following appearance of wild type virus.</td>
</tr>
</tbody>
</table>
### Characteristics of included studies (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Hatano 2000</th>
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</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Uncontrolled, N=26, Non randomized, Open, FUP-reported</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>EC: HIV VL&lt;500 copies/ml for 12 months, confirmed HIV infection, age&gt;18 years, on ART for 12 months, median age 43.5 years, 100% male; PI + 2 NRTI regimen;</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>STI 7 weeks attempted after ART for 12 months, criteria for ART resumption clear.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Metabolic studies: decrease of total cholesterol (P&lt;0.0001) LDL cholesterol, triglycerides; increase in urinary free cortisol (p=.016), no change in insulin resistance profile,</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Transient improvement in metabolic phenomena. Generalization of findings limited due to short duration of ART interruptions, small sample size: Studies on long term effects of metabolic abnormalities.</td>
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<td><strong>Allocation concealment</strong></td>
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<thead>
<tr>
<th>Study</th>
<th>Lori 2002</th>
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</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Uncontrolled, N=16, Non randomized, Open, FUP=8 wks w/o and d/o: reported</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>STI N=9; Controls N=7; EC: STI group CD4 -250-500 cells/microlitre, on Hydroxyurea /Didanosine, Controls: continuous ART, similar VL and CD4 at baseline</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>STI 1 cycle of 8 weeks duration, ART duration pre-interruption 154 weeks, ART Didanosine and Hydroxyurea,</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>STI group: Median VL 2026 copies/ml in PANDA cohort, containment of VL during STI. CD4 count: an increase in CD4 counts observed during therapy interruption (median increase 444 cells/mm³ to 512 cells/mm³ at week 8);</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Cellular arm of immune system controls HIV during therapy discontinuation. Increased HIV specific TH1 type T cells response, characterized by IFN gamma expression of CD4 T lymphocyte; Long 8 weeks HAART interruption could damage immune system; Combination of Hydroxyurea and Didanosine provides a valid addition to the available therapy;</td>
</tr>
<tr>
<td><strong>Allocation concealment</strong></td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Maggiolo 2004</th>
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</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>RCT, N=69, BASTA, Randomized, Open, FUP=64 wks W/o d/o: reported</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>STI N=46; Control N=23</td>
</tr>
</tbody>
</table>
### Characteristics of included studies (Continued)

**Eligibility Criteria:**
- Age > 18yrs
- CD4 > 800
- VL < 50
- Stable HAART
- At baseline: VL undetectable, CD4 1077

**Interventions**
- Randomized 1:2 ratio to continuous treatment group or individualised CD4 guided STI.
- Individualized CD4 guided STI: resume therapy if CD4 < 400 irrespective of viral load; and taken off drugs if CD4 > 800; aim to give shortest possible exposure to drugs.

**Outcomes**
- Primary end point was the proportion of subjects maintaining a CD4 cell count > 400. Secondary end point was to identify the dynamic and predictive variables of CD4 cell loss. Number of patients in the STI group with a CD4 < 400 was not statistically significant from number of people in the control group. Main predictor of decline in CD4 was nadir CD4 with (p < 0.001); Greater viral rebound and greater cell loss reported in low nadir CD4 group. Intention to treat analysis done. In a multivariate model, parameter significantly associated with possibility to stay off therapy and prolong STI was CD4 cell count (B = 1.749, p = 0.001). Duration of first STI was significantly different between STI groups stratified by CD4 nadir levels. No differences in metabolic parameters between groups by t test. 2 patients developed adverse events.
- Overall, pulse therapy seems a strategic option seems to be an alternative strategy for a wide variety of chronic infected HIV individuals responding to HAART.

**Notes**
- Prolonged STI safe in patients with fully suppressed virus and immune reconstitution is safe with good clinical monitoring. The main predictor of CD4 cell decline is nadir CD4 cell count. Long term follow up of clinical outcomes needed.

**Allocation concealment**
- B

---

### Study: Martinez-Picado 2002

**Methods**
- Uncontrolled
- N = 12,
- Non randomized,
- Open,
- FUP = unclear

**Participants**
- EC:
  - Chronic HIV infection, VL < 50 cop/ml for 2 yrs, CD4:CD8 ratio > 1 for 22 months,

**Interventions**
- STI 3 cycles of 30 days, duration of ART monitored with VL, Protease inhibitor and reverse transcriptase 3TC + d4T + IDV, clear description for ART resumption,

**Outcomes**
- Mutation: stepwise increase in M184 V mutation in patient virus population, over successive STI.

**Notes**
- Potential for selection of drug resistant quasi-species. Drug resistant testing useful in STI studies.

**Allocation concealment**
- D

---

### Study: Martini 2002

**Methods**
- Uncontrolled
- N = 10,
- Non randomized
- Open trial
- FUP = 79 days,
- w/o and d/o reported;

**Participants**
- EC:
  - Chronic HIV infection, > 2 yrs on ART < Stable CD4 counts > 12 months, undetectable VL for > 12 months before study entry.
### Characteristics of included studies (Continued)

| Interventions | STI 1 cycle of >1month (42.3±7 days), after ART >2 years, with clear description of criteria for ART<, baseline CD4 698±74 cells/mm³, VL<50 copies/ml |
| Outcomes | VL: rapid plasma HIV RNA >30,000 cop/ml, observed after 28.7±1.8 days, VL increase by 0.3 logs (p<0.05) CD4: drop in CD4 from 698±74 to 489±70 (p<0.05); CD8: increase in near doubling time from 894±125 to 1433±188, Increase in Vgamma2T cells 1 month after STI. A reduction in Vgamma9Vgamma2 was accompanied by functional anergy, this cell subset was affected by acute response to HIV replication. |
| Notes | Increased risk of developing OI's, which underscores the importance of careful application of STI. Soon after HIV RNA rebound, the cell becomes anergic and then undergo profound depletion, the cytopathic effect of HIV forces them to an anergic state. |

| Study | Metzner 2003 |
| Methods | Uncontrolled N=133, SSITT Non randomised, Open, FUP=52 weeks, w/o and d/o=reported |
| Participants | EC: STI n=28 VL<50 for 6months, CD4>300, ART 2/3 drugs for 6 months |
| Interventions | STI 4 cycles of 2 week STI duration |
| Outcomes | Resistance mutations L90M, M184V, detected during STI |
| Notes | HIV-1 Variants carrying drug resistant mutations emerge during periods of HIV-1 replication. |

| Study | Molto 2004 |
| Methods | Uncontrolled Non randomized, N=45 Retrospective chart review Fup: unclear |
| Participants | STI N=15 Control N=30 EC: VL<50 CD4>500 CD4 nadir median 341 (298–464) in STI group |
| Interventions | STI 2 weeks off 4 weeks on ART Treatment resumption: AIDS defining clinical event, VL>100,000 copies/ml, CD4<350cells/mm³, |
| Outcomes | CD4: Decrease in CD4 during STI, median drop 23.5% in 4 weeks, 33% in 8 weeks; STI CD4 nadir 340, Control nadir 560; CD4 T cell was higher in patient remaining off therapy; VL: no difference was seen in patients who resumed treatment by week 48, those who remained off therapy; AIDS defining events: none Resistance: mutation present |
### Characteristics of included studies (Continued)

**ART resumption: virological control achieved**

**Notes**
- CD4 nadir a predictor of treatment re-initiation. Low CD4 T cell and high VL predict treatment re-initiation.
- Previous STI did not influence time off therapy.

**Allocation concealment**
- D

#### Study 1: Montes 2005

**Methods**
- NRCT
- N=45
- Non randomized
- open
- Withdrawals/dropouts: unclear
- Fup: unclear

**Participants**
- STI: 25
  - Control 20 age and sex matched controls;
  - EC: CD4>500, VL<50, HAART for 1 year,
  - At enrolment,
  - CD4>500
  - VL<50 copies/ml at 6 months,
  - ART=3 drug regimen
  - Age and sex matched controls

**Interventions**
- STI: 3 cycles; each cycle 8 weeks on and 4 weeks off ;
- ART: 2 NRTI +1PI regimen

**Outcomes**
- CD4 T cell: significant decrease after interruption;CD4 count decreased from 769 in first cycle to 637 at end of third cycle.
- CD8 T cell: increased in 30% patients;
- VL: undetectable at first cycle to the end of third cycle.
- OI: none
- IL-16 Cytokine: increased after each interruption.

**Notes**
- STI failed to modify immunological parameters. Increased risk of developing OI’s. Soon after HIV RNA rebound, the cell becomes anergic and then undergo profound depletion, the cytopathic effect of HIV forces them to an anergic state.

**Allocation concealment**
- D

#### Study 2: Nuesch 2005

**Methods**
- RCT
- N=71
- Randomized
- Open
- 3 arm trial;
- CD4 guided arm n= 39
- FUP= 108 weeks
  - w/o and d/o=reported

**Participants**
- CD4 guided arm N=23
- WOWO arm N=26
- Control arm N=25
- EC:-
- CD4 before ART 380,
  - Before HAART 732
  - Before STI 766
### Characteristics of included studies (Continued)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral load</td>
<td>Median before ART 4.8, Level&lt;400 before HAART 7, No of STI cycles 1.65+/-.67</td>
</tr>
<tr>
<td>Interventions</td>
<td>STI: total duration 9.6 weeks, total cycles 3; ART: AZT+3TC; d4T +ddl;</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Resistance: Reports on 20 of 23 patients. One major mutation(T215Y) in CD4 arm. Mutations in Cd4 guided arm decreased from 36% pre STI to 6% after STI. VL: No virological failure at 48 weeks. At 108 weeks, 1 virological failure in STI arm, 1 in continuous arm.</td>
</tr>
<tr>
<td>Notes</td>
<td>No major HIV mutation induced in CD4 cell guided STI arm. CD4 guided STI appear to be safe in this patient population.</td>
</tr>
</tbody>
</table>

### Study: Ortiz 2001

<table>
<thead>
<tr>
<th>Study</th>
<th>Ortiz 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>NRCT; N= 12 patients; FUP 38-64 weeks w/o and d/o:reported</td>
</tr>
<tr>
<td>Participants</td>
<td>STI n=8; Control n=4; EC: Subjects with CD4 counts&gt;400 cells/ml for 6 months, VL &lt;400 copies/ml for 3 months, renal, hepatic, hemopoietic function within defined limits, Duration of ART 2.7 years</td>
</tr>
<tr>
<td>Interventions</td>
<td>STI: 2 cycles of 1 month duration and 1 cycle of 3 month duration,</td>
</tr>
<tr>
<td>Outcomes</td>
<td>VL: Viral rebound&gt;10,000 copies/ml; CD4T cell counts decreased but levels never below baseline (&lt;200 cells/microlitre); CD8 T cell increased; Increase in total HIV-1 specific CD8T cell response at the end of last STI (p=0.003); AIDS related events: left cervical lymphadenopathy, rash, hives, reported. On ART resumption, VL re-suppressed to a low level after return to ART; in all 8 subjects, CD4 T cell returned to pre-STI levels after resumption of ART.</td>
</tr>
<tr>
<td>Notes</td>
<td>No clear therapeutic benefit of STI observed;</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>B</td>
</tr>
</tbody>
</table>

### Study: Oxenius 2002

<table>
<thead>
<tr>
<th>Study</th>
<th>Oxenius 2002</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Uncontrolled; N=133, SSITT non randomised, open; FUP=52 weeks w/o and d/o:reported</td>
</tr>
<tr>
<td>Participants</td>
<td>EC: Chronic HIV Infection, plasma VL &lt;50 copies/ml, for 6 months, CD4 &gt;300 cells/mm3 at enrolment, Resumption of ART: baseline CD4 median 740(318-1909) , VL &lt;50 copies/ml,</td>
</tr>
<tr>
<td>Interventions</td>
<td>STI: 4 cycles of 2 week and 8 weeks on ART; PreSTI ART 26 months (8.5-44.5) , Regime not reported.</td>
</tr>
</tbody>
</table>
### Characteristics of included studies (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oxenius 2002a</strong></td>
<td>Uncontrolled SSITT trial, N=15, phase II study, FUP= 52 weeks, w/o and d/o reported</td>
<td>Chronic HIV infection, median age 46 (33-68), inclusion criteria combination ART 2/3 drugs&gt;6months, VL &lt;50 copies/ml for 6 months, CD4&gt;300 cells/ml, baseline VL 34750 (537-561831)</td>
<td>STI 2 weeks duration, total 4 cycles, ART&gt;6months, duration of ART 8-10 weeks;</td>
<td>VL: detected in 11/13 patients, plateau VL after 4 STI was lower than HIVRNA before ART in 10/13 patients, plateau VL correlated with pretreatment VL; viral rebound during STI CD8T cell: Increase in magnitude and breadth of CD8 T cell response. These levels did not correlate with viral setpoints. CD4T cell: Increase in response during STI, maintained in patients with low preART VL.</td>
<td>No correlation between virological improvement and increase in HIV specific CD8 T cell response. STI unable to alter the pre-existing equilibrium between cellular immunity and viral replication nor lower the set point VL.</td>
</tr>
<tr>
<td><strong>Papasavvas 2004</strong></td>
<td>RCT</td>
<td>STI n=21 Repeated Treatment Interruptions=100% male Control n=21 Single Treatment interruption 83% male EC: Age&gt;18 years CD4&gt;400 CD4 nadir&gt;100</td>
<td>STI : 3 cycles of 2,4,6 weeks duration STI arm Phase I STI cycles 2 week, 4 week, 6 week Phase II single treatment interruption in both arms</td>
<td>STI induced boosting of cellular immunity was not associated with changes in viral replication. STI restored preART CD8 T cell response.</td>
<td></td>
</tr>
</tbody>
</table>
**Characteristics of included studies (Continued)**

Control arm: Continuous treatment for 40 weeks, plus one TI
ART: PI + NNRTI+NRTI

| Outcomes | Main outcome: Time to viral rebound (>5000 copies/ml). Secondary outcomes: study defined safety criteria, viral resistance, therapy failure and retention of immune constitution
|          | No significant difference between the two groups w.r.t time to viral rebound during the open ended TI of 4 weeks[1-8] weeks, and STI group 5[4-8] weeks, (p=0.36).
|          | No differences in secondary outcomes noted between groups.STI group: Increase in CD8 T cells in STI group; Resistance mutations STI group 9/18 ; continuous 3/16; STI gp tmt failure 1 patient

| Notes   | Cycles of 2 to 6 weeks time fixed TIs in patients with suppressed HIV infection failed to confer a clinically significant benefit with regard to viral suppression off ART.
|         | Sample size calculations done. Intention to treat analysis done.

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<th>Allocation concealment</th>
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</table>

**Study** | **Plana 2004**

| Methods | RCT; N=45
|         | Randomized
|         | Open
|         | FUP: 2 years
|         | W/o and d/o: none

| Participants | STI n=45
|             | 25 patients from SSITT and 20 patients from pilot study;
|             | Baseline Cd4>400, VL>5000
|             | EC: VL<20 copies/ml for 32 weeks, HAART duration 1year

| Interventions | STI cycles: 4
|              | STI duration: 2 weeks off and 8 weeks on
|              | 5th STI, (after 12th week, VL allowed to reach a setpoint).

| Outcomes | VL: VL set point during final STI was lower, positively correlated to baseline VL before HAART (p<0.0001); Mean VL reduction 0.777log(p<0.001); VL rebound peak declines over time, decreases not statistically significant; Plasma VL positively correlated with CD8 T cell percentage.
|          | CD4: A significant decrease in percentage of CD4 T cells (p<0.0001). CD4 LPR to p24increased significantly (p<0.001) between day 0 of the first STI cycle and 4th STI but decreased thereafter.
|          | CD8T cell response increase in magnitude, between day 0 and week 52 (p<0.0001); In patients with nadir CD4>400, increased HIV-1 specific immune response seen; significant decrease in CD4 T cell percentage (p<0.001);

| Notes   | STI did not control viral replication, possibly because boosted CTL responses lacked durable, strong and sustained helper T cell response. To reset VL set point, alternative approaches that augment helper T cell response need investigation. HIV-1 specific cellular immune responses can be augmented following cycles of therapy interruptions in very early stage HIV-1 chronically infected individuals.

| Allocation concealment | D |

**Study** | **Ruiz 2000**

| Methods | RCT; N=26 patients;
|         | Randomized yes;
|         | Open
|         | FUP=unclear, w/o and d/o=reported

| Participants | STI N= 12; Control N=14; Chronic HIV infection,
Characteristics of included studies (Continued)

EC: 2 years of viral suppression, during ART, CD4:CD8 ratio>1 for 6month, HIV-1 asymptomatic adults >2years, HIV-1RNA <50 copies/ml *24 months, ART regime 5 different combination regimes, median duration of HIV infection 10 years.,

Interventions 3 cycles of STI, ART duration between cycles 90days, cointervention: interleukin used

Outcomes Rebound of HIV-1RNA occured in all the three TI. No significant change in CD4/CD8 cell counts or in memory and naive subpopulations. 5/12 patients developed a p24 specific T helper cell response, HIV specific C8 T cell response detectable at baseline, no significant differences between those on interleukin and those not on interleukin. HIV specific CD8 T cell response detected at baseline,

Notes Scientific support for therapeutic strategies re-exposing immune system to nonpathogenic formulations restoring HIV specific immune response, need for large controlled trials

Allocation concealment B

Study Ruiz 2001

Methods Uncontrolled
N=12, Open, W/o and d/o=reported, FUP=unclear

Participants EC: Chronic HIV Infection, median CD4 1367 cells/mm3, viral load 29496. ART duration pre STI >2years, Regimes interrupted were PI +NRTI based.

Interventions STI :1 cycle of STI 30 day duration, no co-intervention used

Outcomes VL: increased exponentially in 10/12 during interruption period. 2 subjects maintained HIV RNA below detection limits. CD4 and CD8: No CD4 decline. No significant variations in CD4/CD8 T cells percentage nor in proportion of memory and naive T cell subsets when therapy is stopped, level of expression of T cell activation antigen increased significantly. A significant increase in proportion of CD8/CD38 T cells detected.

Notes No immunological impairment in the cohort. Brief duration of interruption and small sample in our pilot study limit generalizability. Interruption not associated with CD4 decline and viral rebound effectively controlled on resuming therapy.

Allocation concealment D

Study Tarwater 2003

Methods Uncontrolled
N=105; Non randomized Open; mixed cohort study Follow up reported

Participants STI N= 105 Lab and clinical criteria used to interrupt therapy; ART 6months;

Interventions STI cycles: variable Median TI duration 114 weeks. Pulse therapy-CD4 maintained above a threshold, using cycles of ART and prolonged interruptions;

Outcomes Three outcomes: 1. Time to treatment resumption TR. 2. Rate of change in CD4 cell count per year after TI: decrease of CD4 80 in non resumers, decrease in CD4 159 in resumers. 3. Mean Viral load during TI 20,000 in non resumers and 64,500 in resumers
Characteristics of included studies (Continued)

CD4: 57% patients with a mean CD4 of 500, did not resume therapy. Compared to baseline CD4 >500, those with CD4<200 were 4.4 times likely to resume treatment; Those with a CD4 200-350 were 2.9 times likely to resume treatment; those with a CD4 350-500 were 1.6 times more likely to resume treatment.

No AIDS defining malignancies.

Notes

- Pretreatment CD4 cell count was best predictor of TI duration. Patients with low virological set points and high CD4 cell count could discontinue therapy for longer periods of time.
- Patients with greatest increase in CD4 post ART had the most rapid decline in CD4 cells.

Allocation concealment  D

<table>
<thead>
<tr>
<th>Study</th>
<th>Tuldra 2001</th>
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<tbody>
<tr>
<td>Methods</td>
<td>NRCT; N=24, Non randomized, open trial, w/o and d/o=reported;</td>
</tr>
<tr>
<td>Participants</td>
<td>STI N=12 Control N=12 EC: Chronic HIV-1 patients, HIV-1 positive, ART&gt;2 years, CD4:CD8 ratio&gt;1, &lt;20 copies of HIVRNA cop/ml for 24 months,</td>
</tr>
<tr>
<td>Interventions</td>
<td>STI cycle: 30 days, total 4 cycles, ART &gt;2 years, duration of ART between cycles 3months,</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Quality of Life better in interrupters compared to control, p=0.03; QOL decreased on therapy re-introduction (p=.003) Self perceived health status improved significantly during interruption (p=0.02) and decreased on treatment resumption; Effort to follow medication greater at first resumption of therapy and feeling of freedom from duty of medication intake reported in 70% participants; No differences found with respect to CD4 and VL after reintroduction of therapy;</td>
</tr>
<tr>
<td>Notes</td>
<td>Significant improvement in QOL in STI. Close follow up of patients undergoing STI is advised to avoid difficulties reported at resumption of treatment.</td>
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<td>Allocation concealment</td>
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Characteristics of excluded studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
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<tbody>
<tr>
<td>Altfeld 2002</td>
<td>Acute HIV-1 Infection</td>
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<tr>
<td>Ananworanich 2003a</td>
<td>Case report</td>
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<tr>
<td>Benson 2001</td>
<td>Review</td>
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<tr>
<td>Chen 2002</td>
<td>Retrospective cohort analyzing unstructured treatment interruptions</td>
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<td>Deeks 2001</td>
<td>Treatment failure category</td>
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<td>Delaugerre 2001</td>
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<td>Devereux 1999</td>
<td>Drug discontinuation studies</td>
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<td>Fagard 2005</td>
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<td>Frost 2002</td>
<td>Modeling and basic sciences</td>
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<td>Garcia 2002</td>
<td>Basic sciences</td>
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Characteristics of excluded studies

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<td>Halfon 2003</td>
<td>Treatment failure</td>
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<td>Haslett 2000</td>
<td>Prospective cohort</td>
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<td>Izopet 2000</td>
<td>Drug discontinuation</td>
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<td>Jaafar 2004</td>
<td>Treatment failure</td>
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<td>Katlama 2004</td>
<td>Treatment failure</td>
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<tr>
<td>Lawrence 2003</td>
<td>Treatment failure</td>
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<td>Lori 2000</td>
<td>Review</td>
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<td>Miller 2000</td>
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<td>Neumann 1999</td>
<td>Primary Infection</td>
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<tr>
<td>Ortiz 1999</td>
<td>Drug discontinuation</td>
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<td>Poulton</td>
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<td>Prado</td>
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<td>Rosenberg 2000</td>
<td>Acute HIV-1 Infection</td>
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<td>Ruiz 2003</td>
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<td>Schweighardt 2002</td>
<td>Basic science</td>
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<tr>
<td>Taffe 2002</td>
<td>Cohort study with unplanned interruptions</td>
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<td>Tebas 2002</td>
<td>Retrospective cohort with drug discontinuation</td>
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<td>Tremblay 2003</td>
<td>Acute HIV infection b</td>
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<td>Yerly 2004</td>
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<td>Treatment failure</td>
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Characteristics of ongoing studies

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<tbody>
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<td>Trial name or title</td>
<td>ISSPART</td>
</tr>
<tr>
<td>Participants</td>
<td>Chronic HIV-1 infection</td>
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<tr>
<td>Interventions</td>
<td>Prospective trial therapy of intermittent therapy</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Immunological and virological response</td>
</tr>
<tr>
<td>Starting date</td>
<td></td>
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<tr>
<td>Contact information</td>
<td>Stephano Vella, MD Research Director, HIV AIDS, Instituto Superiore di Sanita, Rome, Italy</td>
</tr>
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<td>Notes</td>
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<th>Study</th>
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<tbody>
<tr>
<td>Trial name or title</td>
<td>SMART</td>
</tr>
<tr>
<td>Participants</td>
<td>Chronic HIV-1 infection n=6000 HIV positive participants, over 13 years, CD4&gt;350, follow up 3-5 years</td>
</tr>
<tr>
<td>Interventions</td>
<td>STI group WAIT group and continuous therapy group GO group; STI gp treatment reinintiated if CD4 fall below 250,</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Comparing drug conservation strategy to viral suppression strategy, long follow up of clinical, virological and immunological outcomes</td>
</tr>
<tr>
<td>Starting date</td>
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</table>

Structured treatment interruptions (STI) in chronic suppressed HIV infection in adults (Review)
### Characteristics of ongoing studies (Continued)

<table>
<thead>
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<th>Study</th>
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<tbody>
<tr>
<td><strong>Trial name or title</strong></td>
<td>BASTA study</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>on ART CD4&gt;800 VL&lt;50 copies/ml</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>STI or Continuous therapy Treatment resumed if CD4 fell below 400, interrupted above 800</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Patients with high nadir CD4 remained interrupted for longer periods. Patients with high nadir CD4 STI may be safe.</td>
</tr>
</tbody>
</table>

**Contact information**
- NIAID/NIH
- Multicentric trial

**Notes**
- one study published to date, study in progress

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**GRAPHS AND OTHER TABLES**

This review has no graphs.

---

**COVER SHEET**

**Title**
Structured treatment interruptions (STI) in chronic suppressed HIV infection in adults

**Authors**
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**Contribution of author(s)**
- Study concept and design: Pai, Tulsky
- Acquisition of data: Pai, Tulsky
- Analysis and Interpretation of data: Pai, Tulsky, Lawrence
- Drafting of manuscript: Pai, Lawrence, Tulsky, Colford, Reingold
- Critical revision of manuscript for important intellectual content: all authors

**Issue protocol first published**
/

**Review first published**
/

**Date of most recent amendment**
19 August 2005

**What's New**
Information not supplied by author

**Date new studies sought but none found**
Information not supplied by author

**Date new studies found but not yet included/excluded**
Information not supplied by author

**Date new studies found and included/excluded**
Information not supplied by author

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Structured treatment interruptions (STI) in chronic suppressed HIV infection in adults (Review) 36

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