Safety and factors predicting the duration of first and second treatment interruptions guided by CD4+ cell counts in patients with chronic HIV infection

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Objectives: To evaluate the safety of treatment interruption (TI) guided by CD4+ count in HIV-infected patients followed-up prospectively.

Methods: Patients on HAART with a CD4+ cell count >500 cells/mm3 discontinued therapy with instructions to start therapy again before their CD4+ count dropped below 200 cells/mm3.

Results: We report data on 112 HIV-infected patients. The median follow-up after starting the first TI was 34.7 months (IQR: 23.1–43.8). The median duration of the first TI was 12 months (IQR: 5.2–25). In the multivariate analysis the factor which most strongly correlated with the duration of the first TI was the CD4+ cell count at the end of the TI. Among the 34 patients who had completed a second TI, the duration of the two periods of interruption was similar if the treatment was recommenced at the end of the first TI at a CD4+ count higher than the nadir count.

Conclusions: The strategy of TI is safe if the criteria for restarting therapy are applied correctly. The factor with the greatest influence on the duration of the first TI is the number of CD4+ cells at the end of the TI.

Keywords: nadir CD4+ cell count, highly active antiretroviral therapy, immunological set-point

Introduction

Following evidence that it is not possible to eradicate human immunodeficiency virus (HIV) with the currently available treatments,1 and that prolonged administration of highly active antiretroviral therapy (HAART) is often associated with severe side-effects and with a risk of developing extensive drug resistance,2,3 the indications for starting therapy have been changed. Current guidelines recommended that treatment should be delayed in order to reduce the amount of time patients are exposed to drugs. This strategy derives from an analysis of cohort studies, but there is a lack of data from randomized, controlled trials on clinical end-points to guide the decision on when to initiate therapy in patients with >200 CD4+ cells/mm3.4

Exposure to drugs could also be reduced by a strategy involving periodic cyclic treatment interruptions (TIs) if this approach were to be demonstrated safe.

The aim of this study was to evaluate the safety of TI guided by the CD4+ cell count in patients with a good response to HAART and to evaluate which parameters correlate with the duration of the first and second TI.

Patients and methods

In this study we report an update of the results of our cohort of patients who are undergoing carefully managed therapy interruptions, 1 year after the previous analysis.5 In this prospective cohort study we evaluated patients with chronic HIV infection who suspended HAART with the intention of resuming therapy on the basis of predefined criteria. The last US guidelines developed by the panel on clinical practices for treatment of HIV infection convened by the Department of Health and Human Services (DHHS) reported that the option of TI based on CD4+ cell count may be offered to patients with immune reconstitution. Therapy was interrupted only in those patients who gave their verbal informed consent to this management.

This study was strictly observational and all the decisions regarding interruption and resumption of therapy were made by the patient’s clinician. HAART was suspended because of toxicity or following agreement between the doctor and patient. All patients who were offered the possibility of interrupting HAART were informed that during TI the CD4+ cell count would decrease and that there would be rebound viral replication with the risk of disease progression, selection of drug-resistant viruses and increased infectivity.

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Eligible patients were older than 18 years, with a CD4+ lymphocyte cell count above 500 cells/mm³, an undetectable viral load or HIV-RNA detectable, after virological suppression, only in the last follow-up and on HAART for more than 12 months.

The criteria for restarting therapy were (i) patient’s choice, at any level of CD4+ count; (ii) pregnancy; (iii) appearance of symptoms that could be manifestations of HIV infection and (iv) a decreasing CD4+ count before falling below 200 cells/mm³.

Patients receiving HAART with protease inhibitors suspended all treatment simultaneously, whereas the patients receiving HAART containing non-nucleoside reverse transcriptase inhibitors suspended the inhibitors 48 hours before the other drugs in the HAART regimen.

CD4+ count and viral loads were monitored every 2 months during TI. A test of genotypic resistance was planned in cases of viral load >1000 copies/mL at 6 months after reintroducing HAART or in the case of viral rebound >1000 copies/mL.

After restarting HAART, patients were eligible for another TI when the CD4+ count again exceeded 500 cells/mm³ or if signs of HAART-related toxicity developed.

In most cases the therapy used after TI was the same combination of drugs used before the TI, although in some cases the combination was modified because of previous toxicity or to minimize the pill burden.

The study follow-up started at the moment of the first TI. Only patients with a follow-up of at least 12 months were considered in the evaluation of the long-term effects of TI. The data were collected up to 31 June 2004.

The primary endpoint of the study was to evaluate the safety of TI guided by CD4+ counts. Safety was defined as the lack of appearance of AIDS-defining events, the absence of unexpected clinical events and the absence of virological failure (as defined by DHHS guidelines) when therapy was reintroduced.

The secondary endpoint was to evaluate parameters correlated with the duration of the first TI, the behaviour of the CD4+ count after the TI, the immunological response to restarting therapy and the duration of any TI subsequent to the first.

A total of 112 patients were enrolled in the cohort; 6 patients were lost from the follow-up during the observation period. The median age was 42 years (interquartile range [IQR]: 25th–75th percentiles) 37–48 years and 81 (72.3%) of the patients were males. The presumed method of having acquired HIV infection was heterosexual activity in 44 (39.3%), homosexual practices in 38 (33.9%) and intravenous drug use in 30 (26.8%). Twelve patients had had a previous diagnosis of AIDS.

The nadir cell count was defined as the lowest value of CD4+ lymphocytes before starting HAART.

At the time of the first TI the viral load was <50 copies/mL in 93 (83%) patients and >50 copies/mL in 19 (17%, median 2.54 log₁₀ copies/mL, IQR: 2.01–3.21).

**Statistical analysis**

The normal distribution of the variables was evaluated by Shapiro’s test and the data are presented as medians with IQRs (IQR: 25th–75th percentiles); non-parametric tests were used for comparisons between and within groups. Correlates of the duration of the first TI (age, gender, risk, nadir CD4+ cell count, viral load pre-HAART, stage of infection, months of therapy before TI, viral load <50 copies/mL for less than or more than 12 months before the TI, CD4+ cell count at TI, gain of CD4+ cells prior to the TI, CD4+ cell count at the end of TI, and difference between the CD4+ count at the end of the TI and the nadir CD4+ cell count) were determined using Cox model analysis. Repeated measure MANOVA was used to test for statistically significant changes over time and between groups stratified according to the CD4+ nadir. Pearson’s correlation test was used to investigate relationships among variables. Multiple linear regression was used to analyse the factors (age, gender, risk, stage of infection, nadir CD4+ cell count, viral load pre-HAART, months of therapy before TI, viral load <50 copies/mL for less than or more than 12 months before the TI, CD4+ cell count at TI, gain of CD4+ before the TI) possibly correlated with a decrease of CD4+ cell counts at various times after the TI. A P value of <0.05 was considered to be statistically significant. All tests were two-sided. Analyses were performed using Statistica for Windows (StatSoft, Inc. 2002. STATISTICA for Windows, Computer program manual, Tulsa, OK, USA) and using the STATA software (StataCorp, 2002. Stata Statistical Software: release 7.0, College station, TX, USA).

**Results**

After the start of the first TI the median follow-up was 34.7 months (IQR: 23.1–43.8).

The overall duration of the follow-up was 3854.2 months and the total time of therapy suspension (first TI and subsequent ones) was 2380.5 months with a 61.8% HAART time savings.

After the first TI 88 (78.6%) patients restarted therapy while 24 (21.4%) were still off therapy at the end of the follow-up; 54 patients interrupted therapy twice, 17 patients interrupted therapy three times, 7 patients four times, 5 patients five times and 1 patient six times.

Data on pre-HAART viral load was available for 67 patients (median 4.78 log₁₀ copies/mL; IQR: 4.4–5.2). The median viral load in the same patients at the end of the first TI (median duration 12 months IQR: 5–24.9) was 5.0 log₁₀ copies/mL (IQR: 4.6–5.5).

**Clinical events**

During the follow-up, one 73-year-old patient died of cerebral stroke.

**AIDS-defining events.** One case. AIDS-defining events occurred in one 42-year-old male who began HAART because of the onset of fever with a CD4+ count of 350 cells/mm³ and a viral load of 5.9 log₁₀ copies/mL. After 50 months of continuous treatment with a CD4+ count of 1410 cells/mm³ and a viral load <50 copies/mL, TI was agreed. After 18 months of TI the CD4+ cell count was 290 cells/mm³ and the patient complained of a 15 day history of low-grade fever and oral candidiasis. HAART was not restarted and 2.5 months later he developed Pneumocystis carinii pneumonia (PCP). After treatment of the PCP, HAART was recommenced and 10 months later the CD4+ had recovered to 1148 cells/mm³ and the viral load was <50 copies/mL.

**Acute retroviral syndrome-like illness.** Three cases. Symptoms appeared 20, 28 and 40 days after the TI. All these patients had a nadir CD4+ cell count <200 cells/mm³. The duration of HAART prior to the TI had exceeded 4 years in all three; the pre-TI CD4+ cell counts were 725, 875 and 1041 cells/mm³, respectively, and the viral load was <50 copies/mL. The CD4+ cell counts at the onset of the symptoms were 373 and 441 cells/mm³ and the viral loads 5.53 and 6.10 log₁₀ copies/mL (one patient restarted therapy without undergoing laboratory tests). All resumed treatment which resulted in rapid disappearance of symptoms. On specific request, one patient underwent subsequent therapy interruptions without reappearance of symptoms.
Oral candidiasis. Five cases. All these patients had initially started HAART on the occasion of developing oral candidiasis. Their median nadir CD4+ count was 306 cells/mm³ (range 162–505). At the time of reappearance of the oral candidiasis the median CD4+ count was 406 cells/mm³ (range 354–574) and therapy was restarted. These five patients interrupted therapy a second time and four of them once again developed oral candidiasis.

Analysis of the factors related to the duration of the first TI and the decrease in CD4+ cell count during the TI

In the univariate analysis the factors that were most strongly correlated with the duration of the TI were the nadir CD4+ cell count, the CD4+ cell count at the time of TI and the CD4+ cell count at the end of TI (all P < 0.001). The other parameters that were significantly related to the duration of the TI were age (P = 0.002), disease stage (AIDS versus chronic infection; P = 0.004), pre-HAART viraemia (P = 0.005) and viraemia at the end of the TI (P = 0.042). In the multivariate analysis the only factors that were correlated with the duration of the TI were the CD4+ cell count at the end of the TI (P = 0.006) and the viral load at the end of the TI (P = 0.009).

On the basis of these results we divided the patients into three groups according to the difference between the number of CD4+ lymphocytes at the end of the TI and the nadir CD4+ cell count (ΔCD4+). We considered that the TI was concluded at the same level as the nadir CD4+ cell count if the difference was between –49 CD4+ cells/mm³ (with respect to the nadir), at a level higher than that of the nadir if the difference was >49 CD4+ cells/mm³ and at a level lower than that of the nadir if the difference was less than –49 CD4+ cells/mm³. Table 1 reports the durations of the TI in the patients divided according to this stratification, while Table 2 reports the durations of the TI in patients stratified according to their nadir CD4+ cell count.

The pre-HAART viral load was not included in the multivariate analysis because data were available for only 67 patients. An analysis of these patients, using a model in which all the previously listed factors were included, yielded pre-HAART viral load as the only factor correlated with the duration of the TI (P = 0.023).

Table 3 reports the duration of the first TI in patients stratified according to the pre-HAART viral load.

During the first TI the CD4+ cell count dropped rapidly in the first 2 months and then continued to fall more slowly (Figure 1).

The independent factors correlated with a reduction of CD4+ counts (change %) in the first 2 months after the first TI, investigated with multiple regression analysis, were the CD4+ increase during HAART (normalized coefficient: 0.38; P < 0.0001) and nadir CD4+ cell count (normalized coefficient: –0.31; P = 0.001). None of the factors analysed was correlated with the number of CD4+ cells lost in the period from 2 months after the TI until the end of the TI.

By 2 months after the start of TI, a median of 47.5% of the CD4+ cells recovered during HAART had been lost. Evaluating this

Table 1. Duration of the first TI in groups of patients stratified according to the difference between the CD4+ count at the end of the TI and the nadir CD4+ cell count (ΔCD4+)

<table>
<thead>
<tr>
<th>ΔCD4+</th>
<th>≤–49 cells/mm³</th>
<th>ΔCD4+ between ±49 cells/mm³</th>
<th>ΔCD4+ &gt;49 cells/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>26</td>
<td>28</td>
<td>54</td>
</tr>
<tr>
<td>Nadir CD4+ count, median (IQR) (cells/mm³)</td>
<td>435 (374–600)</td>
<td>315 (278–441)</td>
<td>246 (144–350)</td>
</tr>
<tr>
<td>Duration of TI, median (IQR) months</td>
<td>21.6 (12.3–25)</td>
<td>14.2 (8.9–27.6)</td>
<td>8 (4.2–13.5)</td>
</tr>
<tr>
<td>ΔCD4+, median (IQR) (cells/mm³)</td>
<td>–107 (–203, –86)</td>
<td>+17 (–14, +31)</td>
<td>+133 (+88, +186)</td>
</tr>
<tr>
<td>CD4+ count before TI, median (IQR) (cells/mm³)</td>
<td>794 (625–1095)</td>
<td>759 (655–910)</td>
<td>748 (605–952)</td>
</tr>
<tr>
<td>CD4+ count at the end of TI, median (IQR) (cells/mm³)</td>
<td>308 (274–374)</td>
<td>337 (293–406)</td>
<td>392 (289–502)</td>
</tr>
</tbody>
</table>

IQR, interquartile range.

*Analysis on 108 patients: nadir CD4+ count unknown in 3 patients and CD4+ count at the end of TI unknown in 1 patient.

Table 2. Duration of first TI in all patients and in groups stratified according to nadir CD4+ cell count

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>All patients</th>
<th>Patients with nadir CD4+ &lt;200 cells/mm³</th>
<th>Patients with nadir CD4+ between 200 and 349 cells/mm³</th>
<th>Patients with nadir CD4+ &gt;349 cells/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nadir CD4+ count, median (IQR) (cells/mm³)</td>
<td>338 (200–402)</td>
<td>124 (65–165)</td>
<td>294 (262–320)</td>
<td>440 (374–505)</td>
</tr>
<tr>
<td>Duration of treatment before TI, median (IQR) months</td>
<td>36 (24–51)</td>
<td>40 (26.5–65)</td>
<td>29 (18.5–71)</td>
<td>35.1 (20.3–44.7)</td>
</tr>
<tr>
<td>CD4+ count before TI, median (IQR) (cells/mm³)</td>
<td>751 (627–977)</td>
<td>694 (552–875)</td>
<td>701 (627–851)</td>
<td>931 (679–1121)</td>
</tr>
<tr>
<td>Duration of TI, median (IQR) months</td>
<td>12 (5.3–25)</td>
<td>4.8 (2.5–8.8)</td>
<td>11 (5.5–14.4)</td>
<td>24 (12.3–38)</td>
</tr>
<tr>
<td>CD4+ count at the end of TI, median (IQR) (cells/mm³)</td>
<td>343 (280–437)</td>
<td>257 (228–335)</td>
<td>339 (291–404)</td>
<td>416 (313–502)</td>
</tr>
</tbody>
</table>

IQR, interquartile range.

*Nadir CD4+ count unknown in three patients.

*CD4+ count before restarting therapy or last CD4+ value available for patients still in treatment suspension.
proportion in the various groups stratified according to the nadir CD4+ cell count, the median loss was 51.5, 54.8 and 43.8% in the groups with a CD4+ nadir count <200, 200–349, and >349 cells/mm3, respectively (using the Kruskal–Wallis ANOVA test, these differences were not statistically significant; \( P = 0.214 \)).

**Trend in CD4+ counts and viral load after restarting treatment and analysis of the second interruption**

After the first TI 88 patients restarted HAART and all had a rapid increase in CD4+ counts (Table 4).

Among the 88 patients who resumed HAART after the first TI, there was one patient in whom the viral load remained >400 copies/mL despite at least 24 weeks of resumed treatment (820 copies/mL after 10 months of therapy; this patient interrupted therapy a second time and at recommencement of therapy achieved a viral load <50 copies/mL) and two patients with a viral load >50 copies/mL more than 48 weeks after resuming treatment (73 and 101 copies/mL after 12.5 and 20 months, respectively). Both patients had had a viral load >50 copies/mL before the TI (76 and 151 copies/mL, respectively). Thirty-four patients resumed therapy after a second TI and one of these patients had a viral load of 59 copies/mL after 18 months of treatment. Twelve patients resumed treatment after a third TI, six after a fourth TI, two after a fifth TI and one after a sixth TI; none of these patients has suffered virological failure.

In order to compare the duration of the first TI with that of subsequent interruptions, we analysed 34 patients who completed a second TI. Table 5 reports the data concerning the duration of the first and second TI.

**Conclusions**

In patients undergoing TI, once case of AIDS occurred during the follow-up, when PCP developed 20 months after therapy suspension in a patient who had initially started HAART because of the onset of fever with a CD4+ count >300 cells/mm3. The patient developed fever and oral candidiasis 2 months before the appearance of PCP. Fever, constitutional symptoms and/or oral candidiasis are unchallenged criteria for starting therapy in treatment-naive patients, independently of the CD4+ count.4 The recognized predictive value of these symptoms for the appearance of AIDS-defining events in treatment-naive patients indicates that rigorous application of the clinical criteria for starting HAART is the most important factor for guaranteeing the safety of TI as well.

In our analysis, none of the patients who had had a viral load >50 copies/mL before the TI developed AIDS during the follow-up. The cases of acute retroviral syndrome-like illness all occurred in patients with nadir CD4+ counts <200 cells/mm3, an association already described by other authors.5–8

Our analysis shows that the factor with the greatest influence on the duration of the first TI was the CD4+ cell count at the end of the TI. Other studies examining TI have indicated various factors as being predictive of the duration of the TI, with the nadir count emerging as the most constant and influential.5–15 In a previous study, the duration of TI was significantly longer in patients with lower CD4+ counts at the end of the TI.5 In our study, the CD4+ count at the end of the TI was significantly lower in patients who had a longer duration of TI, as compared to patients with a shorter duration of TI. This finding is consistent with the results of other studies that have shown a significant correlation between the duration of TI and the CD4+ count at the end of the TI.2–5,10–14 In our study, the CD4+ count at the end of the TI was significantly lower in patients who had a longer duration of TI, as compared to patients with a shorter duration of TI. This finding is consistent with the results of other studies that have shown a significant correlation between the duration of TI and the CD4+ count at the end of the TI.2–5,10–14

| Patients (n) | 67 | 9 | 12 | 20 | 26 |
| Duration of TI, median (IQR) months | 12 (5–24.9) | 19 (9.3–36.5) | 13.9 (5.5–40) | 11.2 (4.8–25) | 9.6 (4.5–18) |
| \( \Delta CD4+ \), median (IQR) (cells/mm\(^3\)) | +56 (–61, +144) | +100 (+9, +246) | +42 (–103, +107) | +78 (+22, +142) | +7 (–87, +115) |

IQR, interquartile range.

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Median loss (lines: 25th–75th percentiles) of CD4+ cells per month (cells/mm\(^3\)) in various periods after TI in all patients and in groups stratified according to nadir CD4+ cell counts.
study, we also reported that the duration of the first TI was correlated to the nadir CD4+ count. However, we also noted that during TI the time required to lose the CD4+ cells recovered during HAART was similar in all patients and independent of the nadir CD4+ cell count and that the correlation between the duration of the first TI and the nadir CD4+ count was probably due to the fact that, in the various groups stratified according to nadir CD4+ cell count, the resumption of HAART started from CD4+ counts values that were different from the nadir value. In fact, when the CD4+ count at the end of TI was included in the multivariate analysis, the nadir CD4+ count lost its significance and the factor with most influence on the duration of the TI was the CD4+ count at the end of the TI.

Indeed, it seems clear (Table 1) that patients who resumed therapy at CD4+ counts lower than their nadir count had a longer duration of TI than patients who resumed therapy at CD4+ counts higher than their nadir count. It is also obvious that the former situation is possible in patients with higher nadir counts, whereas those patients with lower nadir counts must resume treatment at CD4+ cell counts above the level of their nadir count (Tables 2 and 4).

In the group of patients who restarted therapy respecting the nadir count, the median duration of TI was ~14 months. This is the time necessary to lose the CD4 lymphocytes recovered during the therapy preceding the TI. Similar times for CD4+ cell loss have been reported in other studies.

Data on pre-HAART viral load were only available for 67 patients. Albeit with the limitation inherent in this small sample size, in a statistical model also incorporating CD4+ cell counts at the nadir, at the time of starting TI and at the end of TI, the only factor related in a statistically significant manner with the rate of CD4+ loss during the TI was the pre-HAART viral load. When the patients were stratified according to their pre-HAART viral load (Table 3), patients with more marked viraemia, despite having similar nadir CD4+ cell counts, lost the CD4+ cells recovered during therapy more rapidly, resembling what happens in

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>All patients</th>
<th>Patients with nadir CD4+ count &lt;200 cells/mm³</th>
<th>Patients with nadir CD4+ count between 200 and 349 cells/mm³</th>
<th>Patients with nadir CD4+ count &gt;349 cells/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>88</td>
<td>25</td>
<td>33</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Nadir CD4+ count, median (IQR) (cells/mm³)</td>
<td>296 (180–377)</td>
<td>143 (81–163)</td>
<td>294 (262–320)</td>
<td>428 (377–570)</td>
</tr>
<tr>
<td>CD4+ count before TI, median (IQR) (cells/mm³)</td>
<td>715 (616–895)</td>
<td>683 (552–819)</td>
<td>701 (642–780)</td>
<td>889 (668–1111)</td>
</tr>
<tr>
<td>Duration of first TI: median (IQR) (months)</td>
<td>9 (4.5–16.5)</td>
<td>4.5 (2.5–8)</td>
<td>10.5 (5.5–14)</td>
<td>17.7 (8–24)</td>
</tr>
<tr>
<td>CD4+ count at restarting treatment, median (IQR) (cells/mm³)</td>
<td>323 (268–390)</td>
<td>251 (223–314)</td>
<td>336 (291–386)</td>
<td>374 (307–437)</td>
</tr>
<tr>
<td>Months (median) of therapy after the end of the first TI (IQR)</td>
<td>9 (5.5–15)</td>
<td>9.5 (6.6–14)</td>
<td>7.8 (5.6–12.5)</td>
<td>8.7 (4.9–14.5)</td>
</tr>
<tr>
<td>CD4+ count during therapy after the first TI, median (IQR) (cells/mm³)</td>
<td>582 (477–677)</td>
<td>524 (427–668)</td>
<td>546 (441–651)</td>
<td>613 (559–693)</td>
</tr>
</tbody>
</table>

IQR, interquartile range.

*aNadir CD4+ count unknown in one patient.

*bCD4+ count at the end of therapy for those who started the second TI or last follow-up data for those still in therapy after the first TI.

Table 5. Duration of first and second TIs in all patients who had resumed treatment after a second TI and in the groups of patients stratified according to whether therapy was resumed after the first TI at a CD4+ count higher (A) or lower (B) than the nadir count.

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>All patients</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>275 (119–309)</td>
<td>19.9 (17–32.4)</td>
<td>15.6 (5.5–22.7)</td>
</tr>
<tr>
<td>308 (250–428)</td>
<td>40 (24–91)</td>
<td>794 (593–1056)</td>
<td>382 (257–450)</td>
</tr>
<tr>
<td>321 (272–386)</td>
<td>324 (265–394)</td>
<td>321 (282–386)</td>
<td></td>
</tr>
</tbody>
</table>

IQR, interquartile range.
Strategy of TI in HIV-infected patients

The decline in CD4+ cell counts during the first TI has a biphasic trend, being rapid in the first months and then slower in subsequent months, as described by others.\(^\text{5,10,11,13,15,18}\)

In the first 2 months of the TI ~50% of the CD4+ lymphocytes recovered during the HAART are lost, as reported in other studies\(^\text{10,13,19}\). The absolute number of CD4+ cells lost during the TI is related to the number of these cells gained during the HAART, as described by various authors\(^\text{9,15,18,19}\) and to the nadir CD4+ cell count as described by others.\(^\text{11,13}\) In the former studies, a similar increase in CD4+ cells was observed in patients with different CD4+ nadirs. In the latter, patients with lower nadir CD4+ counts gained the greatest number of CD4+ cells during the HAART. The correlation with either HAART-associated CD4+ cell gain or CD4+ cell nadir reflects differences in populations analysed. The median loss of CD4+, 2 months after the start of TI, was nearly 50% of the cells recovered in all groups of patients stratified according to nadir cell count. These observations suggest that the behaviour of the CD4+ lymphocytes gained during HAART is identical in all patients and that the absolute value of the loss of these cells is proportional only to the number gained during HAART.

After TI the loss of CD4+ lymphocytes gained during HAART, besides being similar in all patients, was much faster than that seen in untreated patients with HIV infection.\(^\text{17}\)

These factors, together with the fact that the duration of HAART, the number of CD4+ cells gained and the time of viral suppression before the TI do not influence the duration of the TI, suggest that the damage to the immune system caused by HIV is not reversible by current therapy, as indeed indicated by other authors.\(^\text{20,21}\) Following the TI, the viral load rebounds to the pre-HAART levels,\(^\text{22–24}\) and in a relatively short time span, CD4+ cell counts similarly tend to return rapidly to the pre-HAART level. As a result, patients who obtain high CD4+ cell counts during treatment cannot be considered identical with treatment-naive patients with the same CD4+ cell count. It is, therefore, probable that an immunological set-point is established during HIV infection, in addition to the described virological set-point.\(^\text{22–24}\)

During the period of antiretroviral therapy, the drugs cause a decrease in viral replication and a consequent increase in the number of circulating CD4+ lymphocytes, thus interrupting the evolution of the HIV infection and reducing HIV-related morbidity and mortality.\(^\text{25}\) However the treatment is not able to modify the equilibrium between the HIV and the host’s immune system that was established at the time of starting therapy. The reappearance during TI of the same clinical events that had necessitated the initiation of HAART is also indirect confirmation of this hypothesis.

When treatment is resumed, there is a rapid increase in the number of CD4+ cells (Table 4) and any viraemia reaches undetectable levels in practically all patients, as observed in other studies.\(^\text{9,12}\) We have already expressed our opinion on the risk of the development of mutated, drug-resistant viral strains as a consequence of TI in a previous study.\(^\text{1}\)

Since treatment of HIV infection is necessarily life-long, a single TI would have a very limited impact on the overall reduction in exposure to therapy. For this reason, the possibility of using CD4+ cell counts to guide repeated TI needs to be explored. The analysis of subsequent TIs after the first TI was limited to those patients who had resumed therapy after at least a second TI. This analysis showed that the second TI was shorter than the first only in those patients who, after the first TI, had resumed therapy at CD4+ counts lower than their nadir count (Table 5). This observation confirms the importance of the CD4+ count at which therapy is resumed in determining the duration of the TI and indicates that in order to have periods of TI of constant duration the nadir count must be respected. Lowering the immunological set-point increases the duration of first TI, but impoverishes the patient’s immune system, increases the levels of viraemia and shortens the duration of the subsequent TI.

In conclusion, we believe that CD4+ cell count-guided TI is a safe strategy if the criteria for resuming therapy are correctly applied. In patients with a nadir CD4+ count <200 cells/mm\(^3\) the duration of the TI is short and therefore the strategy is of limited efficacy in reducing the time exposed to drugs and places the patients at a risk of developing an acute retroviral syndrome-like illness. This strategy can, however, be considered for patients with a nadir CD4+ cell count of >200 cells/mm\(^3\) in order to manage the toxicity of antiretroviral drugs and/or fulfil a patient’s desire to suspend treatment.

Despite the limits of this being a study without a control group, our results shed some light on the possibility of using the strategy of TI also in treatment-naive patients. In these patients HAART could be started at CD4+ levels even higher than 350 cells/mm\(^3\) in order to preserve a more robust and competent immune system, then reducing the time exposed to drugs by using CD4+ cell count-guided TI that respects the nadir count. The validity of this hypothesis requires confirmation from the results of a controlled trial.

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Transparency declarations

None to declare.

References


