

Original Article**Is it Safe and Cost Saving to Defer the CD4+ Cell Count Monitoring in Stable Patients on Art with More than 350 or 500 cells/ μ l?**

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Abstract. Background: CD4+ lymphocyte cell count represents the main immunological marker used to monitor HIV infection. However, frequent monitoring may be unnecessary, could cause anxiety to the patient as well as burdening healthcare with extra expenses.

Objectives and methods: A two-step retrospective (safety and cost-saving) analysis was performed to evaluate the probability of maintaining a safe number of more than 350 CD4+ cells/ μ l in HIV-positive subjects under treatment during a three-year follow up and secondarily to estimate in *real life* the cost of the CD4+ determinations in a 3 years period, speculating on possible cost-saving strategies. The safety analyses was conducted with Kaplan-Meyer method considering: 1) all patients independently from their viral load (VL); 2) patients with 500 > CD4+ \geq 350 cells/ μ l versus (vs) CD4+ \geq 500 cells/ μ l at baseline; 3) patients with VL < 20 copies/ml vs VL > 20 copies/ml. The cost-saving analysis measuring the costs of CD4+ determinations was calculated from April 1, 2013, to March 31, 2016.

Results: In the safety analysis, 253 subjects were enrolled. The median CD4+ count was 623 (489-805) cells/ μ l. Subjects maintaining \geq 350 cells/ μ l in the first, second, and third year were respectively 238 (94.1%), 229 (90.5%), and 226 (89.3%), independently from VL. Within subjects with \geq 350 CD4+/ μ l vs. \geq 500 CD4+/ μ l at baseline, those who maintained \geq 350 cells/ μ l until the third year were respectively 241 (95.3%) and 158 (98.1%). The probability of maintaining these values in the third year was 89.3% for those who had CD4+ \geq 350/ μ l at baseline and 98.1% for those who had CD4+ \geq 500/ μ l. This probability was around 90% vs. 99% for subjects with HIV-RNA above or below 20 copies/ml. In the real-life cost saving analysis, we evaluated subjects with a stable value or more than 500 CD4+ (respectively 343, 364 and 383 in the first, second and third period). We observed mean value of about two determinations patient/year (2.41 in 2013/2014; 2.32 in 2014/2015; 2.18 in 2015/2016), with a significant decrease between the first and the last period ($p < 0.001$). The mean cost patient/year was €101.51 in the first year, €97.61 in the second, €92.00 in the third ($p < 0,001$). Assuming to extend these procedures to all our patients with stable CD4+ cells/ μ l and monitoring CD4+ cell count once in a year, we were able to obtain an overall saving of €19,152/year.

Conclusions: A very high percentage of subjects maintained a high and safe number of CD4+ cells (>350 cells/ μ l) during a three-year follow-up. It could be possible to save up to 66% of the costs by reducing the number of CD4+ count determinations in a year, to have other favorable consequences as well, releasing new resources for patient management.

Keywords: HIV; CD4 monitoring; Saving analysis; Saving cost.

Introduction. It is estimated that HIV infection affects about 37 million people worldwide, with 2 million new infections in 2017 only.¹ To date, CD4+ T-lymphocyte cell count represents the only immunological diagnostic and prognostic marker validated in randomized clinical trials and currently used in clinical practice.^{2,3} This parameter gives us information about the level of immune-depression at baseline and it has led for a long time the beginning of antiretroviral therapy (cART) administration; at the same time, CD4+ cell count highlights the timing of opportunistic infections prophylaxis.^{4,6}

A key finding is that untreated patients have a median decrease of the CD4+ cells count of about 4% per year,⁶ while subjects on ART have an increase of 50-100 cells μ l/year;⁷ this increase is strictly associated with the CD4+ nadir.^{2,8}

Nevertheless, opportunistic infections were reported even with an absolute CD4+ count over the risk threshold (≥ 350 cells/ μ l),^{2,5} although less frequently.² Due to the high variability of absolute numbers, CD4+ percentage should always be evaluated before clinical or therapeutic strategy modification: a decrease below 14% is associated with an increased risk of opportunistic infection.²

At this moment, the key questions are: how to behave if the patient is virologically suppressed? Is it safe to defer the CD4+ cell count monitoring in stable patients on ART with ≥ 350 or 500 cells/ μ l? The role and frequency of CD4+ cell count monitoring in stable HIV-infected subjects remain controversial.^{9,10} In 2012 the Department of Health and Human Services guidelines^{11,12} sentenced that “in patients with suppressed viral loads (VL) and a consistent ART-related immune reconstitution, frequent CD4+ count monitoring may be un-useful, given the continuous clinically irrelevant fluctuations, in addition to causing stress and anxiety both in the patient and in the physician. Therefore, in stable patients whose CD4+ cell count has increased well above the threshold for opportunistic infection risk, CD4+ count can be monitored less frequently than the VL (every 6 or 12 months).”

For this reason, Howard Gale et al.¹³ supported a less frequent CD4+ monitoring in virologically suppressed patients: they demonstrated that stable patients with VL < 200 copies/mL and CD4+ counts ≥ 300 cells/ μ L had a 97.1% probability of maintaining

CD4+ ≥ 200 cells/ μ L for 4 years; when non-HIV causes of lymphopenia were excluded, this probability rose to 99.2%.⁷

Caniglia and colleagues¹⁴ showed that decreasing monitoring frequency when CD4+ cell count > 200 cells/ μ l (compared with when CD4+ cell count > 500 cells/ μ l) results in an increased risk of virologic failure at 24 months of follow up. They also have shown that the mean CD4+ cell count at 18 months was higher than 400 cells/ μ l in the patients virologically suppressed.

Therefore, they concluded that less frequent monitoring for subjects on cART, with confirmed virological suppression, does not change substantially clinical outcomes in 18 months follow up.

Cost-saving is another considerable aspect: Hyle et al.,¹⁵ based on the need for redirecting financing in order to improve healthcare, estimated a potential annual saving of 18 million dollars by reducing CD4+ cell count monitoring.

The problem is how this change could affect some clinical decisions, such as when to start ART or prophylaxis for opportunistic infections (OI).

As far as we know, rarely does a virologically suppressed patient with ≥ 300 CD4+ develop an OI or a rapid CD4+ decline (below 200 cells/ μ l).

Moreover, the most sensitive method to describe a treatment failure is by determining HIV RNA.¹¹ For this reason, the CD4+ count is probably required only for those subjects who are not virologically suppressed and for those with advanced disease.¹⁶ Thus, why do we keep requesting it? Katz MH said that “it is our habit and patients expect it”.¹⁷ Unfortunately, nowadays health funds are not unlimited, and we need to save as much money as possible; this would be a right way to start as well as a challenge for European and US physicians who deal with guidelines.

Although different guidelines proposed CD4+ evaluation every six or twelve months with convenience for patients and public health system,^{2,5} many doctors are not so confident with this strategy.

Objectives. A *safety analysis* was conducted in our outpatient unit to measure the probability of maintaining a safe (above the threshold for OI risk) number of CD4+ (≥ 350 cells/ μ l) when more than 350 cells/ μ l were obtained.

Secondarily, we performed a second *cost-saving*

analysis to evaluate, in a real-life context, if it could be possible to reduce the number and the cost of CD4+ count determinations in a three-year follow-up.

Materials and Methods. A retrospective monocentric study, including patients on cART with CD4+ cell count steadily over 350 cells/ μ l in all determinations during 2011, was performed. Subjects with cirrhosis, OIs, active intravenous drug users (IVDU), pregnant women, patients treated with chemotherapy or peg-IFN plus ribavirin for HCV infection were excluded. All the enrolled patients were monitored for 36 months. The whole CD4+ counts and HIV-RNA determinations recorded were considered. Demographics and clinical data were also evaluated.

Three analyses (Kaplan Meyer method) were performed considering:

1. all patients independently of HIV RNA levels;
2. patients with CD4+ cell count ranging from 350 to 499 cell/ μ l vs. patients with more than 500 cell/ μ l;
3. patients with HIV RNA levels below or above 20 copies/ml.

Statistical comparison of survival curves was performed using the Log-rank (Mantel-Cox) test.

Secondarily, we retrospectively analysed the number of CD4+ cell count determinations patients/year and calculated total- and single- patient costs in all subjects on cART harboring a CD4+ cell count over 350 cells/ μ l in all determinations performed from April 1, 2013 to March 31, 2016. Three annual interval periods were analyzed. Statistical analysis was performed using the Kruskal-Wallis test.

Results. In the first safety analysis, we enrolled 253 patients. At the enrolment (last visit during the year 2011) median age was 47 (IQR 41-54); 175 (69%) were males. The median CD4+ T-cells count was 623 cells/ μ l (IQR 489-805); 161 (63.6%) had CD4+ >500 cells/ μ l. 199 (78.7%) subjects had HIV-RNA <50 copies/ml, 161 (63.3%) HIV-RNA <20 copies/ml. Overall, 2613 samples were analyzed, with a median of 10.3 samples per patient (**Table 1**).

Among subjects with more than 350 CD4+ lymphocyte/ μ l at baseline, independently of HIV RNA levels, those with more than 350 CD4+ cell/ μ l in all determinations in the first, second and third year were

Table 1. Epidemiological and clinical characteristics of subjects enrolled.

CLINICAL STAGE (CDC) CDC A	151 (59.7%)
CDC B	29 (11.5%)
CDC C	73 (28.8%)

respectively 238 (94.1%), 229 (90.5%), 226 (89.3%). (**Figure 1**).

Within the 161 subjects with CD4+ \geq 500 cells/ μ l at baseline, 159 (98.7%), 159 (98.7%), and 158 (98.1%) respectively maintained CD4+ \geq 350 cells/ μ l during the first, second and third year.

Among 161 subjects with more than 500 CD4+ cell count/ μ l at baseline, those who maintained more than 500 cells/ μ l in all determinations in the first, second, and third year were respectively 144 (89.4%), 139 (86.3%) and 138 (85.7%). The probability of maintaining more than 350 cells/ μ l during a three-year follow-up, regardless of HIV-RNA levels, was 89.3% for those who had more than 350 CD4+ T-cells/ μ l at baseline and 98.1% for those who had more than 500 cells/ μ l at baseline (**Figure 2**).

Within the subjects with more than 350 or 500 CD4+ cells/ μ l and VL below 20 copies/ml at baseline (respectively 161 and 108), those who maintained more than 350 CD4+ in all determinations in the first, second and third year were respectively 152 (94.4%), 145 (90.0%), 144 (89.4%) and 107 (99.1%), 107 (99.1%), 107 (99.1%).

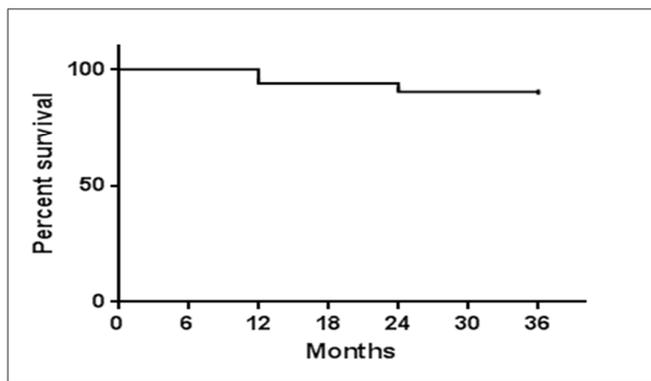


Figure 1. Probability of maintaining > 350 CD4+ cells during a 3-year follow up independently of HIV RNA value in subjects with more than 350 CD4+ cell/ μ l at baseline. Estimated Kaplan Meyer curve.

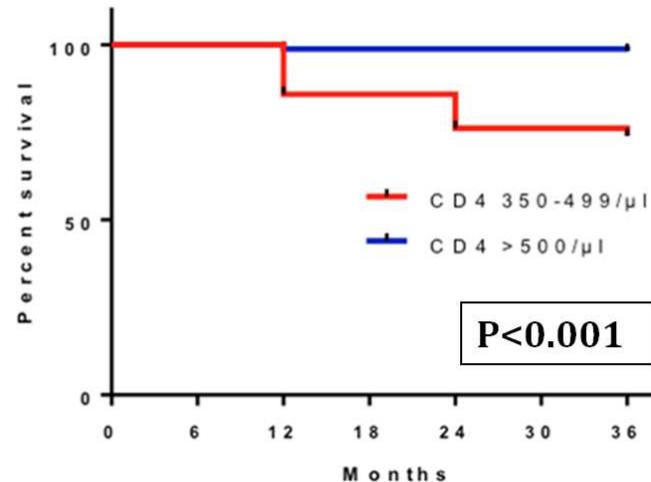


Figure 2. Probability of maintaining > 350 CD4+ cell during a 3-

Age (years), median (IQR)	47 (41-54)
Males/Females, n (%)	175 (69%)/78 (31%)
CD4+ T-cell count (cells/ μ l), median (IQR)	623 (489-805)
CD4+ T-cell count (cells/ μ l) > 500	161 (63.6%)
HIV RNA <50 copies/ml, n (%)	199 (78.7%)
HIV RNA <20 copies/ml, n (%)	161 (63,3%)

year follow up independently of HIV RNA value in subjects with 350-499 and ≥ 500 CD4+ cell/ μ l at baseline. Estimated Kaplan Meyer curve.

Out of 108 subjects with more than 500 CD4+ cells at baseline and HIV-RNA below 20 copies/ml, those who maintained more than 500 CD4+ at in the first, second and third year were respectively 97 (89.8%), 97 (89.8%), 97 (89.8%).

The probability of maintaining more than 350 cells/ μ l during a three-year follow up for patients with HIV-RNA below 20 copies/ml at baseline was around 90% for subjects with more than 350 CD4+ cells at baseline, and around 99 % for subjects with more than 500 CD4+ cells at baseline. This probability was lower for those who had a VL above 20 copies/ml (**Figure 3**).

Then, we performed a cost-saving analysis, evaluating data from all subjects with a stable value of 500 or more CD4+/ μ l throughout three years. They were 343 in 2013/2014, 364 in 2014/2015, and 383 in 2015/2016; the total number of determinations was respectively 829, 846, 839.

We calculated a mean of 2.41 determinations per patient in the first period, 2.32 in the second period, and 2.18 in the third period, with a significant decrease between the first and the third period ($p < 0.001$).

The cost of a CD4+ determination laboratory kit is about €42 times the whole number of determinations done each year; in this way, we calculated the total spending for each period that is €34,818 in 2013/2014, €35,532 in 2014/2015 and €35,238 in 2015/2016.

The cost rose in the last period compared to the first, but there was an increase in the outpatient number at the same time. We compared data about the cost patient/year and we found a mean value of €101.51 in the first period, €97.61 in the second and €92.00 in the third, with a saving of €9.51 per patient. The median value was slightly less than €100.00 per patient per year, with a significant decrease between the first and the third year ($p < 0.0001$).

Discussion. Tolerability and potency of the new antiretroviral drugs, associated with the increasing number of simple regimens based on a single pill or single dose per day, represent an incredible opportunity for all patients in cART to obtain and maintain good

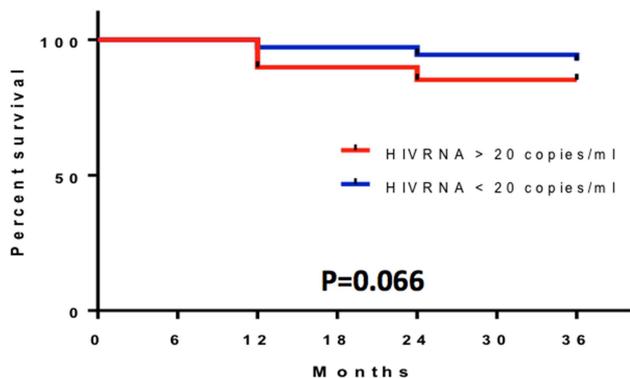


Figure 3. Probability of maintaining > 350 CD4+ cells during a 3-

year follow up in patients with HIV RNA value more or below 20 copies/ml and with > 350 CD4+ cell/ μ l at baseline. Estimated Kaplan Meyer curve.

adherence and optimal viro-immunological control over a long period.

The acceptance of HIV infection and the reduction of HIV-related stigma could be improved by reducing patients' access to hospitals for blood testing or pharmacological refill. Reducing CD4+ count determinations could help with this purpose.

Absolute CD4+ cell number fluctuations are frequent, but their clinical significance is irrelevant.¹⁸

In most cases, CD4+ cell percentage remains unmodified and any changes of absolute CD4+ cell count are due to total leucocytes and/or lymphocytes count oscillations, while the anxiety of patients frequently increases, thus defining the request of a new CD4+ count determination. However, the predictive value of these fluctuations remains inconsistent.¹⁸

It was surprising to find that such a high number of subjects maintained a stable and safe number of CD4+ cells during a three-year follow up after they had already obtained the threshold of 350 CD4+ cells/ μ l.

Our follow up, conducted for a time double in length in comparison to the study of Mocroft et al,⁷ confirms that also in a longer follow up, the decrease of CD4+ is an infrequent event, which becomes rare if more than 500 cells/ μ l are obtained.

Even if HIV replication is not entirely suppressed, our data showed that the probability of maintaining stable CD4+ cell counts is high in these subjects.

Although our approach was very conservative and prudential, the results confirm that a single determination of CD4+ count in a year could not reduce the quality of assistance and that the probability of having a value below the cut-off of 350 cells/ μ l during the follow up is very low. Furthermore, we cannot exclude that some of these low values are only insignificant fluctuations.

More recently, researchers^{19,20} showed a predictive role for CD4+/CD8 ratio in disease progression and immune activation, also in patients with undetectable HIV RNA²¹. This issue remains controversial as debatable is, at the same time, the selection of patients to address to this evaluation. However, the reduction of CD4+ determinations could limit the recording of this data for future analyses.

In the last years, because of the approval of new therapeutic guidelines,²² more and more patients have begun the treatment earlier, regardless of baseline CD4+ count or HIV RNA viremia.

In 2014, in our setting, more than 72% of patients in treatment had >500 CD4+/ μ l and therefore monitoring CD4+ cell count once a year could be a safe strategy.

Although the safety was clearly demonstrated, the cost-saving appears controversial. In fact, in the cost-saving sub-study, during the three-year follow up we

observed a progressive light decrease of CD4+ determinations per patient for year. These results were linked to the progressive change in the follow-up strategies applied in the last years for stable patients, which established the delay of blood testing every six months or more.

Although this trend was statistically significant, more than 50% of patients enrolled still do more than two CD4+ determinations in a year, so the magnitude of the financial result was not as significant as we expected. By extending these procedures to all patients with stable CD4+ cells/ μ l and by monitoring CD4+ cell count once a year, we could obtain, in this cohort, an overall saving of €19,152/year.

In Italy more than 100,000 patients are in cART, more than 90% of them show an HIV-RNA viremia below the cut off of detectability and more than 75% present a CD4+ count above 350 cells/ μ l;²³ taking these numbers into account, the strategy of reducing CD4+ cell determinations could represent a considerable opportunity for saving resources.

A scenario in which just more than 50% of patients could be tested once a year could determine a considerable reduction of costs and the opportunity of employing these funds to monitor other markers.

Giving a precise evaluation of total cost saving is complicated; different centers applied different follow-up strategies (only CD4+; CD4+ and CD8+; CD3+, CD4+, and CD8+; or more complex immunological panels). Moreover, the cost of the same single determination could vary in different laboratories or geographic areas. Also, the strategies to redirect saved money to alternative uses (from management to treatment or assistance) could be controversial, depending on each hospital's economic policy.

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Conclusions. In patients who have already achieved virological suppression with a stable cART regimen, the role of CD4+ testing is questionable.²⁴

Our findings highlighted that a very high percentage of subjects maintained a high and safe number of CD4+ cells (>350 cells/ μ l) during a three-year follow-up. This probability is slightly less than 100% for subjects with more than 500 cells/ μ l at baseline.

Many studies suggest that, although most patients reach a CD4+ count greater than 500 cells/ μ L after several years of cART, CD4+ count restoration is variable, and a few patients might fail to recovery despite virological suppression.^{25,26} Another critical fact is that the variability only in CD4 recovery, with suppressed HIV-RNA, would not change treatment decisions because there is no evidence for changing cART in those with divergence between CD4+ and HIV-RNA.²⁷

Furthermore, the costs of CD4+ tests vary depending on the different laboratories, but it is possible to save from 33% to 66% of the cost by reducing the number of determinations in a year. This saving could have other favorable consequences as well, providing new resources for patient's management. Although a progressive and significant reduction of CD4+ count determinations costs could be achieved in some laboratories, the patient's anxiety related to CD4+ fluctuations remained insolvable. Nevertheless, it is time to rethink our strategies for reducing the amount of CD4+ determinations conducted in a year.²⁴

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