Switch from zidovudine- to non-zidovudine-containing regimens is associated with modest haematological improvement and no obvious clinical benefit: a substudy of the ANRS 099 ALIZE trial

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Background: Zidovudine, the first antiretroviral agent, has short-term haematological toxicity. However, it is unclear whether patients tolerating long-term zidovudine-containing regimens will benefit from a switch to non-zidovudine-containing regimens.

Methods: One hundred and fifty-eight patients enrolled in the ALIZE trial receiving zidovudine at baseline were analysed. These patients were randomized to continue their regimen or to switch to a combination of emtricitabine, didanosine and efavirenz for 48 weeks. Changes from baseline in haemoglobin (Hb), neutrophil and platelet counts were compared between arms as well as the occurrence of cardiovascular events, bacterial infections, use of haematopoietic growth factors, blood transfusion and quality of life using the Medical Outcome Study HIV (MOS-HIV) health survey.

Results: Eighty-one patients continued their regimen and 77 switched. At 48 weeks, mean change from baseline in Hb were 0.73 and -0.37 g/dL in the switch and maintenance groups, respectively (P < 0.01). Mean neutrophil counts increased by 592 and 51 cells/mm³ in the switch and maintenance groups, respectively (P = 0.02). The occurrence of cardiovascular events or bacterial infections was similar in both treatment arms with no use of haematopoietic growth factors or blood transfusion. Also, mean change from baseline in MOS-HIV physical and mental health summary scores was similar in both arms.

Conclusions: A switch from a long-standing zidovudine- to a non-zidovudine-containing regimen modestly improves haematological parameters and is not associated with obvious clinical benefit.

Keywords: HAART, haemoglobin, neutrophil, quality of life, bacterial infection

Introduction

Anaemia and neutropenia are frequent haematological manifestations among patients with HIV infection and AIDS and are associated with a higher risk of morbidity and mortality.1–6 In the era of combined antiretroviral therapy (cART), the rate of severe anaemia has decreased, but mild-to-moderate anaemia remains an important concern.7–9 Anaemia is associated with fatigue, altered...
quality of life (QoL) and a higher risk of cardiovascular events.\textsuperscript{10–12} Neutropenia is also reported to be associated with a higher risk of bacterial or fungal infections.\textsuperscript{13} Zidovudine, a widely used HIV reverse transcriptase inhibitor, is unique among antiretroviral drugs because of its haematological toxicity. Zidovudine-induced anaemia and neutropenia have been well identified as treatment-limiting adverse events in clinical trials and cohort studies.\textsuperscript{1,2,14–21} It remains unclear however if patients who have tolerated long-term therapy with zidovudine-containing regimens will benefit from a switch to a non-zidovudine-containing cART. To address this issue, we performed a post hoc analysis of patients randomized in the ANRS 099 ALIZE trial who were receiving a zidovudine-containing cART at baseline and assessed haematological parameters after switching to a once-daily emtricitabine/didanosine/efavirenz combination.\textsuperscript{22} A secondary objective was to assess the potential clinical benefit associated with the improvement of haematological parameters.

Methods

Study population

The ANRS 099 ALIZE trial design is presented in detail elsewhere.\textsuperscript{22} In brief, ANRS 099 ALIZE was a 48 week, multicentre, randomized, open-label trial comparing the maintenance of a stable protease inhibitor (PI)-containing regimen (maintenance group: \(n = 177\)) with the switch to a once-daily regimen of efavirenz, didano- sine and emtricitabine (switch group: \(n = 178\)) in patients with controlled HIV infection. Adult HIV-1-infected patients were eligible if they had received an unchanged combination antiretroviral therapy for at least 6 months consisting of at least one PI plus two nucleo- side analogues, had a CD4\(^+\) cell count of 100 cells/mm\(^3\) or more and a plasma HIV-1 RNA level of <400 copies/mL for at least 6 months, and had never received non-nucleoside reverse transcriptase inhibitors. All patients gave informed written consent to participate. The study was approved by the Paris Saint-Louis Ethics Committee.

Individual clinical history was collected at trial entry. Patients underwent clinical and laboratory evaluations at the screening visit, baseline, weeks 4 and 8, and then every 8 weeks up to week 48. Errors and missing data of any type were actively searched for during monitoring visits on site. The primary outcome of the trial was the proportion of patients with virological success, defined as plasma HIV-1 RNA levels <400 copies/mL from baseline to week 48, with any missing data replaced by a value >400 copies/mL.

The subset of patients who were receiving zidovudine as a component of their antiretroviral regimen at entry was the focus of this study.

Outcome variables

At 48 weeks of follow-up, mean changes from baseline of the following laboratory variables were compared between treatment arms: haemoglobin (Hb), red cells mean corpuscular volume (MCV), neutrophil, platelet, lymphocyte counts and CD4\(^+\) T cell counts. The proportion of patients with plasma HIV RNA levels <400 or 50 copies/mL was also assessed in each arm through week 48. The severity of anaemia and neutropenia was assessed using the Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (ANRS) toxicity grading scale. In brief, grade 1–2 (mild to moderate) anaemia was defined as an Hb level between 8 and 10.5 g/dL and grade 3–4 anaemia as an Hb level <8 g/dL. Grade 1–2 (mild to moderate) neutropenia was defined as a neutrophil count between 750 and 1500 cells/mm\(^3\) and grade 3–4 neutropenia as a neutrophil count <750 cells/mm\(^3\).

To assess the potential clinical benefit associated with the improvement of haematological parameters, we also compared the occurrence of a first cardiovascular event or a first bacterial infection, the use of haematopoietic growth factors (erythropoietin and granulocyte colony-stimulating factor) and the need for blood transfusion during the 48 weeks of the study.

Cardiovascular events and infections were prospectively collected during follow-up and coded with the MedDRA\textsuperscript{\textregistered} dictionary, version 3.0.\textsuperscript{23} Cardiovascular events were selected using the MedDRA\textsuperscript{\textregistered} entries: High Level Group Term = 'Coronary artery disorders' or Preferred Term = 'myocardial infarction' or 'Angina (pectoris or unstable)' Infections were selected using the MedDRA\textsuperscript{\textregistered} entries: High Level Group Term = 'Infections—pathogen class unspecified' or 'Bacterial infectious disorders'. We then reviewed each preferred term to ensure that they corresponded to proven or probable bacterial infections. We also scanned the whole adverse events list to check that this selection rule was exhaustive for our data. Also, we searched the database for the use of haematopoietic growth factors or receipt of a blood transfusion.

Finally, we assessed the QoL at baseline and week 48 using the self-reporting instrument of the Medical Outcome Study HIV (MOS-HIV) health survey. The MOS-HIV heath survey contains 36 questions measuring physical and mental dimensions of health. These dimensions are scored as summary rating scales ranging from 0 to 100 with higher scores indicating better health. For patients with physical or mental health summary scores above or below 50, it can be inferred that they have better or worse QoL, respectively, than the HIV-infected patient population used to develop these scales. The MOS-HIV has been shown to be a reliable and valid tool.\textsuperscript{24,25} Mean change from baseline in the physical and mental component summary scores (PCS and MCS) of the MOS-HIV SF-36 questionnaire was compared between arms, as these measures have been shown to improve with the increase in Hb levels in patients receiving epoetin alfa.\textsuperscript{12}

Statistical analysis

All analyses were performed on an intention-to-treat basis, using available observed data. Patients who discontinued zidovudine in the maintenance arm or who resumed zidovudine in the switch arm were analysed in their allocated randomization arm. To assess the robustness of the results, an on-treatment analysis was also performed in which data from patients who either definitely discontinued or resumed zidovudine after randomization were censored.

Baseline characteristics of patients receiving zidovudine in their regimen at enrolment were compared with those who were not receiving zidovudine, and similarly, baseline characteristics of patients continuing zidovudine or switching their regimen were compared using the Mann–Whitney–Wilcoxon test. Mean change from baseline to 48 weeks in Hb, MCV, neutrophils, platelets counts and CD4\(^+\) cell count was compared between treatment arms using the two-sided sample \(t\)-test.

Through to week 48, the proportion of patients with at least a grade 1–4 anaemia or neutropenia, and the proportion of patients with plasma HIV RNA levels <400 or 50 copies/mL, were compared using a two-sided Fisher’s exact test.

The rates of cardiovascular events or bacterial infections were compared between treatment arms using a two-sided Fisher’s exact test.

Statistical tests were two-sided with a 5% significance level. SAS software, version 8.2 (SAS Institute, Cary, NC, USA), was used for all calculations and statistical analyses.
Results

Among the 355 patients enrolled in the ANRS 099 ALIZE trial, 158 (44.5%) were receiving a zidovudine-containing regimen at baseline and were part of this study. Baseline characteristics of these 158 patients were first compared with those of the patients not receiving zidovudine in their regimen at enrolment ($n = 197$), 79% of whom received a combination of stavudine plus lamivudine. There was no significant difference between these two populations in terms of weight, sex, HIV risk factors, CDC stage or CD4 cell counts (data not shown).

Among the 158 patients receiving a zidovudine-containing regimen at baseline, 77 were randomized to the switch arm and 81 were randomized to the maintenance arm and continued their zidovudine- and PI-containing regimen (Figure 1). As shown in Table 1, baseline characteristics were similar between groups. Most of the patients were homosexual males with high CD4 cell counts. The median duration of prior treatment with zidovudine did not differ between the maintenance and switch arms (38.6 and 37.8 months, respectively, $P = 0.91$). Four patients (4.9%) in the maintenance arm discontinued zidovudine but not for haematological toxicity. At week 48, mean changes from baseline in Hb levels were +0.73 and −0.37 g/dL in the switch and maintenance groups, respectively ($P < 0.01$) (Table 2). As shown in Figure 2, mean change from baseline in Hb level increased as early as week 8 in the switch group and then remained quite stable, whereas it gradually decreased in the maintenance arm. At baseline, one patient in each arm had an anaemia of grade 1–2. However, only three other patients experienced grade 1–2 anaemia in the maintenance group during follow-up (overall probability of occurrence: 5%; 95% CI: 1.9–12.9) and none in the switch arm (overall probability of occurrence: 1%; 95% CI: 0.2–9; $P = 0.37$). No grade 3 or 4 anaemia was reported in either arm. A significant reduction of the MCV was seen in the switch group compared with the maintenance group (Table 2, $P < 0.0001$).

Mean change from baseline in neutrophil counts increased in both arms during follow-up, but the increase between baseline and week 48 was significantly higher in the switch arm (+592 cells/mm$^3$) compared with the maintenance arm (+51 cells/mm$^3$, $P = 0.02$) (Figure 3). At baseline, four patients in the maintenance arm and six patients in the switch arm had neutropenia. During follow-up, neutropenia was reported in 11 other patients in the maintenance arm (overall probability of occurrence: 17%; 95% CI: 10.7–27.7) and 3 other patients in the switch arm (overall probability of occurrence: 12%; 95% CI: 6.3–21.5, $P = 0.27$). Overall, 28 episodes of grade 1–2 neutropenia were reported in the maintenance arm and 21 episodes of grade 1–2 neutropenia plus 2 episodes of grade 3–4 neutropenia in the switch arm.

Mean change from baseline in platelet counts slightly decreased at week 48 in both arms, with a mean decrease from baseline of 658 and 10 026 platelets/mm$^3$ in the maintenance and switch arms, respectively, ($P = 0.23$). Grade 1–2 thrombocytopenia was reported in two patients (3%; 95% CI: 0.7–10.1) in the switch group and one patient (1%, 95% CI: 0.2–8.6) in the maintenance arm.

Mean change from baseline in CD4 and total lymphocytes counts at week 48 were of +17 and −6 cells/mm$^3$, and of +34 and +27 cells/mm$^3$ in the maintenance and switch arms, respectively ($P = 0.52$ and 0.65, respectively). At week 48, 94.6% and 97.3% of the patients in the maintenance and switch arms, respectively, had plasma HIV RNA levels of <400 copies/mL ($P = 0.44$). Similarly, the proportions of patients with plasma HIV RNA levels <50 copies/mL were 86.5% and 94.7% in the maintenance and switch arms, respectively ($P = 0.10$).

Clinical progression was described after the switch. One patient with a history of toxoplasma encephalitis in the maintenance arm died of generalized seizures. Another patient, in the maintenance arm, experienced an episode of angina pectoris. No myocardial infarction was reported. No use of haematopoietic growth factor was reported during the study, and no blood transfusions were required.

The rate of a first bacterial infection during follow-up did not differ between arms with 17 episodes in the maintenance arm compared with 20 in the switch arm, with estimated probabilities of, respectively, 20% (95% CI: 12.9–30.8) and 26% (95% CI: 17.8–37.7, $P = 0.57$).

With regards to health-related QoL, the mean change from baseline of the PCS and MCS at week 48 were −1.04 and +0.0 U in the maintenance arm compared with −1.76 and +1.01 in the switch arm, respectively ($P = 0.57$ and 0.42) (Table 2). Specific items such as physical function, social function and energy/fatigue remained unchanged in both arms of the study during follow-up (data not shown).

Similar results were obtained in on-treatment analyses censoring data when zidovudine was either discontinued or resumed after randomization (data not shown).

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**Figure 1.** Study flow chart of patients treated with zidovudine (ZDV)-containing regimens at baseline in the ANRS-099 ALIZE trial.

*Reasons for the discontinuation of ZDV in the maintenance arm were virological failure ($n = 3$) or patient’s choice ($n = 1$). Patients with virological failure did not have genotypic resistance to ZDV. ZDV, zidovudine; FTC, emtricitabine; EFV, efavirenz; ddI, didanosine.

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*Patient withdrawal ($n = 1$)
Death (seizure) ($n = 1$)
ZDV discontinuation* ($n = 4$)

79 patients completed 48 weeks of follow-up

77 patients assigned to once-daily therapy with FTC + ddi + EFV

Patient withdrawal ($n = 1$)
ZDV resumed ($n = 4$)

76 patients completed 48 weeks of follow-up

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Table 1. Baseline characteristics of patients treated with zidovudine-containing regimens (n = 158) at randomization in the ALIZE ANRS-099 study

<table>
<thead>
<tr>
<th>Event</th>
<th>Maintenance arm (n = 81)</th>
<th>Switch arm (n = 77)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR), years</td>
<td>41.7 (37–53)</td>
<td>43.2 (38–52)</td>
<td>0.84</td>
</tr>
<tr>
<td>Male, no. (%)</td>
<td>70 (86.4)</td>
<td>65 (84.4)</td>
<td>0.82</td>
</tr>
<tr>
<td>HIV risk factors, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>heterosexual</td>
<td>21 (25.9)</td>
<td>31 (40.3)</td>
<td>0.26</td>
</tr>
<tr>
<td>homosexual/bisexual</td>
<td>44 (54.3)</td>
<td>36 (46.8)</td>
<td></td>
</tr>
<tr>
<td>injection drug use</td>
<td>8 (9.9)</td>
<td>5 (6.5)</td>
<td></td>
</tr>
<tr>
<td>other/unknown</td>
<td>8 (9.9)</td>
<td>5 (6.5)</td>
<td></td>
</tr>
<tr>
<td>AIDS, no. (%)</td>
<td>18 (22.2)</td>
<td>19 (24.7)</td>
<td>0.71</td>
</tr>
<tr>
<td>Weight (median), kg</td>
<td>70.5 (63.4–75)</td>
<td>69 (63–78)</td>
<td>0.74</td>
</tr>
<tr>
<td>Prior duration of ZDV therapy median (IQR), months</td>
<td>38.6 (22–47.9)</td>
<td>37.8 (22.1–48.2)</td>
<td>0.91</td>
</tr>
<tr>
<td>ZDV-associated nucleosides analogues</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lamivudine, no. (%)</td>
<td>78 (96.3)</td>
<td>74 (96.1)</td>
<td></td>
</tr>
<tr>
<td>zalcitabine or didanosine, no. (%)</td>
<td>3 (3.7)</td>
<td>3 (3.9)</td>
<td></td>
</tr>
<tr>
<td>Protease inhibitors used</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ritonavir alone, no. (%)</td>
<td>4 (4.9)</td>
<td>4 (5.2)</td>
<td>0.43</td>
</tr>
<tr>
<td>indinavir, no. (%)</td>
<td>44 (54.3)</td>
<td>33 (42.9)</td>
<td></td>
</tr>
<tr>
<td>nelfinavir, no. (%)</td>
<td>28 (34.6)</td>
<td>31 (40.3)</td>
<td></td>
</tr>
<tr>
<td>saquinavir, no. (%)</td>
<td>5 (6.2)</td>
<td>9 (11.7)</td>
<td></td>
</tr>
<tr>
<td>Plasma HIV RNA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 copies/mL, no. (%)</td>
<td>72/78 (92.3)</td>
<td>67/74 (90.5)</td>
<td>0.78</td>
</tr>
<tr>
<td>&lt; 400 copies/mL, no. (%)</td>
<td>76/78 (97.4)</td>
<td>73/74 (98.6)</td>
<td>1</td>
</tr>
<tr>
<td>Median CD4 count, IQR (cells/mm³)</td>
<td>530 (385–757)</td>
<td>484 (368–709)</td>
<td>0.42</td>
</tr>
<tr>
<td>Median haemoglobin level, IQR (g/dL)</td>
<td>14 (13.1–14.9)</td>
<td>13.9 (13.1–14.8)</td>
<td>0.65</td>
</tr>
<tr>
<td>Median neutrophil count, IQR (cells/mm³)</td>
<td>2910 (2190–3700)</td>
<td>2490 (1855–3349)</td>
<td>0.06</td>
</tr>
<tr>
<td>Median platelet count, IQR (cells/mm³)</td>
<td>248 000 (207 500–292 500)</td>
<td>235 500 (197 000–269 000)</td>
<td>0.06</td>
</tr>
<tr>
<td>Median lymphocyte count, IQR (cells/mm³)</td>
<td>2000 (1615–2330)</td>
<td>1880 (1436–2140)</td>
<td>0.07</td>
</tr>
<tr>
<td>Median MCV, a IQR (mm³)</td>
<td>110.8 (106–116)</td>
<td>112.3 (106–116)</td>
<td>0.76</td>
</tr>
<tr>
<td>Median PCS, b summary score, IQR c</td>
<td>56.5 (50–61.8)</td>
<td>57.4 (51.5–60.4)</td>
<td>0.79</td>
</tr>
<tr>
<td>Median MCS, d summary score, IQR c</td>
<td>40.2 (33.8–45.3)</td>
<td>38.3 (33.4–43.6)</td>
<td>0.44</td>
</tr>
</tbody>
</table>

aMCV, mean red cells corpuscular volume.
bPCS, physical component score.
cOnly 55 patients in the maintenance arm and 56 patients in the switch arm had MOS-HIV SF-36 questionnaires available.
dMCS, mental component score.

Table 2. Mean change from baseline to week 48 in haematological and quality of life variables with standard deviations (in brackets)

<table>
<thead>
<tr>
<th>Events</th>
<th>Maintenance group</th>
<th>Switch group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 cells/mm³</td>
<td>+17 (150)</td>
<td>+34 (169)</td>
<td>0.52</td>
</tr>
<tr>
<td>Lymphocytes/mm³</td>
<td>–6 (448)</td>
<td>+27 (468)</td>
<td>0.65</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>–0.37 (1.24)</td>
<td>+0.73 (0.93)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MCV</td>
<td>–0.87 (6.16)</td>
<td>–12.2 (6.43)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neutrophils/mm³</td>
<td>+51 (1321)</td>
<td>+592 (1561)</td>
<td>0.02</td>
</tr>
<tr>
<td>Platelets/mm³</td>
<td>–658 (54 911)</td>
<td>–10 026 (38 512)</td>
<td>0.23</td>
</tr>
<tr>
<td>QoL SF-36 PCS</td>
<td>–1.04 (4.97)</td>
<td>–1.76 (6.61)</td>
<td>0.57</td>
</tr>
<tr>
<td>QoL SF-36 MCS</td>
<td>0.0 (5.56)</td>
<td>+1.01 (6.04)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

aMCV, mean red cells corpuscular volume.
bQoL, quality of life.
cPCS, physical component score.
dMCS, mental component score.
Figure 2. Mean change from baseline in haemoglobin (Hb) level by treatment arm during the study (intent-to-treat analysis).

Figure 3. Mean change from baseline in neutrophil count by treatment arm during the study (intent-to-treat analysis).
Discussion

Among HIV-infected patients receiving long-term antiretroviral therapy with a zidovudine-containing regimen, switching from zidovudine to other nucleoside analogues was associated with statistically significant improvements in haematological parameters, namely Hb level and neutrophil counts, but these changes are of modest clinical relevance. Indeed, according to the well-known bone marrow toxicity of zidovudine, it is no surprise that a reversal of haematological toxicity could occur once zidovudine is discontinued. Our study shows, however, that among patients with a history of >3 years of zidovudine, there is little additional haematological toxicity if a zidovudine-containing regimen is continued. Therefore, patients who have tolerated zidovudine for a long time are not expected to suffer severe anaemia or neutropenia later on. These data confirm that haematological toxicity of zidovudine is mainly observed during the first weeks to months of treatment. Indeed, among the 81 patients in the maintenance arm of the trial, the mean decrease in Hb was only −0.37 g/dL after 48 weeks, and the neutrophil count remained almost stable with a mean increase of 51 cells/mm³ (Table 2). Also, only three patients experienced grade 1–2 anaemia during follow-up. Furthermore, no patient received red cells transfusion or erythropoietin during the study. There was only one case of angina pectoris in the maintenance arm that was unlikely to be related to anaemia since the Hb level of this patient was of 15.1 g/dL when the event occurred.

We then used QoL assessments to see if the switch in treatment regimen was associated with a benefit as shown in studies where epoetin was used to correct HIV-associated anaemia.11,12 Although QoL questionnaires were available for only 55 and 56 patients in each arm of the study, we were unable to show any improvement in either mental or physical summary scores of the MOS-HIV SF-36 health survey in this study (Table 2).

Similarly, the mean neutrophil count increased by 592 cells/mm³ in the switch arm, but there was no indication in this study of a reduced rate of bacterial or fungal infections in this arm when compared with the maintenance arm. Also, no patient needed granulocyte colony-stimulating factor during follow-up in either arm of the study, and the number of neutropenia episodes was similar between arms with most events being grade 1 or 2. Previous reports have indeed shown that the risk of bacterial infection is very low if the neutrophil count does not fall below 500 cells/mm³ and that neutropenia induced by zidovudine is probably less often complicated by infectious episodes than neutropenia induced by chemotherapy.13–26 Our results are therefore similar to those of Fisher et al.,27 who recently demonstrated in the Sweet study a similar haematological benefit of switching from zidovudine to tenofovir in patients with well-controlled HIV infection. Although their preliminary results were reported at 48 weeks of follow-up, they could not demonstrate a benefit of switching on the proportion of patients who maintained a plasma HIV RNA level of <50 copies/mL. We obtained similar results in our study, and while there was a trend towards a higher rate of patients with suppressed viral replication in the switch arm of our study (86.5% and 94.7% of the patients in the maintenance and switch arm of the study, respectively, achieved a plasma HIV RNA level <50 copies/mL at week 48, \( P = 0.10 \)), we have to remember that patients in this trial also switched from a PI to efavirenz, which could account for these differences.

There might be other reasons, however, to switch from zidovudine- to non-zidovudine-containing regimens in such patients, in particular if the patients are to receive other myelotoxic agents such as ribavirin or interferon for the treatment of hepatitis C virus infection, for example. Also, Fisher et al.27 found some improvements in triglycerides and cholesterol levels after the switch from zidovudine to tenofovir in their study, but there was little change in LDL-cholesterol levels, and the toxicity of the replacement agents must also be kept in mind.

A further potential benefit of switching from zidovudine to another nucleoside analogue such as tenofovir or abacavir could be the reversal of zidovudine-induced lipodystrophy.27,28 We were not able to address this issue in our study since the switch involved not only zidovudine but also PIs that may have a role in lipodystrophy, and no objective measurement of lipodystrophy was performed. However, even in studies where a significant improvement in lipodystrophy was seen, little, if any, clinical improvement was observed by the patient or his/her physician.27,28

Our study has, however, a number of limitations. First, although the switch to once-daily combination regimen was randomized, there was no stratification at the time of randomization on the use of zidovudine in the regimen. We therefore performed a post hoc analysis that might be biased even if the baseline characteristics of our two groups were very similar. Second, since our study was relatively small and of limited duration, we cannot exclude that with a larger study or with a longer follow-up a significant clinical benefit could be associated with the improvement of haematological parameters. Finally, the outcomes of bacterial infections and cardiovascular events were not prospectively defined. Therefore, it is possible that there was under-reporting of these events especially if they did not lead to hospitalization. Other studies will have to be performed to address these issues.

In conclusion, our data suggest that in patients under zidovudine-containing regimens for years, with full suppression of HIV replication and high CD4 counts, a change from zidovudine to other nucleoside analogues is likely to improve Hb level and neutrophil count, but this change might only be associated with limited clinical benefit for the patients in the short run. According to the cost of antiretroviral therapy today, and the availability of generic forms of zidovudine, it seems that a clear clinical benefit should be demonstrated in randomized studies before switching from an effective zidovudine-containing regimen in patients with HIV infection.

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The investigators participating in the ALIZE study are listed below.

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References


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