As this was a retrospective analysis, the primary limitation is that of missing data. Secondly, per protocol analysis tends to overestimate effect size and tolerability of regimens [13,14]. Although incidences of reported side effects and development of new resistance mutations were not reported in this study, we have provided in Table 1, wherever possible, data for patients who have switched regimens or were lost to follow-up.

These results are preliminary and prompt additional investigation into the clinical efficacy of non-PI regimens in treatment of PLWH with baseline resistance. Use of alternative drug classes in resistant HIV might allow for better tolerated treatment options and could translate into further cost-effectiveness strategies.

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Conflicts of interest

All authors were involved in designing the study, data analysis and manuscript preparation. C.L., K.M. and S.K. collected the data.

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References


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Cancers in elite controllers: appropriate follow-up is essential

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Elite controllers may have non-AIDS-defining comorbidities. We describe here 18 cases of cancers diagnosed in two cohorts of controllers, elite and viremic. Cancers are similar to those commonly described in antiretroviral therapy treated patients but also in HIV-negative patients, which underlines the necessity of an appropriate regular follow-up.

Elite controllers are rare HIV-1-infected individuals in whom HIV replication is spontaneously below the limit of detection without antiretroviral therapy (ART) for a prolonged period of time. These patients are intensively studied because they can be an example of effective ‘functional cure’ or ‘remission’. They can experience various comorbidities linked with deleterious effects from HIV infection, other coinfections including hepatitis B or C, or from other exposures including tobacco use. Elite controllers have chronic immune activation with higher percentages of activated CD4+ and CD8+ T-cells than HIV-negative patients [1]. Increased levels of various inflammatory biomarkers have also been observed in elite controllers [2]. These levels of activation/inflammation are greater in a subset of low-grade viremic patients (50 < viral load < 2000) termed ‘viremic controllers’ [3]. Chronic inflammation
is associated with an increase of the cardiovascular risk, and studies have shown that elite controllers are more prone to be hospitalized for cardiovascular events [4] and to have an increase of the carotid intima-media thickness [5]. Chronic inflammation has been also associated with the development of cancer [6]. Except for a case of Kaposi sarcoma [1], no data have been reported to our knowledge about the occurrence of cancer in elite controllers. To investigate this point, we collected all the cases of solid and hematologic cancers reported in two well studied cohorts: the French ANRS CODEX CO21 and the US Military HIV Natural History Study (NHS).

The French ANRS cohort was established in 2009 and includes 272 elite controllers with a median follow-up of 18 years. The NHS was established in 1985 and includes 36 elite controllers and 231 viremic controllers with a median follow-up of 12 years. Viremic controllers are present only in the NHS. The definitions of the elite controllers in each cohort are overlapping and have been described previously [7,8]. Data for both AIDS-defining and non-AIDS-defining cancers are systematically collected in both cohorts.

Six cancers in five elite controllers have been reported in the French cohort but four were diagnosed between 2005 (first descriptions of the ‘controller’ status) and 2009. Five cancers were reported in the elite controllers in the NHS, but one cancer (colon) was diagnosed 10 years before the diagnosis of HIV infection and was excluded. Cancers were reported in eight viremic controllers. Details are provided in Table 1. Among the 18 cases of cancers, only one was an AIDS-defining event, a non-Hodgkin lymphoma (NHL). The patient first had a MALT lymphoma that later evolved into an aggressive diffuse B-cell lymphoma. Five additional cases were cancers commonly observed in HIV-infected patients on ART [9]: two lung cancers in smokers, one hepatocarcinoma in a patient coinfected with hepatitis C (HCV), a case of Hodgkin’s disease, and an intraepithelial anal carcinoma with human papilloma virus (HPV) infection. Other cancers not known to be overrepresented in HIV-infected patients were five skin cancers, including three melanomas, three prostate cancers, and an unclassified brain tumor. Lastly, two rare colonic neuroendocrine tumors were reported.

Median age of the patients at cancer diagnosis was 32 years (range 21–46), and median time since HIV diagnosis was 11 years (range 2–27). There were four women among the 17 patients. All the patients had a symptomatic cancer, except two patients with prostate cancer (prostate-specific antigen increase). The median of the CD4+ T-cell count at cancer diagnosis was 521 cells/µl (range 197–1164). Cancers diagnosed in patients with a CD4+ T-cell count higher than 500 cells/µl were the lung cancers, the hepatocarcinoma, the two neuroendocrine tumors, one brain tumor, one melanoma, and one case of nonmelanoma skin cancer. Medians of the HIV-1 viral load at cancer diagnosis in elite controllers and viremic controllers were, respectively, less than 50 RNA copies/ml (range <50–3002) and 154 RNA copies/ml (range <50–47291). The cancer treatments were conventional: seven patients underwent surgery, four chemotherapy, four radiotherapy, one received combination of the last three strategies, and one received ART only. Interestingly, complete remission of the low-grade NHL was obtained.

Table 1. Characteristics of cancers in HIV controllers.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Sex</th>
<th>Age at HIV diagnosis (years)</th>
<th>Cancer</th>
<th>Year of HIV diagnosis</th>
<th>Year of cancer diagnosis</th>
<th>CD4+ T-cell count at cancer diagnosis/µl</th>
<th>Plasma viral load at cancer diagnosis (RNA copies/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANRS-1</td>
<td>F</td>
<td>31</td>
<td>Lung adenocarcinoma</td>
<td>1988</td>
<td>2009</td>
<td>1070</td>
<td>&lt;50</td>
</tr>
<tr>
<td>ANRS-2</td>
<td>M</td>
<td>27</td>
<td>Hepatocarcinoma</td>
<td>1991</td>
<td>2008</td>
<td>652</td>
<td>&lt;50</td>
</tr>
<tr>
<td>ANRS-3</td>
<td>M</td>
<td>42</td>
<td>Lung adenocarcinoma</td>
<td>1993</td>
<td>2006</td>
<td>521</td>
<td>&lt;50</td>
</tr>
<tr>
<td>ANRS-4</td>
<td>M</td>
<td>33</td>
<td>Gl carcinoid tumor</td>
<td>1996</td>
<td>2006</td>
<td>680</td>
<td>&lt;50</td>
</tr>
<tr>
<td>ANRS-5</td>
<td>F</td>
<td>28</td>
<td>Low-grade NHL</td>
<td>1986</td>
<td>2008</td>
<td>255</td>
<td>3002</td>
</tr>
<tr>
<td>ANRS-5</td>
<td>F</td>
<td>28</td>
<td>High-grade NHL</td>
<td>1986</td>
<td>2013</td>
<td>333</td>
<td>&lt;50</td>
</tr>
<tr>
<td>NHS EC-1</td>
<td>M</td>
<td>41</td>
<td>Squamous cell skin cancer</td>
<td>2002</td>
<td>2009</td>
<td>780</td>
<td>&lt;50</td>
</tr>
<tr>
<td>NHS EC-2</td>
<td>M</td>
<td>36</td>
<td>Prostate cancer</td>
<td>1990</td>
<td>2011</td>
<td>438</td>
<td>1461</td>
</tr>
<tr>
<td>NHS EC-3</td>
<td>M</td>
<td>28</td>
<td>Melanoma</td>
<td>1998</td>
<td>2009</td>
<td>197</td>
<td>&lt;50</td>
</tr>
<tr>
<td>NHS EC-4</td>
<td>M</td>
<td>21</td>
<td>Anal cancer (HPV+)</td>
<td>1986</td>
<td>1999</td>
<td>433</td>
<td>499</td>
</tr>
<tr>
<td>NHS VC-1</td>
<td>M</td>
<td>27</td>
<td>Hodgkin’s lymphoma</td>
<td>1996</td>
<td>2007</td>
<td>418</td>
<td>16 600</td>
</tr>
<tr>
<td>NHS VC-2</td>
<td>M</td>
<td>46</td>
<td>Prostate cancer</td>
<td>1999</td>
<td>2008</td>
<td>389</td>
<td>&lt;50</td>
</tr>
<tr>
<td>NHS VC-3</td>
<td>M</td>
<td>34</td>
<td>Squamous cell skin cancer</td>
<td>2004</td>
<td>2007</td>
<td>333</td>
<td>47 291</td>
</tr>
<tr>
<td>NHS VC-4</td>
<td>M</td>
<td>35</td>
<td>Melanoma</td>
<td>1987</td>
<td>1998</td>
<td>70</td>
<td>248</td>
</tr>
<tr>
<td>NHS VC-5</td>
<td>M</td>
<td>32.6</td>
<td>Prostate cancer</td>
<td>1995</td>
<td>2006</td>
<td>235</td>
<td>787</td>
</tr>
<tr>
<td>NHS VC-6</td>
<td>F</td>
<td>30</td>
<td>Brain tumor</td>
<td>1999</td>
<td>2001</td>
<td>1164</td>
<td>&lt;500</td>
</tr>
<tr>
<td>NHS VC-7</td>
<td>M</td>
<td>38</td>
<td>Neuroendocrine anal tumor</td>
<td>1994</td>
<td>1999</td>
<td>513</td>
<td>1032</td>
</tr>
<tr>
<td>NHS VC-8</td>
<td>M</td>
<td>24</td>
<td>Melanoma</td>
<td>1995</td>
<td>2002</td>
<td>504</td>
<td>1017</td>
</tr>
</tbody>
</table>

EC, elite controller; F, female; GI, gastrointestinal; HPV, human papilloma virus; K, carcinoma; M, male; NHL, non-Hodgkin lymphoma; NHS, Natural History Study; VC, viremic controller.
with start of ART only. Six patients died because of cancer progression (two lung adenocarcinomas, one hepatocarcinoma, one anal neuroendocrine tumor, one brain tumor, and one melanoma).

Two elite controllers had no history of a detectable viral load prior to cancer diagnosis. Only two elite controllers (NHL and prostate) and two viremic controller (Hodgkin lymphoma and skin cancer) experienced loss of controller status with viral load increase and CD4+ cell count decline prior to cancer diagnosis but none received ART. After cancer diagnosis, only one French elite controller, one American elite controller and four viremic controllers received ART. None of the other patients had evidence of sustained, detectable viral replication including those who received cancer chemotherapy. In contrast, all patients who received chemotherapy had a decline in CD4+ T-cell counts.

Spano et al. [10] recently reported that four cancers are the most frequent non-AIDS-defining cancers in HIV-infected individuals: lung, Hodgkin, anal and liver carcinoma. These accounted for only 5 of 18 cancers described among controllers. The limited prolonged immunodepression (if any) among most controllers could explain these different incidences. Although incidence could not be calculated because of the small number of controllers in this study, the data suggest that the incidence of some cancers in elite controller could be similar to those in the general population. Shiels et al. [11] have reported that most types of cancers occur at the same ages in HIV-negative populations and in patients with AIDS, when confounding factors are taken into account. However, in elite controllers who do not have AIDS, no information is available. These patients may potentially develop cancers, such as prostate cancer or squamous cell skin carcinoma, at a younger age than the general population. Skin cancers were common (25%) underlying the necessity to carefully examine the skin of all HIV-infected patients, including HIV controllers. An increase of the risk of skin cancer has been reported in other settings of T-cell immunodeficiencies, such as solid organ graft recipients [12].

The relatively uncommon observation of the AIDS-defining cancers seems to be logical in patients with controlled HIV and presumably functional immune responses. However, clinicians should consider cancer development in controllers with known risk factors, such as tobacco for lung cancer, HPV for anal cancer, and HCV/alcohol for hepatocarcinoma. Thus, it is essential to obtain an appropriate clinical history and inquire about potential symptoms of cancer in HIV controllers. Although some HIV controllers are receiving ART, comorbidities such as cancer can occur, and this study reinforces the necessity to evaluate HIV controllers regularly in the outpatient clinic.

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J.F.O. and O.L. designed the study, analyzed the data, and drafted the manuscript. F.B., D.C., and A.G. contributed to study design and analysis. All authors reviewed and approved the final manuscript.

Conflicts of interest

There are no conflicts of interest.

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References


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