Immuno-virological and clinical impacts of treating cancer in patients living with HIV

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Background: Patients living with HIV (PLHIV) are increasingly being affected by cancer. However, data evaluating the long-term impact of cancer treatment on HIV course are sparse.

Methods: To determine whether anticancer treatments detrimentally impact HIV course, we conducted a retrospective cohort study in seven hospitals in France. Adult PLHIV treated for haematological or solid malignancies were included and compared (1:1) with suitably matched (cancer-free) controls. The primary outcome was the risk of a ≥25% reduction in the absolute CD4+ count during follow-up. The risks for virological failure (i.e. a confirmed plasma viral load >50 copies/mL), incidental AIDS-related illnesses and death over time were also assessed. Multivariate Cox proportional-hazards regression analyses were used to identify the outcome predictors.

Results: One-hundred-and-ten patients with cancer and 110 controls were followed for a median of 4.4 years. In a Cox model, the CD4+ depletion was strongly predicted by external radiotherapy (ERT) exposure (HR = 5.1, 95% CI, 3.0–8.6, P < 0.0001) but not by chemotherapy. For patients exposed to ERT, the magnitude of the CD4+ depletion peaked 6 months after their cancer diagnosis (mean CD4+ drop at this time = 2283 ± 370 cells/mm3). Overall, the cancer patients were also more likely to experience virological failure than the controls (HR = 1.7, 95% CI, 1.1–2.7, P = 0.03). Finally, the incidence of AIDS-related illnesses was similar for both groups.

Conclusions: In PLHIV, cancer treatment increased the risk for prolonged CD4+ depletion and virological failure but had no impact on AIDS-related events when appropriate prophylaxes were implemented.

Keywords: ART, CD4+ depletion, AIDS, virological failure

Introduction

Soon after highly active ARTs were first marketed, the incidence of AIDS-defining illnesses (ADIs) suddenly fell, dramatically reducing patient mortality.1 As a result, ageing has become a common occurrence for patients living with HIV (PLHIV). AIDS-free survival exposes these patients to new health challenges.5 In this setting, cancer is a major concern. Indeed, cancer is increasingly diagnosed in PLHIV; most of these malignancies are non-ADIs.1,4 In France, cancers are currently the leading cause of death among PLHIV.3

Although many studies have described the spectrum, incidence and risk factors of malignancies in PLHIV, few have specifically focused on the impact of cancer treatments on immuno-virological parameters and clinical outcomes. Thus, little is known about the course of HIV after cancer management. Reversible myelosuppression is a major side effect of intravenous cytotoxic chemotherapy and radiotherapy; it exposes patients to transient but potentially severe white blood cell depletion, including T cell depletion, and consequent opportunistic infections. Moreover, it is well known that intravenous chemotherapy causes nausea and vomiting. Finally, significant drug–drug interactions between ART and cytotoxic chemotherapy have been described.6 Together, these issues could have a deleterious impact on the efficacy of and adherence to combination

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antiretroviral therapy (cART) and could worsen the prognosis of HIV infection.

We aimed to investigate whether PLHIV are at a higher risk for severe CD4+ depletion, virological failure, new ADIs and death following the treatment of various haematological or solid tumours compared with a matched population without malignancies.

Methods
Study design and setting
We conducted a retrospective cohort study to evaluate the immunological, virological and clinical outcomes in a group of HIV-infected patients who were diagnosed and treated for malignancies (i.e. the patient group) as compared with a matched group without malignancy (i.e. the control group). This retrospective study was embedded in an ongoing multicentre prospective cohort (the ‘COREVH Centre de Poitou-Charentes’ cohort) following HIV-infected individuals at seven primary care and referral hospitals located in two different geographical areas in France.

We aimed to investigate whether PLHIV are at a higher risk for severe CD4+ depletion, virological failure, new ADIs and death following the treatment of various haematological or solid tumours compared with a matched population without malignancies.

We also examined the factors predicting the CD4+ decrease. The secondary objectives were to assess the risk of virological failure (defined as two consecutive PVLs >50 copies/mL), incidental ADIs (according to the 1993 revised classification of the CDC) and death rates over time between the patients and controls. Virological failure was considered only for patients under cART for ≥6 months at baseline or for those patients who initiated cART within 1 month after baseline (data were censored for these patients until 6 months of cART were completed).

Covariates
Standardized data collection forms, including characteristics of both malignancy and HIV infection, were completed (G. L. M. and L. B.). The baseline data that were collected included demographics (age, gender and ethnicity), characteristics of the malignancy (histological reports, localization, stage and any iconographic or biological results supporting the diagnosis), hepatitis B or C coinfection, current tobacco smoking, alcohol abuse, date of HIV diagnosis, CDC classification, medical and ART history, CD4+ cell count nadir and PVL zenith before treatment.

Follow-up data included the therapeutics used for the cancer treatment (surgery, irradiation, systemic chemotherapy and any other therapy), evolution of the malignancy, death (and its cause), new ADIs, CD4+ cell counts and PVL curves (typically, blood samples were taken three to four times a year, according to national guidelines).

Statistical analysis
Data were expressed as median (IQR), mean ± SD or percentage values. Between-group differences were compared using 2 or Fisher’s exact tests for categorical variables and using the unpaired t-test, Mann–Whitney U-test or Kruskal–Wallis test for continuous variables. Spearman’s rank-order correlation was used to determine linear correlations. Kaplan–Meier curves were drawn for the primary and secondary outcomes, and P values were based on the log-rank test. Cox proportional-hazards regression models were used to compare times to events and to control for covariates. All demographic, baseline clinical and biological variables were evaluated as covariates and considered for inclusion in the final model on the basis of an unadjusted association with different outcomes. All P values were two-tailed, and statistical significance was set at the 0.05 level. Statistical analyses were performed using MedCalc® software version 12.7.5 (MedCalc Software, Ostend, Belgium).

Results
Participant characteristics
During the 6 year enrolment period, 2390 PLHIV were followed, accounting for 12 717 person-years. A total of 115 individuals were diagnosed with cancer, five of whom were excluded because of insufficient data. Finally, 110 patients (78 men and 32 women) were included in the study. Thus, the incidence of cancer in our cohort was 8.7 cases per 1000 person-years. At the time of their cancer diagnoses, 83 of 110 patients (75%) were on cART, but only 61 (55%) had undetectable PVL (<50 copies/mL). In 7 of 110 patients (6%), the cancer revealed HIV infection.

The patients suffered from various solid and haematological malignancies (Figure 1). Although Kaposi sarcoma was the most frequently occurring malignancy, non-AIDS-defining cancers were much more common than AIDS-defining cancers, accounting for 73% and 27% of all diagnoses, respectively.

Of 110 patients, 105 (95%) received specific therapeutics (Table S1), which consisted of systemic cytotoxic chemotherapy (SCC, n = 58), surgery (n = 43), external radiotherapy (ERT, n = 41),

Outcomes
The main objective was to compare the risk of a ≥25% reduction of CD4+ absolute count between the patients and controls during the study period.
ART initiation (n = 9, for Kaposi sarcoma), immunomodulation agents (n = 4) and hormonotherapy (n = 3). Of these 105 patients, 27 received a combination of SCC plus ERT. Finally, 5 of 110 patients (5%) received only comfort care: one patient refused specific therapeutics, and four had incurable tumours. Overall, the patients received 1.4 (mean) specific cancer treatments. Compared with contemporary guidelines, the treatments aligned with the standard of care for all but one patient, who refused any specific treatment.

The patients were matched with 110 controls. The main baseline characteristics of both groups are summarized in Table 1. The

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**Figure 1.** Distribution of malignancies.

Table 1. Baseline characteristics of the patients with cancer and controls

<table>
<thead>
<tr>
<th></th>
<th>Patients (n = 110)</th>
<th>Controls (n = 110)</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (IQR)</td>
<td>47.5 (39.6–55.9)</td>
<td>47.0 (39.4–55.9)</td>
<td>0.96</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>78 (71)</td>
<td>78 (71)</td>
<td>1.0</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>94 (86)</td>
<td>94 (86)</td>
<td>1.0</td>
</tr>
<tr>
<td>Hepatitis B and/or C coinfection, n (%)</td>
<td>27 (25)</td>
<td>24 (22)</td>
<td>0.75</td>
</tr>
<tr>
<td>Previous history of malignancy, n (%)</td>
<td>10 (9)</td>
<td>10 (9)</td>
<td>1.0</td>
</tr>
<tr>
<td>Duration with HIV (years), median (IQR)</td>
<td>10.7 (3.8–16.5)</td>
<td>10.0 (2.7–13.8)</td>
<td>0.23</td>
</tr>
<tr>
<td>CDC clinical category, n (%)</td>
<td></td>
<td></td>
<td>0.27</td>
</tr>
<tr>
<td>A</td>
<td>51</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>17</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>42</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Nadir CD4+ count (cells/mm&lt;sup&gt;3&lt;/sup&gt;), median (IQR)</td>
<td>122 (47–269)</td>
<td>151 (65–276)</td>
<td>0.53</td>
</tr>
<tr>
<td>Highest PVL (copies/mL), median (IQR)</td>
<td>5.1 (5.0–5.7)</td>
<td>5.3 (4.7–5.6)</td>
<td>0.83</td>
</tr>
<tr>
<td>On cART, n (%)</td>
<td>83 (75)</td>
<td>86 (78)</td>
<td>0.75</td>
</tr>
<tr>
<td>CD4+ count (cells/mm&lt;sup&gt;3&lt;/sup&gt;), median (IQR)</td>
<td>359 (214–595)</td>
<td>423 (267–591)</td>
<td>0.34</td>
</tr>
<tr>
<td>PVL &lt;50 copies/mL, n (%)</td>
<td>61 (55)</td>
<td>58 (53)</td>
<td>0.79</td>
</tr>
<tr>
<td>Current alcohol abuse, n (%)</td>
<td>24 (22)</td>
<td>11 (10)</td>
<td>0.03</td>
</tr>
<tr>
<td>Current tobacco smoking, n (%)</td>
<td>58 (53)</td>
<td>45 (41)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

<sup>a</sup>A t-test was used for normally distributed continuous data, the Mann–Whitney U-test was used for non-parametric continuous data and the χ<sup>2</sup> test was used for dichotomous data.
patients and controls had similar characteristics at baseline, except for current alcohol abuse, which was more frequently reported among the patients than among the controls (22% versus 10%, *P*=0.03).

Main outcome

The median follow-up time was 3.6 years (IQR 2.0–5.3) for the patients and 4.8 years (IQR 3.3–6.0) for the controls (*P*=0.001). No patient (or control) was lost to follow-up. During this period, 53 of 110 patients (48%) and 20 of 110 (18%) controls experienced a ≥25% CD4+ depletion compared with the respective baseline value (*P*,0.0001). In an unadjusted analysis, the patients were more likely to experience CD4+ depletion (HR = 3.5; 95% CI, 2.1–5.8; *P*,0.0001) than the controls (Figure 2a). In a Cox proportional-hazards regression model, two variables remained predictive of pre-defined CD4+ depletion: exposure to ERT (HR = 5.1; 95% CI: 3.0–8.6; *P*,0.0001), and a >11 year duration of living with HIV (HR = 2.0, 95% CI, 1.2–3.3, *P*=0.007) (Table 2 and Figure 3a). Notably, type of cancer (AIDS-defining versus non-AIDS-defining, haematological versus non-haematological, infection-related versus non-infection-related), number of myelotoxic drugs used in SCC (0, 1, 2, ≥3) and exclusion of deceased patients had no impact on the incidence of CD4+ depletion in this model (data not shown).

For the patients who received ERT, the magnitude of the CD4+ depletion peaked at 6 months after their cancer diagnoses [mean CD4+ drop at this time = 2283 ± 370 cells/mm³, median = 2174 cells/mm³ (IQR 2352 to 292)]. This decrease in the CD4+ count was significantly greater than for the patients unexposed to ERT and the controls at every follow-up time from month 3 to month 36 (*P*≤0.0001 for all comparisons) (Figure 3b). At the peak of the CD4+ depletion (i.e. month 6), the patients who were exposed to ERT also had a greater decrease in their total lymphocyte count, CD8+ count and CD4+/CD8+ ratio compared with the patients who were unexposed to ERT and the controls (data not shown). Finally, in the ERT-exposed patients, the magnitude of the CD4+ drop at month 6 was highly correlated with the baseline CD4+ count (*r* = −0.8, *P*,0.0001) but not with age, type of cancer, co-administration of SCC, localization of radiotherapy, total dose received (Grays) and mode of administration (hypo- versus normal fractionation, data not shown).

![Figure 2. Kaplan–Meier survival estimates for participants without CD4+ depletion, virological failure, new ADI and death. Curves represent the percentages of patients and controls that remained free of pre-defined CD4+ depletion (main outcome) (a), virological failure (b) and new ADI (c), and who survived (d) from baseline to the last visit.](https://academic.oup.com/jac/article-abstract/70/1/249/2911336/1336)
Other outcomes

Virological failure

A total of 205 patients were eligible for the virological outcome evaluations: 169 patients were undergoing cART at baseline, and 36 started cART within 1 month after baseline. During follow-up, 44 of 104 patients (42%) and 30 of 101 (30%) controls fulfilled the criteria of virological failure ($P = 0.08$). In an unadjusted analysis, the patients were more likely than the controls to experience virological failure over time (HR = 1.7; 95% CI, 1.1–2.7, $P = 0.03$) (Figure 2b). This difference was no longer significant after adjusting for other baseline characteristics; in the multivariate analysis, only the use of NNRTIs and duration with undetectable PVL b (years) remained predictive for viral control (Table 2). In all, 6 PLHIV experienced new ADIs: two patients (candidal oesophagitis, n = 1; Mycobacterium avium infection, n = 1) and four controls (candidal oesophagitis, n = 1; extrapulmonary tuberculosis, n = 1; Pneumocystis jirovecii pneumonia, n = 1; recurrent pneumonia plus wasting syndrome, n = 1). Notably, in both groups, all PLHIV with CD4 + T cell counts, 200 cells/mm$^3$, were prescribed systematic prophylaxis against P. jirovecii pneumonia and toxoplasmosis. Antimycobacterial prophylaxis was also administered to PLHIV with a CD4 + count, 50 cells/mm$^3$.

Deaths

Overall, 31 of 110 patients (28%) died during follow-up; there were no deaths in the control group ($P = 0.0001$) (Figure 2d). This difference was no longer significant after adjusting for other baseline characteristics; in the multivariate analysis, only the use of NNRTIs and the duration with undetectable PVL at baseline (>1 year) remained predictive for viral control (Table 2).

Type of cancer (AIDS-defining versus non-AIDS-defining, haematological versus non-haematological, infection-related versus non-infection-related), number of myelotoxic drugs used in SCC (0, 1, 2, ≥3) and exclusion of patients had no impact on the incidence of virological failure in this model (data not shown).

New ADIs

During follow-up, no significant between-group difference was observed concerning new ADIs (HR = 0.6, 95% CI, 0.1–2.9, $P = 0.5$) (Figure 2c). Overall, six PLHIV experienced new ADIs: two patients (candidal oesophagitis, n = 1; Mycobacterium avium infection, n = 1) and four controls (candidal oesophagitis, n = 1; extrapulmonary tuberculosis, n = 1; Pneumocystis jirovecii pneumonia, n = 1; recurrent pneumonia plus wasting syndrome, n = 1). Notably, in both groups, all PLHIV with CD4 + T cell counts, 200 cells/mm$^3$, were prescribed systematic prophylaxis against P. jirovecii pneumonia and toxoplasmosis. Antimycobacterial prophylaxis was also administered to PLHIV with a CD4 + count <50 cells/mm$^3$.

Deaths

Overall, 31 of 110 patients (28%) died during follow-up; there were no deaths in the control group ($P = 0.0001$) (Figure 2d). The deaths were directly attributable to the progression of cancer in all but two patients (end-stage renal insufficiency, n = 1; aspiration pneumonia complicating severe chronic respiratory failure, n = 1). The proportion of death, according to each type of cancer, was as follows (in order of decreasing frequency, for cancers whose number is ≥4): liver, 4 of 4 (100%); lung, 9 of 12 (75%); colon, 1 of 4 (25%); Hodgkin’s lymphoma, 1 of 5 (20%); breast, 1 of 8 (13%); and non-Hodgkin’s lymphoma, 1 of 14 (7%).

Long-term immuno-virological outcomes

The remaining 79 patients who survived and 110 controls had similar follow-up durations (median 4.6 versus 4.8 years,
respectively, \( P = 0.75 \)). At the last visit, these patients and controls demonstrated comparable outcomes regarding the use of cART (97\% versus 99\%, respectively, \( P = 0.75 \)), immuno-virological parameters (median CD4+ count: 476 versus 496 cells/mm\(^3\), respectively, \( P = 0.26 \)) and percentage with PVL <50 copies/mL (90\% versus 92\%, respectively, \( P = 0.8 \)). Nevertheless, the patients who had been exposed to ERT still had a slightly lower CD4+ count than the non-ERT exposed patients and controls (median, 431, 540 and 496 cells/mm\(^3\), respectively, \( P = 0.056 \) for overall comparisons) because of the persistence of a significant CD4+ decrease compared with the baseline values \( \Delta \)CD4+ count: \(-53, +163 \) and \(+82 \) cells/mm\(^3\), respectively, \( P < 0.05 \) (overall comparison)).

**Discussion**

To the best of our knowledge, the present study is the first to specifically focus on the long-term impact of treating cancer in HIV-infected patients, encompassing both immuno-virological and clinical outcomes. Moreover, our results are reinforced by the fact that we compared the cancer cases (i.e. PLHIV and cancer) with well-matched controls (i.e. PLHIV without malignancies). Mainly, we found that radiotherapy (and not chemotherapy) promptly induced a steep and protracted decline in the peripheral CD4+ count, whereas the patients generally were at increased risk of virological failure compared with the controls. Nevertheless, no harmful consequence (in terms of new ADIs) was observed in the patients undergoing appropriate prophylaxes.

The deleterious effect of localized irradiation on circulating T cells was well described in the late 1980s in HIV-uninfected adults treated for various cancers.\(^8,9\) Irradiation transiently affects all circulating lymphocytes,\(^8,9\) but in the long term it affects CD4+ T cells, particularly naive cells.\(^10\) Two studies have reported that lymphocyte declines can last for up to 5–11 years after radiotherapy.\(^10,11\) Radio-induced cell activation and apoptosis are likely to explain such rapid T cell depletion, whereas thymic involution (in adults) can explain its sustainability, particularly for naive cells.\(^10\) More recently, T cell decline has also been described in small studies of HIV-infected adults,\(^12–14\) but a single study reported long-term outcomes (up to 3 years) for CD4+ count and demonstrated results that were comparable to those for HIV-uninfected patients.\(^15\) The magnitude of CD4+ loss reported in most previous studies (regardless of HIV status) was 150–200 cells/mm\(^3\), which is similar to our findings.\(^10,12,13,15\) Until the present report, it has not been clearly demonstrated whether radio-induced CD4+ T cell depletion clinically could lead to an increased risk of opportunistic infections, particularly in the context of PLHIV who are on
a successful CART.\textsuperscript{16} We concluded that there was no increased risk for opportunistic infections when the prophylactic conditions aligned with the CD4+ count. The effect of SCC on T cell count is more controversial. Hakim et al.\textsuperscript{17} reported a profound decline in CD4+ (>CD8+) T cells for more than 1 year following chemotherapy in the context of HIV-uninfected patients with breast cancer. Conversely, Powles et al.\textsuperscript{18} reported a rapid recovery in CD4+ count following the completion of chemotherapy in PLHIV treated for AIDS-related lymphoma and undergoing cART. These authors postulated that the constant thymic stimulation caused by cART\textsuperscript{19} was responsible for the rapid rise in CD4+ count following the cessation of chemotherapy. Moreover, Sankatsing et al.\textsuperscript{15} concluded that ERT resulted in a significant and prolonged decline in CD4+ counts in PLHIV, whereas SCC did not significantly influence CD4+ cell count recovery. In our study, we found no significant association between SCC use and the incidence of a \geq25\% CD4+ depletion in the multivariate analysis (after adjusting for the use of ERT).

Assessing the specific decay of cells carrying HIV-DNA could be of particular interest. In fact, an increasing body of evidence indicates that a cure for HIV is an attainable goal.\textsuperscript{20,21} The combination of irradiation, systemic chemotherapy and bone marrow graft has been proven to dramatically reduce HIV reservoirs and to sometimes lead to viral control after cART cessation.\textsuperscript{22–24} In this context, PLHIV undergoing treatments for cancer could be a good model to assess the impact of various antitumoral strategies on the biomarkers of HIV reservoirs (as HIV-DNA) in a large number of patients, particularly as such strategies are not ethically evaluable in many patients without malignancy.

We showed that cancer patients had an increased risk of experiencing virological failure compared with matched controls. The use of cART during SCC entails a number of potential complications, including pharmacokinetic interactions and overlapping toxicities that might compromise both cancer treatment and HIV-1 control.\textsuperscript{25} Indeed, as either inducers or inhibitors of the cytochrome P450 pathway, many antiretroviral drugs are metabolized through it. Thus, the co-administration of cART and SCC metabolized through this pathway can result in drug accumulation (and possible toxicity) or, in contrast, decreased concentration (and efficacy) of one or both drugs. Moreover, treatment compliance of PLHIV with cancer may be altered because of the increased side effects resulting from taking drugs for both HIV and cancer. Together, these constraints could explain part of the virological failure that we observed in our patients. Unfortunately, because the data collection was retrospective, we are unable to confirm these hypotheses in the absence of specific drug monitoring or adherence measures. Interestingly, multivariate analysis demonstrated that belonging to the cancer group was no longer a significant predictor of success, along with the duration of virological control before baseline. Recently, Torres et al.\textsuperscript{26} reported that the use of NNRTIs or an integrase strand transfer inhibitor (raltegravir) as the third agent was associated with better efficacy and safety and lower levels of drug–drug interactions during the treatment of cancer than regimens containing PIs. We found similar results concerning the use of NNRTIs, but we had insufficient data to specifically draw any conclusions regarding raltegravir.

This study has some limitations. Because of its retrospective nature, we were unable to explore the mechanism of CD4+ decrease or to compare this decline with that in HIV-uninfected patients treated for the same malignancies. Compared with large, nationwide studies in PLHIV, we found similar patterns concerning the type and relative frequency of cancers\textsuperscript{3,26} Nevertheless, our case collection was not exhaustive and probably missed some relevant cases, as we did not systematically approach all adult oncology departments or paediatric wards. Indeed, our cancer rate was slightly lower than those previously reported in France and the USA (i.e. 13–14/1000 person-years).\textsuperscript{4,26} Our goal was only to assess the impact of cancer on HIV course and not to describe the incidence and risk factors of cancers. Thus, we valued the completeness of medical records rather than the number of cases. Another limitation is that we cannot rule out that the CD4+ depletion was due to the cancer itself rather than the treatment that was received, in particular with patients with haematological malignancy.

An increasing number of PLHIV face cancer because of ageing. Our results support the conclusion that these patients should be treated in a manner similar to HIV-uninfected people and certainly should not receive less vigorous treatment, particularly because nearly all deaths were directly attributable to the evolution of malignancy and not to ADIs. Nevertheless, irradiation strongly impacts CD4+ count for years and warrants special attention to prevent opportunistic infections. Such a CD4+ T cell decline is intriguing and warrants further investigation and better characterization.

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Author contributions
Supplementary data

Figure S1 and Table S1 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

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