As this was a retrospective analysis, the primary limitation is that of missing data. Secondarily, 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

1. McFaul KM, Lim C, Jones R, Asboe D, Pozniak A, Sonecha S, *et al*. **Transmitted antiretroviral resistance in a large HIV directorate 2011–2014: a response.** *AIDS* 2015; **29**:861–862.
2. Churchill D, Waters L, Ahmed N, Angus B, Boffito M, Bower M, *et al*. *BHIVA guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy 2015*. British HIV Association; 2015 .
3. Feng M, Wang D, Grobler JA, Hazuda DJ, Miller MD, Lai MT. **In vitro resistance selection with doravirine (MK-1439), a novel nonnucleoside reverse transcriptase inhibitor with distinct mutation development pathways.** *Antimicrob Agents Chemother* 2015; **59**:590–598.
4. Garrido C, Soriano V, Geretti AM, Zahonero N, Garcia S, Booth C, *et al*. **Resistance associated mutations to dolutegravir (S/GSK1349572) in HIV-infected patients – impact of HIV subtypes and prior raltegravir experience.** *Antiviral Res* 2011; **90**:164–167.
5. Schürmann D, Sobotha C, Gilmartin J, Robberechts M, De Lepeleire I, Yee KL, *et al*. **A randomized, double-blind, placebo-controlled, short-term monotherapy study of doravirine in treatment-naive HIV-infected individuals.** *AIDS* 2016; **30**: 57–63.
6. Van Leeuwen R, Katlama C, Murphy RL, Squires K, Gatell J, Horban A, *et al*. **A randomized trial to study first-line combination therapy with or without a protease inhibitor in HIV-1-infected patients.** *AIDS* 2003; **17**:987–999.
7. Staszewski S, Morales-Ramirez J, Tashima KT, Rachlis A, Skiest D, Stanford J, *et al*. **Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults.** *N Engl J Med* 1999; **341**:1865–1873.
8. Daar ES, Tierney C, Fischl MA, Sax PE, Mollan K, Budhathoki C, *et al*. **Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1: a randomized trial.** *Ann Intern Med* 2011; **154**:445–456.
9. Geretti AM, White E, Beloukas A, Orkin C, Tostevin A, Tilston P, *et al*. **Impact of transmitted thymidine analogue mutations on responses to first-line ART**. *23rd Conference on retroviruses and opportunistic infections (CROI)*. 22–25 February 2016, Boston, USA. 2016. Abstract number 482.
10. Shafer RW. **Rationale and uses of a public HIV drug-resistance database.** *J Infect Dis* 2006; **194 (Suppl 1)**:S51–S58.
11. Bacheler L, Jeffrey S, Hanna G, D'Aquila R, Wallace L, Logue K, *et al*. **Genotypic correlates of phenotypic resistance to efavirenz in virus isolates from patients failing nonnucleoside reverse transcriptase inhibitor therapy.** *J Virol* 2001; **75**:4999–5008.
12. Melikian GL, Rhee SY, Varghese V, Porter D, White K, Taylor J, *et al*. **Nonnucleoside reverse transcriptase inhibitor (NNRTI) cross-resistance: implications for preclinical evaluation of novel NNRTIs and clinical genotypic resistance testing.** *J Antimicrob Chemother* 2014; **69**:12–20.
13. Hernán MA, Hernández-Díaz S. **Beyond the intention-to-treat in comparative effectiveness research.** *Clin Trials* 2012; **9**: 48–55.
14. Stannard CF, Kalso E, Ballantyne J (Eds): *Evidence-based chronic pain management*. Chichester: Wiley-Blackwell/BMJ; 2010.

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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 ($50 < \text{viral load} < 2000$) termed 'viremic controllers' [3]. Chronic inflammation

is associated with an increase of the cardiovascular risk, and studies have showed 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 melanoma, three prostate cancers, and an unclassified brain tumor. Lastly, two rare colic 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.

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

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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Conflicts of interest

There are no conflicts of interest.

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References

1. Hunt PW, Brenchley J, Sinclair E, McCune JM, Roland M, Page-Shafer K, *et al*. **Relationship between T cell activation and CD4$^+$ T cell count in HIV-seropositive individuals with undetectable plasma HIV RNA levels in the absence of therapy.** *J Infect Dis* 2008; **197**:126–133.
2. Noel N, Boufassa F, Lécuroux C, Saez-Cirion A, Bourgeois C, Dunyach-Remy C, *et al*. **Elevated IP10 levels are associated with immune activation and low CD4$^+$ T-cell counts in HIV controller patients.** *AIDS* 2014; **28**:467–476.
3. Pereyra F, Addo MM, Kaufmann DE, Liu Y, Miura T, Rathod A, *et al*. **Genetic and immunologic heterogeneity among persons who control HIV infection in the absence of therapy.** *J Infect Dis* 2008; **197**:563–571.
4. Crowell T, Gebo KA, Blankson JN, Korthuis PT, Yehia BR, Rutstein RM, *et al*. **Hospitalization rates and reasons among HIV elite controllers and persons with medically controlled HIV infection.** *J Infect Dis* 2015; **211**:1692–1702.
5. Hsue PY, Hunt PW, Schnell A, Kalapus SC, Hoh R, Ganz P, *et al*. **Role of viral replication, antiretroviral therapy, and immunodeficiency in HIV-associated atherosclerosis.** *AIDS* 2009; **23**:1059–1067.
6. Shalapour S, Karin M. **Immunity, inflammation, and cancer: an eternal fight between good and evil.** *J Clin Invest* 2015; **125**:3347–3355.
7. Boufassa F, Saez-Cirion A, Lechenadec J, Zucman D, Avettand-Fenoel V, Venet A, *et al*. **CD4 dynamics over a 15 year-period among HIV controllers enrolled in the ANRS French observatory.** *PLoS One* 2011; **6**:e18726.
8. Okulicz JF, Marconi VC, Landrum ML, Wegner S, Weintrob A, Ganesan A, *et al*. **Clinical outcomes of elite controllers, viremic controllers, and long-term nonprogressors in the US Department of Defense HIV Natural History Study.** *J Infect Dis* 2009; **200**:1714–1723.
9. Lanoy E, Spano JP, Bonnet F, Guiguet M, Boué F, Cadranel J, *et al*. **The spectrum of malignancies in HIV-infected patients in 2006 in France: the ONCOVIH study.** *Int J Cancer* 2011; **129**:467–475.
10. Spano JP, Poizot-Martin I, Costagliola D, Boue F, Rosmorduc O, Lavolé A, *et al*. **Non-AIDS-related malignancies: expert consensus review and practical applications from the multidisciplinary CANCERVIH working group.** *Ann Oncol* 2016; **27**:397–408.
11. Shiels MS, Pfeiffer R, Engels EA. **Age at cancer diagnosis among persons with AIDS in the United States.** *Ann Intern Med* 2010; **153**:452–460.
12. Yu SH, Bordeaux JS, Baron ED. **The immune system and skin cancer.** *Adv Exp Med Biol* 2014; **810**:182–191.

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