Letter to the Editor

Drastic decrease of the HIV reservoir in a patient treated with nivolumab for lung cancer

Amélie Guihot[1,2,3], Anne-Geneviève Marcelin[3,4,5], Marie-Ange Massiani[6], Assia Samri[2], Cathia Soulié[4], Brigitte Autran[2,3], Jean-Philippe Spano[3,4,7]

1- APHP, Hôpital Pitié Salpêtrière, Département d'Immunologie, Paris, France

2- INSERM, U 1135, CIMI, Paris, France

3- Sorbonne Universités, UPMC Univ Paris 06, Paris, France.

4- INSERM, UMRS 1136, Institut Pierre Louis d'épidémiologie et de Santé Publique, F75013, Paris, France

5- AP-HP, Hôpital Pitié-Salpêtrière, Service de Virologie, Paris, France

6- Institut Curie - Centre René Huguenin, Saint Cloud, France

7- Department of Medical Oncology, Groupe hospitalier Pitié-Salpêtrière-Charles Foix, AP-HP, Paris, France

Word count: 504

1 figure

Keywords: nivolumab, PD-1, HIV, reservoir, immune check points

Dear Editor,

Therapy with immune check-points inhibitors (ICPIs) may have dual benefits in HIV infection by acting not only on the cancers frequently associated but also by helping to purge the HIV reservoirs that indefinitely persist despite antiretroviral therapy. Indeed it is hypothesized that ICPIs could de-repress the blockade of HIV transcription in the reservoirs concentrated in memory CD4 T cells co-expressing ICPs and simultaneously restore functions in exhausted HIV-specific T cells displaying high PD-1 levels [1]. This hypothesis has not been confirmed yet. Two case reports of HIV-infected patients treated for cancer with an anti-CTLA-4 [2], or an anti-PD1 [3] monoclonal antibody showed a good safety profile that was recently confirmed by two series of patients treated for melanoma (N=9) [4] or lung cancer (N=10) [5]. However, no clear effect on HIV reservoirs was reported despite some transient increase in HIV transcription after anti-CTLA-4, and in HIV-specific T cells after anti–PD1 therapy [2,3]. Here we report for the first time a new case with a drastic and sustained decrease of the HIV reservoir paralleling the increase in HIV-specific CD8 T cells under anti-PD1 therapy.

A 51 year-old man, smoker, HIV-infected since 1995, diagnosed with stage IIIa EGFR -/BRAF-/Kras-/PDL-1- non small cell lung cancer in May 2015 was treated with lobectomy and adjuvant chemotherapy (cisplatin and pemetrexed). Relapse occurred less than 6 months after the end of chemotherapy and nivolumab was introduced as a second line in December 2016 upon the CANCERVIH network recommendations. Pre-treatment plasma HIV load was undetectable (<20 copies/mL) under emtricitabin, tenofovir and dolutegravir started in August 2016. Fifteen injections were administered every 14 days until July 2017, with a stable disease, and a good tolerance with stable CD4 and CD8 counts despite a slight CD4 drop at D30 (Figure 1A). The plasma HIV load progressively and modestly increased up to 101 copies/mL at D45, decreasing afterwards to 31 copies/ml at D120. In parallel T cell activation

slightly increased between D14 and D45 while PD-1+ CD4 and CD8 T cells declined at D30 (Figure 1B, C). Then frequencies of HIV RT- and nef -specific CD8 T cells markedly increased from D30 to D120 (Figure 1D). Finally, the cell associated HIV-DNA showed a drastic and persistent decrease from 369 at D0 to 30 copies/10^6 cells at D120 (Figure 1A).

Taken together, those results suggest that nivolumab in this patient had induced synergistic "shock and kill" mechanisms: 1) a transient reactivation of HIV replication within infected CD4 T cells together with a T cell activation, 2) a decrease in exhausted CD4 and CD8 T cells followed by a durable and major restoration of HIV-specific CD8 T cells function that might have killed the HIV-producing cells, altogether resulting in a drastic and durable diminution of the reservoir.

This first report of a successful depletion of the HIV reservoirs opens new therapeutic perspectives towards an HIV cure. Whether this encouraging result is reproducible is also currently being analyzed in the French cohort of HIV-infected people treated with immune check-point inhibitors (ANRS-CO24, OncoVIHAC cohort).

Figure 1.

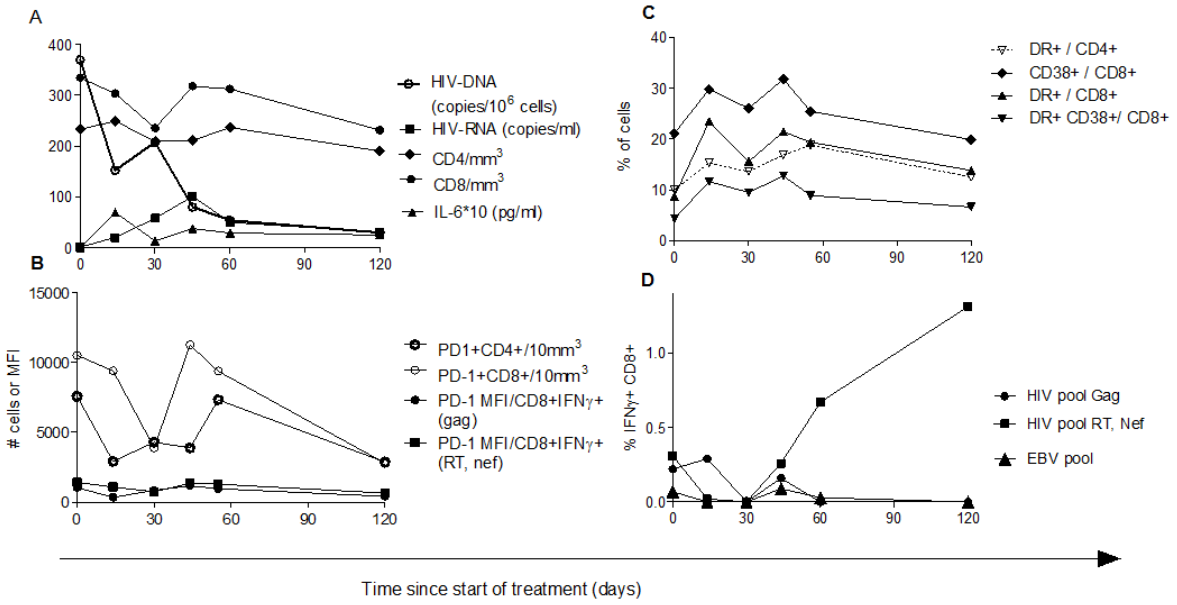

A
400
300
200
100
0
0
30
60
90
120
HIV-DNA (copies/10^6 cells)
HIV-RNA (copies/ml)
CD4/mm^3
CD8/mm^3
IL-6*10 (pg/ml)
B
15000
10000
5000
0
cells or MFI
PD1+CD4+/10mm^3
PD-1+CD8+/10mm^3
PD-1 MFI/CD8+IFNγ+ (gag)
PD-1 MFI/CD8+IFNγ+ (RT, nef)
C
40
30
20
10
0
% of cells
DR+ / CD4+
CD38+ / CD8+
DR+ / CD8+
DR+ CD38+/ CD8+
D
1.0
0.5
0.0
% IFNγ+ CD8+
HIV pool Gag
HIV pool RT, Nef
EBV pool
Time since start of treatment (days)

Figure Legend.

Immunovirological modulations under anti-PD-1 therapy in an HIV-infected patient treated for lung cancer. **A.** CD4 cell count, IL-6 plasma levels, HIV-1 plasma viral load measured with ultrasensitive technique (USVL), and total HIV-DNA (DNA copies/million cells) through time. **B.** PD-1 expression on total CD4+ and CD8+ T cells, on HIV Gag-specific CD8+ T cells, and on HIV RT/Nef-specific CD8+ T cells. Results are expressed as absolute number of total PD-1+ T cells/mm^3MFI, or Mean Fluorescence Intensity for HIV-specific T cells. **C.** HLA-DR and CD38 activation markers expression on total CD4 and CD8 peripheral T cells. **D.** Frequencies of HIV Gag, RT/Nef, and Epstein Barr Virus (EBV)-specific IFNγ+CD8+ T cells (stimulation with optimal CD8 peptides).

References

1- Deeks SG, Lewin SR, Ross AL, et al; International AIDS Society Towards a Cure Working Group. International AIDS Society global scientific strategy: towards an HIV cure 2016. Nat Med. 2016;22:839-50.

2- Wightman F, Solomon A, Kumar SS, et al. Effect of ipilimumab on the HIV reservoir in an HIV-infected individual with metastatic melanoma. AIDS. 2015;29:504-6.

3- Le Garff G, Samri A, Lambert-Niclot S, et al. Transient HIV-specific T cells increase and inflammation in an HIV-infected patient treated with nivolumab. AIDS. 2017;31:1048-1051.

4- Heppt MV, Shlaak M, Eigenlter TK, et al. Checkpoint blockade for metastatic melanoma and Merkel cell carcinoma in HIV-positive patients. Ann Oncol 2017, Sep 18.

5- A. Samri, A. Lavolé, S. Even, et al. Immunovirological evolution in HIV-infected patients treated with anti-PD-1 therapy. IAS 2017, Abstract#MOPEB0362.