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Malignant Melanoma in People Living with HIV/AIDS: Can We Know More, Can We Do Better?

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Abstract

Thanks to the advancement in understanding of molecular mechanisms driving immune surveillance, we have now approached a revolutionary era for the treatment of malignant melanoma (MM). Meanwhile, people living with HIV/AIDS (PLWHA) are aging and non-AIDS-related cancers have become a leading cause of death. Both HIV infection and melanoma share common immune-pathological pathways: immune checkpoints are being targeted for melanoma immunotherapy and investigated as a "shock and kill" strategy for latency reversion among HIV-positive individuals. Nevertheless, a substantial lack of information exists on epidemiology, clinical features, and management of MM in HIV, due to compartmentalized approaches and poor awareness about the problem. In this narrative review, we aimed at analyzing available data regarding MM in PLWHA to point out key knowledge gaps and future opportunities from an integrated dermatology, oncology, and infectious diseases standpoint. To date, a strong association between HIV infection and MM risk still needs to be effectively demonstrated; nevertheless, once this cancer has developed in HIV-positive people, it shows more aggressive course, worse prognosis, and seemingly peculiar clinical and histological features. Despite these challenges, a syndemic framework should lead us toward a tailored and multidisciplinary approach not to miss valuable opportunities from the worst situations including the enrolment of HIV-positive patients in the ongoing trials with immune checkpoint inhibitors. **(AIDS Rev. 2019;21:65-75)**

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Key words

HIV. Melanoma. Cancer. Immune checkpoint inhibitors. Programmed cell death 1.

Introduction

Over the past decade, we have witnessed revolutionary changes regarding both malignant melanoma (MM) and HIV infection. While MM prognosis promises to change rapidly thanks to signaling pathway-targeted and immune therapy[1], life expectancy of people living with HIV/AIDS (PLWHA) is going to match the one of the general populations[2]. A more in-depth insight into immune surveillance, escaping, and microenvironment

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have been milestones for changing route of both these chronic conditions. Despite these striking steps forward, when their pandemics overlap, resulting outcomes may overcome the positive goals attained in both the individual fields and progress decelerates if it is compartmentalized, not sustained by a translational approach of multidisciplinary interchange and the "one size fits all" rule still prevails. Although new therapeutic strategies and earlier diagnosis, MM death rates are expected to remain stable until 2030[3]. Meanwhile, in highly active antiretroviral therapy (HAART) era, PLWHA age and non-AIDS-defining cancers (nADCs) have become a relevant cause of death[4]. Cancer in PLWHA has a more aggressive course[5]; additionally, HAART together with MM immunotherapies may reciprocally influence both the diseases so that MM in this population should require a tailored management. Nevertheless, until recently, PLWHA have experienced an unmet need being excluded from all the immunotherapy trials[6]. Comparing the immune checkpoints similarities and differences would not only benefit PLWHA suffering from MM but it may also synergistically push forward advancements in both the fields. Furthermore, revolutionary changes such as HAART introduction first and then HAART administration to anyone at any stage modified what we already knew about the co-occurrence of these conditions from pre-HAART era. There is an increasing need of better understanding the natural history, the standard of care and the possible therapies interactions, and opportunities for MM in PLWHA. Therefore, in this narrative review, we analyzed recent data and pointed out key knowledge gaps about MM epidemiology, clinical aspects, and new therapies among PLWHA from an integrated dermatology and infectious diseases point of view.

Epidemiology: do PLWHA have a higher risk for MM?

MM incidence among PLWHA has been reported around 16.4-175.7/100.000 persons-years during early HAART era in selected American and European cohorts[4,7-11]. While overall projected nADCs incidence rates are expected to decrease until 2030[12], MM incidence is increasing in the general population[3,13,14]. In 2018, 91,270 and 144,209 new cases of MM have been estimated in the United States and Europe, respectively[13,14]. From pre-HAART era to the first decade of the current century, four studies reported no cumulative MM incidence trend among PLWHA[7,15-17] and only one observed an increasing incidence[4]. Standardized incidence rate (SIR) and other effect measures of risk for MM in PLWHA in pre- and post-HAART era are listed in Table 1. In both the periods, the overall pooled SIR has been reported to be close to 1, suggesting that MM incidence in PLWHA is increasing in parallel with the one of the general population without differences in terms of incidence and risk rates. Nevertheless, some studies were featured by high prevalence of African ethnicity people, where an overall lower risk for MM compared to Caucasian has been found both for HIV-negative and HIV-positive individuals[10,18,19]. Interestingly, an increased MM risk has been reported among PLWHA in India, but no evaluation according to skin pigmentation was made[20]. The possibility that HIV infection by itself may overcome or attenuate ethnicity-related factors protecting from MM development is still far from being understood. Moreover, study design and analyses were very heterogeneous[8,10,17,19-26] with possible representativeness, surveillance, case definition/inclusion, comparison, and/or computational bias, while AIDS-related competing risks may have not always been considered by pre-HAART era studies. Nevertheless, despite the wide variability in methods and sample populations which may explain the apparently contradictory data, some studies may still point toward a higher prevalence of MM among PLWHA, if only Caucasian ethnicity would be taken into account[10,19,27,28]. In accordance with this, a recent meta-analysis on MM risk in PLWHA reported a significant heterogeneity and a pooled relative risk of 1.3 and 1.5 after ethnicity-adjustment during pre- and post-HAART eras, respectively[27]. This 20% increase in MM risk between the periods seems to be more explainable by the longer longevity of PLWHA, rather than by HAART-induced carcinogenic risks as hypothesized by some[15]. In fact, age has been reported as a significant risk factor for melanoma[29] and higher MM rates have been associated with older age also in PLWHA[8,19]. If any increment in MM risk is ascribable to HIV infection, then the evidence of HIV-related risk factors should be investigated. Cases of eruptive dysplastic nevi have been reported among patients soon after progressing into AIDS[30]; still, no attempt to demonstrate that HIV-induced immune deficiency may promote nevi development has been successful: PLWHA may have higher number of small nevi, but similar amount of larger and atypical nevi compared to age, sex, and hair color matched controls[31]. Ultraviolet/sun exposure, fair skin (phototypes 1-2), higher number of common and atypical nevi, and family history are acknowledged risk factors for MM[18]. Sunbath use is more common among

Table 1. Effect measures of MM risk in PLWHA from the pre-HAART era to current days

Period	Location	Cohort	Effect Measure	Features	References
Pre-HAART and early HAART era					
1981-1996	USA	AIDS ≥ 60 years old patients	RR 1.5 (0.8-2.6)	Cross-matched registries §	21
1988-2003	USA	HIV/AIDS military	RR 10.5 (9.0-11.9)		10
1980-2002	USA, Europe, Australia	HIV/AIDS adults	SIR 1.24 (1.0-1.5)	Meta-analysis	28
1995-2004	South Africa	HIV/AIDS African ethnicity adults	aOR 1.7 (0.7-3.8)	Cancer questionnaires	24
1980-2004	USA	AIDS adults	SIR 1.3 (1.1-1.4)	Cross-matched registries §	19
1987-2002	USA	HIV ≥ 66 years old	OR 0.89 (0.6-1.3)		22
1978-1996	USA, Europe, Australia	HIV/AIDS adults	pRR 1.26 (1.1-1.4)-1.28 (1.1-1.5)*	Meta-analysis	27
1997-2009			pRR 1.26 (0.9-1.6)-1.50 (1.1-2.0)*		
Early and Late HAART era					
1996-2008	USA	HIV/AIDS veterans	SIR 1.04 (0.8-1.4) versus 2.50 (2.1-3.0)	Cancer registries versus ICD-9 codes §	25
1996-2008	Pune (India)	HIV/AIDS patients	SIR 6.0 (1.2-17.4)	Cross-matched registries §	20
1996-2009	USA, Canada	HIV/AIDS Caucasian adults only	SIR 1.15 (0.9-1.4)		8
1996-2012	USA	HIV/AIDS adults	SIR 0.87 (0.7-1.1)-0.85 (0.7-1.0) in HIV-AIDS	Registry-linkage study	26
1995-2017	Denmark	HIV/AIDS ≥ 16-year-old Danish patients	IRR 0.60 (0.3-1.3)	Scarcity of MM events	23

MM: malignant melanoma; PLWHA: people living with HIV/AIDS; SIR: standardized incidence rate.

Only the most recent publication from the same clinical cohorts and studies not included in the listed meta-analyses were reported in the table. HAART: highly active antiretroviral therapy; RR: rate ratio; SIR: standardized incidence ratio; aOR: adjusted odds ratio; OR: odds ratio; pRR: pooled relative risk; NA: not available; IRR: incidence rate ratio; MM: malignant melanoma. *After ethnicity adjustment; §SEER: surveillance, epidemiology and end results program) data, for which no information/specification is available about the immune status of the cohort individuals, was used as control.

Table 2. Effect measures of risk of MM according to viroimmunological parameters in PLWHA

Viroimmunological parameters (cutoff/Model)	Effect measure of association	References
AIDS episodes	HRi 2.81 (0.38-20.87)	15
Length of HIV infection (5 years)	HRi 1.04 (0.14-7.91)	15
CD4 + T cells Nadir (≤ 200 cells/mmc)	HRi 0.10 (0.01-1.04)	15
Current CD4 + T-cells		
(≤ 200 cells/mmc)	RRu 2.1 (0.8-5.0)/RRi 1.8 (0.6-6.0)	8, 11
(201-499 cells/mmc)	RRu 2.5 (1.6-3.9)/RRi 2.3 (1.0-5.3)	
(≥ 500 cells/mmc)	RRu 1.1 (0.5-2.1)	
(Every 100 cells/mmc less)	HRi 1.0 (0.92-1.09)	
Being on HAART	HRi 0.38 (0.05-2.69)-HRi 1.45 (0.83-2.55)	8, 15
Time on HAART		
(10% increase over prior 2 years)	HRi 1.16 (1.03-1.3)	8
(10% increase over prior 180-900 days)	HRi 1.14 (1.01-1.28)	
Plasma HIV-RNA		
(>10,000 cp/mL)	RRu 2.6 (1.3-5.1)/RRi 1.9 (0.8-4.6)	8,11
(501-9999 cp/mL)	RRu 2.2 (1.0-5.0)/RRi 1.5 (0.6-3.8)	
(< 500 cp/mL)	RRu 1.5 (1.0-2.4)	
(Every Log10 more)	HRi 1.08 (0.9-1.32)	

MM: malignant melanoma; PLWHA: people living with HIV/AIDS
AIDS: acquired immunodeficiency syndrome; HAART: highly active antiretroviral therapy. Effect measures (HR: hazard ratio; RR: rate ratio) are reported with "u" as subscript if the ratio is between rate in HIV-positive versus rate in HIV-negative patients, with an "i" if the ratio is between rates within HIV-infected patients

homosexual and bisexual people than in the general population[32] and some authors have observed higher MM risk solely in this HIV-positive group[19]. While specific extrinsic risk factors for melanoma have a higher prevalence among community more at risk for HIV, the reported data can induce us to speculate for a negative indirect association between lower phototype and atypical mole syndrome toward HIV risk. Nevertheless, no specific HIV-related risk factor has been clearly identified to date, as shown in Table 2. Recently, Park et al. observed that in different nADCs, including MM, the longer is the period of continuous viral suppression, the lower is the cancers incidence[33], but no studies have investigated possible associations between MM and HIV-induced chronic inflammation, immune activation, immune senescence, and possible legacy effect and no data are available after the START study. Probably, a 10-year span is still necessary to evaluate any change in melanoma incidence among PLWHA starting HAART immediately after HIV diagnosis. To date, a modest number of MM cases have been included in larger and varied nADCs cohorts so that studies specifically designed to assess MM risk and incidence in PLWHA are poorly represented and stratifying for subgroup analyses according to HIV-related parameters can be hardly performed.

Clinical features of MM in PLWHA: same face, same story?

While a strong association between HIV infection and MM still needs to be effectively established, once this cancer develops in PLWHA, a second question to be answered is whether the presentation and prognosis are similar to those of the general population. In 2018, 27,147 and 9320 deaths due to MM have been estimated in Europe and the United States, respectively[13,14]. Up to 2011, MM deaths were 0.2-3% of all the deaths due to nADCs among PLWH[5,34]; current data are missing. We know that nADCs occur at more advanced stages at diagnosis and that PLWHA are less likely than the HIV negatives to receive any first-line course of cancer therapy[5]. In the USA, during 1996-2010, PLWHA showed a significantly higher cancer-specific mortality for overall MM cases (HR 1.72) and for locoregional stages (HR 2.27), even after adjusting for receipt first course cancer treatment (HR 1.93)[5]. In Italy, during 2006-2011, people with AIDS diagnosed with MM died of cancer-related causes 10 times more frequently than the HIV-negative patients with MM (overall sex-/age-standardized mortality ratio of 10.9)[34]. Similar data should be carefully collected and assessed nowadays, after the introduction of new targets

and immunotherapies. This higher mortality could also be due to the greater portion of patients diagnosed with late-stage disease: PLWHA are more than twice as likely to have a distant metastasis from MM and almost twice as likely a regional lymph node metastasis from MM at diagnosis compared to HIV-negative cases matched for age, sex, and race[35]. Furthermore, they showed reduced disease-free survival (16 vs. 42 months) compared to HIV negatives matched for age, sex, histotype, primary site, and thickness[36]. Whether the worse prognosis and the more aggressive clinical course are mainly influenced by HIV-related sociodemographic, clinical or viroimmunological factors have not yet been clearly addessed. MM case reports from HAART era are listed in Table 3. To date, there have been over 30 English published reports from pre- and post-HAART eras; nowadays, patients with concurrent MM and HIV infection are predominantly Caucasian males and do not seem to differ in terms of age from HIV-negative cases (median age 50 years). The median Breslow thickness is 1.4 mm; 64.3% has metastatic disease at the diagnosis. Some authors reported the trunk as preferential primary site[16,31] and rarer localizations have been described[37-44] with SIR of MM of atypical sites reported as the highest among PLWHA[19]. Nevertheless, possible publication bias limits the generalizability of this picture. No association between $CD4^+$ T-cells count and overall survival or Breslow thickness at diagnosis has been observed[36], but higher $CD4^+$ count has been related with longer disease-free survival[36]. Interestingly, a lack or scarcity of tumor-infiltrating lymphocyte (TIL) has been repeatedly described[45-47]; if MM among PLWHA was confirmed as a more prevalent non-brisk TIL type, also this would explain its poorer prognosis. In fact, the presence of TIL and histological regression has been associated to lower risk of sentinel lymph node involvement and to more favorable prognosis in HIV-negative patients[48]. Moreover, atypical presentations including multiple MMs in the context of not familial melanoma[46,47,49] and "animal type" histotype[50] have also been reported, but to date, there is no evidence that rarer forms of MM are more common in PLWHA.

Clinical management of MM in PLWHA: the untold story

Tailored guidelines for screening and managing MM in PLWHA do not exist and HIV is not included among those factors determining the extent of investigations and follow-up of MM. Awareness about the problem is still poor, and the current scientific debate in MM clinical management includes several hot topics urgently requiring an international consensus that, however, may differ for PLWHA:

1. The sentinel node biopsy controversy: after MSLT-II trial, several ***pros*** and ***cons*** emerged to choose between complete lymph node dissection and active nodal basin surveillance with ultrasonography following a positive sentinel node[51]. HIV-related lymphoid hyperplasia as well as infective and lymphoproliferative lymphadenopathies may affect histological evaluation (ulceration, regression, infiltrating lymphocytes, and micro/macrosatellitosis) and should be carefully taken into consideration. While surgical or ultrasonography options should be ideally discussed case by case, in the light of current knowledge, the latter option seems to be more risky to undertake in PLWHA. Ultrasound-guided fine-needle aspiration cytology may prove to be an intermediate option to identify candidates for the complete nodal dissection in a population presenting a wide range of alternative causes of palpable nodes. Furthermore, the promising application of serum S-100β and osteopontin as predictive markers of metastasis in non-sentinel and sentinel nodes[52] should also be carefully evaluated, considering that both have been described as altered by HIV infection[53,54].
2. The excision margins controversy: most of the current guidelines now recommend 2 cm as the maximum margins around thicker MM[55]. To date, no strong data may inform us to prefer wider elective excision margins in PLWHA, but the lack of evidence of higher risk of local recurrence and different microsatellites distribution in this group of patients is not the evidence of their absence and further studies are warranted.
3. The biomarkers challenges: circulating microRNAs (miRNAs) are emerging as potential diagnostic, prognostic, and predictive biomarkers of MM[52]. Furthermore, miRNAs literature in HIV is proliferating leading to the almost daily discovery of miRNAs alterations. Considering the possibility of shared or opposite up- and down-regulated miRNAs, diagnostic and prognostic miRNA clusters should be carefully assessed in PLWHA versus HIV-negative patients with and without MM, avoiding over- or under-estimation of cancer burden and prognosis in the former group.
4. The accompanying HAART: nelfinavir, an old protease inhibitor for HIV infection, repeatedly

Table 3. MM in PLWHA: case reports from the HAART era

Sex	Age (years)	Ethnicity	Breslow's thickness (mm)	Stage*	Primary Site	CD4 count (cells/mmc)	Treatment	Outcome	Note	References
M	33	–	–	IV	Unknown	> 500	IFN-α, γ-knife radiosurgery	Death	Seminal vesicles metastasis	38
M	54	–	1.3	IV	Scalp	> 200	–	–	Fine-needle biopsy	39
M	53	Caucasian	5.6	IV	Lower limb	190	IFN-α, IL-2, vindesine	Death	–	76
M	27	African	2.7	IIb	Thigh	42	–	–	Animal type	50
M	60	Hispanic	–	-	Esophagus	–	Esophagectomy	–	–	40
M	50	Caucasian	3.01	IIIc	Trunk	700	IFN-α, temozolomide	Death	–	77
M	50	–	–	IV	Unknown	320	IL-2, ipilimumab	Stable 8 months	First report of anti-CTLA-4	64
M	48	Caucasian	–	IV	Cheek	38	Ipilimumab, stereotactic radiosurgery	Stable 9 months	–	37
F	30	African	1.45	Ib	Oral mucosa	177	–	DF 21 months	Pregnancy	41
M	47	Caucasian	0.8	Ia	Trunk	–	Ipilimumab, IL-2, dabrafenib/ trametinib, pembrolizumab	Death	First report of anti-PD1	65
M	51	–	–	IV	-	610	Ipilimumab, nivolumab	Death	CD4, CD8, HIV-RNA and HIV-DNA kinetic during anti- CTLA-4	59, 66
NA	NA	African	–	NA	Orbit	–	Orbital exenteration	LFU	Achromic MM	42
M	33	Indian	–	IV	Lower limb, multiple	< 200	–	LFU	–	49

(Continue)

Table 3. MM in PLWHA: case reports from the HAART era *(Continued)*

Sex	Age (years)	Ethnicity	Breslow's thickness (mm)	Stage*	Primary Site	CD4 count (cells/mmc)	Treatment	Outcome	Note	References
F	53	–	–	I	Retro-orbital	–	Orbital exenteration, RT	DF 3.5 years	–	43
M	66	–	–	I	Anorectal	–	Chemotherapy	Death	Anorectal cytology	44
M	72	Caucasian	6.0	IIIc	Lower limb	–	Ipilimumab, nivolumab, RT	Death	–	67

MM: malignant melanoma; PLWHA: people living with HIV/AIDS
M: male; F: female; MM: malignant melanoma; RT: radiotherapy; LFU: lost to follow-up; DF: disease free; CTLA-4: cytotoxic t-lymphocyte antigen 4; PD-1: programmed cell death protein 1. *Stage at diagnosis according to the American Joint Committee on Cancer classification

investigated for its broad antitumor activity, can inhibit MM cell lines proliferation *in vitro* and suppress PAX3/microphthalmia-associated transcription factor pathway, implicated in MM metastatic phenotype and resistance to MAPK inhibitors[56]. No other HIV protease inhibitors have been investigated in this respect nor preferable antiretrovirals combination exists in case of coexisting MM. Therefore, studies addressing all these issues are highly required, also considering the possibility of shared properties among protease inhibitors and their alternative use as a booster for cancer therapies.

Despite MM in PLWHA presents a more aggressive course, worse prognosis, and probably peculiar clinical and histological features, no tailored recommendations on threshold for biopsy, timing for skin examination, staging, frequency, and procedures of follow-up can be drafted based on current available data. Prospective studies and trials are advocated and until then, a strong cooperation between infectious diseases, dermatology and oncology specialists is strongly advisable.

New perspectives in MM therapy: friend or foe in HIV settings?

Over the past decade, improved molecular and immunologic understanding turned MM into a model prototype for studying cancer immune editing processes[1,57]. The most remarkable step forward has been represented by immune checkpoint inhibitors (ICIs). These monoclonal antibodies target key regulatory pathways in immune T-cell, inducing a response toward cancer cells[1,57]. Specifically, by blocking programmed cell death protein 1 (PD-1, nivolumab and pembrolizumab) and cytotoxic t-lymphocytes antigen 4 (CTLA-4, ipilimumab), ICIs have unprecedently prolonged MM relapse free, distant metastasis free, and overall survival times[1]. A schematic representation of PD-1 and CTLA-4 immune checkpoints pathways and their role in MM is depicted in Figure 1. The current standard of care for Stage IV melanoma is now mono/combination therapy with ICIs following or not anti-BRAF/MEK (according to BRAF mutant status)[1]. Considering that their use in BRAF/MEK mutant MM is still under debate and that adjuvant immunotherapy has proved to give survival benefit in patients without evidence of distant metastases too[1], further additional indications for ICIs are expected to be released soon. Surprisingly, HIV is able to exploit the same immune

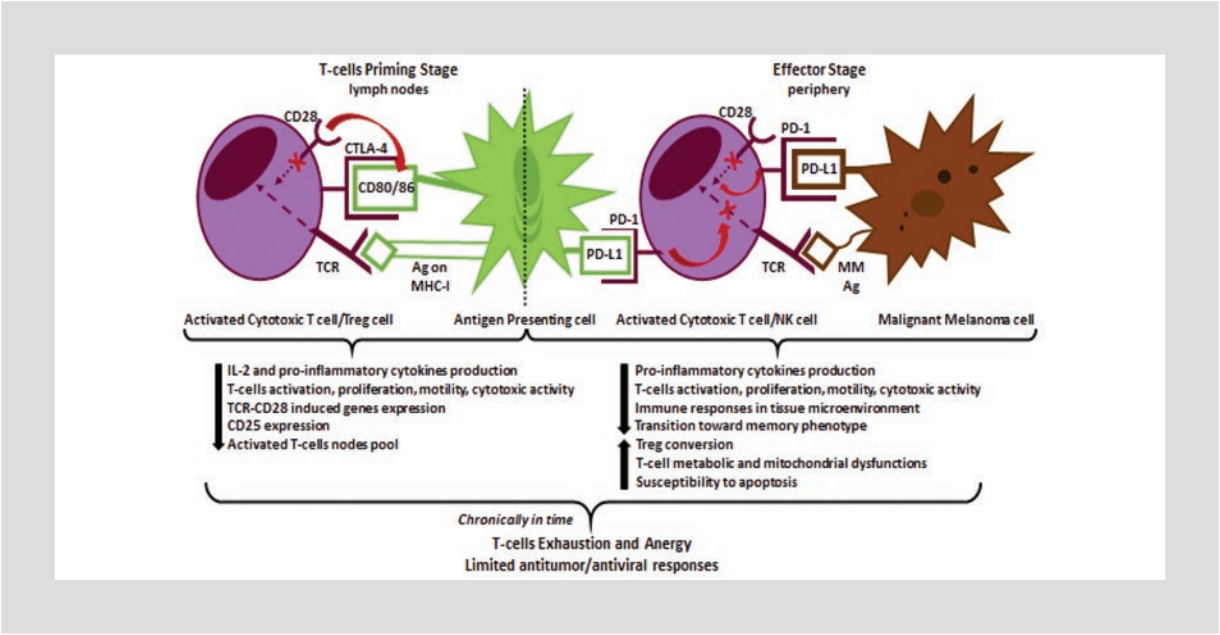

Figure 1. *Major schematic stages of the role of PD-1 and CTLA-4 immune checkpoints in T-cellular responses against viral and tumoral threats. The figure shows some of the major mechanisms by which Cytotoxic T-Lymphocytes Antigen 4 (CTLA-4) and Programmed cell Death protein 1 (PD-1) immune checkpoints limit T-cells activation in melanoma (the same mechanisms are shared with chronic HIV infection). While these pathways normally regulate exaggerate or prolonged T-cells responses, their persistent activation by cancers or chronic infections leads to T-cell exhaustion. During T-cells priming, antigen presenting cells (APCs) present tumor antigen (Ag) to T-cells receptor (TCR) of D8+ cytotoxic T-cells by major histocompatibility complex- I (MHC-I); concurrent costimulatory binding of CD80/86 to CD28 drives lymphocytes towards an activated phenotype. In the presence of CTLA-4, possessing higher affinity than CD28 for CD80/86, the costimulation is prevented and TCR downstream signaling is interrupted, leading to energy. Similarly, in tumor microenvironment APCs and melanoma cells express PD-ligand 1 (PD-L1) which binds to PD-1 of activated T-cells; interfering with TCR-CD28 downstream signaling leading to T-cell functions supression.*

checkpoints for suppressing host immune defences[57-59], proving to possess further mechanisms by which it may facilitate MM development. Nevertheless, at least until recently, immunotherapies have not been investigated in HIV to the same extent as they have been in MM since PLWHA have been considered trial ineligible due to fear of impaired efficacy of ICIs, burst of immune reconstitution inflammatory syndrome (IRIS), or more frequent immune-related adverse events (IRAEs)[6,60,61]. Therefore, most of the available current data come from *in vitro, ex vivo,* and animal models. CTLA-4 is overexpressed on $CD4^+$ T-cells and correlates with loss of HIV-specific T-cells functions and disease progression[57], while PD-1 has been identified as one of the major drivers of T-cell exhaustion and viral latency in HIV/SIV infection[57-59,62,63]. Its expression is the highest on HIV-specific human $CD4^+$ and $CD8^+$ T-cells, correlates with HIV antigen burden and disease progression, and is downregulated by HAART[57-59,62,63]. In SIV-positive macaques, PD-1 blockade reduced plasma viremia, delayed viral rebounds after HAART interruption, and improved overall survival by restoring HIV-specific T- and B-cells functions[58,62]. Preliminary animal models suggest a role for PD-1 blockade also in reducing microbial translocation, immune activation, and incidence of opportunistic infections[58]. So far, 14 cases of metastatic MM treated with ICIs in PLWHA have been described[6,37,64-67]: they were all on HAART but one, and no drug-drug interactions were observed. Pooled viroimmunological dynamics, IRAEs, and treatment outcome are depicted in Figure 2. Despite Chang et al. reported a significantly higher number of IRAEs for PLWHA[60], the vast majority were Grade 1-2 reactions not requiring therapy discontinuation[60] and other studies did not raise concerns about ICIs safety and tolerability[61,68]. No studies observed IRIS nor worrying changes in median $CD4^+$ count and viral load[60,61,68]; on the contrary, favorable $CD4^+$ T-cells increase, similar response rates compared to HIV-negative patients and durable benefit regardless of baseline $CD4^+$ count were documented[60]. Given current evidence, only fear about more frequent IRAEs may be justified, but HIV-related anomaly in absolute number and functions of Th17[69], determinant drivers of IRAEs[70], should raise questions. ICIs safety concerns are currently undergo-

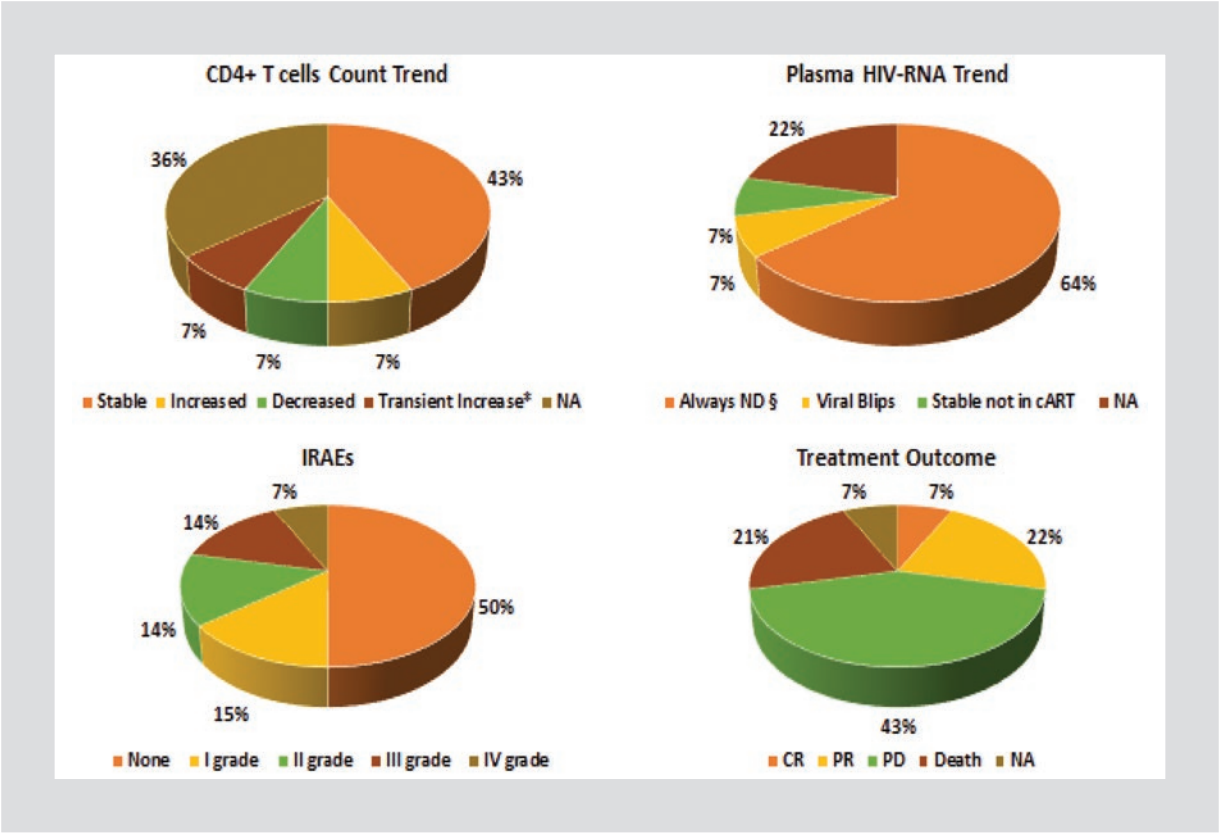

Figure 2. *Pooled clinical and viroimmunological outcomes of the 14 reported cases of metastatic malignant melanoma treated with anti-PD1 and/or anti-CTLA-4 in HIV-positive patients from literature.*
**This single patient was assessed for and presented a transient increase of CD4+ activation, CD4+ total memory and effector memory cells and CD8+ cells after each Ipilimumab infusion[66]; §For 1 patient single-copy assay HIV-RNA, cell-associated unspliced HIV-RNA in CD4+ T-cells and HIV-DNA were assessed after Ipilimumab infusion and found to decrease, increase and remain stable, respectively[66]. NA: Not available data; ND: Not Detectable plasma HIV-RNA; IRAEs: Immune-Related Adverse Events; CR: Complete Response; PR: Partial Response; PD: Progressive Disease.*

ing evaluation through Phase-I trials for PLWHA (NCT03304093; NCT02595866; NCT03239899). Under investigation is also the possible role of ICIs in reverting HIV latency. Dynamics of cell-associated unspliced HIV-RNA in CD4+ T-cells, HIV-DNA, and plasma ultrasensitive or single-copy HIV-RNA have been reported with significantly variable trends after nivolumab or ipilimumab administration for different cancers, including MM, in single case reports[59,66,71-73] and preliminary prospective studies[68] (CROI conference 2018, abstract 656LB), either suggesting or questioning possible effects on destabilizing latent viral reservoir. Recently, pembrolizumab proved to decrease HIV latency establishment when administered before HIV infection in CD4+ T-cells *in vitro*[59]. Whether or not ICIs may be exploited as a "shock and kill" strategy, reverting latency while concurrently reactivating HIV-specific immune responses may also depend on ICIs molecules and doses, presence and type of cancer, concomitantly involved immune checkpoints and corresponding inhibitors, and specific viroimmunological features of subgroups of patients so that no conclusion but hopes can be drawn to date. Furthermore, about 70% of MM shows primary or secondary resistance to PD-1 inhibition[1]. Increased understanding of resistance mechanisms could help in developing predictive biomarkers for ICIs response; among them, PD-1 expression, presence and location of TIL and Th17, and composition of gut microbiome are under investigations[1,69,70]. All of them are variably altered by HIV infection. Studies regarding HIV-related dendritic cells and lymphocyte migration as well as the precise definition of the entity, frequency, and role of TIL in MM of PLWHA may improve our current knowledge about immune-histological prognostic and predictive markers of treatment response, advantaging both HIV-positive and negative patients. Considering further the respective positive and negative correlations between CD4+ count and viral load with PD-1/PD-L1 expression on different cell types[57,58,62,63], the opportunity of ex-

ploiting routine HIV-related parameters as predictive biomarkers of ICIs response should be evaluated. As a gathering framework for all of this, Vitamin D, largely acknowledged for its immunomodulatory properties and highly deficient among PLWHA[74], affects MM onset and prognosis through intricate networks of intra/intercellular pathways[75]. Interactions between Vitamin D and ICIs may take place at different levels including antiproliferative activity against MM cells, PD-L1 upregulation, and Th17 inhibition[75] so that further studies are warranted to define possible adjuvant role of Vitamin D supplementation in MM and HIV.

Conclusions

We have entered a revolutionary era for the treatment of both MM and HIV. Although MM risk factors and incidence among PLWHA are still hazy, considering what follows such a diagnosis, HIV clinicians must keep an extremely high attention threshold toward the problem, becoming experienced with simple tools such as the ABCDE rule and the revised Glasgow checklist in their routine practice; on the other hand, dermatologists and oncologists must recognize that more than ever the management of these patients requires a tailored multidisciplinary approach to be defined case by case. When the Berlin patient underwent stem cells transplant for acute myeloid leukemia, despite the planned selection of a CCR5Δ32-mutated donor, no one would have certainly expected the impressive resulted outcome, the cure of HIV. Taking into account the promising premises, trials based on ICIs and immune-pathological studies specifically retailed for MM among PLWHA are, therefore, heartily solicited being conceivable that they may pave a way forward further Berlin patients.

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