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Neurological manifestations of coinfection with HIV and human T-lymphotropic virus type 1

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HIV-individuals are at risk for human T-lymphotropic virus (HTLV) coinfection and neurological diseases. Little is known about the impact of HAART among coinfected patients. In this study, 47 out of 428 HIV individuals were coinfected with HTLV (10.9%). Coinfection was an independent variable associated with neurological outcome (odds ratio 8.73). Coinfection was associated with myelopathy [chi square (X^2) = 93, $P < 0.001$], peripheral neuropathy ($X^2 = 6.5$, $P = 0.01$), and hepatitis C virus infection ($X^2 = 36.5$, $P < 0.001$). HAART did not appear to protect against neurological diseases and had no impact on HTLV proviral load.

HIV/human T-lymphotropic virus (HTLV) coinfection is expected both in people from HTLV endemic areas and in intravenous drug users. Furthermore, both viruses affect nervous system [1,2]. Little is known about the impact of HAART on HIV/HTLV coinfection, as majority of studies were performed before or in the initial years of HAART [1,3–5]. We aimed to determine the prevalence of HIV/HTLV coinfection and related neurological diseases in a cohort of HIV patients on HAART.

From 2678 HIV individuals, 500 on HAART were randomized to HTLV antibody analysis (HIV/HTLV group or HIV-control group). Additionally, 92 out of 726 HTLV individuals were randomly selected (HTLV group). All participants were submitted to neurological examination, CD4 cell counts, HIV viral load, HCV antibody test, and HTLV proviral load. A specific diagnostic form was used to identify peripheral neuropathy and myelopathy [6,7].

A logistic regression was employed to clarify whether independent variables could predict neurological outcome. We employed two models of multiple binary logistic regression. Potential risk factors were sex, age, CD4 cell count, virological group, and HCV infection. In the first model, the variable virological group contained three categories (HIV/HTLV, HIV, and HTLV group); in the second model, it contained only HIV/HTLV and HIV group. Additionally, we used correlation coefficient to quantify the strength of a relationship between coinfection and neurological outcomes. As variables were dichotomous, φ coefficient was used [$r\varphi = \sqrt{(X^2/N)}$]. Correlations can range from −1 (negative) to 1 (positive relationship). A correlation of 0 indicates no relationship. To interpret the effect size, we used the effect size threshold [8]. We calculated the strength of association ($r\varphi$) using X^2-test. The following score was used to categorize $r\varphi$ value and the effect size: $r\varphi = 0.1$ or less, small; $r\varphi$ more than 0.1 and 0.3 or less, medium; and $r\varphi$ more than 0.3, large effect size.

Four hundred and twenty-eight out of 500 HIV-individuals underwent HTLV testing; 72 were not available to complete the study. HIV/HTLV coinfection was diagnosed in 47 (10.9%). Neurological disease was more prevalent in HIV/HTLV than in HIV group (24 out of 47 vs. 57 out of 381, respectively; $r\varphi = 0.3302$, $X^2 = 51.8$). In logistic regression, age and coinfection were the only variables to predict neurological outcome; odds ratio (OR) for any neurological outcome was 8.73 (confidence interval 4.1–18.4) considering coinfection. Myelopathy was diagnosed in 12 and isolated peripheral neuropathy in another 12 coinfected individuals. Because HCV infection is also associated with peripheral neuropathy, we excluded all HCV-patients. Despite this, peripheral neuropathy was more prevalent in coinfected patients (23 vs. 11.2%; $r\varphi = 0.0818$, $X^2 = 2.7$; see Table 1).

Baseline CD4 cell counts were higher in the HIV/HTLV than in the HIV group, but not after HAART had been initiated. HTLV proviral load was similar in the HIV/HTLV and HTLV groups. Prevalence of peripheral neuropathy was higher in coinfected compared with HTLV patients ($r\varphi = 0.2260$, $X^2 = 7.1$, $P = 0.007$). Otherwise, myelopathy was more prevalent in the HTLV than in the HIV/HTLV group ($r\varphi = 0.1838$, $X^2 = 4.7$, $P = 0.02$).

HIV/HTLV coinfection was diagnosed in 10.9% of HIV-individuals on HAART from an HTLV endemic area. Coinfected patients were more likely to have peripheral neuropathy, myelopathy, and HCV infection. Furthermore, neither HTLV proviral load nor CD4 cell counts were influenced by HAART. Perhaps, the higher CD4 cell counts in coinfected patients reflect HTLV-1-associated lymphocyte proliferation; CD4 cell count cutoff values should be reviewed in this setting [9].

HTLV-1 is the causative agent of HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP).

Table 1. Clinical and laboratorial characteristics of the HIV/human T-lymphotropic virus, HIV control, and human T-lymphotropic virus control groups.

	HIV/HTLV group ($n=47$)	HIV group ($n=381$)	HTLV group ($n=92$)	X^2 (P)
Age	47.6 (SD 8.8)	41.7 (SD = 9.6)	52.2 (SD = 14.5)	NA ($P=0.004$)
HTLV serotype	34 HTLV-1 (72%) 3 HTLV-2 (6.4%) 5 HTLV-1/2 (10.6%) 5 Indeterminate (10.6%)	NA	87 HTLV-1 (94.6%) 3 HTLV-2 (3.3%) 2 HTLV-1/2 (2.2%) 0 Indeterminate	
HCV+	31.9%	7.9%	7.6%	36.5 ($P<0.001$)
Nx disease	24 (51%)	57 (15%)	NA	51.8 ($P<0.001$)
PN	12 (25%)	52 (13%)	NA	6.5 ($P=0.01$)
Myelopathy	12 (25%)	2 (0.5%)	NA	93 ($P<0.001$)
1. CD4 cell count	385 (SD = 108)	281.5 (SD = 146)	NA	NA ($P=0.02$)
2. CD4 cell count	516 (SD = 302)	448.5 (SD = 212)	NA	NA ($P=0.5$)
HTLV PVL	6.1	NA	7.2	NA ($P=0.17$)

Age, median age of patients (SD); HCV+, HCV infection; HTLV PVL, median human T-lymphotropic virus proviral load per 100 leukocytes; Nx disease, number of patients with some neurological disease; PN, number of patients with peripheral neuropathy; 1. CD4 cell count, median CD4 cell count at admission/μl; 2. CD4 cell count, median CD4 cell count on neurological assessment/μl.

Additionally, other neurological conditions have been associated with HTLV-1, emphasizing its ability to affect the nervous system [10]. Noteworthy, a high proviral load is associated with the development of neurological diseases [11].

Similarly, several HIV-neurological diseases have been described since the beginning of HIV epidemic. HIV has been associated with vacuolar myelopathy that is clinically similar to but histopathologically distinct from HAM/TSP. In pre-HAART era, about 10% of AIDS patients were affected by vacuolar myelopathy, but nowadays it is rarely diagnosed.

It is estimated that the lifetime risk of HAM/TSP in HTLV-1 individuals is around 2%, but there are evidences that the rates are higher in coinfected patients; this increased risk may result from upregulated HTLV-1 levels, as suggested by the finding that HTLV-1 tax/rex mRNA expression levels are higher in coinfected patients [12]. In addition, HTLV-1 proviral load might increase during immune reconstitution with HAART owing to expansion of the reservoir of CD4 cells containing HTLV-1 provirus [13]. It is unknown whether HAART effects play a role in the neuropathogenesis of HTLV diseases. However, as patients on HAART survive longer, long-term complications, such as myelopathy and peripheral neuropathy, might emerge.

Berger *et al.* [14] were the first to report that HIV could increase susceptibility to the development of myelopathy in coinfected patients. They described four coinfected patients and all except one had a myelopathy similar to HAM/TSP. In another study in the pre-HAART era, myelopathy was more prevalent in coinfected patients (11 out of 15 coinfected patients, OR = 14, $P<0.00004$) [15].

Beilke *et al.* [3] described four cases of myelopathy among 41 HIV/HTLV-1 patients, wherein only two of those were taking antiretroviral drugs (zidovudine as monotherapy). In our cohort, all patients were using HAART and 12 (25.5%) had myelopathy. Whether HAART predisposes coinfected individuals to develop myelopathy is still a matter of speculation.

Isolated peripheral neuropathy has also been described in association with HTLV. Zehender *et al.* [16] studied 30 HIV/HTLV-2 patients and reported a higher frequency of peripheral neuropathy (OR 3.3, $P<0.009$). In our cohort, peripheral neuropathy was also more prevalent in coinfected individuals even when we excluded HCV patients. It is noteworthy that unlike the report of Zehender *et al.*, majority of our coinfected patients were infected with HTLV-1, highlighting its role in the pathogenesis of peripheral neuropathy as suggested [10].

Summarizing, we found a 10.9% prevalence of HIV/HTLV coinfection in a cohort of HIV individuals from a HTLV endemic area. Coinfection was associated with an increased risk of neurological diseases. HAART did not appear to protect against neurological diseases and had no impact on HTLV proviral load and CD4 cell counts. It remains an open question whether higher prevalence of neurological diseases was due to longer survival of HIV-patients on HAART. If this idea proves to be true, we should expect an increasing number of neurological complications among coinfected individuals in the future.

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There are no conflicts of interest.

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Anogenital pseudotumoral herpes and HIV infection: a new challenge for diagnosis and treatment

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HIV-infected patients may develop rare anogenital pseudotumoral herpes potentially mimicking epidermoid carcinoma. We assessed treatment in five new cases with a median follow-up of 3.3 years. Recurrence and clinical nucleoside analog resistance were observed in all patients. All drug treatments were only temporarily curative and clinical responses varied between patients and recurrences. Foscavir seemed to be the most appropriate second-line treatment and cidofovir or thalidomide should be considered as alternative treatments.

Genital herpes simplex virus (HSV) may be deceptive in HIV-infected patients [1]. Chronic HSV infection masquerading as carcinoma vegetans was first described in 1983 by Leming *et al.* [2]. Thirty-three cases in HIV-infected patients [3–22] and seven in immunocompromised patients without HIV infection [2,23–28] have since been published. We report five new HIV-related cases, focusing in treatment options and long-term follow-up.

Between 2007 and 2009, we identified five cases of pseudotumoral herpes in a cohort of more than 500 HIV-infected patients. Tumoral lesions with HSV infection documented by PCR and immunochemistry on a proper excisional biopsy specimen, with histological features excluding invasive carcinoma, were considered to be pseudotumoral herpes. Clinical data were extracted retrospectively.

The patients studied were four women and one man, aged from 39 to 48 years, all originally from Congo. Highly-active antiretroviral therapy had increased their CD4 cell counts to 154–616 cells/μl, and the virus had been undetectable for the last 6 months. All patients reported previous recurrent genital herpes.

The four women had vulval tumors, with three bifocal perineal localizations. The man had a tumor at the base of the penis that recurred in the perianal area and the groin. The location often changed between recurrences in a given patient. The lesions ranged from 1.5 to 7 cm in diameter.

During the median follow-up period of 3.3 years, all patients presented recurrences, despite surgical excision and/or drug treatment. No event was correlated with CD4 cell count. Recurrences and initial lesions often occurred at different sites. Clinical responses differed considerably between patients and recurrences. The size of the lesion was not predictive of the effect of drug treatment.

Recurrences were observed in all four cases treated by complete local excision, with a disease-free period of 1 month to 4 years.

Oral nucleoside analogs (2–3 g/day valacyclovir) were initially administered to all patients, with no improvement. Case 1 received high doses of intravenous acyclovir (15 mg/kg/8 h for 15 days), but two courses of this treatment did not result in complete remission.

Intravenous foscavir treatment was successful in four patients, who received 80 mg/kg/day until complete remission, with a maximum of 4 weeks of treatment. Complete remission was observed after 15 days (cases 2, 3 and 5), 1 (case 3) and 2 months (case 1; Fig. 1a and b). The disease-free period lasted from 0 to 2 years.

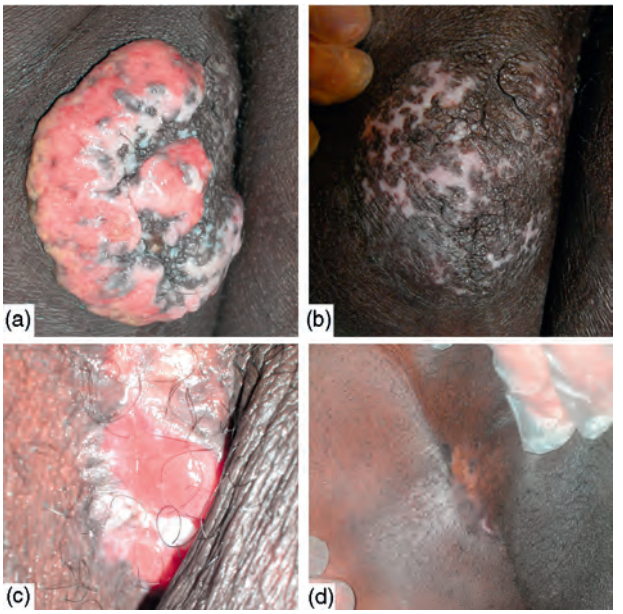

Fig. 1. Perineal pseudotumoral herpes in an HIV-infected woman, (a) before and (b) after one cycle of foscavir; pseudotumoral herpes in an HIV-infected man (c) before and (d) after 5 weeks of 100 mg thalidomide per day.

Three cases received topical treatment with 1% cidofovir, which was applied to lesions, 5 days per week, until complete remission. This drug was used alone (cases 1 and 2) or in combination with valacyclovir (cases 1 and 4). Complete remission was achieved in three patients, after 1–3 months of treatment. A recurrence occurred in one patient after 7 months (case 1), but the reinitiation of topical cidofovir treatment led to secondary cure.

Thalidomide (100 mg/day for 1.5 months) cured recurrences in two cases (Fig. 1c,d), but with one dissociated response in a bifocal tumor. Imiquimod was used in combination with valacyclovir in one case, with the complete resolution of two of the three lesions.

Foscavir was not given in case 4 because renal failure had occurred during previous treatment with foscavir for chronic genital herpes. No adverse effects of any of the treatments used were reported during this study.

It is difficult to compare the results of different studies because diverse treatments are administered and follow-up times are short [9]. Whatever the treatment, lesions often recur in the longer term.

Surgery provides immediate resolution of the lesion but does not protect against short-term recurrence, with possible problems of surgical closure in cases of large and/or periorificial lesions [11]. In our opinion, drugs should, therefore, be preferred for first-line treatment.

Nucleoside analogs are the approved first-line treatment for HSV infection. Unfortunately, such treatments decrease the size of most pseudotumoral lesions but do not eliminate them completely. This persistence of tumors may be accounted for by the presence of mixed resistant and wild populations of HSV [15], and may explain why acyclovir continues to be efficient at preventing other forms of herpes.

For patients displaying either resistance or an inadequate response to nucleoside analogs, intravenous foscarnet is recommended. We report the largest ever series of cases of pseudotumoral herpes treated with foscavir. Our experience and published findings suggest that this drug should be offered as a first-line intravenous treatment.

Topical treatments have been developed because relapses are frequent and systemic treatments have potential side effects. Topical applications of 1–2% cidofovir and 2.4% foscarnet have been reported to be effective. We consider such treatments to be of potential value when used in combination and/or in relay with systemic antiviral treatment. Immunomodulation treatments have also recently been tested. Interferon-α is produced principally by plasmacytoid dendritic cells, which are lacking in patients with AIDS; this cytokine plays a critical role in the control of viral infection. Imiquimod has been successfully used in three published cases [16,18] and in case four reported here.

Thalidomide is known to downregulate proinflammatory cytokines and to be antiangiogenic, antiproliferative and proapoptotic. Following the successful treatment of recurrent aphthous ulceration in HIV-infected patients [29] with thalidomide, this drug was successfully used to treat five HIV-infected individuals with genital hypertrophic herpes [14], and two further cases treated by us. As thalidomide may exacerbate the immunodeficiency associated with HIV and/or the secondary effects of some antiviral drugs, we restrict its use to cases of resistance to systemic antiviral drugs and multiple recurrences.

Finally, if the lesion does not regress rapidly despite the use of these various drug treatments, surgery should be carried out to prevent the misdiagnosis of carcinoma.

In HIV-infected patients with a good immune status and recurrent genital herpes, pseudotumoral herpes should be considered on the basis of a proper excisional biopsy, in the differential diagnosis of anogenital carcinoma, to prevent unnecessary major surgery. The disparity of the results obtained for treatments that were only temporarily curative and the short follow-up period for this series made it impossible to draw firm conclusions about treatment. However, we suggest that drugs should be favored as a first-line treatment, with surgery limited to small or resistant lesions.

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