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Contributing awareness of autoimmune hepatitis in HIV patients

Alterations in liver function tests (LFTs) are frequent in people living with HIV, being present in 21–32% of them. This alteration can be due to a chronic coinfection with hepatitis B virus or hepatitis C virus (HCV), drug liver toxicity, neoplasms and, rarely, autoimmune diseases [1,2]. Autoimmune hepatitis (AIH) is a chronic, progressive hepatitis of unknown cause. The diagnosis is based on the histology, clinical manifestations, circulating autoantibodies and abnormal levels of serum globulins [3]. AIH has been rarely described in HIV-infected patients. Our review of the literature has identified 34 reported cases [4–20]. We contribute with seven cases from our cohort, the second largest series described in HIV-infected patients, and we also present a review of the literature.

A retrospective study from May 2007 to 31 December 2016 was carried out in the HIV Unit of Hospital Clinic in Barcelona, where a cohort of 5000 HIV-positive patients is followed.

Seven patients with abnormal liver enzymes and positive auto antibodies were included in this case series. Table 1 summarizes demographic and clinical features of these patients.

Six patients had undetectable HIV viral load at presentation. $CD4^+$ cell count ranged from 534 to 1175 cells/μl (median 899 cells/μl).

Five of the patients fulfilled the revised score for the diagnosis of AIH [3]. The other two were considered as probable AIH.

Four patients presented HCV coinfection. Two were receiving treatment with peg-interferon when LFT elevation started and treatment had to be interrupted. The third patient achieved sustained viral response 4 years before the LFT elevation, and the last one had and active HCV infection at the time of LFT alteration and the HCV was treated when the AIH was in clinical remission. This was the only symptomatic patients, presenting severe hepatitis with jaundice and international normalized ratio (INR) prolongation.

Regarding antiretroviral therapy, five of the patients were on the same antiretroviral regimen before developing LFT alterations (between 11 and 86 months). Two of them presented LFT elevation a few months after an antiretroviral treatment switch. In one patient, antiretroviral was switched to the previous one, suspecting-related toxicity, without improvement after the change. In the other one, the same antiretroviral treatment was maintained. In both cases, AIH was confirmed by biopsy, and both improved with specific AIH medications.

Six patients had elevated IgG titres. Five had both antinuclear antibodies (ANA) and smooth muscle antibodies (SMA) antibodies; one of them had only ANA and the last one exclusively presented SMA. One of them also had antisoluble liver antigen autoantibodies and other showed antiliver cytosol-1. Only four of the patients underwent a liver biopsy, being all of them compatible with AIH (interface hepatitis and lymphoplasmocytic infiltrates).

Pharmacological therapies for AIH are recorded in Table 1. One patient presented spontaneous remission without specific treatment. None of the patients developed complications related to immunosuppressive treatment.

We found in the literature 34 cases of AIH related to HIV infection, and a total of 17 published articles. AIH was predominant in female patients, with a median age of 42 years (29–65 years). The HIV viral load was undetectable in most cases and the $CD4^+$ cell count was over 150 cells/μl in the onset of AIH. Two severe cases of AIH related to HIV-infected patients have been reported. The first one with acute liver failure and death and the second one required liver transplantation. Treatment with prednisone and azathioprine proved good response in the rest of the cases. As in our cohort, a case with spontaneous remission without treatment was described [6].

Some publications have illustrated the triggers of AIH in HIV-infected patients; one of them is HIV itself [2,17]. Two reports of interferon-induced AIH in coinfected patients with HIV and HCV have been described [15,16].

Recently, two cases of AIH in the context of HCV treatment with new direct-acting antivirals, have been published. Nevertheless, these cases have been described in patients without HIV infection [21,22].

The most reported trigger is the HIV-associated to immune reconstitution syndrome, a viral response to ARV therapy and clinical deterioration of an infectious or inflammatory condition temporally related to antiretroviral initiation, without other explanation for the symptoms [13]. Ten reports describe immune reconstitution-related AIH [5–14].

Finally, drugs can have direct cytotoxic effect and lead to drug-induced AIH, which is a well described clinical

Table 1. Demographic and clinical features of study patients.

Case	1	2	3	4	5	6	7
Age	45	55	43	47	55	49	36
Sex	M	F	F	M	F	M	M
Race	White	White	White	White	White	White	White
Alcohol intake	Occasional	No	No	No	No	No	No
Nadir $CD4^+$ cell count (cells/μl)	418	141	344	114	398	781	220
$CD4^+$ at presentation	734	696	1166	1175	1128	859	534
HIV viral load (copies/ml)	<37	91	<50	<37	<37	<37	<37
ARV treatment	Atripla	Kaletra + Truvada	Kivexa + Atazanavir	Kivexa + Atazanavir	Atripla	Kivexa + Raltegravir	Kivexa + Edurant
Duration of ARV regimen at LFT elevation (months)	48	24	60	86	18	11	4
Duration of any ARV (years)	10	24	19	18	18	14	8
Coinfection	No	HCV	HCV	No	HCV	HCV	No
Laboratory tests at presentation							
AST (IU/l and ×ULN)	71 (×1.77)	200 (×5)	389 (×9.7)	121 (×3)	207 (×5)	1135 (×28)	178 (×4.5)
ALT (IU/l and ×ULN)	193 (×4.8)	299 (×7.5)	300 (×7.5)	242 (×6)	343 (×8.5)	583 (×14.5)	373 (×9)
ALP (IU/l and ×ULN)	250 (×2)	337 (×3)	480 (×4)	162 (×1.5)	311 (×2.7)	184 (×1.6)	151 (×1.3)
IgG (g/l)	15	–	26	12	15.2	17	20
Positive autoantibodies	ANA 1/640 ASMA 1/80 (anti f-actin)	ANA 1/160 ASMA 1/80 (anti f-actin) anti-LC	ANA 1/640 ASMA 1/160 (anti f-actin)	ANA 1/640	ANA1/80 ASMA 1/80 (anti f-actin) anti-SLA	ASMA 1/80	ANA 1/640 ASMA 1/320
R value (ALP ÷ ALT)	1.295	1.127	1.600	0.669	0.907	0.316	0.405
Laboratory tests after treatment							
AST (IU/l)	17	62	36	23	25	151	29
ALT (IU/l)	27	66	42	25	17	122	24
ALP (IU/l)	158	175	225	137	114	172	94
Histology	–	Compatible with AIH	–	Compatible with AIH	–	Compatible with AIH	Compatible with AIH
AIH SCORE (pretreatment)	12 (prob)	11 (prob)	9 (prob)	13 (prob)	15 (prob)	11 (prob)	15 (prob)
AIH simple score (pretreatment)	5 (prob)	5 (prob)	4	6 (def)	6 (def)	5 (prob)	7 (def)
AIH treatment	None	PDN + AZA	PDN + AZA	PDN	PDN	PDN	AZA + UDCA

Revised score: 10–15 probable, more than 15 definite AIH. Simplified score: at least six probable AIH, at least seven definite AIH. AIH, autoimmune hepatitis; ALP. alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibodies; anti-LC, antiliver cytosol; anti-SLA, antisoluble liver antigen; ARV, antiretroviral; ASMA, antismooth muscle antibodies; AST, aspartate aminotransferase; AZA, azathioprine; HCV, hepatitis C virus; LFT, liver function test.; PDN, prednisone; UDCA, ursodesoxicolic acid; ULN, upper limit of normal.

entity. There is one description in the literature of AIH secondary to an antiretroviral medication change in the series published by Kia *et al.* [4], but not directly related to any specific antiretroviral medication.

The concern about treating HIV patients with immunnossupressors, in our experience, as in other reported cases is good. No complications have been seen in well controlled HIV patients.

Consideration of this uncommon, but potentially treatable clinical entity should be included in the differential diagnosis of LFTs elevation in the course of HIV infection.

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Conflicts of interest

There are no conflicts of interest.

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Acute myocarditis after switch to dolutegravir: a reminder of potential toxicity of integrase inhibitor-including HAART

The spectrum of cardiac disease that can occasionally complicate the course of HIV infection is broad and varied. Focal myocarditis was not an unusual autopsy finding in the pre-HAART era [1], although clinically evident disease is rare. Myocarditis in HIV-infected patients occasionally results from an infectious [2] or neoplastic [3] insult. A direct or indirect effect of HIV itself on myocardial cells, as well as selected nutritional deficiencies, may also play a role in heart muscle disease in some HIV-infected patients [4]. Antiretroviral therapy, most notably regimens that include zidovudine, a drug known to induce toxic myopathy, has been reported as a potential cause of cardiomyopathy in individual patients [5,6]. Recently, Mahlab-Guri *et al.* [7] reported two cases of severe myocarditis associated with the integrase inhibitor (INI) dolutegravir. An additional patient is known to have been diagnosed with acute myocarditis while on a dolutegravir study [8]. We wish to report the case of a Brazilian HIV-infected man who developed acute myocarditis a few weeks after switching his antiretroviral therapy to a dolutegravir-including regimen.

A 35-year-old HIV-infected white male patient presented with acute precordial and retrosternal pain that started 90 min after preforming vigorous-intensity physical activity (running). The pain radiated to the right mammary and palmar region. There was no preceding fever, constitutional, or cardiovascular symptoms. He was an otherwise healthy, athletic man who engaged in regular physical activity. The patient did not smoke, had no history of hypertension, alcohol, cocaine, or other illicit drug use, and did not use athlete performance or dietary supplements. He had no family history or other risk factors for cardiovascular disease other than HIV infection and antiretroviral treatment. The diagnosis of HIV infection had been made 6 years previously when he developed an acute retroviral syndrome and seroconversion of the previously negative HIV serologies was documented. Two months later, the HIV plasma viral load was 21 968 (4.34 log) copies/ml and the $CD4^+$ cell count was 420 cells/μl. An antiretroviral regimen consisting of lamivudine, tenofovir, and efavirenz was then initiated. Transient, generalized rash attributed to efavirenz was recorded 8 days after treatment initiation. Treatment was not interrupted and the plasma HIV viral load dropped to consistently bellow detection limits. Secondary syphilis was diagnosed and treated 5 years earlier. Six months before the current presentation, the $CD4^+$ cell count was 687/μl. Two