Severe strongyloidiasis in AIDS: relative risk obscured by absolute rarity

*Strongyloides stercoralis* infects millions of people worldwide, and is mostly endemic in the tropics and subtropics. It can complete its life-cycle within a human host (auto-infection); hence, carrier status may be lifelong [1]. Carriers with compromised immunity are at risk for acceleration of the auto-infective cycle, resulting in a clinical syndrome termed hyperinfection. Moreover, disseminated disease can occur whenever larvae migrate to distant organs such as the brain, liver or kidney. In strongyloides hyperinfection and dissemination (SHaD), numerous larvae are found in the lungs and gastrointestinal tract. Autoinfection (mostly corticosteroid therapy) is the main risk factor for SHaD in developed countries. Infection with human T-lymphotropic virus type 1 (HTLV-1) also correlates with increased risk of SHaD [2]. The mortality rate of SHaD is above 60% [3].

Since the emergence of AIDS, there has been an ongoing dispute in the medical literature regarding the role of advanced HIV disease as a risk factor for SHaD. Initially, SHaD was listed as an AIDS-defining illness following the prediction that it would be very common among AIDS patients due to the overlap in the geographical endemicity of HIV and *Strongyloides stercoralis*, and the role of T-cell immunity dysfunction leading to SHaD [4]. However, over the years, only several dozen cases of SHaD in AIDS patients have been described in the medical literature, and some of them were related to concomitant corticosteroid use or to immune reconstitution syndrome [3,5,6]. This relative paucity of SHaD cases in AIDS was suggested to be due to the preservation of type 2 T-helper cell activity in HIV disease [7]. Additionally, it was suggested that in AIDS patients the development of *Strongyloides stercoralis* larvae into noninfectious rather than infectious forms is favored [8].

Ultimately, not only was SHaD removed from the list of AIDS-defining illnesses, but AIDS was no longer considered an established risk factor for SHaD. Some current medical texts question or even dismiss the role of AIDS as an independent risk factor for SHaD [9,10].

In Israel, immigrants from Ethiopia, a country endemic for *Strongyloides stercoralis*, are often diagnosed as *Strongyloides stercoralis* carriers, sometimes decades after immigration. In a survey conducted in 1989, 4.5% of more than 5000 single stool samples of newly arrived immigrants were found positive for *Strongyloides stercoralis* larvae [11]. The rate of HIV infection in immigrants from Ethiopia is around 1.8% [12]. In contrast, their rate of HTLV-1 infection is negligible [13].

Kaplan Medical Center is a 550-bed secondary care institution that serves a population of 700 000, among them about 20 000 Jews of Ethiopian descent, nearly half of them Ethiopian-born. The affiliated HIV clinic follows around 700 HIV carriers of Ethiopian descent. Most patients are highly compliant, but 20–30 patients present each year with symptomatic disease, mostly due to low compliance or as a newly diagnosed case. Over the last 13 years, in a cohort of 307 admissions due to complications of HIV in this population, we identified eight cases of SHaD. All had a CD4⁺ cell count less than 120. None received immunosuppressive therapy. Five of these patients were tested for HTLV-1, and found negative. The diagnosis of SHaD was based on the identification of filariform larva in appropriate specimen obtained according to the presenting clinical syndrome. The pertinent clinical and laboratory characteristics of each patient are presented in Table 1. Five additional cases of SHaD were diagnosed in this time in HIV negative Ethiopian-born patients with established risk factors (not shown).

The lower than expected incidence of SHaD in AIDS patients in endemic countries may indeed be due to the above mentioned immunologic factors or host–pathogen interactions. It is suggested that it can also be in part related to the under diagnosis or misdiagnosis of this rare, highly fulminant and clinically nonspecific syndrome. This trend may be further perpetuated by the dismissal of SHaD as a direct consequence of AIDS in the medical literature. Nonetheless, the paucity of diagnosed cases should not have been interpreted as low relative risk. The occurrence of SHaD in HIV carriers only upon progression to severe immunosuppression, as shown herein, directly defines AIDS as a risk factor.

Re-inclusion of AIDS as a risk factor for SHaD should be reconsidered. We further call for clinician awareness of the possibility of this co-infection in advanced AIDS patients who reside in, or emigrated from endemic areas. Above all, the delayed diagnosis and poor prognosis of SHaD calls for prevention through preemptive screening for *Strongyloides stercoralis* and subsequent deworming of all HIV patients at risk.
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Table 1. Characteristics of the 8 AIDS patients with severe strongyloidiasis in Kaplan Medical Center, Rehovot, Israel (2002–July 2015).

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>CD4+</th>
<th>Clinical presentation</th>
<th>Diagnosis</th>
<th>HTLV-1 serology</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>35/F</td>
<td>91</td>
<td>Fever, vomiting and hematemesis, abdominal pain, <em>E. coli</em> bacteremia and respiratory distress.</td>
<td>Duodenal biopsy</td>
<td>Neg.</td>
<td>Death</td>
</tr>
<tr>
<td>44/M</td>
<td>70</td>
<td>Recurrent admissions due to fever, abdominal pain, vomiting, respiratory distress and cough.</td>
<td>Intestinal biopsy</td>
<td>ND</td>
<td>Death</td>
</tr>
<tr>
<td>49/M</td>
<td>10</td>
<td>Vomiting and diarrhea. <em>E. coli</em> bacteremia of unknown origin.</td>
<td>Stool O&amp;P</td>
<td>Neg.</td>
<td>Death in 1 month</td>
</tr>
<tr>
<td>35/F</td>
<td>1</td>
<td>Vomiting and diarrhea. <em>E. coli</em> bacteremia of unknown origin.</td>
<td>Duodenal aspirate</td>
<td>ND</td>
<td>Death in 2 months (sepsis-like syndrome and respiratory failure)</td>
</tr>
<tr>
<td>36/F</td>
<td>72</td>
<td>Postpartum sepsis, <em>K. pneumonia</em> bacteremia and respiratory failure.</td>
<td>Gastric aspirate</td>
<td>Neg.</td>
<td>Death</td>
</tr>
<tr>
<td>44/F</td>
<td>56</td>
<td><em>E. coli</em> bacteremia followed by ESBL pos. <em>E. coli</em> meningitis.</td>
<td>Stool O&amp;P + pos. PCR in CSF</td>
<td>ND</td>
<td>Death</td>
</tr>
<tr>
<td>37/F</td>
<td>43</td>
<td>Abdominal pain and hematemesis, followed by sepsis-like syndrome and respiratory failure.</td>
<td>Sputum</td>
<td>Neg.</td>
<td>Death</td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid; ESBL, extended spectrum beta-lactamase; ND, not determined; O&P, ova and parasites.

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**Conflicts of interest**

There are no conflicts of interest.

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**References**


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**Atazanavir use and carotid intima media thickness progression in HIV: potential influence of bilirubin**

Cardiovascular disease (CVD) deaths are an important cause of mortality in HIV-infected patients. As a predictor of cardiovascular outcome, carotid intima media thickness (CIMT) has been shown as an independent predictor of CVD events [1]. We read with great interest the study by Stein et al. [2] in which they report that treatment-naive HIV-infected individuals randomized to an initial antiretroviral therapy (ART) regimen including
atazanavir/ritonavir (ATV/r) experienced slower progression of CIMT than those assigned darunavir/ritonavir (DRV/r) or raltegravir. Accordingly, we conducted retrospective analysis of the longitudinal Hawaii Aging with HIV Cardiovascular Study to assess the relationship of ATV/r on CIMT in a cohort of HIV-infected individuals on stable ART. Additionally, the baseline plasma biomarkers and total serum bilirubin were analyzed for differences between participants currently receiving ATV/r compared with participants not on ATV/r. Group differences between participants receiving ATV/r versus those not taking ATV/r were assessed using multivariable regression.

A total of 62 study participants enrolled in the Hawaii Aging with HIV Cardiovascular Study had available CIMT measures at baseline and year 2. A total of 11 study participants (18%) were receiving ATV/r and 51 (82%) were not receiving ATV/r (non-ATV/r). In the non-ATV/r group, 55% were on non-nucleoside reverse transcriptase inhibitors, 18% were on a protease inhibitors other than ritonavir as a booster, and none were on an integrase inhibitor. Entry criteria for the cohort required study participants to be on stable ART for at least 3 months, and 82% of these study participants were virologically suppressed with a plasma HIV RNA level of less than 50 copies/ml on ATV/r and 82% were suppressed on non-ATV/r. The median CD4 cell count was 370 cells/μl (Q1: 249, Q3 : 612) for the ATV/r group and 502 (349, 660) cells/μl for the non-ATV/r group (P = 0.10). Baseline median Framingham Risk Score were: ATV/r 0.03 (0.01, 0.14), non-nucleoside reverse transcriptase inhibitors 0.04 (0.02, 0.14), and protease inhibitors 0.08 (0.04, 0.20) (P = 0.53). Median duration on ART did not differ between the ATV/r and non-ATV/r groups, 14.2 years (6.4, 14.6) versus 12.6 years (7.8, 16.2), respectively. The median in CIMT over 2 years was 0.009 mm (0.005, 0.022) for the ATV/r group compared with 0.022 mm (0.013, 0.034) in the non-ATV/r group (P < 0.001). ATV/r use continued to be associated with slower CIMT progression compared with the non-ATV/r group after adjusting for age, sex, hypertension, diabetes mellitus, current smoking status, low-density lipoprotein cholesterol, and systolic blood pressure (P = 0.012) (Table 1).

The rate of CIMT change was similar to the findings presented by the A5260 study. Interestingly, we also found a significant correlation between increasing baseline total serum bilirubin level and reduced CIMT progression (Table 1). The A5260 study reported a significant reduction in CIMT with bilirubin as a binary cut-off point of 0.6 mg/dl at weeks 4 and 24, with similar trends seen for higher cut-off points. Bilirubin has an antioxidant effect as well as an association with reduced inflammation [3]. The antioxidant and anti-inflammatory effects of bilirubin metabolism have been reported with lower serum IL-6, C-reactive protein (CRP), and serum amyloid P (SAP) level [4–6]. In our study, log total bilirubin levels correlated with log SAP (r = −0.329, P = 0.009) and log CRP (r = −0.288, P = 0.023), but not with other biomarkers such as IL-6, matrix metalloproteinase-9, tissue plasminogen activator inhibitor-1, soluble intercellular adhesion molecule, soluble vascular cell adhesion molecule, myeloperoxidase, monocyte chemoattractant protein-1, acute phase protein (Serum amyloid A, vascular endothelial growth factor). Total bilirubin was also negatively correlated with the intermediate (CD14+CD16+) monocyte subset (r = −0.267, P = 0.048). None of these baseline biomarkers or intermediate monocyte subsets were associated with change in CIMT [7]. The article by Stein et al. [2] did not report on the correlations between bilirubin, biomarkers, and monocyte subsets. Although there were no direct associations between biomarkers and monocyte subsets, we still speculate a potential role of total bilirubin in slowing CIMT progression. Hereditary conditions such as Gilbert syndrome, where serum bilirubin levels in these individuals are elevated, are reported to have much lower rates of ischemic heart disease compared with the general population [8]. A cardioprotective role of bilirubin, heme oxygenase, and UDP-glucuronosyltransferase has been speculated [9]. This retrospective study is limited by its small sample size and nonrandomized design. Despite these differences, our findings have important implications and suggestions for future research. Our data demonstrated similar CIMT findings with ATV/r as in the A5260 study. The exact mechanism of ATV/r on CIMT progression remains unclear, but total serum bilirubin may play a potential role in modifying CVD risk.

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### Conflicts of interest

There are no conflicts of interest.

<table>
<thead>
<tr>
<th>Predictor of interest</th>
<th>β</th>
<th>Standard error</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current atazanavir use</td>
<td>−0.269</td>
<td>0.103</td>
<td>0.012</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>−0.123</td>
<td>0.056</td>
<td>0.031</td>
</tr>
</tbody>
</table>

Change in carotid intima media thickness has been log10 transformed to adjust for normality. P ≤ 0.05 was regarded as statistically significant. Risk factors adjusted for both the models include: age, sex, hypertension, diabetes mellitus, current smoking status, low-density lipoprotein cholesterol, and systolic blood pressure.

### Table 1. Multivariable linear regression of 2-year change in carotid intima media thickness of the common carotid artery predicted by atazanavir use and separately for baseline total bilirubin as a continuous variable.
Atypical ocular manifestation of primary varicella zoster virus infection as the first manifestation of AIDS

Varicella zoster virus (VZV) infection is a common infection in HIV compromised patients associated with frequent reactivations [1]. VZV ocular involvement in HIV patients most commonly manifests as an acute retinal necrosis with potentially secondary optic neuritis without chiasmal impairment [2], associated with poor prognosis [3]. Isolated retrobulbar optic neuritis damage has been reported in very few cases, all of them with unilateral involvement [3], including only one case in an HIV-infected patient with ophthalmic zoster [4]. Treatment of this severe localization of VZV reactivation in the immunosuppression context is not clearly defined. We report, to our knowledge, the first case of a primary VZV infection, complicated by bilateral retrobulbar optic neuritis, with chiasmal involvement, revealing HIV.

A 42-year-old Afro-Caribbean man, presented with a 7-day history of decrease bilateral visual acuity, vomiting and severe headaches. Past medical history was unremarkable except oral candidiasis 1 month before. At admission, he presented with fever and different-aged vesicular and crusted lesions on the trunk and limbs. His son had been diagnosed with chickenpox 2 weeks before. Neurological examination was normal. Pupil examination demonstrated a sluggish light reflex in the right eye and nonreactive mydriasis in the left eye. Visual acuity was 1.00 LOGMAR in the right eye and 0.5 LOGMAR in the left eye. Slit lamp and fundus examination were normal in both eyes, except for two cotton-wool spots in the right eye. Fluorescein angiography was normal (Fig. 1a). Kinetic visual field showed bitemporal hemianopia with bilateral central scotomas (Fig. 1b, 1, 2) suggestive of bilateral optic neuropathy associated with chiasmal lesion.

Routine blood testing was normal except for liver cytolysis (alanine aminotransferase 6x upper limit normal and lymphopenia (1.22 x 10^3/μl). MRI demonstrated hypersignal and edema of both retrobulbar optic nerves and chiasma in T1 and T2 gadolinium injection (Fig. 1c). These findings were associated with hypersignal of the internal face of the temporal lobe, suggestive of limbic encephalitis (Fig. 1d) associated with a vasculitis. Cerebrospinal fluid (CSF) analysis showed 14 cells/μl with mixed formula, a glucose level of 4.4 mmol/l and protein level of 0.74 g/l. CSF quantitative polymerase chain reactions (qPCR) were negative for herpes simplex virus, cytomegalovirus, Epstein–Barr virus, adenovirus and Toxoplasma gondii. CSF Gram stain, bacterial culture, acid-fast bacilli and fungal stain were negative, as well as the VDLR testing. qPCR for VZV was positive in CSF with more than 25 x 10^6 copies/ml and, in blood, 6125 copies/ml. Presumptive intravenous aciclovir (10 mg/kg/day) was started on day 1 after admission, 2 weeks after first symptoms. Following VZV results, aciclovir dosage was increased (25 mg/kg/8 h) and foscarnet (90 mg/kg/12 h) added. Two days after initiation of antiviral treatment, slit
Lamp examination revealed a bilateral granulomatous keratic precipitates with cellular reaction in the anterior chamber, associated with anterior synechia in the right eye. Topical steroids (dexamethasone) and atropine 1% were added.

HIV-1 test, realized after VZV PCR results, was positive with a plasma viral load (pVL) at 144,050 copies/ml, 4560 copies/ml in CSF and a CD4 cell count of 5 cells/μl. Antiretroviral treatment with tenofovir/emtricitabine (300/200 mg) combined to dolutegravir (50 mg/day) for a rapid effect on HIV pVL was initiated at day 7 as recommended [5].

During the follow-up, visual acuity gradually but slowly improved with, after 3 months, a corrected visual acuity of 20/200 in the right eye, and 20/50 in the left eye. The central scotoma in the right eye decreased in size whereas the one of the left eye disappeared (Fig. 1b, 3, 4). Some degree of bitemporal hemianopsia persisted on final visual field, although it had improved compared with initial visual field. Optical coherence tomography performed after 3 months of follow-up demonstrated early retinal nerve fiber layer loss, diffuse in the right eye, and predominating in nasal quadrant in the left eye. These findings were consistent with bilateral optic neuropathy associated with chiasmal involvement. Secondary prophylaxis by valaciclovir (3 g/day) was initiated at day 65. Two months after cART introduction, the HIV pVL was less than 20 copies/ml, 54 copies/ml in CSF and VZV CSF, 2982 copies/ml and CD4 cell count, 86 cells/μl.

We present the first case of bilateral retrobulbar neuropathy with optic chiasm damage, without retinal necrosis, secondary to a primary VZV infection revealing AIDS. The evolution was favorable, despite a significant therapeutic delay and severe ophthalmological damage. This evolution could be explained by prolonged and high dose antiviral association, associated with a fast HIV virological control by integrase inhibitors.

Management of this entity is difficult due to delay in diagnosis, choice of treatment and secondary prophylaxis and their respective duration.

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