Clinical characteristics of a group of HIV patients with ocular lesions

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Research Article

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Abstract

**Background:** The study was to analyze HIV dynamics across BRB and the relevant risk factors for HIV-associated ocular complications.

**Methods:** This study included a prospective case series of 40 HIV-positive patients with ocular lesions. Clinical and laboratory examinations included plasma and intraocular VL were evaluated.

**Results:** HIV VL on paired aqueous/plasma samples was available for 40 patients. Aqueous VL was negatively associated with ART duration ($p = 0.02$ and $p < 0.05$), plasma VL was independent of ART duration ($p = 0.53$). An aqueous/plasma discordance was found in 19/40 (47.5%) patients, eight of whom (20%) had detectable aqueous VL despite a suppressed plasma VL (escape). There were significant differences in CD4$^+$ T-lymphocyte levels ($p=0.012$ and $p < 0.05$) and ART duration ($p=0.007$ and $p < 0.05$) between the patients with HIV-associated ocular complications and the patients without.

**Conclusion:** This study provides rationale for initiating ART early in the course of infection to reduce HIV VL in the aqueous humor, and raises the possibility of the ocular sanctuary where HIV replicate. Meanwhile, early and standard ART would be optimal option to protect against ocular opportunistic infection.

**Trial registration:** Participants enrolled in the research signed informed consent and the study was approved by the institutional ethics committee of Huashan Hospital affiliated with Fudan University (protocol number: KY2021-837).

Introduction

There is a growing concern about sanctuaries of local human immunodeficiency virus (HIV) replication as it has already been documented for the central nervous system (CNS)(1). HIV might persist in these sanctuaries during antiretroviral treatment (ART) and theoretically cause the generation and dissemination of drug-resistant viruses. It has been found that detectable intraocular HIV viral load (VL) was higher in patients with the absence of retinal lesions, or ocular VL largely exceeded that of plasma(2). Among some patients with uveitis attributed to HIV, aqueous humor sequences had less genetic diversity compared to plasma, aqueous humor HIV sequences were compartmentalized from plasma(3). All these suggest the possibility of the existence of intraocular HIV repository.

The application of ART has effectively controlled the incidence of acquired immune deficiency syndrome (AIDS), and HIV-associated ocular complications have also decreased significantly. However, the latest data showed that 20%-30% patients still suffered from ocular complications, which mainly included opportunistic infections caused by immunodeficiency(4, 5). Our group found that cytomegalovirus retinitis (CMVR) accounted for the first place (about 10.6%), followed by the retinopathy induced by the invasion of HIV, which was associated with severe vision impairment (9.4%)(6).

So, we assessed the clinical characteristics and HIV VL of plasma and aqueous humor in 40 HIV-infected patients and attempted to analyze HIV dynamics across the blood–retinal barrier (BRB). Since the HIV patients suffer from high incidence of ocular complications, we would like to discuss the relevant risk factors and whether it's associated with the persistence of ocular HIV.

Study Design

This is a retrospective study including data recorded from 57 HIV positive subjects for medical consultations and treatments in our institute between 2018 and 2021 due to blurred vision or black shadows. The study was approved by the institutional ethics committee of Huashan Hospital affiliated with Fudan University (protocol number: KY2021-837), and the treatment was performed under the tenets of the Declaration of Helsinki. The patients enrolled in the study signed the written informed consent for the publication of their data and examinations.
Paired blood and aqueous humor were evaluated for HIV VL. HIV VL was quantified in plasma and aqueous humor by COBAS TaqMan HIV-1 Test (Roche Molecular Systems, Inc., Branchburg, New Jersey, USA) with a detection limit of 20 copies/mL both in plasma and aqueous humor. The aqueous humor/plasma ratio of HIV-RNA was calculated, an aqueous humor/plasma ratio > 1 (indicating levels of HIV-RNA in aqueous humor higher than those in plasma) was labeled as a “discordance” between aqueous humor and plasma. Ocular “escape” was defined as detectable aqueous humor HIV VL in the setting of suppressed plasma VL.

**Patient Characteristics**

57 Patients were involved, mostly males (82.5%) with a median age of 44.3 years (IQR 34.0–53.0), females (17.5%) with a median age of 47.6 years (IQR 34.3–70.0), and the majority of them (96.4%) had acquired HIV infection through sexual intercourse. When patients were enrolled, median CD4⁺ T-lymphocyte level was 301 cells/µl (IQR, 183–410), and 33 (57.8%) patients were diagnosed with HIV-associated ocular complication, which included CMVR, acute retinal necrosis (ARN), immune restorative uveitis (IRU), ocular infection of Syphilis and Aeruginosa. Overall, 2 (3.5%) patients have not yet received any antiretroviral therapy, other patients were receiving an ART regimen with a median duration of 34.1 months (IQR, 8.0–36.0).

**Viral Load**

HIV VL on paired aqueous/plasma samples was available for 40 patients. Aqueous VL was detected in 22/40 patients (55%), plasma VL was detected in 22/40 patients (55%), and both can be detected in 14/40 (35%). Median aqueous and plasma HIV VL were 2.44 log₁₀ cp/ml (IQR 1.30–3.60 log₁₀ cp/ml) and 2.10 log₁₀ cp/ml (IQR 1.30–2.74 log₁₀ cp/ml), respectively. Aqueous VL was independent of CD4⁺ T-lymphocyte level (p = 0.28), plasma VL was negatively correlated with CD4⁺ T-lymphocyte levels (p = 0.009 and p < 0.05). Aqueous VL was negatively associated with ART duration (p = 0.02 and p < 0.05), plasma VL was independent of ART duration (p = 0.53).

An aqueous/plasma discordance was found in 19/40 (47.5%) patients, eight of whom (20%) had detectable aqueous VL despite a suppressed plasma VL (escape). The aqueous/plasma discordance was independent of CD4⁺ T-lymphocyte level (p = 0.19) and treatment time (p = 0.24).

**Risk Factors For HIV-associated Ocular Complications**

The patients were divided into two groups according to whether they were diagnosed with HIV-related ocular complications. There were significant differences between the two groups in CD4⁺ T-lymphocyte levels (p = 0.012 and p < 0.05) and ART duration (p = 0.007 and p < 0.05). In patients with HIV-associated ocular involvement and those without, no differences were found in the plasma VL (p = 0.145), aqueous VL (p = 0.062) and aqueous/ plasma VL ratio (p = 0.75) at the time of ocular examination. (The detail is shown in Table 1.)

**Statistics**

Multiple variables per patient and different groups of patients were compared, including the aqueous humor and plasma HIV VL, age, sex, ART duration and CD4⁺ T-lymphocyte levels. Comparisons between groups were performed by means of Student’s t-test for continuous data and chi-square test for categorical data. The relationships between variables were evaluated with Pearson’s correlation analysis. Two-tailed p values < 0.05 were considered statistically significant. Our study was conducted with the approval of the medical ethical committee of Huashan Hospital, Fudan University. All patients were informed about these investigations and their consent was obtained.

**Discussion**
We documented the presence of intraocular HIV in 55% of HIV patients. HIV entrance into the eye was repeatedly reported and was attributed to the entrance of infected lymphocytes. HIV has been found in retina, vitreous humor, iris, cornea, conjunctiva and tears (7–9). Breakdown of BRB was suggested as determinants of the positive intraocular HIV (10, 11), and being on HAART had a significant impact on aqueous humor HIV RNA levels (12). In our study, the HIV VL in the eye showed a negative association with ART duration, indicating that sufficient antiviral therapy would effectively reduce the HIV VL in the eye. This provides further rationale for initiating ART early in the course of infection to inhibit HIV replication in the eye.

In the present study, aqueous/plasma discordance was found in 47.5% of HIV patients and significantly more frequent ($p < 0.0001$) in patients with lower plasma viral load. An explanation for this finding can be offered by the particular structure of the BRB which is characterized by tight junctions and the lack of intercellular pores thereby preventing most molecules from entering the eye (13, 14). Therefore, the presence of BRB plays an important role in reducing drug penetration and suboptimal drug concentration (15), resulting in an incomplete suppression of HIV replication in the eye. Moreover, it's postulated that protease inhibitors and several of the nucleoside analogues have limited penetration into the brain, which is associated with increased HIV VL and mutations in cerebrospinal fluid (16). By inference, the same situation may occur when HIV passes through the BRB, allowing HIV replication and evolution in the eye. So far, the causes of viral persistence in eye are still controversial and not completely understood, paired aqueous/plasma HIV gene sequences would be essential in the future to evaluate viral evolution for further clarifying the question of intraocular repository.

In this study, there's obvious differences in CD4$^+$ T-lymphocyte count ($p = 0.012$ and $p < 0.05$) and ART duration ($p = 0.007$ and $p < 0.05$) between groups with HIV-related ocular complications and those without. Insufficient ART duration and low CD4$^+$ T-lymphocyte count are associated with higher prevalence of ocular manifestation as shown in this study, part of the reason is that patients might have already developed ocular manifestation before initiation of ART. On the other hand, even though patients are on ART and their CD4$^+$ T-lymphocyte count increases, the newly formed lymphocytes are not enough for functional maturity and patients are not protected (17, 18). In clinical work, we found that the treatment of HIV-related ocular infection is a tricky and long-term process, if treated not promptly, vision will be severely damaged, and even lead to blindness. Therefore, early and comprehensive fundus should be routinely examined to detect peripheral lesions for HIV patients. And more importantly, standard ART would be optimal option to build immunity, further to protect against ocular opportunistic infection.

**Declarations**

**Ethics approval and consent to participate** The research was performed under the tenets of the Declaration of Helsinki. The patient enrolled in the study have provided written informed to participate this study.

**Consent for publication** Not applicable.

**Availability of data and material** Not applicable.

**Authors' contributions:** Xin Che and Yang Zhang contributed equally to this work. Zhiliang Wang and Luoziyi Wang contributed equally to this work. Design of the study (XC, ZLW), data collection (XC, YZ, QJL, LZYW), preparation of the manuscript (XC, YZ). All authors have read and approved the manuscript to be published.

**Competing interests** The authors declare no competing financial interests.

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**References**


Table

Table 1. HIV patients were divided into two groups according to whether they were diagnosed with HIV-associated ocular complications. Relevant data about sex, age, plasma HIV load, ocular HIV load, ocular/plasma viral load ratio, CD4+ T-lymphocyte and ART duration of HIV patients.
<table>
<thead>
<tr>
<th>Ocular lesions</th>
<th>CMVR</th>
<th>ARN</th>
<th>IRU</th>
<th>Syphilis</th>
<th>Aeruginosa</th>
<th>RD</th>
<th>DM</th>
<th>Cataract</th>
<th>BRVO</th>
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</thead>
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<tr>
<td></td>
<td>35%</td>
<td>20%</td>
<td>2.5%</td>
<td>2.5%</td>
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<td>10%</td>
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</tr>
<tr>
<td></td>
<td>(14/40)</td>
<td>(8/40)</td>
<td>(1/40)</td>
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<td>(1/40)</td>
<td>(6/40)</td>
<td>(4/40)</td>
<td>(4/40)</td>
<td>(1/40)</td>
<td></td>
</tr>
</tbody>
</table>

HIV-1 associated eye disease
Yes
No

Sex (n)
Male (22) Female (3)
Male (13) Female (2)

0.902<sup>a</sup>

Age (IQR range)
44.04 (33.0, 54.5)
52.2 (48.0, 55.0)

0.048<sup>b</sup>

Median Plasma RNA load (IQR range)
2.11 (1.30, 2.74)
2.07 (1.30, 3.34)

0.145<sup>b</sup>

Median Ocular RNA load (IQR range)
2.73 (1.30, 3.62)
1.96 (1.30, 2.39)

0.062<sup>b</sup>

Ocular/Plasma RNA load (IQR range)
1.47 (0.91, 1.60)
1.34 (0.38, 2.80)

0.75<sup>b</sup>

Median CD4+ T-lymphocyte (IQR range) cells/ul
245 (100, 400)
372 (312, 501)

0.012<sup>b</sup>

Median ART duration (IQR range) (Month)
20.84 (5.50, 36.00)
58.00 (24.00, 108.00)

0.007<sup>b</sup>

<sup>a</sup>chi-square test; <sup>b</sup>t-test.