EClinicalMedicine 31 (2021) 100646

Contents lists available at ScienceDirect

EClinicalMedicine

journal homepage: https://www.journals.elsevier.com/eclinicalmedicine

The value and implementation of routine ophthalmic examination in the era of HAART

Wangting Li[a,1], Xiaoli Wang[b,1,2], Lanqin Zhao[a,1], Duoru Lin[a], Yahan Yang[a], Zhenzhen Liu[a], Xiaohang Wu[a], Jinghui Wang[a], Yi Zhu[c], Chuan Chen[c], Xiayin Zhang[a], Ruixin Wang[a], Ruiyang Li[a], Xiaoman Huang[a], Wenyong Huang[a,2], Haotian Lin[a,d,2,*]

[a] State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, Guangdong, 510000, China
[b] Guangzhou Eighth People's Hospital, Guangzhou Medical University, Guangzhou, Guangdong 510000, China
[c] Department of Molecular and Cellular Pharmacology, University of Miami Miller School of Medicine, Miami, Florida 33136, United States
[d] Center of Precision Medicine, Sun Yat-sen University, Guangzhou, Guangdong, 510000, China

ARTICLE INFO

Article History:
Received 9 June 2020
Revised 31 October 2020
Accepted 2 November 2020
Available online xxx

Keywords:
HIV infection
Chronic diseases
Ocular manifestation
Ophthalmic examination

ABSTRACT

Background: The high prevalence of ocular manifestations (OMs) in patients with human immunodeficiency virus (HIV) infection and chronic diseases such as diabetes has become a global health issue. However, there is still a lack of an appropriate ophthalmic diagnostic procedure for the early detection of OMs in this population, leading to the risk of an irreversible visual impairment that substantially affects the quality of life of these patients.

Methods: The Guangzhou HIV Infection Study was a retrospective study that enrolled hospitalised HIV-infected patients in Guangzhou between January 2005 and December 2016, period corresponding to the highly active antiretroviral therapy (HAART) era in China. We collected data on OMs, systemic diseases, hospitalisation, and demographic characteristics. We classified the patients into 3 groups according to the ophthalmic examination mode they underwent: the non-ophthalmologist examination group (patients hospitalised in 2005–2011 who were only treated by infectious disease physicians), the on-demand ophthalmic examination group (patients hospitalised in 2012–2013 who were referred for a consultation with an ophthalmologist), and the routine ophthalmic examination group (patients hospitalised in 2014–2016 who routinely underwent standard ophthalmic examinations). Binary logistic regression models were used to investigate the factors related to OMs.

Findings: A total of 8,743 hospitalised HIV-infected patients were enrolled. The prevalence of detected OMs were 1.5% in the non-ophthalmologist examination group, 1.9% in the on-demand ophthalmic examination group, and 12.8% in the routine ophthalmic examination group. The odds of detection of OMs were highest in the routine ophthalmic examination group (adjusted odds ratio [aOR]=9.24, [95%CI, 6.51–13.12], compared to the non-ophthalmologist examination group). The detection of all types of OMs increased substantially, with keratitis, retinitis and vascular abnormalities increased the most (by 15.8–20.0 times). In the routine examination group, patients who were older than 50 years, males, with medical insurance, and were not resident in Guangzhou, had higher odds to have OMs. Several systemic diseases also increased the odds of OMs, with the highest odds among patients with a cytomegalovirus infection (aOR=5.59, [95%CI, 4.12–7.59]). Patients with retinitis, retinopathy and conjunctivitis had higher odds of having a $CD4^+$ T cell counts less than 200 cells/μL compared to the patients that did not have these referred OMs.

Interpretation: The implementation of a routine ophthalmic examination has improved the odds of OM detection by approximately 9 times and increased the diagnosis rates of all types of OMs. Therefore, we encourage all HIV-infected patients to undergo regular ophthalmic examinations. Patients with OMs, especially retinopathy and retinitis, need to be evaluated for immune function (such as $CD4^+$ T cell counts) and systemic diseases.

Funding: The Science and Technology Planning Projects of Guangdong Province (2018B010109008), the Key Research Plan for the National Natural Science Foundation of China in Cultivation Project (91846109), the Science Foundation of China for Distinguished Young Scholars (81822010), and the National Natural Science Foundation of China (81770967, 81873675, and 81800810).

* Corresponding author.
E-mail addresses: gddlht@aliyun.com, linht5@mail.sysu.edu.cn (H. Lin).
[1] Co-first authors
[2] Co-senior authors

https://doi.org/10.1016/j.eclinm.2020.100646

Research in context

Evidence before this study

Non-fatal complications of human immunodeficiency virus (HIV) infection, such as ocular manifestations (OMs), substantially affect quality of patient life. We searched PubMed for studies published before Jun 30, 2020, using the search terms "HIV", "AIDS", and "ocular". Up to 48% of HIV-infected patients have OMs in the highly active antiretroviral therapy (HAART) era, and many have already developed visual impairments before they visit a doctor. Moreover, we reviewed the hospital clinical data and found that even in Guangzhou, one of the most prosperous cities in China, less than 10% of OMs were diagnosed and treated in a timely manner.

Added value of this study

To our knowledge, this study is the first to compare different modes of ophthalmic diagnosis in the management of OMs. Moreover, no study has reported the prevalence of OMs in HIV-infected patients in China in the past 5 years.

Implications of all the available evidence

A routine ophthalmic examination is crucial to improve the early diagnosis of OMs; this study provides reliable clinical evidence regarding the management of OMs in patients infected with HIV and patients with other chronic diseases.

1. Introduction

Human immunodeficiency virus (HIV) infection has become a manageable chronic disease with the universal use of highly active antiretroviral therapy (HAART). Mortality has been significantly reduced, but the resulting prolonged life spans have led to an increase in the number of non-fatal complications [1–5], including ocular manifestations (OMs) that seriously affect the quality of patient life [6–13].

Similar to diabetes, HIV infection can cause various OMs, which have become a global health problem in patients with chronic diseases. Although the OMs prevalence has decreased compared to the pre-HAART era, as many as 48% of HIV-infected patients have been diagnosed with OMs in the HAART era [6,11,14-22]. Early diagnosis of OMs is critical for the timely treatment and determination of the prognosis of HIV infection, as the impaired visual function can decrease productivity [9,17,18,23,24], and increase the cost of treatment [25,26].

However, the diagnosis of OMs in HIV-infected patients is often delayed. Many patients with OMs are not diagnosed until a severe visual impairment has developed [6,8-10,18,27]. Methods to balance medical resources and develop appropriate ophthalmic examination procedures to ensure that patients obtain a timely ophthalmic diagnosis and necessary treatments, have been a problem for patients with HIV infection and many chronic diseases [3,5,28-31].

To explore the appropriate pattern for the early detection of OMs in patients with HIV infection and similar chronic diseases, we conducted the Guangzhou HIV Infection Study, which enrolled hospitalised HIV-infected patients in Guangzhou Eighth People's Hospital, the designated infectious disease treatment centre for patients diagnosed with HIV infection. We 1) analysed the association of the ophthalmic examination mode with the prevalence of detected OMs, 2) investigated the variation in detected OMs, and 3) analysed the association of demographic characteristics and systemic diseases with the presence of OM. The study provides reliable evidence and suggestions for the management of non-fatal complications in patients with HIV infection and other chronic diseases.

2. Methods

2.1. Study design and participants

The Guangzhou HIV Infection Study was a retrospective study that enrolled HIV-infected patients hospitalised in Guangzhou between Jan 1, 2005, and Dec 31, 2016. All the enrolled inpatients met the HIV diagnostic criteria. They received HAART according to the *Chinese guidelines for AIDS diagnosis and treatment* [32,33]. All the data was extracted from the Guangzhou Eighth Hospital medical record and the related ophthalmologic consultation records. Because the data was initially checked and recorded by the hospital staff during the admission procedures, there was no missing data. Data on the discharge diagnosis and demographic characteristics were then extracted. The unknown information was initially recorded as 'unknown' or 'other' and was categorized as "other or unspecified" for analysis.

Patients diagnosed with ophthalmic diseases during hospitalisation, excluding ocular trauma and congenital eye diseases, were defined as patients with OMs. The remaining patients were defined as normal patients. The selected hospitalisation for analysis were 1) the first hospitalisation of normal patients and 2) the first hospitalisation with any OM diagnosis of patients with OMs. Every participant was counted once. Fig. 1 shows the enrolment of patients.

This study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Zhongshan Ophthalmic Center (2019KYPJ177), Guangzhou, China. Written consent was waived because many patients were lost to follow-up, and the study did not involve personal identifiers or commercial interests. All patient records and information were anonymised and deidentified before analysis.

2.2. Ophthalmic examination procedure

To compare the influence of the mode of ophthalmic examination, the patients were divided into three groups according to the ophthalmic examination mode they underwent: the non-ophthalmologist examination group (2005-2011), the on-demand ophthalmic examination group (2012–2013) and the routine ophthalmic examination group (2014–2016).

In the non-ophthalmologist examination group (2005–2011), the patients were treated by infectious disease physicians without referral to an ophthalmologist. Due to the lack of ophthalmic equipment and professional eye examination, OMs were diagnosed based on inquiry and previous medical history. In the on-demand ophthalmic examination group (2012–2013), as an ophthalmology department had been established, patients were referred to an ophthalmologist if they had OM-related symptoms. In the routine ophthalmic examination group (2014–2016), the ophthalmic examination was routinely provided at admission. Every hospitalised HIV-infected patient was referred to the ophthalmology department for ophthalmic examinations if the patient's condition permitted the examination.

In the on-demand ophthalmic examination group (2012–2013) and the routine ophthalmic examination group (2014–2016), the patient who was referred to the ophthalmology department would be offered ophthalmic examinations, including a visual acuity test, a non-contact intraocular pressure test, slit-lamp examination, and fundoscopy, performed by a qualified ophthalmologist. The visual acuity test includes a naked visual acuity test and a best-corrected visual acuity test at a distance of 5 m. If the visual acuity was less than 6/60, the distance would be reduced, and the visual acuity was calculated accordingly. A visual acuity below 1/60 would be recorded as finger counts (FC), hand movements (HM), perceives light (PL) and

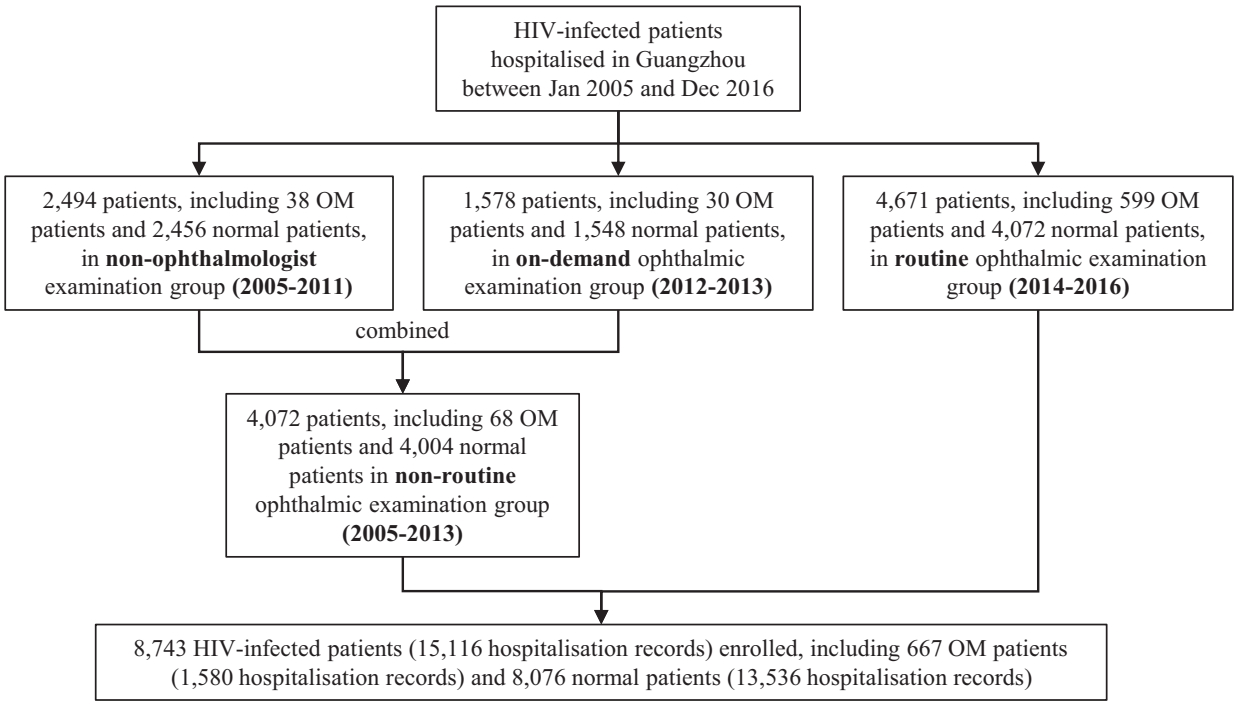

Fig. 1. Flowchart of the Guangzhou HIV Infection Study and the classification of the patients. A total of 8,743 hospitalised HIV-infected patients were enrolled in this study. OMs were detected in 38 (1.5% of 2,494) HIV-infected patients in the nonophthalmologist examination group (2005-2011), 30 (1.9% of 1,578) in the on-demand ophthalmic examination group (2012-2013), and 599 (12.8% of 4,671) in the routine ophthalmic examination group (2014-2016).

unable to perceive light (NPL) accordingly. The slit lamp examination was performed with both diffuse light and slit light to examine the anterior segment before dilation. If the patient does not have a history or risk factor of glaucoma, a dilated fundoscopy exam would be performed. Further examinations, such as ultrasound biomicroscopy and optical coherent tomography scans, were also performed if needed. The OM diagnosis was then recorded on the consultation record, which is part of the discharge diagnosis after hospitalisation.

2.3. Classification of discharge diagnosis

The ocular diagnosis was extracted from the discharge diagnosis, and was classified according to the location and the type of the OMs [10]. Cases which were of small numbers or not able to classify were assigned to the "other disorders" category. When regarding the location of lesion, this category includes pterygium, glaucoma, herpes zoster ophthalmicus, endophthalmitis, ophthalmitis, and blindness. When regarding the type of the lesion, this category additionally includes vitreous opacity, retinal detachment and unclassified uveitis.

Systemic diseases with high prevalence rates or significant effects on survival outcomes were also classified to analyse their association with the presence of OM.

2.4. Statistical analysis

When comparing the distributions of characteristics between groups, Student's t test was used to compare the age as a continuous variable, while the chi-square test was used for other categorical variables, including sex, age group, location of the permanent residence, job classification, payment method, and marital status. Since the number of patients with OMs was small in both the non-ophthalmologist examination group (2005–2011) and the on-demand ophthalmic examination group (2012–2013), and no significant difference in the prevalence of detected OMs was observed between these two groups, the two groups were combined into a non-routine ophthalmic examination group (2005–2013) for the characteristic comparison.

Binary logistic regression was used to assess the association between OMs and potential related factors. All the variables, including ophthalmic examination mode and the other factors (sex, age group, location of the permanent residence, job classification, payment method, marital status, whether diagnosed with a disease, and immunity outcome [whether CD4+ T cell count $<$ 200 cell/μL]), were used as categorical variables in the regression models.

To analyse the association of ophthalmic examination mode with the detection of OM, the odds ratio (OR) of the ophthalmic examination mode was calculated without and with adjustments for age group, sex and other potential confounding factors. These factors include the location of the permanent residence, job classification, payment method, and marital status.

To further analyse the association of these potential confounding factors with the presence of OM, and also to analyse the association of systemic diseases with the presence of OM, the data was restricted to the data from the routine examination group (2014–2016). Because all the hospitalised HIV-infected patients in this group underwent routine ophthalmic examinations, the prevalence of detected OMs could therefore represent the true prevalence of OMs in this period.

Data analysis was performed using STATA version 14.0 (Stata Corp., College Station, TX). All tests were two-sided, and P values less than 0.05 were considered statistically significant.

2.5. Role of funding

The source of funding played no role in the design of the study protocol; the data collection, analysis, and interpretation; the writing of the report; or the decision to submit the manuscript for publication.

3. Results

3.1. Association of ophthalmic examination mode with OM detection

A total of 8,743 hospitalised HIV-infected patients with 15,116 hospitalisation records were enrolled in this study (Fig. 1). 667

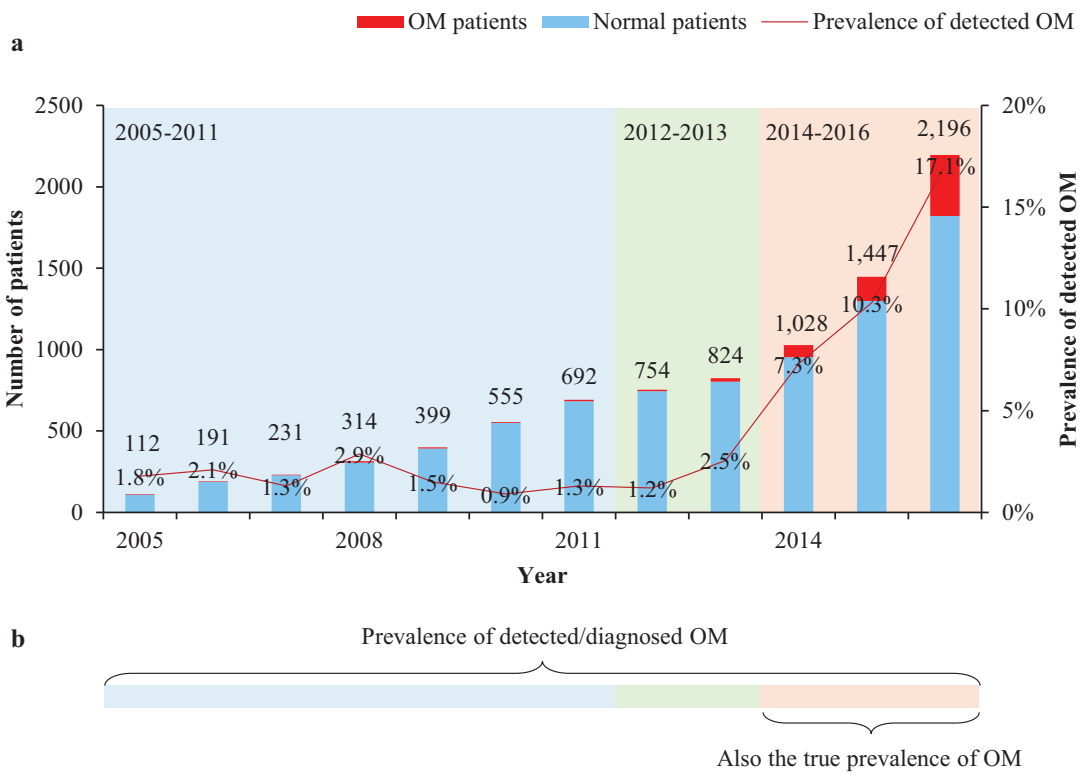

Fig. 2. The overall trend of hospitalized HIV patients and the prevalence of detected ocular manifestations (OM). a. The upper number above the square bar represents the total number of hospitalised HIV patients in the year. The lower number represents the prevalence of detected OM. There was an increase in the number of hospitalized HIV patients, while the annual prevalence of detected OM remained low, ranging between 0.9% and 2.9% before 2013. After 2014, as the ophthalmic examinations became a routine practice in hospitalized HIV-infected patients, the annual prevalence of detected OM sharply increased from 7.3% to 17.1%. b. The prevalence of detected OM was not the true prevalence of OM in the first two periods. After the ophthalmic examination became routine in the 2014-2016 time period, the prevalence of detected OM was able to represent the true prevalence of OM.

patients (7.6%) with 1,580 records had OMs. Despite the overall increase in the number of hospitalised HIV-infected patients, the annual prevalence of detected OMs remained low, ranging between 0.9% and 2.9% before 2013 (Fig. 2). After 2014, the prevalence increased substantially from 7.3% to 17.1%, as ophthalmic examinations became a routine practice in hospitalised patients with an HIV infection.

Therefore, OMs were detected in 38 (1.5% of 2,494) HIV-infected patients in the non-ophthalmologist examination group, 30 (1.9% of 1,578) in the on-demand ophthalmic examination group, and 599 (12.8% of 4,671) in the routine ophthalmic examination group (Table 1). The characteristics of patients were compared in Table 2. The unadjusted odds of detection of OMs were highest in the routine ophthalmic examination group (odds ratio [OR]=9.51, [95%CI, 6.82−13.25], compared to the non-ophthalmologist examination group) in model 1 in Table 1.

After adjusting for the demographic characteristics in Table 2, the odds of detection of OR remained the highest in Table 1 (in model 2 that was adjusted for age group and sex, adjusted OR [aOR]=8.93, [95%CI, 6.40−12.45], compared to the non-ophthalmologist examination group; in model 3 that was additionally adjusted for more demographic characteristics, aOR=9.24, [95%CI, 6.51−13.12], compared to the non-ophthalmologist examination group). However, no significant difference was observed between the non-ophthalmologist examination group and the on-demand ophthalmic examination group.

To analyse the association of demographic characteristics with the presence of OMs, we restricted the analysis to the routine ophthalmic examination era (a total of 4,671 patients, Table 3). The results show that females were less likely to develop OMs (aOR = 0.71, [95%CI, 0.56−0.90], compared to males). Patients who paid without health insurance also had lower odds of having OMs (aOR = 0.69, [95%CI, 0.55−0.87], compared to the self-paying patients). Patients of 50-59 years old (aOR = 1.52, [95%CI, 1.14−2.01]) and more than 60 years old (aOR = 1.92, [95%CI, 1.43−2.57]) were more likely to develop OMs, compared to the patients of 30-39 years old. The local patients (patients resident in Guangzhou City) had lower odds of having OMs (aOR = 0.45, [95%CI, 0.35−0.57]), compared to patients not resident in Guangzhou City. Therefore, patients that were older than 50 years old, males, paid with medical insurance, and were not resident in Guangzhou, would have higher odds to have OMs.

3.2. Variation in OMs

Although opportunistic infections had the highest prevalence of detection in both the non-routine ophthalmic examination group and the routine ophthalmic examination group, several differences were noted in the locations and nature of OMs (Fig. 3 and Supplementary Table 1). First, conjunctivitis was detected the most common infection in the non-routine ophthalmic examination group (17 patients [0.4%]), whereas vascular abnormalities (229 patients [4.9%]) and retinitis (181 patients [3.9%]) became the most common in the routine ophthalmic examination group (Fig. 3a). Second, from the non-routine ophthalmic examination period to the routine ophthalmic examination period, the prevalence of all types of detected OMs has increased substantially, with keratitis, retinitis and vascular abnormalities increased the most (by 15.8-20.0 times, Supplementary Table 1). At the same time, the prevalence of diagnosed corneal diseases increased from 0.1% to 1.8% (82 patients), and the prevalence of diagnosed retinal disorders increased from 0.4% (11 patients) and 0.8% (12 patients) to 8.3% (386 patients) (Fig. 3b).

Table 1
Association between the ophthalmic examination mode and the detection of ocular manifestations (OMs). The detection of OMs was set as the outcome of the regression model. All the factors were used as categorized factors. Model 1: Univariate logistic regression model. Model 2: Logistic regression model adjusted for age group and sex. Model 3: Logistic regression model adjusted for age group, sex, location of the permanent residence, job classification, payment method, and marital status. OR: odds ratio. Ref.: reference.

Ophthalmic examination group	No. (prevalence) of OM detection	Model 1		Model 2		Model 3	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Non-ophthalmologist examination group (2005-2011)	38 (1.5%)	Ref.		Ref.		Ref.	
On-demand ophthalmic examination group (2012-2013)	30 (1.9%)	1.25 (0.77, 2.03)	0.361	1.22 (0.75, 1.97)	0.425	1.25 (0.76, 2.04)	0.381
Routine ophthalmic examination group (2014-2016)	599 (12.8%)	9.51 (6.82, 13.25)	<0.001	8.93 (6.40,12.45)	<0.001	9.24 (6.51, 13.12)	<0.001

Table 2
Demographic characteristics of the participants in different ophthalmic examination groups. 2005-2013: non-routine ophthalmic examination group. 2014-2016: routine ophthalmic examination group.

Parameter	2005-2013	2014-2016	P
Diagnosis of any ophthalmic manifestation			<0.001
No	4,004 (98.3%)	4,072 (87.2%)	
Yes	68 (1.7%)	599 (12.8%)	
Sex			<0.001
Male	2,867 (70.4%)	3,613 (77.3%)	
Female	1,205 (29.6%)	1,058 (22.7%)	
Mean age in years (std.)	39.2 (13.1)	41.6 (13.7)	<0.001
Age group (years)			<0.001
<20	138 (3.4%)	94 (2.0%)	
20-29	700 (17.2%)	848 (18.2%)	
30-39	1,467 (36.0%)	1,248 (26.7%)	
40-49	977 (24.0%)	1,267 (27.1%)	
50-59	452 (11.1%)	689 (14.8%)	
≥60	338 (8.3%)	525 (11.2%)	
Location of the permanent residence			<0.001
Guangzhou city	820 (20.1%)	1,470 (31.5%)	
Other cities in Guangdong Province	2,374 (58.3%)	1,947 (41.7%)	
Outside Guangdong Province	878 (21.6%)	1,254 (26.8%)	
Job classification			<0.001
Clerical work	222 (5.5%)	308 (6.6%)	
Physical work	1,130 (27.8%)	1,553 (33.2%)	
In between jobs	340 (8.3%)	25 (0.5%)	
Other or unspecified	2,380 (58.4%)	2,785 (59.6%)	
Payment method			<0.001
With health insurance	277 (6.8%)	1,069 (22. 9%)	
Without health insurance	3,795 (93.2%)	3,602 (77.1%)	
Marital status			0.119
Married	3,045 (74.8%)	3,464 (74.2%)	
Unmarried	884 (21.7%)	1,072 (23.0%)	
Divorced or widowed	143 (3.5%)	135 (2.9%)	

Table 3
Association between the demographic parameters with the prevalence of ocular manifestations. The logistic regression analysis was conducted based on 4,671 participants in the routine ophthalmic examination group (2014-2016). The presence of OMs was set as the outcome of the logistic regression model. All the factors were used as categorized factors. Model 1: Univariate logistic regression model. Model 2: Logistic regression model that adjusted for age group, sex, location of the permanent residence, job classification, payment method, and marital status. OR: odds ratio. Ref.: reference.

Parameter	Model 1 OR (95% CI)	P	Model 2 OR (95% CI)	P
Sex (female)	0.67 (0.53, 0.84)	<0.001	0.71 (0.56, 0.90)	0.004
Age group (years)				
<20	0.63 (0.29, 1.39)	0.254	0.66 (0.29, 1.50)	0.324
20-29	0.92 (0.70, 1.22)	0.564	0.92 (0.69, 1.23)	0.580
30-39	Ref		Ref	
40-49	1.06 (0.83, 1.36)	0.628	1.03 (0.80, 1.33)	0.798
50-59	1.46 (1.11, 1.91)	0.006	1.52 (1.14, 2.01)	0.004
≥60	1.92 (1.45, 2.53)	<0.001	1.92 (1.43, 2.57)	<0.001
Location of the permanent residence				
Guangzhou City	0.53 (0.42, 0.66)	<0.001	0.45 (0.35, 0.57)	<0.001
Other cities in Guangdong Province	Ref		Ref	
Outside Guangdong Province	0.89 (0.72, 1.08)	0.239	0.95 (0.77, 1.16)	0.609
Job classification				
Clerical work	Ref		Ref	
Physical work	1.30 (0.90, 1.88)	0.166	1.01 (0.68, 1.50)	0.950
In between jobs	1.00 (0.28, 3.50)	0.998	0.86 (0.24, 3.05)	0.817
Other or unspecified	0.97 (0.67, 1.39)	0.859	0.82 (0.56, 1.21)	0.313
Payment method (without health insurance)	0.92 (0.75, 1.12)	0.410	0.69 (0.55, 0.87)	0.002
Marital status				
Married	Ref		Ref	
Unmarried	0.76 (0.61, 0.95)	0.014	0.94 (0.72, 1.22)	0.627
Divorced or widowed	1.19 (0.74, 1.91)	0.478	1.35 (0.84, 2.18)	0.214

In the routine ophthalmic examination group, the opportunistic infection was also the main type of OM in all age groups (Fig. 4, Supplementary Table 2). Retinitis was the most common infection (1.1−5.4%), followed by conjunctivitis (1.3−3.4%), keratitis (0-2.2%) and uveitis (0-1.3%) (Fig. 4a). Vascular abnormalities were the second most common OM (3.2-7.2%). Cataract was very common (10.5%) in patients older than 60 years old. Notably, the patients younger than 29 or patients older than 50 had a higher prevalence of ocular surface diseases, including conjunctivitis, keratitis, and infection in eyelid or adnexa (Fig. 4b). In contrast, the patients of 30-49 years olds had a higher prevalence of posterior segment diseases, including retinitis and uveitis.

3.3. Association of systemic diseases with any OM

Table 4 shows the association between systemic diseases and the presence of OM in HIV-infected patients in the routine ophthalmic examination group. In the multivariate model adjusted for all the diseases in Table 4, patients with cytomegalovirus infection had the highest odds of OMs (aOR=5.59, [95%CI, 4.12−7.59], compared to the patients without cytomegalovirus infection), followed by three metabolic diseases (electrolyte disturbance [aOR=2.24, [95%CI, 1.74−2.88]], hypoproteinaemia [aOR=2.12, [95%CI, 1.29−3.49]], and diabetes [aOR=1.74, [95%CI, 1.14−2.64]], compared to the patients without the referred disease). Patients with diseases of the respiratory system (pulmonary infection), digestive system (liver cysts and enteropathy), and nervous system (encephalopathy) had less high odds of developing OMs compared to the patients without the referred disease. In contrast, patients with marasmus, heart failure, and infection of *Pneumocystis carinii* had lower odds of having OMs compared to the patients without the referred disease.

Table 5 shows the associations between common ocular disorders with immunodeficiency. In the multivariate model adjusted for age group, sex and all the diseases in Table 5. Patients with retinitis (aOR=3.66, [95%CI, 2.29−5.86]), retinopathy (aOR=2.59, [95%CI,

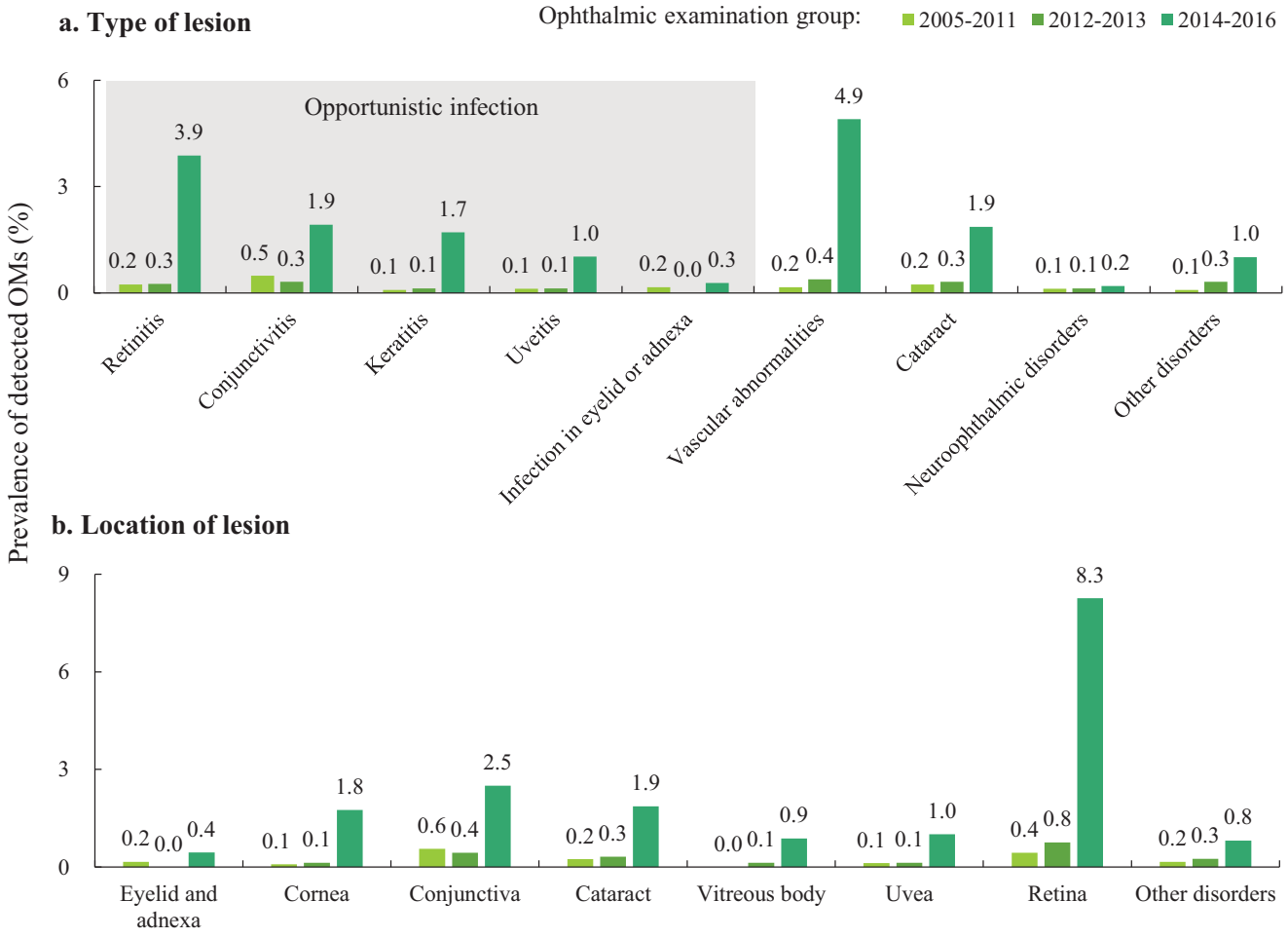

Fig. 3. Prevalence variation of detected ocular manifestations (OMs) in different ophthalmic examination groups. 2005-2011: non-ophthalmologist examination group. 2012-2013: on-demand ophthalmic examination group. 2014- 2016: routine ophthalmic examination group. The number of hospitalised HIVinfected patients in each ophthalmic examination group was used as the denominator (2,494 individuals in 2005-2011, 1,578 individuals in 2012-2013, and 4,671 individuals in 2014-2016). a. The prevalence of all types of detected OMs increased substantially, with keratitis, retinitis and vascular abnormalities increased the most (by 15.8-20.0 times, Supplementary Table 1). b. The prevalence of detected OMs of different locations also increased. Both panel a and b indicate an improved accuracy of the OM diagnosis.

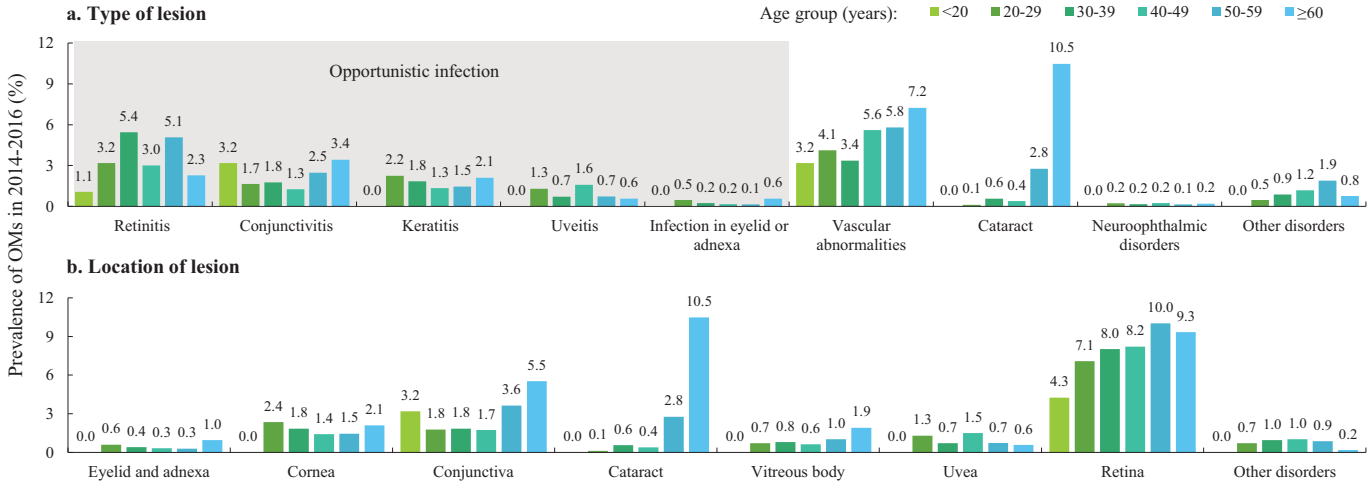

Fig. 4. Prevalence variation of ocular manifestations (OMs) in different age groups in the routine ophthalmic examination group (2014-2016). The number of all the hospitalised HIV-infected patients in each age group in the ophthalmic examination group (2014-2016) was used as the denominator (94 individuals in '<20', 848 individuals in '20-29', 1,248 individuals in '30-39', 1,267 individuals in '40-49', 6,89 individuals in '50-59', 525 individuals in '≥60. a. Opportunistic infection was also the main type of OM in all age groups. b. Ocular surface diseases were more common in patients that were younger than 29 or older than 50, while the patients of 30-49 years old had a higher prevalence of the posterior segment diseases of the eye.

Table 4
Association between systemic diseases and the prevalence of ocular manifestations. The logistic regression analyses were conducted based on 4,671 participants in the routine ophthalmic examination group (2014-2016). Model 1: Logistic regression model that includes three variables (age group, sex, and the selected disease). Model 2: Logistic regression model that includes age group, sex, and all the diseases in the table. OR: odds ratio. The reference was without the selected systemic disease.

Parameter	N (%)	Model 1 OR (95%CI)	P	Model 2 OR (95%CI)	P
Respiratory system					
Pulmonary infection	2,426 (51.9)	1.87 (1.56, 2.25)	<0.001	1.40 (1.08, 1.80)	0.010
Digestive system					
Oral candidiasis	740 (15.8)	1.36 (1.09, 1.69)	0.006	1.31 (0.66, 2.60)	0.439
Viral hepatitis	1,064 (22.8)	0.95 (0.78, 1.17)	0.656	0.95 (0.75, 1.19)	0.646
Toxic/drug hepatitis	353 (7.6)	1.27 (0.94, 1.73)	0.122	0.90 (0.63, 1.27)	0.542
Liver cysts	380 (8.1)	1.76 (1.35, 2.30)	<0.001	1.68 (1.26, 2.26)	<0.001
Enteropathy	698 (14.9)	1.58 (1.27, 1.96)	<0.001	1.28 (1.00, 1.63)	0.049
Metabolic system					
Marasmus	298 (6.4)	0.80 (0.55, 1.16)	0.238	0.48 (0.32, 0.73)	0.001
Electrolyte disturbance	570 (12.2)	2.80 (2.26, 3.46)	<0.001	2.24 (1.74, 2.88)	<0.001
Diabetes	177 (3.8)	1.79 (1.23, 2.59)	0.002	1.74 (1.14, 2.64)	0.010
Hypoproteinaemia	107 (2.3)	3.30 (2.18, 5.01)	<0.001	2.12 (1.29, 3.49)	0.003
Anaemia	330 (7.1)	0.94 (0.65, 1.35)	0.736	0.84 (0.56, 1.27)	0.414
Urinary system					
Renal cyst	376 (8.1)	1.29 (0.97, 1.72)	0.081	1.10 (0.79, 1.53)	0.590
Kidney stone	393 (8.4)	1.36 (1.03, 1.79)	0.032	1.16 (0.84, 1.59)	0.371
Renal failure	238 (5.1)	1.25 (0.88, 1.78)	0.213	1.02 (0.68, 1.52)	0.935
Cardiovascular system					
Hypertension	233 (5.0)	1.07 (0.74, 1.54)	0.732	1.02 (0.68, 1.55)	0.908
Heart failure	175 (3.8)	0.65 (0.39, 1.09)	0.104	0.34 (0.19, 0.59)	<0.001
Intracerebral haemorrhage	13 (0.3)	0.48 (0.06, 3.77)	0.489	0.37 (0.03, 4.16)	0.421
Nervous system					
Encephalatrophy	267 (5.7)	1.75 (1.28, 2.40)	<0.001	1.45 (1.02, 2.07)	0.038
Meningitis	123 (2.6)	1.89 (1.21, 2.94)	0.005	1.42 (0.78, 2.59)	0.255
Infection					
Bacterial	1,282 (27.5)	1.38 (1.15, 1.66)	0.001	0.83 (0.66, 1.04)	0.102
Fungal	1,596 (34.2)	1.74 (1.46, 2.07)	<0.001	1.33 (1.01, 1.76)	0.043
Viral	3,329 (71.3)	1.49 (1.21, 1.83)	<0.001	0.97 (0.76, 1.24)	0.804
Specific pathogen					
Pneumocystis carinii	413 (8.8)	1.25 (0.94, 1.66)	0.119	0.56 (0.39, 0.82)	0.003
Tuberculosis	1,062 (22.7)	1.66 (1.38, 2.01)	<0.001	1.25 (0.99, 1.57)	0.062
Treponema pallidum	584 (12.5)	1.31 (1.03, 1.67)	0.029	1.24 (0.96, 1.62)	0.105
Candida	828 (17.7)	1.32 (1.07, 1.63)	0.010	0.56 (0.28, 1.10)	0.091
Herpes virus	247 (5.3)	1.31 (0.92, 1.86)	0.134	1.10 (0.74, 1.63)	0.639
Cryptococcus	128 (2.7)	1.58 (1.00, 2.49)	0.050	0.71 (0.38, 1.30)	0.264
Cytomegalovirus	405 (8.7)	5.04 (4.02, 6.32)	<0.001	5.59 (4.12, 7.59)	<0.001

Table 5
The relationship between ocular manifestations (OMs) and CD4+ T cell counts <200 cells/μL. The logistic regressions were conducted based on 599 patients with OMs in the routine ophthalmic examination group (2014-2016). Whether CD4+ T cell count < 200 cell/μL, was used as a categorical variable and the outcome of the regression models. Model 1: Logistic regression model that includes age group, sex, and the selected disease. Model 2: Logistic regression model that includes age group, sex, and all the diseases in this table. The reference was without the selected OM. OR: odds ratio.

	Model 1 OR (95%CI)	P	Model 2 OR (95%CI)	P
Retinopathy	2.09 (1.25, 3.49)	0.005	2.59 (1.51, 4.44)	0.001
Retinitis	2.58 (1.69, 3.94)	<0.001	3.66 (2.29, 5.86)	<0.001
Uveitis	0.72 (0.47, 1.10)	0.129	0.75 (0.47, 1.18)	0.216
Cataract	0.38 (0.23, 0.60)	<0.001	0.47 (0.28, 0.77)	0.003
Pterygium	1.17 (0.61, 2.22)	0.640	1.39 (0.70, 2.73)	0.347
Keratitis	1.14 (0.52, 2.47)	0.747	1.46 (0.65, 3.27)	0.359
Retinal attachment	0.54 (0.28, 1.04)	0.065	0.51 (0.25, 1.02)	0.056
Fundus haemorrhage	0.75 (0.33, 1.73)	0.502	1.30 (0.54, 3.16)	0.560
Conjunctivitis	1.44 (0.84, 2.44)	0.182	2.19 (1.24, 3.87)	0.007
Maculopathy	0.79 (0.37, 1.70)	0.541	0.97 (0.43, 2.19)	0.934

1.51−4.44]) and conjunctivitis (aOR=2.19, [95%CI, 1.24−3.87]) had significantly higher odds to have immunodeficiency (defined as a CD4+ T cell count <200 cells/μL) compared to the patients without the referred OM. In contrast, patients with cataract had lower odds of having immunodeficiency (aOR=0.47, [95%CI, 0.28−0.77]).

4. Discussion

In this study, we collected data from 8,743 HIV-infected patients hospitalised in Guangzhou and investigated the prevalence of detected OMs determined using different ophthalmic examination modes over the 12 years of the HAART era. Our study has two significant findings. First, the implementation of routine ophthalmic examinations plays a critical role in OM detection and the management of patients with an HIV infection. Second, in HIV-infected patients, a strong correlation is observed between systemic diseases and the presence of OM.

Despite the wide accessibility of HAART in China, a high prevalence of OMs (12.8%) was still present in the routine ophthalmic examination group. Retinal disorders were seen in 8.3% of patients in the routine ophthalmic examination group (Supplementary Table 1) accounted for 64.4% of OMs, which were the primary cause of vision loss reported in previous studies [12,34]. Early diagnosis is the key to timely treatment to decrease vision loss. The implementation of routine ophthalmic examinations significantly improved the odds of OM detection by approximately 9 times, and improved the detection of three common vision-threatened OMs, keratitis, retinitis and vascular abnormalities, by 15.8−20.0 times compared to the other two groups. The increased accuracy and detection of all types of OMs in the routine ophthalmic examination group highlights the role of the ophthalmology department, ophthalmologists and examination equipment, suggesting the need for appropriate ophthalmic

examinations. Moreover, compared to the non-ophthalmologist examination group, the establishment of an ophthalmology department without routine examinations of every HIV-infected patient (as was the case for the on-demand ophthalmic examination group) did not significantly improve the detection of OMs. Therefore, both high-quality ophthalmic examinations and appropriate medical regulations are crucial for the early and accurate diagnosis of OMs in HIV-infected patients.

Notably, the changing need for hospitalisation was inversely having an influence on the prevalence of OM in our study period. The patients were admitted to the hospital with a better condition of HIV infection than before with the upgraded Guideline for AIDS management in China [32,33] emphasizing the importance of timely initiation of HAART (once the HIV infection is confirmed, the HAART should be initiated timely) and the improving capacity of the Chinese hospitals. Our study also found a decreased hospitalisation duration of hospitalised HIV-infected patients, revealing that the patients had a less severe condition than before. Moreover, the efficacy of the "Four Frees and One Care" policy for HIV-infected patients is also crucial in encouraging more patients to visit a doctor and adhere to long-term drug regimens, as early treatments lead to improved outcomes and decreased OMs [35–37]. Considering the fact that the prevalence of detected OMs ultimately increased because of the application of the routine ophthalmic examinations, we recommended that even HIV-positive individuals without a need for hospital treatment should undergo regular eye examinations because of its essential role for the early diagnosis of vision-threatening OMs.

Our results also show that patients who were older than 50 years old, males, paid with medical insurance, and that were not resident in Guangzhou, had higher odds of having OMs, which were not entirely consistent with the previous studies. Some researchers found that the increasing age was a risk factor of OMs, while sex was not associated [20]. In another study, neither ages nor sex was associated with OMs [38]. Although the floating population and medical insurance payments were not discussed in the previous studies, we noted that patients are more likely to see doctors for non-fatal complications when they have access to medical insurance [39,40]. Based on our research, future prevention and control efforts should pay attention to these populations. We will also further investigate the interaction between OMs and these demographic characteristics in the future study.

The association between systemic diseases, immunodeficiency and the presence of OM indicates that OMs represent a potential confounding factor of systemic diseases and patient immunity, adding value to the examination and diagnosis of OMs. Therefore, on the one hand, patients with documented immunodeficiency should be examined carefully for OMs. On the other hand, infectious diseases, especially the cytomegalovirus infection, are becoming a much more common cause of vision loss and blindness in eye clinic [41,42]. Missed diagnosis and misdiagnosis increased because of the growing number of HIV-infected patients [43]. One of the important reasons was that the patients came to the eye clinic without knowing their condition or deliberately concealing their history of HIV infection [44]. Therefore, to avoid missed diagnosis and misdiagnosis, patients with OMs should also focus on their systemic conditions and should undergo additional immune function tests, such as a T cell test, particularly if they are diagnosed with retinopathy or retinitis.

We constructed a model to illustrate the possible interrelationships among these factors in our study (Fig. 5). The observed prevalence of OMs is influenced by a combination of the true prevalence of OMs and their diagnosis in the real world. The OMs refer to the patients' true eye conditions, which are influenced by treatment. The diagnosis of OMs is related to the mutual influence of external factors such as the patient's willingness to seek ophthalmic examinations and the quality of treatment. In this study, the prevalence of OMs in the routine ophthalmic examination group reflected the true prevalence of OMs in hospitalised HIV-infected patients, whereas the prevalence was much lower in the non-routine ophthalmic examination group as a result of differences in ophthalmic examination modes, medical insurance, and other factors.

There are a few limitations in the study. First, potential factors that may affect the prevalence of detected OMs, including pregnancy [45] and drug use [46], were not characterised in our study. Second, according to the *Guidelines for AIDS diagnosis and treatment in China*, after 2012, the first-line HAART changed from stavudine + lamivudine + efavirenz/nevirapine to tenofovir/zidovudine + lamivudine + efavirenz/nevirapine, as stavudine was reported to cause severe adverse reactions in many cases [47]. The

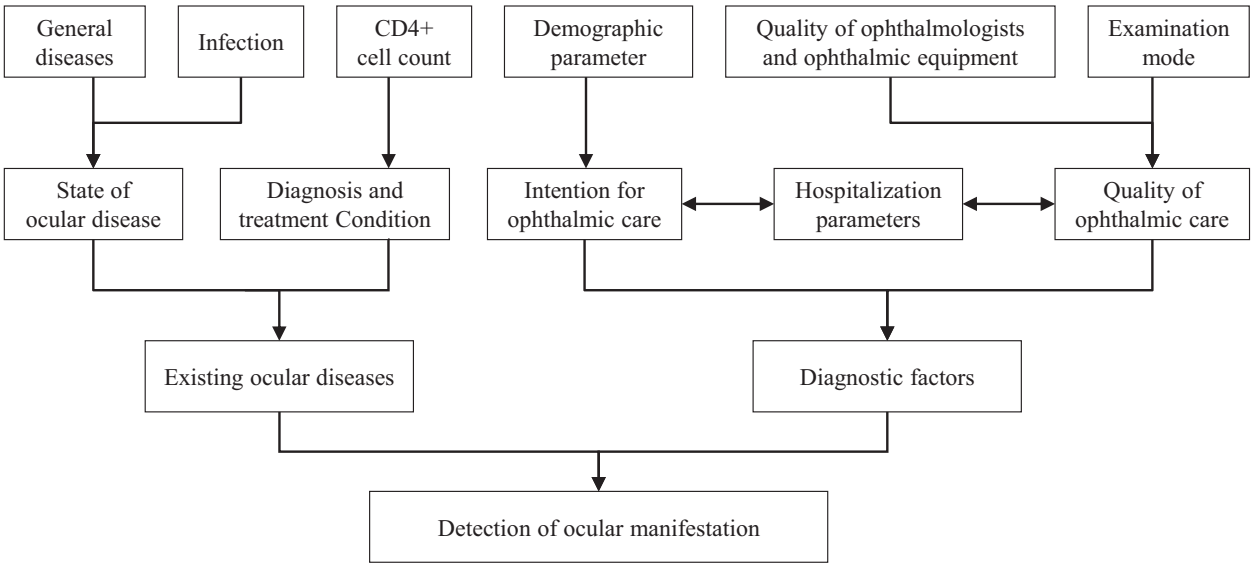

Fig. 5. The model of ocular manifestation (OM) detection and its related factors. The arrow represents having effect on the pointing object. The observed prevalence of OMs is influenced by a combination of the true prevalence of OMs and their diagnosis in the real world. The OMs refer to the patients' true eye conditions, which are influenced by treatment. The diagnosis of OMs is related to the mutual influence of external factors such as the patient's willingness to seek ophthalmic examinations and the quality of treatment. In this study, the prevalence of OMs in the routine ophthalmic examination group reflected the true prevalence of OMs in hospitalised HIV-infected patients, whereas the prevalence was much lower in the non-routine ophthalmic examination group as a result of differences in ophthalmic examination modes, medical insurance, and other factors.

prevalence of detected OMs before 2012 may have been slightly influenced as well [46]. Third, although the percentage of patients with severe condition decreased, most of the hospitalised HIV-infected patients required certain inpatient treatment, indicating an overall more severe condition than the outpatients. Therefore, the results presented here may not be generalizable to the HIV-infected population overall. Fourth, this study was based on data collected from hospitalised HIV-infected patients in one of the most prosperous cities in China; therefore, the data may not wholly represent the general condition of OMs in HIV-infected patients in this country.

In conclusion, the implementation of routine ophthalmic examinations, including both high-quality ophthalmic examinations and appropriate medical regulations, is crucial for the early and accurate diagnosis of OMs in HIV-infected patients. Timely diagnosis of eye diseases may not only promote early treatment and improved prognoses but also allow patients to be alerted to additional systemic diseases. Therefore, in addition to increasing the awareness of OMs and other non-fatal complications in HIV-infected patients, we suggest ophthalmic examinations as a routine procedure to improve the early diagnosis of OMs and decrease vision loss in patients with the management of HIV infection and other chronic diseases.

Author contributions

H Lin conceived and designed the study. X Wang, W Li, D Lin, Z Liu, X Wu, J Wang, X Zhang, Y Yang, R Wang, and R Li collected and interpreted the data. W Li and L Zhao carried out the statistical analysis. W Li wrote the manuscript. H Lin, W Huang, D Lin, Y Zhu, C Chen, and X Huang reviewed and edited the manuscript. All authors have seen the final version of the manuscript and approved it for publication. The corresponding author had full access to all data in the study and assumed final responsibility for the decision to submit the manuscript for publication.

Data sharing statement

The deidentified participant dataset are available for research purposes from the corresponding authors on reasonable request.

Funding

This study is funded by the Science and Technology Planning Projects of Guangdong Province (2018B010109008, 2019B030316012), the Science Foundation of China for Distinguished Young Scholars (81822010), and the National Natural Science Foundation of China (81770967, 81873675, and 81800810).

Declaration of Competing Interest

The authors declare no competing financial interests.

Acknowledgments

We are grateful to the staff of the Zhongshan Ophthalmic Center and Guangzhou Eighth People's Hospital for their assistance during data collection. We also thank all the participants, their families, and the institutions for supporting this study.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2020.100646.

References

[1] The L. The global HIV/AIDS epidemic-progress and challenges. Lancet 2017;390 (10092):333.
[2] Nathanson N. HIV/AIDS epidemic: the whole truth. Science 2016;351(6269):133.
[3] Sued O, Figueroa MI, Cahn P. Clinical challenges in HIV/AIDS: hints for advancing prevention and patient management strategies. Adv Drug Deliv Rev 2016;103:5–19.
[4] Maartens G, Celum C, Lewin SR. HIV infection: epidemiology, pathogenesis, treatment, and prevention. Lancet 2014;384(9939):258–71.
[5] Beyrer C, Das P, Horton R, Ryan O, Bekker LG. The International AIDS Society-Lancet Commission on the future of the HIV response and global health. Lancet 2017;390(10092):344–5.
[6] Singalavanija T, Ausayakhun S, Tangmonkongvoragul C. Anterior segment and external ocular disorders associated with HIV infections in the era of HAART in Chiang Mai University Hospital, a prospective descriptive cross sectional study. Plos One 2018;13(2):e193161.
[7] Butler NJ, Thorne JE. Current status of HIV infection and ocular disease. Curr Opin Ophthalmol 2012;23(6):517–22.
[8] Stewart MW. Human immunodeficiency virus and its effects on the visual system. Infect Dis Rep 2012;4(1):e25.
[9] Shah SU, Kerkar SP, Pazare AR. Evaluation of ocular manifestations and blindness in HIV/AIDS patients on HAART in a tertiary care hospital in western India. Brit J Ophthalmol 2008;93(1):88–90.
[10] Holland GN. AIDS and ophthalmology: the first quarter century. Am J Ophthalmol 2008;145(3):397–408.
[11] Bekele S, Gelaw Y, Tessema F. Ocular manifestation of HIV/AIDS and correlation with CD4+ cells count among adult HIV/AIDS patients in Jimma town, Ethiopia: a cross sectional study. Bmc Ophthalmol 2013;13(1):20.
[12] Ford N, Shubber Z, Saranchuk P, et al. Burden of HIV-related cytomegalovirus retinitis in resource-limited settings: a systematic review. Clin Infect Dis 2013;57 (9):1351–61.
[13] Newman H, Gooding C. Viral ocular manifestations: a broad overview. Rev Med Virol 2013;23(5):281–94.
[14] Agarwal A, Singh R, Sharma A, Gupta V, Dogra MR. Ocular manifestations in patients with human immunodeficiency virus infection in the pre-HAART versus the HAART era in the north Indian population. Ocul Immunol Inflamm 2017;25 (3):396–404.
[15] Amsalu A, Desta K, Nigussie D, Delelegne D. Ocular manifestation and their associated factors among HIV/AIDS patients receiving highly active antiretroviral therapy in Southern Ethiopia. Int J Ophthalmol 2017;10(5):776–81.
[16] Martin-Odoom A, Bonney EY, Opoku DK. Ocular complications in HIV positive patients on antiretroviral therapy in Ghana. Bmc Ophthalmol 2016;16(1):134.
[17] Sittivarakul W, Benjhawaleemas T, Aui-Aree N, Jirarattanasopa P, Liabsuetrakul T. Incidence rate and risk factors for contralateral eye involvement among patients with AIDS and cytomegalovirus retinitis treated with local therapy. Ocul Immunol Inflamm 2016;24(5):530–6.
[18] Sharew G, Azage M. Predictors of HIV/AIDS related ocular manifestations among HIV/AIDS patients in Felege Hiwot Referral Hospital, Northwest Ethiopia. J Ophthalmol 2015;2015:965627.
[19] Kim YS, Sun HJ, Kim TH, Kang KD, Lee SJ. Ocular manifestations of acquired immunodeficiency syndrome. Korean Journal of Ophthalmology 2015;29(4):241.
[20] Nishijima T, Yashiro S, Teruya K, et al. Routine eye screening by an ophthalmologist is clinically useful for HIV-1-infected patients with CD4 count less than 200 /muL. Plos One 2015;10(9):e136747.
[21] Kim SJ, Park SJ, Yu HG, Kim NJ, Jang HC, Oh MD. Ocular manifestations of acquired immunodeficiency syndrome in Korea. J Korean Med Sci 2012;27(5):542–6.
[22] Kaleem MA, Ramsahai S, Del FK, et al. Ocular findings in human immunodeficiency virus patients in Washington. Int Ophthalmol 2012;32(2):145–51.
[23] Gogri PY, Misra SL, Kothari RN, Bhandari AJ, Gidwani HV. Ophthalmic manifestations of HIV patients in a rural area of western Maharashtra, India. Int Sch Res Notices 2014;2014:347638.
[24] Biswas J, Sudharshan S, Babu RB. Ocular lesions in AIDS: Indian scenario. Am J Ophthalmol 2008;146(2):331–2 331.
[25] Reddy PA, Congdon N, MacKenzie G, et al. Effect of providing near glasses on productivity among rural Indian tea workers with presbyopia (PROSPER): a randomised trial. The Lancet Global Health 2018;6(9):e1019–27.
[26] Uchino M, Uchino Y, Dogru M, et al. Dry eye disease and work productivity loss in visual display users: the Osaka study. Am J Ophthalmol 2014;157(2):294–300.
[27] Luo J, Jing D, Kozak I, et al. Prevalence of ocular manifestations of HIV/AIDS in the highly active antiretroviral therapy (HAART) era: a different spectrum in central South China. Ophthal Epidemiol 2013;20(3):170–5.
[28] Poudel AN, Newlands D, Simkhada P. The economic burden of HIV/AIDS on individuals and households in Nepal: a quantitative study. Bmc Health Serv Res 2017;17(1):76.
[29] Deeks SG, Lewin SR, Ross AL, et al. International AIDS Society global scientific strategy: towards an HIV cure 2016. Nat Med 2016;22(8):839–50.
[30] Shubber Z, Mills EJ, Nachega JB, et al. Patient-reported barriers to adherence to antiretroviral therapy: a systematic review and meta-analysis. Plos Med 2016;13 (11):e1002183.
[31] Piot P, Abdool KS, Hecht R, et al. Defeating AIDS—advancing global health. Lancet 2015;386(9989):171–218.
[32] AIDS Professional Group SOID. The third edition of Chinese guidelines for AIDS diagnosis and treatment (2015). Chi J Clin Infect Dis 2015;5(8):385–401.
[33] AIDS Professional Group SOID. The second edition of Chinese guidelines for AIDS diagnosis and treatment (2011). Chin J Clin Infect Dis 2011;29(10):629–40.

[34] Hui-hong LU, Zhi-liang W, Yin-zhong S, Hong-zhou LU, Xianqun F. A study of eye complications and causes of blindness and in patients initially diagnosed with AIDS in Shanghai. Chin J Optometry Ophthalmol Visual Sci 2013;15(2):120–4.
[35] Wu Z, Wang Y, Detels R, Bulterys M, McGoogan JM. HIV/AIDS in China: epidemiology. Prevention and Treatment: Springer 2019.
[36] Li L, Ji G, Lin C, Liang L, Lan C. Antiretroviral therapy initiation following policy changes. Asia Pacific J Public Health 2016;28(5):416–22.
[37] Sun X, Lu F, Wu Z, et al. Evolution of information-driven HIV/AIDS policies in China. Int J Epidemiol 2010;39 (Supplement 2): i4-13.
[38] Jabs DA, Ahuja A, Van Natta ML, Lyon AT, Yeh S, Danis R. Long-term outcomes of cytomegalovirus retinitis in the era of modern antiretroviral therapy: results from a United States Cohort. Ophthalmology 2015;122(7):1452–63.
[39] Xiong X, Zhang Z, Ren J, et al. Impact of universal medical insurance system on the accessibility of medical service supply and affordability of patients in China. Plos One 2018;13(3):e193273.
[40] Li L, Fu H. China's health care system reform: progress and prospects. The International J Health Plan Manage 2017;32(3):240–53.
[41] PATHANAPITOON K, AUSAYAKHUN S, KUNAVISARUT P, et al. Blindness and low vision in a tertiary ophthalmologic center in Thailand. Retina 2007;27(5):635–40.
[42] Yen M, Ausayakhun S, Chen J, et al. Telemedicine diagnosis of cytomegalovirus retinitis by nonophthalmologists. Jama Ophthalmol 2014;132(9):1052–8.
[43] Wei WB, Zhou N. [Efforts to improve the level of clinical diagnosis and treatment of infectious fundus diseases]. Zhonghua Yan Ke Za Zhi 2019;55(4):241–5.
[44] Parekh P, Oldfield EC, Marik PE. Progressive outer retinal necrosis: a missed diagnosis and a blind, young woman. Case Reports 2013;2013 (apr22 1): r2013009333.
[45] Rutar T, Youm J, Porco T, et al. Ophthalmic manifestations of perinatally acquired HIV in a US cohort of long-term survivors. Br J Ophthalmol 2015;99(5):650–3.
[46] Urban B, Bakunowicz-Lazarczyk A, Michalczuk M. Immune recovery uveitis: pathogenesis, clinical symptoms, and treatment. Mediators Inflamm 2014; 2014:971417.
[47] Chowta MN, Kamath P, Ramapuram JT, Shenoy KA, Hadigal S. Evaluation of Adverse Drug Reaction Profile of Drugs Used as First-Line Antiretroviral Therapy. Interdiscip Perspect Infect Dis 2018;2018:8095609.