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HIV-infected individuals on long-term antiretroviral therapy are at higher risk for ocular disease

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SUMMARY

Introduction of antiretroviral therapy (ART) has dramatically reduced the incidence of infectious ocular diseases in human immunodeficiency virus (HIV)-infected individuals. However, the effects of long-term ART and chronic HIV infection on the eye are ill-defined. This study determined the occurrence and severity of ocular diseases among 342 participants in a rural South African setting: HIV-naïve ($n = 105$), HIV-infected ART-naïve ($n = 16$), HIV-infected on ART for <12 months (short-term ART; $n = 56$) and HIV-infected individuals on ART for >36 months (long-term ART; $n = 165$). More HIV-infected participants presented with an external eye condition, in particular blepharitis, than HIV-naïve individuals (18% *vs.* 7%; age-adjusted odds ratio (aOR) = 2·8, $P < 0·05$). Anterior segment conditions (particularly keratoconjunctivitis sicca and pterygium) were also more common (50% *vs.* 27%; aOR = 2·4; $P < 0·01$). Compared with individuals on short-term ART, participants receiving long-term ART were more likely to have clinically detectable cataract (57% *vs.* 38%; aOR = 2·2, $P = 0·01$) and posterior segment diseases, especially HIV retinopathy (30% *vs.* 11%; aOR = 3·4, $P < 0·05$). Finally, long-term ART was significantly associated with presence of HIV retinopathy ($P < 0·01$). These data implicate that ocular disease is more common and of more diverse etiology among HIV-infected individuals, especially those on long-term ART and suggest that regular ophthalmological monitoring of HIV-infected individuals on ART is warranted.

Key words: ART, HIV, ocular disease, rural South Africa.

INTRODUCTION

Human immunodeficiency virus (HIV) infection is a major public health problem in sub-Saharan Africa [1]. During the course of HIV infection individuals are at increased risk of developing ocular disease. Lifetime prevalence of ocular disease among

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HIV-infected individuals was estimated at more than 70% in the pre-antiretroviral therapy (ART) era [2, 3]. In most of those cases, ocular disease was caused by opportunistic infections associated with advanced immunosuppression [2–4]. For example, 40% of individuals was affected by cytomegalovirus retinitis whereas Kaposi's sarcoma of the eyelids or conjunctiva occurred in up to 5% of HIV-infected individuals before ART became available [2, 3, 5]. Management of these conditions was difficult without simultaneous provision of ART, commonly resulting in serious ocular morbidity [2, 3].

The large-scale introduction of ART has resulted in substantial reduction in infectious ocular conditions among HIV-infected individuals [6, 7]. However, a shift in spectrum of ocular disease among HIV-infected individuals has occurred. Immune recovery following ART initiation may lead to occurrence of ocular conditions such as immune recovery uveitis, especially among individuals with relatively low CD4 count at start of ART [8]. Currently many individuals receive lifelong ART, but the long-term effects of ART on occurrence and severity of ocular disease in chronically HIV-infected individuals are largely unknown. Metabolic and vascular changes associated with extended use of ART may affect the eye resulting in ocular diseases such as retinopathy [7]. Furthermore, the process of accelerated ageing and frailty among HIV-infected individuals on ART may also affect ocular structures such as the lens [9]. Finally, persistent immune activation, suboptimal HIV containment and incomplete immune restoration may predispose to various ocular conditions [10].

There is widespread scientific interest in the effects of chronic HIV infection and ART on systemic processes in the body (e.g. accelerated development of cardiovascular and ageing-related conditions), but the effects on the eye are ill-defined [11, 12]. Moreover, many chronic systemic diseases present with ocular co-morbidity, but limited attention has been paid to the impact of chronic HIV infection and long-term use of ART on the eye. Such impact of HIV infection and ART on the eye that could result in visual impairment, may greatly affect HIV-infected individuals' quality of life in both the short and long term [13]. Thus, a better understanding of the effects of HIV infection and ART on the eye is warranted.

The aim of this study was to describe the occurrence and spectrum of ocular diseases among patients in different phases of the HIV treatment program to determine the clinical effects of HIV infection and short and long term ART on the eye.

METHODS

Study design

Four groups of adult individuals were recruited: (1) HIV-naïve individuals ($n = 105$), (2) HIV-infected individuals not on ART ($n = 16$), (3) HIV-infected individuals on ART for <12 months (defined as short-term ART; $n = 56$) and (4) HIV-infected individuals on ART for >36 months (defined as long-term ART; $n = 165$). Recruitment took place in rural South Africa (Mopani district) between August 2014 and March 2015 at three hospitals and three primary healthcare (PHC) facilities that are in walking distance of the hospitals. Potential participants were approached and recruited at the general clinic of the PHC facility and HIV/ART clinic at the hospitals. If interested in participating, written informed consent was obtained and questionnaires completed. Individuals were eligible if they met the following criteria: adult ($\geqslant 18$ years), visiting the healthcare facility for any reason other than eye complaints and with a documented HIV status based on their patient file. Individuals classified as HIV naïve had been tested through routine HIV testing facilities on the day of recruitment. Participants were requested to visit the ophthalmology outpatient department at one of the three hospitals on the day of recruitment for full ocular examination. A list of patients referred from the hospital HIV/ART clinic and the PHC facility was compiled to determine selection bias in these referrals. All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. This study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (Johannesburg, South Africa; M140318).

Study procedures

Demographic, clinical, and HIV laboratory data (viral load and CD4 cell count) were collected with a questionnaire and from the patient records. A viral load of <400 copies/ml was defined as a suppressed HIV load. Visual acuity was measured using an 'illiterate E' Snellen chart at a distance of 6 m. In case visual acuity

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was reduced (<6/6 by Snellen chart), a pinhole disk was utilized to determine the BCVA (best-corrected visual acuity) as alternative to refraction methods that were unavailable. Visual impairment was defined according to the International Classification of Diseases on the basis of the individual's visual acuity [14]. Furthermore, slit lamp examination, determination of intraocular pressure using the Icare TA01i (Icare Finland Oy; Helsinki, Finland) and dilated indirect funduscopy were performed to complete ophthalmic examination.

Ocular disease was diagnosed based on clinical history and ocular characteristics observed during examination as per generally accepted international criteria and guidelines of the American Academy of Ophthalmology [15]. In case of keratoconjunctivitis sicca, diagnosis was based on epithelial health of the cornea (ocular surface staining), and the tear film stability (tear break-up time) after the application of fluorescein dye as the Schirmer test was unavailable [16]. A diagnosis of clinically detectable cataract was based on the detection of ocular lens density; a diagnosis of clinically significant cataract was based on the simultaneous detection of ocular lens density and visual acuity of <6/12. Appropriate treatment was provided as per local guidelines and available resources.

Data analysis

Data were double-entered into EPI-INFO version 3.5.4 (Centers for Disease Control; Atlanta, GA) and analyzed using IBM SPSS Statistics version 22 (IBM; New York City, NY). Standard descriptive overview of demographic factors and ocular conditions was provided including proportions, mean with standard deviation and median with range. To determine the effect of HIV infection on the occurrence of ocular disease, we compared demographic factors and frequency of ocular conditions between HIV-uninfected individuals and HIV-infected individuals, excluding those on long-term ART as effects of long-term ART use may bias these results. We categorized the ocular conditions based on anatomic location: external eye, anterior segment, posterior segment and/or neuro-ophthalmic structure affected. The occurrence of ocular conditions was compared between groups using χ^2 for dichotomous variables, with Fisher's Exact test if appropriate, and the Mann–Whitney U test for continuous variables. Odds ratio (OR) with 95% confidence interval (CI), adjusted for age (aOR) where appropriate, was calculated using logistic regression. Similarly, factors associated with specific ocular conditions were identified. Age, recent and nadir CD4 count, viral load, time on ART, and ART regimen, as well as all variables with a P-value $\leqslant 0{\cdot}10$ in univariate analysis, were included in multivariate analysis using logistic regression (forward likelihood ratio) to identify factors independently association with ocular conditions. As outcome measures, all ocular conditions were included in the multivariate analysis as well as all four eye disease categories based on anatomic location.

RESULTS

Demographics of the study population

We recruited a total of 367 individuals at the HIV/ART clinics: 192 (52%) individuals at the hospitals and 175 (48%) at the general PHC facilities. Of these individuals, a total of 342 (93%) attended the ophthalmology outpatient department for full ophthalmic examination of which 181 of 192 (94%) individuals were recruited at the hospitals and 161 of 175 (92%) at PHC facilities. No relevant differences in demographic variables were observed between individuals enrolled and those that were excluded from further analysis for not having visited the ophthalmology outpatient department. Distribution of participants across the four groups with different HIV/ART status was as follows: 105 individuals were HIV naïve, 16 HIV-infected not on ART, 56 on short-term ART and 165 on long-term ART. HIV-infected participants were significantly older than those without HIV infection (median age of 46 (range 20–75) years *vs.* 32 (range 18–85) years; $P < 0{\cdot}001$) and individuals on long-term ART were older than participants receiving short-term ART (median age of 47 (range 22–75) years *vs.* 32 (range 20–69) years; $P = 0{\cdot}001$). Additional significant differences between the four study groups were the number of male participants and education level (Table 1). Nadir CD4 cell count at ART initiation was lower in individuals with long-term *vs.* short-term ART (median of 146 (range 1–473) cells/mm^3 *vs.* 187 (range 6–346) cells/mm^3; $P < 0{\cdot}05$). In contrast, the most recent documented CD4 cell count was higher among the long-term ART group (median of 463 (range 2–1266) cells/mm^3 *vs.* 207 (6–904) cells/mm^3; $P < 0{\cdot}001$). The number of individuals with a suppressed viral load was not

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Table 1. *Demographic and clinical characteristics among HIV naïve and HIV-infected individuals* (n = *342*)

	HIV naïve no ART (*n* = 105)	HIV-infected no ART (*n* = 16)	HIV-infected short-term ART (*n* = 56)	HIV-infected long-term ART (*n* = 165)
Demographics				
Age (years)*	32 (18–85)	43 (21–67)	43 (20–69)	47 (22–75)
Gender*				
Female	96 (91)	12 (75)	39 (70)	115 (70)
Male	9 (9)	4 (25)	17 (30)	50 (30)
Low educational status*	15 (14)	7 (44)	23 (41)	75 (46)
Low financial status	35 (33)	7 (44)	23 (41)	89 (54)
Clinical history				
Diabetes mellitus	6 (6)	1 (6)	1 (2)	6 (4)
Hypertension	11 (11)	1 (6)	7 (13)	27 (16)
History of herpes zoster scar**	3 (3)	4 (25)	11 (20)	48 (29)
History of treatment for tuberculosis**	6 (6)	1 (6)	14 (25)	61 (37)
Time on ART (months)	na	na	6 (1–12)	66 (37–179)
ART regimen				
TDF+FTC/3TC + EFV	na	na	52 (93)	142 (86)
d4T/AZT + 3TC + EFV	na	na	3 (5)	9 (6)
Lopinavir-containing regimen	na	na	1 (2)	7 (4)
Other combinations	na	na	0 (0)	7 (4)
HIV status				
Nadir CD4 (cells/mm^3)	na	na	187 (6–346)	146 (1–473)
Most recent CD4 (cells/mm^3)	na	461 (130–745)	207 (6–904)	463 (2–1266)
Most recent viral load				
<400 copies/ml	na	na	12 of 18 (67)	117 of 149 (79)
>400 copies/ml	na	na	6 of 18 (33)	32 of 149 (21)

HIV, human immunodeficiency virus; ART, antiretroviral therapy; na, not applicable; TDF, tenofovir; FTC, emtricitabine; 3TC, lamivudine; EFV, efavirenz; d4T, stavudine; AZT, zidovudine.
Data are shown as number (%) or median (range). Short-term and long-term ART is defined as <12 months and >36 months ART at inclusion, respectively.
*Significant difference (age adjusted $P<0{\cdot}001$) between HIV-infected *vs.* HIV-naïve participants.
**Significant difference (age adjusted $P<0{\cdot}01$) between HIV-infected *vs.* HIV-naïve participants.

different between participants receiving short-term and long-term ART.

Clinical history and findings on ocular examination

Overall, 218 (64%) participants reported at least one eye complaint: blurred vision (42%) was the most common complaint followed by excessive tearing (33%) and foreign body sensation (27%). Eye complaints were more often reported by HIV infected (74%) (aOR = 2·7; 95% CI 1·3–5·5, $P = 0{\cdot}005$) than HIV-naïve individuals (46%). No difference in occurrence of ocular complaints was observed between those on short-term *vs.* long-term ART (70 *vs.* 71%; $P = 0{\cdot}9$). On ophthalmic examination, 52 individuals (15%) were visually impaired, including 39 individuals (75%) with visual impairment of both eyes. Thirty-one of the 39 visually impaired individuals (79%; 9·1% of study population) had severe visual impairment; including 14 individuals with both eyes affected. There was no difference in frequency of visual impairment between the four study groups.

Ocular disease between HIV-infected and uninfected individuals

HIV-infected participants had more frequently an external eye condition (13 of 72 (18%)) compared with HIV-naïve individuals (7 of 105 (7%); aOR = 2·8; 95% CI 1·0–7·6, $P < 0{\cdot}05$); blepharitis was especially common (9 of 13 (69%)) among HIV-infected individuals with external eye conditions. Additionally, anterior segment conditions were more common among HIV-infected (36 of 72 (50%)) than HIV-naïve individuals (28 of 105; (27%); aOR = 2·4; 95% CI 1·2–4·6, $P < 0{\cdot}01$) (Table 2). The main

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Table 2. *Ocular conditions among HIV naïve and HIV-infected individuals* (n = *177*)

	HIV-naïve individuals (*n* = 105)	HIV-infected individuals (*n* = 72)	Age-adjusted crude odds ratio (95% CI)	*P*-value
External eye disease	7 (7)	13 (18)	2·8 (1·0–7·6)	0·04
Blepharitis	6 (6)	9 (13)	–	0·1
Hordeolum	0 (0)	1 (1)	–	0·3
Eyelid scar	1 (1)	4 (7)	–	0·1
Eyelid entropion or ectropion	0 (0)	1 (1)	–	0·3
Proptosis	1 (1)	0 (0)	–	0·1
Anterior segment disease	28 (27)	36 (50)	2·4 (1·2–4·6)	0·009
Pterygium	5 (5)	13 (18)	3·5 (1·1–10·5)	0·03
Keratoconjunctivitis sicca	13 (12)	17 (24)	–	0·3
Anterior uveitis	0 (0)	5 (7)	–	0·06
Clinically detectable cataract	17 (16)	29 (40)	3·5 (1·7–7·0)	0·001
Posterior segment disease[a]	10 (10)	8 (11)	–	0·4
HIV retinopathy	0 (0)	1 (1)	–	0·2
Old inactive retinitis	0 (0)	1 (1)	–	0·2
Posterior vitreous detachment	6 (6)	4 (6)	–	0·7
Retinal detachment	1 (1)	1 (1)	–	0·8
Hypertensive retinopathy	2 (2)	1 (1)	–	0·3
Diabetic retinopathy	1 (1)	0 (0)	–	0·2
Neuro-ophthalmic disease[a]	8 (8)	5 (7)	–	0·3
Glaucoma	8 (8)	5 (7)	–	0·3

HIV, human immunodeficiency virus; ART, antiretroviral therapy.
Data are shown as numbers (%). Age adjusted crude odds ratios were calculated between HIV-infected and HIV-naive individuals.
[a] The posterior segment, including the optic disc could not be evaluated in one participant short-term ART participant.

conditions affecting the anterior segment among HIV-infected individuals were clinically detectable cataract (81%), keratoconjunctivitis sicca (47%), and pterygium (36%). HIV-infected participants had more frequently pterygium (aOR = 3·5; 95% CI 1·1–10·5, $P < 0·03$) and clinically detectable cataract (aOR = 3·5; 95% CI 1·7–7·0, $P < 0·001$). Frequency of posterior segment and neuro-ophthalmic conditions were not different between both groups (Table 2).

Ocular disease among HIV-infected individuals taking ART for a short *vs.* long period of time

The posterior eye segment was more often affected in individuals on long-term than short-term ART (30 *vs.* 9%; aOR = 3·4; 95% CI 1·2–9·2, $P < 0·05$), but there was no difference observed for the external eye, anterior segment and neuro-ophthalmic segment (Table 3). HIV retinopathy (10%) and posterior vitreous detachment (9%) were the most common posterior eye segment conditions observed. A trend was observed for HIV retinopathy ($P = 0·07$) between long-term (10%) *vs.* short-term ART use (2%), but vitreous detachment was equally common in both groups (9% *vs.* 4%; $P = 0·3$). Although the anterior segment was not more commonly affected in individuals on long-term ART, we observed a significant difference for lens status with long-term ART participants more likely to have clinically detectable cataract (57%; aOR = 2·2; 95% CI 1·2–4·1, $P = 0·01$) compared with short-term ART participants (38%). However, there was no difference in occurrence of clinical significant cataract between these groups (age-adjusted $P = 0·6$).

Factors associated with specific ocular disease among HIV-infected individuals on ART

We assessed the association of several clinical and laboratory factors (i.e. age, recent CD4 count, viral load, nadir CD4 count, time on ART, and ART regimen) with the most common eye diseases in HIV-infected individuals taking ART for a short and long period of time (Table 4). Participants with an external eye condition were more likely to have a non-suppressed viral load (aOR = 2·5; 95% CI 1·0–6·2, $P < 0·05$); this association was also observed for blepharitis (aOR = 3·3; 95% CI 1·2–8·8, $P < 0·05$) representing the most common diagnosis in this group. Older age was associated with keratoconjunctivitis sicca (median age 49 (range 25–75) *vs.* 44 (range

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Table 3. *Ocular conditions among HIV-infected individuals participants on short-term and long-term ART (n = 221)*

	HIV-infected short-term ART ($n = 56$)	HIV-infected long-term ART ($n = 165$)	Age-adjusted crude odds ratio (95% CI)	*P*-value
External eye disease	11 (20)	27 (16)	–	0·6
Blepharitis	9 (16)	22 (13)	–	0·6
Chalazion	0 (0)	1 (1)	–	0·5
Hordeolum	1 (2)	1 (1)	–	0·4
Molluscum contagiosum	0 (0)	1 (1)	–	0·4
Eyelid scar	2 (4)	3 (2)	–	0·4
Eyelid entropion or ectropion	1 (2)	2 (1)	–	0·6
Facial nerve paresis	0 (0)	2 (1)	–	0·4
Anterior segment disease	30 (54)	87 (53)	–	0·4
Pterygium	11 (20)	40 (24)	–	0·8
Keratoconjunctivitis sicca	16 (29)	62 (38)	–	0·6
Anterior uveitis	3 (5)	4 (2)	–	0·3
Clinically detectable cataract	21 (38)	94 (57)	2·2 (1·2–4·1)	0·01
Posterior segment disease[a]	5 (9)	49 (30)	3·4 (1·2–9·2)	0·02
HIV retinopathy	1 (2)	17 (10)	–	0·07
Infectious retinitis	0 (0)	1 (1)	–	0·6
Old inactive retinitis	1 (1)	4 (3)	–	0·9
Posterior vitreous detachment	2 (4)	15 (9)	–	0·3
Retinal detachment	1 (2)	1 (1)	–	0·6
Hypertensive retinopathy	0 (0)	2 (1)	–	0·7
Diabetic retinopathy	0 (0)	4 (3)	–	0·3
Age-related macular degeneration	0 (0)	1 (1)	–	0·8
Neuro-ophthalmic disease[a]	4 (7)	19 (12)	–	0·7
Glaucoma	4 (7)	14 (9)	–	0·9
Optic atrophy	0 (0)	5 (3)	–	0·3

HIV, human immunodeficiency virus; ART, antiretroviral therapy.
Data are shown as numbers (%). Short-term and long-term ART is defined as <12 months and >36 months ART at inclusion, respectively. Age-adjusted crude odds ratios were calculated between HIV-infected individuals on long-term ART and short-term ART.
[a] The posterior segment, including the optic disc could not be evaluated in one participant short-term ART participant and in two long-term ART participants.

20–74) years) for those without keratoconjunctivitis sicca (OR = 1·04; 95% CI 1·02–1·07, $P = 0·001$). No associations were observed for clinically detectable cataract. Three cases of immune recovery anterior uveitis were observed in HIV-infected participants on short-term ART; all of whom had nadir CD4 count <50 cells/mm^3 and a clinically mild presentation.

Posterior eye segment conditions were associated with increased time on ART (median months of ART use 63 (range 3–179) *vs.* 48 months (range 1–132)) for those without posterior condition (aOR = 1·02; 95% CI 1·01–1·03, $P < 0·01$). This was also observed for HIV retinopathy (75 months (range 3–179) *vs.* 52 months (range 1–171), aOR = 1·02; 95% CI 1·01–1·03, $P < 0·01$). A trend towards lower nadir CD4 count (<50 cells/mm^3) and HIV retinopathy was observed ($P = 0·06$), but not for viral load ($P = 0·1$). Additionally, an association for increased occurrence of HIV retinopathy was observed for participants using a lopinavir-containing ART regimen (2/8; 25%) compared with participants using tenofovir with emtricitabine or lamivudine and efavirenz, (14/192 (7%); aOR = 6·0; 95% CI 1·0–35·7, $P < 0·05$) but there was no difference for participants using a tenofovir-containing regimen (14/192; 7%) compared with those using a stavudine or zidovudine-containing ART regimen (0/11; $P = 0·3$), albeit with low numbers for all these comparisons.

DISCUSSION

This study reports on ocular disease manifestations among HIV-infected individuals in different phases

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Table 4. *Factors associated with specific ocular disease among HIV-infected individuals on ART (n = 221)*

	Numbers (%) or median (range) among participants with ocular disease	Numbers (%) or median (range) among participants without ocular disease	Age-adjusted crude odds ratio (95% CI)	Age-adjusted *P*-value
Blepharitis (*n* = 31)				
Age (years)	47 (25–65)	46 (20–75)	–	0·9
CD4 cell count (cells/mm^3)	345 (6–1260)	403 (2–1245)	–	0·6
Viral load				
>400 copies/ml	9 (45)	29 (20)	3·3 (1·2–8·8)	0·02
<400 copies/ml	11 (55)	118 (80)		
Nadir CD4 cell count (cells/mm^3)	162 (6–328)	150 (1–473)	–	0·6
Time on ART (months)	53 (1–120)	56 (1–179)	–	0·3
ART regimen				
TDF + FTC/3TC + EFV	28 (90)	166 (87)	1·0	–
d4T/AZT + 3TC + EFV	2 (7)	10 (5)	–	0·8
Lopinavir-containing regimen	1 (3)	7 (4)	–	0·9
Other combinations	0 (0)	7 (4)	–	0·3
Keratoconjunctivitis sicca (*n* = 78)				
Age (years)	49 (25–75)	44 (20–74)	1·04 (1·02–1·07)	0·001
CD4 cell count (cells/mm^3)	365 (2–1266)	404 (11–1163)	–	0·9
Viral load				
>400 copies/ml	17 (28)	21 (20)	–	0·1
<400 copies/ml	43 (72)	86 (80)		
Nadir CD4 cell count (cells/mm^3)	139 (1–328)	158 (3–473)	–	0·9
Time on ART (months)	60 (2–171)	53 (1–179)	–	0·5
ART regimen				
TDF + FTC/3TC + EFV	71 (91)	123 (86)	1·0	–
d4T/AZT + 3TC + EFV	4 (5)	8 (6)	–	0·6
Lopinavir-containing regimen	1 (1)	7 (5)	–	0·2
Other combinations	2 (3)	5 (3)	–	0·7
HIV retinopathy (*n* = 18)				
Age (years)	49 (30–75)	46 (20–74)	–	0·2
CD4 cell count (cells/mm^3)	377 (127–866)	403 (2–1266)	–	1·0
Viral load				
>400 copies/ml	1 (7)	36 (24)	–	0·1
<400 copies/ml	14 (93)	113 (76)		
Nadir CD4 cell count (cells/mm^3)	112 (8–473)	158 (1–416)	–	0·2
Time on ART (months)	75 (3–179)	52 (1–171)	1·02 (1·01–1·03)	0·005
ART regimen				
TDF + FTC/3TC + EFV	14 (78)	178 (89)	1·0	–
d4T/AZT + 3TC + EFV	0 (0)	11 (5)	–	0·3
Lopinavir-containing regimen	2 (11)	6 (3)	6·0 (1·0–35·7)	0·048
Other combinations	2 (11)	5 (3)	5·1 (1·0–28·6)	0·07

HIV, human immunodeficiency virus; ART, antiretroviral therapy; TDF, tenofovir; FTC, emtricitabine; 3TC, lamivudine; EFV, efavirenz; d4T, stavudine; AZT, zidovudine.
Data are shown as number (%) or median (range).

of the HIV/ART treatment program in rural South Africa. We observed that ocular disease is more common among HIV-infected individuals, especially those on long-term ART, and causes substantial ocular morbidity in our study population.

The spectrum of ocular conditions observed in our study is different from what has been reported in the pre-ART period: lower frequency of infectious eye conditions such as retinitis was observed [2, 3, 5, 7]. Instead, blepharitis, pterygium, keratoconjunctivitis sicca, and cataract formation were the main ocular diseases in our HIV-infected population. Different pathophysiological processes may play a role in the increased susceptibility of HIV-infected individuals

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to these conditions. HIV-induced immunosuppression, i.e. low CD4 cell counts, may lead to a reduced ability to control the normal bacterial flora in the cutaneous glands of the eye lids. Changes in this flora may lead to development of blepharitis and other conditions of the external eye [17, 18]. Furthermore, destruction of the lacrimal glands and damage to the conjunctiva resulting from HIV-mediated immune activation and lymphocytic infiltration may progress the development of keratoconjunctivitis sicca and pterygium development [18, 19]. Finally, accelerated immunosenescence has been associated with HIV infection and may cause accelerated formation of age-related eye conditions in particular cataract [9].

Posterior segment disease, especially HIV retinopathy, was more common in HIV-infected individuals on long-term ART. The 10% prevalence of HIV retinopathy observed in patients on ART in our study resembled data from a study in Italy reporting a reduction of HIV retinopathy from 41% before ART to 10% among those treated with ART [7]. A low nadir CD4 count, as also observed in our study, appeared to increase the risk of HIV retinopathy, especially if CD4 counts were below 100 cells/mm^3 [2]. Since HIV-infected individuals are initiating ART at increasingly higher CD4 count, it is expected that the prevalence of this condition will decrease. On the other hand, the effect of longstanding suboptimally suppressed HIV on the retina in patients taking ART is unclear, but microvascular changes might continue to occur. In addition, geographic and genetic factors may play a role in the occurrence of HIV retinopathy [20].

Likewise a Danish nationwide population-based study describing ART introduction as a risk factor for cataract, long-term ART use in our study was associated with clinically detectable cataract [21]. The higher risk for surgery of clinically significant cataract after ART initiation observed in the Danish population suggests that it is likely that patients in our study with clinically detectable cataract will develop clinically significant cataract over time, i.e. associated with visual impairment. This is supported by data from Cape Town that reported an increased risk of cataract for HIV-infected individuals with low nadir CD4 cell counts (<200 cells/mm^3) compared with HIV-uninfected individuals [9]. When comparing similar groups in our study population, the same association is observed: 51% (69/135) of individuals with CD4 count <200 cells/mm^3 present with cataract and 16% (17/105) of HIV-uninfected individuals (aOR = 2·3; 95% CI 1·1–5·0, $P = 0·03$). The potential increase in cataract and demand for surgery among HIV-infected individuals will have major consequences for the South African healthcare system, and likely for many developing countries, as their rates of cataract surgery are already low [22].

The association between low nadir CD4 cell count for HIV retinopathy and cataract reported here suggests that the nadir CD4 cell count is a potential risk factor of non-infectious ocular diseases. Notably, other studies also identified lower nadir CD4 cell count and more prolonged ART use as risk factors for non-infectious HIV-related conditions such as cardiovascular disease and diabetes mellitus [11, 12]. In our study, limited associations were observed between ocular conditions and specific ART drugs. Although the number of individuals using a lopinavir-containing ART regimen was low, the data suggest that its use is associated with the development of HIV retinopathy. In line with this observation, protease inhibitors have been suggested to increase the risk of ocular conditions such as chalazion and different types of retinopathy [7].

None of the participants of this study visited the healthcare facility on the day of recruitment for eye complaints, although on request the majority reported at least one eye complaint. Possible reasons for this unexpected finding include the poor status of public eye care in South Africa, especially in rural settings such as the Mopani District. Many challenges affect the system including lack of knowledge and community awareness, inaccessibility of treatment and poor referral systems (Schaftenaar *et al.*, unpublished data). In our study, HIV-infected individuals reported eye complaints and were diagnosed with eye disease more often than those without HIV infection. Although frequency of visual impairment was similar between these groups, a number of these conditions will result in visual impairment and irreversible eye damage over time if they remain unrecognized and are left untreated (e.g. cataract and uveitis). Moreover, although not directly resulting in visual impairment, ocular diseases such as blepharitis, keratoconjunctivitis sicca and pterygium will also have a negative impact on the quality of life and may result in ocular surface damage if left untreated [23].

Although the main conclusion of our study is that HIV-infected individuals in the population studied, especially those on long-term ART, are at increased risk of developing ocular disease, some limitations of

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the study should be considered. First, it was conducted in a rural setting with limited available resources for ocular examination. We cannot rule out that some of the ocular conditions observed have been misclassified, and that others have been missed. Second, to determine the effects of both HIV infection and ART regiment we recruited participants in four groups in different stages of the national HIV treatment program. This selection was chosen due to the skewed ART program uptake over time in our district, with higher numbers of individuals taking ART between 12 and 36 months. We expect that this selection only had a minimal impact on our results. Nonetheless, as the number of HIV-infected ART-naïve individuals was low, we cannot exclude effects of short-term ART in our HIV-infected *vs*. uninfected analyses. Also, the burden of ocular disease that we observed may be an underestimation as we excluded individuals consulting with eye complaints on the day of recruitment. Finally, recruitment took place at PHC facilities and HIV/ART clinics of participating hospitals. A small number of individuals recruited did not visit the ophthalmology outpatient department for full ocular examination and were excluded from further participation. Although it seems more likely that individuals with eye complaints would visit the ophthalmology department, we did not observe any statistical significant differences between these groups. As most of the recruited individuals participated, we expect this type of selection bias to be minimal.

Taking together, our findings warrant increased awareness among healthcare providers of early clinical symptoms and signs of ocular disease in HIV-infected patients on ART. The increased risk of ocular disease with associated development of visual impairment is of concern as the numbers of individuals on long-term ART is growing rapidly. Therefore implementation of systematic ophthalmologic screening of HIV-infected individuals in the ART program is warranted for early identification of ocular disease and to prevent a future large burden of visual impairment.

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DECLARATION OF INTEREST

None.

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