African Vision and Eye Health
ISSN: (Online) 2410-1516, (Print) 2413-3183

Loss of function of the meibomian glands among HIV and AIDS individuals undergoing antiretroviral therapy

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Dates:
Received: 30 May 2023
Accepted: 07 Feb. 2024
Published: 11 Apr. 2024

How to cite this article:
Mathebula SD, Ntsoane MD. Loss of function of the meibomian glands among HIV and AIDS individuals undergoing antiretroviral therapy. Afr Vision Eye Health. 2024;83(1), a866. https://doi.org/10.4102/aveh.v83i1.866

Background: Meibomian gland dysfunction (MGD) is one of the most encountered diseases in the clinical practice but appears to be underappreciated as it does not cause blindness. Meibomian gland dysfunction is a multifactorial and complex disorder of the ocular surface.

Aim: This study aims to evaluate the characteristics of the meibomian glands in individuals living with HIV and AIDS undergoing antiretroviral therapy.

Setting: The study was conducted at the antiretroviral (ARV) clinic, Mankweng Hospital.

Methods: This was a prospective study conducted with 37 HIV and AIDS participants and 20 healthy controls. All participants were assessed using the Ocular Surface Diseases Index (OSDI) score and, tear break-up time and lid margin regularity (using the slit-lamp biomicroscopy). The loss of the meibomian glands was evaluated using the Marx's line. For this study, this line represented a clinical parameter of meibomian function.

Results: The OSDI score was significantly higher in the HIV and AIDS group than that of the control participants (39.95 ± 18.65 and 13.00 ± 9.09, respectively, $P < 0.05$). The tear breakup time (TBUT) for the HIV and AIDS study group was lower than that of the control group (7.95 ± 3.54 and 9.90 ± 3.70, respectively, $P < 0.05$). The HIV and AIDS participants showed greater meibomian gland loss relative to the healthy controls (9.30 ± 4.97 and 5.70 ± 2.1, $P < 0.05$).

Conclusion: The loss of eyelid meibomian glands is common in people living with HIV and AIDS in comparison with healthy controls.

Contribution: Although there is a decrease in sight-threatening complications in the era of ARVs, ocular surface disorders (OSD) are still commonly found, which may reduce the quality of life of HIV and AIDS individuals.

Keywords: AIDS; dry eye; HIV; meibomian gland; meibomian gland dysfunction; ocular surface; tear film.

Introduction

One of the most common ocular surface disorders (OSD) in HIV and AIDS patients is meibomian gland dysfunction (MGD), which has implications for dry eye diseases (DED).[1,2,3] The meibomian glands are found on the upper and lower eyelids and they play a crucial role in the healthy tear film and ocular surface.[2,3,4,5,6,7,8,9] A stable preocular tear film plays a vital role in providing protection to the ocular surface as well as lubricating the cornea and the palpebral and bulbar surfaces. The human meibomian gland orifices secrete clear meibomian lipid called *meibum* on the skin of the eyelid margin and is spread onto the preocular tear film with each blink.[6,7,8,9,10,11] Meibum provides tear film stability and protects the ocular surface against microbial agents and organic matter. The tear film lipid layer plays an important role in stabilising the tear film and it also provides a barrier to tear evaporation. A stable preocular tear film is a sign of good ocular health.

Meibomian gland dysfunction is a chronic abnormality of the meibomian glands with a multifactorial aetiology.[6,7] It is characterised by abnormality of terminal duct obstruction and qualitative or quantitative changes in glandular lipid secretion, which will eventually impair ocular homeostasis. Meibomian gland dysfunction causes lipid deficiency in the tear film and results in the evaporation of tears. This, then produces alteration of the tear film, giving rise to symptoms of ocular irritation or discomfort that ultimately affect the quality of life.[9,11]

There are several clinical methods to evaluate meibomian gland function.[10] Some are fast, simple, and cost-effective while others are time-consuming. The cost-effective methods to examine the ocular surface include the slit-lamp biomicroscopy but more sophisticated technologies include meibography and interferometry. Although these advanced technologies are valuable, a simple and comprehensive technique that could rapidly and accurately screen and evaluate meibomian gland function is needed for routine clinical practice, especially in poor communities with limited medical support. When a fluorescein dye solution is applied to the lid margin a clear narrow line (called the Marx line) running along the inner eyelid is observed using a slit-lamp. The Marx line represents the border between the tear film and the skin of the eyelid margin.[12,13,14,15] It runs parallel to meibomian orifices along the conjunctival border in healthy individuals. The superficial location of the meibomian glands on the tarsal plates allows their orifices to be quantified and graded using the Marx line.[12,13,14] The meibomian orifices are displaced at regular intervals along the lid margin and are surrounded by a characteristic ring-shaped architecture.[6] The loss of this architecture can be an important clinical sign for MGD.

Most ophthalmic studies on HIV and AIDS patients placed maximum emphasis mostly upon posterior segment disorders and studies characterising the OSD in the era of highly active antiretroviral therapy (HAART) are lacking or few. Hence, the purpose of this study was to investigate whether people living with HIV and AIDS would demonstrate MGD, which is considered to be present if there are subjective symptoms of ocular discomfort, displacements of Marx's line, presence of meibomian gland loss (dropout), and lid abnormalities.[6,7,8,9]

Methods

The study included 37 HIV and AIDS participants as the study group recruited from the Antiretroviral treatment (ART) Clinic and 20 healthy controls between April 2016 and October 2021. All HIV and AIDS participants were on antiretroviral therapy and between the ages of 20 and 40 years. The controls were healthy volunteers recruited from general optometric patients and all were HIV-negative by self-report. All study (HIV-positive) and control participants gave written informed consent prior to performing any test procedures. Inclusion criteria for both groups were visual acuity of at least 6/9 monocularly, no history of ocular diseases, ocular trauma or ocular surgery, and no eyelid abnormality, chalazions, or hordeolums. Participants using contact lenses, or those with allergic conjunctivitis, infectious corneal and conjunctiva, taking topical medications, HIV-positive not on antiretroviral (ARVs), and having systemic disease that could affect the synthesis and function of tear lipids were excluded. The procedures complied with the principles of the Helsinki Declaration for human subjects and its subsequent revisions.

Procedure

Each participant completed a validated Ocular Surface Diseases Index (OSDI) questionnaire, which consisted of 10 specific MGD symptoms. Each question was on a scale of 0 to 10, with 0 for no symptom and 10 for severe. Participants graded their symptoms under the guidance of the researcher to make sure all participants understand. Score for each question and total scores for all 10 questions were calculated to assess the severity of MGD symptoms.

Slit-lamp biomicroscopy was used to assess the tear breakup time (TBUT) in seconds, eyelid margins, and meibomian gland loss. The interval between a complete blink and the appearance of the first dark or dry spot was recorded after the installation of fluorescein. The lid margin was evaluated for abnormality under the diffuse illumination of the slit lamp. The abnormality of eyelid margin was defined as zero (0) for normal and one (1) for irregular. The central two-third meibomian glands were observed and squeezed to assess the meibum.

A moistened fluorescein strip was inserted into the lower fornix of the conjunctiva and participants were asked to blink several seconds. The strip was moistened with a drop of saline. After the instillation, the eyelids were examined using the slit lamp biomicroscopy and a stained line (Marx's) was observed. The fluorescein was chosen over other stains as it is widely used in clinical practice. Both the upper and lower eyelids were everted and the slit lamp was used to observe the line. The fluorescein-stained line was observed to extend along the entire length of the inner surface of both the upper and lower eyelids with a similar pattern. A score was assigned to the line based on its location in relation to the meibomian orifices: 0 = the line runs entirely along the conjunctival side of the meibomian orifices; 1 = parts of the line touch the meibomian orifices; 2 = the line ran through the meibomian orifices; 3 = the line was on the anterior to the meibomian orifices, that is, ran along the eyelid margin.

The observed patterns of the fluorescein-stained lines were used to predict the loss of meibomian glands for each eye lid. The score was graded using the following grades: 0 = no loss of meibomian glands; 1 = meibomian gland loss involve less than 1/3 of the total meibomian gland area (33%); 2 = loss between 1/3 and 2/3 of the total meibomian gland area and 3 = loss of more than 2/3 of the total meibomian gland area.[16,17]

Both the upper and lower eyelids were everted and the slit lamp was used to detect the meibomian gland dropout. The ultraviolet Burton lamp was used to grade the meibomian gland loss.[18,19] Meibomian gland loss or dropout was graded from 0 to 3, where 0 is no meibomian gland loss, 1 was 4 glands loss, 2 was 5–10 gland loss, and 3 was > 10 gland loss. It was also expressed as the percentage when the areas of meibomian gland loss were divided by the total area of the everted eyelid. The score of the upper and lower eyelids were then added to obtain the total meiboscore ranging from 0 to 6.[16,17]

Stable pressure was applied on the central third of the lids and the number of glands with secretions were noted. The degree of ease in expressing meibomian secretion was graded on a scale from 0 to 3, where grade 0 = easy expression, 1 = mild expression, 2 = moderate, and 3 could not be expressed. The meibomian lipid was graded as 0 = clear, 1= mild cloudy, 2 = cloudy, and 3 = thick. The secretion of the meibomian glands was examined by applying compression on selected glands and the colour of the secretions were noted and graded as: 0, clear fluid; 1, cloudy fluid; 2, cloudy-yellow with some viscosity; 3, white think secretions; and 4, no secretions.

Statistical analysis

All statistical analysis was performed by using the SPSS version 24 (SPSS Inc.; Chicago, IL, USA). Shapiro—Wilk test was used to determine the normality of quantitative measurements. Measurements were presented with means and standard deviations. Spearman's correlation analysis was used to explore the correlation between variables. Statistical significance was considered when the *P*-value was less than 0.05. For brevity, only the results of the right eyes are presented in this article.

Results

This was a prospective study performed on 39 HIV and AIDS participants and 20 healthy controls who were believed to be HIV-negative (as mentioned earlier). The study group consisted of 23 females and 14 males with an average age of 29.22 ± 6.0 (age range: 20–40) years. The control group consisted of 12 females and eight males, ages from 20 to 40 years with an average of 30.35 ± 6.4 years of age. As each sample was less than 200, the Shapiro–Wilk test was used to assess the normality of measurements and all measurements were normally distributed.

Table 1 shows the descriptive statistics of all variables for the study and control participants. All measurements of interest showed statistically significant differences among the two groups, $P < 0.05$. The most common reported symptoms by the HIV and AIDS participants were dryness, burning sensation, foreign body sensation, and photophobia with the other symptoms being less than 50% of the time. Figure 1 shows the distributions of meibomian glands parameters. The TBUT of HIV and AIDS group was significantly smaller than that of control group, $P < 0.05$. The average meibomian glands for the study group was 28.81 ± 4.1 and 24.51 ± 3.5 for the upper and lower eyelids while for the control group were 32.9 ± 5.5 and 25.5 ± 3.2 for upper and lower eyelids, respectively. Meibomian gland loss (average of the upper and lower eyelids) was higher in HIV and AIDS group compared with the control participants. Based on the number of meibomian glands, there was a corresponding 5–6 gland loss in HIV and AIDS compared with 0–2 in the control group.

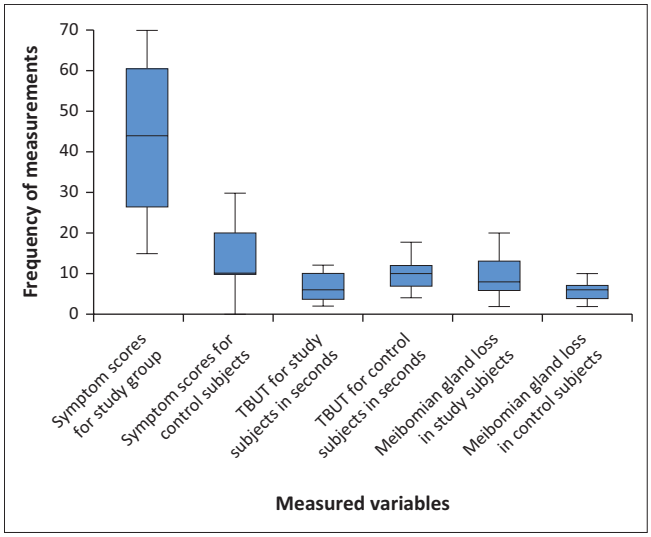
TABLE 1: Descriptive statistics for the right eyes for participants in their two groups.

Variables	Study participants	Control participants	*P*
Mean ages and standard deviations of participants (in years)	29.22 ± 6	30.35 ± 6.4	0.34
Gender (F/M)	23/14	12/8	0.29
CD4+ cell count	398.95 ± 105	Not available	None
TBUT (s)	7.95 ± 3.54 Range: 2–14 s	9.90 ± 3.7 Range: 4–18 s	0.00
OSDI symptom score	39.95 ± 18.6 Range: 15–70	13.00 ± 9.1 Range: 5–30	0.00
Meibomian gland upper lid	28.81 ± 4.5 Range: 20–36	32.90 ± 5.5 Range: 24–40	0.03
Meibomian glands lower lid	24.51 ± 3.5 Range: 20–32	25.45 ± 3.2 Range: 20–30	0.41
Meibomian gland loss	9.30 ± 4.9 Range: 2–20	5.70 ± 2.1 Range: 2–10	0.00
Quality of expressed meibum	1.51 ± 0.5 Range: 1–3	0.65 ± 0.7 Range: 0–2	0.00

TBUT, tear breakup time; OSDI, Ocular Surface Diseases Index.

The Marx's line moved anteriorly to encroach the orifices, then lying at the same level, and end-up moving anteriorly to the meibomian orifices. The obstructed or opaque orifices were more visible than the normal ones. The obstructed orifices were statistically higher (67%) in HIV and AIDS than the controls (24%), $P = 0.00$. The quality of meibomian secretion was graded 3 in 53.7% of HIV and AIDS and only up to grade 2 in 34.5% control participants. The degree of non-expressibility in meibomian orifices symbolised the degree of obstruction of the meibomian glands. The HIV and AIDS participants presented with 19.6% of individuals with most glands that could not be expressed. The Marx's line was irregular and showed displaced orifices in most study participants, and the mean was higher in HIV and AIDS (2.8 ± 1.7) than the controls (1.6 ± 2.5), $P = 0.05$.

Correlation analysis was performed to explore the relationships between the CD4+ cell count and the other variables within the HIV and AIDS sample (Figure 2). The highest correlation (moderate) was between the CD4+ cell count and the TBUT, $r = 0.48$, $P = 0.00$. The correlations



TBUT, tear breakup time.

FIGURE 1: Box plots for the variables of concern using medians and interquartile ranges (IQR).

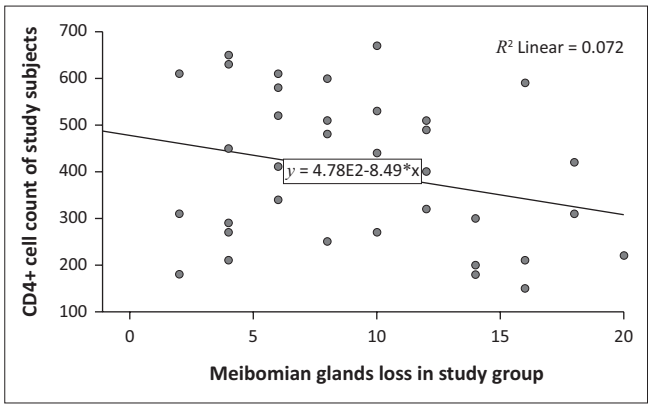


FIGURE 2: Scatter plot between meibomian gland loss and CD4+ cell count (R = 0.036, P < 0.00).

between the CD4+ cell count and symptom scores and meibomian gland loss in study participants were r = 0.30, P = 0.07 and r = –0.30, P = 0.01. There was no correlation between TBUT and OSDI symptom scores. The regression equation was used to explore if the CD4+ cell count could be used to predict the meibomian gland loss. The formula generated: meibomian gland loss = 12.68 – 0.08 (CD4+ cell count). However, the meibomian gland loss was not correlated with the duration of HIV and AIDS infection (P > 0.05).

Discussion

Highly active antiretroviral therapy restores the CD4+ T-cell immunity and lowers the plasma HIV and AIDS viral load to undetectable levels.[20] It has improved the length and quality of life of individuals with HIV and AIDS. However, HIV and AIDS cannot be eliminated completely because of various reservoirs in the human body, including the meibomian glands. Tears are mostly secreted by the lacrimal glands, and there is additional contribution from the meibomian glands and goblet cells.[21,22] HIV has been isolated from tears of patients with undetectable plasma viral load who were on long-term HAART. This shows that the meibomian glands and other tear-associated tissues can serve as reservoirs or compartment of HIV. Reservoir means the persistence of HIV in tissues even in the presence of an effective immune response and ARV therapy.[21]

In the healthy eye, the meibomian glands provide the meibomian lipids that form the lipid layer of the tear film and increases its TBUT.[11] Hyperkeratinisation of the meibomian glands causes MGD. The MGD is the most common encountered disease in the ophthalmic practice. The most common symptoms of MGD include dry eye, irritation, burning sensation, photophobia, foreign body sensation, pain, tearing, asthenopia, blurred vision, redness, eyelids swelling, itching, and secretions.[2,3,4] Meibomian gland dysfunction does not exist in isolation but is linked to other ocular and systemic conditions. Defining the dysfunction is a challenge as it is associated with multiple complex patho-aetiological mechanisms. Furthermore, it is unknown as to whether MGD is a disease of the eyelids, tear film, or the entire ocular surface. The presence of MGD is strongly associated with the symptoms and signs of DED, hence, differentiating MGD-related dry eye from other ocular surface diseases is a challenge. The diagnostic sequence for assessment of MGD include patient questionnaire using subjective symptoms, TBUT, eyelid margin, and evaluation of MGD dropout (loss).[17]

The participants' symptoms were assessed using the OSDI questionnaire. The results of this study showed that HIV and AIDS participants had significantly higher OSDI score when compared with the control group, P = 0.00. We used a grading scale of 0 to 10, with 0 for never and 10 for severe. In this study, we found dryness, photophobia, foreign body sensation, and itching as the most common symptoms affecting the daily quality of life of HIV and AIDS participants. This suggests that ophthalmic clinicians should evaluate meibomian glands signs while examining patients with such symptoms.

The TBUT is an indicator of tear film stability and a score of less than 10 s indicates an inadequate balance between aqueous and lipid layers of the tear film.[17] The average TBUT score for our study group was significantly lower compared to that of the controls (7.95 ± 3.54 and 9.90 ± 3.70, respectively, P = 0.09). Generally, TBUT is regarded as a test for diagnosis of evaporative dry eye but is more relevant in the diagnosis of MGD as the core mechanisms of dry eye is tear instability, which is dependent on meibomian gland function.[1,6] A low TBUT implies a possibility of the compromised tear film lipid layer, hence MGD, while a high TBUT measure is regarded as suggesting a normal lipid layer and healthy meibomian gland function.[6] There is a source of variability in TBUT because of the volume of fluorescein to be delivered. It is unknown whether the moistened fluorescein strip should be shaken before installation and whether the strip should be applied on the superior, inferior, temporal, or nasal bulbar conjunctive or the tear meniscus. In this study the strip was placed on the temporal lower fornix of the conjunctiva.

Eyelid margin irregularity was seen in 21 (56.8%) HIV and AIDS participants and only in four (10.8%) controls. Features observed in this study included thickening of the eyelids margin and an association between a low TBUT and a compromised eyelid margin irregularity. The cause of irregularities of the lid margin is unknown but could be because of narrowing of meibomian orifices because of hyperkeratinisation of the meibomian glands. However, the diagnosis of MGD is not made on the irregular lid margin but on meibomian gland dropout or loss and expression.[17,23]

Loss of meibomian glands or dropout was determined using the slit lamp and Burton lamp. The meiboscore was higher in the study group, which was the HIV and AIDS sample. Meibomian gland loss (meiboscore ≥ 3) was seen in 83.7% of HIV and AIDS and 37.8% in the control group. The prevalence

of MGD in HIV people who were under antiretroviral therapy was also reported in 2018 by Singalavanija et al.[18] It has been reported that contact lens wear also experiences about 50% meibomian gland loss, which is somehow less than what has been observed in this study. Mathers and Lane[8] in 1998 also found MGD of about one gland per four assessed areas of the eyelid in healthy adult population. A recent study by Nguyen et al.[23] also found greater meibomian gland dropout in HIV-positive patients. This study shows that the HIV and AIDS participants were significantly associated with a greater degree of meibomian glands loss when compared with healthy controls. Meibomian gland loss is significantly correlated with altered tear film lipid layer stability, ocular surface damage, and the quality of the expressed meibum.

The cause of meibomian glands loss is unknown but could be because of any combination of six separate conditions, which are obstruction of meibomian glands, abnormal secretion of the meibomian glands, eyelid inflammation, corneal and conjunctival inflammation and epithelial damage, and microbiological changes.[2,3,4,5,6,7,8,9,16,17] Hyperkeratinisation of the meibomian glands causes obstruction of the meibomian glands.[6] The inflammatory mediators are the possible causes of hyperkeratinisation of the epithelial lining of the mebomian glands duct. The orifices of the meibomian glands then become obstructed, preventing meibum to be secreted onto the ocular surface. The inability of the meibum to be excreted results in increased pressure that causes the dilation of the meibomian glands duct. The ductal dilation leads into acinar degeneration and atrophy that lead to loss of meibocytes. So, the stagnation of the meibum causes the alterations to the meibomian secretions, which include the thickening and loss of clarity and pouting of the meibomian orifices and loss of tear film integrity.

Blockage of the meibomian glands leads to stasis of the meibum inside the gland duct, which then promote bacterial and mite proliferation and cause inflammation of the eyelids and possibly the conjunctiva.[16,17] Furthermore, the upper and lower eyelids laxity may exacerbate reduced meibum drainage through decreased muscle pressure on the meibomian glands. The ingrowth of bacteria enhances the production of lipid-degrading lipases and esterases that increase the viscosity of the meibum, reducing its secretion onto the surface of the tear film.[19,20,21] The absence of the normal meibum reduces the lipid content of the tear film, in which the lipid-deficient tear film promotes increased tear evaporation, hyperosmolarity, and inflammation.

Tears play an important role in refraction of light, preventing infection, and maintaining homeostasis of the ocular surface.[2] It has been reported that HIV-1 can be detected in tears of HIV-positive patients who were under long-term HAART with undetectable blood viral load.[22] This suggest that tear-associated tissues could be new reservoirs of HIV. However, the causes of persistent viral loads in eyes are still controversial and not completely understood but one possibility is the limited entry of some anti-HIV drugs because of ocular barriers. A recent study by Qian et al.[24] found that the tear viral load is positively correlated with plasma viral load while negatively correlated with CD4+ cell count. Although HAART can successfully reduce plasma HIV viral load to undetectable levels in most HIV-infected individuals, HIV virus cannot be eliminated completely, suggesting that the lacrimal gland may be the new HIV reservoir that needs effective antiretroviral regimens[25] in the eye or the ocular organ could be a viral sanctuary. While the meibomian gland dropout may be because of either direct infiltration of the meibomian gland by HIV or alteration of the meibomian gland morphology and function as a by-product of ART, future studies should report the individual medications comprising ART.

This study has possible limitations. Although we used a standardised OSDI questionnaire designed for DED, sample sizes were small, and the unavailability of the latest imaging modalities influenced the study. Newer imaging technologies would provide valuable information on the morphology and architecture of the meibomian glands. We did not assess the whole ocular surface unit, which limits the full understanding of the MGD. The ultraviolet Burton lamp is limited in some operations. It lacks variability of illumination and magnification control.

Another limitation was that controls were not evaluated directly regarding their HIV status but were regarded through self-assessment as healthy and HIV-negative. CD4+ cell count was only available for the study participants but the duration of the HIV and the HAART were not recorded. Despite the limitation, significant differences in variables of interests were observed for the study (HIV-positive) participants and controls.

Another possible issue was that grading scales as used herein are subjective and highly dependent upon examiner experience and skills. Furthermore, the control group was also smaller in size than for the HIV and AIDS group and this could have had unknown but potentially important effects upon the findings from this study. Issues such as the duration of HIV and AIDS and the duration of treatment for the condition might also be important when considering the results herein.

Conclusion

Meibomian glands are important contributors to the maintenance of a healthy ocular surface. Many pathologies can disrupt their functioning causing the quality and quantity of meibum to be altered with a negative impact on the ocular surface. The main finding of this study is the presence of several meibomian gland loss with HIV and AIDS individuals relative to normal healthy controls.

This study showed that the prevalence of meibomian gland loss among individuals with HIV and AIDS was 87%. The cause of meibomian gland loss in HIV and AIDS individuals is unknown but may be because of either direct infiltration of the meibomian gland by the HIV or an alteration of the gland as a by-product of ART.

Individuals with HIV and AIDS are at a greater risk of developing OSD. Meibomian gland morphology and function should be routinely evaluated for the occurrence of MGD and subsequent OSD.

Acknowledgements

The authors thank individuals who volunteered to participate and the Medical Research Council of South Africa.

Competing interests

The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.

Authors' contributions

S.D.M. and M.D.N. contributed equally to this research article.

Ethical considerations

Ethical clearance to conduct this study was obtained from the University of Limpopo, Turfloop Research Ethics Committee. The ethics approval number is TREC/196/2015:IR.

Funding information

The funding for this study was provided by the South African Medical Research Council.

Data availability

The data that support the findings of this study are available from the corresponding author, S.D.M., upon reasonable request.

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