



# Ocular surface disorder among HIV and AIDS patients using antiretroviral drugs



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**Background:** Ocular disorders occur in 50% – 80% of HIV and AIDS patients, and dry eye has been reported as one of the most common anterior segment manifestations in these patients.

**Aim:** The aim of this study was to investigate ocular surface disorders (OSDs) or dry eye in people living with HIV and AIDS on antiretroviral (ARVs) in a controlled setting.

**Setting:** Mankweng Hospital, ARV Clinic.

**Methods:** This study included 130 HIV and AIDS participants attending an ART Clinic at Mankweng Hospital and 48 controls. Each participant had an anterior and posterior segment eye examination with a slit lamp and fundus camera, respectively. The dry eye or OSD was investigated with Schirmer's test and invasive fluorescein tear breakup time (TBUT).

**Results:** The means of the Schirmer's test and TBUT were 6.7 mm ± 4.0 mm and 6.9 ± 4 seconds in HIV and AIDS participants, while the means in the control group were 13.5 mm ± 3 mm and 14.2 ± 3 s, respectively. The correlations between the severity of dry eye and the level of CD4 cell count were positive and significant.

**Conclusion:** There was decreased tear production as measured by the Schirmer's test and TBUT in our study participants. Statistically significant correlations were found between the severity of dry eye and the level of CD4 cell count. Although the entire pathogenesis of dry eye in HIV and AIDS patients remains unclear, it may be associated with lymphocytic infiltration and destruction of the lacrimal gland.

## Introduction

Since its first report in 1981, acquired immunodeficiency syndrome (AIDS) has emerged as a major public health disease.<sup>1,2,3,4</sup> This disease is caused by a retrovirus called human immunodeficiency virus (HIV) and it is a potentially lethal multisystemic disease affecting various systems and organs of the body including the eye.

Ocular lesions are a common finding, and studies have shown that 50% – 80% of HIV and AIDS patients will have at least one ocular manifestation at some point in time during the course of the disease.<sup>5,6,7,8,9</sup> The ocular lesion can involve any part of the eye from the adnexa and anterior segment to the posterior segment.

Dry eye (also called keratoconjunctivitis sicca or dry eye syndrome) appears to be more common among patients with HIV and AIDS.<sup>10,11,12,13,14,15</sup> The Tear Film and Ocular Surface Society (TFOS) Dry Eye Workshop (DEWS) II defined dry eye as follow:

a multifactorial disease of the ocular surface characterised by a loss of homeostasis of the tear film and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.<sup>16,17,18</sup>

In physiology, homeostasis is described as the state of equilibrium of the body with respect to its various functions, and chemical composition of the fluids and tissues.<sup>17</sup> The open eye is constantly subjected to environmental stresses (low humidity, wind, cold and physical, chemical or microbial agents) through evaporation of the tears but is protected from damage by the homeostatic mechanisms that regulate tear secretion (mainly from lacrimal glands) and distribution in response to signals from the ocular surface. Failure of homeostatic mechanisms may lead to a quantitative or qualitative deficiency of tears that induces tear film instability. This then may initiate a chain of inflammatory events that characterise dry eye or ocular surface disorder (OSD).<sup>16</sup> Disruption of tear film homeostasis describes the fundamental process in the

development of dry eye. Loss of homeostasis in the definition seems to account for the things that are unknown and those that we cannot yet grasp.

Dry eye is a common disorder of the precocular tear film that results in damage to the ocular surface and can cause ocular discomfort. It is characterised by instability of the tear film that can be caused by deficient or insufficient amount of tear production or because of poor quality of tear film, which results in increased evaporation of the tears.<sup>19,20,21,22,23,24,25,26,27</sup> The symptoms of discomfort are due to insufficient tears which cause damage to the interpalpebral ocular surface.<sup>17,18,21</sup> It is also accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.<sup>27,28</sup> Although dry eye is a common condition causing discomfort and affecting the quality of life, it is widely underdiagnosed but is generally not sight threatening.

The normal tear film and its anti-inflammatory constituents provide lubrication and protection for the tissues of the palpebral and bulbar surface, and the tears also provide a smooth refracting surface for light entering the visual system.<sup>28</sup> A lack of tear production exposes the ocular surface to the risk of damage provoked by environmental factors. The purpose of this study was to investigate dry eye in HIV and AIDS patients on antiretroviral drugs and to establish whether there is any correlation between the dryness of the eyes with the level of the CD4 cell counts.

## Methods

In this explorative and descriptive study, 130 HIV and AIDS patients with any duration (of the condition after initial diagnosis) between the ages of 20 and 40 were recruited to participate in the study and 48 healthy controls of similar age seeking medical attention for refractive errors were recruited. The study was conducted at Mankweng Hospital, ART Clinic, Limpopo Province from May 2016 to November 2017.

Convenience sampling was used as all participants available on the day of investigation and willing to participate were enrolled. All HIV and AIDS cases and controls suffering from corneal or conjunctival pathology, contact lens users, diabetes mellitus or refractive surgery were excluded from the study as these conditions could independently cause dry eye. All HIV and AIDS and controls with any form of retinopathy were excluded. Also, participants on topical and/or systemic medications known to cause dry eye, such as topical glaucoma therapy, were excluded.

## Procedures

All HIV and AIDS participants and controls were subjected to ophthalmologic examination that included distance and near visual acuities, detailed anterior segment examination with a slit lamp and non-mydratic fundus imaging. All participants were investigated for dry eye with Schirmer's test and sodium fluorescein invasive tear breakup time

(TBUT) measurements. (A possible minor limitation of our study was that a standardised questionnaire about dry eye symptoms was not used.)

## Schirmer's test

Schirmer's test was performed using Schirmer's strips. The Schirmer's test quantitatively measures the aqueous tear production by the lacrimal gland during a fixed time period.<sup>23</sup> The test was performed by placing prepacked sterile paper strips without anaesthetic simultaneously in both inferior conjunctival sac away from the cornea, allowing the strips to remain there for 5 minutes. Installation of a topical anaesthetic could induce reflex tearing and the instilled volume itself could contribute to wetting of the Schirmer's strip.<sup>26</sup> Participants were instructed to close their eyes during the test. Serin et al.<sup>23</sup> suggested that administering the Schirmer's test with the patient's eyes closed produces less variable results and greater repeatability. After 5 min, the strip was removed and the length of the wetting of the strip, starting from the indentation, was measured in millimetres. A wetting length of less than 10 mm within 5 min was considered tear production deficiency.<sup>26</sup>

## Sodium fluorescein tear breakup time

Tear breakup time is the time required for the tear film to break up following a blink. It is a quantitative test for the measurement of the tear film stability.<sup>24,26</sup> A fluorescein dye strip wetted with one to two drops of non-preserved saline solution was applied in the lower conjunctival sac. Participants were instructed to blink five times to distribute the dye throughout the tear film and then asked to look straight ahead without blinking.<sup>24,26</sup> The participants were also asked to refrain from talking during the procedure. Two minutes after the application of fluorescein, the broad-beam of the slit lamp biomicroscope with a cobalt blue filter was used to examine the appearance of the first dry spot or hole on the cornea without artificially holding the lids open.<sup>26</sup> The time period elapsed between the last complete blink and the first appearance of a dry spot in the tear film was recorded as the TBUT in seconds. Breakup time of less than 10 s was considered as suggesting an unstable tear film.<sup>24,26</sup>

On the basis of Schirmer's and sodium fluorescein TBUT tests, grading of dry eye was classified into three types: mild, moderate and severe.<sup>17,18,23,24,25,26,27</sup> Mild dry eye was defined in participants who had a Schirmer's test result of 10 mm – 15 mm in 5 min and TBUT more than 10 s. Moderate dry eye was Schirmer's test result of 5 mm – 10 mm in 5 min and TBUT of 5–10 s. In severe dry eye, the Schirmer's test result was less than 5 mm in 5 min and TBUT less than 5 s. Normal values of Schirmer's test are more than 15 mm in 5 min,<sup>23</sup> while for TBUT are 20 s.<sup>24</sup>

## Statistical analysis

The IBM SPSS version 23 (SPSS Inc., Chicago, IL, United States) was used to analyse the data. Descriptive and

inferential statistical analyses were applied. The normality of the continuous data obtained was tested using the Shapiro–Wilk test. Results for these measurements are presented using means and standard deviations. The statistical significance was set at  $p < 0.05$  for all tests and 95% confidence intervals were quoted. Data for the right eyes were used for all analyses.

## Ethical considerations

The study was approved by the University of Limpopo and University of Pretoria Research Ethics Committees and was conducted in accordance with the principles contained in the Declaration of Helsinki. All HIV and AIDS and control participants provided consent to participate in the study after explanation of the nature and possible consequences of the study.

## Results

A total of 178 participants, including 130 HIV and AIDS patients (102 females and 28 males) and 48 healthy individuals of similar age as controls (30 females and 18 males), were included in the study. The mean age ( $\pm$  standard deviation) of HIV and AIDS participants was  $30.8 \pm 6$  years and  $30.4 \pm 6$  years in the control group,  $p > 0.05$  (see Table 1). Most of the participants (53.8%) were in the age range of 31–40 years.

**TABLE 1:** Descriptive statistics for 178 participants, aged 20–40 years.

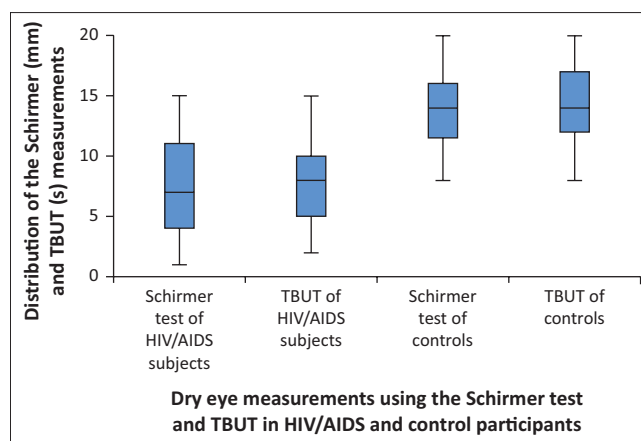
Variable	HIV and AIDS	Controls
<b>Sex</b>		
Female (N)	102	30
Male (N)	28	18
Total (N)	130	48
<b>Mean age and SD (years)</b>		
	<b><math>30.8 \pm 6</math></b>	<b><math>30.4 \pm 6</math></b>
<b>Mean Schirmer's and SD test in mm over 5 min and 95% confidence interval</b>		
Minimum	6.35	12.60
Maximum	8.82	14.40
<b>Mean TBUT and SD in seconds and 95% confidence interval</b>		
Minimum	7.07	13.21
Maximum	9.14	15.21
<b>Medians</b>		
Schirmer's test	7.50	14.00
TBUT	8.00	14.00
<b>Skewness</b>		
Schirmer's test	0.36	0.29
TBUT	0.31	0.28
<b>Kurtosis</b>		
Schirmer's test	-1.07	-0.37
TBUT	-0.83	-1.06
<b>Mean CD4+ cell count and SD</b>		
Cell/ $\mu$ L	275 $\pm$ 150	-
Range	80–680	-

N, number; CI, confidence interval; SD, standard deviation; TBUT, tear breakup time; HIV and AIDS, human immunodeficiency virus/ acquired immunodeficiency syndrome; CD4, T-lymphocyte cell bearing CD4 receptor.

Note: Mean differences, Schirmer's test and fluorescein TBUT (HIV and AIDS):  $-0.18 \pm 3$ , 95% CI,  $-0.7$  to  $-0.4$  ( $p = 0.49$ ); mean differences, Schirmer's test and fluorescein TBUT (control):  $-0.7 \pm 4$ , 95% CI,  $-1.9$  to  $0.5$  ( $p = 0.25$ ). Mean difference of Schirmer's test between HIV and AIDS cases and controls:  $-5.9 \pm 5$ , 95% CI,  $-7.3$  to  $-4.6$  ( $p = 0.00$ ); mean difference of TBUT between HIV and AIDS cases and controls:  $-6.1 \pm 4$ , 95% CI,  $-7.4$  to  $-4.8$  ( $p = 0.00$ ). Standard deviations (SD) are also provided. The units for Schirmer's test are in millimetres (mm) and seconds (s) for sodium fluorescein TBUT.

The mean dry eye value was significantly reduced in HIV and AIDS participants as compared to the controls,  $p < 0.01$  (see Table 1 and Figure 1). The Schirmer's test showed 80% of HIV and AIDS participants had dry eye, while the TBUT less than 10 s was seen in 85.4% of the study participants. Approximately 18% of the control participants had mild dry eyes (see Table 2). The mean differences between the Schirmer's test and TBUT in the HIV and AIDS and control group were  $-0.18$  (95% CI,  $-0.7$  to  $-0.4$ ),  $p = 0.49$  and  $-0.7$  (95% CI,  $-1.9$  to  $0.5$ ),  $p = 0.3$ . These mean differences were, however, not found to be statistically significant. However, the mean differences of Schirmer's test and TBUT between the HIV and AIDS and controls were statistically significant  $-5.9$  (95% CI,  $-7.3$  to  $0.46$ ) and  $-6.1$  (95% CI,  $-7.4$  to  $-4.8$ ),  $p = 0.00$ , respectively. Tables 3–4 and Figure 2 show the CD4+ cell count in groups of 100. Most participants (60.8%) had CD4+ cell count between 100 mm/ $\mu$ L and 300 mm/ $\mu$ L. Table 5 shows the association of dry eye or OSD with the CD4+ cell count ranges.

Visual inspection of the distributions may be used for assessing normality, although this approach is usually unreliable. The boxplot (box and whisker plot) is one approach for checking normality visually. The boxplot shows the median as a bold horizontal line inside the box and the interquartile range (range between the 25th and 75th percentiles) as the length of the box (see Figure 1). The whiskers (line extending from the top and bottom of the box) represent the minimum and maximum values when they are within 1.5 times the interquartile range from either end of



TBUT, tear breakup time; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.

**FIGURE 1:** The boxplots display the distributions and medians of Schirmer's test and TBUT in study and control participants.

**TABLE 2:** Dry eye results for 178 participants.

Range of dry eye	HIV and AIDS cases				Controls			
	Schirmer's		TBUT		Schirmer's		TBUT	
	N	%	N	%	N	%	N	%
0–5 (severe)	67	51.5	56	43.1	0	0.0	0	0.0
5–10 (moderate)	37	28.5	55	42.3	9	18.8	10	20.8
6–10 (mild)	24	18.5	18	13.9	20	41.7	24	50.0
> 15	2	1.5	1	0.8	19	39.6	14	29.2

N, number; TBUT, tear breakup time; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.

**TABLE 3:** Results for CD4+ cell count in mm/ $\mu$ L for 138 human immunodeficiency virus/acquired immunodeficiency syndrome participants.

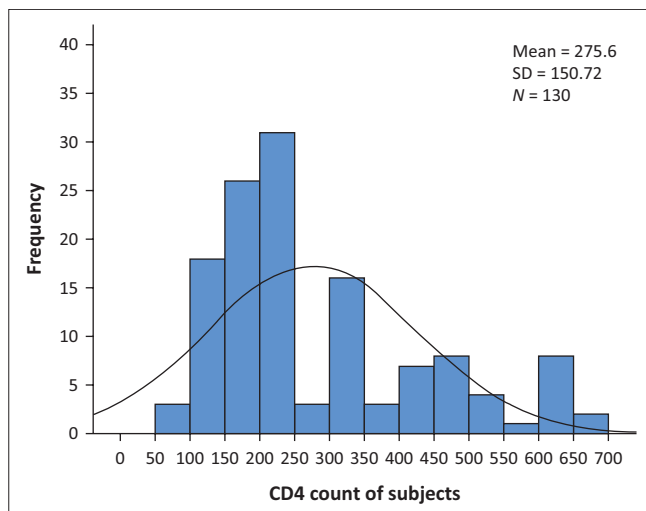
Ranges of CD4+ cell counts	N	%	Sex	
			Females	Males
0–100	8	6.2	6	2
101–200	52	40.0	39	13
201–300	27	20.8	22	5
301–400	16	12.3	13	3
401–500	14	10.8	12	2
501–600	9	6.9	7	2
> 600	4	3.0	3	1
<b>Total</b>	<b>130</b>	<b>100.0</b>	<b>102</b>	<b>28</b>

N, number; CD4, T-lymphocyte cell bearing CD4 receptor.

**TABLE 4:** Descriptive statistics of the CD4+ cell count.

Statistics	CD4+ cell count (mm/ $\mu$ L)
Mean $\pm$ SD	275.60 $\pm$ 150.72
Lower bound (95% CI)	249.45
Upper bound (95% CI)	301.75
Median	214.50
Minimum	80
Maximum	600
Interquartile range	178
Skewness	0.99
Kurtosis	-0.04

CI, confidence interval; SD, standard deviation; CD4, T-lymphocyte cell bearing CD4 receptor.



Note: Mean, 275.6; SD, 150.72; N, 130.

N, number; CD4, T-lymphocyte cell bearing CD4 receptor; SD, standard deviation.

**FIGURE 2:** Frequency histogram of the distribution of CD4 cell count of 130 study participants. SD, standard deviation;

the box, hence the term box and whisker plot. The boxplots were essentially symmetric since the median lines were approximately at the centre of the box and symmetric with the whiskers, implying normal distributions.

The median (interquartile range) of Schirmer and TBUT for HIV participants were 7.00 (7) mm and 8.00 (5) s, respectively, while for controls they were 14.00 (5) mm and 14.00 (6) s, respectively ( $p < 0.05$ ).

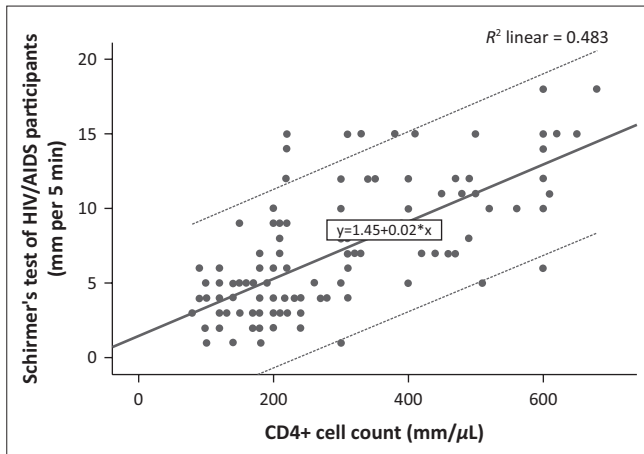
Boxplots are a useful way of comparing two or more data sets. The frequency histogram was used to check for normality for the CD4+ cell counts because it gives a picture of the data and shows the distribution of the data set (see Table 4 and Figure 2). The CD4+ cell counts were not normally distributed; there is a lack of symmetry (skewness) and pointiness (kurtosis). The values of the skewness and kurtosis should be zero in a normal distribution. A positive skew was seen in Figure 2, where the right tail is longer and the mass of the CD4+ cell count distribution was concentrated on the left of the figure. Kurtosis of any normal distribution is three (3). Distribution with a kurtosis less than three is platykurtosis (see Table 4). Platykurtosis does not imply the peakedness, but it means a distribution that produced less extreme outliers than the normal distribution. Shapiro–Wilk test of normality was performed and showed that  $p < 0.01$ , which means the CD4+ cell count was not normally distributed.

The correlation and regression analyses were performed for the CD4+ cell count with the Schirmer's test and TBUT measurements, respectively. Figure 3 shows the regression between the CD4+ cell count and the Schirmer's test. The Pearson's correlation ( $r$ ) was 0.7, while the correlation between CD4+ and TBUT was 0.457 (see Figure 4). Values greater than 0.7 are regarded as strong correlation, while values between 0.5 and 0.7 are treated as good correlation.<sup>29</sup> Values between 0.3 and 0.5 are treated as moderate or fair correlation, while any value less than 0.3 are interpreted as poor correlation.<sup>29</sup> A coefficient of determination ( $r^2$ ) was determined to denote the proportion of the variability of Schirmer's test and TBUT that can be attributed to their linear relation with the CD4+ cell count. It is denoted as  $R^2$  in Figures 3 and 4. As  $r = 0.7$  and 0.45, 49% and 20.9% of

**TABLE 5:** Association of dry eye with CD4 cell count ranges.

Variable	CD4 cell count ranges							Total
	0–100	101–200	201–300	301–400	401–500	501–600	> 600	
<b>Schirmer's test grading</b>								
0 mm–5 mm	7	42	14	3	0	1	0	67
5 mm–10 mm	1	10	9	7	6	4	0	37
11 mm–15 mm	0	0	4	6	8	4	4	24
> 15 mm	0	0	0	0	0	1	1	2
<b>Total</b>	<b>8</b>	<b>52</b>	<b>27</b>	<b>16</b>	<b>14</b>	<b>10</b>	<b>5</b>	<b>130</b>
<b>TBUT grading</b>								
0–5 s	6	29	10	6	3	1	1	56
5–10 s	1	21	12	7	8	4	2	55
11–15 s	1	2	5	3	3	4	1	18
> 15 s	0	0	0	0	0	0	1	1
<b>Total</b>	<b>8</b>	<b>52</b>	<b>27</b>	<b>16</b>	<b>14</b>	<b>9</b>	<b>5</b>	<b>130</b>

TBUT, tear breakup time; CD4, T-lymphocyte cell bearing CD4 receptor; s, second; mm, millimetre.



CD4+, T-lymphocyte cell bearing CD4 receptor; mm, millimetre.

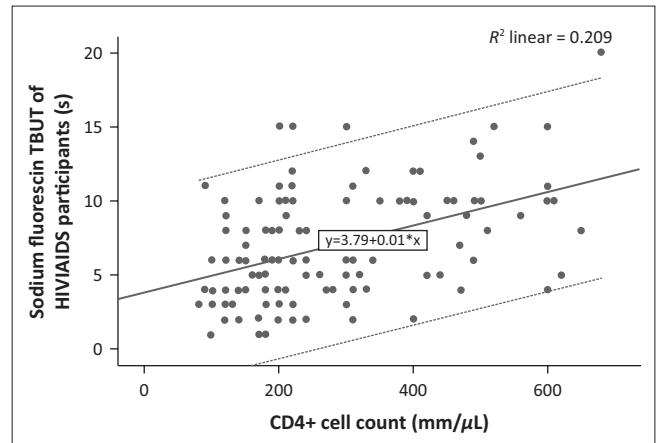
**FIGURE 3:** Scatter plot showing the correlation between CD4 cell count and Schirmer's test results. There appears to be a good linear correlation,  $r = 0.7$ ,  $p < 0.05$ . The solid line represents the regression line for TBUT and CD4+ cell count and the dotted lines represent the 95% confidence interval. The  $R^2$  (coefficient of determination) gives information about the goodness-of-fit model. It denotes the proportion of variability of measurements that can be attributed to its linear relation with the level of CD4+ cell count. The equation of the regression line is given.  $R^2$  linear, 0.483.

the variability in Schirmer's test and TBUT are because of variation with CD4+ cell count, respectively. In regression analysis, the  $r^2$  gives information about the goodness-of-fit of a model. As the Schirmer's test, CD4+ cell count and TBUT and CD4 cell count are correlated, regression technique was used to predict the value of Schirmer's test or TBUT from the value of CD4 cell count. The straight line or regression line is the line of best fit for the measurement points on the scatter plot.<sup>29</sup> The regression line is given by  $y = a + bx$ . As the values of 'a' and 'b' are known, the expected value of  $y$  can be predicted from any given value of  $x$  and vice versa.<sup>29</sup> The associations are graphically shown on scatter plots as can be seen in Figures 3 and 4. The level of CD 4 cell count is statistically associated with the severity of dry eye,  $p < 0.05$ .

## Discussion

A stable precorneal tear film is one of signs of satisfactory ocular health and is a vital component of vision. The tear film provides lubrication and protection to the cornea and ocular surface and is a major refractive surface for light entering the visual system.<sup>16,17,18</sup> Disruption of homeostasis of the tear film is the fundamental process in the development of dry eye, resulting in hyperosmolar and unstable tear film.<sup>17</sup> The tear film instability is the component of all forms of dry eye, while tear hyperosmolarity is a key mechanism of ocular surface damage.

Results from this study showed that the tear production as measured with Schirmer's test and sodium fluorescein TBUT, was significantly reduced in HIV and AIDS participants as compared to the healthy control group. These results indicate that dry eye is a significant feature of the HIV and AIDS disorders. According to the results of this study, approximately 80% of HIV and AIDS participants had dry eye. The results of this study agree with previous studies which showed that



TBUT, tear breakup time; CD4+, T-lymphocyte cell bearing CD4 receptor.

**FIGURE 4:** Scatter plot showing the correlation between CD4 cell count and sodium fluorescein TBUT test. There is a weak-to-moderate linear correlation,  $r = 0.457$ ,  $p < 0.05$ . The solid line represents the regression line for TBUT and the CD4+ cell count, and the dotted lines represent the 95% confidence interval.  $R^2$  linear, 0.209.

dry eye is one of the most common ophthalmologic disorders in HIV and AIDS patients.<sup>30</sup> Also, this study found that there is a statistically association between the level of CD4 cell count and the severity of dry eye. However, some studies found that the association of dry eye with CD4 cell count was inconclusive.<sup>13,14</sup> It seems the dry eye is more likely to correlate with CD4 cell count below 200 cells/ $\mu$ L.

Similar to this study, several authors have reported that tear production or secretion is significantly reduced in HIV and AIDS patients. Lucca et al.<sup>10,11</sup> reported a 21.4% prevalence of dry eye in nine patients with HIV and AIDS infection. However, the study was based on individual symptoms of dry eye and the clinical examination used a non-standardised test. DeCarlo et al.<sup>12</sup> also reported dry eye in HIV infection. Geier et al.'s<sup>13</sup> data demonstrated that decreased tear production occurs in approximately 20% – 25% of patients with HIV infection, but this decrease in tear production was not associated with the severity of HIV diseases or with the CD4+ cell count. According to Burtin et al.,<sup>30</sup> 70% – 80% of HIV-positive patients presented dry eye symptoms and signs. The prevalence in their study was similar to the result of our study. A recent study by Gowda et al.<sup>14</sup> showed decreased tear production in 50% of the HIV patients. However, the decreased tear production was not associated with the level of CD4+ cell count. Our study found a statistically significant positive correlation between the severity of dry eye and the level of CD4 cell count.

The cause of tear deficiency in HIV and AIDS participating patients is unclear and remains elusive but may be associated with dysfunction or disturbance of the lacrimal functional unit (LFU).<sup>19,20,21,22</sup> Lacrimal functional unit is composed of the cornea, conjunctiva, lacrimal gland, meibomian gland, lids and sensory and motor nerves that connect them. The LFU plays a regulatory role in tear secretion and tear film formation and maintains the normal physiology of the ocular surface.<sup>17,20</sup> Damage to any component of the LFU may lead to tear deficiency or evaporative dry eye.

The blood–brain barrier (BBB) provides protection against microbial invasion of the brain. Both the BBB and the blood–retinal barrier (BRB) are derived from the same embryonic primordium.<sup>31,32</sup> Their endothelial cells form extremely tight cell to cell junctions that are distinct from the tight junctions of endothelia and epithelia elsewhere in the body. As they lack fenestrations, they have high numbers of mitochondria for providing the energy required to maintain the structure and function. The BRB is composed of inner and outer BRB that controls solute and fluid permeability between circulating blood and neural retina.<sup>31,32</sup> During HIV infection there is alteration of the BRB resulting in the permeability of the barrier. *Tat* protein, which is only protein that is actively secreted by HIV infected cells, causes the paracellular permeability of retinal pigment epithelium cells simultaneously with changes in the expression of the tight junctions.<sup>33,34,35,36</sup> Once inside the eye, HIV can replicate itself and cause direct or indirect damages. HIV is then released in the LFU through the infiltration of the CD4+ T cells, macrophages and dendritic cells.<sup>35,36,37</sup> Viral infection is often associated with inflammation. The inflammatory process can then initiate the production of viral proteins, proinflammatory cytokines, chemokines and matrix metalloproteinases which can lead to further damage of the LFU. Dysfunction of the LFU then causes changes in the composition of the tear fluid and tear film stability, leading to inflammation of the ocular surface. This then causes activation of inflammatory cells including T-lymphocytes by immune system of the body. T cells release cytokines which cause inflammation of the ocular surface and lacrimal glands, thereby resulting in abnormal tears and dry eye symptoms.

Despite the advent of HAART, ocular lesions still occur as complications in HIV and AIDS patients. A detectable HIV-1 viral load has been found in tears, even in patients who are under long-term HAART who have an undetectable plasma viral load.<sup>34</sup> It is believed HIV gets into the tears through the CD4+ T cells, macrophages and dendritic cells, and then infiltrates into the lacrimal gland. These cells could release the HIV into the tears after initial infection.<sup>34</sup> It is unknown why HAART could not suppress the virus in tears. Perhaps the drug is not distributed effectively in tears or the enzymes in tears suppress or block the drug activity, or the genetic information of the HIV in tears is different from the one in the plasma. This suggests that the lacrimal gland and/or other tear-associated tissues could be new reservoirs of HIV. Persistent of HIV in the eye may lead to the formation of an HIV ocular reservoir, even in the presence of an effective immune response and antiretroviral therapy. HIV can replicate itself within the eye and cause intraocular disorders. The intraocular viral load may be more likely to correlate with ophthalmic manifestations of HIV and AIDS.

## Conclusion

A healthy and comfortable ocular surface requires a stable tear film. Dysfunction of any component of tear film may lead to dry eye. Dry eye appears to be more prevalent among individuals with HIV and AIDS than in the general

population. Statistically significant correlation was found between dry eye and CD4 cell count. According to this study, 51.5% of the study participants had dry eye as tested through Schirmer's test and TBUT. Ocular involvement may be the initial symptom or sign and may often precede systemic manifestation in HIV infection; hence, routine examination of tear function should be an integral part of assessment of HIV and AIDS patients. Early detection and treatment is necessary to improve the patient's comfort and minimise or prevent further structural damage to the ocular surface.

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## Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

## Authors' contributions

S.D.M. conceptualised the study. P.S.M. collected the data, reviewed the literature and wrote the first draft. S.D.M. analysed the data and edited the article. Both authors read and approved the final version of the manuscript.

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## References

1. Centre for Disease Control (CDC). Pneumocystis pneumonia-Los Angeles. MMWR Morb Mortal Wkly Rep. 1981;30(21):250–252.
2. Gottlieb MS, Schroff R, Schanker HM. Pneumocystic pneumonia and mucosal candidiasis in previously healthy homosexual men: Evidence of a new acquired cellular immunodeficiency. N Engl J Med. 1981;305:1425–1431. <https://doi.org/10.1056/NEJM198112103052401>
3. Gallo RC, Montagnier L. The discovery of HIV as the cause of AIDS. N Engl J Med. 2003;349(24):2283–2285. <https://doi.org/10.1056/NEJMp038194>
4. Martin SS, Peter S. HIV and eye: A global perspective. Expert Rev Ophthalmol. 2009;4(2):113–114. <https://doi.org/10.1586/eop.09.2>
5. Holland GN, Gottlieb MS, Yee RD, Schanker HM, Pettit TH. Ocular disorders associated with a new severe acquired cellular immunodeficiency syndrome. Am J Ophthalmol. 1982;93(4):393–402. [https://doi.org/10.1016/0002-9394\(82\)90127-1](https://doi.org/10.1016/0002-9394(82)90127-1)
6. Kim YS, Sun HJ, Kim TH, Kang KD, Lee SJ. Ocular manifestations of acquired immunodeficiency syndrome. Korean J Ophthalmol. 2015;29(4):241–248. <https://doi.org/10.3341/kjo.2015.29.4.241>
7. Kusagur S, Gururaj KJ. Clinical study of ocular manifestations in HIV/AIDS and its correlation with CD4+ t cells. Int J Biol Med Res. 2013;4(3):3284–3289.
8. Ifeanyi AR, Ezenwa U, Tarilah T, Opubiri IR. Ocular manifestation of HIV/AIDS infection among patients receiving highly active antiretroviral therapy (HAART) in a tertiary eye care centre. J AIDS HIV Res. 2013;5(9):322–327.
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. Br J Ophthalmol. 2009;93(1):88–90. <https://doi.org/10.1136/bjo.2008.149237>
10. Lucca JA, Kung JS, Farris RL. Keratoconjunctivitis sicca in female patients infected with human immunodeficiency virus. CLAO J. 1994;20(1):49–51.
11. Lucca JA, Farris RL, Bielory L, Caputo AR. Keratoconjunctivitis sicca in male patients infected with human immunodeficiency virus type 1. Ophthalmology. 1990;97(8):1008–1010. [https://doi.org/10.1016/S0161-6420\(90\)32472-7](https://doi.org/10.1016/S0161-6420(90)32472-7)

12. DeCarlo DK, Penner SL, Schamerloh RJ, Fullard RJ. Dry eye among males infected with the human immunodeficiency virus. *J Am Optom Assoc.* 1995;66(9):533–538.
13. Geier SA, Libera S, Klaus V, Goebel FD. Sicca syndrome in patients infected with the human immunodeficiency virus. *Ophthalmology.* 1995;102(9):1319–1324. [https://doi.org/10.1016/S0161-6420\(95\)30868-8](https://doi.org/10.1016/S0161-6420(95)30868-8)
14. Gowda HT, Krishnamurthy T, Tanushree V, Nayak S. Correlation of CD4 count and severity of dry eye in human immunodeficiency virus positive patients. *Int J Sci Stud.* 2015;3(5):68–71.
15. Coll J, Tomas S, Corominas JM, Gutierrez J. Sicca syndrome associated with human immunodeficiency virus infection: An immunohistochemical study. *Arthritis Rheum.* 1993;36(6):875–876. <https://doi.org/10.1002/art.1780360621>
16. Tsubota K, Yokoi N, Shimazaki J. New perspectives on dry eye definition and diagnosis: A consensus report by the Asian Dry Eye Society. *Ocul Surf.* 2017;15(1):65–76. <https://doi.org/10.1016/j.jtos.2016.09.003>
17. Craig JP, Nichols KK, Akpek EK. TFOS DEWS II definition and classification report. *Ocul Surf.* 2017;15(3):276–283. <https://doi.org/10.1016/j.jtos.2017.05.008>
18. DEWS Definition and Classification. The definition and classification of dry eye diseases: Report of the definition and classification subcommittee of the International Dry Eye Workshop. *Ocul Surf.* 2007;5(2):75–92. [https://doi.org/10.1016/S1542-0124\(12\)70081-2](https://doi.org/10.1016/S1542-0124(12)70081-2)
19. Javadi MA, Feizi S. Dry eye syndrome. *J Ophthalmol Vis Res.* 2011;6(3):192–198.
20. Stern ME, Gao J, Siemasko KF, Beuerman RW, Pflugfelder SC. The role of the lacrimal functional unit in the pathophysiology of dry eye. *Exp Eye Res.* 2004;78(3):409–416. <https://doi.org/10.1016/j.exer.2003.09.003>
21. Behrens A, Doyle JJ, Stern L. Dysfunctional tear syndrome: A Delphi approach to treatment recommendations. *Cornea.* 2006;25(8):900–907. <https://doi.org/10.1097/01.icc.0000214802.40313.fa>
22. Baudouin C. The pathology of dry eye. *Surv Ophthalmol.* 2001;45(Suppl):S211–S220. [https://doi.org/10.1016/S0039-6257\(00\)00200-9](https://doi.org/10.1016/S0039-6257(00)00200-9)
23. Serin D, Karshoglu S, Kiyani A, Alagoz G. A simple approach to the repeatability of the Schirmer test without anesthesia: Eyes open or closed? *Cornea.* 2007;26(8):903–906. <https://doi.org/10.1097/ICO.0b013e3180950083>
24. Vanley GT, Leopold IH, Gregg TH. Interpretation of tear film breakup. *Arch Ophthalmol.* 1977;95(3):445–448. <https://doi.org/10.1001/archoph.1977.04450030087010>
25. Bourcier T, Acosta MC, Borderie V, et al. Decreased corneal sensitivity in patients with dry eye. *Invest Ophthalmol Vis Sci.* 2005;46(7):2341–2345. <https://doi.org/10.1167/iovs.04-1426>
26. Nichols KK, Nichols JJ, Zadnik K. Frequency of dry eye diagnostic test procedures used in various modes of ophthalmic practice. *Cornea.* 2000;19(4):477–482. <https://doi.org/10.1097/00003226-200007000-00015>
27. Tukenmez-Dikmen N, Yildiz EH, Imamoglu S, Turan-Vural E, Sevim MS. Correlation of dry eye workshop dry eye severity grading system with tear meniscus measured by optical coherence tomography and tear osmolarity. *Eye Contact Lens.* 2016;42(3):153–157. <https://doi.org/10.1097/ICL.0000000000000168>
28. Hessen M, Akpek EK. Dry eye: An inflammatory ocular disease. *J Ophthalmol Vis Res.* 2014;9(2):240–250.
29. Liu J, Tang W, Chen G, Lu Y, Feng C, Tu XM. Correlation and agreement: Overview and clarification of competing concepts and measures. *Shanghai Arch Psychiatry.* 2016;28(2):115–120.
30. Burtin T, Guepratte N, Bourges JL, Garcher C, Le Hoang P, Baudouin C. Abnormalities of the ocular surface in patients with AIDS. *J Fr Ophthalmol.* 1982;21(9):637–642. Article in French.
31. Che X, Fan XQ, Wang ZL. Mechanism of blood-retinal barrier breakdown induced by HIV-1. *Exp Ther Med.* 2014;7(4):768–772. <https://doi.org/10.3892/etm.2014.1521>
32. Bail L, Zhang Z, Zhang H, et al. HIV-1 Tat protein alter the tight junction integrity and function of retinal pigment epithelium; An in vitro study. *BMC Infect Dis.* 2008;8:77. <https://doi.org/10.1186/1471-2334-8-77>
33. Han Y, Wu N, Zhu W, et al. Detection of HIV-1 viruses in tears of patients even under long-term HAART. *AIDS.* 2011;25(15):1925–1927. <https://doi.org/10.1097/QAD.0b013e32834b3578>
34. Pathanopitoun K, Riemens A, Kongyai N. Intraocular and plasma HIV-1 RNA loads and HIV uveitis. *AIDS.* 2011;25(1):81–86. <https://doi.org/10.1097/QAD.0b013e328340fe91>
35. Ogawa Y, Kuwana M, Yamazaki K. Periductal area as the primary site for T-cells activation in lacrimal gland chronic graft-versus-host diseases. *Invest Ophthalmol Vis Sci.* 2003;44(5):1888–1896. <https://doi.org/10.1167/iovs.02-0699>
36. Forrester JV, Xu H, Kuffova L. Dendritic cell physiology and function in the eye. *Immunol Rev.* 2010;234(1):282–304. <https://doi.org/10.1111/j.0105-2896.2009.00873.x>
37. Willshire C, Buckley RJ, Bron AJ. Central connections of the lacrimal functional unit. *Cornea.* 2017;36(8):898–907. <https://doi.org/10.1097/ICO.0000000000001250>