Early and late stage ocular complications of herpes zoster ophthalmicus in rural South Africa

Erik Schaftenaar, MD[1-3*], Christina Meenken, PhD[4], G. Seerp Baarsma, MD[2,5], James A. McIntyre, FRCOG[3,6], Georges M.G.M. Verjans, PhD[1,7], Remco P. H. Peters, PhD[3,8]

Affiliations:

1. Department of Viroscience, Erasmus Medical Center, Rotterdam, The Netherlands
2. Rotterdam Eye Hospital, Rotterdam, The Netherlands
3. Anova Health Institute, Johannesburg and Tzaneen, South Africa
4. Department of Ophthalmology, VU University Medical Center, Amsterdam, The Netherlands
5. Rotterdam Ophthalmic Institute, Rotterdam, The Netherlands
6. School of Public Health & Family Medicine, University of Cape Town, Cape Town, South Africa
7. Research Center for Emerging Infections and Zoonoses, University of Veterinary Medicine, Hannover, Germany
8. Department of Medical Microbiology, University of Pretoria, Pretoria, South Africa

* Corresponding author, Anova Health Institute, PostNet Suite 242, Private Bag X30500, 2041 Houghton, Johannesburg, South Africa. E-mail: e.schaftenaar@gmail.com. Tel.: +27(0)115815011.

Word count:

Abstract: 243 words

Text: 2053 words

ABSTRACT

Objectives. To describe the spectrum of ocular complications of herpes zoster ophthalmicus (HZO) in rural South Africa.

Methods. Patients presenting with visual complaints and active or healed HZO at the ophthalmology outpatient department of three hospitals in rural South Africa were included in this study. Demographic and clinical data were collected and HIV status was determined for all participants.

Results. Forty-eight patients were included and the majority (81%) were HIV-infected. Poor vision was reported by 94% of patients, painful eye by 79% and photophobia by 63%. A diverse spectrum of ocular complications was observed with corneal inflammation and opacification as the most frequent (77%) followed by anterior uveitis (65%). The majority of patients (65%) presented with late stage ocular complications associated with irreversible loss of vision whereas early stage complications, such as punctate epithelial keratitis and anterior uveitis were less common. Blindness of the affected eye was observed in 68% of patients with late stage complications. There was a considerable delay between onset of symptoms and first presentation to the ophthalmology outpatient department (median time 35 days; range 1-2500 days) and longer delay was associated with late stage ocular complications (p = 0.02).

Conclusions. HZO patients present with relatively late stage ocular complications and blindness among these patients is common. The delayed presentation to the ophthalmology outpatient department of hospitals in our rural setting is of concern and efforts to improve this situation are of paramount importance to improve ocular outcomes of HZO.

INTRODUCTION

Herpes zoster ophthalmicus (HZO) is the clinical manifestation of reactivation of latent varicella-zoster virus (VZV) infection located within the ophthalmic branch of the trigeminal nerve.[1-4] Due to impaired cell-mediated immunity, human immunodeficiency virus (HIV)-infected individuals are at increased risk of developing HZO (relative incident risk of 6.6) compared to HIV-uninfected individuals.[5-8] If cutaneous HZO is left untreated, ocular involvement occurs in more than half of patients and leads to chronic debilitating pain, visual impairment and eventually (unilateral) blindness.[1-3,9] These ocular complications are more common among HIV-infected individuals and have a more severe clinical presentation and higher recurrence rate, especially in individuals with low CD4 count.[1,3,6,8]

The spectrum of ocular complications of HZO is diverse. Corneal inflammation and opacification (49-89%) and anterior uveitis (43-92%) are the most common complications, but ocular cranial-nerve palsies, neuralgia, eyelid deformities, (blepharo-)conjunctivitis, (epi-)scleritis and optic neuritis may also occur.[1-4,7,9-13] In the acute phase of HZO 'early' corneal complications are may develop such as punctate epithelial keratitis and dendritic keratitis; these are associated with minimal risk of visual impairment. However, if left untreated, progression to chronic, late-stage corneal complications with serious visual impairment due to corneal opacification and ulceration may develop.[1,3] Additionally, in cases where uveitis occurs, mild HZO-associated acute anterior uveitis may progress to sight-threatening stages due to chronic inflammation leading to corneal oedema, iris atrophy, posterior synaechiae and cataract formation.[3,7] Thus, early recognition of ocular involvement in HZO patients and subsequent initiation of targeted oral and topical treatment is essential to prevent ocular morbidity.

South Africa is highly affected by the HIV epidemic and the clinical presentation of dermal HZO is relatively common.[14] Data on ocular manifestations of HZO in HIV-infected sub-Saharan Africans are scarce.[9,14,15] The aim of this study was to describe the spectrum of ocular complications

of HZO and, in particular, to distinguish between early and late stage ocular complications as these impact on visual prognosis.

METHODS

Study setting and population

This study was conducted at the ophthalmology outpatient department of three hospitals in rural South Africa (Mopani District) and is a sub-analysis of data collected in Anova's Mopani Eye Project. Briefly, this project aimed to improve eye care through a combination of clinical research and health systems strengthening activities. For this analyses, cases were selected from three ongoing clinical studies initiated with the following objectives: to determine the (1) aetiology of uveitis, (2) aetiology of infectious keratitis and (3) impact of HIV infection and antiretroviral therapy (ART) on the eye (Schaftenaar E, Mopani Eye Project 2015, unpublished data). Adults (≥18 years old) with a clinical diagnosis of uveitis or infectious keratitis were included in the first two studies and adults with documented HIV infection, regardless presence of eye complaints, were included in the third study. Individuals presenting in either of these studies with active or healed HZO were included in the current analysis.

HZO diagnosis was defined as presence of a primary vesiculomacular and dysesthetic skin rash or typical scar (with matching clinical history of HZO) within the ophthalmic dermatome.[7,16] Demographic and clinical data were collected at enrolment in all three studies. Each participant had a full ophthalmic examination, including measurement of visual acuity, slit-lamp examination and dilated indirect ophthalmoscopy. Visual acuity testing was performed using an "illiterate E" Snellen chart at a distance of 6 meter and visual acuity was defined as the lowest line value where at least half the letters were correctly identified by the participant without correction of the affected eye. If visual acuity was <6/60, the distance between the Snellen chart and patient was reduced to 3 or 1

meter. If visual acuity was <1/60, “hand movements”, “light perception” or “no light perception” was recorded. Visual impairment was defined according to the International Classification of Diseases (ICD-10, version 2010) on basis of the individual’s visual acuity.[17] The studies were approved by the Human Research Ethics Committee (University of the Witwatersrand; Johannesburg, South Africa) and written informed consent (including ocular photography) was obtained from all participants.

Classification of early and late ocular complications

Ocular complications were classified as “early” or “late” based on stage of disease progression and (potential) restoration of normal vision. The following manifestations were classified as early stage: eyelid oedema, (blepharo-)conjunctivitis, (epi-)scleritis, punctate epithelial keratitis, pseudodendritic or dendritic keratitis, nummular keratitis and/or anterior uveitis.[7] Late stage ocular complications were in case of eyelid scarring, trichiasis, entropion, ptosis, deep stromal keratitis, disciform keratitis, corneal ulceration, neurotrophic keratopathy, necrotising retinitis, retinal detachment and optic neuritis. Although necrotising retinitis and optic neuritis may also occur in the early phase, we decided to include both as late stage ocular complications due to their devastating effect on visual acuity.[7]

Data analysis

Data were double-entered and validated using EPI-INFO version 3.5.4 (Centers for Disease Control; Atlanta, GA) and analysed using IBM SPSS Statistics version 22 (IBM; New York City, NY). Description of study population, clinical and laboratory findings were performed using number with proportion and median with range. Comparison was done by Chi-squared tests with Fisher’s Exact if appropriate for categorical variables and Mann-Whitney for continuous variables. Data are presented as odds ratio (OR) with 95% confidence interval (CI), mean with standard deviation (SD) or as median with range.

RESULTS

The study sample (n=48) consisted of 10 (21%) men and 38 (79%) women with a median age of 40 years (range 18-72 years). Thirty-nine (81%) individuals were HIV-infected, with a median CD4 count of 260 cells/mm^3 (range 43-813 cells/mm^3), of which 25 (64%) received ART. Most cases (n=39; 81%) presented with healed (no active skin lesions) and 9 patients (19%) with active HZO. HZO was unilateral except for two cases. Median days between reported onset of eye complaints and first presentation to the ophthalmology outpatient department was 35 days (range 1-2500 days).

Poor vision (94%) was the most common ocular symptom, followed by a painful eye (79%) and photophobia (63%). A diverse spectrum of ocular HZO complications was observed (**Figure 1**), with corneal inflammation and opacification (77%) as the most common ocular complication followed by anterior uveitis (65%) (**Table 1**). Intraocular complications were more common among HIV-infected than HIV-uninfected individuals (OR = 5.8; 95% CI: 1.2–27.6, $p < 0.05$). Scleritis, cranial nerve palsy and optic neuritis was not observed. The majority (n=31; 65%) of patients presented with late stage ocular complications. These patients reported longer time between onset of eye symptoms and presentation to the ophthalmology outpatient department (median of 18 vs. 46 days; $p = 0.02$) and presented more frequently with healed than active HZO (OR = 5.1; 95% CI: 1.1–24.0, $p = 0.05$) than those with early stage complications (**Table 2**). However, among individuals presenting with healed HZO, early ocular complications were observed in only 11 (28%) patients and late stage ocular complications were observed in three (33%) patients with active HZO. Visual impairment (81%), including blindness (23 of 39 individuals; 59%), was common and late stage ocular complications were associated with blindness of the affected eye (OR = 15.8; 95% CI: 3.0–82.5, $p = <0.001$).

DISCUSSION

This study reports on the early and late stage ocular complications of HZO patients presenting to the ophthalmology outpatient department of three hospitals in rural South Africa. A diverse spectrum of ocular HZO complications was observed. Most patients had late stage ocular complications, which was associated with blindness of the affected eye.

Corneal inflammation and opacification were the most common complication followed by anterior uveitis. This observation is in line with previous studies from Africa and the Unites States.[9,11,12] Intraocular complications were more common among HIV-infected than HIV-uninfected individuals. HIV-related immunodeficiency might lead to rapid breach of the corneal defence mechanisms resulting in intraocular inflammation in case of VZV-infection, which is in line with previous studies in which HIV infection was associated with more severe ocular disease in HZO.[1,3,6,8] At enrolment we observed a significant rate of visual disability and blindness (81%). Although we did not report on visual acuity after HZO-specific treatment, we expect the final rate of visual disability and blindness to be high since the majority presented with late stage manifestations associated with often irreversible visual impairment and blindness.[1,3,7] The observed high rate of visual disability was similar to two previous studies from Africa twenty years ago.[9,15]

There was a considerable delay (median time of 35 days) between onset of symptoms and first presentation to the ophthalmology outpatient department; such delay was associated with late stage ocular complications. The association between delay to the ophthalmology outpatient department and late stage complications might be due to delayed initiation of antiviral treatment as early initiation thereof (≤72 hours after onset of rash) reduces the risk of progression to late stage ocular complications.[3,18] The delay observed in our study is long and much higher than reported by a similar study conducted at the ophthalmology outpatient department of the Groote Schuur Hospital (Cape Town, South Africa) in which a median delay of 5 days was reported.[14] Both patient- and healthcare system-associated factors may have contributed to this discrepancy. First, patient delays

are generally more common in rural (e.g. Mopani District) than urban (e.g. Cape Town) South African settings. To our knowledge no studies have reported on patient delay in case of HZO or eye complaints, but substantial delays have been reported for other conditions between such settings.[19,20] Second, healthcare system delays are likely to occur, especially in rural settings where ophthalmological expertise and resources are limited and the referral process for ophthalmologic examination is complicated. Unfortunately, we did not record if individuals visited primary healthcare facilities before presenting to our ophthalmology outpatient departments.

Healed HZO was associated with late stage ocular complications. However, seemingly contradictory, early ocular complications were observed in 11 (28%) patients, all of whom were HIV-infected, presenting with healed HZO. Although no demographic and clinical characteristics, including CD4 count, were associated with these 11 patients, the early stage ocular complications observed in these healed HZO patients may be due to higher frequency of local (e.g. corneal) recrudescence of VZV due to HIV-induced immune senescence.[5-8] Also, late stage ocular complications were observed in three (33%) HIV-infected patients with active HZO. Since HIV infection is associated with more severe ocular disease in HZO, these three patients may have developed late stage ocular complications early after onset of disease.[1,3,6,8] Most HZO patients included in our study were HIV infected and were significant younger than HIV-uninfected individuals. This is in agreement with previous HZO studies from sub-Saharan Africa.[9,12,14] Among the HIV-infected individuals, four (10%) HZO patients were tested reactive for HIV for the first time as they were offered provided-initiated HIV testing based on their clinical presentation. This highlights the importance of providing HIV testing to individuals presenting with HZO as advocated in previous studies.[1,8,10,21,22]

A potential limitation is the study design whereby potential HZO patients were selected from three different clinical studies. However, selection bias is unlikely, because any individual with HZO presenting with ocular complaints was eligible for participation in one of our studies. Due to selection of individuals with ocular HZO complications, no inferences could be made about the

prevalence of ocular HZO complications in the general population of the Mopani District. Finally, because diagnosis was solely based on the patient's history and clinical characteristics, not all observed ocular HZO complications may be caused directly by VZV as involvement of other viruses or even an ocular bacterial superinfection are optional. However, the latter is unlikely because the sensitivity and specificity of the clinical characteristics in combination with active or healed HZO lesions are very disease-specific.[16,23]

In this study, we demonstrated that HZO patients presenting to the ophthalmology outpatient department of three hospitals in rural South Africa have relatively late stage ocular complications and that this is associated with serious visual impairment and blindness. This emphasizes the importance of early recognition of ocular involvement in HZO and subsequent initiation of appropriate antiviral treatment at primary healthcare level with prompt referral to hospitals with ophthalmology departments to reduce these sight-threatening ocular complications. As such, appropriate antiviral treatment should be available at primary healthcare level, even in rural settings. Furthermore, to prevent HZO-associated ocular morbidity, development of clinical guidelines and training programmes for healthcare workers as well as health system strengthening and community awareness are of paramount importance. These efforts will improve prevention and clinical management of ocular HZO complications and reduce the burden of avoidable visual impairment and blindness in South Africa.

AUTHORS' CONTRIBUTIONS STATEMENT

Erik Schaftenaar: literature search, study design, data collection, data analysis, data interpretation and writing. Christina Meenken: data analysis, data interpretation and writing. G. Seerp Baarsma: data analysis, data interpretation and writing. James A. McIntyre: writing. Georges M.G.M. Verjans: data analysis, data interpretation and writing. Remco P.H. Peters: literature search, study design, data analysis, data interpretation and writing.

ACKNOWLEDGMENTS

This study was in part funded by the Rotterdamse Stichting Blindenbelangen and the Rotterdam Global Health Initiative. Anova Health Institute receives a grant from the US President's Emergency Plan for AIDS Relief (PEPFAR) program via the US Agency for International Development under Cooperative Agreement No AID-674-A-12-00015. The views expressed in this report do not necessarily reflect those of PEPFAR or USAID. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

We thank all patients who participated in this study. Our further gratitude goes to the staff of Anova Health Institute (Johannesburg and Tzaneen, South Africa) and the staff of the ophthalmology outpatient department of the three hospitals in the Mopani District that participated in this study for their invaluable contribution, efforts and support. We also thank Vincent Schaftenaar for refining the figure included in this manuscript.

CONFLICT OF INTEREST

The authors have no conflict of interest to matters presented in the report.

REFERENCES

1. Vafai A, Berger M. Zoster in patients infected with HIV: a review. *Am J Med Sci* 2001; **321:** 372–80.
2. Marsh RJ, Cooper M. Ophthalmic herpes zoster. *Eye (Lond)* 1993; **7:** 350–70.
3. Liesegang TJ. Herpes zoster virus infection. *Curr Opin Ophthalmol* 2004; **15:** 531–6.
4. Kaufman SC. Anterior segment complications of herpes zoster ophthalmicus. *Ophthalmology* 2008; **115:** S24–32.
5. Buchbinder SP, Katz MH, Hessol NA, et al. Herpes zoster and human immunodeficiency virus infection. *J Infect Dis* 1992; **166:** 1153–6.
6. Hodge WG, Seiff SR, Margolis TP. Ocular opportunistic infection incidences among patients who are HIV positive compared to patients who are HIV negative. *Ophthalmology* 1998; **105:** 895–900.
7. Shaikh S, Ta CN. Evaluation and management of herpes zoster ophthalmicus. *Am Fam Physician* 2002; **66:** 1723–30.
8. Veenstra J, Krol A, Van Pragg RM, et al. Herpes zoster immunological deterioration and disease progression in HIV-1 infection. *AIDS* 1995; **9:** 1153–8.
9. Bayu S, Alemayehu W. Clinical profile of herpes zoster ophthalmicus in Ethiopians. *Clin Infect Dis* 1997; **24:** 1256–60.
10. Ritterband DC, Friedberg DN. Virus infections of the eye. *Rev Med Virol* 1998; **8:** 187–201.
11. Womack LW, Liesegang TJ. Complications of herpes zoster ophthalmicus. *Arch Ophthalmol* 1983; **101:** 42–5.
12. Kestelyn P, Stevens AM, Bakkers E, et al. Severe herpes zoster ophthalmicus in young African adults: a marker for HTLV-III seropositivity. *Br J Ophthalmol* 1987; **71:** 806–9.
13. Harding SP, Lipton JR, Wells JC. Natural history of herpes zoster ophthalmicus: predictors of postherpetic neuralgia and ocular involvement. *Br J Ophthalmol* 1987; **71:** 353–8.

14. Richards JC, Maartens G, Davidse AJ. Course and complications of varicella zoster ophthalmicus in a high HIV seroprevalence population (Cape Town, South Africa). *Eye (Lond)* 2009; **23:** 376–81.
15. Lewallen S. Herpes zoster ophthalmicus in Malawi. *Ophthalmology* 1994; **101:** 1801–4.
16. Liesegang TJ. Herpes zoster ophthalmicus natural history, risk factors, clinical presentation, and morbidity. *Ophthalmology* 2008; **115:** S3–12.
17. World Health Organisation. ICD-10 Classifications of Mental and Behavioural Disorder: Clinical Descriptions and Diagnostic Guidelines. Geneva: World Health Organisation; 2015.
18. Nithyanandam S, Joseph M, Stephen J. Ocular complications and loss of vision due to herpes zoster ophthalmicus in patients with HIV infection and a comparison with HIV-negative patients. *Int J STD AIDS* 2013**; 24:** 106–9.
19. Otwombe KN, Variava E, Holmes CB, et al. Predictors of delay in the diagnosis and treatment of suspected tuberculosis in HIV co-infected patients in South Africa. *Int J Tuberc Lung Dis* 2013; **17:** 1199–205.
20. Kong VY, Van der Linde S, Aldous C, et al. Quantifying the disparity in outcome between urban and rural patients with acute appendicitis in South Africa. *S Afr Med J* 2013; **103:** 742–5.
21. Nasoodi A, Lim LT, Al-Ani A, et al. What you can see in your patient's eyes? Review of ocular manifestations of HIV in HAART era. *Int J STD AIDS* 2008; **19:** 4–11.
22. Cunningham ET Jr, Margolis TP. Ocular manifestations of HIV infection. *N Engl J Med* 1998; **339:** 236–44.
23. Takase H, Kubono R, Terada Y, et al. Comparison of the ocular characteristics of anterior uveitis caused by herpes simplex virus, varicella-zoster virus, and cytomegalovirus. *Jpn J Ophthalmol* 2014; **58:** 473–82.

TABLES

Table 1. Distribution of ocular complications of herpes zoster ophthalmicus by HIV status.

	HIV-infected (n=39)	HIV-uninfected (n=9)	Total (n=48)
Eyelid and conjunctiva			
Eyelid oedema	7 (18)	3 (33)	10 (21)
Eyelid scarring	10 (26)	0 (0)	10 (21)
Eyelid trichiasis	2 (5)	0 (0)	2 (4)
Entropion	1 (3)	0 (0)	1 (2)
Ptosis	8 (21)	0 (0)	8 (17)
Blepharoconjunctivitis	5 (13)	2 (22)	7 (15)
Conjunctivitis	13 (33)	3 (33)	16 (33)
Episclera and sclera			
Episcleritis	3 (8)	0 (0)	3 (6)
Scleritis	0 (0)	0 (0)	0 (0)
Cornea			
Corneal inflammation and opacification	29 (74)	8 (89)	37 (77)
Punctate epithelial keratitis	8 (21)	7 (78)	15 (31)
Pseudo dendritic keratitis	3 (8)	0 (0)	3 (6)
Dendritic keratitis	2 (5)	3 (33)	5 (10)
Nummular keratitis	4 (10)	0 (0)	4 (8)
Stromal keratitis	7 (18)	3 (33)	10 (21)
Disciform keratitis	3 (8)	1 (11)	4 (8)
Corneal ulceration	4 (10)	2 (22)	6 (13)
Neurotrophic keratopathy	14 (36)	3 (33)	17 (35)
Abnormal corneal sensation	12 (31)	2 (22)	14 (29)
Anterior chamber			
Anterior uveitis	28 (72)	3 (33)	31 (65)
Keratouveitis	17 (44)	2 (22)	19 (40)
Posterior synechiae	11 (28)	2 (22)	13 (27)
Posterior segment			
Posterior involvement	4 (10)	0 (0)	4 (8)
Necrotising retinitis	3 (8)	0 (0)	3 (6)
Retinal detachment	2 (5)	0 (0)	2 (4)
Optic neuritis	0 (0)	0 (0)	0 (0)

Data are shown as numbers (%). HIV, human immunodeficiency virus.

Table 2. Early versus late stage ocular complications of herpes zoster ophthalmicus.

	Early stage ocular complications (n=17)	Late stage ocular complications (n=31)	Crude odds Ratio (95% CI)	*p*-Value
Age in years	40 (24-72)	40 (18-71)	na	0.470
Gender				
Male	4 (40)	6 (60)	1.3 (0.3–5.4)	0.727
Female	13 (34)	25 (66)		
HIV-status				
HIV-infected	14 (36)	25 (64)	1.1 (0.2–5.2)	1.000
HIV-uninfected	3 (33)	6 (67)		
CD4 cell count in cells/mm3	301 (32-813)	244 (52-670)	Na	0.598
HZO				
Active HZO	6 (67)	3 (33)	5.1 (1.1–24.0)[a]	0.051
HIV-infected	3	3		
HIV-uninfected	3	0		
Healed HZO	11 (28)	28 (72)		
HIV-infected	11	22		
HIV-uninfected	0	6		
Time between onset of eye complaints and presentation to the ophthalmology outpatient department	18 (1-131)	46 (2-2500)	Na	0.016
Reported ocular symptom				
Poor vision	14 (82%)	31 (100%)	-	0.039
Painful eye	17 (100%)	21 (68%)	-	0.009
Photophobia	15 (48%)	15 (88%)	8.0 (1.6–41.0)	0.006
Visual acuity of the affected eye				
≥ 6/18	9 (100)	0 (0)	15.8 (3.0–82.5)[b]	<0.001
< 6/18 but ≥ 6/60	5 (36)	9 (64)		
< 6/60 but ≥ 3/60	1 (50)	1 (50)		
< 3/60	2 (9)	21 (91)		

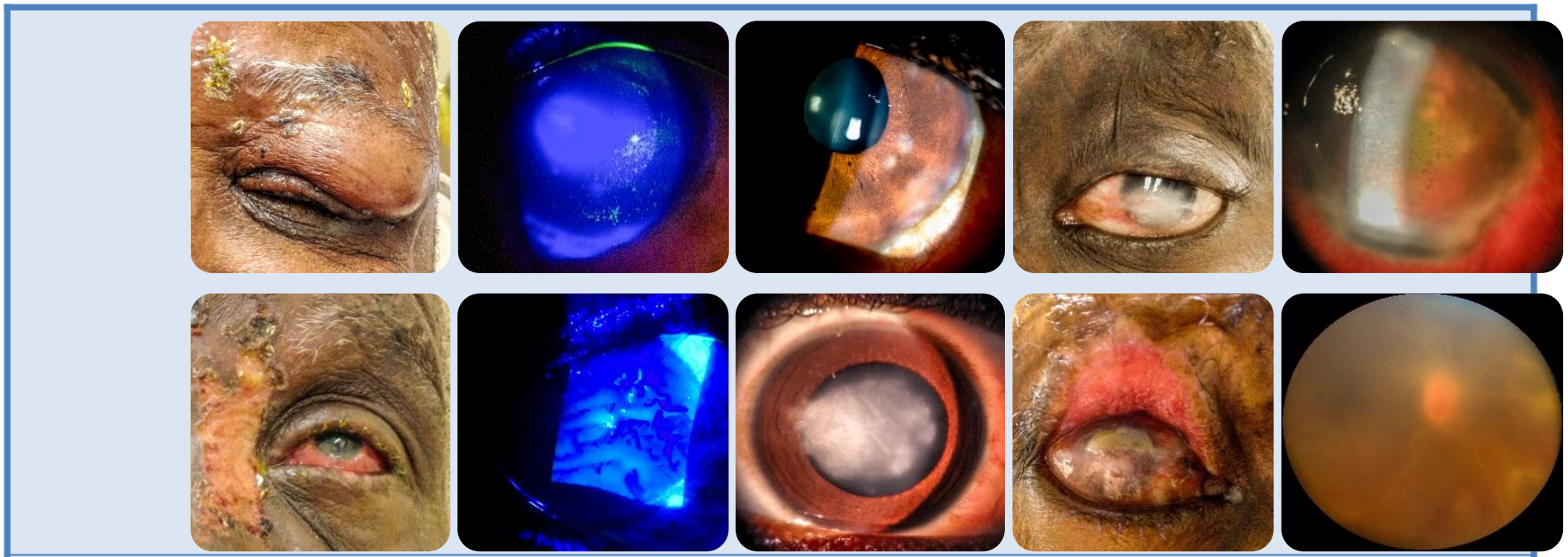
Data are shown as numbers (%) or median (range). HIV, human immunodeficiency virus; HZO, herpes zoster ophthalmicus; CI, Confidence interval; *p*-Value, Pearson Chi-square or Mann–Whitney *U* test; na, not applicable.

[a]Crude odds ratio and *p*-Value were calculated for active HZO vs. healed HZO between early and late stage ocular complications.

[b]Crude odds ratio and *p*-Value were calculated for visual acuity ≥ 3/60 vs. < 3/60 between early and late stage ocular complications.

FIGURE PANELS

Figure 1. Spectrum of ocular complications of herpes zoster ophthalmicus.



Clinical stage	Eyelid and conjunctival involvement	Early corneal involvement	Corneal involvement	Late corneal complications and eyelid deformities	Anterior and posterior segment involvement
Clinical signs	Cutaneous macular rash and vesicles with oedema of the superior eyelid Cutaneous macular rash and vesicles and blepharoconjunctivitis	Punctate epithelial keratitis: multiple, focal swollen corneal surface epithelial cells (Pseudo)dendritic keratitis: elevated plaques of swollen epithelial cells that form a branching pattern	Nummular keratitis: multiple fine infiltrates immediately beneath corneal surface Stromal keratitis: deep stromal inflammation with lipid infiltrates	Eyelid scarring and neurotrophic keratopathy: generalised corneal epithelial erosions with or without ulceration, calcareous plaque formation, and corneal neovascularisation Severe upper eyelid scarring and corneal opacification due to neurotrophic keratopathy	Anterior keratouveitis: localized stromal oedema, keratic precipitates, cells and flare in the anterior chamber, and posterior synechiae Necrotizing retinitis: vitreous inflammation, necrotizing retinitis, and occlusive vasculitis