



## RESEARCH NOTE

**REVISED** **Ophthalmic signs in Ugandan adults with HIV-associated cryptococcal meningitis: A nested analysis of the ASTRO-CM cohort [version 2; referees: 2 approved]**

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**v2** **First published:** 27 Jun 2018, 3:80 (doi: [10.12688/wellcomeopenres.14666.1](https://doi.org/10.12688/wellcomeopenres.14666.1))  
**Latest published:** 12 Oct 2018, 3:80 (doi: [10.12688/wellcomeopenres.14666.2](https://doi.org/10.12688/wellcomeopenres.14666.2))

### Abstract

Cryptococcal meningitis is a leading cause of morbidity and mortality among HIV-infected persons, accounting for 15% of AIDS-related deaths. Visual disturbance is commonly reported, and a wide range of ophthalmic signs may be present on examination. There is limited published literature to date describing the range and incidence of ophthalmic signs in HIV-associated cryptococcal meningitis. Nested within the Adjunctive Sertraline for the Treatment of HIV-Associated Cryptococcal Meningitis (ASTRO-CM) trial (ClinicalTrials.gov number: NCT01802385), we conducted an observational study of 696 Ugandan adults with HIV-associated cryptococcal meningitis. Patients were screened for visual disturbance and external ophthalmic signs at initial presentation and at follow-up appointments over 18 weeks. Assessment comprised simple clinical history and basic examination and required no specialist equipment.

More than a quarter of our cohort demonstrated ocular signs or symptoms, which were observed throughout the study period. A broad range of ocular signs were demonstrated: these included neurological signs (10.9%), localized ocular pathology (4.5%), and evidence of concurrent systemic disease (12.9%).

The range of signs observed demonstrates the complexities of case management in patients with advanced HIV and cryptococcosis and also the importance of basic ocular examination in low resource settings.

There remains an urgent need for studies conducting comprehensive ocular examination in patients with HIV-associated cryptococcal meningitis; these studies should include formal assessment of visual acuity, slit lamp examination and dilated indirect ophthalmoscopy. Prospective studies should investigate whether there is a correlation between reported visual disturbance and objective signs, in order to further clarify the underlying mechanisms and to guide effective diagnosis, follow-up and management.

### Keywords

Cryptococcus, cryptococcal meningitis, HIV, visual, ocular, ophthalmic

### Open Peer Review

Referee Status:

	Invited Referees	
	1	2
<b>version 2</b> published 12 Oct 2018		
<b>version 1</b> published 27 Jun 2018	 report	 report

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Comments (0)

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**Competing interests:** No competing interests were disclosed.

**Grant information:** This research was supported by the Wellcome Trust [210772/Z/18/Z] to FVC and through the Joint Global Health Trials scheme jointly funded by the UK Medical Research Council, UK Department for International Development and the Wellcome Trust [M007413/1]. This work was also funded by the National Institute of Neurologic Disorders and Stroke and Fogarty International Center [R01NS086312, R25TW009345], and the National Institute of Allergy and Infectious Diseases [T32AI055433].

*The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

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**How to cite this article:** Atherton RR, Ellis J, Cresswell FV *et al.* **Ophthalmic signs in Ugandan adults with HIV-associated cryptococcal meningitis: A nested analysis of the ASTRO-CM cohort [version 2; referees: 2 approved]** Wellcome Open Research 2018, 3:80 (doi: [10.12688/wellcomeopenres.14666.2](https://doi.org/10.12688/wellcomeopenres.14666.2))

**First published:** 27 Jun 2018, 3:80 (doi: [10.12688/wellcomeopenres.14666.1](https://doi.org/10.12688/wellcomeopenres.14666.1))

**REVISED Amendments from Version 1**

We have taken into account the considered and constructive analysis of our manuscript by the two reviewers. We have addressed individual comments and submit this revised version 2.

We have highlighted that we identified only external ophthalmic signs in our cohort, and have recognised a possible trial effect of multiple lumbar punctures on apparently low incidence of neurological signs. We also acknowledge the added limitation in not extracting data regarding co-morbidities or medications.

See referee reports

**Background**

Cryptococcal meningitis is the commonest neurological complication in patients with advanced HIV, accounting for 15% of AIDS-related deaths<sup>1</sup>. Visual disturbance is a frequent presenting symptom including reduced visual acuity, blurred vision, diplopia and photophobia. In a South African study of patients with HIV-associated meningitis due to *Cryptococcus neoformans*, 47% (40/86) had decreased visual acuity<sup>2</sup>. Visual loss may occur secondary to raised intracranial pressure or be due to direct fungal invasion of the optic nerve, optic chiasm or optic tracts<sup>3,4</sup>.

Papilloedema is reported to be the most common ophthalmic sign in cryptococcal meningitis, prevalence ranging between 33% and 48%<sup>5-7</sup> in case series. Other ophthalmic signs described in case reports include: retinal haemorrhages<sup>8</sup>, multi-focal choroiditis<sup>9</sup>, optic atrophy<sup>10</sup>, vascular tortuosity<sup>11</sup>, exudative retinal detachment<sup>12</sup> and intraocular cryptococcoma<sup>13</sup>. Ophthalmic signs in patients with cryptococcal meningitis may be indicative of neurological dysfunction including cranial nerve palsies<sup>14,15</sup> or may reflect concurrent systemic disease in patients with advanced HIV.

We conducted an observational study of HIV-infected adults with acute cryptococcal meningitis to describe the range and relative incidence of external ophthalmic signs.

**Methods**

The study was nested within the Adjunctive Sertraline for the Treatment of HIV-Associated Cryptococcal Meningitis (ASTRO-CM) trial (ClinicalTrials.gov number: [NCT01802385](https://clinicaltrials.gov/ct2/show/study/NCT01802385)). ASTRO-CM was a phase III randomized controlled trial to evaluate whether adjunctive sertraline improved survival when added to standard amphotericin-based therapy for cryptococcal meningitis. Primary outcome was 18-week survival. We enrolled HIV-infected adults ( $\geq 18$  years) presenting with cryptococcal meningitis (diagnosed by cerebrospinal fluid (CSF) cryptococcal antigen positivity) to Mulago National Referral Hospital, Kampala or Mbarara Regional Referral Hospital, Uganda between August 2013 and May 2017. Patients were required to be willing to undergo protocol-specified lumbar punctures; and were excluded if they had already received 3 doses of amphotericin B, if they had jaundice or known liver cirrhosis, or were pregnant or currently breastfeeding. Patients were hospitalized for 2 weeks and thereafter seen every 2 weeks as outpatients through 18 weeks.

Standard clinical and examination data were collected as part of the randomized controlled trial. We screened participants for visual disturbance and external ophthalmic signs at baseline and at each follow-up appointment, via clinical history and examination with a simple light source such as a pen torch. Incident ophthalmic symptoms and signs were ascribed by the attending study physician when first observed based on standard clinical case definitions (abnormal signs which persisted were not re-recorded at each follow-up visit).

Analysis was primarily descriptive and was performed using Microsoft Excel® 2016. We summarized the observational data as proportions or medians with inter-quartile ranges (IQR). For the descriptive analysis, we categorized ophthalmic abnormalities into three groups: (i) neurological signs (ii) localized ocular pathology (iii) evidence of concurrent systemic disease.

**Results**

We screened 696 adults with HIV-associated cryptococcal meningitis for visual disturbance and external ophthalmic signs. 87.2% of patients presented as a first episode of cryptococcal meningitis, with the remaining 12.8% having had a previous episode. The mean age was 36 years (range 18–70 years), and 60% (421/696) were men. All patients had advanced HIV with a median CD4 count 16 cells/mm<sup>3</sup> (IQR 6 - 49) and mean hemoglobin of 11.6 g/dL. Diagnostic lumbar punctures were undertaken on all patients and revealed a median opening pressure of 270 mmHg (IQR 180 – 410), and a median CSF fungal burden of 38,000 cfu/ml (IQR 790 – 236,750).

Overall, 184 participants (26.4%) displayed external ophthalmic signs or symptoms during the study period, with a total of 227 abnormal findings documented (Table 1). Thirty-eight participants (5.5%) displayed more than one sign or symptom, either concurrently or sequentially (median 2; range 2–4). Ophthalmic signs were diagnosed throughout the study period: at initial assessment (n=80; 11.5%); during inpatient consultation (n=92; 13.2%); and during outpatient consultation (n=65; 9.3%).

Ninety participants (12.9%) displayed ophthalmic manifestations of systemic disease, with conjunctival pallor the most frequently reported sign (n=48; 6.9%). Sixty-three patients (9.1%) had ocular signs or symptoms, the most common being 'reported visual disturbance' (n=32; 4.6%) – a disparate category which grouped all subjective visual deficit in the absence of other objective signs. Conjunctivitis was also frequently noted on examination (n=22; 3.2%). Cranial nerve palsies (III, IV, VI or VII) occurred in 49 patients (7.0%), with the most common being a unilateral VI palsy (n=17; 2.4%). Other neurological symptoms were less commonly seen and included conjugate gaze palsy (n=6), nystagmus (n=2) and bilateral miosis (n=1).

**Conclusions**

Ophthalmic signs and symptoms were present in more than a quarter of our cohort of Ugandan adults with HIV-associated cryptococcal meningitis, consistent with previous literature reporting ophthalmic findings to be common in this population<sup>1,2,8,16,17</sup>, although heterogeneity in study design should be noted. The complexity of this patient group is demonstrated

**Table 1. Frequency of external ophthalmic signs and symptoms in Ugandan adults with HIV-associated cryptococcal meningitis.** I) Initial assessment (baseline); II) During inpatient stay; III) During subsequent outpatient consultations. Results displayed as raw data and as a percentage of the total study population (N=696). <sup>a</sup>Reported Visual Disturbance represents the only patient-reported variable; otherwise signs are reported as judged by the clinician. <sup>b</sup>Not otherwise specified.

Sign or Symptom (N=696)	Baseline n (%)	Inpatient n (%)	Outpatient n (%)	Total n (%)
<b>Any Ophthalmic Sign or Symptom</b>	80 (11.5)	92 (13.2)	65 (9.3)	<b>184 (26.4)</b>
<b>Systemic</b>				
Pallor/Anaemia	12 (1.7)	21 (3.0)	15 (2.2)	<b>48 (6.9)</b>
Jaundice/Icterus	2 (0.3)	16 (2.3)	2 (0.3)	<b>20 (2.9)</b>
Dehydration/Sunken Eyes	1 (0.1)	3 (0.4)	3 (0.4)	<b>7 (1.0)</b>
Periorbital Oedema	4 (0.6)	3 (0.4)	0 (0.0)	<b>7 (1.0)</b>
Abnormal Periorbital Skin	4 (0.6)	4 (0.6)	0 (0.0)	<b>8 (1.1)</b>
<b>Total</b>	23 (3.3)	47 (6.8)	20 (2.9)	<b>90 (12.9)</b>
<b>Ocular</b>				
<i>Reported Visual Disturbance<sup>a</sup></i>	14 (2.0)	10 (1.4)	8 (1.1)	<b>32 (4.6)</b>
Conjunctivitis/Redness	6 (0.9)	3 (0.4)	13 (1.9)	<b>22 (3.2)</b>
Conjunctival Haemorrhage	1 (0.1)	3 (0.4)	1 (0.1)	<b>5 (0.7)</b>
Exophthalmos/Proptosis	3 (0.4)	0 (0.0)	0 (0.0)	<b>3 (0.4)</b>
Cataract	0 (0.0)	1 (0.1)	0 (0.0)	<b>1 (0.1)</b>
<b>Total</b>	24 (3.4)	17 (2.4)	22 (3.2)	<b>63 (9.1)</b>
<b>Neurological</b>				
Abnormal Pupillary Light Reflex				
Unilateral	5 (0.7)	2 (0.3)	2 (0.3)	<b>9 (1.3)</b>
Bilateral	2 (0.3)	5 (0.7)	2 (0.3)	<b>9 (1.3)</b>
III Palsy				
Unilateral	5 (0.7)	2 (0.3)	2 (0.3)	<b>9 (1.3)</b>
Bilateral	0 (0.0)	0 (0.0)	1 (0.1)	<b>1 (0.1)</b>
IV Palsy				
Unilateral	1 (0.1)	0 (0.0)	2 (0.3)	<b>3 (0.4)</b>
Bilateral	0 (0.0)	0 (0.0)	0 (0.0)	<b>0 (0.0)</b>
VI Palsy				
Unilateral	12 (1.7)	4 (0.6)	1 (0.1)	<b>17 (2.4)</b>
Bilateral	1 (0.1)	2 (0.3)	1 (0.1)	<b>4 (0.6)</b>
VII Palsy				
Unilateral	0 (0.0)	2 (0.3)	1 (0.1)	<b>3 (0.4)</b>
Bilateral	0 (0.0)	0 (0.0)	0 (0.0)	<b>0 (0.0)</b>
Squint/CN Palsy NOS <sup>b</sup>	7 (1.0)	2 (0.3)	3 (0.4)	<b>12 (1.7)</b>
Conjugate Gaze Palsy				
Lateral	1 (0.1)	2 (0.3)	2 (0.3)	<b>5 (0.7)</b>
Vertical	0 (0.0)	1 (0.1)	0 (0.0)	<b>1 (0.1)</b>
Nystagmus				
Horizontal	1 (0.1)	0 (0.0)	0 (0.0)	<b>1 (0.1)</b>
Vertical	0 (0.0)	1 (0.1)	0 (0.0)	<b>1 (0.1)</b>
Bilateral Miosis	1 (0.1)	0 (0.0)	0 (0.0)	<b>1 (0.1)</b>
<b>Total</b>	36 (5.2)	23 (3.3)	17 (2.4)	<b>76 (10.9)</b>

in the breadth of signs present, both those indicative of systemic disease and those representing concurrent ocular and neurological pathology.

Abnormal examination findings were diagnosed throughout the study period and were equally incident across initial examination, inpatient and outpatient assessment; it is therefore essential that a high clinical vigilance is maintained at every stage of management in these patients.

All reported signs and symptoms were elicited through basic clinical history and examination, requiring only a simple light source such as a pen torch. This demonstrates the potential for identifying a large spectrum of systemic, ocular and neurological disease even in a low-resource setting. The absence of equipment such as Snellen charts in our study may partly explain the low incidence of reported visual disturbance in our population (4.6%), when compared to previously published case series<sup>2,8,16,17</sup>. The apparently low incidence of neurological signs (10.9%) is likely to be attributable in part to the effect of protocol-specified lumbar punctures on intracranial pressure.

Of note, signs of systemic disease such as conjunctival pallor (6.9%) and scleral icterus (2.9%) were particularly incident in our population. Anaemia is a common feature of advanced HIV disease and a side-effect of amphotericin B-based induction therapy, with increased mortality in patients with anaemia at baseline<sup>18</sup>. Hepatotoxicity is less common, but also well-described for both amphotericin B and fluconazole, as well as several commonly-used antiretroviral (ARV) drugs such as nevirapine and efavirenz. Jaundice may signal concomitant infection with chronic hepatitis C virus (HCV) or hepatitis B virus (HBV), as well as other opportunistic infections such as cytomegalovirus (CMV) and tuberculosis (TB). Simple ophthalmic examination can provide a mechanism for identifying these potentially complicating issues - both prior to and during anti-fungal treatment - and prompt further investigation.

Our data afford several advantages compared to previous case series. Firstly, the size of our study population (N=696) is considerably larger than those previously examined, allowing for a more comprehensive description of signs and symptoms and their relative incidence. Secondly, we assessed patients regularly across a range of time-points. Systematic screening at baseline allowed for identification of early ophthalmic signs, with prolonged (18-week) follow-up ensuring late manifestations were also captured. Finally, the simplicity of clinical examination allowed a wide range of presentation severities to be assessed, in contrast to previous studies limited to co-operative patients able to consent to comprehensive ophthalmological assessments<sup>2</sup>.

However, we recognise several limitations to our study. Firstly, although visual disturbances were systematically screened for, due to the nested nature of the study formal visual acuity testing was not performed, and therefore it is likely that we underestimated the proportion of patients with objective visual

disturbance. Secondly, neither slit lamp examination nor indirect ophthalmoscopy was performed and therefore we are unable to comprehensively report on the prevalence of asymptomatic anterior chamber or retinal pathology in our cohort. Thirdly, in most cases, no attempt was made to establish aetiology of reported visual disturbance. The use of dilated indirect ophthalmoscopy in conjunction with intracranial pressure measurement and imaging, would have aided in dividing ocular from neurological pathology. Mechanisms for visual loss have been discussed elsewhere<sup>2,19</sup>. In addition, we did not extract data regarding co-morbidities or medications with ophthalmic consequences, such as diabetes mellitus or ethambutol. Finally, our study was underpowered to detect an association between visual disturbance, cryptococcal disease severity and outcome.

Currently, limited published data exist describing ophthalmic features observed in HIV-associated cryptococcal cohorts. Prospective study - including routine slit lamp and indirect ophthalmoscopic examination - is urgently required into the correlation of reported visual disturbance with objective signs, in order to further clarify the underlying mechanisms and to guide effective diagnosis, follow-up and management.

### Consent

Ugandan (MREC 429) and Minnesota (1304M31361) Institutional Review Boards approved the ASTRO-CM trial protocol. All participants (or a surrogate, should the former demonstrate altered mental status or otherwise lack capacity) provided written informed consent.

### Data availability

The database contains individual level data and as such is not available through an open-access data repository. The database is stored on a secure server at University of Minnesota. Researchers interested in accessing the data can contact the corresponding author (RRA; [rachelatherton@doctors.org.uk](mailto:rachelatherton@doctors.org.uk)), the last author (DRB; [boulw001@umn.edu](mailto:boulw001@umn.edu)) or the Division of Biostatistics at the University of Minnesota ([sph-ask@umn.edu](mailto:sph-ask@umn.edu)). Data access will be granted to active researchers in the field with the agreement of the authors.

### Grant information

This research was supported by the Wellcome Trust [210772/Z/18/Z] to FVC and through the Joint Global Health Trials scheme jointly funded by the UK Medical Research Council, UK Department for International Development and the Wellcome Trust [M007413/1].

This work was also funded by the National Institute of Neurologic Disorders and Stroke and Fogarty International Center [R01NS086312, R25TW009345], and the National Institute of Allergy and Infectious Diseases [T32AI055433].

*The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

## References

1. Rajasingham R, Smith RM, Park BJ, *et al.*: **Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis.** *Lancet Infect Dis.* 2017; **17**(8): 873–881.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
2. Moodley A, Rae W, Bhigjee A, *et al.*: **Early Clinical and Subclinical Visual Evoked Potential and Humphrey's Visual Field Defects in Cryptococcal Meningitis.** *PLoS One.* 2012; **7**(12): e52895.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
3. Moodley A, Bhigjee A: **Visual loss in HIV-associated cryptococcal meningitis: A case series and review of the mechanisms involved.** 2007; 1–9.
4. Merkler AE, Gaines N, Baradaran H, *et al.*: **Direct Invasion of the Optic Nerves, Chiasm, and Tracts by *Cryptococcus neoformans* in an Immunocompetent Host.** *Neurohospitalist.* 2015; **5**(4): 217–222.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
5. Mao F, Sun H, Li D: **[Ophthalmic manifestations in acquired immune deficiency syndrome patients with cryptococcal meningitis].** *Zhonghua Yan Ke Za Zhi.* 2015; **51**(5): 364–368, Accessed October 6, 2017.  
[PubMed Abstract](#) | [Publisher Full Text](#)
6. Kestelyn P, Taelman H, Bogaerts J, *et al.*: **Ophthalmic manifestations of infections with *Cryptococcus neoformans* in patients with the acquired immunodeficiency syndrome.** *Am J Ophthalmol.* 1993; **116**(6): 721–727, Accessed October 6, 2017.  
[PubMed Abstract](#) | [Publisher Full Text](#)
7. Okun E, Butler WT: **Ophthalmologic Complications of Cryptococcal Meningitis.** *Arch Ophthalmol.* 1964; **71**: 52–57, Accessed October 6, 2017.  
[PubMed Abstract](#) | [Publisher Full Text](#)
8. Battu RR, Biswas J, Jayakumar N, *et al.*: **Papilloedema with peripapillary retinal haemorrhages in an acquired immunodeficiency syndrome (AIDS) patient with cryptococcal meningitis.** *Indian J Ophthalmol.* 2000; **48**(1): 47–9.  
[PubMed Abstract](#)
9. Andreola C, Ribeiro MP, de Carli CR, *et al.*: **Multifocal Choroiditis in Disseminated *Cryptococcus neoformans* Infection.** *Am J Ophthalmol.* 2006; **142**(2): 346–348.  
[PubMed Abstract](#) | [Publisher Full Text](#)
10. Espino Barros Palau A, Morgan ML, Foroozan R, *et al.*: **Neuro-ophthalmic presentations and treatment of Cryptococcal meningitis-related increased intracranial pressure.** *Can J Ophthalmol.* 2014; **49**(5): 473–7.  
[PubMed Abstract](#) | [Publisher Full Text](#)
11. Aderman CM, Gorovoy IR, Chao DL, *et al.*: **Cryptococcal choroiditis in advanced AIDS with clinicopathologic correlation.** *Am J Ophthalmol Case Rep.* 2018; **10**: 51–54.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
12. Chen J, Chai C, Teoh SC: **Cryptococcal-related exudative retinal detachment.** *Eye (Lond).* 2011; **25**(9): 1234–1235.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
13. Wykoff CC, Albin TA, Couvillion SS, *et al.*: **Intraocular Cryptococcoma.** *Arch Ophthalmol.* 2009; **127**(5): 700–2.  
[PubMed Abstract](#) | [Publisher Full Text](#)
14. Krishnamoorthy A, Joel A, Abhilash KP: **Cryptococcal Meningitis with Multiple Cranial Nerve Palsies: A Review of Literature.** *J Glob Infect Dis.* 2015; **7**(3): 123–124.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
15. Liyanage DS, Pathberiya LP, Gooneratne IK, *et al.*: **Cryptococcal meningitis presenting with bilateral complete ophthalmoplegia: a case report.** *BMC Res Notes.* 2014; **7**(1): 328.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
16. Sloan D, Parris V: **Cryptococcal meningitis: epidemiology and therapeutic options.** *Clin Epidemiol.* 2014; **6**: 169–82.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
17. Kuriakose CK, Mishra AK, Vanjare HA, *et al.*: **Visual Disturbance in Patients with Cryptococcal Meningitis: The Road Ahead.** *J Neurosci Rural Pract.* 2017; **8**(1): 151–152.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
18. Tugume L, Morawski BM, Abassi M, *et al.*: **Prognostic implications of baseline anaemia and changes in haemoglobin concentrations with amphotericin B therapy for cryptococcal meningitis.** *HIV Med.* 2017; **18**(1): 13–20.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
19. Rex JH, Larsen RA, Dismukes WE, *et al.*: **Catastrophic visual loss due to *Cryptococcus neoformans* meningitis.** *Medicine (Baltimore).* 1993; **72**(4): 207–224, Accessed June 6, 2018.  
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# Open Peer Review

Current Referee Status:  

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## Version 2

Referee Report 22 October 2018

doi:[10.21956/wellcomeopenres.16207.r34063](https://doi.org/10.21956/wellcomeopenres.16207.r34063)



**Emilio Dodds**<sup>1</sup>, **Héctor Pérez**<sup>2</sup>

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**Competing Interests:** No competing interests were disclosed.

**We have read this submission. We believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

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## Version 1

Referee Report 08 October 2018

doi:[10.21956/wellcomeopenres.15968.r34000](https://doi.org/10.21956/wellcomeopenres.15968.r34000)



**Héctor Pérez**<sup>1</sup>, **Emilio Dodds**<sup>2</sup>

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This work was evaluated jointly, with Dr. Emilio Dodds, who is a reference of the ophthalmology service and consultant of the infectious diseases division of the Juan A. Fernandez Hospital, in the city of Buenos Aires, with extensive experience in diagnostic, treatment and monitoring of more than four thousand patients since 1982, with multiple studies published, continuing their work for more than thirty-five years, and training resident doctors, as well as dictating the subject in the undergraduate program. These are our conclusions.

Overall it is a nice study with a big population, however the ophthalmic study is limited and the authors clearly state that condition. Some comments:

1. The title is misleading: I would say external ophthalmic findings instead of ophthalmic signs, since this is exactly what they studied and they did not look for the whole ophthalmic signs.
2. To clarify I would add external ophthalmic signs every time they mention ophthalmic signs (abstract, row 10; Background, last row; Methods, second paragraph, 3 row; Results, 2 row)

3. Conclusion: ophthalmic signs and symptoms were present in more than a quarter of our cohort...consistent with previous reports (references 1, 2, 8, 16,17). These studies are not comparable since they are looking at different things: external findings and not the whole signs.
4. Page 5, first column, last paragraph, row 5: they say the underestimate number of patients with visual disturbances but they could also overestimate it because they are not checking for refractive errors.

**Is the work clearly and accurately presented and does it cite the current literature?**

Yes

**Is the study design appropriate and is the work technically sound?**

Partly

**Are sufficient details of methods and analysis provided to allow replication by others?**

Partly

**If applicable, is the statistical analysis and its interpretation appropriate?**

I cannot comment. A qualified statistician is required.

**Are all the source data underlying the results available to ensure full reproducibility?**

Yes

**Are the conclusions drawn adequately supported by the results?**

Yes

**Competing Interests:** No competing interests were disclosed.

**We have read this submission. We believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Referee Report 02 July 2018

doi:[10.21956/wellcomeopenres.15968.r33421](https://doi.org/10.21956/wellcomeopenres.15968.r33421)



**Mosepele Mosepele**<sup>1,2</sup>

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Study question, setting & population, study measures, data analysis, data reporting & interpretation are clearly stated. In this ophthalmic complications study nested within a CM trial, the investigators described ophthalmic complications among 696 HIV-CM adults in Uganda. At any point in time (at admission, during admission, post-discharge), rate of ophthalmic complications ranged between 9 and 13%. Clinically significant findings such as subjective decrease in visual acuity were however, uncommon.

Suggestions for data reporting:

1. Would have been useful to "trend" out the TYPE(S) of ophthalmic complications over time (even though the total frequencies were similar throughout follow-up). For instance, give baseline median

haemoglobin of 11g/dl, the reported 48 participants may indicate complications of Amphotericin (late in course of treatment) vs at presentation. A figure or bar chart or some other graphical representation of major findings at each setting: at admission vs during admission vs post-discharge may be informative re the type of further care/evaluation that could be recommended for patients (systemic disease will be for the treating clinician) while ocular/neuro symptoms may indicate need for eye clinic referral.

2. In this setting, proportion of patients started on Ethambutol (or even anti-tuberculous therapy) containing antimicrobial therapy should be reported if available - or these limitation discussed as Ethambutol may cause decrease in visual acuity.

Conclusions:

1. Neurologic complications seem very low. Discussing the trial effect, e.g., intensive CSF drainage vs opening pressure monitoring as per standard of care, should be discussed.
2. Evaluation of other conditions that may results in ophthalmic conditions such as Diabetes, etc were not evaluated. This should be discussed in the study limitations section.

**Is the work clearly and accurately presented and does it cite the current literature?**

Yes

**Is the study design appropriate and is the work technically sound?**

Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

Yes

**Are all the source data underlying the results available to ensure full reproducibility?**

Partly

**Are the conclusions drawn adequately supported by the results?**

Partly

**Competing Interests:** No competing interests were disclosed.

**Referee Expertise:** HIV in resource limited setting, including both infectious and non-infectious complications

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

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