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Telemedicine Screening for Cytomegalovirus Retinitis at the Point of HIV Care

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Abstract

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Author Contributions:
Study concept and design: Jirawison, Margolis, Keenan.
Acquisition of data: Jirawison, Yen, Leenasirimakul, Chen, Guadanant, Margolis, Keenan.
Analysis and interpretation of data: Jirawison, Yen, Kunavisarut, Patikulsila, Watanachai, Ausayakhun, Heiden, Holland, Margolis, Keenan.
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Conflicts of Interest: Gary N. Holland has served on Advisory Boards for the following companies: Genentech, Incorporated; Novartis International AG; Santen, Incorporated; and Xoma (US) LLC. Todd P. Margolis has pending intellectual property with the University of California describing a mobile phone camera for retinal imaging. At the current time this intellectual property has no financial value. Jirawison, Yen, Leenasirimakul, Chen, Guadanant, Kunavisarut, Patikulsila, Watanachai, Ausayakhun, Heiden, and Keenan do not have any conflicts of interest to disclose.

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Importance: Cytomegalovirus (CMV) retinitis is a leading cause of blindness in many developing countries, likely the result of inadequate screening. Telemedicine screening for CMV retinitis instituted at the point of HIV care may allow for earlier detection.

Objective: To determine the diagnostic accuracy of retinal photography in detecting CMV retinitis at the point of HIV care, and to characterize the clinical manifestations of CMV retinitis detected through the screening program.

Design: Mosaic fundus photographs were captured through a dilated pupil using a digital fundus camera. An experienced on-site ophthalmologist masked to the results of the fundus images subsequently examined each eye with indirect ophthalmoscopy and recorded the clinical findings on a standardized form. Three remote graders evaluated each image for CMV retinitis.

Setting: Hospital HIV clinic in Thailand.

Participants: 103 participants were enrolled from a population of 258 HIV patients with a CD4<100 cells/μl.

Main Outcomes and Measures: Sensitivity and specificity of telemedicine diagnosis of CMV retinitis relative to indirect ophthalmoscopy, and clinical features of CMV retinitis lesions.

Results: Sixteen (15.5%) patients were diagnosed with CMV retinitis, of which 5 (31.3%) had bilateral disease. Of the 21 (10.2%) eyes with CMV retinitis, 33.3% had visual symptoms. Retinitis lesions occupied <10% of the total retinal surface area in 61.9% of eyes, and did not involve the posterior pole (i.e., zone 1) in 71.4% of eyes. Average visual acuity in affected eyes was 20/50 (95%CI 20/25–20/100). The mean sensitivity for the 3 remote graders in detecting eyes with CMV retinitis on fundus photography was 30.2% (95% CI 10.5% to 52.4%), and mean specificity was 99.1% (95%CI 97.8% to 100.0%). CMV retinitis lesions missed by the remote graders (false negatives) were more likely to be small (P=0.001) and located in the peripheral retina (P=0.04).

Conclusion and Relevance: Patients screened at an HIV clinic had less extensive retinitis than recent reports from a local ophthalmology clinic. Retinal photography with the camera used in this study was not highly sensitive in detecting CMV retinitis, but may identify immediately vision-threatening disease. Improved accuracy will require a camera that can more easily image the peripheral retina.

Introduction

Cytomegalovirus (CMV) retinitis is a leading cause of blindness in many developing countries with a high burden of the acquired immunodeficiency syndrome (AIDS).[1–5] The condition causes full thickness retinal necrosis and irreversible blindness if left untreated.[6,7] It is therefore important to detect CMV retinitis before the patient loses vision. The standard of care is to screen patients who have a CD4 count below 100 cells/μl with indirect ophthalmoscopy every 3 months. However, screening is not routinely performed in many developing countries due to limited ophthalmic care.[8–11] Patients often have severe disease by the time they present to care.[12,13] New strategies are needed to increase the number of patients who are diagnosed with CMV retinitis before it causes vision loss. Because CD4

testing is the primary indication for screening, it would be most effective if screening were initiated by the HIV clinician.[2,13,14]

Telemedicine using retinal photography is one potential method to screen for CMV retinitis in a primary care setting. Prior studies found that telemedicine has high sensitivity and specificity in detecting CMV retinitis.[15–17] However, these studies recruited participants from ophthalmology centers. In practice, telemedicine screening would occur in HIV clinics. It is unclear whether the diagnostic performance of telemedicine would differ in an HIV clinic, where non-ophthalmic personnel would obtain photographs and the disease would likely be less extensive. The purpose of the present study was two-fold: first, to determine the diagnostic accuracy of fundus photography in detecting CMV retinitis when used in an HIV clinic setting, and second, to determine whether the cases identified at the point of HIV care have less extensive disease than those reported in prior studies of ophthalmology clinic based screening programs.

Methods

Ethical approval was obtained from the Committee on Human Research at the University of California, San Francisco and the Nakornping Hospital Institutional Review Board. This study adhered to the tenets of the Declaration of Helsinki. All participants gave written informed consent prior to enrollment. No patients were harmed during data collection.

Between June 18, 2010 and June 15, 2012, we enrolled patients with a CD4 count below 100 cells/μl from the HIV clinic at Nakornping Hospital, a tertiary medical center in Chiang Mai, Thailand. We intended to enroll all consecutive patients, but this was logistically difficult. Patients who were pregnant, under the age of 18, or carried a previous diagnosis of CMV retinitis were excluded. We trained an HIV clinic staff member (SG) with no previous experience in ophthalmology or fundus photography to use the Topcon TRC-NW 6S digital fundus camera (sensor resolution 10.1 megapixels; Topcon, Tokyo, Japan). In one training session prior to enrolling participants, we trained her to use the internal fixation settings to obtain a standard set of 9 overlapping 45-degree fundus images. Her skills were deemed to be adequate by the end of this session. We directly monitored all photography for the first 6 weeks, and periodically thereafter. This individual took all photographs in the study. Images of both eyes from each patient were captured after dilating each eye with 1% tropicamide. A composite mosaic image covering an 85-degree retinal field was created using i2kRetina software (DualAlign LLC, Clifton Park, NY). The photographer was masked to all clinical and demographic information about the patient.

A fellowship-trained retina specialist (CJ) with extensive experience diagnosing and treating CMV retinitis subsequently examined each eye for CMV retinitis using indirect ophthalmoscopy, masked to the findings from fundus photography. Clinical characteristics of retinitis lesions were recorded on a standardized form. For each eye with CMV retinitis, a detailed drawing of the lesion was made on a template that showed important retinal landmarks as well as the 3 zones used to denote CMV retinitis location.[18] The in-clinic ophthalmologist categorized retinitis lesion size as a percentage of total retinal surface area, and assessed the degree of opacity of the lesion border against standard photographs from a

previously described system.[18] Study participants were offered repeat examination and photography every three months until their CD4 count increased to 100 cells/μl or greater. Eyes that developed CMV retinitis at any point in the study were subsequently censored.

The mosaic image for each eye was uploaded to a secure server and transferred to 3 fellowship-trained retina specialists with expertise in diagnosing CMV retinitis (PK, DP and NW). After completing a training session, remote graders used a standardized form to assign to each image a diagnosis of “CMV retinitis present”, “CMV retinitis absent”, or “unknown”. Experts also determined the gradability of each image. Gradability was defined as “good” if the image was both in focus and covered the full 85-degree field; “acceptable” if the image was either slightly out of focus or did not cover the full 85-degree field, but a definitive diagnosis could be made; and “poor” if the image was either so out of focus or covered such a small degree of the retina that definitive diagnosis could not be made. Eyes were evaluated independently and in random order. Graders received no demographic information and were masked to the clinical diagnosis that was made both on indirect ophthalmoscopy and by the other graders.

We calculated the sensitivity and specificity of each grader relative to the in-clinic examination as the reference standard. The purpose of telemedicine screening is to identify all potential cases of CMV retinitis for referral to an ophthalmologist. Therefore, we considered as a positive diagnosis both “CMV retinitis present” and “unknown.” Sensitivity and specificity was calculated using 1) individual eyes and 2) the person as the unit of analysis. For eye-level analyses, eyes were excluded if the on-site ophthalmologist could not determine with certainty the presence or absence of CMV retinitis. For person-level analysis, the study participant was excluded if the on-site ophthalmologist diagnosed both eyes as “unknown” or diagnosed one eye as “unknown” and the other as “CMV retinitis absent.” Participants were considered positive for CMV retinitis if at least one eye was found to have CMV retinitis, and negative for CMV retinitis if neither eye had CMV retinitis.

Positive predictive values (PPV) and negative predictive values (NPV) were determined using the prevalence of CMV retinitis in this study population. Cohen’s kappa coefficient (κ) was used to measure 1) intra-grader agreement for each remote grader using 50 randomly selected and randomly presented repeat images, and 2) inter-grader agreement between all 3 graders. To account for the non-independence of two eyes from the same patient as well as multiple images of the same eye on different visits, we calculated bootstrap percentile 95% confidence intervals for diagnostic test statistics with resampling at the patient level (9999 repetitions). *P*-values were calculated using Fisher’s exact test for categorical variables and the Wilcoxon rank sum for continuous variables. All statistical analyses were performed with Stata software version 13 (Statacorp, College Station, Texas, USA).

Results

HIV Clinic Screening Population:

We enrolled 103 of 258 eligible individuals (i.e. patients seen in the HIV clinic during the study period with a CD4<100 cells/μl as documented by the hospital laboratory), 30 of

whom were screened multiple times. Those who enrolled were similar to those who did not: 62 (60.2%) participants were male compared with 144 (55.8%) non-participants; the average age was 37.5 years (SD 9.1) for participants versus 37.8 (SD 8.4) for non-participants; and the average CD4 count was 30.2 cells/μl, (SD 19.1) in participants versus 29.5 cells/ μl (SD 19.2) in non-participants. In total, we performed 277 separate eye examinations of 205 eyes. Table 1 shows the clinical and demographic characteristics of the study population.

The study-site ophthalmologist diagnosed CMV retinitis by indirect ophthalmoscopy in 21 (10.2%, 95%CI 6.5–15.2%) distinct eyes from 16 (15.5%, 95%CI 9.1–24.0%) distinct study participants. CMV retinitis was detected at the initial screening examination in 17 eyes of 13 participants and at the 3-month repeat screening examination for 4 eyes of 3 participants. The on-site ophthalmologist could not give a definitive diagnosis in 5 eyes of 4 participants. All 5 eyes were excluded from eye-level analyses, and 3 of the 4 participants were excluded from person-level analyses. The participant not excluded from the person-level analyses had CMV retinitis in one eye and an unknown diagnosis in the contralateral eye.

CMV Retinitis Characteristics:

Five participants (5/16; 31.3%) with CMV retinitis had bilateral disease at the time of diagnosis. Of the 21 eyes diagnosed with CMV retinitis, the average logMAR visual acuity was 0.41 (95%CI 0.11 to 0.71; Snellen equivalent 20/50, 95%CI 20/25 to 20/100). Seven eyes (7/21; 33.3%) of 6 (6/16; 37.5%) participants had visual symptoms at the time of diagnosis. The extent of retinitis was less than 10% of the total retinal surface area in the majority of eyes. Lesions extended into zone 1 in 6 (28.6%) eyes.

Remote Diagnosis:

Three retina specialists remotely graded the 272 eligible images. Photographic quality was high, with 262 of 272 photographs deemed to be of acceptable or good quality by 2 of the 3 graders (Figure). The diagnostic accuracy of each grader relative to indirect ophthalmoscopy is shown in Table 2. On average, remote graders had a sensitivity of 30.2% (95% CI 10.5% to 52.4%) and specificity of 99.1% (95%CI 97.8% to 100.0%) in diagnosing individual eyes for CMV retinitis. Assuming the study prevalence of 10.2%, average PPV and NPV were 78.7% (95%CI 61.7% to 89.4%) and 92.6% (95%CI 91.4% to 93.6%), respectively. Intra-rater κ was 1.00 for all graders. Inter-rater κ was 0.92 (0.74 to 1.00). Sensitivity was slightly higher and specificity slightly lower in the person-level analyses (Table 2).

False negatives:

Table 3 shows the characteristics of the 21 eyes diagnosed with CMV retinitis by indirect ophthalmoscopy, stratified by whether CMV retinitis was detected by at least 2 remote graders. The 15 eyes for which the graders did not diagnose CMV retinitis (i.e. false negatives) had smaller (P=0.001) and more peripheral (P=0.04) lesions with less border opacity (P<0.001). To assess which lesion characteristics were most important, we stratified false negatives by the most posterior retinitis location (Table 4). Of particular interest were 2 eyes from 1 patient in which the in-clinic ophthalmologist documented retinitis in zone 1—a location that should have been detected on photography. Both of these eyes had lesions that occupied <10% of the total retina and had minimal (1+) border opacity. We retrospectively

reviewed the medical records of this patient; at subsequent clinic visits the in-clinic ophthalmologist determined that neither eye had CMV retinitis. The false negative cases were also evaluated by 3 unmasked uveitis experts (DH, GNH, and TPM). Of the 15 images reviewed, they found potential abnormalities in 3 eyes, each of which had been classified as having CMV retinitis in zone 2 or anterior by the in-clinic ophthalmologist. One of the eyes had a possible small focus of retinitis at the image border and 2 eyes had lesions thought unlikely to be CMV retinitis but requiring close follow-up.

False positives.—Two eyes without CMV retinitis on indirect ophthalmoscopy were classified as having CMV retinitis by remote graders (i.e. false positives). One image was rated as having poor gradability and diagnosed as “unknown” by all of the graders; the other was found by the 3 unmasked uveitis experts to have a nonspecific inactive chorioretinal scar.

Discussion

In this study we report the results of a CMV retinitis telemedicine screening program that was instituted at the point of HIV care. In contrast to previous studies from ophthalmology referral centers in Thailand that have found CMV retinitis in up to one-third of HIV patients, we diagnosed CMV retinitis in 15.5% of those screened.[19] Although this should be interpreted with caution since we screened only 40% of patients with a CD4 < 100 cells/μl, these results likely provide a more accurate estimate of the burden of CMV retinitis in the Thai HIV population. The retinitis detected in this point-of-care screening program was less extensive than previous reports from nearby Thai ophthalmology clinics, suggesting disease was detected earlier.[15,17] Remote CMV retinitis screening by telemedicine did not perform as well in the HIV clinic setting as it had in a previous study from a tertiary ophthalmology referral clinic, but may be useful for identifying patients with immediately vision-threatening disease.

Fundus photography, as implemented in a single HIV clinic in Thailand, detected approximately one-third of CMV retinitis cases. This performance is inferior to that of telemedicine diabetic retinopathy screening, for which the sensitivity typically exceeds 85%.[20,21] The majority of missed lesions were small and located in the peripheral retina outside the photographable range of the camera, whose internal fixation targets do not image zone 3 or the anterior portion of zone 2. Two small lesions missed by the remote graders but classified as being in zone 1 by the in-clinic ophthalmologist were later determined to not have CMV retinitis by the treating physician, suggesting the reference diagnosis was misclassified in these cases. Thus, fundus photography with the study camera detects the vast majority of vision-threatening lesions in the posterior pole but misses disease confined to the peripheral retina. Obtaining a wider view of the retina would likely increase the sensitivity of telemedicine CMV retinitis screening. This could be accomplished with a camera that has a wider angle lens, or by using an external fixation light instead of the internal fixation light used in the present study. Neither of these limitations are easily overcome. Fundus cameras with wider fields of view are cost-prohibitive for resource-constrained settings, and obtaining peripheral retinal images with an external fixation target is technically challenging and may not be feasible in the hands of personnel with minimal

training. A potential alternative would be to train HIV clinicians to use indirect ophthalmoscopy to diagnose CMV retinitis.[22]

Even an imperfect screening test could increase the number of patients with CMV retinitis detected by the health care system. Fundus photography detected cases that were more likely to have larger lesions, zone 1 involvement, and poorer visual acuity. Telemedicine may therefore identify patients in urgent need of referral to an ophthalmologist due to immediately sight-threatening disease.[6,23] However, untreated peripheral lesions may grow into the posterior pole and may also increase the risk for retinal detachment.[24–27] Patients would therefore need to be re-screened periodically for previously missed lesions that progress into the viewable range of the camera. This may be feasible at the early stages of HAART, when most cases of CMV retinitis in Thailand are diagnosed, because patients see their provider every few weeks for routine HIV care.[12] Nevertheless, a more sensitive screening test that reliably identifies early retinitis would clearly be preferable.

The CMV retinitis diagnosed at this HIV clinic was less extensive compared with previous studies done at ophthalmology clinics, likely because diagnosis occurred earlier. CMV retinitis patients in Thailand must be referred to an ophthalmologist sometimes several hundred kilometers away for diagnosis and treatment.[9] This situation likely leads to disease progression before diagnosis, permanent vision loss, and decreased quality of life.[28] This study provides evidence that integrating screening for CMV retinitis into routine HIV clinical care allows for earlier detection. Compared to the study conducted at the nearby ophthalmology referral center, we found less bilateral retinitis (31.3% versus 46.2%), fewer visual symptoms (33.3% versus 90.8%), better visual acuity (median 20/50 versus 20/80), smaller lesion sizes (28.6% of lesions occupied more than one-quarter of the total retinal surface area in the present study, versus 56.7%), and less zone 1 involvement (28.6% versus 61.8%).[12] Notably, the disease profile of the HIV clinic patients in this study was closer to that observed in Western populations.[29–32]

Our goal was to screen all HIV patients with a CD4 < 100 cells/μl. Although we used an established protocol to recruit participants, we enrolled only 39.9% of eligible patients, resulting in a relatively small sample size. Although non-participation may limit the generalizability of the study if CMV retinitis affected participants and non-participants differently (e.g., in terms of location or severity), we found no evidence suggesting this was the case, since CD4 counts were similar in those who did and did not enroll. We did not prospectively record why prospective study participants did not enroll in the study. However, we retrospectively solicited the impressions of clinic personnel, which uncovered 3 major reasons for non-participation: (1) some patients, especially those unaccompanied by a caretaker, did not want to be dilated over concerns of difficulty driving home after dilation; (2) some patients, especially those without visual symptoms, did not want to spend the extra time to participate; and (3) on busy days, clinic staff often did not have time to obtain informed consent. These three factors must be addressed before screening is adopted as a clinic policy.

Our research had several other limitations. We did not follow study participants after diagnosis and cannot comment on the long-term visual outcomes or complication rates of

our patients. Based on the results of a prior study,[15] we trained the photographer to use the internal fixation lights to create mosaic retinal images of the posterior retina. This strategy limited the ability of the camera to detect far peripheral disease, which likely reduced the sensitivity of the test. Finally, patients were recruited from an urban medical center, and residents here likely have better access to medical care than those living in rural areas.[33,34] Retinal photography may have a higher sensitivity in detecting CMV retinitis if instituted at a rural clinic, where patients are more likely to present at a later stage of their disease.

In conclusion, instituting photographic CMV retinitis screening with the systems and protocols described in this paper is feasible at the primary care level and could lead to earlier diagnosis. Retinal imaging with the camera used in this study did not have a high sensitivity for detecting CMV retinitis because cases with less extensive and more peripheral disease were missed. However, our data shows that telemedicine can identify lesions that are immediately vision-threatening and require immediate attention by an ophthalmologist. A camera that can more easily image the entire retina would increase the accuracy of telemedicine in detecting CMV retinitis among at-risk patients and would be even more valuable in an HIV clinic.

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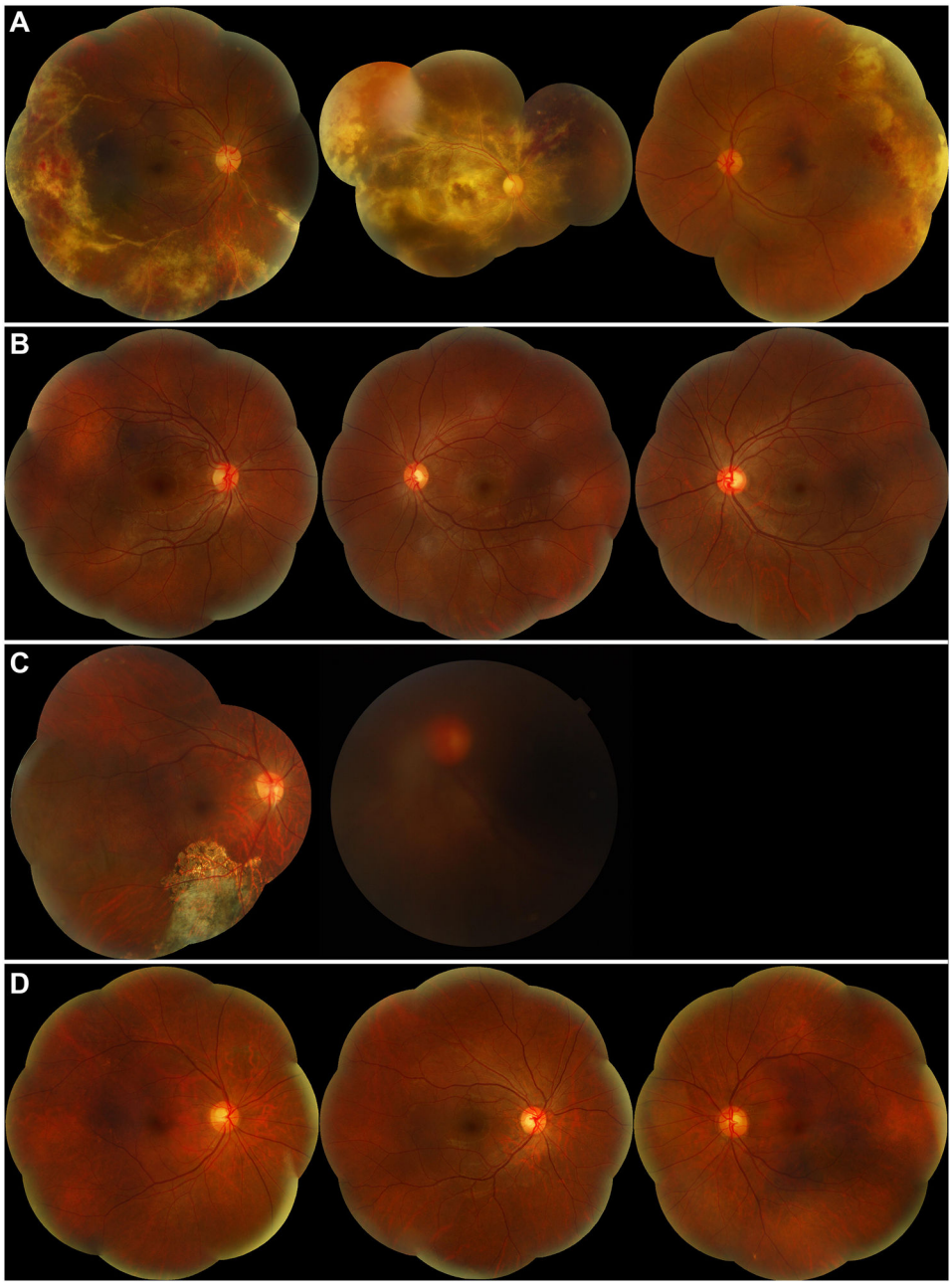

Figure 1: Representative sample of mosaic fundus images, stratified by telemedicine results.
A stratified random sample of (A) true positives, (B) true negatives, (C) false positives, and (D) false negatives is shown, defined based on the consensus grade from 2 of 3 photographic graders relative to the in-clinic ophthalmologist.

Table 1:

Characteristics of 103 study participants screened for cytomegalovirus retinitis at an HIV clinic in Thailand

Characteristic	n(%) or Median (IQR)
Age, years	36 (30–44)
Female	41 (39.8%)
CD4 Count, cells/μl	
Nadir	22 (12–39)
Most Recent	27 (14–41)
Taking HAART	79 (76.7%)
Time from HAART, months[a]	1.8 (0.7–4.0)
Number of screening examinations	
Baseline only	103 (100%)
Baseline and Month 3	30 (29.1%)
Baseline, Month 3, and Month 6	6 (5.8%)

HAART=highly active antiretroviral therapy

[a]Among 79 study participants on HAART

Table 2:

Diagnostic accuracy of telemedicine for cytomegalovirus retinitis, relative to indirect ophthalmoscopy

	Grader 1	Grader 2	Grader 3	Average
Eye-Level[a]				
Sensitivity	28.6% (9.5–52.0)	33.3% (13.1–55.0)	28.6% (9.5–52.0)	30.2% (10.5–52.4)
Specificity	99.2% (97.9–100.0)	98.8% (97.3–100.0)	99.2% (97.9–100.0)	99.1% (97.8–100.0)
PPV	80.3% (46.7–95.0)	76.0% (46.9–91.9)	80.3% (46.7–95.0)	78.7% (61.7–89.4)
NPV	92.4% (90.3–94.1)	92.9% (90.6–94.6)	92.4% (90.3–94.1)	92.6% (91.4–93.6)
Patient-Level[b]				
Sensitivity	31.3% (12.5–56.3)	37.5% (12.5–62.5)	31.3% (12.5–56.3)	33.3% (12.5–56.3)
Specificity	98.3% (95.7–100.0)	97.5% (94.2–100.0)	98.3% (95.7–100.0)	98.1% (95.4–100.0)
PPV	77.5% (42.1–94.2)	73.3% (43.2–90.9)	77.5% (42.1–94.2)	75.9% (57.7–87.9)
NPV	88.6% (84.8–91.6)	89.5% (85.3–92.6)	88.6% (84.8–91.6)	88.9% (86.8–90.7)

PPV= Positive Predictive Value

NPV= Negative Predictive Value

[a]Based on 272 distinct eye examinations of 200 eyes, 21 of which had CMV retinitis; assumes 10.2% prevalence of CMV retinitis for predictive values

[b]Based on 136 distinct patient examinations (of both eyes) of 100 patients, 16 of whom had CMV retinitis; assumes 15.5% prevalence of CMV retinitis for predictive values

Table 3:

Characteristics of eyes with cytomegalovirus retinitis, stratified by telemedicine results

Characteristic	Detected on photography[a] (True positives; N=6)	Not detected on photography[a] (False negatives; N=15)	*P*- Value[b]
	n(%) or Median (IQR)	n(%) or Median (IQR)	
Visual Acuity	6/120 (6/18 to HM)	6/6 (6/6 to 6/9)	0.006
Visual symptoms	5 (83.3%)	2 (13.3%)	0.006
Lesion Size			
<10%	0 (0%)	13 (86.7%)	0.001
10%−24%	1 (16.7%)	1 (6.7%)[b]	
25%−50%	3 (50.0%)	1 (6.7%)[b]	
>50%	2 (33.3%)	0 (0%)	
Most Posterior Zone			
1	4 (66.7%)	2 (13.3%)	0.04
2	2 (33.3%)	6 (40.0%)	
3	0 (0%)	7 (46.7%)	
Border Opacity			
1+	0 (0%)	9 (60.0%)	<0.001
2+	1 (16.6%)	5 (33.3%)	
3+	0 (0%)	1 (6.7%)	
4+	5 (83.3%)	0 (0%)	
Photograph gradability[c]			
Good	1 (16.7%)	11 (73.3%)	0.04
Acceptable	4 (66.7%)	4 (26.7%)	
Poor	1 (16.7%)	0 (0.0%)	

HM=Hand Motions

[a]Results stratified by the consensus grade given by at least 2 of 3 remote graders

[b]Fisher's exact or Wilcoxon rank sum test

[c]Gradability score given by at least 2 graders

Table 4:

Characteristics of CMV retinitis, stratified by the most posterior zone involved and by telemedicine results

	Detected on photography[a] (True positives)		Not detected on photography[a] (False negatives)		
	Most posterior zone		Most posterior zone		
	Zone 1 (N=4)	Zone 2 (N=2)	Zone 1 (N=2)	Zone 2 (N=6)	Zone 3 (N=7)
Lesion Size					
<10%	0 (0%)	0 (0%)	2 (100%)	4 (66.6%)	7 (100%)
10%−24%	0 (0%)	1 (50.0%)	0 (0%)	1 (16.7%)	0 (0%)
25%−50%	2 (50.0%)	1 (50.0%)	0 (0%)	1 (16.7%)	0 (0%)
>50%	2 (50.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Border Opacity					
1+	0 (0%)	0 (0%)	2 (100%)	2 (33.3%)	5 (71.4%)
2+	0 (0%)	1 (50.0%)	0 (0%)	3 (50.0%)	2 (28.6%)
3+	0 (0%)	0 (0%)	0 (0%)	1 (16.7%)	0 (0%)
4+	4 (100%)	1 (50.0%)	0 (0%)	0 (0%)	0 (0%)

[a]Results stratified by the consensus grade given by at least 2 of 3 remote graders