

CMV Retinitis Diagnosis by Non- ophthalmologists: Learning Curve Over a 4-Day Training Workshop

To the Editors:

Cytomegalovirus (CMV) retinitis is a blinding opportunistic infection that primarily affects people with AIDS in resource-limited settings. Screening for CMV retinitis is important because the infection can cause irreversible retinal destruction before the onset of visual symptoms. Routine screening is recommended for patients with CD4 counts less than 100 cells per microliter and consists of a dilated fundus examination with an indirect ophthalmoscope. However, screening rarely occurs in low- and middle-income countries because ophthalmologists are usually not available. As a result, clinical outcomes are poor, with roughly one-third of eyes already blind by the time they are diagnosed with CMV retinitis.¹

Given the lack of CMV retinitis screening for its HIV population, the Médecins Sans Frontières Yangon Project initiated a program in 2006 to train its AIDS physicians how to diagnose and treat CMV retinitis at the point-of-care.² An outside ophthalmologist (D.H.) designed and implemented a 4-day training program to transfer the skills of binocular indirect ophthalmoscopy for CMV retinitis diagnosis. The workshop has been repeated every year since. In this study, we retrospectively reviewed the records from 2 of the workshops to determine the sensitivity and specificity of CMV retinitis

diagnosis by non-ophthalmologists over the course of a 4-day training workshop.

METHODS

Two training workshops, each attended by 5 different HIV/AIDS physicians, were administered over 2 consecutive weeks in Yangon, Myanmar, in February 2012. The 4-day training workshop is described in detail elsewhere.² Briefly, the workshop consisted of didactic lectures about retinal diseases, instruction in the use of the binocular indirect ophthalmoscope, and practical sessions using the indirect ophthalmoscope—first on model eyes and then on patients with AIDS. Two of the trainees had completed the workshop before 1–2 years and had been performing indirect ophthalmoscopy at their respective clinics in the interim. The remaining physicians had no experience with indirect ophthalmoscopy. All were medical school graduates with 1 to 5 years of experience in general medical practice; all had been working in clinics dedicated to patients with HIV/AIDS for at least 1 year. The workshops were led by 3 ophthalmologists and included both classroom didactics and clinical examinations of patients with HIV/AIDS.² During clinical examinations, trainees and ophthalmologists recorded on a standardized form whether each eye had CMV retinitis (present, absent, unknown). By workshop design, each trainee and ophthalmologist was masked to the results of each other's examination until everyone had examined a particular patient, at which time one of the ophthalmologists would review the findings of that patient and provide directed guidance to trainees.

We assessed agreement between the 3 masked ophthalmologists with a Cohen's kappa statistic. For subsequent analyses, we constructed a consensus diagnosis, defined as the diagnosis agreed on by at least 2 ophthalmologists. We modeled the sensitivity of indirect ophthalmoscopy over the 4 days of the workshop using mixed effects linear regression with trainee as a random effect and using only the subset of eyes classified as having CMV retinitis by the consensus grade. We used a similar model to estimate: (1) specificity, using the subset of eyes classified as not

having CMV retinitis by the consensus diagnosis and (2) the rate of indeterminate tests, separately for patients with and without the consensus diagnosis of CMV retinitis. We constructed 95% confidence intervals for all statistical tests using bootstrapping (1000 replications), with resampling at the patient level to account for nonindependence of eyes. We used Stata 12 (Statacorp, College Station, TX) for all analyses. The study was reviewed by the University of California, San Francisco Committee for Human Research, which deemed that the study did not require ethical approval because it used retrospective deidentified data.

RESULTS

Of 171 eyes examined by trainees, 89 were examined by all 3 ophthalmologists. Agreement between the 3 ophthalmologists was high for the diagnosis of CMV retinitis ($\kappa = 0.85$, 95% CI: 0.77 to 0.91).

We constructed a consensus diagnosis for CMV retinitis for the 147 examinations where at least 2 ophthalmologists agreed. Of these 147 eyes, CMV retinitis was present by ophthalmologist consensus in 89 (60.5%). For those eyes with a consensus diagnosis of CMV retinitis, novice trainees demonstrated a remarkable improvement in the ability to detect CMV retinitis over the 4 days of the workshop (from 25.1% to 83.9%; $P < 0.001$), as well as a reduction in the number of diagnoses coded as "unknown" (from 46.7% to 7.5%; $P = 0.002$) (Fig. 1A). In contrast, experienced trainees had near perfect sensitivity throughout the entire 4 days of the workshop and no evidence for change during the workshop ($P = 0.62$ for CMV retinitis diagnoses and $P = 0.40$ for "unknown" diagnoses; Fig. 1B).

Of 58 eyes without CMV retinitis by consensus diagnosis, novice trainees had a relatively high rate of correct diagnosis early in the week, which demonstrated a slight but nonsignificant reduction throughout the 4 days (from 79.7% to 62.0%; $P = 0.16$) and was accompanied by a relatively stable rate of "unknown" diagnoses ($P = 0.72$) (Fig. 1C). The experienced trainees showed a similar pattern, with near perfect specificity early in

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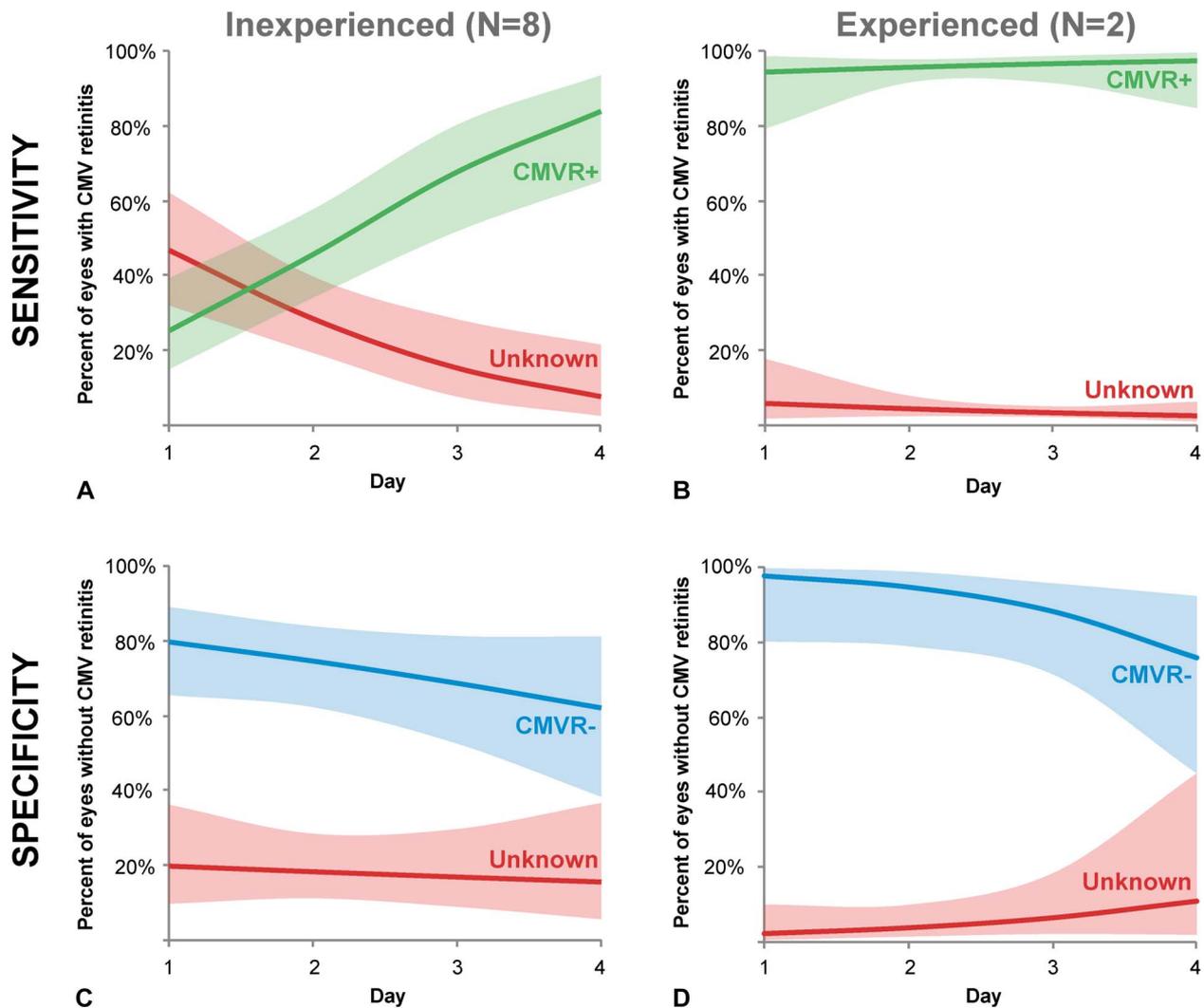


FIGURE 1. Sensitivity and specificity of trainee diagnosis of CMV retinitis over a 4-day indirect ophthalmoscopy training course in Myanmar. A and B, Depict sensitivity over time by showing the proportion of eyes diagnosed with CMV retinitis by ophthalmologist consensus that were diagnosed with CMV retinitis (green) or not given a diagnosis (red) by inexperienced (A) and experienced (B) trainees. C and D, Depict specificity by showing the proportion of eyes with no CMV retinitis by ophthalmologist consensus that were diagnosed as not having CMV retinitis (blue) or not given a diagnosis (red) by inexperienced (C) and experienced (D) trainees.

the week that decreased nonsignificantly throughout the 4 days of the workshop (from 97.7% to 75.8%; $P = 0.08$) and was accompanied by a nonsignificant slightly increased rate of “unknown” diagnoses (from 2.0% to 10.7%; $P = 0.24$) (Fig. 1D).

DISCUSSION

Our data show that non-ophthalmologists with no prior experience in eye examination can quickly learn indirect ophthalmoscopy, with enough skill to diagnose CMV retinitis with high accuracy. Physicians who had learned indirect ophthalmoscopy at a prior workshop and had been examin-

ing patients in the interim maintained their diagnostic accuracy at a high level.

The steep learning curve observed in this study may owe itself in part to the obvious clinical findings of CMV retinitis, as well as the high probability that any retinal abnormality in a patient with AIDS is due to CMV infection.³ Moreover, because only trainees who had voiced interest in the program were selected for the workshop, the trainees were by definition highly motivated to learn indirect ophthalmoscopy.

This study supports the idea that HIV/AIDS clinicians can diagnose CMV retinitis in settings with poor access to ophthalmologists. Once diagnosed, the

HIV provider could institute oral valganciclovir if available or could even perform intravitreal ganciclovir injections.^{2,4} With proper training and monitoring, HIV/AIDS physicians can provide primary management of CMV retinitis, just as they do all other opportunistic infections.

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REFERENCES

1. Ausayakhun S, Keenan JD, Ausayakhun S, et al. Clinical features of newly diagnosed cytomegalovirus retinitis in northern Thailand. *Am J Ophthalmol.* 2012;153:923–931 e1.
2. Heiden D, Tun N, Maningding E, et al. Training clinicians treating HIV to diagnose cytomegalovirus retinitis. *Bull World Health Organ* 2014;92:903–908.
3. Ausayakhun S, Watananikom S, Ittipunkul N, et al. Epidemiology of the ocular complications of HIV infection in Chiang Mai. *J Med Assoc Thai.* 2003;86:399–406.
4. Heiden D, Ford N, Wilson D, et al. Cytomegalovirus retinitis: the neglected disease of the AIDS pandemic. *PLoS Med.* 2007;4:e334.

Nationwide Study of Cancer in HIV-Infected Taiwanese Children in 1998–2009

To the Editors:

We previously reported an increased incidence of cancers in a nation-

wide registry of 15,269 HIV/AIDS patients in Taiwan in 1998–2009.¹ Excluded from that cohort were HIV-infected patients younger than 15 years. In this study, we determined the cancer incidence in this group of HIV-infected children and compared their incidence to that of noninfected children in the general population.

With approval from the National Health Research Institutes, Taiwan, the National Health Insurance Research Database (NHIRD) was searched for children younger than 15 years with HIV/AIDS in the 1998–2009 databases as previously described.¹ Patients subsequently diagnosed with cancer were identified based on the ICD-9-CM diagnosis codes. To calculate expected rates of cancer, data were obtained from a database linked by the Office of Statistics of the Department of Health using the NHIRD and death certificate database. This data set consisted of 1.8 million individuals randomly sampled from the Registry for Beneficiaries of the NHIRD, which contains registration and original claim data of every person who was a beneficiary of the National Health Insurance program during the period 1998–2009 (approximately 23.72 million individuals). All individuals under the age of 15, totaling 297,387 individuals, were then selected as the control group.

The incidence density (ID) and standardized incidence rate (SIR) for each cancer type were calculated. Person-years analysis was performed in strata of age, calendar period, and cancer type to estimate the ID and SIR. The start date for the calculation of person-years was the date of first HIV/AIDS clinic visit and the end date was December 31, 2009, as no deaths occurred during the follow-up period. The ID of each type of cancer after HIV infection was calculated by dividing the number of observed cancer cases by the total person-years at risk for that cancer. The SIR for each cancer type was calculated by dividing the observed number of cases by the number that would be expected if age-, sex-, and calendar period-specific rates of the comparison population applied.² The 95% confidence interval (CI) was calculated by Poisson distribution. All analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC). A 2-tailed *P* value of <0.05 was considered statistically significant.

A total of 230 HIV-infected children were identified. There were 131 males and 99 females. Seven of these children were diagnosed with cancer (Table 1). When compared with non-HIV-infected children, increased SIRs were seen in HIV-infected children with Kaposi sarcoma (SIR = 30,513.7, 95% CI: 3426.89 to 110,169.44), cancer of the lung and bronchus (SIR = 108.32, 95% CI: 1.42 to 602.67), and cancer of the testis (SIR = 106.86, 95% CI: 1.4 to 594.53).

Most of the reported cases of cancer in children with HIV are AIDS-defining cancers such as Kaposi sarcoma and Non-Hodgkin lymphoma or non-AIDS-defining cancers such as leukemia. Our study showed cancers of the lung and testis, which are very uncommon in children. A case of primary lung cancer in a child with AIDS was previously reported by Biggar et al.³ This study identified the first case of testicular cancer in a child with HIV. Unfortunately, the histopathology of the testicular tumor in this child is unknown.

The only previous study in Asia was performed in Thailand, which reported a 10-time higher incidence of cancers in HIV-infected children compared with non-HIV-infected children, but this study was performed in children born before perinatal antiretroviral therapy.⁴ In the advent of antiretroviral therapy, the incidence of AIDS-defining cancers in children has decreased dramatically⁵ but that of non-AIDS-defining cancers has continued to rise. Epidemiologic data suggest that antiretroviral therapy may reduce the incidence of AIDS-defining cancers in children because of improved immunosurveillance induced by antiretroviral therapy.^{6,7} However, immune dysregulation has been reported to persist in some children on antiretroviral therapy.^{8,9} A limitation of this study was that there were no perinatal antiretroviral therapy exposure data, as these data would help confirm whether the cancer incidence was related to antiretroviral exposure. Many of the cancers have been associated with an infectious etiology in HIV-infected adults¹ and children.¹⁰ Although a causal role has not yet been established for some cancers, human papilloma virus (HPV) infection has been associated with lung cancer¹¹ and testicular cancer¹² in adults.

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