Author's response to reviews

Title: Prevalence and Clinical Management of Cytomegalovirus Retinitis in AIDS patients in Shanghai, China

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Author's response to reviews: see over
Dear Editors:

Thank you for your advice and I have revised my manuscript. We have modified the article. The following is our answer about the review.

**Reviewer: Miles R Stanford**

1. It would be useful to know over what actual time period this cohort was derived and whether there was an alteration in the management of CMV retinitis over this time.

   The actual time period is from October 2005 to December 2007.

   Generally ganciclovir (5mg/kg) was administered twice a day by intravenous injection for two to three weeks (according to the severity) during the inductive phase. Then ganciclovir (5mg/kg) was given once a day intravenously or ganciclovir (1000 mg) three times a day orally during the maintenance phase.

2. Did the patients who received HAART (21 patients – P6) fare differently?

   The drugs of HAART in every patient were different according to personal health such as allergy, infection and so on.

3. Do the authors mean ganciclovir or valganciclovir as an oral medication (P6)

   Ganciclovir as an oral medication. We have no valganciclovir.
4. Please explain what is meant by an opaque and transparent vitreous (P8) what was the state of the vitreous in the other 12 eyes?
The vitreous were opaque in 7 eyes and transparent in 28 eyes. But the opaque vitreous is not vitreous inflammation. So I decide to remove it and avoid ambiguity.

5. Please explain more clearly the point of view of Chinese culture on health (p10)
In our understanding from a point of view of Chinese culture on their health and cost concern about doctor’s visits, minor vision problem was and will not be the main reason for the AIDS patients to seek medical attention in comparison with other vital signs and symptoms at the later stage of disease course. Some patients only visited the doctor when their diseases were very serious. So many of them died from other infections or complications before CMV retinitis had been diagnosed.

6. The discussion could be shortened by 1/3 without loss to science. I have modified it.

Reviewer: Sophia Pathai

Abstract:
Introduction, last sentence: it is not clear if this is a study of CMV
retinitis associated with HIV or AIDS (as in the text it is mentioned that only 23/303 patients had AIDS), please clarify.

This study was to investigate the prevalence and clinical management of the cytomegalovirus retinitis AIDS in a large municipality of China. I have modified it.

Methods – sentence 1: again it is not clear if these patients had AIDS or HIV.

Clinical and laboratory data from 23 cytomegalovirus retinitis patients (35 eyes) out of 303 hospitalized AIDS individuals in a single medical center were analyzed retrospectively. The patients were all AIDS patients.

Results – please provide confidence intervals for the estimate provided.

The confidence intervals were [10.4%, 25.0%], [1.1%, 14.9%], [0.0%, 7.8%] and [0.0%, 5.5%] respectively.

Line four should read ‘mean CD4 T lymphocyte count. Median CD4 count and inter-quartile range would be a more informative value.

The median CD4 was 20 cells/ul with inter-quartile range of [5, 36].

Conclusion – This should be revised; at present it only contains results. What do the authors feel is the overall ‘take home’ message for this paper? Are there any recommendations based upon the findings of this study?
The CMV retinitis in the AIDS patients was response well to ganciclovir therapy. Several important factors have been identified for early clinical diagnosis of CMV retinitis and prophylactic treatment of anti-CMV drug is recommended when the CD4+ T lymphocyte count is less than 50 cells/µl in AIDS patients. We should check their eyes routinely in the patients with CD4+ T lymphocyte < 50 cells/µl.

Background:

Last sentence – again, please clarify whether this is a cohort of patients with advanced AIDS or advanced HIV.

This data reflects the incidence of CMV retinitis in advanced AIDS patients and current status of clinical management on this opportunistic infection in China. The patients were all AIDS patients.

Methods:

Paragraph 1: Please provide more information about the study population. How was demographic data collected?

According to history and clinical data in hospital

What demographic and clinical data were collected?

Age, mode of transmission, HARRT, CD4, CMV viral load, CMV IgG\IgM, HIV viral load, vision acuity exam, examination with slitlamp microscope, funds examination in dilate pupil, funds photo.
These data were in Result according to journal editor suggestion

Were patients asked directly about ocular symptoms?
Yes, we check every patient’s eyes in hospital routinely.

Did they report any symptoms?
Some patients did not report any symptoms, some complained Blurred vision, some complained muscae volitantes.

Were the ophthalmic examiners masked to demographic or clinical characteristics (which might bias their diagnosis e.g. extremely low CD4 count may make a diagnosis of CMV retinitis seem more likely).
No, the ophthalmic examiners know demographic or clinical characteristics. Non-blind study.

How did patients come to attend this hospital i.e. what were the sources of referral (e.g. from other specialties, self-referral etc).
Our hospital, Shanghai Public Health Clinical Center, is the designated hospitals for AIDS patients. If a patient is found HIV(+), he or she will refer to our hospital from other hospital. If the AIDS patients need admitting in hospital, they all are admitted in our hospital. We check every patient’s eyes in hospital routinely.

Did patients already have a positive HIV test at the time of referral to the hospital?
They were all HIV positive, which were diagnosed by Shanghai
Center for Disease Control in accordance with the diagnosis criteria proposed by American Center for Disease Control.

Over what period of time was this cohort of 303 participants examined?

From October 2005 to December 2007.

Were all participants examined regardless of the presence of ocular symptoms?

Yes, we check every patient's eyes in hospital routinely.

Paragraph 2: The sentence “ophthalmoscopic appearance of typical retinopathy” is confusing. Please clarify whether referring to the appearance of CMV retinitis.

Yellow-white retinal lesions with granular border or arciform retinal lesion with or without hemorrhage along with vessels


Yes

Please provide more details about method of examination: was visual acuity measured using a Snellen chart, LogMAR – and at what distance?

Snellen chart, 20 feet
How was dilated fundus examination performed – with an indirect ophthalmoscope?

We exam the dilated fundus with an indirect ophthalmoscope.

Some cases underwent fluorescein angiography – please indicate the indication for why some cases underwent this procedure and others did not.

Some patients were allergy and some patients did not agree to undergo fluorescein angiography. I think the significance of fluorescein angiography was not obvious, I have removed it.

Paragraph 3, sentence 4 – please clarify the selection criteria for the 21 patients who received HAART.

The 21 AIDS patients were all CMV retinitis. The other 2 patients died soon, so did not give HAART.

Sentence 6 – please describe the time periods over which “improvement” and “non-improvement” were reported to occur. These only were defined ourselves. So we have modified it avoiding ambiguity.

How often was follow-up?

Once a week.

Was fluorescein angiography used as an adjunct to examination?

(Yes, but not generally.)

Were fundus photographs taken to document
progression/regression? Yes

Results

First paragraph – 2nd sentence it is not clear why the mode of transmission is only given for 23 participants out of all 303.

Because we study the AIDS patients with CMV retinitis in the study, the mode of transmission is only given for 23 participants.

It would be informative to have some description of the clinical characteristics of the clinical population: Were the participants staged according to WHO clinical stage? If so, what were the relative proportions?

They were all HIV positive and staged clinical stage 3 or 4.

How many participants had other opportunistic infections, particularly systemic CMV, or TB? (I see this is in the next section, but would be better placed here, along with numbers involved)

Oral fungal infection(3 patients), Pulmonary fungal infection(2 patients), Herpes Zoster(1 patient) , Lymphoma(1 patient), CMV myelitis(1 patient), Pneumocystis jiroveci pneumonia(6 patient), tuberculosis(4 patient), Pancreatitis(1 patient), Cryptococcal meningitis(1 patient). I have placed the table 2.

Second paragraph – please provide confidence intervals for the overall estimate.

I have provided. The confidence intervals were [10.4%, 25.0%],
[1.1%, 14.9%], [0.0%, 7.8%] and [0.0%, 5.5%] respectively. I have placed the table 1.

Please provide Snellen equivalents for visual acuity values.

I have modified it.

Sentence 4 – please provide a description of ‘vaginae vasorum’.

I have modified it.

Sentence 7 – please give some further description to the opaque vitreous and keratic precipitates seen in some of the cases as CMV retinitis would not normally produce an inflammatory reaction in the anterior segment or vitreous – were these cases related to IRU?

The opaque vitreous is not vitreous inflammation. So I decide to remove it and avoid ambiguity. When keratic precipitates was found in 2 eyes, HAART did not begin. So we don’t think IRU

Third paragraph – please give the viral load level as log-transformed values; this will also make the values in Tables 2 and 3 easier to interpret.

I have modified it in table 2.

Why did the authors choose mean CD4 count? Perhaps the median and interquartile range is more informative?

I have modified it.

Did the authors note any other retinal opportunistic infections or e.g. HIV retinopathy?
Yes, HIV retinopathy is in some patients.

It would be interesting to know the spectrum of retinal pathology seen.

HIV retinopathy, CMV retinitis, Toxoplasma retinitis.

It would also be of interest to know the proportion of participants who had low vision or blindness due to CMV retinitis.

In the article: The vision acuity was less than 20/400 in 7 eyes and between 20/400 and 20/63 in 15 eyes. The proportion of blindness is 7/35,20%. The proportion of low vision is 15/35,42.9%.

Discussion

There is little discussion about the strengths and weaknesses of this study. A key strength is that this is a large study, more so if participants were not an ‘enriched’ population (i.e. just those with ophthalmic symptoms or referred for an ophthalmic examination). A limitation is that this estimate is based upon a study population with advanced HIV and high mortality and so the prevalence may be falsely low; the authors do point this out.

Yes, I have modified it.

Tables

Table 1 – please provide confidence intervals for the estimates in the fourth column.

I have modified it.
Tables 2 and 3 should be combined to form a composite table that reflects all of the clinical data so that parameters that may change following treatment can be clearly compared.

Yes.

In Table 2 the HIV VL column – for ease of comparability it would better to undertake log transformation for these values. This should be done similarly for CMV VL levels.

I have modified it.

It is not clear if the visual acuity is decimal or LogMAR – please provide details about this.

I have modified it with Snellen chart.

To avoid ambiguity of the side affected in bilateral cases the visual acuity column should be further subdivided into ‘right’ and ‘left’ accordingly.

I have modified it.

In Table 2 – is the CD4 count column reflective of baseline, nadir or current CD4 count? Please clarify.

The CD4 count is recorded when diagnosed CMV retinitis.

Table 3 - column ‘Time since HAART received’ – is this since diagnosis?

From begin HAART to stop follow-up.

How was this information obtained? Please clarify.
From history and clinical data in hospital.

This also applies to the next column ‘Time anti-CMV treatment received’ – it is not clear what timepoint this is referring to.

From begin ganciclovir treatment to stop ganciclovir treatment.

Table 3 – prognosis. Please provide more information. It is mentioned in the text that some participants had complications such as IRU, RD and relapse. Please make this clear in the table of cases. Maybe a ‘treatment/complications’ column would be helpful.

I have modified it.

Minor essential revisions

Background: Sentence 1 – please clarify by what is meant by ‘largest’ of the herpes viruses – is this size?

Genome

Please provide a reference(s) for sentence 2.

I have modified it.

Discretionary revisions

Results

I think it would be easier for the reader to follow if the first paragraph is split into Study Population results and ocular manifestations results. Yes, I have modified it.

Third paragraph - Please refer to my comments about Tables 2 and
3 which should make this paragraph clearer.

Yes, I have modified it.

N.B I do not see any reference to the tables in this section and it would be helpful to refer the reader to the table in the text rather than in the last paragraph.

I have modified it.

Reviewer: Gary Holland

Major Compulsory Revisions

1. What defines the study population?

They were all in hospital.

The cohort appears to consist of all patients seen in one facility during a set period of time; if so, how was that period chosen?

When they were in hospital to finishing examming eyes in outpatient

How were patients with eye disease identified at that facility?

Every patient in hospital were all exam eyes routinely

Were all patients with HIV disease screened for the possible presence of asymptomatic disease?

Yes

Was CMV retinitis first diagnosed at the start of the study, or did some patients have previously diagnosed, long-standing eye disease at study entrance?
Some were diagnosed in our hospital and some were referral when other hospital suspected CMV retinitis.

This information should be provided in the Methods section.

2. The prevalence of 7.6% is not meaningful, as the population is heterogeneous in terms of severity of immune deficiency, but probably does not represent a random sampling of the total AIDS population in Shanghai. A more meaningful figure to be featured in the Abstract, because it can be used for comparison to other studies, is the prevalence of disease among those at risk: patients with CD4+ T-lymphocyte cell counts less than 50, as reported in other studies.

We think so, too and we have modified it.

3. What was the temporal relationship between CD4+ T-lymphocyte cell counts and diagnosis of CMV retinitis? CD4+ T-lymphocyte cell counts were lower, the possibility of CMV retinitis was larger.

Were they obtained at the same time?

Yes.

4. Were retinal lesions active in those patients with high CD4+ T-lymphocyte cell counts, or did they have old, inactive scars?

This information is critical for understanding the relationship
between CMV retinitis and CD4+ T-lymphocyte cell counts that they report.

Retinal lesions were active, not old, inactive scars.

5. Some sort of time-dependent analysis of response to treatment is needed. It is not appropriate to state that a certain percentage of patients did not respond to treatment with ganciclovir, when they were lost to follow-up or died before treatment had time to work.

Review of Table 3, third and fourth columns, seems to show a clear, direct relationship between time on anti-CMV treatment and response (recovery, improved, non-improved). The issue of differential patient follow-up, and analysis techniques to address this problem, are discussed in the following two publications, which may be helpful to the authors: (1) Jabs DA. Improving the reporting of clinical case series. Am J Ophthalmol 2005;139:900-5; and (2) DiLoreto DA Jr, Bressler NM, Bressler SB, Schachat AP. Use of best and final visual acuity outcomes in ophthalmic research. Arch Ophthalmo 2003;121:1586-90.

Some patients refused ganciclovir treatment because cost was large. So their ganciclovir treatment time is short.

6. The definitions of “recovery” and “improvement,” in terms of treatment, need to be clarified further. How did they determine
disease to be “active”? How would a patient be categorized if activity regressed, but vision did not improve (their definition of recovery)? The categories should be mutually exclusive, and all treated patients should fit into one category.

I have modified it.

7. In 7 patients, vitreous was opaque, presumably from inflammation. Why were those patients not considered to have IRU (only 2 patients had IRU, according to the authors)?

The opaque vitreous is not vitreous inflammation. So I decide to remove it and avoid ambiguity. When keratic precipitates was found in 2 eyes, HAART did not begin. So we don’t think IRU.

What was their definition of IRU?

Clinical diagnosis: HAART for 2 weeks above, CD4 count increase, vitreous inflammation, keratic precipitate or cystoid macular edema et al was found

8. “Cotton-wool spot” (e.g. Abstract, Results section; pages 8,11-12; and Figure 1C) is not a term that should be used to describe early CMV retinitis lesions, as implied by the authors. Cotton-wool spots are distinct lesions related to focal ischemia of the retinal nerve fiber layer.

The presence of cotton-wool spots is predictive for the development of CMV retinitis. International Journal of STD & AIDS.
Minor Essential Revisions

1. The authors should define the type of study in the Methods section. retrospective study

2. Is the descriptive information provided about patients (disease characteristics, laboratory tests) all from a single examination?

From the history and clinical data in hospital and in outpatient

The study is not strictly cross-sectional, however, as at least some patients were followed longitudinally to provide data on treatment response. Were all patients followed, and if not, how were patients chosen for follow-up? What defines the length of time that patients were followed?

All patients follow up at least 6 months in hospital and in outpatient but the dead patients

3. The authors should acknowledge and discuss the fact that their cohort is probably not representative of the Chinese AIDS population in general. Because they examined only hospitalized patients, their series will undoubtedly be skewed to individuals who are more sick and therefore at greater risk for CMV retinitis. I think it is more likely that they have over-estimated the prevalence than
under-estimated it, as they claimed on page 11.

We think so, too and modified it.

4. The authors should define what is meant by “large” lesions (e.g. Page 8, first paragraph under “Clinical Manifestations”, and page 11, last paragraph). It would be helpful if they provided an estimate of retinal area involved for each eye and location of lesions, as has been done for many previous studies of CMV retinitis. Lesion size gives an estimate of disease duration (larger lesions are older) prior to diagnosis, and has implications for risk of vision loss.

Lesions of 20 eyes in posterior pole retina and 13 eyes in mid periphery retina. “large” is not defined strictly, so we removed it.

5. If all patients had been followed for the same length of time, the long-term course of those with “recovery”, “improvement”, and “non-improvement” may have been the same. Thus, the comparison of laboratory values between these groups (pages 9-10) is not very meaningful. Yes, we think so. We have modified it.

6. More information should be given about the person with relapse of CMV retinitis. Was the patient on HAART?

Yes

If so, for how long?

1.5 months

Was the patient still immunosuppressed?
Yes

Was the patient followed longer than those without relapse?

No, he was not longer than those without relapse when he relapsed

7. The fourth column of Table 3 should be labeled “Response to Treatment”, “Status of Retinitis,” or a similar term. The information provided does not provide a “prognosis”.

I think so. I have modified it.

8. It is unlikely that CMV load in the blood will be a useful diagnostic measure to differentiate CMV retinitis from other retinal infections. At the level of immunodeficiency that is associated with CMV retinitis, patients will be susceptible to multiple infectious agents simultaneously, and thus, CMV in the blood does not rule out the possibility of a different infection in the eye. Also there have been reports of multiple, concurrent infections with CMV and other agents in the retina.

Yes, we have modified it.

Reviewer: David Heiden

Discretionary Revisions

1. RESULTS, clinical manifestations pre- and post-HAART, paragraph 2:

IMMUNE RECOVERY UVEITIS – the next to last sentence states
that IRU occurred in 3 eyes yet in paragraph 1 it is stated that the vitreous was opaque in 7 eyes. This would presumably be due to IRU unless another cause is stated. Perhaps the IRU data should be reviewed and this aspect of the paper clarified.

The opaque vitreous is not vitreous inflammation. So I decide to remove it and avoid ambiguity. When keratic precipitates was found in 2 eyes, HAART did not begin. So we don’t think IRU.

2. RESULTS, clinical manifestations pre- and post-HAART, paragraph 1: other opportunistic infections: a table describing this would be interesting if the data is available.

We have modified it into table 2.

3. Clinical management. A closer review of the huge western literature would improve this aspect of the paper. First, the standard of care for treatment in western countries is oral valganciclovir, a well-absorbed prodrug of ganciclovir that gives blood levels equivalent to intravenous treatment, and is equally effective.

We know valganciclovir is more effective, but our hospital does not provide valganciclovir, so we give patients ganciclovir oral.

Cost is the issue in China, with Roche being allowed to hold a patent monopoly and maintain an exorbitant pricing that has not been challenged, despite the availability of generic versions from Cipla and Rambaxi. Second, the duration of treatment has been
extensively studied and discussed in the literature, with general agreement that therapy should be continued until the retinitis is completely inactive, the CD4 count above 100, and the patient on ART for at least 3 months.

We end the ganciclovir treatment according to the above standard, but some patients refuse treatment after short time ganciclovir treatment, so the time of ganciclovir treatment in some patients is short.

Third, the dose of oral ganciclovir used in the paper (1 gram/day) is at variance with the initial reported dose of 3 grams/day (3) or the higher doses studied by Lalezari.

Ganciclovir (1g) orally should be three times one day

Finally, the lowest cost alternative treatment—intravitreal injection of ganciclovir—actually has been performed several places in China (Guanxi Province, Xinjiang Province), but has not yet been reported.

Because the patients with CMV retinitis all have very low CD4 counts, the patients are afraid of complication such as endophthalmitis, vitreous hemorrhage et al. We can’t give intravitreal injection without their agreement.

Minor Essential Revisions

1. VISUAL ACUITY In the table the Va is given as 0.1, whereas in
the discussion it is described as less than 0.1. This needs to be clarified.

The vision acuity such as 0.08, 0.05, HM/BE, LP is less than 0.1

Also, in table 2, patient 22, does the author mean NLP (no light perception)? – I don’t know what ND stands for.

ND is non-detectable, I have give NA (not available) instead of ND

Also, what is the common definition of blindness that is being used?

The definition of blindness is the vision acuity less than 0.05 (20/400)

It simplifies the presentation, and emphasizes the results if a tally of “blind” outcomes can be reported.

We have modified it.

2. The term “vaginae vasorum” is not part of the CMV vocabulary.

In English “vagina” refers to a private part of a woman’s anatomy.

I’ve been told by a Chinese speaking friend that “vaginae vasorum” literally means “sheathing of the vessels.” There is commonly subtle sheathing of vessels in patients with CMV retinitis. The flamboyant examples that occasionally occur (demonstrated in photograph B) are termed “frosted Branch angiitis”

We have modified it.

3. Abstract, Results: as now written there is confusion between the two most commonly observed retinal complications of patients with
advanced AIDS, with the implication that HIV retinopathy, commonly characterized clinically by cotton-wool spots (CWS) progresses to CMV retinitis. Better say something like “the two most common retinal abnormalities were CWS in __/__ patients and CMV retinitis in __/__ patients. Or probably best leave this descriptive data to the body of the text and entirely remove from the abstract. 

We have modified it.

4. DISCUSSION, the next to last sentence in the first paragraph makes an outstanding point that I fully support regarding the importance of screening asymptomatic patients and generally addressing the problem of CMV retinitis at the first patient visit. However, I would change the wording: …"special medical attention to vision examination of AIDS patients…” which might be construed to imply that measurement of visual acuity might be adequate. I would remove any ambiguity by saying:” special attention to full exam of the entire retina thru a fully dilated pupil using an indirect ophthalmoscop”

Yes

Major Compulsory Revisions:

1. CLARIFICATION OF PATIENT SELECTION AND DATA COLLECTION:

ABSTRACT, METHODS, and also METHODS, STUDY
POPULATION, and also DISCUSSION, line 2: Patient selection needs to be clarified. It appears that the report is a retrospective review of a consecutive series of 303 AIDS patients who were hospitalized at a single Infectious Disease Hospital, and screened for CMV retinitis over a period of ? 16 months?

Yes, average follow-up time is 16 months

And that the initial diagnosis of HIV infection was established and the requirement for hospitalization was established at the Shanghai Public Health Center? Or at the Shanghai Center for Disease Control? Please clarify.

The initial diagnosis of HIV infection was established at the Shanghai Center for Disease Control and the requirement for hospitalization was established at the Shanghai Public Health Center

ABSTRACT, METHODS: I don’t understand the period of data collection.

Was the average patient followed the indicated period of time?

Yes

Was there a retrospective review of 303 patients admitted to the hospital over 15.69 months?

No, the follow-up time of the patients with CMV retinitis is 15.69 months, including in hospital and follow up in outpatient
2. BLINDNESS: 15/35 eyes, 42.8% were blinded by CMV retinitis at the time they were enrolled in the study (and would have presumably stayed blind if they all survived and were not treated). This is a disastrous consequence of a disease. It should be stated in the abstract, as well as the number of eyes that were blind at the end of the treatment period.

   No, the definition of blindness is the vision acuity less than 0.05(20/400). So I have modified the number in Result. Before treatment, 20%(7/35) were blinded, 12.5% (3/24) were blinded at the end of the treatment period (excluded 7 patients (11 eyes) dead).

3. MORTALITY: The mortality information needs to be re-evaluated and rewritten, both in the Abstract section, and in the Results, clinical manifestation…para 2, section. 7/23, 30%, of patients with CMV retinitis died within 2 weeks of “because of other complications and infections.” Unless there is careful autopsy data, extra-ocular CMV infection can not be excluded as the cause of death, or as contributing to death. The patient with transverse myelitis almost certainly died of extraocular CMV disease. There is a large body of information linking increased mortality with CMV disease, and a well accepted viewpoint that CMV retinitis is a systemic disease and a potential cause of mortality. A number of lines of evidence support the view that CMV disease causes
increased mortality. In autopsy series about half of AIDS patients have evidence of active CMV infection, with evidence of disseminated infection in 38% - 59%. Determining the precise cause of AIDS mortality is difficult, even at autopsy, with most patients having malignancy and/or multiple opportunistic infections. However, CMV infection has been identified as the primary cause of death in 1% - 19% of AIDS patients. In addition, data from both before and after the introduction of HAART in developed countries demonstrates that CMV viremia predicts mortality, and a recent report from Cambodia demonstrated that CMV viremia was associated with a doubling of mortality. CMV retinitis also predicts mortality (16,18), with reports showing mortality was reduced in patients with CMV retinitis when these patients received systemic anti-CMV treatment. At the very least, the presence of CMV retinitis identifies patients at extraordinary risk of mortality in the patient population they studied. This must be acknowledged as a justification for the importance of identifying patients with CMV retinitis, and for the importance of devoting attention to CMV disease.

We think so, we have modified it. But we have no autopsy data. No patient was taken to autopsy.

4. METHODS, DIAGNOSIS OF CMV RETINITIS: CMV retinitis is a
clinical diagnosis, and the “gold standard” is examination of the entire retina through a fully dilated pupil with an indirect ophthalmoscope.

The methods need to specify the instrument used to examine the retina (direct ophthalmoscope, Indirect ophthalmoscope, slit lamp with fundus lens with specifying what type of lens). It needs to specify whether the entire retina was studied or whether only the posterior pole was examined.

Indirect ophthalmoscope through a fully dilated pupil

5. CMV PCR:. Again, a closer review of the western literature would improve this aspect of the paper. DISCUSSION para 4 needs to be re-written with clarification of the role of vitreous sample for CMV, and peripheral blood sample for CMV. Peripheral blood PCR strongly correlates with risk of end-organ disease and mortality. But it is not a clinically useful tool for diagnosis of CMV retinitis in the individual patient, since viremia may pre-date retinitis or be intermittent.

However, detection of viremia may be important for diagnosis of extra-ocular CMV disease that may be fatal (22), and may not be easily detect or suspected on clinical grounds alone. Regarding vitreous sampling for CMV PCR: this is an infrequently used or needed means of establishing the diagnosis of CMV retinitis.
Again, diagnosis of CMV retinitis is based on clinical examination, and this is sufficient in 90%+ of cases. Vitreous sampling is reserved for unusual cases with atypical features, where clinical findings are ambiguous and there needs to be clarification between a potential toxoplasma or herpetic infection, or very rarely, with suspicion of intraocular lymphoma.

We think so, and we have modified it. But some references we have no full text.

Thank you very much!

Sincerely yours,

Taiwen He