Proposed Clinical Case Definition for Cytomegalovirus–Immune Recovery Retinitis

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Background. Cytomegalovirus (CMV) retinitis has been extensively described in patients with advanced or late human immunodeficiency virus (HIV) disease under ineffective treatment of opportunistic infection and antiretroviral therapy (ART) failure. However, there is limited information about patients who develop active cytomegalovirus retinitis as an immune reconstitution inflammatory syndrome (IRIS) after successful initiation of ART. Therefore, a case definition of cytomegalovirus–immune recovery retinitis (CMV-IRR) is proposed here.

Methods. We reviewed medical records of 116 HIV-infected patients with CMV retinitis attending our institution during January 2003–June 2012. We retrospectively studied HIV-infected patients who had CMV retinitis on ART initiation or during the subsequent 6 months. Clinical and immunological characteristics of patients with active CMV retinitis were described.

Results. Of the 75 patients under successful ART included in the study, 20 had improvement of CMV retinitis. The remaining 55 patients experienced CMV-IRR; 35 of those developed CMV-IRR after ART initiation (unmasking CMV-IRR) and 20 experienced paradoxical clinical worsening of retinitis (paradoxical CMV-IRR). Nineteen patients with CMV-IRR had a CD4 count of ≥50 cells/µL. Six patients with CMV-IRR subsequently developed immune recovery uveitis.

Conclusions. There is no case definition for CMV-IRR, although this condition is likely to occur after successful initiation of ART, even in patients with high CD4 T-cell counts. By consequence, we propose the case definitions for paradoxical and unmasking CMV-IRR. We recommend close follow-up of HIV-infected patients following ART initiation.

Keywords. IRIS; ART; HIV; AIDS; CMV–immune recovery retinitis.

Before the widespread use of antiretroviral therapy (ART), cytomegalovirus (CMV) retinitis typically occurred in subjects with advanced or late human immunodeficiency virus (HIV) disease and CD4 T-cell counts <50 cells/µL [1, 2]. The incidence of CMV retinitis has decreased by 80%–90% nowadays [3], but it remains one of the most common opportunistic ocular infections in HIV-infected patients [4].

Late presentation for HIV care and the consequent low CD4 T-cell counts at the start of ART increase the risk of immune reconstitution inflammatory syndrome (IRIS). In patients with healed CMV retinitis under successful ART, IRIS has been defined as a process of immune recovery uveitis (IRU), characterized by any type of ocular inflammation such as anterior uveitis, vitritis, papillitis, cystoid macular edema, or epiretinal membrane [5, 6]. IRU has long been described in the context of inactive retinitis, and frequencies as high as 37.7% of IRU have been reported in patients with healed CMV retinitis [7]. In contrast, the effects of ART-induced immune reconstitution in subjects with active CMV retinitis have only been documented in a few case reports and case series [8, 9]. Therefore, in this retrospective study we describe a group of patients with active CMV retinitis in the current context of successful ART initiation, and propose a case definition for active CMV retinitis-associated IRIS. Because IRU is a well-characterized uveitis form of IRIS that occurs mainly in patients with inactive CMV retinitis, the clinical syndrome described here involving active retinitis...
METHODS

Study Population
This study was conducted at the Center for Research in Infectious Diseases at the National Institute of Respiratory Diseases (INER), a tertiary referral center in Mexico City. The medical workup at the INER for HIV-infected patients includes a medical history with demographic data, assessment of underlying medical conditions, physical examination, routine laboratory tests, CD4 T-cell counts, HIV RNA load, and comprehensive ophthalmologic examinations. Of the 1200 HIV-infected patients receiving regular ophthalmologic follow-up at the INER, we reviewed the medical records of 116 patients with CMV retinitis who started ART between January 2003 and June 2012. The Research and Ethics Committee of the INER approved the study.

Procedures
Ophthalmologic examinations were performed on the anterior segment using a slit lamp, and funduscopic explorations were carried out via indirect ophthalmoscope. Fundus photographs were obtained to record the lesions for follow-up comparisons. Frequency of ophthalmologic examinations was based on CD4 T-cell count, HIV RNA load, and current or future ART initiation. Patients were examined on the following schedule according to CD4 T-cell count: those with <50 cells/µL were examined weekly; 50–100 cells/µL, biweekly; >100–150 cells/µL, every 3 weeks; >150–200 cells/µL, every 4 weeks; >200–250 cells/µL, every 6 weeks; >250 cells/µL, every 6 months. Patients with CMV retinitis on initial ophthalmologic examination were treated with oral valganciclovir (900 mg every 12 hours) [10].

Inclusion and Exclusion Criteria
We included HIV-infected patients with CMV retinitis who had the following assessments before ART initiation and within the subsequent 6 months: ophthalmologic examinations, determinations of CD4 and CD8 T-cell counts, and HIV RNA load. All patients were examined by the same expert ophthalmologist, a retina and uveitis specialist. Criteria for exclusion from this study were the lack of an ophthalmologic examination before ART initiation; ART failure (defined as a persistent viral load >40 HIV RNA copies/mL or a reduction <1 log in the viral load during the first 6 months); lack of adherence to CMV treatment; and insufficient follow-up.

Case Definitions for CMV-IRR
Diagnosis of IRIS was based on the consensus criteria of the International Network for the Study of HIV-Associated IRIS, specified as follows: (1) response to ART by (a) receiving HIV ART and (b) virologic response with >1 log_{10} copies/mL decrease in HIV RNA (if available); (2) clinical deterioration of an infectious or inflammatory condition temporally related to ART initiation; and (3) inability to explain symptoms by (a) expected clinical course of a previously recognized and successfully treated infection; (b) medication side effect or toxicity; (c) treatment failure; (d) complete nonadherence [11]. Patients with unmasking CMV-IRR were those being followed prospectively by ophthalmology without a diagnosis of CMV retinitis. IRU was defined by completely healed CMV retinitis with any of the following types of ocular inflammation under successful ART: anterior uveitis, vitritis, papillitis, cystoid macular edema, or epiretinal membrane [13].

Statistical Analysis
Baseline characteristics of the patients with CMV-IRR were compared with those of patients who had improvement of CMV retinitis with successful ART and valganciclovir. Demographic categorical data were compared using the Fisher exact test. Comparison of CD4 and CD8 T-cell counts and percentages and HIV RNA loads before ART initiation was performed using the nonparametric Wilcoxon rank-sum test. We also compared the risk of CMV-IRR in patients with CD4 counts <50 cells/µL vs those with CD4 counts ≥50 cells/µL on ART initiation.

RESULTS

During the period between January 2003 through June 2012, 116 HIV-infected patients initiating ART were diagnosed with CMV retinitis. Of those, 41 were deemed ineligible due to exclusion criteria. Of the 75 patients included in the study, 20 had improvement of CMV retinitis with successful ART (26.6%); 35 had unmasking CMV-IRR (46.6%); and 20 had paradoxical CMV-IRR (26.6%).
### Table 1. Characteristics of Study Participants

<table>
<thead>
<tr>
<th></th>
<th>CMV-IRR (n = 55)</th>
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<th>CMV Retinitis Improvement (n = 20)</th>
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<tr>
<td></td>
<td>Unmasking (n = 35)</td>
<td>Paradoxical (n = 20)</td>
<td>Total (n = 55)</td>
<td>Unmasking (n = 35)</td>
</tr>
<tr>
<td><strong>Male sex, No. (%)</strong></td>
<td>32 (91.4)</td>
<td>19 (95)</td>
<td>51 (92.7)</td>
<td>18 (90)</td>
</tr>
<tr>
<td><strong>Time to IRIS after ART initiation, wk, median (IQR)</strong></td>
<td>4 (3–7)</td>
<td>6 (3.25–9.5)</td>
<td>4 (3–8)</td>
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<tr>
<td>Prior to ART initiation</td>
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<tr>
<td>CD4 count, cells/µL, median (IQR)</td>
<td>19 (13–56)</td>
<td>50 (15–91.25)</td>
<td>26 (15–76)</td>
<td>26 (12.5–88)</td>
</tr>
<tr>
<td>CD4 %, median (IQR)</td>
<td>4 (2–7)</td>
<td>5.5 (4–10.5)</td>
<td>5 (3–8)</td>
<td>6.5 (3–10)</td>
</tr>
<tr>
<td>CD8 count, cells/µL, median (IQR)</td>
<td>454 (223–697)</td>
<td>389.5 (216.7–727.5)</td>
<td>428 (223–697)</td>
<td>504 (133–680)</td>
</tr>
<tr>
<td>CD8 %, median (IQR)</td>
<td>60 (53–75)</td>
<td>56 (45–65.75)</td>
<td>57 (52–72)</td>
<td>62 (46–72)</td>
</tr>
<tr>
<td>CD4/CD8, median (IQR)</td>
<td>0.07 (0.03–0.12)</td>
<td>0.1 (0.07–0.15)</td>
<td>0.08 (0.04–0.15)</td>
<td>0.09 (0.06–0.19)</td>
</tr>
<tr>
<td>HIV RNA copies/mL, median (IQR)</td>
<td>379 359 (205 330–602 000)</td>
<td>491 369 (79 474–769 553.25)</td>
<td>412 963 (168 692–675 000)</td>
<td>495 559.5 (274 162.5–809 376.25)</td>
</tr>
<tr>
<td>Log HIV RNA, copies/mL, median (IQR)</td>
<td>5.56 (5.23–5.77)</td>
<td>5.54 (4.89–5.86)</td>
<td>5.56 (5.15–5.8)</td>
<td>5.62 (5.36–5.86)</td>
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<tr>
<td>After ART initiation</td>
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<tr>
<td>CD4 count, cells/µL, median (IQR)</td>
<td>92 (38–170)</td>
<td>128.5 (67.2–191.5)</td>
<td>93 (47–189)</td>
<td>173 (78.5–263)</td>
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<tr>
<td>CD4 %, median (IQR)</td>
<td>10 (6–17)</td>
<td>13 (7.2–15.7)</td>
<td>11 (7–16)</td>
<td>11 (8–14)</td>
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<tr>
<td>CD8 count, cells/µL, median (IQR)</td>
<td>657 (387–1069)</td>
<td>431.3 (275.5–845)</td>
<td>614 (307–872)</td>
<td>792 (423.25–1176.25)</td>
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<tr>
<td>CD8 %, median (IQR)</td>
<td>61 (44–76)</td>
<td>49 (42–58)</td>
<td>52 (43–68)</td>
<td>47 (37–60)</td>
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<tr>
<td>CD4/CD8, median (IQR)</td>
<td>0.19 (0.1–0.3)</td>
<td>0.25 (0.18–0.39)</td>
<td>0.22 (0.12–0.32)</td>
<td>0.23 (0.15–0.35)</td>
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<tr>
<td>HIV RNA copies/mL, median (IQR)</td>
<td>54 (39–907)</td>
<td>286 (54–796.7)</td>
<td>82 (39–880)</td>
<td>39 (39–112.7)</td>
</tr>
<tr>
<td>Log HIV RNA copies/mL, median (IQR)</td>
<td>1.73 (1.59–2.96)</td>
<td>2.43 (1.73–2.88)</td>
<td>1.91 (1.59–2.94)</td>
<td>1.59 (1.59–2.04)</td>
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<td>ART-induced changes</td>
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<tr>
<td>Decrease in log HIV RNA copies/mL, median (IQR)</td>
<td>3.46 (2.73–3.97)</td>
<td>3.1 (2.27–3.56)</td>
<td>3.2 (2.46–3.9)</td>
<td>3.78 (3.42–4.22)</td>
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<tr>
<td>Increase in CD4 cells/µL, median (IQR)</td>
<td>50 (5–152)</td>
<td>70.5 (4.5–147.7)</td>
<td>54 (5–151)</td>
<td>103 (47.7–183.2)</td>
</tr>
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Abbreviations: ART, antiretroviral therapy; CMV, cytomegalovirus; HIV, human immunodeficiency virus; IQR, interquartile range; IRIS, immune reconstitution inflammatory syndrome; IRR, immune recovery retinitis.
General Characteristics of Patients Before ART Administration

The median age of patients included in the study was 33 years (interquartile range [IQR], 29–39). There were 69 men (92%) and 6 women (8%). The median CD4 count was 26 cells/µL (IQR, 14–72); the median CD8 count was 451.5 cells/µL (IQR, 221.2–684.2). The median viral load was 5.58 log10 copies/mL (IQR, 5.25–5.82). No significant differences between the group of patients with CMV retinitis improvement vs the group with CMV-IRR were found regarding age, CD4 and CD8 cell counts and percentages, CD4/CD8 ratios, and HIV RNA load before ART (Table 1). Sixty patients (80%) had other associated opportunistic infections. Of those, 30 had pneumocystis pneumonia, 18 had mycobacterial infection, 4 patients had fungal disseminated diseases, 4 had Kaposi sarcoma, and 4 had other infections or tumors (cryptococcal meningitis, tonsil lymphoma, CMV hepatitis and pneumonia, and herpes pneumonia). CMV retinitis was the only opportunistic infection in 15 patients.

Patients With Unmasking or Paradoxical CMV-IRR and IRU

The median time to unmasking CMV-IRR was 4 weeks (IQR, 3–7) after ART initiation, and the median time to paradoxical CMV-IRR was 6 weeks (IQR, 3.25–9.5) after ART initiation. The fundus photographs of a case with unmasking CMV-IRR are shown in Figure 1. Of the 55 patients with CMV-IRR, 36 had a CD4 count <50 cells/µL; 12 had a CD4 count of 50–100 cells/µL; and 7 had a CD4 count >100 cells/µL. Therefore, 19 patients with CMV-IRR had ≥50 CD4 T-cells/µL. Interestingly, 6 of the 7 patients who developed IRU previously had unmasking or paradoxical CMV-IRR. The first and the second patients had paradoxical CMV-IRR and anterior uveitis after 7 and 10 weeks, respectively, on ART. The third patient had paradoxical CMV-IRR with vitritis, subretinal mass, and vasculitis distant from the originally affected zone after 8 weeks on ART. The fourth patient had paradoxical CMV-IRR after 4 weeks on ART, and 14 weeks later he had a focus of choroiditis next to the original retinitis. The fifth patient had unmasking CMV-IRR.

![Figure 1.](image-url) Paradoxical cytomegalovirus (CMV)–immune recovery retinitis. The patient developed CMV retinitis with a CD4 count of 2 cells/µL and a viral load of 260 000 HIV RNA copies/mL. After 16 weeks on oral valganciclovir, CMV retinitis was completely resolved (inferior nasal retina with dramatic improvement of CMV retinitis and areas of retinal atrophy in the right and left eye are shown in panels A and B, respectively). ART was then initiated and 8 weeks later, paradoxical worsening of CMV retinitis was diagnosed with a CD4 count of 558 cells/µL and a viral load of 1210 HIV RNA copies/mL (white edematous lesions with microhemorrhages on previously inactive retinal nasal borders in the right and left eye are shown in panels C and D, respectively).
and anterior uveitis after 7 weeks on ART. The sixth patient had unmasking CMV-IRR after 6 weeks on ART, and 40 weeks later he developed cystoid macular edema. The seventh patient had retinitis improvement with CMV treatment, but he developed an epiretinal membrane after 10 weeks on ART.

No difference in risk for CMV-IRR was found in patients with a CD4 count of <50 cells/µL vs those with ≥50 cells/µL (relative risk, 1; 95% confidence interval, 74–1.32; P = .99 Fisher exact test).

**DISCUSSION**

CMV retinitis has been extensively described in HIV-infected patients with CD4 counts <50 cells/µL under ineffective treatment of opportunistic infection and ART failure [14]. Due to the fact that these patients have active CMV infection, they are usually treated with ganciclovir or valganciclovir, and steroids are contraindicated. Once CMV infection has healed, approximately one-third of these patients will develop IRU with ART-induced immune reconstitution. Patients with IRU may develop cataract, vitritis, papillitis, cystoid macular edema, and epiretinal membrane. At this point, the use of steroids is recommended for the control of the inflammatory process involving different intraocular structures.

Here we found a high frequency of patients who developed unmasking or paradoxical CMV-IRR under successful ART initiation. This condition has only been described in a few case reports and case series [8, 9], but a standardized clinical case definition for CMV-IRR is needed. Due to active CMV infection in these patients, the use of ganciclovir or valganciclovir is recommended, and steroids are contraindicated.

The fact that 4 patients with paradoxical CMV-IRR and 2 patients with unmasking CMV-IRR developed IRU leads to the hypothesis that active CMV retinitis might be an initial stage of a continual process leading to healed CMV retinitis observed in IRU. In addition, the interval between ART initiation and IRU diagnosis reported in the literature is often on the order of a year or more [15, 16], in contrast to the data presented in this study, where most patients with CMV-IRR were diagnosed within 3 months of ART initiation. In any case, a closer follow-up of patients initiating ART would help to define the possible etiologic and temporal relation between active retinitis in CMV-IRR and IRU.

We did not find a higher risk for IRIS in patients with a CD4 count <50 cells/µL at the start of ART, as was reported in previous studies [7]. Contrasting results might be explained by the use of different diagnostic criteria for IRIS; the nonprospective design here and in the studies cited; and the fact that previous studies reported mainly patients with IRU, whereas we are reporting IRIS in patients with active, nonhealed CMV retinitis. Our patients, as well as those included in previous studies, had a low CD4 T-cell count at the start of ART. Therefore, late presentation for HIV care prevails in the past and current context of CMV retinitis.

Relapse of retinitis has been described in immunocompromised patients despite the use of valganciclovir. However, our patients were unlikely to have a simple relapse as the clinical diagnosis of retinitis was performed in the context of clinical deterioration of an infectious or inflammatory condition temporally related to successful ART initiation. As shown in Table 1, 80% of the patients with unmasking CMV-IRR had a median increase of 50 CD4 T cells/µL on ART. At that time, the median CD4 count was 92 cells/µL; only 10 of 35 patients (28.5%) had a CD4 count <50 cells/µL, and 48.5% had a CD4 count >100 cells/µL, which is definitely atypical. In the group with paradoxical CMV-IRR, the median CD4 count on diagnosis of clinical deterioration was 128.5 cells/µL; only 3 of 20 patients (15%) had a CD4 count <50 cells/µL, and 55% had a CD4 count >100 cells/µL. In sum, this is not the expected clinical course of CMV retinitis. The diagnosis of CMV retinitis was based on the clinical findings of an expert ophthalmologist familiarized with the clinical features of this condition [17, 18], and supported by the clinical response to valganciclovir treatment. Thus, confirmation of active CMV infection by detection of viral DNA in aqueous humor was not performed.

Regular ophthalmologic follow-up has been recommended at 3-month intervals [19, 20]. Nevertheless, considering that CMV-IRR occurred with CD4 counts >100 cells/µL, that the incidence of IRIS peaks 2–8 weeks after ART initiation [21], and that ophthalmologic examination is the only way to diagnose and prevent severe forms of CMV-IRR, we suggest a closer ophthalmologic follow-up for patients initiating ART. During the first 2 months on ART, we recommend weekly examinations for patients with CD4 counts <50 cells/µL and biweekly examinations for those with 50–150 cells/µL. For patients with higher CD4 counts or those with IRU who have healed retinitis, examinations at 4- to 6-week intervals would be reasonable.

### Notes

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**Potential conflicts of interest.** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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