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LYMPHOID NEOPLASIA

# Relapse of HHV8-positive multicentric Castleman disease following rituximab-based therapy in HIV-positive patients

Alessia Dalla Pria,[1] David Pinato,[1] Jennifer Roe,[2] Kikeri Naresh,[3] Mark Nelson,[2] and Mark Bower[1]

[1]Department of Oncology, The Chelsea and Westminster Hospital, London, United Kingdom; [2]Department of HIV Medicine, The Chelsea and Westminster Hospital, London, United Kingdom; and [3]Department of Pathology, Imperial College School of Medicine, London, United Kingdom

## Key Points

- HIV-associated MCD remains a relapsing remitting disease despite rituximab-based therapy.
- Most patients can be salvaged at relapse by retreating with rituximab, but the risk of developing HHV8-associated lymphomas remains.

**Successful treatment of HIV-associated multicentric Castleman disease (HIV+MCD) with rituximab-based approaches has dramatically improved survival and reduced the risk of human herpesvirus 8 (HHV8)-associated lymphoma. Longer term outcomes including relapse rates have not been described and are important to establish the potential role of maintenance therapy. A prospective cohort of 84 patients with biopsy-proven HIV+MCD were treated with risk-stratified rituximab-based therapy. Four patients (5%) died of refractory HIV+MCD and 80 achieved clinical remission. The median follow-up for the 80 patients was 6.9 years and their 5-year overall survival was 92% (95% confidence interval [CI], 85 to 99). Eighteen have relapsed (all histologically confirmed), including 5 with concomitant HHV8-associated lymphoma and MCD at relapse. The 5-year relapse-free survival is 82% (95% CI, 72 to 92). No clinical or laboratory findings that were present at MCD diagnosis predicted subsequent relapse, and the median time to first relapse was 30 months (maximum, 10 years). There were no significant differences in clinico-pathological features at initial diagnosis and at relapse. All patients were successfully retreated at relapse with rituximab-based therapy. Only 1 patient died of relapsed MCD (at fifth relapse 9.4 years after initial diagnosis). Despite the use of rituximab, the risk of developing HHV8-associated lymphoma was significantly elevated in this cohort, with an incidence of 11.4/1000 person-years. The relatively low relapse rate and high salvage rates at relapse reduce the potential benefit of maintenance therapy; this should only be advocated in the context of a clinical trial. (*Blood*. 2017;129(15):2143-2147)**

## Introduction

HIV-associated multicentric Castleman disease (HIV+MCD) is an uncommon lymphoproliferative disorder associated with human herpesvirus 8 (HHV8).[1] Epidemiologic studies suggest that MCD is more common in people living with HIV, but the elevated risk is not associated with immunodeficiency (CD4 cell count) or the use of combination antiretroviral therapy (cART). The incidence of HIV+MCD seems to be rising in the cART era, although case-identification bias may play an important role.[2]

HIV+MCD is a waxing and waning acute febrile illness characterized by various clinical findings, including diffuse lymphadenopathy, splenomegaly, and anemia.[3] The definitive diagnosis requires histological confirmation. The main characteristic is the presence of enlarged abnormal plasmablasts within the B-cell follicles of pathological lymph nodes. These plasmablasts express high levels of cytoplasmic polyclonal monotypic, immunoglobulin M-λ–restricted immunoglobulins and have positive immunohistochemistry for HHV8 latent nuclear antigen-1.[4,5] The diagnosis of active MCD requires not only the histopathological findings, but also clinical correlates of active disease.

Although there are no evidence-based gold standard criteria for establishing a diagnosis of active MCD, both the French Agence Nationale de Recherche sur le syndrome d'immunodéficience acquise 117 CastlemaB trial group[6] and the National Cancer Institute[7] have described clinical criteria to define an attack of MCD. We have previously applied both scoring schemes to confirm disease activity in a cohort of 75 patients with HIV+MCD.[8]

The management of HIV+MCD was revolutionized by the introduction of rituximab-based immunochemotherapy in 2003. Rituximab is a chimeric monoclonal antibody against CD20, a B-cell marker. It leads to B-cell depletion via complement- and antibody-mediated cytotoxicity. Even though HHV8-infected plasmablasts frequently do not express high levels of CD20,[9] numerous case series and 3 open-label studies have used rituximab in HIV+MCD, dramatically improving the prognosis of patients with this disease.[6,10,11] In a cohort study of 61 patients with HIV+MCD, the overall survival (OS) for 46 patients treated with rituximab-based treatment was 90% at 5 years compared with 33% before the introduction of rituximab.[12]

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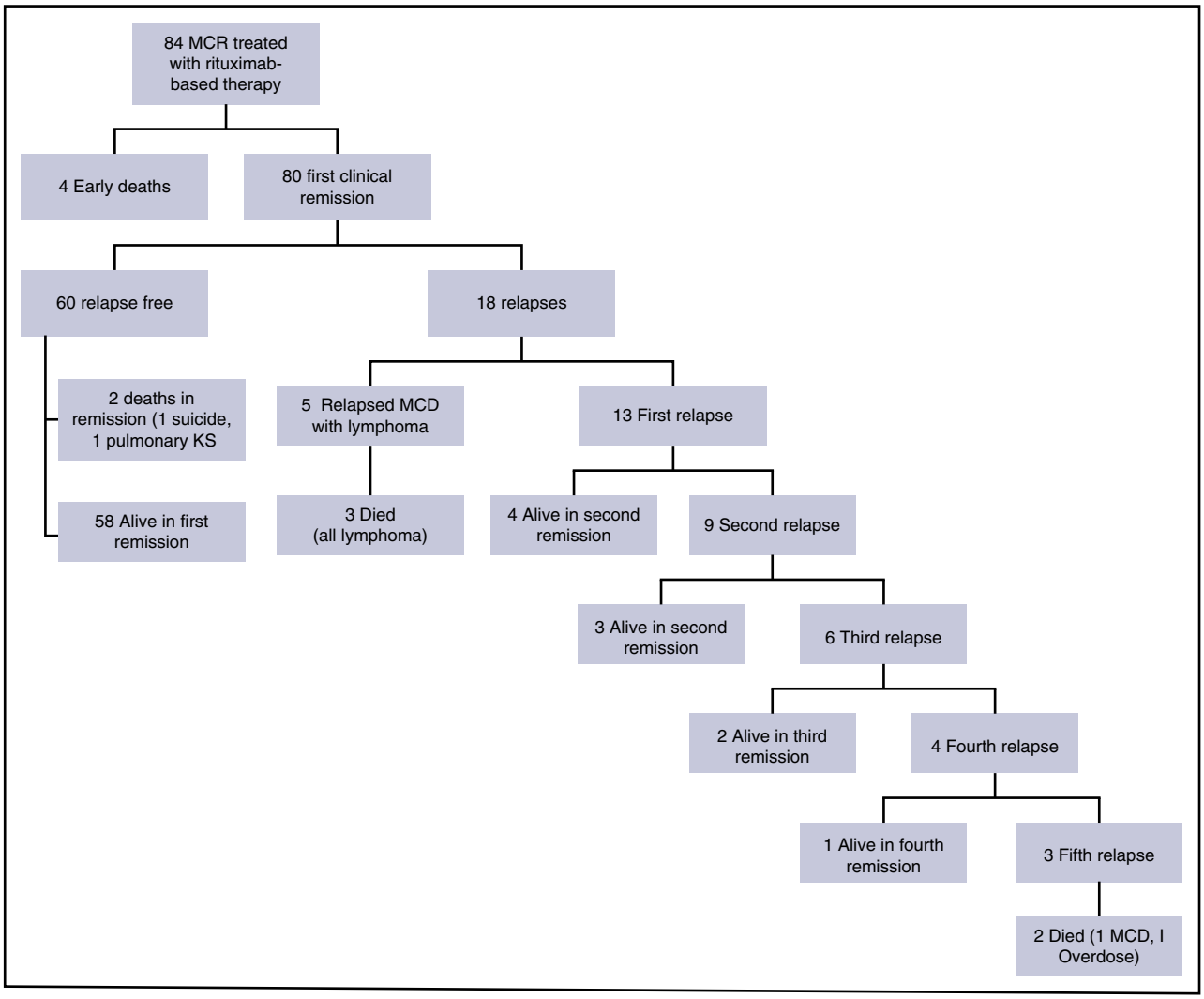


**Figure 1. Flowchart for entire cohort of 84 patients with HIV+MCD.**

Despite the efficacy of rituximab-based treatment in acute HIV+MCD, relapses may occur following treatment; however, the frequency, clinicopathological features, and outcomes after relapse of HIV+MCD have not been described.

## Methods

From a prospective database, we retrospectively reviewed clinical and pathological data of 84 patients treated for HIV+MCD with rituximab-based therapy since 2003 at the National Centre for HIV Malignancy at Chelsea and Westminster Hospital, London. All HIV+MCD diagnoses have been confirmed by central histological review, including HHV8 latent nuclear antigen-1 immunostaining and immunoglobulin Mλ expression of lymph node, spleen, or bone marrow biopsies (K. Naresh). All relapses were confirmed by repeat biopsy. All patients had radiological staging with computed tomography or positron emission tomography/computed tomography.

Survival was calculated from HIV+MCD diagnosis until death (OS), relapse (relapse-free survival), or last follow-up, and from MCD relapse diagnosis until death or last follow-up. Survival curves were plotted according to the Kaplan-Meier method. Cox proportional hazards model was used to test for the effects of covariates on relapse-free survival.[13] Comparison of variables between groups was by Fisher's exact test for nominal variables and Mann-Whitney test for nonparametric continuous variables; all *P* values are 2-sided.

## Results

Eighty-four patients (72 males; mean age, 42 years) were treated with rituximab-based immunotherapy for HIV+MCD. These 84 patients include all those treated with rituximab that were also in a previously published series from this center.[8,12,14,15] Fifty-two patients were treated with single-agent rituximab (375 mg/m$^2$ IV every week for 4 weeks) and 32 with combined rituximab and etoposide (rituximab, 375 mg/m$^2$; etoposide, 100 mg/m$^2$ both administered IV every week for 4 weeks), following a risk-stratified approach. This strategy, which was introduced in 2006, uses combined rituximab and etoposide treatment of patients with a poor performance status (Eastern Cooperative Oncology Group [ECOG] >2) or end-organ damage (involvement of organs other than spleen and lymph nodes, hemophagocytic syndrome, or hemolytic anemia). Rituximab monotherapy is used for patients with less aggressive disease who do not fulfill these high-risk criteria.[16] Patients are followed with clinical examination and blood tests, including plasma HHV8 viral load every 3 months. Radiological

**Table 1. Comparison of clinicopathological features present at initial diagnosis and at relapse in HIV+MCD**

| | First diagnosis | First relapse (no lymphoma) | *P* value |
|---|---|---|---|
| Mean age, y (range) | 42 (21-69) | 44 (31-59) | MW: .83 |
| Male sex | 72/84 (86%) | 12/13 (92%) | FET: 1.0 |
| **Ethnicity** | | | |
| Black African | 26 (31%) | 5/13 (38%) | |
| White | 56 (67%) | 8/13 (62%) | |
| Other | 2 (2%) | 0/13 (0%) | |
| **On cART** | 41/84 (49%) | 13/13 (100%) | FET: .0004 |
| Mean time on cART, y (range) | 1.9 (0-16) | 4.6 (0.2-9.6) | MW: .0018 |
| Mean CD4 (range) | 283 cells/mL (24-834) | 536 cells /mL (79-1457) | MW: .026 |
| Mean CD4% (range) | 17% (2-35) | 20% (10-33) | MW: .16 |
| Mean CD8 (range) | 912 cells/mL (164-2558) | 1340 cells/mL (279-3570) | MW: .060 |
| Mean CD8% (range) | 55% (25-83) | 52% (32-79) | MW: .29 |
| Mean CD19 (range) | 272 cells/mL (8-1508) | 474 cells /mL (55-1451) | MW: .28 |
| Mean CD19% (range) | 16% (0.2-53) | 15% (4-33) | MW: .77 |
| Mean NK (range) | 87 cells/mL (4-493) | 184 cells /mL (32-772) | MW: .050 |
| Mean NK% (range) | 5% (0.4-29) | 6% (2-15) | MW: .49 |
| VL undetectable | 27/83 (33%) | 6/13 (46%) | FET: .36 |
| VL <400 copies/mL | 45/83 (54%) | 12/13 (92%) | FET: .013 |
| Median duration of symptoms, mo (range) | 3 (1-48) | 2 (1-4) | MW: .036 |
| ECOG >1 | 42/84 (50%) | 5/13 (38%) | FET: .56 |
| Median plasma HHV8 (range) | 237 200 copies/mL (200-554 000 000) | 177 500 copies/mL (19 800-23 000 000) | MW: .61 |

FET, Fisher's exact test; MW, Mann-Whitney test; VL, plasma HIV RNA viral load.

examinations for relapse are based on symptoms and laboratory findings, and relapses are confirmed by repeat biopsy and histological examination. The last patient was treated in December 2015 and follow-up was censored in June 2016.

Four patients (5%) died of refractory or progressive HIV+MCD, all within 2 weeks of initiating first-line combined rituximab and etoposide treatment, whereas 80 (95%) patients achieved a clinical first remission. Eighteen of these 80 (22%) patients have relapsed with biopsy-proven relapsed HIV+MCD, including 5 patients with concomitant HHV8-associated lymphomas. The lymphoma histological subtypes identified using the 2016 revision of the World Health Organization classification were 4 HHV8-associated diffuse large B-cell lymphoma not otherwise specified and 1 primary effusion lymphoma extracavity[17]; there were 3 lymph node samples with histological evidence of coexisting MCD. Three of these patients died of lymphoma. Two of the remaining 62 patients died in first remission (1 suicide, 1 pulmonary Kaposi sarcoma [KS]). Thus, 13 patients had a first relapse without lymphoma and received second-line therapy using the same stratified rituximab-based approach. Two patients with relapsed MCD without lymphoma died, both after 5 relapses, 1 from MCD and 1 from an overdose in sixth remission (Figure 1).

The clinicopathological features at first relapse for 13 patients who relapsed without lymphoma is shown in Table 1 and compared with the findings at initial HIV+MCD diagnosis for all 84 patients. At relapse, more patients were established on cART ($P = .0004$), the median CD4 cell count was higher ($P = .03$), and more had a plasma HIV viral load <400 copies/mL ($P = .01$). At relapse, fewer were anemic ($P = .004$), but more had nasal obstruction ($P = .03$) and the duration of symptoms was shorter ($P = .04$). In other respects, there were no significant differences in clinical criteria of acute HIV+MCD using both Agence Nationale de Recherche sur le syndrome d'immunodéficience acquise and National Cancer Institute criteria. Similarly, there were no differences in other immune cell subsets (CD8, CD19 [B cells], CD16/56 [natural killer (NK) cells]). Finally, there were no differences in ECOG performance status or in plasma HHV8 viral load.

For the entire cohort of 84 patients, the 2- and 5-year OSs are 91% (95% confidence interval [95% CI], 85-98) and 88% (95% CI, 80-96), respectively (Figure 2). Four patients did not achieve a clinical remission and the median follow-up for the remaining 80 patients is 6.9 years with 2- and 5-year OSs of 96% (95% CI, 91-100) and 92% (95% CI, 85-99), respectively. Of the 80 patients who achieved a first remission, 7 have died: 3 from HHV8-related lymphomas, 1 from pulmonary KS in MCD remission, 1 from suicide in MCD remission, 1 from MCD at fifth relapse, and 1 from overdose at fifth MCD relapse. Eighteen of 80 (19%) who achieved remission have relapsed at least once with biopsy-confirmed relapsed MCD (including 5 patients with concurrent HHV8-associated lymphoma). The median time to first relapse (excluding the 5 patients with lymphoma) is 30 months (range, 3-124). At first relapse, all 13 had symptoms of median duration 2 months (compared with 3 months at first diagnosis) and detectable plasma HHV8 viremia (median, 177 500 copies/mL). The median CD19 (B-cell) count at relapse was 474/mL (15%), suggesting full recovery of B lymphocytes following rituximab first-line therapy.

The 2- and 5-year relapse-free survival rates for the 80 patients achieving remission were 89% (95% CI, 82-96) and 82% (95% CI, 72-92) (Figure 3). Using multivariate modeling, the risk of relapse was not influenced by sex ($P = .88$), age ($P = .052$), time since HIV diagnosis ($P = .17$), prior AIDS diagnosis ($P = .12$), plasma HIV viremia ($P = .48$), use of antiretroviral therapy ($P = .49$), CD4 ($P = .80$), CD8 ($P = .67$), CD19 (B cell) ($P = .98$), or CD16/56 (NK cell) ($P = .68$) counts. The plasma HHV8 at initial HIV+MCD diagnosis ($P = .45$) and the addition of etoposide chemotherapy to rituximab for high-risk patients ($P = .71$) similarly did not affect the risk of relapse.

All 13 patients with no lymphoma at relapse were retreated with rituximab-based immunotherapy following the same risk-stratified approach; all achieved a second clinical remission. Nine have had second relapses also successfully treated, 6 have had third relapses, 4 have had fourth relapses, and 3 fifth relapses including 1 patient who died of progressive HIV+MCD at fifth relapse 9.4 years after first HIV+MCD diagnosis. The rate of second relapse for the 13 patients who entered a second remission of HIV+MCD is substantially higher than the rate of first relapse, with 53% relapsing by 5 years after second remission. The median time from second remission to relapse is 2.9 years.

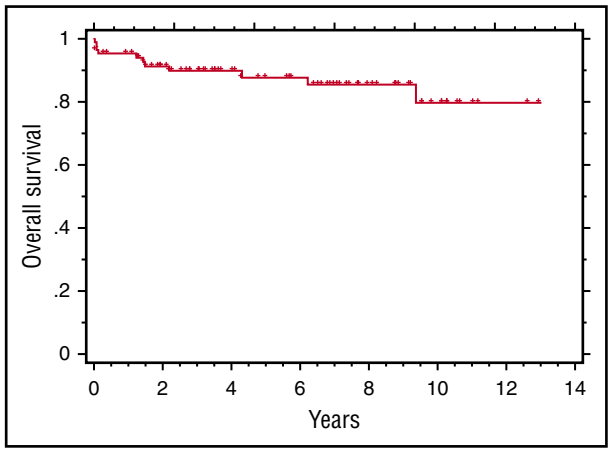


**Figure 2. Kaplan-Meier curve showing the OS of 84 patients treated with rituximab-based immunotherapy for HIV-associated MCD.**

Five patients developed HHV8-associated lymphomas, all at the time of their first relapse with HIV+MCD. The lymphoma incidence for HIV+MCD patients achieving remission is 1140 per 100 000 person-years. The median interval from initial HIV+MCD diagnosis to lymphoma was 2.2 years (range, 0.3-6.9). Three have died of lymphoma, so that lymphoma accounts for 3/11 (27%) of deaths compared with 5/7 (45%) from HIV+MCD.

## Discussion

Rituximab has revolutionized treatment of HIV+MCD and has markedly improved the prognosis[6,10,18] and reduced the risk of developing HHV8-associated lymphomas.[19] It has converted a once rapidly fatal illness into a relapsing and remitting disease. Rituximab treatment may lead to progression of KS in this group of patients, and we have previously reported KS progression in 38% of 24 patients from this cohort who had both MCD and KS at diagnosis.[12] This has led some clinicians to advocate for the use of liposomal anthracycline in combination with rituximab in patients with dual diagnosis of HIV+MCD and KS.[11] The natural history of HIV+MCD following treatment to clinical remission with rituximab-based therapy has not been documented, and is important because maintenance therapies have been advocated by some clinicians.[7]

This manuscript describes the patterns of relapse in a single-center cohort of 84 patients with newly diagnosed HIV+MCD treated with a consistent risk-stratified approach based on rituximab monotherapy or in combination with etoposide. With a median follow-up of 6.9 years, the 5-year OS for the entire cohort is 88%. Four patients died of progressive refractory MCD before completing the 4-week course of treatment and only 1 other patient died of MCD following 5 relapses. In addition, 5 patients developed HHV8-associated lymphomas; 3 of these patients died of the lymphoma. The OS rate in this cohort is comparable to published HIV+MCD cohorts treated with rituximab-based treatment that reported 2-year OS of 93%[19] and 1-year OS of 94%.[18]

Despite the excellent OS achieved, this study demonstrates that HIV+MCD follows a relapsing and remitting clinical course even after primary therapy with rituximab. The relapse rate at 5 years following first remission is 18%, and all achieved a second remission. The relapse rate following second remission was even higher at 53% at 5 years, but despite this only 1 patient died of relapsed HIV+MCD.

The clinical presentation of HIV+MCD at relapse is similar to the first episode of MCD and the median time to first relapse is 30 months, although late relapses occurred up to 10 years after first line therapy. It is noteworthy that at the time of biopsy-proven relapse, all patients had detectable HHV8 viremia and that the circulating B cells (CD19) had recovered to normal ranges following the prior rituximab-based treatment. The risk of relapse of HIV+MCD was not significantly influenced by patient characteristics, use of cART, plasma HIV viral load, or lymphocyte subset counts. Although age at HIV+MCD diagnosis was predictive of relapse in the previous analysis of 52 patients,[14] this variable did not achieve statistical significance in this Cox proportional hazards model of 80 patients, possibly for mathematical rather than biological reasons. Similarly, initial HHV8 viremia and the addition of etoposide chemotherapy to rituximab for high-risk HIV+MCD did not affect relapse risk. A previous publication that included 52 patients from this cohort confirmed that a rising plasma HHV8 DNA load during remission predicted relapse of MCD.[14] This analysis has not included response to first-line therapy in terms of clinical response, radiological response, or suppression of HHV8 viremia as predictors of subsequent relapse.

The duration of symptoms at relapse was shorter than at initial diagnosis, presumably resulting from greater vigilance by both patients and physicians.

Retreatment of patients with histologically confirmed HIV+MCD relapse with rituximab-based therapy achieved second remissions and in 37 patients and in subsequent relapses only 1 patient died of active MCD. Some clinicians have advocated maintenance rituximab as studied in the CastlemaB trial,[6] or the oral antiherpes agent valganciclovir.[20,21] This idea is supported by the finding in our cohort that at relapse, B-cell counts had recovered to normal following rituximab therapy, so perhaps maintenance rituximab could reduce the risk of relapse. However, the relatively modest relapse rate after first-line treatment of 18% at 5 years and the high OS with only 1 death attributable to relapsed HIV+MCD suggests that the value of maintenance is limited. Of interest, the relapse rate following second remission is much higher (53% at 5 years); maintenance therapy may offer greater benefit at this time. This requires validation in an adequately powered randomized clinical trial and the findings from our cohort could inform design of such a trial.

The maturity of this cohort with a median follow-up of 6.9 years allows further elaboration on the incidence of HHV8-associated

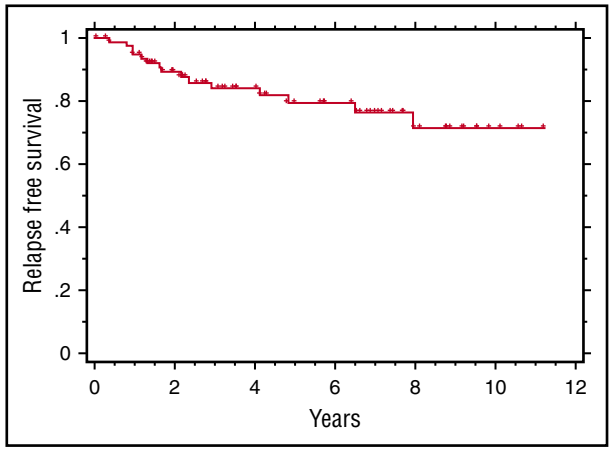


**Figure 3. Kaplan-Meier curve showing the relapse-free survival for all 80 patients achieving remission from HIV-associated MCD following rituximab-based first-line therapy.** In this analysis, the development of HHV8-associated lymphoma is taken as a relapse even if the biopsy did not include the presence of MCD.

lymphomas following immunotherapy for HIV+MCD. A high incidence of lymphoma following HIV+MCD diagnosis was noted in an early cohort series of 60 patients with a median follow-up of 20 months.[22] Fourteen of 60 patients, none of whom received rituximab-based therapy, developed lymphomas and the incidence was 101/1000 patient-years. The French collaborative cohort reported that the incidence of lymphoma in the pre-rituximab era was 69.6/1000 patient-years and fell to 4.2/1000 PY patient-years following the introduction of rituximab-based therapy.[19] In our study, the incidence is 11.4/1000 patient-years which is approximately 3 times higher than in the general population of people living with HIV.[23]

## Conclusions

Relapse following rituximab-based treatment of MCD is not infrequent and may occur after recovery of CD19 (B-cell) counts. Clinical, virological, and immunological predictors of relapse have not been identified. Multiple rechallenges with rituximab-based immunochemotherapy are safe and efficacious. The risk of lymphoma remains significantly elevated even in patients with HIV+MCD who are successfully treated with rituximab-based approaches. The successes in salvaging patients with relapses need to be taken into account when designing studies to address the role of maintenance therapies in HIV+MCD. Our current follow-up strategy is no maintenance treatment, but clinical follow-up every 3 to 6 months and patient awareness about the risk of HIV+MCD recurrence with recommendation to seek quick medical attention in the specialist center as soon as symptoms recur.

## Authorship

Contribution: A.D.P., D.P., J.R., M.N., and M.B. collected the data and analyzed and interpreted the results; K.N. performed all histopathological examinations; and all authors contributed to the writing of the manuscript and approved the final version submitted.

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Correspondence: Mark Bower, Department of Oncology, Imperial College School of Medicine, The Chelsea and Westminster Hospital, 369 Fulham Rd, London SW10 9NH, United Kingdom; e-mail: m.bower@imperial.ac.uk.

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