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ORIGINAL ARTICLE

Cytomegalovirus infection among people living with HIV in Sweden: Case profiles, treatment strategies and patient outcomes at Karolinska University Hospital 2010–2020

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Abstract

Objectives: In countries with access to early antiretroviral treatment (ART), opportunistic infections caused by cytomegalovirus (CMV) in people living with HIV (PLWH) are becoming increasingly rare. As potential complications are severe, it is critical to remain aware of this important diagnosis. However, clinical characteristics and prognosis of CMV infection in PLWH in the era of modern ART have not been well described.

Methods: Here, we compiled the clinical presentation, management and outcome of CMV infection in PLWH treated at the infectious diseases clinic of Karolinska University Hospital during 2010–2020.

Results: We identified 51 cases of active CMV infection, based on detection of CMV-DNA, mainly diagnosed in patients with CD4 T-cell count <200 cells/μL (86%). Median time from HIV diagnosis to detection of CMV infection was 16 days. In 20 cases (39%), CMV infection was symptomatic with retinitis identified as a manifestation in 70% of cases. Symptomatic CMV infection was treated for 73 (20–313) days upon diagnosis, mostly using valganciclovir. One-year mortality was 22% and was associated with longer time to ART initiation from HIV diagnosis and with comorbidities, but not with CMV-DNA levels or CD4 count. Immune reconstitution was not significantly compromised in patients with symptomatic CMV, although CD4/8 ratio tended to be lower in patients with systemic CMV infection.

Conclusions: Retinitis remains the most common manifestation of symptomatic CMV infection in PLWH. Recognizing CMV infection is important, especially in the management of 'late presenters'. Adequate duration of antiviral therapy and appropriate follow-up must be ensured to avoid complications.

KEYWORDS

AIDS, cytomegalovirus, HIV, opportunistic infections, retinitis

INTRODUCTION

Cytomegalovirus (CMV) is a betaherpesvirus with a prevalence of 60–70% in the United States [1], 83% in Sweden [2] and nearly 100% in some African countries [1]. The primary infection is often acquired in early childhood, after which latent infection is established in cells of the myeloid lineage, where the virus remains for the rest of the host's life. Reactivation of the infection may occur repeatedly, often in association with inflammatory conditions or stress. In immunocompetent individuals, reactivation or reinfection is usually asymptomatic, although it may present with fever. However, in immunocompromised individuals, CMV infections can lead to severe, or even fatal, end-organ disease (EOD). In HIV-infected individuals, the risk of symptomatic CMV infection further increases when the CD4 T-cell count falls below 100 cells/μL [1]. CMV EOD is an AIDS-defining condition. The most common manifestation of CMV EOD is retinitis [3]; other sites of manifestation include the gastrointestinal tract, central nervous system, lungs and liver.

There are about 8000 people living with HIV (PLWH) in Sweden [4], with 400–500 newly registered HIV diagnoses per year (both newly diagnosed people and immigrants with previously known HIV) [5]. The infectious diseases outpatient clinic at Karolinska University Hospital provides care to 2300 PLWH. Prior to the era of effective antiretroviral treatment (ART), 21–44% of people with AIDS were estimated to have CMV disease [6]. Following the START trial [7], ART has been recommended for all PLWH, regardless of CD4 count, in many countries. Subsequently, the incidence of new cases of CMV EOD in HIV-infected individuals has declined by ≥95% in the United States [8, 9]. The Swedish HIV treatment guidelines were updated accordingly in 2014 [10]. Current opinion does not support the need for early CMV treatment in addition to ART in treatment-naïve patients with low CD4 counts [11].

As the burden of CMV disease in PLWH decreases, there is a risk of loss of clinical experience and awareness that may lead to suboptimal treatment of PLWH with CMV infection. The incidence, clinical characteristics and prognosis of CMV in HIV-infected individuals in the era of modern ART is not well described [12]. To address this, we aimed to characterize CMV infection in PLWH at our clinic during 2010–2020, by reviewing clinical presentation, management and outcome as defined by 1-year mortality and immune reconstitution. We found that CMV continues to be an important pathogen in HIV patients, especially 'late presenters'. Our results may be used to improve patient care in this neglected area.

METHODS

Study population

We identified PLWH with positive CMV-DNA results in polymerase chain reaction (PCR) analyses of blood, bronchoalveolar lavage (BAL) fluid, cerebrospinal fluid or tissue biopsy treated at our clinic in the years 2010–2020. For patient identification, we used three parallel approaches: electronic patient records, the national HIV patient database InfCare HIV and the local laboratory database. Electronic patient records of in-patients treated at the infectious diseases clinic of Karolinska University Hospital in Huddinge during 2010–2020 were screened for relevant ICD-10 codes. Patient records with one code corresponding to HIV infection and one code corresponding to CMV disease or eye disease were further reviewed and included in cases where concurrent HIV and CMV infection was found **(**Table S1**)**. The HIV national patient database InfCare HIV was used to identify patients with CMV diagnosis, identifying both in- and outpatients treated at our clinic. We also performed a search within the local laboratory database of the Karolinska University Hospital microbiology department (wwLab) to identify samples analysed for CMV-DNA analysis from the in- and outpatient clinics of the infectious diseases clinic from 1 January 2010 to 8 December 2020. Samples with CMV-DNA >500 IU/mL were matched with the InfCare HIV database, thus identifying cases with concomitant HIV and CMV infection. This approach allowed us to cover cases of CMV infection registered by the clinicians, as well as laboratory-confirmed cases of CMV infection in PLWH.

Data analysis

The patient records of the identified cases were reviewed (Ethical permit: Dno 2015/1521-31/1, Dno 2022-01933-01) in terms of dates of HIV and CMV diagnoses, respectively, immune status at time of diagnosis, HIV-RNA levels, CMV-DNA levels, antiretroviral treatment, and antiviral treatment. Restoration of CD4 count 1 year after CMV diagnosis and survival was documented. CMV retinitis diagnoses were based on ophthalmological examinations performed by consults at St Erik Eye Hospital, Stockholm, Sweden. Ophthalmological examinations of patients sometimes yielded equivocal results, such as 'suspected retinitis'. Those cases have been labelled as 'EOD' in this study. CMV manifestations were graded on a scale of 1–3, where 1 represents asymptomatic CMV infection, 2 represents CMV EOD, and 3 represents systemic CMV disease, which was characterized by CMV viraemia as well as

manifestation of CMV disease in multiple organs, or fever and manifestation in at least one organ. One-year mortality was selected as an outcome, and data analysis was performed in JMP 16 (SAS). Depending on data type, *p*-values were calculated using Welch's test, Mann–Whitney test or Fisher's exact test. Graphs were made with Graphpad Prism 9.

RESULTS

We identified 51 cases of CMV infection in HIV-infected individuals. They had a mean age of 48 years (range 25–69) and 71% were male **(**Table 1**)**. At the time of CMV diagnosis, 46 (90%) individuals were receiving in-patient care. The cases were unevenly distributed over the study period, with 19 (37%) diagnosed with CMV infection during 2010–2015. In total, 16 (31%) patients were diagnosed with HIV before 2014, in the period when start of ART was delayed until the CD4 count declined below 350 cells/μL. In this group, median time to CMV diagnosis from HIV diagnosis was 1658 days, as compared with 7 days for the patients who received HIV diagnosis from 2014 and onwards **(**Table 1**)**, indicating that, in general, CMV tests were sent when the clinician recognized that the patient had low CD4 counts.

Median HIV-RNA level in plasma was 276 000 (interquartile range 1450–1 460 000) copies/mL at the time of CMV diagnosis. CMV-DNA levels in blood did not correlate with HIV-RNA levels ($p = 0.784$, Spearman's correlation). Of the 16 patients who were diagnosed with HIV prior to 2014, 10 (63%) started ART within 60 days of HIV diagnosis. On average, these patients started ART 721 days after diagnosis (range 3–3317). By contrast, 97% of patients diagnosed with HIV from 2014 onwards were started on ART within 60 days from HIV diagnosis, reflecting the change in treatment guidelines. An integrase inhibitor (INSTI)-based regimen was prescribed for 85% of the patients at the time of CMV diagnosis.

In the whole cohort, the median CD4 count was 60 (20–110) cells/μL **(**Table 1**)** at the time of CMV diagnosis and 86% of the patients had CD4 count < 200 cells/μL. Patients with symptomatic CMV infection presented with very low CD4 count [50 (20–70) cells/μL]. The highest CD4 count was 1020 cells/μL (5%), in an individual with newly diagnosed HIV, asymptomatic CMV infection and no comorbidities or other opportunistic infections (OIs).

Cytomegalovirus EOD was present in 15 (29%) of the cases **(**Table 1**)**. Retinitis was verified in six of these patients, and it was suspected in three. Systemic CMV infection was found in five patients, all of whom also were considered to have retinitis (verified in four, suspected in one). Thus, signs of CMV retinitis were present in 14 out of 20 (70%) of the patients with symptomatic CMV infections. Differential diagnoses such as retinitis caused by syphilis, cryptococcosis, toxoplasmosis and *Candida* were excluded by serological testing as well as correlations to clinical symptoms. The remaining 31 patients (61%) had positive CMV DNA only, with no symptoms recorded.

The CMV-DNA levels were lower in PLWH with asymptomatic CMV infection compared with those with symptomatic CMV infection; however, the difference was not statistically significant ($p = 0.05$; Figure 1). Although some of the patients with the highest CMV-DNA levels were among those with the lowest CD4 counts, there was no direct correlation between CD4 count and CMV-DNA levels (Figure 2).

Ten cases of malignancies were noted in the studied cohort (Table S2), of which diffuse large B-cell lymphoma (DLBCL) was the most common ($n = 5$, 50% of malignancies). Two of the patients with DLBCL died within 1 year of CMV diagnosis. Other comorbidities included autoimmune diseases, cardiovascular diseases and drug abuse. In all, 80% of the patients had at least one other OI, of which *Pneumocystis jirovecii* pneumonia (PJP), *Candida* and atypical mycobacterial infections were the most common (Table S2).

Cytomegalovirus treatment was given to 18 (90%) cases with symptomatic CMV infection and seven (23%) cases with asymptomatic CMV infection. Valganciclovir was the most common treatment of choice – used as primary therapy in 83% of the cases, dosed according to treatment guidelines, i.e. 900 mg every 12 h in the first 14–21 days with renal adjustments when needed. Treatment duration for the first course of antiviral treatment was a median 73 days (range 20–313) for patients with symptomatic CMV infection. All but two patients with CMV retinitis received treatment; 10 were treated with valganciclovir and two with ganciclovir as first-line therapy. Only one patient received intravitreal injections of ganciclovir in addition to systemic treatment. Treatment duration for the first course of CMV retinitis treatment was 112 days (21–386). Of the 31 patients with asymptomatic CMV viraemia, seven were treated with valganciclovir for viraemia with median CMV-DNA at 6308 IU/mL (1218–33 000). Treatment duration of valganciclovir for asymptomatic CMV was a median of 12 (6–19) days.

The 1-year mortality of the studied cohort was 22% ($n = 11$). Five (45%) of the deceased patients were diagnosed before 2014, accounting for 31% of the patients who were diagnosed with HIV before 2014. A total of 36% of the deceased patients received CMV treatment as compared with 51% of the patients who were alive 1 year

TABLE 1 Characteristics of the 51 patients with HIV and cytomegalovirus (CMV) coinfection at the infectious diseases clinic of Karolinska University Hospital during 2010–2020.

PLWH with CMV infection diagnosed at Karolinska University hospital 2010–2020	**51**
Age (years)[a]	48 (25–69)
Male sex[b]	36 (71)
In-patient care[b]	46 (90)
CMV diagnosis during 2010–2015[b]	19 (37)
ART[b]	
Start at CMV infection	46 (90)
Start >6 months prior to CMV infection	3 (6)
No ART	2 (4)
HIV-RNA at CMV infection, copies/mL[c]	276 000 (1450–1 460 000)
Time since HIV diagnosis[b]	
<1 year	39 (76)
>1 year	10 (20)
Missing data	2 (4)
HIV diagnosis year[b]	
Before 2014	16 (31)
2014–2020	35 (69)
Time since HIV diagnosis at CMV diagnosis (days)[c]	
Before 2014	1658 (30–4109)
2014–2020	7 (3–31)
CD4 T-cell count at CMV infection (cells/μL)[c]	60 (20–110)
CD4/8 ratio at CMV infection[a]	0.15 (0.01–0.91)
Other concomitant OIs[b]	41 (80)
Missing data	3 (4)
Comorbidities[b]	31 (61)
Missing data	1 (2)
CMV infection manifestation[b]	
Viraemia (no symptoms)	31 (61)
End organ disease	15 (29)
Retinitis	9 (18)
Colitis	3 (6)
Systemic/disseminated	5 (10)
Retinitis	5 (10)
CMV-DNA (IU/mL)[c]	3400 (1200–13 000)
CMV sample material[b]	
Blood/plasma	43 (84)
BAL	4 (8)
CSF	1 (2)
Colon biopsy	1 (2)
No sample	2 (4)
Received CMV treatment[b]	25 (49)
Days of CMV treatment[c]	28 (14–112)
1-year mortality (after CMV infection)	11 (22)

Abbreviations: ART, antiretroviral therapy; BAL, bronchial alveolar lavage; CSF, cerebrospinal fluid; PLWH, people living with HIV; OI, opportunistic infection.
[a]Mean (range).
[b]*n* (%).
[c]Median (interquartile range). Missing data: two patients had CMV diagnosis without a CMV sample. Systemic/disseminated CMV infection: retinitis + systemic infection, e.g. fever, malaise, diarrhoea. Time of CMV treatment refers to first treatment course upon discovery of CMV infection; some patients received multiple treatment courses.

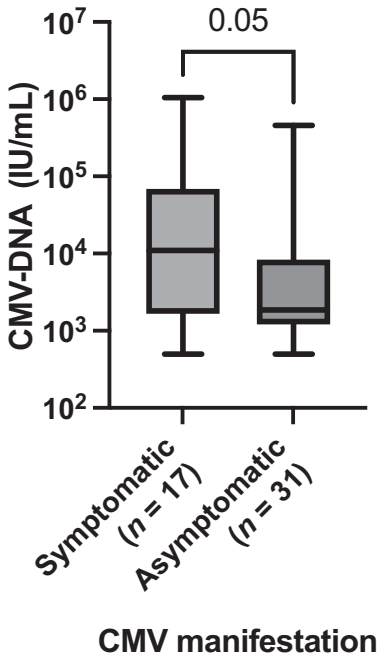

FIGURE 1 Cytomegalovirus (CMV) DNA levels were lower in asymptomatic patients, but the difference was not statistically significant ($p = 0.0510$). Of the 20 symptomatic patients, CMV-DNA levels were missing in three.

after CMV diagnosis, respectively (Table 2**).** In the patients who were deceased within 1 year of CMV diagnosis, all were admitted to hospital and all but two

started or restarted on ART at the time of CMV diagnosis. Moreover, the deceased patients exhibited a substantially longer duration between HIV diagnosis and initiation of ART, in addition to a significantly higher prevalence of coexisting medical conditions as compared with the rest of the cohort (including conditions such as malignancies, intravenous drug use and cardiovascular diseases). There were no significant differences in CD4 nadir, CMV-DNA titre, HIV-RNA titre, time to HIV viral load <50 copies/mL, CD4/8 ratio at time of CMV infection or presence of other OIs between the two groups (Table 2). However, maximum CD4 count in the 1-year mortality group was 300 cells/μL, with the remaining 10 patients in the range 9–110 cells/μL. In six of the 11 patients, CMV was found at the same time or a maximum of 2 months after HIV diagnosis, further indicating advanced HIV infection at the time of diagnosis.

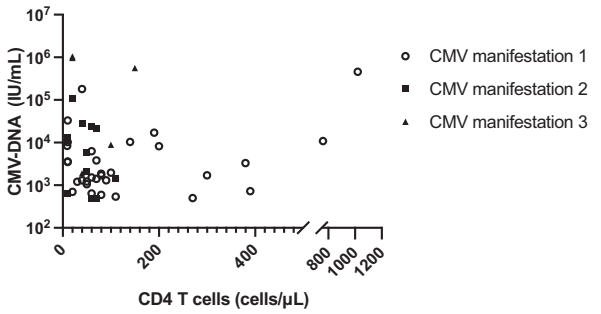

FIGURE 2 Cytomegalovirus (CMV) DNA levels did not correlate with CD4 T-cell levels. All patients with symptomatic CMV infection had CD4 count < 200 cells/μL . CMV manifestation: 1, asymptomatic viraemia; 2, end-organ disease; 3, systemic infection.

At follow-up, patients with systemic CMV infection had lower CD4/8 ratio than those with CMV EOD or asymptomatic CMV infection. However, there were no significant differences in the different groups regarding immune reconstitution, as measured by CD4/8 ratio. CMV retinitis recurred in three patients, prompting several courses of antiviral treatment, one of which also included intravitreal ganciclovir.

TABLE 2 Comparisons of pertinent data between patients who died within 1 year and patients who were alive at 1 year after diagnosis of cytomegalovirus (CMV) infection. Of the 51 patients in the study, 39 were alive at 1 year after CMV infection, 11 were deceased, and one was lost to follow-up. Results are shown as median (interquartile range) or quantity (%).

	Deceased within 1 year ($n = 11$)	Alive 1 year after CMV infection ($n = 39$)	p
Age (years)	55 (35–60)	48 (39–56)	ns[a]
CMV infection manifestation			
DNAemia	7 (64)	23 (60)	ns[b]
EOD	3 (27)	12 (31)	ns[b]
Systemic	1 (9)	4 (10)	ns[b]
Received CMV treatment	4 (36)	20 (51)	ns[b]
CD4 nadir	20 (10–70)	30 (10–80)	ns[b]
CD4 T cells at CMV infection	50 (10–100)	65 (28–143)	ns[c]
Time to ART from HIV diagnosis (days)	20.5 (7–1467)	6 (3–10)	0.0055[c]
CMV-DNA (IU/mL)	1971 (1300–13 000)	3543 (844–15 500)	ns[c]
HIV-RNA (copies/mL)	319 000 (3253–1 460 000)	159 000 (1430–1 630 000)	ns[c]
Time to viral load <50 copies/mL since start of ART (days)	90 (54–114)	146 (71–202)	ns[c]
CD4/8 ratio at CMV infection	0.12 (0.03–0.21)	0.095 (0.0475–0.185)	ns[c]
Presence of other OI	10 (91)	30 (77)	ns[b]
Comorbidities	10 (91)	20 (51)	0.0333[b]

Note: For the 'alive' group, CMV-DNA data was missing for three patients; HIV-RNA and time to viral load (VL) < 50 copies/mL missing from four patients; CD4/8 ratio and information on other OIs missing for one patient. For the 'deceased' group, time since HIV diagnosis at start of ART was missing for oen patient; HIV-RNA missing for two patients; time to VL < 50 copies/mL not applicable for five patients as it was never achieved. In the 'deceased' group, the patients who received CMV treatment were those with EOD or systemic infection.

Abbreviation: ART, antiretroviral therapy; EOD, end-organ disease; OI, opportunistic infection.

[a]Welch's *t*-test.

[b]Fisher's exact test.

[c]Mann–Whitney test.

DISCUSSION

The introduction of the early ART strategy in the past decade has improved the management and prognosis of HIV infection. As a result, OIs such as CMV infections have become increasingly rare in countries with high access to ART. However, CMV infection remains an important concern in 'late presenters' and must not be neglected in patients with newly diagnosed HIV and poor immune status. Here, we have described the shared characteristics of PLWH diagnosed with CMV infection at the infectious diseases department of Karolinska University hospital during 2010–2020, a setting comparable to other clinics of similar size and socioeconomic conditions from high-income countries.

We found that a majority of the CMV-infected patients in the studied cohort were individuals with newly diagnosed HIV/AIDS, belonging to the category 'late presenters' [13]. CMV retinitis was found in 27% of the patients with CMV infection, which correlates well with studies from the pre-ART era [6]. Comorbidities were significantly more prevalent in the patients who died within 1 year after CMV diagnosis compared with those who did not. Considering the severity of these comorbidities and the presence of concurrent OIs, the causes of death in these cases were not directly attributable to the CMV infection itself. There was no correlation between nadir CD4 count and 1-year mortality. The number of CMV infections identified per year increased from 3.2 in 2010–2015 to 6.4 in 2016–2020. In patients diagnosed with HIV during 2014–2020, CMV infection was often diagnosed in proximity of HIV diagnosis (median 7 days), indicating an increased awareness of testing for CMV infection in 'late presenters'. It is also possible that these patients are being more closely monitored for immune reconstitution reactions with in-patient care at the time of start of ART.

All 20 patients with symptomatic CMV infection had CD4 count <200 cells/μL, and 15 (75%) had CD4 count <100 cells/μL. These low nadir CD4 counts most likely mirrored low number of CMV-specific CD4 T cells, which are an important part of the antiviral immunity to CMV. The CMV-specific CD4 T cells developed in response to primary CMV infection persist in the T-cell repertoire of healthy adults. In stem cell as well as solid organ transplant recipients, presence of CMV-specific CD4 T cells is associated with lower risks of developing CMV disease by reactivation of latent virus [14]. At the same time in PLWH, CMV coinfection may have an impact on immune reconstitution [15, 16] and the latent HIV reservoir [17]. Christensen-Quick et al. [18] found that detectable CMV at the start of ART in PLWH was associated with higher CD4 T-cell activation and lower CD8 T-cell degranulation, which may contribute to slower decay of the size of the HIV reservoir during CMV replication. A recent study showed that immune reconstitution after ART was superior in PLWH treated with INSTI-based regimens [19], which were prescribed for 85% of our patients. Notably, the same study also showed lower probability of immune reconstitution in patients with positive CMV serology.

Preventive therapy with oral valganciclovir is not recommended for HIV-infected individuals at high risk of CMV EOD due to cost, toxicity and lack of shown therapy benefits [20]. Treatment for CMV retinitis comprises initial therapy with parenteral ganciclovir or peroral valganciclovir with or without intravitreous injections of ganciclovir or foscarnet, followed by chronic maintenance therapy for at least 3–6 months. Routine ophthalmological follow-up is recommended after cessation of chronic maintenance therapy, so that relapse or immune reconstitution uveitis can be detected early [20]. Other CMV EODs are treated with the same agents, but duration of therapy varies with the site of manifestation. Our study shows that the median time of CMV treatment in general was shorter than what is recommended by current guidelines, demonstrating that duration of treatment more often was decided individually by the treating physician.

Previous studies have found that CMV viraemia is predictive of CMV disease in PLWH [21], and CMV DNA load is an independent marker of CMV disease and survival in patients with AIDS [22]. In addition, CMV reactivation is associated with worse outcome in PLWH with poor immune status [23]. Although we have not found an association between CMV DNA load and 1-year mortality in our cohort, we noted that immune reconstitution tended to be inferior in patients with systemic CMV infection. Indeed, Bigliano et al. [23] found that the diagnosis of serious OIs and the presence of CMV-DNA at follow-up (within 6 months) were associated with poor clinical outcome. Early initiation of ART is key in preventing AIDS-related morbidity and mortality, including that caused by CMV, regardless of anti-CMV treatment. However, close monitoring for persistent CMV viraemia in PLWH with poor immune reconstitution despite ART treatment may be an important practice in the management of this patient group. Indeed, while our results align with previous research indicating that CMV viraemia does not independently predict disease progression or mortality in patients with advanced HIV initiating ART [11], a recent meta-analysis has highlighted the potential advantages of pre-emptive therapy in preventing CMV EOD in PLWH [24].

Our study faces limitations due to the absence of a control group comprising PLWH who do not have CMV

infection. Given our retrospective methodology, we could not employ propensity score matching. This was primarily because CMV is not routinely tested in all patients, making any such analysis inherently biased. Additionally, the study's scope is constrained by the relatively small number of participants. Nevertheless, the study achieves its objective of identifying and characterizing CMV infection cases in PLWH treated at our clinic from 2010 to 2020, including an examination of symptoms and management strategies following the introduction of modern ART. The focus on CMV DNA, which is not regularly measured in PLWH, most likely represents a selection of patients with compromised immune function, as clinicians are more prone to conduct extensive opportunistic infection testing, including for CMV, in such cases.

In summary, we have found that CMV EOD continues to pose a risk for PLWH. Since 2014, most individuals who present with AIDS are late presenters and may benefit from screening for CMV viraemia by PCR at the time of HIV diagnosis. Given that retinitis represents the most prevalent symptomatic manifestation of CMV infection in this cohort, it is crucial for clinicians to actively inquire about patients' vision-related issues and to consult ophthalmologists when necessary. In PLWH with poor immune reconstitution despite effective ART, repeated CMV monitoring may be warranted. In these cases, anti-CMV treatment for an adequate duration of time may be considered also for asymptomatic CMV viraemia, along with increased attention for other OIs.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets used in this study are not publicly available due to privacy concerns and the proprietary nature of the database but can be accessed upon reasonable request through the corresponding author.

ETHICS APPROVAL STATEMENT

This work was approved by the Swedish Ethical Review Authority, Dno 2015/1521-31/1 and Dno 2022-01933-01.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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