

From Persistent to Undetectable: Cerebrospinal Fluid CMV DNA Clearance During PD-1 Blockade treatment With Sintilimab in a HIV-Associated Lymphoma Patient

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Case Report

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Abstract

Background

Cytomegalovirus (CMV) neurologic disease is an uncommon but severe complication of advanced HIV infection. Evidence guiding management is limited, and the implications of programmed cell death protein 1 (PD-1) blockade when low-level cerebrospinal fluid (CSF) CMV DNA remains detectable are unknown.

Case presentation

A 57-year-old man with HIV-associated Epstein-Barr virus-encoded RNA-positive diffuse large B-cell lymphoma had CD4⁺ T-cell counts persistently below 100 cells/ μ L. He subsequently developed fever, dizziness, and somnolence. During the diagnostic evaluation, CSF CMV DNA was 1.53×10^7 IU/mL, compared with 96,000 IU/mL in paired plasma. Major alternative Central Nervous System (CNS) opportunistic infections and CNS lymphoma were not identified, supporting a diagnosis of probable CNS CMV disease. Prolonged ganciclovir-based therapy with foscarnet coadministration reduced CSF CMV DNA to 150 IU/mL one day before the first sintilimab dose, which was administered for lymphoma consolidation. CSF CMV DNA was first documented as undetectable 27 days later and remained undetectable through October 2025. Serial monitoring showed recovery of the absolute peripheral CD8⁺ T-cell count from a pre-sintilimab nadir, early enrichment of the effector CD8⁺ T-cell compartment, later partial re-equilibration of effector-memory CD8⁺ T cells, subset-specific PD-1⁺ T-cell dynamics, and selective CSF cytokine activation without clinically apparent inflammatory worsening.

Conclusions

The overall virologic decline was primarily attributable to anti-CMV therapy. The temporal association among PD-1 blockade, transient T-cell immunophenotypic remodeling, and the first documented undetectable CSF CMV DNA result raises the hypothesis that sintilimab-associated immune modulation may have contributed to the final conversion of residual low-level CSF CMV DNA to undetectability. However, causality cannot be established because antiviral therapy and broader immune recovery were ongoing. This report provides limited tolerability information for PD-1 blockade under continued antiviral coverage and a low residual CSF CMV DNA burden.

Introduction

Cytomegalovirus (CMV) neurologic disease is an uncommon but potentially life-threatening complication of advanced HIV infection. Management is particularly challenging when profound cellular immunodeficiency coexists with hematologic malignancy and recent cytotoxic therapy, and evidence in this setting remains limited to guidelines, small studies, and case reports.^{1–4}

Programmed cell death protein 1 (PD-1) blockade may be considered for cancer control, but its use before complete resolution of an opportunistic central nervous system infection is poorly characterized. Existing literature provides only indirect evidence and does not define the virologic course or safety of treatment when low-level cerebrospinal fluid (CSF) CMV DNA remains detectable.^{5–8} We report a patient with HIV-associated Epstein–Barr virus-encoded RNA-positive diffuse large B-cell lymphoma who received sintilimab as individualized lymphoma consolidation during continued anti-CMV therapy, with longitudinal virologic, immunologic, and clinical assessment.

Case Presentation

A 57-year-old man presented with a neck mass, without fever, headache, altered consciousness, limb weakness, or visual impairment. In June 2024, he was concurrently diagnosed with HIV infection and stage IV diffuse large B-cell lymphoma (DLBCL), without bone marrow or CNS involvement. The lymphoma was positive for Epstein-Barr virus-encoded RNA by in situ hybridization. At diagnosis, the CD4⁺ T-cell count was 110 cells/ μ L and plasma HIV RNA was 232,000 copies/mL. ART with bictegravir/emtricitabine/tenofovir alafenamide was initiated promptly, and the patient received R-DA-EPOCH-based chemotherapy together with prophylactic intrathecal therapy. Complete remission was achieved in December 2024. Plasma HIV RNA declined rapidly and remained at a low level (48.1 copies/mL at the last follow-up), whereas CD4⁺ T-cell recovery was slow and the count remained below 100 cells/ μ L for a prolonged period (nadir, 73 cells/ μ L), indicating persistent severe cellular immunodeficiency. The overall clinical course is summarized in Fig. 1.

On August 29, 2024, plasma CMV DNA was 22,900 IU/mL and was undetectable on repeat testing on September 10 after ganciclovir-based therapy. On November 11, 2024, the patient was readmitted with fever, dizziness, and somnolence, and plasma CMV DNA had risen to 170,000 IU/mL. On November 21, plasma CMV DNA was 96,000 IU/mL, whereas CSF CMV DNA measured on the same day was 1.53×10^7 IU/mL, approximately 159-fold the paired plasma level. Available CSF biochemical results included a protein concentration of 0.59 g/L, glucose of 2.5 mmol/L, and chloride of 117 mmol/L. Dilated fundoscopic examination showed no CMV retinitis, and cranial magnetic resonance imaging showed lacunar infarction without radiographic evidence of encephalitis. Microbiologic testing for *Cryptococcus*, *Mycobacterium tuberculosis*, and other major CNS opportunistic pathogens was negative. Given the compatible neurologic syndrome, high-level CMV DNA in CSF, exclusion of major alternative CNS infections, and absence of CNS lymphoma involvement, probable CNS CMV disease was diagnosed. Long-term ganciclovir-based therapy was administered sequentially, including oral ganciclovir, oral valganciclovir, and intravenous ganciclovir at the intervals shown in Fig. 1. Foscarnet was administered intravenously at 3 g every 12 hours from November 13, 2024, through March 3, 2025, with dose adjustment according to renal function and tolerability.

Serial monitoring demonstrated discordant plasma and CSF CMV DNA kinetics (Fig. 2). CSF CMV DNA declined from 1.53×10^7 IU/mL on November 21, 2024, to 665 IU/mL on February 13, 2025, and further to 150 IU/mL on February 24, one day before the first sintilimab dose, but remained detectable. After

multidisciplinary review and informed consent, the patient received sintilimab 100 mg intravenously on February 25, March 27, and April 24, 2025, as individualized consolidation therapy for lymphoma. Monitoring of CMV virologic and immunologic variables was exploratory and was performed during treatment. After the November rebound, plasma CMV DNA was again documented as undetectable on March 4, 2025. CSF CMV DNA was first documented as undetectable on March 24 (day 27 after the first sintilimab dose) and remained undetectable on repeat lumbar punctures on April 22 and October 26, 2025. No CMV retinitis, recurrent neurologic symptoms, or other CMV end-organ disease was observed during follow-up.

Peripheral blood T-cell counts and phenotypes and CSF cytokine concentrations were monitored serially during sintilimab therapy (Fig. 3). After reaching a nadir before sintilimab, the absolute CD8⁺ T-cell count increased during subsequent follow-up (Fig. 3A). From D + 1 to D + 27, the proportion of effector CD8⁺ T cells increased and remained elevated at D + 58, whereas the effector-memory CD8⁺ T-cell proportion declined through D + 27 and showed a modest partial recovery by D + 58 (Fig. 3B). PD-1⁺ T-cell subsets showed subset-specific, non-monotonic changes (Fig. 3C): the CD3⁺PD-1⁺ and CD8⁺PD-1⁺ fractions decreased markedly by D + 7 and remained below D + 1 levels at D + 27, whereas the CD4⁺PD-1⁺ fraction declined later; all three subsets showed partial recovery by D + 58. In CSF, IFN-γ and IL-8 increased over time, IL-6 increased and then partially declined, and TNF-α remained low after D – 1 (Fig. 3D). Despite these immunologic changes, no clinical worsening of CMV disease, neurologic deterioration, or clinically significant inflammatory reaction was observed during follow-up.

Discussion

This case highlights three clinically relevant features: discordant plasma and CSF CMV DNA kinetics, the temporal sequence between sintilimab exposure and the first documented undetectable CSF CMV DNA result, and the absence of clinically apparent inflammatory worsening during PD-1 blockade. The compatible neurologic syndrome, high-level CSF CMV DNA, exclusion of major alternative CNS infections, and virologic response to anti-CMV therapy supported the diagnosis of probable CNS CMV disease. The CSF CMV DNA peak was markedly higher than the paired plasma level, and CSF CMV DNA remained detectable after plasma CMV DNA had transiently become undetectable, indicating delayed CNS virologic clearance. This difference is insufficient to establish virologic compartmentalization and may reflect differences in local viral replication and clearance, immune conditions, and CNS drug exposure. Serial quantitative CSF CMV DNA may therefore complement clinical assessment when CNS disease is suspected, although no validated CSF PCR threshold exists for treatment discontinuation.^{1,3,4}

Ganciclovir-based therapy with foscarnet coadministration reduced CSF CMV DNA from 1.53×10^7 IU/mL to 150 IU/mL, an approximately 5.0- $\log_{10}$ reduction, demonstrating a substantial antiviral effect before sintilimab was administered. An in vitro study showed that PD-1 blockade could partially restore T-cell function in Epstein-Barr virus-positive DLBCL, providing biological support—but not clinical efficacy evidence—for checkpoint blockade in this lymphoma subtype.⁹ Nevertheless, residual low-level CSF CMV DNA remained detectable one day before the first sintilimab dose and was first documented as

undetectable at D + 27. It remained undetectable on the available subsequent lumbar punctures, including the final examination on October 26, 2025, more than four months after oral ganciclovir had been discontinued. Although the sparse CSF sampling interval does not exclude transient fluctuations, this absence of documented rebound is compatible with durable virologic control after the final transition to undetectability. This temporal sequence, together with the concurrent immunophenotypic observations, raises the hypothesis that PD-1 blockade might have contributed to the final conversion of residual low-level CSF CMV DNA to undetectability. However, ganciclovir-based therapy remained ongoing, foscarnet continued through day 6 after the first sintilimab dose, and the observation occurred in the broader context of ART-related immune recovery, prior completion of chemotherapy, and ongoing lymphoma remission. The case therefore cannot establish whether sintilimab altered the pre-existing trajectory of viral decline.

The hypothesis is biologically plausible but remains indirect. PD-1 expression on CMV-specific CD4⁺ T cells has been associated with attenuated T helper 1 cytokine production, providing a rationale for considering whether checkpoint blockade might influence anti-CMV immunity.⁵ PD-1 blockade has also been explored in progressive multifocal leukoencephalopathy; in a small study, some patients had lower JC virus loads, enhanced virus-specific T-cell responses, and clinical improvement or stabilization, but responses were heterogeneous.⁶ These studies provide conceptual support for an immune-restorative mechanism but do not constitute direct evidence that PD-1 blockade promotes CMV clearance in the CNS.

The longitudinal immune findings should be regarded as hypothesis-generating. After reaching a nadir before sintilimab, the absolute CD8⁺ T-cell count increased during subsequent follow-up. In the more densely sampled subset analysis, the proportion of effector CD8⁺ T cells increased from D + 1 to D + 27 and remained elevated at D + 58, whereas the effector-memory CD8⁺ T-cell proportion declined through D + 27 and showed a modest partial recovery by D + 58. Taken together, these findings are compatible with dynamic remodeling of the peripheral CD8⁺ T-cell compartment, characterized by quantitative CD8⁺ recovery, early enrichment of an effector phenotype, and later partial re-equilibration of the effector-memory compartment. CMV-specific T-cell responses can occupy a substantial fraction of the memory compartment, and CMV-specific CD8⁺ T cells can exhibit differentiated effector phenotypes with persistent cytolytic features.^{10,11} In transplant cohorts, functional CMV-specific CD8⁺ T-cell responses have been associated with faster resolution of CMV viremia,¹² while ex vivo PD-1/PD-L pathway blockade has restored proliferation and cytokine responses in dysfunctional CMV-specific T cells.¹³ These observations are compatible with, but do not prove, expansion or functional reinvigoration of an antiviral CD8⁺ T-cell compartment during sintilimab therapy. Because CMV antigen specificity, degranulation, granzyme or perforin expression, direct cytotoxicity, and T-cell receptor clonality were not assessed, neither CMV-specific CTL expansion nor a causal antiviral effect of sintilimab can be established.

PD-1⁺ T-cell subsets also showed a subset-specific, non-monotonic trajectory during sintilimab therapy. The CD3⁺PD-1⁺ and CD8⁺PD-1⁺ fractions decreased early and remained below D + 1 levels at D + 27, whereas the CD4⁺PD-1⁺ fraction declined later; all three subsets showed partial recovery by D + 58. The early decline, occurring alongside enrichment of effector CD8⁺ T cells, may be compatible with an early shift away from a PD-1–high inhibitory phenotype and toward an effector-enriched circulating T-cell compartment. The subsequent partial recovery may reflect activation-associated PD-1 re-expression and re-establishment of homeostatic inhibitory feedback during later immune re-equilibration, rather than a simple reversal of the earlier response. PD-1 expression can be induced following T-cell activation, and proliferating effector-like PD-1⁺CD8⁺ T-cell responses have been observed after PD-1-targeted therapy.^{14,15} However, the first measurement was obtained at D + 1 rather than before treatment, and the assay quantified the proportion of PD-1-positive cells rather than receptor-expression intensity. These observations therefore support dynamic PD-1-related phenotypic remodeling but do not establish direct pharmacologic downregulation, subsequent restoration of PD-1 expression, or CMV-specific functional reinvigoration.

Concurrent CSF cytokine changes suggested a nonuniform pattern of local immune activation: IFN- γ and IL-8 increased over time, IL-6 rose and then partially declined, whereas TNF- α remained low after D – 1. These cytokines are not CMV antigen-specific, and several measurements were obtained at or after the first documented undetectable result; they should therefore be considered accompanying immune signals rather than direct evidence of viral clearance.^{16,17} Importantly, the cellular and biochemical immune changes were not accompanied by worsening neurologic symptoms, progression of CMV disease, or a clinically significant inflammatory syndrome. This combination is compatible with controlled immune activation during the final transition of residual CSF CMV DNA to undetectability, although the respective contributions of sintilimab, ongoing antiviral therapy, ART-related immune recovery, and lymphoma remission cannot be separated.

Taken together, the virologic course, peripheral CD8⁺ T-cell remodeling, non-monotonic PD-1⁺ T-cell dynamics, and selective CSF cytokine activation without overt inflammatory worsening form a coherent, hypothesis-generating pattern of immune adaptation during sintilimab therapy. This pattern may have contributed to the final control of residual low-level CNS CMV, but it cannot distinguish an independent effect of PD-1 blockade from the continuing effects of antiviral treatment and broader immune recovery. Immune checkpoint blockade may exert bidirectional effects in the setting of opportunistic infections. CMV infection and CMV disease have been reported during immune checkpoint inhibitor therapy, particularly in patients receiving corticosteroids or other immunosuppressive agents for immune-related adverse events; the respective contributions of the checkpoint inhibitor, underlying malignancy, and subsequent immunosuppression are often difficult to disentangle.⁷ Early clinical studies have shown an acceptable safety profile of PD-1 blockade in selected ART-treated people with HIV and cancer, generally with CD4⁺ T-cell counts of at least 100 cells/ μ L, but these data do not address active CNS CMV disease or prolonged CD4⁺ T-cell counts below 100 cells/ μ L.⁸ In the present case, sintilimab was administered while CSF CMV DNA remained detectable at 150 IU/mL, under continued antiviral

coverage, without subsequent clinical worsening of CMV disease, neurologic deterioration, or a clinically significant inflammatory syndrome. This observation provides case-level tolerability information for a low residual viral burden under effective antiviral therapy, but it cannot be extrapolated to uncontrolled or high-viral-load CNS CMV disease.

This report has several limitations. It describes a single uncontrolled case and therefore cannot support reliable causal inference. CSF was not sampled between the low-level positive result on February 24, 2025, and the first undetectable result on March 24, 2025, precluding determination of the precise date of conversion to undetectability or calculation of a post-sintilimab viral decline slope. Ongoing antiviral therapy, ART-related immune recovery, prior completion of chemotherapy, and lymphoma remission were substantial confounders. The diagnosis was probable rather than histopathologically confirmed, and magnetic resonance imaging did not show typical encephalitic changes. The peripheral immunophenotype lacked a true pretreatment baseline. The first PD-1 measurement was obtained at D + 1, and the assay quantified PD-1-positive fractions rather than receptor-expression intensity. CMV antigen-specific T-cell function, proliferative activity, activation markers, direct cytotoxicity, and T-cell receptor clonal expansion were not assessed.

In summary, CSF CMV DNA declined progressively during prolonged anti-CMV therapy and remained detectable at 150 IU/mL one day before the first sintilimab dose; it was first documented as undetectable 27 days later. This interval coincided with transient peripheral T-cell phenotypic changes and dynamic CSF cytokine responses. The overall virologic response was primarily attributable to antiviral therapy. These temporal and immunologic observations generate the hypothesis that PD-1 blockade may have contributed to the final conversion of residual low-level CSF CMV DNA to undetectability; however, its independent contribution requires evaluation in studies incorporating standardized pretreatment baselines, CMV-specific immune endpoints, more frequent CSF sampling, and appropriate controls.

Declarations

Ethics approval and consent to participate

In this study, the patient was informed about the survey, and he fully agreed to share his previous medical records and treatment history.

Consent for publication

Written informed consent was obtained from the patient.

Competing interests

The authors declare no competing interests.

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Author Contribution

BD, KW and XP wrote the main manuscript text and YY prepared figures 1-3. All authors reviewed the manuscript

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Figures

Figure 1. Clinical course and treatment timeline

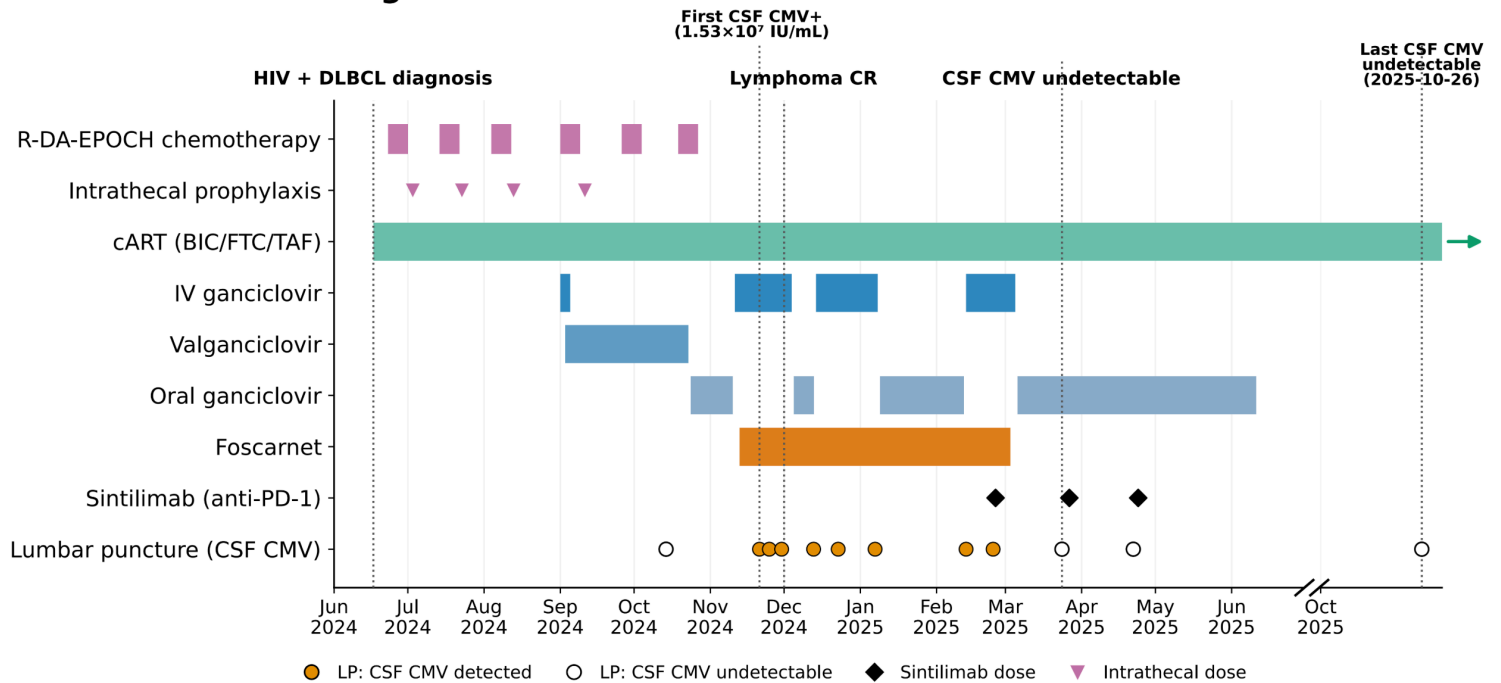


Figure 1

Clinical course and treatment timeline. Swim lanes show R-DA-EPOCH chemotherapy cycles, intrathecal prophylaxis, combination antiretroviral therapy with bictegravir/emtricitabine/tenofovir alafenamide, intravenous ganciclovir, valganciclovir, oral ganciclovir, foscarnet, sintilimab doses, and lumbar puncture results. Filled circles indicate detectable CSF CMV DNA, and open circles indicate undetectable CSF CMV DNA. Dotted vertical lines mark key clinical and virologic milestones. A broken x-axis compresses the interval between June and October 2025; cART continued throughout the omitted interval, whereas oral ganciclovir ended on June 11, 2025. CSF CMV DNA was first documented as undetectable on March 24, 2025, and remained undetectable at the last documented lumbar puncture on October 26, 2025.

Figure 2. Plasma versus CSF CMV DNA kinetics

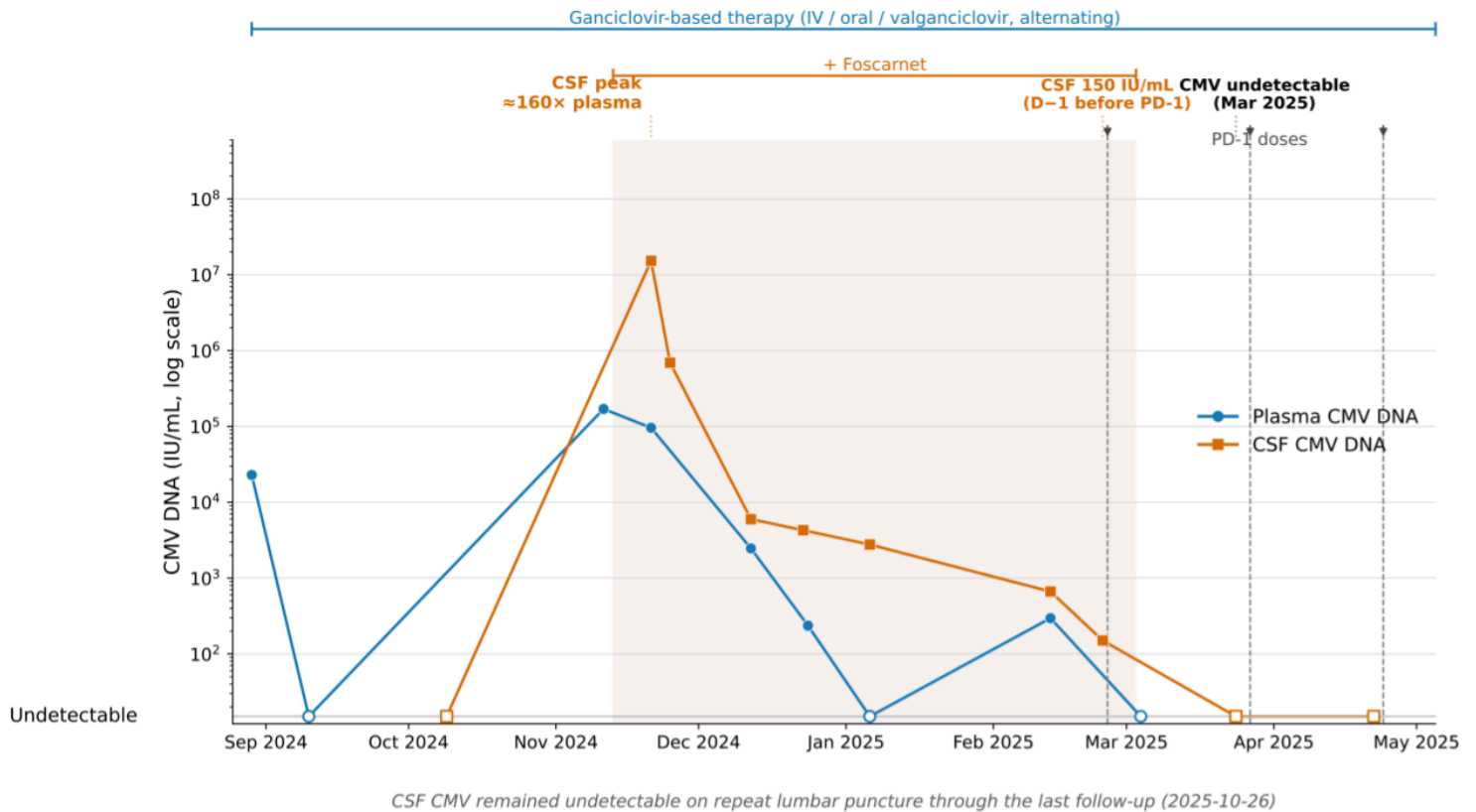


Figure 2

Plasma versus CSF CMV DNA kinetics (log scale, IU/mL). The CSF peak was $\sim 160\times$ the contemporaneous plasma value. Under prolonged ganciclovir-based therapy plus foscarnet, plasma CMV DNA initially became undetectable, subsequently rebounded, and then declined again, whereas CSF CMV declined more slowly (150 IU/mL before the first PD-1 dose) and became undetectable during the sintilimab treatment period, remaining undetectable on repeat lumbar puncture through 2025-10-26.

Figure 3. Longitudinal immune and virologic dynamics

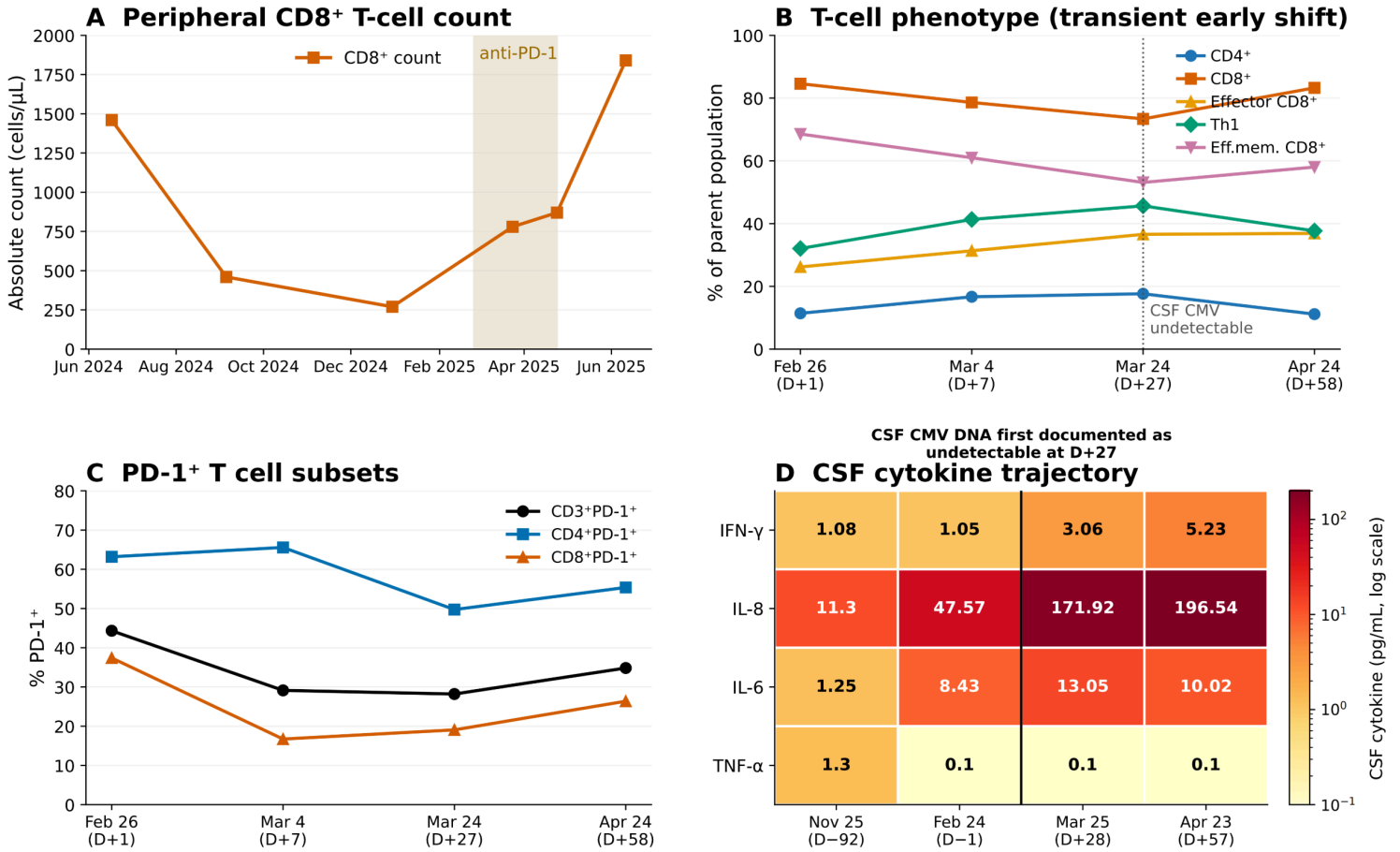


Figure 3

Longitudinal immune and virologic dynamics. (A) Absolute peripheral CD8⁺ T-cell counts during the peri- and post-sintilimab period. The shaded region indicates the sintilimab treatment interval. (B) Longitudinal peripheral T-cell phenotypes, including CD4⁺, CD8⁺, effector CD8⁺, effector-memory CD8⁺, and T helper 1 cell proportions, measured from D+1 to D+58 after the first sintilimab dose. The dotted vertical line marks D+27, when CSF CMV DNA was first documented as undetectable. (C) Subset-specific longitudinal changes in CD3⁺PD-1⁺, CD4⁺PD-1⁺, and CD8⁺PD-1⁺ T-cell proportions. CD3⁺PD-1⁺ and CD8⁺PD-1⁺ fractions decreased early, whereas CD4⁺PD-1⁺ declined later; all three subsets showed partial recovery by D+58. The pattern is presented as an exploratory measure of PD-1-related immune remodeling during sintilimab therapy.