Thirdly, Naccarato *et al.* [1] pointed out that, according to their single-case experience, the combination of dolutegravir and metformin should be avoided in elderly patients with sub-optimal renal function. However, looking at their Table 1, the patient had serum creatinine concentrations ranging from 65 to 70 μmol/l (0.7–0.8 mg/L), thus hardly reflecting the presence of a clinically relevant kidney dysfunction. Remarkably, three out of the 15 patients in our cohort who are more than 65 years old and with serum creatinine concentrations ranging from 83 to 143 μmol/l (0.9–1.63 mg/l) showed an optimal tolerability to dolutegravir with metformin therapy. These results are in line with those by Masich *et al.* [5] reporting no cases of lactic acidosis in patients treated with this drug combination.

Therefore, for all that detailed above, we believe that the DDI-based mechanism proposed by the authors for the observed episode of hyperlactatemia is not sustainable either from pharmacokinetic, pharmacodynamic and clinical viewpoints. Unfortunately, the lack of detailed information on the clinical status immediately before the first episode of hyperlactatemia and for the first 2 weeks after the second episode did preclude the identification of the real triggering event (i.e. acute renal failure? Dehydration? Other acute events?).

In conclusion, we agree with Naccarato *et al.* [1] on the importance that physicians continue to monitor, as per clinical practice, HIV-infected patients on metformin who start (or stop) dolutegravir. However, at the same time, we believe that a priori suggestions such as to 'limit the daily dose of metformin' or 'avoid the combined use of metformin and dolutegravir' may provide misleading information for clinicians, eventually leading to suboptimal blood glycemic control in subset of patients treated with this drug combination. In the era of precision medicine, personalized strategies should be advocated instead of 'one-size fits all approaches'.

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Conflicts of interest

There are no conflicts of interest.

Dario Cattaneo[a,b], Chiara Resnati[c], Giuliano Rizzardini[c,d] and Cristina Gervasoni[b,c], *[a]Unit of Clinical Pharmacology, ASST Fatebenefratelli Sacco University Hospital, [b]Gestione Ambulatoriale Politerapie (GAP) Outpatient Clinic, ASST Fatebenefratelli Sacco, [c]Department of Infectious Diseases, ASST Fatebenefratelli Sacco University Hospital, Milan, Italy, and [d]Faculty of Health Science, School of Clinical Medicine, University of the Witwatersrand, Johannesburg, South Africa.*

Correspondence to Cristina Gervasoni, MD, Department of Infectious Diseases, ASST Fatebenefratelli Sacco University Hospital, Via GB Grassi 74, 20157 Milan, Italy.
E mail: cristina.gervasoni@unimi.it

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Cytomegalovirus encephalitis in the post-HAART era: is there a gold standard for treatment?

Reports of cytomegalovirus (CMV) encephalitis in the post-HAART era have rarely been described in the literature [1,2]. Today, this infection presents in HIV patients who have not initiated or had bad adherence to antiretroviral therapy (ART). Treatments regimens tend to be based on little clinical experience from the pre-HAART era [3–5].

A 32-year-old Caucasian man with HIV infection and no adherence to ART was admitted with fever and dyspnea. He was diagnosed with pnemocystis pneumonia. Despite treatment, he progressed to severe respiratory insufficiency, requiring noninvasive mechanical ventilation. During week 1 of hospitalization, he reported cephalea and diplopia. Brain MRI, cerebrospinal fluid (CSF), and

fundoscopy found no abnormalities. Microbiologic cultures were negative. The patient progressed to a worsening level of consciousness, reaching obtundation, and a multidirectional nystagmus was detected. Follow-up brain MRI showed a diffuse linear increase of fluid attenuation inversion recovery (FLAIR) signal on the ependymal surface (Fig. 1). New CSF analysis showed a white blood count of 20 cells/mm^3 with 41% mononuclear cells, protein level of 83 mg/dl, glucose 34 mg/dl, and a positive qualitative CMV PCR. CMV blood viral load was 7890 IU/ml (log 3.90).

Diagnosis of CMV-associated ventriculitis was performed, and induction doses of ganciclovir (GCV) were initiated. After 5 days of treatment, he presented bilateral facial paralysis and left VI cranial nerve palsy. Blood CMV viral load was 5620 IU/ml (log 3.75). As a result of clinical deterioration and limited viral load decrease, a combined therapy with foscarnet 90 mg/kg per dose, twice daily was added. By the fifth day of combined therapy, the patient showed clinical improvement, decreasing nystagmus, and a recovering consciousness. CMV viral load was 577 IU/ml (log 2.76). Brain MRI displayed less ventricular and ependymal enhancement. CSF analysis showed a negative CMV PCR. Because of patient improvement and negative CMV PCR on CSF, foscarnet was discontinued, completing 18 days of combined therapy. A GCV-resistance study (with 18 mutations in codons 440–645) was performed. Results were negative for mutations. ART was started on day 18 of CMV therapy. Maintenance treatment with oral valgancyclovir was initiated after 37 days of GCV therapy. Upon being discharged from the hospital, the patient was alert, with mild attention deficit, minor nystagmus, and recovering facial paralysis. Four months after discharge, valganciclovir was discontinued with a negative blood CMV viral load. Twenty months after discharge, the patient was in good neurological condition, only showing secuelar diplopia. HIV and CMV viral load have been undetectable during follow-up.

Reports of CMV encephalitis are uncommon. The infection presented more frequently in the pre-HAART era because AIDS-associated CMV encephalitis occurs almost exclusively in patients with $CD4^+$ counts less than 50 cells/μl [1,7]. Currently, HIV patients at the highest risk of developing this infection are those who have no access to medication, or are poorly compliant with ART [7].

CMV encephalitis presents clinically as rhomboencephalitis, exhibiting rapidly progressive encephalopathy and in some cases cranial nerve palsies and seizures [1,2,8,9]. The most frequently reported pattern in brain MRI is periventricular enhancement with or without ventriculomegaly [1,9].

Treatment of CMV encephalitis is difficult, and reports show multiple therapeutic failures. This could be explained by previously irreversible neurological damage caused by CMV and by poor antiviral diffusion in the CNS [3]. Treatment consists of GCV or foscarnet, and is based on only a few case reports. GCV is the first-line treatment; however, in case of poor response, foscarnet could be supplemented because of their synergistic action inhibiting CMV replication [3,11]. As GCV is a highly polar molecule, the drug has poor permeability across biologic membranes [12], unlike foscarnet, that has a good penetration in both retinal and brain tissues [13]. Duration of treatment is not well defined, but, in immunocompromised patients, it frequently requires long-term use of antiviral agents [14], and it should be considered the same duration as retinitis or until symptoms resolve and CMV replication clears [15].

Almost all previous reports were published before the HAART era [3–5]. All cases reported high mortality rate, even in the presence of anti-CMV therapy. In the post-HAART era, there are very few reports, one with clinical improvement [2]. It seems that ART is the most significant strategy in the treatment of CMV disease.

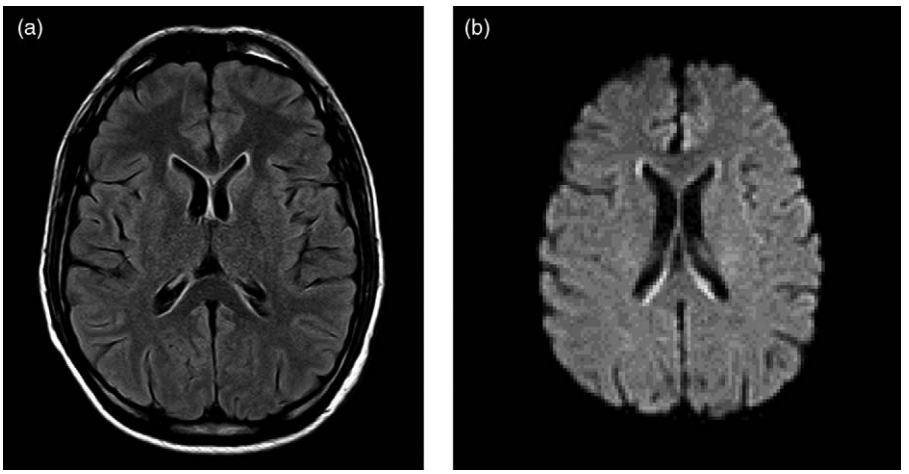

Fig. 1. Cerebral MRI: diffuse linear signal increase of the ependymal surface of third, fourth, and both lateral ventricles on FLAIR (a) and DWI (b). FLAIR, fluid attenuation inversion recovery; DWI, diffusion weighted imaging.

Immune reconstitution from ART results in a significant decline in CMV viremia, perhaps even in the absence of anti-CMV therapy [6,10].

In conclusion, cases of CMV encephalitis in the post-HAART era are uncommon. It usually presents as rhomboencephalitis and CNS images could be very useful. This patient was successfully treated after combined therapy with GCV and foscarnet. Withstanding control of this infection is only possible after immune reconstitution is achieved with ART.

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Maria E. Ceballos[a], Ignacio Rodriguez[a], Patricio Sandoval[b], Eduardo Abbot[c] and Jaime Labarca[a], *[a]Department of Infectious Diseases, [b]Department of Neurology, and [c]Department of Internal Medicine, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile.*

Correspondence to Jaime Labarca, MD, Department of Infectious Diseases, School of Medicine, Pontificia Universidad Católica de Chile, Diagonal Paraguay 362, 6th floor, Santiago, Chile. Tel: +56 223543508; e-mail: jlabarca@med.puc.cl

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