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HIV cure strategies: response to ignore the central nervous system at your patients' peril

We read with interest the recent article published in *AIDS* by Gama *et al*. [1], highlighting evidence for a significant central nervous system (CNS) reservoir in simian immunodeficiency virus macaque models despite effective long-term peripheral viral suppression by antiretroviral therapy. This was followed by an informative editorial by Spector and Rappaport [2], cautioning those involved in HIV cure research not to overlook this important viral reservoir. Future cure strategies, which test the impact of interventions on measures of viral reservoir in peripheral body compartments, may not assume that they have the same efficacy in the CNS and thereby mitigate the effectiveness of HIV cure interventions.

Although we acknowledge and fully agree with this potential lack of efficacy for HIV cure strategies if sanctuary sites are overlooked, we would like to highlight additional potential perils facing HIV cure strategists with respect to the CNS; namely adverse CNS outcomes that may include toxicities of HIV cure therapies, direct immune-mediated CNS pathogenesis or the impact of viral reactivation on the brain [3].

Mechanisms of negative outcomes on the CNS and neuronal tissue due to cure strategies could include, first, adverse effects on brain function secondary to the removal or elimination of latently infected neuronal cells with crucial function for brain health, such as microglial cells and astrocytes [4]. Second, neuronal damage from either drug utilized during cure research strategies or neuronal damage from viral proteins, the expression of which may be upregulated during cure treatments. An example being the gene upregulation resulting from histone deacetylase (HDAC) inhibitor use. Finally, a further adverse outcome, which could be a catastrophic event, is immune reconstitution inflammatory syndromes occurring in the CNS compartment. This could occur due to cytokine storms caused by immunotherapeutic agents modifying neuroinflammatory responses, or immune activation following viral rebound and blips caused by HDAC inhibitors (and similar agents) or viral rebounds associated with antiretroviral treatment interruptions. Cases of HIV encephalopathy associated with viral rebound and cerebrospinal fluid viral escape are well described in the literature [5]. In addition, cure approaches that include the use of therapeutic HIV vaccines that induce HIV-specific $CD8^+$ cytotoxic cells have the potential to trigger $CD8^+$-mediated encephalitis [6].

To date and to our knowledge, no significant adverse effects on CNS function have been observed in HIV cure trials, but limited data are available. One small study has reported on the effects of HIV-latency-reversing agents on CNS parameters in HIV-positive participants with no adverse impact on cerebrospinal-fluid neuroinflammatory or degenerative soluble biomarkers observed [7]. Such results are reassuring. However, one should be weary of the results from other fields such as cancer studies, from which some of the agents used in HIV cure strategies originate. The syndrome of chemotherapy-related cognitive dysfunction or 'chemobrain' is being increasingly recognized with the use of modern oncological treatments, although the pathophysiology of this condition remains elusive [8].

For HIV cure strategists and researchers, consideration of and monitoring for CNS adverse events within HIV cure studies will be crucial. Monitoring for CNS adverse events is challenging given the closed anatomical sanctuary site of the brain and the complexity of monitoring nervous system function. Brain biopsies are clearly not possible, and repeated cerebrospinal fluid examinations are costly and not practical for every study. However, monitoring clinical parameters such as cognitive function and patient-related outcome measures of cognitive health, coupled with the monitoring of sensitive peripheral markers of neuronal integrity, such as highly sensitive plasma neurofilament light protein [9], and noninvasive neuroimaging could be practical approaches to consider.

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Conflicts of interest

There are no conflicts of interest.

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Dolutegravir plasma levels after gastric bypass surgery

With successful combined antiretroviral therapy, HIV-infected individuals are increasingly overweight or obese at a rate similar to the general population [1]. As a consequence, bariatric surgery is also performed in HIV-infected individuals to obtain long-term weight loss and thereby prevent complications such as diabetes and cardiovascular diseases. Gastric bypass surgery is currently considered as the best treatment option for morbid obesity in international guidelines for the general obese population [2]. The Roux-en-Y gastric bypass is a common procedure consisting of creating a small portion of the stomach and attaching it directly to the small intestine, thereby causing a substantial amount of food to bypass the stomach and the upper intestine and not be absorbed [3]. As a consequence, this procedure has also the potential to alter the absorption of drugs which, in the case of antiretroviral drugs, can have deleterious implications on the virological suppression. Thus, the measurement of antiretroviral drug levels is of utmost importance to characterize the impact of bariatric surgery on antiretroviral drug absorption and thereby provide guidance on how to adjust dosage to maintain optimal antiretroviral drug coverage.

We report four HIV-infected patients undergoing gastric bypass surgery. In three patients, HIV primary infection occurred 6 months or 3 years after the surgery and, in the fourth patient, HIV infection was already present before the procedure. It was decided to treat all four patients with dolutegravir (DTG) due to its high antiviral potency, good tolerability and rapid intestinal absorption [4]. DTG was combined with abacavir/lamivudine in two patients and with tenofovir/emtricitabine in the other two. DTG levels were quantified by liquid chromatography coupled with tandem mass spectrometry using an adaptation of a previously published method [5].

Overall, 17 DTG plasma levels were measured in four patients at different time points after drug intake. Patient 1 was initiated on DTG 50 mg once daily, but his viral decay was slower than expected despite acceptable DTG levels and therefore he subsequently received DTG 50 mg twice daily (BID) for 7 months. Patient 1 achieved viral suppression and was definitively switched back to DTG 50 mg once daily. Patients 2 and 3, who directly started DTG at 50 mg once daily, achieved DTG levels that were in the expected range of DTG concentrations for once daily administration and therefore were able to continue this drug schedule. Finally patient 4, who acquired HIV infection before the bariatric surgery, was started on DTG 50 mg once daily. DTG level measured 2 weeks after the procedure was 0.5 μg/ml 11.5 h after drug intake. Given the risk of suboptimal drug coverage at the end of the dosing interval, DTG was increased to 50 mg BID. The subsequent DTG level under BID schedule (2 months postsurgery) was good, and therefore it was decided to lower DTG to 50 mg once daily, which allowed repeatedly optimal DTG levels to be achieved thereafter (Fig. 1). Durable viral suppression was achieved in all four patients.

The current report describes for the first time DTG levels in patients with gastric bypass. Our observations show reassuringly that patients with gastric bypass achieve in the long term DTG levels well above the concentration inhibiting viral replication by 90% (IC_{90}) [6] and mostly