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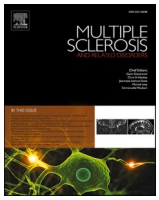

Editorial

In the era of antiviral trials for MS, the answer lies in the details

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After a seminal epidemiological study linked infection with the Epstein-Barr virus (EBV) to multiple sclerosis (MS), there is a consensus that EBV is the primary cause of MS (Bjornevik et al., 2022). Now, the question remains: How does EBV lead to MS, given that the majority of infected individuals do not develop the disease? Hypotheses addressing this question can be divided into two groups: (1) EBV acts as a trigger of self-perpetuating autoimmunity, or (2) EBV acts as a driver of MS pathology (Sollid, 2022). If EBV is solely a trigger, vaccination strategies to prevent EBV infection may lower the incidence of MS; however, these interventions would not be helpful after an MS diagnosis. On the other hand, if EBV is a driver of MS, then targeting EBV using antiviral therapies could reduce disease activity in patients with established MS. In this issue, we present three compelling case reports of MS patients treated with prodrugs of tenofovir, a nucleotide analogue that inhibits the EBV DNA polymerase (Drosu et al., 2020). These cases have important clinical implications, as they provide insights on whether EBV may act as a driver in MS and how EBV can be targeted in future trials.

To review the cases briefly, the first Torkildsen et al. (2024) is an update to a case previously published by the authors (Torkildsen et al., 2020). It involves a patient with highly active relapsing-remitting MS (RRMS) and HIV, whose MS symptoms improved on tenofovir prodrugs and who remained radiologically stable on tenofovir alafenamide. When the patient's HIV therapy was switched to a new regimen not containing tenofovir, there was a rapid recurrence of new MRI lesions and a clinical relapse. The second case Drosu et al. (2024) involves a patient with RRMS who had a significant burden of disease at diagnosis. Despite two relapses and clinical decline while on fingolimod, her symptoms improved after stopping fingolimod and starting treatment with tenofovir prodrugs for HIV. She has unexpectedly remained clinically and radiologically stable for nearly a decade. The third case Drosu and Levy (2024) is also an update to a prior publication from 2018 (Drosu et al., 2018). An HIV-negative patient with aggressive RRMS improved on lamivudine/zidovudine (Combivir), a drug with known anti-EBV activity. When the medication was interrupted, the patient experienced new disease activity and recurrence of MS symptoms. After starting pre-exposure prophylaxis with a tenofovir-based regimen, the patient has been clinically and radiologically stable for four years.

Evidence from epidemiological studies suggests that the risk of MS is lower in patients with a diagnosis of HIV (Gold et al., 2015). This includes findings from a recent, large registry-based study where being HIV positive was associated with nearly half the risk of MS compared to those not HIV positive (McKay et al., 2023). The key question that these studies raise is whether it is HIV itself or the treatment of HIV that modifies the disease course in MS. Interestingly, the reduction in MS risk in the latter study was observed even when the virus was suppressed by antiretroviral treatment, hinting that HIV treatment may lower the expected incidence of MS by reducing disease activity (McKay et al., 2023). The case reports in this issue provide additional support for the hypothesis that selective HIV drugs with anti-EBV activity may contribute to this observed effect and, therefore, that targeting EBV after a diagnosis of MS may open new avenues for treatment.

However, the success of EBV treatment strategies depends on the pathogenic mechanisms of the disease, which have yet to be elucidated. Recently, the EMBOLD trial (NCT03283826), a Phase II placebo-controlled trial of T-cells targeting EBV latent antigens, failed to reach its primary endpoint in progressive MS. However, a previous Phase I open-label study showed that over 25.5 patient-years, 16 out of 26 MRIs (62 %) revealed new lesions, and 100 % of the participants who completed the 3-year follow-up had at least one new lesion (Ioannides et al., 2021). Early signals for high MRI disease activity, as was observed, should not be discounted because this lowers the likelihood of subsequent positive trial results and may predict that certain treatment strategies targeting EBV will be ineffective. Previous placebo-controlled trials using acyclovir and valacyclovir in RRMS did not reach statistical significance, but there was a modest trend toward benefit in the treatment groups for annualized relapse rate (ARR) and MRI disease activity (Lycke, 2017). Prodrugs of tenofovir are different not only because they are more potent against EBV but also because their metabolism is independent of viral enzymes (Drosu et al., 2020). This unique feature may prove critical to efficacy in MS if the pathogenic process depends on

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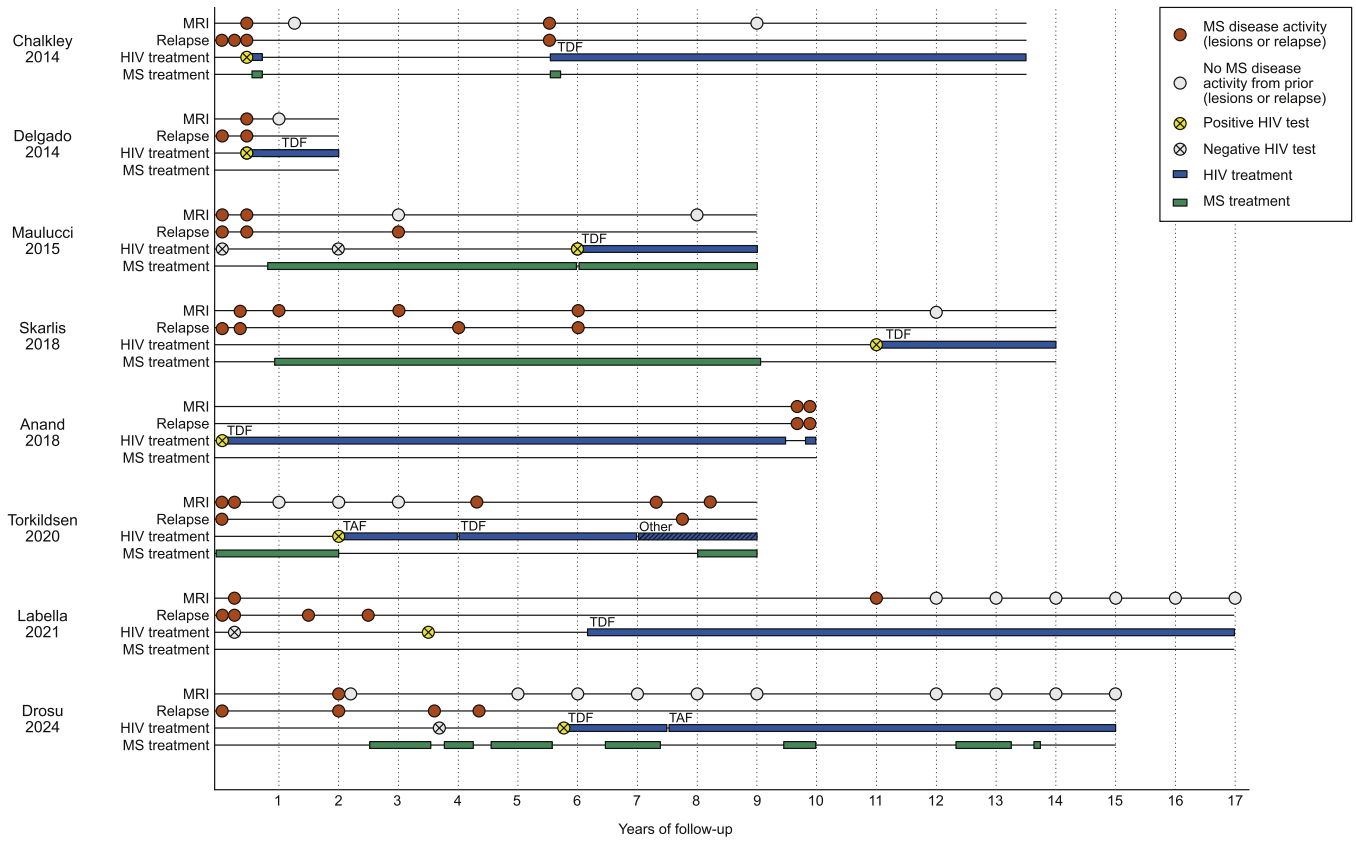

Fig. 1. Case reports of patients with HIV and MS treated with prodrugs of tenofovir. Timelines of case reports published in the literature of patients with HIV and MS on a HAART regimen containing prodrugs of tenofovir (tenofovir disoproxil [TDF] or tenofovir alafenamide[TAF]).

preventing viral antigen presentation rather than preventing viral infection of new cells.

Since there is limited knowledge about how EBV causes MS and a lack of relevant EBV biomarkers, using an approach that starts from clinical observations to guide scientific methods may be useful in developing strategies to target EBV in MS. In retrospect, outcomes of Phase III trials evaluating anti-CD20 monoclonal antibodies (Hauser et al., 2017; Montalban et al., 2017) were largely predictable from early case reports of patients treated with rituximab, including the dramatic effects on MRI lesions and relapses, with less significant benefits for progressive MS (Stüve et al., 2005; Petereit et al., 2008; von Büdingen et al., 2017).

In light of this, we undertook a review of all prior cases of MS patients who were treated with tenofovir prodrugs. A comprehensive list of these cases is provided in Fig. 1 (Anand and Saylor, 2018; Chalkley and Berger, 2014; Delgado et al., 2014; Drosu et al., 2024; Labella et al., 2021; Maulucci et al., 2015; Skarlis et al., 2018; Torkildsen et al., 2020, 2024). In the approximate 40.5 person-years of cumulative exposure to tenofovir prodrugs in people treated for at least three months after a confirmed MS diagnosis, only 2 of the 21 MRIs (10 %) revealed new lesions, and no new relapses were observed (ARR <0.025). Before initiation of tenofovir prodrugs, 13 out of 19 MRIs (68 %) revealed new lesions, and 22 relapses occurred during approximately 37 person-years (ARR 0.6). The increased MS disease activity one patient experienced after switching to a tenofovir-free HIV regimen Torkildsen et al. (2024) and the new disease activity another patient experienced five years after HIV diagnosis, but before starting tenofovir (Chalkley and Berger, 2014), hint that the difference may be attributed to tenofovir prodrugs rather than to HIV. No cases reported disease progression, with most showing at least partial symptomatic improvement of MS after starting treatment with tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF). While existing drugs are clearly not completely effective, doses used for the treatment of HIV are likely too low for EBV. Future approaches may build on tenofovir prodrugs but should pay careful attention to dosing studies.

Evidence from these collective cases suggests that antivirals targeting the EBV DNA polymerase, like tenofovir prodrugs, may control disease activity in MS. When examined as a group, these reports also strongly imply that MRI disease activity and clinical relapses in early MS should be the primary endpoints for a trial evaluating whether EBV acts as a driver of MS. Rigorously conducted trials are now needed to provide more definitive evidence, which will be critical for addressing key questions and advancing the understanding and management of MS.

Declaration of competing interest

None.

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