



## Correspondence

## Tenofvir as a treatment option for multiple sclerosis



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## SUMMARY

Some antiretroviral medications are also inhibitors of EBV. We describe a patient with highly active MS who was infected with HIV and started HIV-treatment containing tenofvir alafenamide (TAF), a potent inhibitor of EBV lytic reactivation. Her MS was in complete remission during this treatment, and she had new radiological disease activity again after switching to tenofvir disoproxil fumarate, a HIV drug with less potent activity against EBV replication. Based on the recently detected mechanism of TDF and TAF, we suggest that further studies on these drugs in MS are warranted.

## 1. Introduction

We read with great interest two recent publications by Drosu et al. (Drosu et al., 2018, 2020). In the first article, the authors described a case report of one patient with multiple sclerosis (MS) treated by antiretroviral therapy (Drosu et al., 2018). In the second, they demonstrated that the antiretroviral medications tenofvir disoproxil fumarate (TDF) and tenofvir alafenamide (TAF) are potent inhibitors of EBV lytic reactivation, raising the question whether these drugs could be a treatment option for EBV associated diseases (Drosu et al., 2020).

One disease that has consistently been linked to EBV infection is MS (Abrahamyan et al., 2020; Levin et al., 2010). Further, anti-CD20 monoclonal antibody therapies are highly effective (Hauser et al., 2017), and one of the proposed mechanisms of therapeutic action is through eradication of EBV infected B-cells (Bar-Or et al., 2020).

Following these publications, we identified one highly interesting Norwegian MS-patient in the clinic of one of the authors.

## 2. Case report

The patient is a 34-year-old woman with relapsing-remitting (RR) MS. She was referred to neurological examination in 2015, after an episode of left facial paralysis and numbness in the right leg and truncus. A full neurological evaluation was performed. Her visual evoked potential (VEP) was delayed on both sides, consistent with subclinical optical neuritis. Her brain MRI showed multiple T2- and gadolinium enhancing lesions consistent with MS, and she had oligoclonal bands in her cerebrospinal fluid. She was subsequently diagnosed with RR-MS. It was concluded that she probably experienced her first MS-symptom in 2002 in the form of diplopia.

Based on a high number of MRI T2- and gadolinium enhancing lesions, her MS-disease was considered to be highly active, and she started disease-modifying therapy with fingolimod after the initial diagnosis. A new MRI was performed three weeks after initiation of fingolimod, showing new gadolinium enhancing lesions, but after about three months of fingolimod treatment, she was clinically stable, with no new relapses in the following two years. Her MRI was also stable with no new MRI-lesions detected in 2015, 2016, and 2017. Still, her MS symptoms persisted, especially fatigue and neuropathic pain.

She was diagnosed with HIV in 2017. Her lymphocyte count was then  $2.8 \times 10^9/l$  (lymphocytes  $0.4 \times 10^9/l$ , CD4  $0.02 \times 10^9/l$ , CD4/CD8 ratio of 0.05 and 27,000 copies of HIV RNA/ml). Her initial HIV-treatment was an integrase strand transfer inhibitor (INSTI) based single-tablet regimen with three active agents consisting of a combination of elvitegravir, cobicistat, emtricitabine, and TAF. The HIV-treatment was successful, and in January 2018, her CD 4 levels were  $1.06 \times 10^9/l$  and the CD4/CD8 ratio was 1.06, with no detectable copies of HIV RNA/ml.

After the HIV-infection was discovered, her neurologist decided to stop treatment with fingolimod. This was done to avoid a potential increased risk of infectious side effects due to the combination of HIV and the immunosuppressive effect of fingolimod. Discontinuation of fingolimod is frequently associated with rebound-disease activity, but our patient was stable without new disease activity. A new MRI was performed in 2017, three months after stopping fingolimod, and further in 2018, without signs of new T2-lesions. Thus, she was stable during the following two consecutive years without any MS-treatment, with no MS-relapses, MRI-activity, or disability progression. Following the initiation of HIV-therapy, her MS-symptoms that she had experienced since 2015, unexpectedly also resolved. She especially experienced less neuropathic pain, a symptom that commonly persists in MS patients, even after initiation of disease-modifying therapy.

As the patient was planning a pregnancy in 2019, the INSTI regimen was changed to a two-tablet regimen containing raltegravir, emtricitabine, and TDF. A new MRI-scan was performed four months after the switch of HIV medication, showing one new gadolinium-enhancing lesion, a sign of new MRI disease activity occurring during the last months. Except for this single gadolinium-enhancing lesion, her MRI remained stable. Her clinical status has been unchanged after switching treatment, and she has not experienced new relapses or disability worsening. She did not become pregnant during the follow-up period and has continued with the two-tablet regime until now, without any additional disease-modifying therapy for her MS. She has still less MS-related symptoms than when she used fingolimod.

## 3. Discussion

Studies on antiviral agents have previously been carried out in MS

(Bech et al., 2002; Friedman et al., 2005; Lycke et al., 1996). There have also been some case reports of potential effects of antiretroviral treatments (Drosu et al., 2018), but we have not found previously published cases of MS being successfully resolved by a combination of elvitegravir, cobicistat, emtricitabine, and TAF. Given its potent effect against EBV reactivation, one could speculate that TAF was the main cause of the potential effect in MS. It is, however, also possible that the boosting effect of cobicistat or elvitegravir could have contributed.

The intracellular drug concentrations reached on TAF are higher than on TDF (Drosu et al., 2020). Thus, negative results in earlier studies on antiviral medications could have been influenced by their low efficacy against EBV reactivation. Still, as an HIV infection in itself is associated with a significantly decreased risk of developing MS (Gold et al., 2015), it is uncertain whether our observations reflect immunosuppression induced by chronic HIV infection or antiretroviral medications. Our findings appear, however, to corroborate an earlier report that chronic MS-symptoms, like fatigue and pain, may be relieved by antiretroviral treatment (Drosu et al., 2018).

#### 4. Conclusion

Our patient with a highly active MS disease was in complete remission during a combination treatment containing TAF, and had new radiological disease activity again after switching to an HIV drug with less potent activity against EBV replication. Based on the recently detected mechanism of TDF and TAF (Drosu et al., 2020), we suggest that further studies on these drugs are warranted. One possibility could be to test TAF and TDF as add-on therapies to conventional MS-treatment, and to determine if patients taking TAF shed EBV compared with patients who take TDF.

#### Disclosure

The authors report no conflicts of interest.

#### Declaration of Competing Interest

None.

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