Clinical Infectious Diseases

EDITORIAL COMMENTARY

Dolutegravir Appears to Lower HTLV-1 Proviral Load: The Emerging Rational Approach to Treatment of HTLV-1 Associated Myelopathy

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While the vast majority of the estimated 10-20 million people worldwide living with human T-cell lymphotropic virus type 1 (HTLV-1) infection have apparent subclinical or asymptomatic cases, around 5% develop one of two severe complications: adult T cell leukemia/lymphoma (ATLL) or HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP). HAM/TSP is a chronic, relentlessly progressive neurologic condition, notable for debilitating spastic weakness (most commonly in the lower extremities), as well as bowel/bladder dysfunction, and severe neuropathic pain.[1] HAM/TSP is a truly neglected disease, with no approved treatments to date.

In this issue of *Clinical Infectious Diseases*, Dr. Brites and colleagues report an open-label randomized trial of dolutegravir (DTG) 50 mg daily versus oral vitamin C (VTC) 500 mg daily over 48 weeks for people with HTLV-1 infection enrolled at a referral center in Salvador, Brazil. Study participants had confirmed HTLV-1 infection by Western blot or PCR and were excluded if they had HIV-1 coinfection, received corticosteroids within 30 days, or were wheelchair-dependent at baseline. The final analyzed cohort included 46 individuals with HAM/TSP (25 and 21 in DTG and VTC groups, respectively) and 24 patients with asymptomatic HTLV-1 infection (13 and 11 in DTG and VTC groups, respectively). At baseline >50% of symptomatic patients had

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DOI: 10.1093/cid/ciag164

increased lower limb spasticity, and the majority were functionally independent with mild to moderate objective neurologic dysfunction as measured on validated clinical assessment tools.

While the trial did not meet its primary endpoint of change in timed 10-meter walk test, individuals receiving DTG were found to have a statistically significant decline in proviral load (PVL) by week 24 compared to baseline that was sustained through week 48, with no change in PVL in the VTC group. Additionally, some significant improvements in neurologic function were found in the DTG but not VTC participants, including lower extremity spasticity and nocturia (fewer voids per night). On closer analysis the authors identified three phenotypes among symptomatic participants in the DTG-treated group: 12 individuals had low baseline PVL that did not change over time, 12 had high baseline PVL that decreased over time, and 1 had high baseline PVL that did not significantly change over time. Among those with high baseline PVL that decreased on DTG, significant improvement in neurofunctional status was observed, but not for those in the group with unchanging low PVL.

The authors should be congratulated for carrying out this important and logistically challenging study that advances our understanding of HTLV-1 persistence and provides important insights into treatment strategies for HAM/TSP. While a high HTLV-1 PVL set point has long been recognized as a key risk factor for developing HAM/TSP[2], clonal expansion of T-cells infected with latent HTLV-1 virus rather than active viral replication was long believed to be the primary mechanism of HTLV-1 persistence, casting doubt on the potential role of antiretrovirals (ARVs). However, more recent work has suggested that, in addition to clonal expansion, active viral replication followed by cell-to-cell transmission of HTLV-1 via a virological synapse is essential to maintaining HTLV-1 PVL, with the set point essentially a steady state between infected cells and those cleared by cytotoxic CD8+ T-cells.[3,4] That the current study found DTG was associated with decreased PVL is consistent with the theory that active viral replication contributes to maintenance of the PVL set point.

DTG, and potentially other ARVs, join other promising candidates for treatment of HAM/TSP. For years, corticosteroids have been the mainstay of treatment for HAM/TSP, after small observational studies reported improvement in rapidly progressing patients treated with high-dose pulse steroids and in those with a more gradual decline placed on long-term low maintenance doses (e.g., prednisone 5 mg daily).[5] The use of steroids, or occasionally steroid-sparing immunomodulators, remains common practice, though patients often eventually develop disease progression. Intravenous mogamulizumab (moga) – a humanized anti-CCR4 monoclonal antibody – has also shown promise as an agent for HAM/TSP. The agent has been studied in a small, randomized trial in Japan where it was associated with significant reduction in PVL as well as markers of CSF inflammation (neopterin), but no significant difference in objective neurologic findings at 24-weeks.[6] Moga decreases PVL by a different mechanism than DTG – it leads to antibody dependent clearance of CCR4+, CD4+ T-cells, the cell type harboring most HTLV-1 virus. ARVs from several classes have long shown *in vitro* activity against HTLV-1[7] and with

increasing evidence supporting the role of viral replication in maintenance of PVL set point, there is a strong rationale to continue to test them clinically.

It is not surprising that the study did not meet its preselected primary outcome and that overall findings for functional outcomes were modest. Other studies of promising agents like moga have also failed to show a clear impact on neurologic findings. Since elevated PVL and the associated immune inflammatory response in the central nervous system over years or decades is the cause of HAM/TSP symptoms, preventing the onset of neurologic symptoms may require earlier antiviral treatment during the asymptomatic phase. This could potentially be studied via universal screening of high-risk individuals and RCTs of DTG given over many years. Determining whether treatment that lowers PVL will slow progression of HAM/TSP requires longer follow up, likely a minimum of 5-10 years. It is notable that Brites and colleagues found that those with the highest baseline PVL that declined with DTG showed some evidence of improvement in neurologic dysfunction. This should be studied in larger samples and suggests that, at least in some individuals, HAM/TSP-associated neurologic symptoms might be partially reversed if treatment is initiated in time. The seemingly very different phenotypes identified by the authors reflect the heterogeneity of clinical presentations of people with HTLV-1 infection and HAM/TSP, and the complexity of studying treatments in such a landscape.

To date far too little clinical and research interest has been focused on HTLV-1 infection and its complications, perhaps because so many of the people living with HTLV-1 infection are marginalized with too little political or economic power. Fortunately, there has been building scientific interest in the condition and clinical researchers have been working with patients to advance the field in search for a more complete understanding of the virology and pathophysiology of the infection and for effective treatments. Since high PVL set point has been repeatedly associated with risk for HAM/TSP, it is a reasonable hypothesis that a sustained decrease in PVL at the right time in the disease course might avert HAM/TSP onset. Even after the onset of HAM/TSP symptoms, agents that lower PVL and associated inflammation might slow disease progression or potentially partially reverse neurologic symptoms. Finally, combination therapy either with multiple antiretrovirals as in HIV infection or using agents with complementary mechanisms of action such as DTG and moga should be studied. While there remains much work to be done and many questions still to be answered, this study is an important step forward. We need increased awareness, testing, and funding to continue to push the field further and to reduce the burden of HTLV-1 in our patients.

Funding: No funding supported this work

Conflict of Interest: The author declares no conflict of interest

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