Dolutegravir-induced colitis in an HIV-infected patient

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Sir,

Many of the gastrointestinal (GI) conditions associated with HIV disease have become much less frequent over the past two decades. Diarrhoea from opportunistic infections has become less common, and HIV-associated diarrhoea is now more often due to non-infectious causes such as ART-related adverse events and HIV enteropathy.1 Diarrhoea associated with ART is most commonly caused by PIs, which may damage the intestinal epithelial barrier and/or alter chloride ion secretion. Less is known about the diarrhoea associated with the other classes of ART.

Newer antiretroviral agents offer improvements in potency and activity as well as tolerability. Dolutegravir was approved by the US FDA in August 2013 and is currently recommended as initial treatment in HIV-infected patients, both as part of the fixed-dose combination tablet including abacavir/lamivudine/dolutegravir and separately with tenofovir/emtricitabine.2 The efficacy of dolutegravir has been demonstrated in several randomized clinical trials (SPRING-1, SPRING-2, SINGLE, FLAMINGO and SAILING).3–7 In a recent safety review of dolutegravir, nausea, diarrhoea and headache were the most commonly reported treatment-related adverse effects. Diarrhoea occurred more often in patients on PI-based therapy (darunavir/ritonavir) than in those on dolutegravir, and the diarrhoea observed with dolutegravir was generally mild in intensity and typically did not prompt discontinuations or changes in treatment.8 Notably, treatment-emergent diarrhoea of at least moderate intensity occurred in <1% of patients receiving dolutegravir.5,7

We report the case of a woman with chronic HIV infection who, after 18 months of treatment with abacavir/lamivudine and efavirenz, switched to abacavir/lamivudine and dolutegravir to accommodate a new job with a varied schedule including night shifts. The patient’s CD4 cell count was 780 cells/mm3 and HIV RNA concentration was <20 copies/mL prior to making the ART change. Her medical history included chronic kidney disease stage 3, hyperlipidaemia, hypothyroidism, osteopenia and allergic rhinitis. Medications aside from ART included alendronate, cholecalciferol, levothyroxine, loratadine, montelukast and pravastatin, all of which she had been taking for at least 2 years.

Approximately 3 weeks after the change from efavirenz to dolutegravir, she developed moderate diarrhoea characterized by 6–10 loose watery stools per day associated with urgency and occasional incontinence. She had no fevers or chills and denied any anorexia, nausea, vomit or abdominal pain. She denied any sick contacts and had not received any recent antimicrobials or other new medications. The results of initial evaluations, including a stool assay for Clostridium difficile and a multiplex PCR test using the FilmArray GI Panel, which detects 22 common viruses, bacteria and parasites that cause infectious diarrhoea, were negative. Pathogens included in the FilmArray GI Panel are as follows: Campylobacter (jejuni, coli and upsaliensis), Clostridium difficile (toxin A/B), Plesiomonas shigelloides, Salmonella, Yersinia enterocolitica, Vibrio species (including a specific target for Vibrio cholerae), enteric-aggregative Escherichia coli, enteropathogenic E. coli, enterotoxigenic E. coli It/st, Shiga-like toxin-producing E. coli stx1/stx2 (including a specific target for E. coli O157), Shigella/enteroinvasive E. coli, adenovirus F40/41, astrovirus, noro-virus GI/GII, rotavirus A, sapovirus (I, II, IV and V), Cryptosporidium, Cyclospora cayetanensis, Entamoeba histolytica and Giardia lamblia.

The patient’s symptoms persisted for an additional 2 weeks, so she underwent colonoscopy with biopsy. The colon and terminal...
ileum appeared normal, but colon biopsies demonstrated at most minimal crypt architectural disarray with active inflammation in the background of diffuse, prominent apoptotic crypt epithelial injury (Figure 1). The results of immunoperoxidase stains for adenovirus and cytomegalovirus were negative. Since apoptotic crypt injury is a typical histological pattern seen with certain drugs, such as mycophenolate mofetil, drug-induced colitis was suspected. Dolutegravir was discontinued, and the patient was switched back to efavirenz. Her diarrhoea resolved within 2 weeks of stopping the dolutegravir.

Dolutegravir is currently a recommended first-line agent for the treatment of HIV in treatment-naive patients. In clinical trials, dolutegravir was non-inferior to raltegravir-containing regimens and superior to darunavir/ritonavir- and efavirenz-containing regimens, largely because of more discontinuations due to adverse events in the comparator arms. Less than 1% of patients receiving dolutegravir in the above-referenced clinical trials experienced diarrhoea, and dolutegravir is often selected because of its tolerability and benign adverse-effect profile. However, post-marketing experience with dolutegravir is still accumulating. Since diarrhoea negatively affects health-related quality of life and is a common reason for ART discontinuation, clinicians should be aware of this severe and clinically relevant adverse event.

Written consent was obtained from the patient for publication of the study.

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**Transparency declarations**

None to declare.

**References**