Possible Drug–Herb Interaction between Herbal Supplement Containing Horsetail (*Equisetum Arvense*) and Antiretroviral Drugs: Report of 2 Cases

Ezequiel Cordova, MD¹, Laura Morganti, MD¹, and Claudia Rodriguez, MD¹

Abstract
The use of alternative medicines, including herbs, is common among HIV-positive patients, even in those on antiretroviral treatment. *Equisetum arvense*, known as “horsetail,” is mainly used for its diuretic properties. There are limited data about the pharmacological properties of this compound and the potential drug–herb interactions. The authors report 2 cases in which a possible drug–herb interaction may have led to virological breakthrough in patients who were maintained on the same regimen for many years, including lamivudine (3TC)/zidovudine (ZDV)/efavirenz (EFV) and emtricitabine (FTC)/tenofovir (TDF)/EFV, respectively. Therefore, a drug–herb interaction may be expected when these agents are taken concurrently. Until additional data are available, the authors advise clinicians to avoid this combination when possible.

Keywords
herb–drug interactions, HIV treatment, horsetail, *Equisetum arvense*

Introduction
In recent decades, the consumption of medicinal herbal products has increased, both in developed and undeveloped countries.¹ The use of alternative medicines, including herbs, is common among HIV-positive patients, even in those on antiretroviral treatment. Case reports, clinical trials, and in vitro studies have shown that there are significant risks of interactions between herbal medicines and antiretroviral drugs.²⁻⁴ However, there is a belief that such products are natural, safe, without providing adverse effects or interactions with other medicinal products, which extends its consumption, and due to which the patients do not report their consumption to the physicians.⁵ We report 2 cases of possible interactions between medicinal herbs and antiretroviral drugs.

Case 1
A 49-year-old woman, otherwise healthy, was diagnosed with HIV in 2001 and started antiretroviral therapy that same year with zidovudine (ZDV), lamivudine (3TC), and nevirapine (NVP). In 2007, NVP was changed to efavirenz (EFV). Her baseline viral load and CD4 count were 23 000 copies/mL and 374 cells/mm³, respectively. She had excellent adherence and sustained virologic suppression until 2013 when she had 2 consecutive detectable viral loads (96 copies/mL and 57 copies/mL) in the lapse of 5 months, while her CD4 count remained stable. On direct questioning, the patient denied any missed doses, immunizations, infectious diseases, and concomitant medications but revealed that recently she started the use of several herbal supplements. Two months prior the first detectable viral load, she started taking daily supplements containing “horsetail” (*Equisetum arvense*) for its analgesic and anti-kidney stone effect. The patient was advised to stop using horsetail because of concerns of a possible negative drug interaction with the antiretroviral drugs. A viral load performed 1 month after the discontinuation of the herbal supplement showed the viral load resuppressed at less than 50 copies/mL, and all subsequent viral loads have thus far remained undetectable, and the patient did not resume taking horsetail.

Case 2
A 75-year-old man, otherwise healthy, was diagnosed with HIV in 1998. He started antiretroviral therapy in 2004 with ZDV, 3TC, and EFV. He continued on this same antiretroviral

¹ Infectious Diseases Unit, Hospital Cosme Argerich, Buenos Aires, Argentina

Corresponding Author:
Ezequiel Cordova, Infectious Diseases Unit, Hospital Cosme Argerich, Pi y Margall 750, Buenos Aires, Argentina.
Email: dr_ecordova@hotmail.com
regimen with excellent adherence and sustained virologic suppression until 2013 when his antiretroviral treatment was simplified to a fixed-dose combination of emtricitabine (FTC), tenofovir (TDF), and EFV. Four months and 9 months after simplification, he had 2 consecutive detectable viral loads of 71 copies/mL and 1590 copies/mL, respectively. On direct questioning, the patient denied any missed doses, immunizations, infectious diseases, and concomitant medications but revealed that recently he started the use of herbal supplements including mainly horsetail for its diuretic effect. The patient was advised to stop using horsetail because of concerns of a possible negative drug interaction with antiretroviral drugs. A viral load performed 1 month after the discontinuation of the herbal supplement showed the viral load resuppressed at less than 50 copies/mL, and all subsequent viral loads have thus far remained undetectable, and the patient did not resume taking horsetail.

Discussion

Our patients experienced a virological breakthrough after being undetectable for 8 and 10 years, respectively, which supports a history of excellent adherence. Different causes or circumstances that could lead to virological breakthrough, such as changes in adherence, infectious complications, recent immunizations, and concomitant medications were ruled out. Based on all these, we suppose that a negative interaction between the consumption of herbal supplements containing horsetail and antiretroviral drugs occurred in our patients.

_Equisetum arvense_, known as horsetail, is mainly used for its diuretic properties. Equisetum is also used as analgesic, hemostatic, astringent, and for treatment of digestive disorders and kidney/bladder stones.

There are limited data about the pharmacological properties of this compound and its possible CYP450 metabolism. Moreover, no previous reports can be found in the literature of drug interactions compromising this herb. For these reasons, horsetail has been listed as an herb of undefined safety by the US Food and Drug Administration.

Both of the reported cases were receiving an antiretroviral regimen including EFV and 2 nucleoside analog reverse transcriptase inhibitors. Efavirenz is a substrate of CYP450 and is primarily metabolized by the CYP2B6 isofrom and to a lesser extent CYP3A4. Drugs that inhibit or induce significantly these enzymes could then increase or decrease EFV exposure, respectively. Therefore, EFV has numerous pharmacokinetic interactions with other pharmacological agents, including herbs such as Ginkgo biloba, St-John-wort, Asian and American ginseng, among others.

Equisetum contains flavonoids and phenols among compounds that could induce CYP450. Despite this, no studies have evaluated their role as potential CYP450 inducers. By contrary, a study found its role as a potential inhibitor of CYP1A2, CYP2D6, without significantly affecting CYP3A4.

Moreover, due to its diuretic properties, _Equisetum arvense_ may increase renal excretion of other drugs, because of which a possible negative interaction with antiretroviral drugs with primarily renal elimination of 3TC, FTC, and TDF cannot be rule out.

Another explanation could be that there was an impairment of the absorption of the antiretroviral drugs by the concomitant use of this herb. The evaluation of these cases with the resolution of the event after the avoidance of the herb supplements would support the causal relationship derived from a possible subtherapeutic concentrations of antiretroviral drugs. Using the Drug Interaction Probability Scale proposed by Horn et al to evaluate drug interaction cases, our proposed causal relationship of virological breakthrough due to a drug interaction between horsetail infusions and antiretroviral drugs was calculated. Positive findings of this scale such as the event being consistent with the known or reasonable time course of the interaction (onset and/or offset), the event resolving upon dechallenge of the herb supplement, and the lack of reasonable alternative causes for the event support our case.

It would have been very useful to perform therapeutic drug monitoring (TDM) for antiretroviral drugs during and after the use of horsetail infusions. Unfortunately, at that moment, we did not have TDM at our facilities.

Finally, it should be taken into account that both the reported patients consumed this herbal medicine as a comminuted herb. For this reason, the exact composition of the herbal supplement cannot be guaranteed and it can be mixed or adulterated with other herbal products.

In conclusion, we report 2 cases of a possible drug interaction between an herbal supplement containing horsetail and antiretroviral drugs. To our knowledge, these are the first reports of this kind of drug–herb interaction. Pharmacokinetic studies are needed to fully elucidate the effect _Equisetum arvense_ and other herbal supplements has on the different antiretroviral drugs. Until additional data are available, we suggest avoiding horsetail and other herbal supplements, with no information regarding drug interactions in patients under antiretroviral therapy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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