antibiotic therapy and therapeutic drug monitoring is available for only a handful of antibiotics. This is important, as suboptimal antibiotic therapy is associated with worse outcomes.\textsuperscript{9} Systematic research using ex vivo circuits, large animal models\textsuperscript{10} and population PK studies are indicated to improve antibiotic prescription and, hence, patient outcomes during ECMO.

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Transparency declarations
None to declare.

References

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Sialolithiasis in an HIV-1-infected patient treated with atazanavir/ritonavir monotherapy

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Sir,

An adult Caucasian HIV-infected male attended the infectious diseases department of Pitié-Salpêtrière Hospital in February 2012 for a painful submandibular tumefaction.

His medical history presented several notable events: HIV infection (diagnosed in 1986); a chronic hepatitis C with a genotype 1 virus diagnosed in 1993 and cured after pegylated interferon and ribavirin therapy in 2004; and sialolithiasis that occurred in 2009 without stone examination at that time. Occasional use of alcohol, tobacco and cannabis was noted in his file.

His CD4 count nadir was 204 cells/mm\textsuperscript{3} and antiretroviral treatment was initiated in 1991. At no time did he present any AIDS-related event, but he experienced several antiretroviral combinations (lamivudine, zidovudine, stavudine, didanosine, abacavir, nevirapine, indinavir/ritonavir and lopinavir/ritonavir) because of persistent plasma HIV-RNA after poor tolerance and adherence difficulties. A regimen combining atazanavir/ritonavir + tenofovir/emtricitabine was initiated in 2006, and plasma HIV-RNA <50 copies/mL and CD4 counts >600 cells/mm\textsuperscript{3} were obtained. Simplification to atazanavir/ritonavir (300/100 mg, once daily) monotherapy was undertaken in March 2011.

The cervical tumefaction comprised an infection of the left submandibular gland with a blocked parotid duct. The ultrasound examination revealed a size-increased submandibular gland (52 \( \times \) 30 mm) and a parotid duct dilated (8 mm internal diameter) by the presence of four calculi (3.4, 4.2, 5.8 and
The patient received symptomatic treatment with spiramycin, metronidazole, prednisone and acetaminophen; in addition, opioid analgesia was necessary. At day 3, a salivary stone was spontaneously released and collected to determine its composition.

After solubilization of the yellowish calculus in acid aqueous solvent (10.2 mg stone weight; 3.4 mm internal diameter), the antiretroviral concentration was determined using liquid chromatography coupled with tandem mass spectrometry, as previously described. Atazanavir was identified as the main component of the salivary stone at 140 \( \mu \text{g/g} \). At the time of calculi collection, the atazanavir plasma concentration 24 h after the last intake (\( C_{24h} \)) was 1775 ng/mL, which is consistent with the median (IQR) value of the atazanavir \( C_{24h} \) obtained in frozen plasma during the past 78 months: 1349 ng/mL (1155–1597; \( n = 7 \)). During this follow-up, the intrapatient variability of the atazanavir \( C_{24h} \) was 25% (Figure 1).

To our knowledge, only one case of lithiasis in the salivary glands has been described in an HIV-infected patient treated with an atazanavir/ritonavir-containing regimen. However, no pharmacokinetic data were reported in that case to illustrate a potential atazanavir overdose.

Here, we report a second case of sialolithiasis with obstruction of the parotid duct in an HIV-infected patient without any previous occurrence of renal or biliary lithiasis. Atazanavir was identified in the extracted stone and the median atazanavir \( C_{24h} \) was \(~10\)-fold higher than the effective target atazanavir \( C_{24h} \) (150 ng/mL). Moreover, since the introduction of atazanavir/ritonavir in this patient’s treatment, the atazanavir \( C_{24h} \) was always >850 ng/mL, which is considered the upper limit of safety for the atazanavir \( C_{24h} \).

Since its approval in HIV treatment in June 2003, atazanavir/ritonavir has been known to be associated with renal and biliary lithiasis. Given the literature on this subject, the mechanistic hypothesis of atazanavir stone formation is in situ precipitation consecutive to the pH-dependent solubilization of atazanavir, enhanced by high plasma concentrations, saturation or inhibition of efflux transporters and waning renal (diuresis) and biliary (metabolic) clearances.

The mechanism of atazanavir-related sialolithiasis occurrence is not well established, but among the possible factors we can list are those that might be connected with the present case: bacterial infection increasing the salivary pH, dry mouth worsened by HIV infection and tobacco/cannabis use. In addition, regarding our findings, we suggest adding the high atazanavir \( C_{24h} \) as another potential factor.

Given the wide use of atazanavir in the medical management of HIV, knowledge of sialolithiasis as a potential long-term atazanavir-associated complication is important for physicians and patients, and our results should encourage prescribers to be more vigilant for antiretroviral pharmacokinetic variations.

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**References**


