that the rate of oral absorption varied from dose to dose. Typical linezolid peak concentrations are 12–26 mg/L ~2 h after oral doses and trough concentrations are typically 3–9 mg/L.\(^1,3\) In this infant, despite q8h dosing, peak and trough concentrations were lower than typically seen. The volume of distribution divided by bioavailability (Vz/F), clearance divided by bioavailability (CL/F), elimination rate constant (k\(\text{el}\)) estimated with three concentrations, half-life (t\(\text{1/2}\)) and AUC\(\text{0–8}\) were estimated at 3.48 L, 1.75 L/h, 0.50 h\(^{-1}\), 1.38 h and 16.56 mg·h/L, respectively.

The pharmacokinetic profile of oral linezolid in our infant differed from what has been published in the literature for full-term infants. Full-term infants who received single doses of iv linezolid had much higher peak plasma concentrations, a larger AUC and a slower clearance.\(^8\) Our infant was born >3 months premature and was treated at a post-gestational age of 1 month (not equivalent to a full-term infant of the same age); therefore, direct correlation is challenging due to the differences in characteristics of the infants in the published studies.\(5,6,8,9\) The C\(\text{max}\) and AUC were lower in our infant and apparent elimination t\(\text{1/2}\) faster than what has been reported in full-term infants. Reasons for this may include incomplete absorption (F < 1), faster clearance or a smaller actual volume of distribution. We were only able to estimate Vz/F, leaving our assessment of this parameter less than optimal. Pharmacokinetic data reported in studies in infants and neonates have utilized the iv formulation of linezolid and studied the disposition of the drug after a single dose, whereas our infant received oral linezolid suspension and pharmacokinetic analysis was done at steady-state. This also may explain some of the differences in pharmacokinetic parameters. Kosaka et al.\(10\) reported plasma levels in four children (aged <30 months) receiving linezolid for MRSA mediastinitis. A serum concentration of <2 mg/L linezolid was needed to inhibit growth for 90% of organisms (MIC\(90\)). Two patients were treated iv with a 90 min infusion at 10 mg/kg q8h initially and were switched to an oral regimen at the same dose. Two other patients were given linezolid orally at a dose of 10 or 15 mg/kg q8h. The linezolid trough concentrations were ≥3.5 mg/L in patients treated with iv linezolid. Lower trough concentrations were seen with oral administration of linezolid. In one 3-month-old child, who was the youngest, undetectable serum trough concentration (<0.1 mg/L) was documented when iv linezolid was changed to oral therapy at a dose of 10 mg/kg q8h; hence, the dose of linezolid was increased from 10 to 15 mg/kg.

Preterm infants are at increased risk of nosocomial bacterial infection with multiresistant Gram-positive pathogens. Linezolid seems to be a safe and potent alternative treatment for these infants. The benefits of linezolid compared with vancomycin include its availability as an oral formulation. Owing to the variability of linezolid kinetics in infants, especially in premature infants as in our case, we would recommend therapeutic serum concentrations be monitored at steady-state and dosage adjusted accordingly. Additional studies are needed to evaluate the steady-state pharmacokinetic disposition of oral linezolid in children.

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### Transparency declarations

None to declare.

### References

The prevalence of obesity (a BMI >30 kg/m²) among HIV-infected individuals in the USA is approaching parity with the general population and is particularly high among women and minorities.¹⁻³ Few medications are available for the treatment of obesity. Presently, the only FDA-approved drugs for the long-term treatment of obesity are orlistat, lorcaserin, phentermine/topiramate, naltrexone/bupropion and liraglutide. ⁴ Orlistat, a potent selective inhibitor of pancreatic and gastric lipases taken at doses of 27 or 60 mg (available over-the-counter) or 120 mg (prescription only) for treatment of obesity, reduces the dietary absorption of fat, potentially altering the absorption of lipophilic drugs, reducing their bioavailability and eventually limiting their effectiveness.⁵⁻⁶ We report here the case of an HIV-infected patient who experienced HIV load rebound 6 weeks after starting orlistat.

An HIV-infected woman in her early forties was on stable ART with 300/100 mg of atazanavir/ritonavir once daily plus tenofovir/emtricitabine (since 2010). Her HIV-RNA was undetectable (<37 copies/mL) for years and her CD4+ cell count was always >800 cells/µL. At her scheduled follow-up visit in June 2015, her HIV-RNA level had risen to 120 copies/mL (the test repeated 1 week later resulted in 440 copies/mL). An HIV genotype test performed on the second blood sample showed no antiretroviral drug resistance mutations. The patient reported that she had been perfectly adherent to ART but that she had begun taking orlistat, purchased over-the-counter from her local pharmacy in May 2015, in order to lose weight (her BMI was 27.2 kg/m²). She took three 60 mg tablets daily at each meal and, as expected, she experienced episodes of mild diarrhoea, particularly after ingesting fatty foods. Orlistat was discontinued and the patient’s HIV-RNA level had returned to undetectable when tested 2 months later. At the last available follow-up (November 2015), the patient’s plasma HIV-RNA and CD4+ T cell count were <37 copies/mL and 1172 cells/µL, respectively. Atazanavir trough evaluations performed immediately before stopping orlistat evidenced drug concentrations (50 ng/mL) that were subtherapeutic according to available literature.⁷ Notably, such concentrations were remarkably low compared with trough atazanavir values measured about 1 year earlier (210 ng/mL), as well as with atazanavir concentrations determined 2 months after orlistat discontinuation (195 ng/mL).

Orlistat blocks the absorption of approximately one-third of all dietary fat in the intestine and theoretically may alter the absorption kinetics of highly lipophilic drugs.⁸⁻¹⁰ After treatment with orlistat, subtherapeutic levels of serum cyclosporine in renal-transplant patients⁶ and reduced absorption of amiodarone by approximately one-quarter in healthy volunteers⁷ have been reported. Chronic use of orlistat can also lead to reduced absorption of fat-soluble vitamins (A, D, E and K)⁵ and interfere with warfarin dosage.¹⁰

Atazanavir is a highly lipophilic drug belonging to Biopharmaceutics Classification System (BCS) class II, with poor water solubility and high permeability.¹¹ Its absorption is, therefore, expected to be reduced by orlistat, providing the most probable cause of the loss of virological control observed in the case described. To the best of our knowledge, no previous studies have reported the effect of orlistat on the exposure to antiretroviral medications. The only case published to date described only a temporal relationship between orlistat use and loss of control of viraemia of HIV in a patient on efavirenz-based ART that resolved after orlistat discontinuation. However, no data on efavirenz pharmacokinetics were given. Conversely, here we provide evidence that our patient—being already at risk for atazanavir underexposure per se as documented by drug trough concentrations just above the therapeutic threshold of 150 ng/mL, probably related to a high level of distribution of atazanavir in the adipose tissue associated with obesity¹³—experienced a significant drop in atazanavir trough concentrations, favouring the reactivation of HIV and the subsequent virological failure.

In conclusion, the main take-home message from this case is that concomitant administration of orlistat is associated with reduced absorption of atazanavir, greatly increasing the risk of virological failure in selected patients with HIV. This anti-obesity drug should be, therefore, used with caution in HIV-infected patients taking highly lipophilic antiretroviral medications. This finding is particularly relevant considering that orlistat is available on the market also as an over-the-counter medication, thus potentially escaping the control of clinicians.

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**Author contributions**

C. G. contributed to the study design, supervised all stages of the study, performed statistical analyses and wrote the first draft of the manuscript. D. C. and S. C. performed pharmacokinetic analyses. A. R., V. D. C. and E. G. recruited and followed the patient. E. C. reviewed the manuscript. All authors contributed to writing the manuscript.

**References**

11 Benet LZ, Broccatelli F, Oprea TI. BDDCS applied to over 900 drugs. AAPS J 2011; 13: 519–47.