ceftazidime. Interspecies variations were observed, especially concerning colistin, co-trimoxazole, fluoroquinolones and piperacillin/tazobactam. Clinical data is now required to establish the optimal treatment of *Cupriavidus* infections.

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Transparency declarations

None to declare.

Supplementary data

Tables S1 and S2 and Figure S1 are available as Supplementary data at *JAC* Online.

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Pharmacokinetics of once-daily doravirine over 72 h following drug cessation

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Sir,

Successful combination ART (cART) relies on daily adherence to cART.[1,2] The 'optimal' adherence pattern may be difficult to adopt as cART is for life and doses can be forgotten or delayed, making antiretrovirals with long half-lives ($t_{1/2}$s) desirable. Such drugs may allow for missed or delayed doses when drug concentrations are maintained at therapeutic levels until the next dose is administered.

Data on drug persistence and terminal $t_{1/2}$ are available for different cARTs and have been useful to advise clinicians and patients on delayed or missed doses.[3] Herein, we investigated the pharmacokinetic (PK) 'forgiveness' of the new NNRTI doravirine. Doravirine was recently approved to treat HIV infection as a single entity (Pifeltro®) and as a fixed-dose combination with tenofovir disoproxil fumarate and lamivudine (Delstrigo®).[4] Since the PK forgiveness of tenofovir disoproxil fumarate and lamivudine has been extensively studied,[5,6] in the present study we characterized the persistence of doravirine in the absence of other agents.

Regulatory and ethical approvals (London Westminster Research Ethics Committee 19/LO/0666) were obtained before initiating the study. Written informed consent was obtained from participants prior to study enrolment. In this Phase I, open-label, PK study, the participants received 100 mg of doravirine once daily for 7 days to

Table 1. Doravirine steady-state PK parameters measured over 24 and 72 h

	0–24 h		0–72 h	
Parameter	GM (95% CI)	coefficient of variance (%)	GM (95% CI)	coefficient of variance (%)
AUC_{0-24} or AUC_{0-72} (ng·h/mL)	18 354 (16 395–21 410)	25.3	26 338 (23 080–31 743)	30.2
C_{max} (ng/mL)	1286 (1162–1488)	23.5	1286 (1188–1462)	23.5
C_{trough} at 24 h or 72 h (ng/mL)	420 (373–526)	35.1	39 (33–61)	56.4
$t_{1/2}$ (h)	14.56 (13.19–16.59)	21	13.97 (12.77–15.68)	19.5

establish steady-state doravirine. Intensive PK visits were scheduled between Day 7 and Day 10. Blood samples were collected pre-dose and at 2, 4, 8, 12, 24, 30, 36, 48, 60 and 72 h post-dose. Doravirine plasma concentrations were measured using a previously reported method with modifications.[7] PK parameters were calculated using non-compartmental modelling techniques (WinNonlin Phoenix Version 8.1; Pharsight, Mountain View, CA, USA): trough concentration (C_{trough}), maximum concentration (C_{max}), elimination $t_{1/2}$ to last measurable timepoint and total drug exposure [expressed as the area under the plasma concentration–time curve from 0 to 24 h after dosing (AUC_{0-24}) and from 0 to 72 h (AUC_{0-72})].

A total of 15 volunteers were screened. One withdrew in keeping with the exclusion criteria and 14 were enrolled and completed the study. Of the 14 subjects, the median age was 33 years (range 22–51 years) and median BMI was 23.3 kg/m^2 (range 19.8–34.3 kg/m^2). Seven (50%) were cis-female, nine were Caucasian, four were black African–Caribbean and one was Hispanic. All subjects completed the study.

Geometric mean (GM) values and 95% CIs for the steady-state PK parameters measured over 24 and 72 h for doravirine are summarized in Table 1. The GM (95% CI) $t_{1/2}$ at 24 h of doravirine was 14.56 h (13.19–16.59 h), which was similar to that at 72 h [13.97 h (12.77–15.68 h)]. At 48 and 72 h post-dose, all subjects had doravirine concentrations higher than the IC_{50} for WT virus (5.2 ng/mL).[8]

Doravirine was well tolerated and no serious adverse events occurred during the study. The most common adverse events reported were hay fever and headache, observed in four and two of the volunteers, respectively. No clinically relevant changes in laboratory parameters were reported.

Although doravirine minimum effective concentration is unclear, during drug development, a putative target for dose selection was a C_{trough} of 23 ng/mL, which is a plasma concentration based on an *in vitro* estimate of 95% efficacy in the presence of 50% normal human serum against the NNRTI K103N/Y181C double substitution.[8] In the current study, all 14 participants had plasma concentrations of doravirine above 23 ng/mL at 54 h post-dose. At 48 h and even 72 h post-dose, all subjects had doravirine concentrations higher than the IC_{50} for WT virus (5.2 ng/mL).[8] Thus, combined with tenofovir disoproxil fumarate and lamivudine, both of which have prolonged $t_{1/2}$, doravirine provides favourable PK forgiveness.

The main study limitation was recruitment of HIV-negative volunteers rather than HIV-infected patients, who may exhibit modestly different PK to volunteers, and the use of mainly young subjects not fully representative of the ageing HIV population in many countries. Steady-state GM doravirine C_{max}, AUC_{0-24} and C_{24} were 962 ng/mL, 16 090 ng·h/mL and 396 ng/mL in people living with HIV, respectively.[9] These were 25%, 12% and 5.7% lower than the corresponding PK parameters of HIV-negative individuals in our study. However, whether this is a real difference between populations or an inter-study difference remains unclear.

In conclusion, our study characterized the PK forgiveness of doravirine following drug cessation. Doravirine plasma concentrations were maintained above the IC_{50} 72 h following a missed dose. This is important in the context of HIV treatment management, as drug-resistant strains may emerge when drug concentrations drop to subtherapeutic concentrations due to poor compliance. Doravirine may be administered with tenofovir disoproxil fumarate and lamivudine, as these are characterized by prolonged $t_{1/2}$s, providing a balanced cART in terms of PK forgiveness.

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