

SHORT REPORT

Food intake and darunavir plasma concentrations in people living with HIV in an outpatient setting

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AIMS

Patients receiving darunavir are advised to take it concomitantly with food. The objectives of the present cross-sectional study were to evaluate the actual concomitant food intake of patients visiting an HIV outpatient clinic.

METHODS

Sixty participants treated with darunavir/ritonavir once daily were subjected to a food recall questionnaire concerning their last concomitant food intake with darunavir. Darunavir trough concentrations were calculated.

RESULTS

The median food intake was 507 (0–2707) kcal; protein intake, 20 (0–221)g; carbohydrate intake, 62 (0–267)g; fat intake: 14 (0–143)g; and dietary fibre: 4 (0–30)g. Twenty-five patients (42%) ingested their drug with between-meal snacks. No relationship was found between food intake and trough concentrations.

CONCLUSIONS

Clear advice on the optimal caloric intake is needed, to avoid high caloric intake in patients who already have an increased risk of cardiovascular disease due to their HIV infection.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- In healthy volunteers, administration of 400 mg darunavir in a fasting state has been shown to result in a peak plasma concentration and area under the curve decrease of approximately 30% compared with administration after a standard meal.
- No significant differences have been observed in darunavir plasma concentrations between the different diets tested.
- The advice on concomitant food intake in patient brochures varies highly in caloric intake.

WHAT THIS STUDY ADDS

- Concomitant food intake in a real-life outpatient setting varied greatly and was often unnecessarily high.
- A large number of people using darunavir take their drug with a between-meal snack.
- Healthcare providers and patient brochures should ensure that their advice on concomitant food intake does not contribute to an unhealthy diet.

Introduction

Darunavir (DRV) is a protease inhibitor (PI) that is administered with low-dose **ritonavir** (RTV) to provide a pharmacokinetic boost by inhibiting drug metabolism, thereby enhancing plasma concentrations over time [1]. Although DRV is considered to be a safe and efficacious drug, a considerable pharmacokinetic variability has been observed [2].

The observed variability may be partly explained by a food effect. In a prior study assessing the food effect on the bioavailability of DRV 400 mg (with RTV) in healthy volunteers, the bioavailability increased by 30% with food intake compared with the fasting state, and no significant differences were observed between the different diets tested [3].

Partly because of this food effect study, patients using DRV are advised to ingest their drug concomitantly with food. However, there is no clear-cut advice on how much nutritional content (e.g. number of calories, and amount of fat, protein and carbohydrate) a meal should contain. The patient product brochures seem to focus more on caloric intake than on a healthy diet, as meals with a high caloric value are often recommended [4–6]. As earlier studies were conducted in controlled settings, little attention was paid to the clinical implications in a real-life outpatient setting. The primary objective of the present study was to determine how people living with HIV, using once-daily DRV/RTV cope with the concomitant food intake advice given by their care givers and patient product brochures. Same-day DRV trough concentrations (C_{trough}) were measured and compared with cut-off values used in clinical care.

Methods

Study design and participants

In the HIV outpatient clinic of the University Medical Center Groningen (UMCG), patients with an appointment between 23 April 2014 and 28 July 2014 were asked to participate if they were using DRV/RTV 800/100 mg once daily. Consenting participants were subjected to a validated and structured food recall questionnaire, filled in by a trained researcher (A.D.) to record participants' food intake (± 30 min) with the last DRV administration before their appointment and the time of DRV ingestion. After performing diagnostic tests for standard care, residual blood was analysed to

determine the DRV plasma concentration. The blood was drawn from the patient on the same day that the food intake questionnaire was obtained. Data concerning patient characteristics, blood chemistry (e.g. renal and hepatic function) and disease-specific results (CD4+ cell count and viral load) were extracted from the medical records. We aimed to enrol 60 patients within the study period, as this sample size was estimated to provide a representative overview of the concomitant food intake. Written informed consent was obtained from all participants prior to any study procedure. The ethical review board of the UMCG reviewed the study and concluded that it was in accordance with Dutch law (METc 2014.115).

Nutritional assessment

The validated food recall questionnaire consisted of the time of food intake, food preparation and an accurate description of the food and drink consumed. To assess the food quantity, the researcher used household measures and photographic tools, using the double-check method on products such as milk, sugar and spices that are known to be under-reported in such questionnaires. The Dutch National Food Consumption Survey 2012–2016 was used as a reference, in addition to the questionnaire used, to determine the type of meal (breakfast, lunch or dinner, or a between-meal snack [7]). The food recall questionnaire was analysed by D.D. using EvryDietist, 6.2.9.9 (Nevo 2011 data, Evry bv, Alphen aan den Rijn, Netherlands). The following nutritional values were calculated: energy (kcal), protein (g), carbohydrate (g), total fat (g) and dietary fibre (g). During the second half of the study, four questions were added to the food recall questionnaire in order to optimize the interpretation of the food intake. The first three additional questions asked were:

1. Did your care providers advise you to eat concomitantly with DRV?
2. If yes, what food intake did your care providers advise?
3. What amount of food do you consider appropriate for intake concomitantly with DRV?

In the fourth question, we asked if patients changed their food pattern as a consequence of DRV and its concomitant food intake advice. We disregarded this question; interpretation of the answer was not possible without information on the antiretroviral therapy taken before the start of the DRV administration.

Pharmacokinetic assessment

Participants were asked at which time point DRV was ingested. The time of blood sampling was recorded. The concentrations of DRV in human plasma were analysed using a validated liquid chromatography–tandem mass spectrometry (LC–MS/MS) method. All analyses were performed on a Thermo Fisher Scientific Inc. (San Jose, CA, USA) triple quadrupole LC–MS/MS with a Finnigan™ Surveyor® LC pump and a Finnigan™ Surveyor® autosampler. The mobile phase consisted of an aqueous buffer (containing ammonium acetate 5 g l⁻¹, acetic acid 35 ml l⁻¹ and trifluoroacetic anhydride 2 ml l⁻¹ water), water and acetonitrile and had a flow rate of 0.3 ml min⁻¹. The calibration curves were linear within the concentration range 0.335–33.5 mg l⁻¹ for DRV and had a correlation coefficient (R²) of 0.999. The lower limit of quantification (LLOQ) for DRV was 0.27 mg l⁻¹. This method is precise and accurate: within-day precision ranged between 2.2% and 3.2% for DRV, and between-day precision from 3.0% to 5.2%. The calculated accuracy ranged from 0.0% to 11.8%.

The DRV C_{trough} was defined as the plasma concentration at 24 h after intake of the dose. To estimate the C_{trough}, we used a DRV iterative two-stage Bayesian population pharmacokinetic model using the software package MWP Pharm Research version 3.82 (Mediware, Groningen, the Netherlands) [8]. The model for DRV is a one-compartment model with input and elimination from the central compartment. Parameters for this model are: a volume of distribution of the central compartment of 2 l kg⁻¹ [standard deviation (SD) 0.5 l kg⁻¹], total body clearance of 6.3 l h⁻¹ 1.85 m⁻² (SD 1.57 l h⁻¹ 1.85 m⁻²), first-order absorption constant of 1 h⁻¹ (SD 0.25 h⁻¹) and a bioavailability of 0.8 (in combination with RTV). This model was built in-house and derived from data provided in the literature [9]. A median population pharmacokinetic curve was used as a cut-off value for follow-up as in standard care [10, 11]. A DRV C_{trough} below 1.07 mg l⁻¹ is an indication for follow-up, in accordance with the treatment protocol. The median population pharmacokinetic curve is seen as a cut-off value for the once-daily dosage and not as the minimally effective concentration.

Further, the medical records of all participants were studied for medication potentially influencing the DRV concentrations.

Statistical analysis and data processing

C_{trough} levels vs. the calculated kcal, carbohydrate, protein, total fat and dietary fibre values were presented in a scatter plot. Curve estimation tests were performed to find the best fit. All descriptive analyses were performed using SPSS for Windows, version 22.0 (IBM SPSS, Chicago, IL, USA).

Nomenclature of targets and ligands

Key ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [12].

Results

Participant characteristics

Sixty patients were enrolled, of whom 50 were male. Participant demographic characteristics are presented in Table 1. Forty-seven per cent of the participants were overweight [body mass index (BMI) ≥25 kg m⁻²], of whom 13% were classified as obese (BMI ≥30 kg m⁻²).

Nutritional analysis

The medians of the calculated nutritional values for the meal concomitantly ingested with DRV are shown in Table 2. Eleven participants ingested DRV with breakfast, even with lunch, 14 with dinner and three without concomitant food, and 25 participants took their DRV with a between-meal snack.

Twenty-eight (85%) of the participants interviewed about the advice received at start of the treatment confirmed that the care provider advised them to eat concomitantly with the ingestion of DRV. Twenty-four participants (73%) indicated that they did not know the amount of food intake recommended with DRV ingestion.

Pharmacokinetic analysis

The median (interquartile range) DRV C_{trough} for the 60 participants was 2.3 (1.51–3.67) mg l⁻¹. Seven participants (12%) had a DRV C_{trough} below the used cut-off value of 1.07 mg l⁻¹. No pattern could be detected in the DRV C_{trough} and the caloric intake. A biologically expected S-curve did not fit the data (P = 0.260), as presented in Figure 1. A linear model fitted slightly better compared with the other curve estimations but still showed no correlation (rho = -0.178, P = 0.173). Similar results were found for the other nutritional values (protein, carbohydrate, total fat and dietary fibre; not

Table 1

Baseline demographic characteristics of the 60 study participants

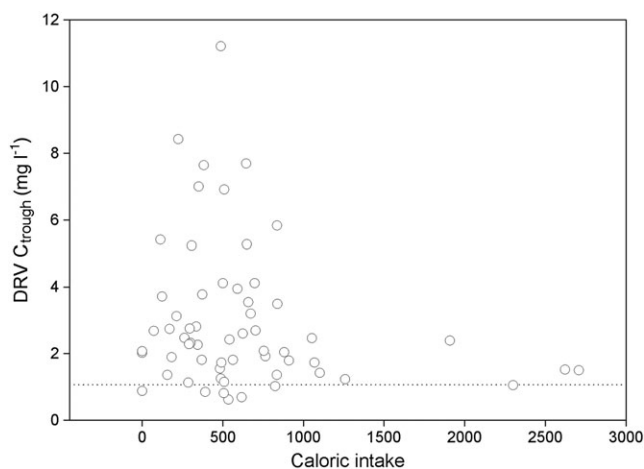
Characteristics	Value (range)
Mean age (years)	45 (20–66)
Median body mass index (kg m ⁻²)	24.66 (16.80–39.18)
Gender (m/f)	50 male 10 female
Mean creatinine clearance (ml min ⁻¹)	99 (46.1–166.0)
Median ASAT	29 (18–261)
Median ALAT	23 (10–784)
Mean CD4+ cell count	510 (130–1200)
Viral load (n = 44)	Undetectable
Median viral load (n = 16) (copies ml ⁻¹)	92 (56–1340)
Duration darunavir use (months)	20 (0.50–59)

ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase

Table 2

Median (range) food intake categorized according to nutritional value for the study participants

Nutritional value	Median (range)
Energy (kcal)	507 (0–2707)
Protein (g)	20 (0–221)
Carbohydrate (g)	46 (0–267)
Total fat (g)	14 (0–143)
Dietary fibre (g)	4 (0–30)

**Figure 1**

Scatter plot of energy intake (kcal) vs. the calculated darunavir (DRV) trough concentrations (C_{trough}). The dotted line represents the reference population median C_{trough} for the once-daily dosage of DRV (1.07 mg l^{-1})

shown). The medical records of the participants did not show use of medication interacting with DRV/RTV.

Discussion

To the best of our knowledge, this was the first study to evaluate the concomitant food intake in people using the once-daily DRV dosage in a real-life setting. Our findings showed that people using DRV often have an unnecessarily high caloric intake and that a large number of the patients take DRV with high caloric between-meal snacks.

Patients using DRV are advised to ingest their drug concomitantly with food, although detailed advice on the type of food and number of calories is not given. This is reflected in the current study as the concomitant food intake among participants varied greatly and no relationship was found with DRV C_{trough} . The high BMI ($>25 \text{ kg m}^{-2}$) of participants in the present study may partly be a consequence of the between-meal snacks and subsequent high caloric intake.

The use of antiretroviral therapy has been associated with a higher risk of cardiovascular and metabolic disorders, such as hyperlipidaemia, insulin resistance, metabolic syndrome and diabetes [13–16]. Therefore, it is important to ensure that the advice on concomitant food intake while using DRV does not lead to an unnecessarily higher caloric intake. Based on the findings by Sekar *et al.* [3] and our findings, we suggest that much of the food advice shown in the DRV patient brochures can be adapted to healthier dietary advice [4, 5].

Due to the observational nature of the study, it is possible that a recall bias on food intake was introduced, despite taking a careful history using a validated food recall questionnaire. Furthermore, the C_{trough} was estimated using one blood sample, which could have given a distorted view. However, repeated blood samples would alter the actual (cross-sectional) study design, and the use of Bayesian estimation in combination with patient characteristics, dosage and time of ingestion is a widely accepted method in daily practice to interpret drug level results [8, 17]. Despite potential weaknesses, the results of the present study provide a good insight into the daily concomitant food intake in patients.

A controlled food effect study in patients is needed to optimize recommendations on the minimal amount of concomitant food intake to prevent unnecessary high-caloric and high-fat food intake in a patient group with already increased risks for cardiovascular and metabolic diseases.

Competing Interests

There are no competing interests to declare.

Contributors

A.D., W.F.W.B., J.G.W.K., J.W.C.A. and Y.S. were responsible for the concept and design of the study. The acquisition of laboratory and clinical data was performed by A.D., D.D., D.A.W. and T.S.W. The data was analysed by A.D. and Y.S. Both the drafting and the later critical revision of the article was conducted by A.D., T.S.W., J.W.C.A. and Y.S. The final approval of the manuscript was done by all authors.

References

- Ortiz R, Dejesus E, Khanlou H, Voronin E, van Lunzen J, Andrade-Villanueva J, *et al.* Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1-infected patients at week 48. *AIDS* 2008; 22: 1389–97.
- Arab-Alameddine M, Lubomirov R, Fayet-Mello A, Aouri M, Rotger M, Buclin T, *et al.* Swiss HIV Cohort Study. Population pharmacokinetic modelling and evaluation of different dosage regimens for darunavir and ritonavir in HIV-infected individuals. *J Antimicrob Chemother* 2014; 69: 2489–98.
- Sekar V, Kestens D, Spinosa-Guzman S, De Pauw M, De Paepe E, Vangeneugden T, *et al.* The effect of different meal types on the

- pharmacokinetics of darunavir (TMC114)/ritonavir in HIV-negative healthy volunteers. *J Clin Pharmacol* 2007; 47: 479–84.
- 4 Janssen-Cilag BV. Information for people who use Prezista®, PHNL/PRE/0113/0250 Edition. Netherlands: Janssen-Cilag B.V., 2013.
 - 5 Janssen Therapeutics, Division of Janssen Products, LP. How should I take PREZISTA®?. Beerse, Belgium, 2014.
 - 6 Janssen-Cilag BV. Prezista® Patient information, December 2010 edn. Breda, Netherlands: Janssen-Cilag b.v., 2010.
 - 7 National Institute for Public Health and Environment. Food consumption survey 2012–2016. 2017.
 - 8 Proost JH, Meijer DK. MW/pharm, an integrated software package for drug dosage regimen calculation and therapeutic drug monitoring. *Comput Biol Med* 1992; 22: 155–63.
 - 9 Truven Health Analytics LLC. Micromedex® solutions Darunavir. 2017.
 - 10 Burger DM. TDM protocollen/TDM protocols 2017. 2014.
 - 11 Boffito M, Miralles D, Hill A. Pharmacokinetics, efficacy, and safety of darunavir/ritonavir 800/100 mg once-daily in treatment-naïve and -experienced patients. *HIV Clin Trials* 2008; 9: 418–27.
 - 12 Southan C, Sharman JL, Benson HE, Faccenda E, Pawson AJ, Alexander SPH, *et al.* The IUPHAR/BPS guide to PHARMACOLOGY in 2016: towards curated quantitative interactions between 1300 protein targets and 6000 ligands. *Nucleic Acids Res* 2016; 44: D1054–68.
 - 13 Panel of experts from the Metabolic Disorders Study Group (GEAM), National Aids Plan (SPNS), Aids Study Group (GeSIDA). Executive summary of the consensus document on metabolic disorders and cardiovascular risk in patients with HIV infection. *Enferm Infecc Microbiol Clin* 2014; 33: 41–7.
 - 14 Samaras K. The burden of diabetes and hyperlipidemia in treated HIV infection and approaches for cardiometabolic care. *Curr HIV/AIDS Rep* 2012; 9: 206–17.
 - 15 Cheruvu S, Holloway CJ. Cardiovascular disease in human immunodeficiency virus. *Intern Med J* 2014; 44: 315–24.
 - 16 Achhra AC, Mocroft A, Reiss P, Sabin C, Ryom L, de Wit S, *et al.* D:A:D Study Group. Short-term weight gain after antiretroviral therapy initiation and subsequent risk of cardiovascular disease and diabetes: the D:A:D study. *HIV Med* 2016; 17: 255–68.
 - 17 van der Meer AF, Touw DJ, Marcus MA, Neef C, Proost JH. Influence of erroneous patient records on population pharmacokinetic modeling and individual Bayesian estimation. *Ther Drug Monit* 2012; 34: 526–34.