The effect of veno-venous ECMO on the pharmacokinetics of Ritonavir, Darunavir, Tenofovir and Lamivudine

DOI:

[10.1016/j.jcrc.2017.03.010](https://doi.org/10.1016/j.jcrc.2017.03.010)

Document Version

Accepted author manuscript

[Link to publication record in Manchester Research Explorer](#)

Citation for published version (APA):

Suliman, M. A. G., Ogungbenro, K., Kosmidis, C., Ashworth, A., Barker, J., Szabo-Barnes, A., Davies, A., Feddy, L., Fedor, I., Hayes, T., Stirling, S., & Malagon, I. (2017). The effect of veno-venous ECMO on the pharmacokinetics of Ritonavir, Darunavir, Tenofovir and Lamivudine. *Journal of Critical Care*, 40, 113-118. <https://doi.org/10.1016/j.jcrc.2017.03.010>

Published in:

Journal of Critical Care

Citing this paper

Please note that where the full-text provided on Manchester Research Explorer is the Author Accepted Manuscript or Proof version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version.

General rights

Copyright and moral rights for the publications made accessible in the Research Explorer are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

Takedown policy

If you believe that this document breaches copyright please refer to the University of Manchester's Takedown Procedures [<http://man.ac.uk/04Y6Bo>] or contact uml.scholarlycommunications@manchester.ac.uk providing relevant details, so we can investigate your claim.

Accepted Manuscript

The effect of veno-venous ECMO on the pharmacokinetics of Ritonavir, Darunavir, Tenofovir and Lamivudine

Mohamed A. Ghazi Suliman, Kayode Ogungbenro, Christos Kosmidis, Alan Ashworth, Julian Barker, Anita Szabo-Barnes, Andrew Davies, Lee Feddy, Igor Fedor, Tim Hayes, Sarah Stirling, Ignacio Malagon

PII: S0883-9441(16)30981-9
DOI: doi: [10.1016/j.jcrc.2017.03.010](https://doi.org/10.1016/j.jcrc.2017.03.010)
Reference: YJCRC 52447

To appear in:

Please cite this article as: Mohamed A. Ghazi Suliman, Kayode Ogungbenro, Christos Kosmidis, Alan Ashworth, Julian Barker, Anita Szabo-Barnes, Andrew Davies, Lee Feddy, Igor Fedor, Tim Hayes, Sarah Stirling, Ignacio Malagon , The effect of veno-venous ECMO on the pharmacokinetics of Ritonavir, Darunavir, Tenofovir and Lamivudine. The address for the corresponding author was captured as affiliation for all authors. Please check if appropriate. Yjcrc(2017), doi: [10.1016/j.jcrc.2017.03.010](https://doi.org/10.1016/j.jcrc.2017.03.010)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Title Page**Title**

The effect of veno-venous ECMO on the pharmacokinetics of Ritonavir, Darunavir, Tenofovir and Lamivudine.

Author names and affiliations

Mohamed A. Ghazi Suliman^A, Kayode Ogungbenro^B, Christos Kosmidis^C, Alan Ashworth^A, Julian Barker^A, Anita Szabo-Barnes^A, Andrew Davies^A, Lee Feddy^A, Igor Fedor^A, Tim Hayes^A, Sarah Stirling^A, Ignacio Malagon^A

^A The North West Heart and Lung Centre, The University Hospital of South Manchester, Manchester M23 9LT, United Kingdom

^B Manchester Pharmacy School, The University of Manchester, Manchester M13 9PT, United Kingdom

^C The Infectious Diseases Unit, The University Hospital of South Manchester, Manchester M23 9LT, United Kingdom

Corresponding author

Dr Mohamed A Ghazi Suliman MRCP FRCA¹,

Email address: mzyvmas@yahoo.co.uk

¹ Department of Anaesthesia, The Royal Liverpool and Broadgreen University Hospital NHS Trust, Prescott Street, Liverpool L7 8XP, United Kingdom

Abstract

Introduction: To our knowledge, there is no published data on the pharmacokinetic (PK) profile of antiretroviral (ART) drugs on patients undergoing extracorporeal membrane oxygenation (ECMO) therapy. We present PK analyses of Ritonavir, Darunavir, Lamivudine and Tenofovir in a patient with HIV who required veno-venous ECMO (VV-ECMO).

Methods: Plasma concentrations for Ritonavir, Darunavir, Tenofovir and Lamivudine were obtained while the patient was on ECMO following pre-emptive dose adjustments. Published population PK models were used to simulate plasma concentration profiles for the drugs. The population prediction and the observed plasma concentrations were then overlaid with the expected drug profiles using the individual Bayesian post-hoc parameter estimates.

Results: Following dose adjustments, the PK profiles of Ritonavir, Darunavir and Tenofovir fell within the expected range and appeared similar to the population prediction, although slightly different for Ritonavir. The observed data for Lamivudine and its PK profile were completely different from the data available in the literature.

Conclusions: To our knowledge, this is the first study reporting the PK profile of ART drugs during ECMO therapy. Based on our results, dose adjustment of ART drugs while on VV-ECMO may be advisable. Further study of the PK profile of Lamivudine is required.

Introduction

Veno-venous Extracorporeal Membrane Oxygenation (VV ECMO) has become an established rescue therapy for patients with severe acute respiratory failure that is refractory to conventional mechanical ventilation (MV)^[1]. Furthermore, there are several reports in the literature of the successful treatment of ARDS in human immunodeficiency virus (HIV)-positive patients using VV ECMO^[2-3].

There is limited data available regarding the pharmacokinetics of drugs while on ECMO. Even when available these are mostly in neonates and not in critically ill adults. Available data indicate variability and lack of consistency in the effect of ECMO on the PK of drugs. The most common effects of ECMO on the PK of drugs are sequestration in the circuit, increased volume of distribution and decreased drug elimination. These changes are compounded by the physiological changes seen in critically ill patients when compared to other patient populations. Consequently, drug plasma concentrations and their therapeutic effects are also affected^[4-5].

Several studies investigating the pharmacokinetics of ART drugs on patients undergoing intermittent haemodialysis have indicated that dosage adjustments were often necessary, primarily for two reasons: Firstly, the influence of end-stage renal failure on the pharmacokinetic phases of drugs in general (e.g. distribution, protein binding, elimination, etc.). And secondly, drug dialysability and dialysis clearance and their impact on drug and metabolite elimination^[6].

To our knowledge, there is no data on the PK profile of ART drugs on patients treated with VV-ECMO.

We present pharmacokinetic analyses of Ritonavir, Darunavir, Lamivudine and Tenofovir in a patient with HIV who required VV ECMO treatment following the development of acute respiratory failure not responding to conventional treatment.

Written informed consent was sought and obtained from the patient for the purpose of publishing this manuscript.

Case Report

A 50 year old man, diagnosed with HIV and treated for several years, presented to hospital with shortness of breath and stridor. His past medical history included a history of recurrent laryngeal papillomas which required debulking surgery in the past. His pre-admission immuno-virological profile was CD4 counts above 500 cells per cubic ml of blood and an undetectable viral load. His drug history included Truvada (Tenofovir disoproxil 245mg, Emtricitabine 200mg) once daily (OD), Darunavir 800mg OD and Ritonavir 100mg OD.

A bedside flexible nasoendoscopy was performed by the ear nose and throat (ENT) surgical team. This revealed bilateral papillomas on the arytenoids and on the right vocal cord, with a normal epiglottis and an otherwise patent airway. He was listed for urgent papilloma debulking surgery. In the meantime, he received dexamethasone and nebulized adrenaline for symptomatic relief, with some initial improvement. Co-Amoxiclav antibiotic treatment was started empirically.

Following an initial period of stability, his oxygen requirements increased. He was admitted to the intensive care unit with Type II respiratory failure 5 days following his initial admission, and required endotracheal intubation and mechanical ventilation shortly afterwards. VV ECMO therapy was initiated 14 days following his admission to the referring intensive care unit.

Microbiology screening revealed Influenzae A (CT 29) on a throat swab, and a H1N1 (9) strain was also isolated. Sputum showed a scanty coliform growth. A computed tomography (CT) chest scan revealed extensive consolidation and ground glass changes in the upper lobes with centrilobular emphysema. Later in his admission, a bronchoalveolar lavage grew *Aspergillus*, which raised the suspicion of invasive Aspergillosis.

He was treated with Piperacillin/Tazobactam (later changed to Meropenem), Clarithromycin, Metronidazole, Tamiflu (later switched to IV Zanamivir due to gastrointestinal ileus), prophylactic Co-trimoxazole, and Ambisome.

The critical care team sought advice from the hospital's HIV and infectious diseases specialists about the effect of ECMO on the PK profile of the ART drugs, and whether there was utility in monitoring their plasma concentrations whilst on ECMO. An extensive literature search revealed no data was available to provide guidance in this subject.

Doses of ARTs were increased pre-emptively. Monitoring of the patient's CD4 count and viral load was performed to check for the therapeutic adequacy of the adjusted dosing of the ARTs and for breakthrough viraemia.

Ritonavir and Darunavir were increased to twice daily (BD) dosing on day 18, four days after initiation of VV ECMO therapy. Tenofovir and Lamivudine were substituted for Truvada due to a supply problem with the latter. On day 35, three weeks after the initiation of VV ECMO therapy, the patient had an undetectable viral load and a CD4 count of 131.

The patient's respiratory function and lung mechanics gradually improved. He was successfully weaned off VV ECMO on day 37 of his hospital admission. In total, he received 23 days of VV ECMO therapy. He was switched back to his usual ART regime (Truvada, Darunavir, Ritonavir), and later transferred to the general intensive care unit on day 38 for ongoing respiratory weaning. He was repatriated to his original referring hospital on day 45 of his hospital admission and was finally discharged home six months after his initial admission following a prolonged period of respiratory and physical rehabilitation.

Methods

Plasma concentration data were obtained for Ritonavir, Darunavir, Tenofovir and Lamivudine. Plasma concentration data were obtained while the patient was on ECMO and no samples were obtained before or after ECMO therapy. The dosage regimens of the drugs were also modified during ECMO:

- Ritonavir – 100 mg once daily before ECMO and 100 mg twice daily during ECMO

- Darunavir – 800 mg once daily before ECMO and 800 mg twice daily during ECMO
- Lamivudine – 300 mg twice daily during ECMO only
- Tenofovir – 245 mg once daily before ECMO, changed to twice daily dosing (245mg and 123 mg respectively) during ECMO.

The above dosage regimens were used to simulate expected plasma concentration profiles for the drugs using already available population pharmacokinetic models published in the medical literature. 95% prediction intervals were obtained for each drug and this was overlaid with the observed plasma concentration in the patient. The prediction intervals represent expected range of plasma concentrations of these drugs in the population based on the dosage regimen used by the patient, assuming the patient characteristics were similar to the individuals used to develop the original population pharmacokinetic models.

It was expected that if there were no effect of ECMO on the pharmacokinetic profiles of the drugs, the observed plasma concentrations would be within the population-based prediction intervals. The simulations were done using MATLAB® 2016a (The MathWorks Inc, 1 Apple Hill Drive, Natick, MA 01760-2098, United States).

The models were also used to obtain individual Bayesian post-hoc parameter estimates for each of the drugs. This was done using NONMEM® 7.3.0 (ICON PLC, 820 W. Diamond Avenue, Suite 100, Gaithersburg, MD 20878, United States). These parameter estimates can be interpreted as the estimates for this individual if the individual was part of the original analysis that was used to develop the original population pharmacokinetic model.

The expected drug profiles using the individual Bayesian post-hoc parameter estimates were overlaid with the population predictions and the observed data. Plots of the individual predictions using the Bayesian post-hoc parameter estimates against observed data were obtained for each of the drugs.

During simulation, it was assumed that the patient had been on Ritonavir, Darunavir, and Tenofovir for at least one month prior to hospital admission, a time period long

enough for the drugs to be at a steady state. Conversely, the patient started Lamivudine during ECMO and this was reflected in the data that was used for the simulation.

Pharmacokinetic Properties

Ritonavir

Ritonavir is a potent HIV protease inhibitor. It has very good oral absorption – between 0.6 and 0.8 fractions of the dose is absorbed. It is highly protein bound (99%), and possesses a relatively large volume of distribution ranging between 20 to 40L. It is extensively metabolised, mainly by CYP3A enzymes, and has a terminal half-life of 3 to 5 hours^[7-8]. Ritonavir is also a potent CYP3A4 inhibitor.

Darunavir

Darunavir is a very potent HIV protease inhibitor. Darunavir is rapidly absorbed following oral administration, reaching its peak after 2.5-4 hours. Absolute bioavailability is approximately 0.37 which increases by more than two-fold when co-administered with Ritonavir. Darunavir is 95% protein bound at clinically relevant plasma concentrations, mainly to α 1-acid glycoprotein. Its volume of distribution is approximately 90L. It is extensively metabolised by CYP3A enzymes with a terminal half-life of 15 hours^[8-9].

Tenofovir

Tenofovir is a nucleotide reverse transcriptase inhibitor administered as a pro-drug (Tenofovir disoproxil fumarate). Following oral administration, Tenofovir is rapidly absorbed reaching its peak at 0.8 – 1 hour of administration. Its oral bioavailability is approximately 25%. Tenofovir's plasma protein binding is low (less than 1%) and its volume of distribution is approximately 56L. Tenofovir is eliminated mostly unchanged in the urine and its terminal half-life is approximately 17 hours^[10].

Lamivudine

Lamivudine is a nucleotide reverse transcriptase inhibitor used in the treatment of HIV. Lamivudine is rapidly absorbed orally, reaching maximum concentration at 0.5 – 1 hour after the dose and its absolute bioavailability is approximately 82%. Plasma

protein binding of Lamivudine is concentration dependent (approximately 35-50% at 100µg/L plasma concentration). The volume of distribution is roughly 90L. Approximately 70% of the administered dose is eliminated unchanged in the urine and the terminal half-life is around 5-7 hours ^[11].

Results

A summary of the doses and plasma sample during ECMO is shown below:

	Ritonavir		Darunavir		Tenofovir		Lamivudine		
Time (hours)	Dose (mg)	Conc (mg/L)	Dose (mg)	Conc (mg/L)	Dose (mg)	Conc (mg/L)	Time (hours)	Dose (mg)	Conc (mg/L)
0	100	-	800	-	245	-	0	300	0
21.5	-	0.246	-	-	-	0.095	7.75	-	1.038
22	100	-	800	-	245	-	10	300	-
34	100	-	800	-	123	-	10.75	-	0.686
38	-	0.264	-	9.204	-	-	19.5	-	1.675
45.75	-	0.128	-	6.262	-	0.085	22	-	1.29
46	100	-	800	-	245	-	24	300	-
48.75	-	0.269	-	9.825	-	0.308	31.67	-	1.577
57.5	-	0.089	-	5.843	-	0.135	34	300	-
58	100	-	800	-	123	-	34.17	-	1.549
60	-	0.244	-	12.994	-	0.206	43.5	-	2.713
69.67	-	0.097	-	5.427	-	0.1	46	-	2.189
70	100	-	800	-	245	-	48	300	-
72.17	-	0.36	-	12.942	-	0.405	55.5	-	2.794
81.5	-	0.149	-	7.114	-	0.172			
82	100	-	800	-	123	-			
84	-	0.639	-	12.959	-	0.306			
93.5	-	0.15	-	6.481	-	0.147			

Population PK models

Data on population pharmacokinetics of several antiretroviral (ART) drugs used in the treatment of patients diagnosed with HIV is widely available in the literature. The population PK models for Ritonavir and Darunivir were obtained from Molto et al^[12]. For Ritonavir, this was based on a one compartment first order absorption model. For Darunivir, this was based on a two compartment first order absorption model. For Tenofovir, the population PK model was obtained from Baheti et al^[13], and this was based on a two compartment first order absorption model. The population PK model for Lamivudine was obtained from Bazzoli et al^[14]. This was based on a one compartment zero order absorption model.

Simulations

Simulated 95% prediction intervals (grey area), observed data (dark circles) and individual prediction based on Bayesian post-hoc estimates (red line) are shown in the figure below on linear and logarithmic scales. The x-axis was also truncated in the second plot to focus on the area of interest, i.e. when the blood samples were collected whilst the patient was on ECMO.

Ritonavir

Darunavir

Tenofovir

Lamivudine

Observed vs Prediction plot

Plots of the observed plasma concentrations and the individual predictions using Bayesian post hoc estimates are shown below. The red squares represent the model prediction for a typical individual in the population (based on the data used during model development by the authors), and the blue circles are the predictions (using Bayesian post hoc estimates) for this individual.

Ritonavir

Tenofovir

Darunavir

Lamivudine

Discussion

There are several reports in the literature describing the use of extracorporeal circuits, namely haemodialysis, in HIV-infected patients. These reports indicate that factors such as molecular weight, protein binding and water solubility affect the pharmacokinetic profiles of antiretroviral drugs. The use of therapeutic drug monitoring of ARTs in patients undergoing haemodialysis has led to appropriate dose adjustments as well as changes in the timing of drug administration to ensure antiretroviral therapy remained effective ^[15 - 16].

To our knowledge, this is the first study that looked at the pharmacokinetic profile of antiretroviral drugs during veno-venous extracorporeal membrane oxygenation therapy. In theory, ART plasma concentrations may be lower during ECMO due to possible drug sequestration, the associated systemic inflammatory response, and fluid shifts related to critical illness.

There are numerous publications on population pharmacokinetic analyses of antiretroviral drugs that provide data on the pharmacokinetic profiles of these drugs

[17]. Analysis of pharmacokinetics data using the population approach has been widely used in drug development and it has now become a standard tool in the pharmaceutical industry and a key component of model-based approaches to drug development [18 - 19]. The approach uses mathematical equations that have been derived from compartmental models to obtain population parameter estimates that describe a mean profile in the data, and individual deviations from these are estimated as a measure of variability in the data. An important advantage of the approach is its ability to combine sparse data from individuals which otherwise cannot be used to obtain individual parameter estimates but can be used for a joint analysis, while individuality in the data is still maintained. The model summarizes the pharmacokinetic property of a drug and can be used to simulate plasma concentrations of the drug under a different scenario i.e. dose.

A population PK model already developed and validated can also be used as prior information to obtain *maximum a priori* (MAP) Bayesian estimates for the individual using limited sample from the individual in dedicated softwares. This approach has been used for Bayesian dose individualization where the population PK model provides information about the PK of the drug in the general population and, combined with a number of samples in the individual, parameter estimates that describe the PK of the drug in the individual can be obtained. The individual parameter estimates can be used to simulate PK profiles mainly to determine the dosage regimen for that individual that will achieve a target exposure that has been linked to efficacy [20].

Because the population PK model provides some information about the PK of the drug during the determination of the *maximum a priori* (MAP) Bayesian estimates for an individual, and the PK of drugs are affected by patients characteristics such as disease condition, it is therefore important that the individual used for MAP estimation as well as the population used to develop the original model both have similar characteristics. Therefore, an assumption was made that our patient's characteristics were similar to the population on which the original analyses was performed.

The observed data for Ritonavir, Darunavir and Tenofovir in this patient fell within the expected range based on the model prediction using the dosage regimen

received by the patient. However, the drug levels of Ritonavir and Tenofovir in this patient were lower than the expected concentrations for a typical individual in the population. Conversely, the observed data for Darunavir was higher than expected concentration for a typical individual in the population.

The profile obtained using the individual Bayesian post-hoc estimate for Ritonavir appeared to be slightly different from the model prediction. This may suggest changes in the PK of the drug during ECMO. The profile obtained using the individual Bayesian post-hoc estimate for Darunavir and Tenofovir appeared to be similar to the population prediction by the published models.

The observed data for Lamivudine in this patient was outside of the model prediction using the dosage regimen received by the patient. The profile obtained using the individual Bayesian post-hoc estimate is also different from the population PK prediction using the published model. Therefore, based on our data, it appears that the pharmacokinetics of Lamivudine under ECMO is completely different from the predicated PK of the drug based on the published population model.

Based on these results, the decision taken by our multidisciplinary team to pre-emptively increase the dosage regimens of ARTs during VV ECMO therapy seems appropriate. Prospective measurement of the viral load and CD4 count indicated no breakthrough viraemia. The CD4 count of 131 may have been influenced by the severity of critical illness and the concomitant infections, namely H1N1 influenza and invasive Aspergillosis.

There are several limitations in this study. It was assumed that the patient had been compliant with the ART drug therapy in the period prior to their admission. More importantly, the lack of drug plasma concentrations prior to ECMO did not allow us to determine precisely the mechanism of the effects of ECMO, if any, on the PK of the drugs. Data prior to ECMO is needed to provide reference for changes in plasma concentration that have been caused by ECMO. Parameter estimates obtained prior to ECMO and during ECMO will provide insight into the mechanism of the effect of ECMO on the PK of the drugs.

There was also significant delay in obtaining antiretroviral plasma concentrations results, and hence, mathematical analyses were done subsequent to the patient's discharge from hospital. Furthermore, only single measurements of viral load and CD4 count were obtained during the period of ECMO therapy. A series of measurements would have been more helpful to obtain a trend and assess treatment efficacy more accurately.

These drugs were enterally administered, and at times their bioavailability and pharmacokinetics may have been influenced by periods of intestinal ileus and malabsorption.

Conclusion

To our knowledge, this is the first study reporting the pharmacokinetic profile of antiretroviral drugs during ECMO therapy. The PK profiles of Darunavir and Tenofovir fell within the expected range based on the model prediction following the adjusted dosage regimen. The profile obtained for Ritonavir appeared to be slightly different from the model prediction, which may suggest changes in the PK of the drug during ECMO.

On the other hand, the PK profile of Lamivudine was completely different from the data available in the literature. The observed data for Lamivudine was outside of the model prediction and the profile obtained using the individual Bayesian post-hoc estimate was also different from the population PK prediction. Therefore, it appears that the pharmacokinetics of Lamivudine under ECMO is completely different from the population-based PK predictions of the drug.

Based on our results, and until more data is available in the literature, we conclude that dose adjustments may be advisable for Darunavir, Tenofovir and Ritonavir while on VV-ECMO. Further research is required to study the pharmacokinetic profile of Lamivudine during ECMO therapy.

References

1. Terragni P, Faggiano C, Ranieri V. Extracorporeal membrane oxygenation in adult patients with acute respiratory distress syndrome. *Current Opinion in Critical Care*. 2014; 20(1): 86-91.
2. Samalavicius R, Serpytis M, Ringaitiene D, Grazulyte D, Bertasiute R, Rimkus B, Matulionyte R, Ambrazaitiene R, Sipylaite J, Kacergius T, Griskevicius L. Successful use of extracorporeal membrane oxygenation in a human immunodeficiency virus infected patient with severe acute respiratory distress syndrome. *AIDS Research and Therapy*. 2014; 11:37. doi: 10.1186/1742-6405-11-37.
3. De Rosa F, Fanelli V, Corcione S, Urbino R, Bonetto C, Ricci D, Rinaldi M, Di Perri G, Bonora S, Ranieri M. Extra Corporeal Membrane Oxygenation (ECMO) in three HIV-positive patients with acute respiratory distress syndrome. *BMC Anesthesiology*. 2014; 14:37. doi: 10.1186/1471-2253-14-37.
4. Boucher B, Wood G, Swanson J. Pharmacokinetic changes in critical illness. *Critical Care Clinics*. 2006; 22(2): 255-71, vi.
5. Shekar K, Fraser JF, Smith M, Roberts J. Pharmacokinetic changes in patients receiving extracorporeal membrane oxygenation. *Journal of Critical Care*. 2012; 27(6): 741. e9-18. doi: 10.1016/j.jcrc.2012.02.013.
6. Izzedine H, Launay-Vacher V, Baumelou A, Deray G. An appraisal of antiretroviral drugs in hemodialysis. *Kidney Int*. 2001; 60(3): 821-30.
7. Hsu A, Granneman G, Bertz R. Ritonavir. *Clinical Pharmacokinetics*. 1998; 35: 275-291.
8. Molto J, Xinarianos G, Miranda C, Pushpakom S, Cedeno S, Clotet B, Owen A, Valle M. Simultaneous pharmacogenetics-based population pharmacokinetic analysis of darunavir and ritonavir in HIV-infected patients. *Clinical Pharmacokinetics*. 2013; 52: 543-553.
9. Rittweger M, Arastéh K. Clinical Pharmacokinetics of Darunavir. *Clinical Pharmacokinetics* 2007; 46: 739-756.
10. Kearney BP, Flaherty JF, Shah J. Tenofovir Disoproxil Fumarate. *Clinical Pharmacokinetics*. 2004; 43: 595-612.
11. Johnson M, Moore K, Yuen G, Bye A, Pakes G. Clinical Pharmacokinetics of Lamivudine. *Clinical Pharmacokinetics*. 1999; 36: 41-66.

12. Moltó J, Xinarianos G, Miranda C, Pushpakom S, Cedeño S, Clotet B, Owen A, Valle M. Simultaneous pharmacogenetics-based population pharmacokinetic analysis of Darunavir and Ritonavir in HIV-infected patients. *Clinical Pharmacokinetics*. 2013; 52(7): 543-53. doi: 10.1007/s40262-013-0057-6.
13. Baheti G, Kiser J, Havens P, Fletcher C. Plasma and intracellular population pharmacokinetic analysis of Tenofovir in HIV-1-infected patients. *Antimicrobial Agents and Chemotherapy*. 2011; 55(11): 5294-9. doi: 10.1128/AAC.05317-11.
14. Bazzoli C, Bénech H, Rey E, Retout S, Salmon D, Duval X, Tréluyer J, Mentré F. Joint population pharmacokinetic analysis of Zidovudine, Lamivudine, and their active intracellular metabolites in HIV patients. *Antimicrobial Agents and Chemotherapy*. 2011; 55(7): 3423-31. doi: 10.1128/AAC.01487-10.
15. Giguère P, La Porte C, Zhang G, Cameron B. Pharmacokinetics of Darunavir, Etravirine and Raltegravir in an HIV-infected patient on haemodialysis. *AIDS*. 2009; 23(6): 740-742
16. Joseph A, Khoo S. Value of therapeutic drug monitoring in the management of patients with HIV infection undergoing haemodialysis. *International Journal of STD and AIDS*. 2004; 15(1): 67-8.
17. Aarons L. Population pharmacokinetics. *International Journal of Clinical Pharmacology, Therapeutics and Toxicology*. 1992; 30: 520-522.
18. Aarons L. Population pharmacokinetics: theory and practice. *British Journal of Clinical Pharmacology*. 1991; 32: 669-670.
19. Musuamba FT, Mourad M, Haufroid V, De Meyer M, Capron A, Delattre IK, Verbeeck RK, Wallemacq P. Statistical tools for dose individualization of mycophenolic acid and tacrolimus co-administered during the first month after renal transplantation. *British Journal Clinical Pharmacology*. 2013; 75: 1277-1288.
20. Vikram L, Singh R, Sandeep S, Tarun J, Mohan D. Population pharmacokinetics of antiretroviral agents: An overview. *International Research Journal of Pharmacy*. 2012; 3(7): 75-85

Conflicts of interest: None

Highlights

This is the first study investigating the PK profile of antiretrovirals during ECMO.

Population-based predications were compared with plasma drug concentrations on ECMO.

Ritonavir, Darunavir and Tenofovir were in the expected range after dose adjustments.

The observed data for Lamivudine was completely different from predictions.

We conclude that dose adjustments of ART drugs while on VV-ECMO may be advisable.