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Research Article

Treatment of Infants and Children HIV- or Coronavirus-Infected with Lopinavir/Ritonavir: Clinical Pharmacology of Lopinavir/Ritonavir

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Abstract

Lopinavir is structurally similar to ritonavir but is 3- to 10-fold more potent against HIV-1. This agent is active against HIV-1 and HIV-2. Lopinavir is co-formulated with ritonavir which is a CYP3A4 inhibitor. Ritonavir is a peptidomimetic HIV protease inhibitor and is active against HIV-1 and HIV-2. The formulation of lovirapin/ritonavir is available in tablets and in oral solution, may be administered on the basis on body-surface-area or body-weight, and lovirapin/ritonavir dose is 300/75 mg/m^2 twice-daily in infants aged 14 days to 12 months, 200/50 and 400/100 mg twice-daily in children with a body-weight <40 kg and >40 kg, respectively. Lovirapin/ritonavir was found efficacy and safe in infants and children. Lopinavir half-life is about 4 and 6 hours in infants and children, respectively. Lopinavir/ritonavir interacts with drugs and induces adverse-effects in infants and children. Treatment with lopinavir/ritonavir successfully cured HIV- and coronavirus-infected infants and children, and the prophylaxis with this drug combination was found useful in naïve- and experienced infants and children HIV- or coronavirus-infection, and it is recommended in breastfeeding newborn infants whose mothers are infected in order to prevent vertical transmission of HIV or coronavirus. Some HIV may become resistant to lopinavir/ritonavir and the mechanism of resistance is the mutation of protease which impairs its efficacy. The aim of this study is to review the published data on lopinavir/ritonavir-dosing, efficacy, safety, pharmacokinetics, interaction with drugs, adverse-effects, treatment, prophylaxis, infants and children use in pregnancy, and viral-resistance in infants and children.

Keywords: Lopinavir/Ritonavir; Pharmacokinetics; Adverse-effects; Treatment; Prophylaxis; Pregnancy

Introduction

Mechanism of action of lopinavir/ritonavir (Kaletra®) and antiviral activity

Ritonavir is a peptidomimetic Human Immunodeficiency Virus (HIV) Protease Inhibitor (PI) designed to complement the C2 axis of symmetry of the enzyme active site. Ritonavir is active against bot HIV-1 and HIV-2. Ritonavir is mostly used as a pharmacokinetic enhancer (CYP3A4 inhibitor). Lopinavir is structurally similar to ritonavir but is 3-to 10-fold more potent against HIV-1. This agent is active against HIV-1 and HIV-2. Lopinavir/ritonavir is also used to treat coronavirus infection. Lopinavir is available only in combination with low-doses of ritonavir [1].

Absorption and distribution of lopinavir/ritonavir

The interindividual variability of ritonavir is high, with variability exceeding 6-fold the trough concentration in patient given 600 mg or ritonavir twice-daily as capsules. The adult lopinavir/ritonavir dose is 400/100 mg (2 tablets) twice-daily or 800/200 mg (4 tablets) once-daily. Lopinavir/ritonavir should not be dosed once-daily in treatment-experienced patients. Lopinavir/ritonavir is approved for the use in paediatric patients, aged 14 days or older, with dose based either on body-weight or body-surface-area. A paediatric tablet formulation is available for use in children aged >6 months. Lopinavir is absorbed rapidly after oral administration. Food has a minimal effect on bioavailability. Although the tablets contain lopinavir/ritonavir in a fixed 4:1 ratio, the observed plasma concentration ratio for these two drugs following oral administration is nearly 20:1, reflecting the sensitivity of lopinavir to the inhibitory effect of ritonavir on CYP3A4. Both lopinavir and ritonavir are highly bound to plasma proteins, mainly α1-acid glycoprotein, and have a low fractional penetration into the cerebrospinal fluid and semen [1] The molecular structures of lopinavir and ritonavir are shown in figure 1a and 1b respectively.

Literature search

The literature search was performed electronically using PubMed database as search engine and the cut-off point was the 2nd of December 2020. The following key words were used: "lopinavir/ritonavir efficacy, safety infants, children", "lopinavir/ritonavir pharmacokinetics infants, children", "lopinavir/ritonavir drug interactions", "lopinavir/ritonavir adverse-effects infants, children", "lopinavir/ritonavir treatment infants, children", "lopinavir/ritonavir prophylaxis infants, children", "lopinavir/ritonavir during pregnancy", and "lopinavir/ritonavir viral-resistance". In addition, the books: The pharmacological basis of therapeutics, Neonatal Formulary, and The British National Formulary for Children were consulted. The manuscript is written according to the "Instructions for authors".

Results

Administration schedules of lopinavir/ritonavir to infants and children

Oral administration to infants [2]: Administration by solution**:** *Infants aged 14 days to 12 months. Give: 300/75 mg/m^2 (i.e. 300 mg of lopinavir and 75 mg of ritonavir). Administration twice-daily seems to offer adequate serum levels.

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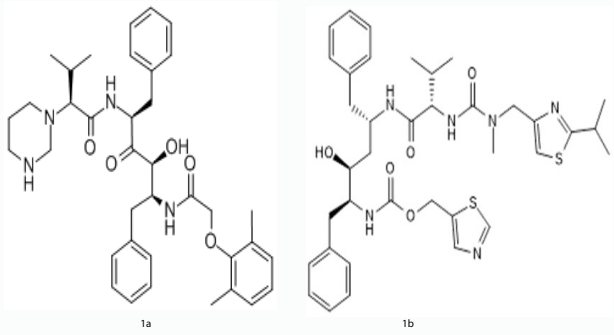

Figure 1a: Molecular structure of lopinavir (molecular weight = 1350 grams/mole).
Figure 1b: Molecular structure of ritonavir (molecular weight = 721 grams/mole).

Older infants. Give: 230/57.5 mg/m^2 twice-daily.

*Lopinavir/ritonavir should not be administered to infants aged <14 days.

Oral administration to children [3]: Administration by tablets: Children aged 2 to 17 years (body-weight up to 40 kg and body-surface-area 0.5 to 0.7 m^2). Give: 200/50 mg twice-daily.

Children aged 2 to 17 years (body-weight up to 40 kg and body-surface-area 0.8 to 1.1 m^2). Give: 300/75 mg Children aged 2 to 17 years (body-weight of 40 kg and above and body-surface-area 1.2 m^2 and above). Give: 400/100 mg twice-daily.

Administration by oral solution: Children aged 6 months to 17 years. Give: 2.9 ml/m^2 surface-area twice-daily (maximum per dose = 5 ml).

Lopinavir/ritonavir efficacy and safety in infants and children

Despite higher clearance in infants, aged 6 weeks to 6 months, a twice-daily-dose of 300/75 mg/m^2 of lopinavir/ritonavir provided similar exposure to that in older children, was well tolerated and provided favourable virological and clinical efficacy [4]. The safety, tolerability, and efficacy of lopinavir/ritonavir in infants aged, ≥ 6 weeks to <6 months were observed following a standard-dose of lopinavir/ritonavir [4]. A lopinavir/ritonavir low-dose of 0.9 mg/m^2 was safe and effective as higher doses in children [5].

Pharmacokinetics of lopinavir/ritonavir in infants

Verweel et al. [6], determined whether the recommended dose of 230/57.5 mg/m^2 of lopinavir/ritonavir results in optimal lopinavir exposure in all age groups. Twenty-three HIV-infected children, aged 5.6 years (range, 0.4 to 13.2) were enrolled. The $AUC_{0\text{-}12\ hours}$, Peak, and trough concentrations of lopinavir are: 75.3 ±33.7 µg*h/ml, 9.33±3.27 µg*h/ml, and 3.68±2.48 µg/ml, respectively, and their interindividual variability is high. Through concentration was inadequate in 7 of 23 children (30.4%). Significantly more children, aged <2 years, had inadequate trough concentration compared to children aged >2 years. Dose increase to 300/75 mg/m^2 of lopinavir/ritonavir led to trough concentration >1.0 µg/ml. The studied dosing-regimens provided excellent viral suppression for naïve and pre-treated children. Lopinavir exposure is significantly reduced in children <2 years. Prospective pharmacokinetic studies using 300/75 mg/m^2 of lopinavir/ritonavir in this age population are urgently warranted.

Chadwick et al. [7], investigated the pharmacokinetics of lopinavir/ritonavir in 21 infants infected by HIV-1, aged 14.7 weeks (range, 6.9 to 25.7) weighing ≤ 2.5 kg who were treated with lopinavir/ritonavir at a dose of 230/57.5 mg/m^2, and two infants discontinued the therapy prior to 24 weeks of treatment. Pharmacokinetic parameters were available in 18 infants and Table 1 shows the pharmacokinetic parameters of lopinavir and ritonavir. This table shows that there is a large interindividual variability of pharmacokinetic parameters.

Best et al. [8], compared lopinavir/ritonavir exposure between whole and crushed tablets in 12 HIV-infected children with a median age of 13 years (range, 10 to 16) who took lopinavir/ritonavir at a daily dose of 550/138 mg/m^2 divided in 2 equal parts which were given twice-daily. Table 2 shows lopinavir and ritonavir pharmacokinetic parameters obtained with whole and crushed tablets. Lopinavir $AUC_{0\text{-}24\ hours}$, peak concentration, and the concentration at 12 hours (trough concentration) after dosing (C_{12}) were greater following the administration of whole tablets in spite of the longer time to obtain peak concentration (Tmax), thus the lopinavir exposition is greater with whole tablets. In contrast, no difference of these parameters was observed for ritonavir.

Chokephaibulkit et al. [9], reported the pharmacokinetics of lopinavir/ritonavir in 12 HIV-1 infected children with median age and body-weight of 13.1 years (range, 9.3 to 17.7), and 40.8 kg (range, 26.8 to 50.3), respectively, who received lopinavir/ritonavir at a dose of 300/75 mg twice-daily or 350/87.5 mg once-daily. Concomitant therapy included tenofovir and lamivudine in six children and lamivudine, efavirenz in five children, and efavirenz alone in one child. The median duration of lopinavir/ritonavir exposure was 2.06 years (range, 1.4 to 3.0). Table 3 shows the pharmacokinetic parameters of lopinavir and ritonavir given twice-daily or once-daily. Lopinavir exposition assessed as the $AUC_{0\text{-}24\ hours}$ was not different according to the two dosing-regimens, thus once-daily regimen is a simplified administration scheme. Lopinavir trough concentration was significantly lower in children who received efavirenz, but all children were able to maintain viral suppression (<40 copies/ml) up to 48 weeks with once-daily regimen. The impact of efavirenz (CYP3A4 inducer) on lopinavir trough concentration was more pronounced in once-daily dosing-regimen.

Puthanakit et al. [5], assessed the pharmacokinetics of lopinavir and ritonavir at a stand-dose and low-dose to 24 children with median and (inter quartile range) of age, body-weight and body-surface-area of 9.5 years (range, 7.0 to 12.3), 22 kg (range, 19 to 31), and 0.9 mg/m^2 (range, 0.8 to 1.2), respectively. Table 4 shows the standard-dose and the low-dose and Table 5 summarizes the pharmacokinetics of lopinavir and ritonavir according to the two doses. The pharmacokinetic parameters of lopinavir and ritonavir are not different according the two doses bud there is a large interindividual variability in the pharmacokinetic parameters obtained with the two drugs.

Jullien et al. [10] investigated the pharmacokinetics of lopinavir in 157subjects HIV-infected aged from 3 days to 18 years, the age and body weight were: 9.1±4.8 years and 29.0±14.9 kg, respectively. The mean lopinavir dose was109±3.7 mg/kg or 288±66 mg/m^2 and this dose was administered twice-daily. Table 6 shows the effect of covariates (body-weight and age) on the objective function and Table 7 summarizes the population pharmacokinetic parameters. For the basic model, estimates of the values for TBC/F, DV/F and the constant rate of absorption (K_a) were: 2.86±0.15 L/h, 24.8±11.8 L, and

Table 1: Baseline data, lopinavir and ritonavir pharmacokinetic parameters which were obtained in 12 infants with a median age and a body-surface-area of 14.7 weeks and 0.31 m^2, respectively. Lopinavir/ritonavir was administered at a dose of 300/75 mg/m^2, by Chadwick et al. [4].

	Baseline data				Non-compartmental parameters			Lopinavir compartmental parameters				
	Age (months)	Weight (kg)	BSA (m^2)	Dose (mg)	LVP C_{pre} (µg/ml)	LPV AUC (µg*h/ml)	RTV AUC (µg*h/ml)	TBL/F (L/h/kg)	TBC/F (L/h/m^2)	K_a	V/F	t1/2
Mean	3.7	6	0.32	87.6	2.68	74.5	2.8	0.23	4.3	0.77	1.2	4.2
Median	3.4	5.5	0.31	80	2.37	67.2	2.6	0.19	3.7	0.36	0.92	3.7
± SD	1.4	1.5	0.05	16.6	2.7	37.9	1.5	0.14	2.5	1.38	0.86	2.8
% CV	39	25	15	19	95	51	53	60	58	178	69	67
Minimum	1.6	4.4	0.25	64	<0.1	23.7	1	0.07	2.34	0.18	0.34	1.2
Maximum	5.9	10.5	0.44	128	8.4	164	5.8	0.61	11.3	6.2	3.97	13.1

LPV = Lopinavir; RTV = Ritonavir; BSA = Body Surface Area; $LVPC_{pre}$ = Predose Concentration of Lopinavir; AUC = Area under the Concentration-Time Curve; TBC = Total Body Clearance adjusted for body-weight (kg) or body-surface-area (m^2); K_a = Absorption Rate Constant; F = bioavailability; V/F = distribution volume; $t_{1/2}$ = half-life; %CV = %coefficient of variation.

Table 2: Pharmacokinetic parameters of lopinavir and ritonavir which were obtained with whole or crushed tablets. Figures are the median and (interquartile range), by Best et al. [8].

Parameter	Whole tablets[1]	Crushed tablets[1]	Crushed/wohle[2]	*P-value
Lopinavir				
$AUC_{0\text{-}12hours}$ (mg*h/L)	144 (101 - 202)	92 (79 - 103)	0.55 (0.45 - 0.69)	0.003
TBC/F (L/h/m^2)	2.3 (1.3 - 2.6)	3.2 (2.5 - 3.5)	1.8 (1.5 - 2.2)	0.003
Tmax (h)	4.0 (2.0 - 4.0)	2.0 (1.5 - 4.0)	NA	NA
Peak conc. (µg/ml)	11.3 (9.3 - 13.8)	9.4 (7.2 - 11.4)	0.75 (0.61 - 0.92)	0.021
C_0 (µg/ml)	4.7 (<0.1 - 8.8)	5.7 (4.2 - 8.0)	1.3 (0.64 - 2.6)	0.505
C_{12} (µg/ml)	6.8 (5.2 - 10.1)	5.0 (2.8 - 5.9)	0.56 (0.40 - 0.78)	0.016
Ritonavir				
$AUC_{0\text{-}12hours}$ (mg*h/L)	13.3 (9.6 - 17.9)	7.0 (4.5 - 11.1)	0.53 (0.40 - 0.71)	0.006
TBC/F (L/h/m^2)	5.0 (4.5 - 7.1)	8.2 (6.4 - 16.1)	1.89 (1.41 - 2.53)	0.008
Tmax (h)	4 (3 - 5)	2 (2 - 4)	NA	NA
Peak conc. (µg/ml)	0.9 (0.8 - 1.7)	0.8 (0.6 - 1.20.69)	0.70 (0.51 - 0.97)	0.075
C_0 (µg/ml)	0.2 (< 0.1 - 0.8)	0.5 (0.2 - 0.8)0.45	1.0 (0.56 - 1.8)	0.69
C_{12} (µg/ml)	0.5 (0.3 - 0.6)	0.4 (0.2 - 0.6)	0.87 (0.67 - 1.12)	0.45

[1]Median; [2]Geometric mean (90% confidence interval); $AUC_{0\text{-}12hours}$ = area under the plasma concentration-time curve; Tmax = time post-dose of maximum concentration; C_0 = pre-dose concentration; F = bioavailability; TBC/F = oral total body clearance; *Level of difference between whole and crushed tablets assessed by Student t test.

Table 3: Pharmacokinetic parameters of lopinavir (with or without efavirenz)which were obtained following lopinavir/ritonavir administered at a dose of 300/75 mg twice-daily or 350/87.5 mg once-daily orally to12 children with median age and body-weight of 13.1 years and 40.8 kg, respectively. Figures are the median and (range), by Chokephaibulkit et al. [9].

	All children (N = 12)	Regimen without EFV (N = 6)	Regimen with EFV (N = 6)
Lopinavir/Ritonavir twice-daily (300/75 mg)			
Lopinavir dose (mg/m^2/dose)	277 (255 - 338)	271 (255 - 283)	303 (273 - 338)
$AUC_{0\text{-}24\ hours}$ (µg*h/ml)	170[a] (124 - 201)	172[a] (125 - 201)	168[a] (124 - 190)
Peak concentration (µg/ml)	9.5 (7.4 - 12.9)	8.8 (7.4 - 9.8)	10.3 (9.5 - 12.9)
Tmax (hours)	3.0 (1.0 - 6.0)	3.0 (1.8 - 6.0)	3.0 (1.0 - 4.0)
Trough concentration (µg/ml)	3.1 (1.2 - 6.5)	4.2 (2.0 - 6.5)	3.1 (1.2 - 3.4)
Trough concentration >1.0 (µg/ml)	12-Nov	6-Jun	6-Jun
TBC (L/h)	4.2 (3.2 - 6.4)	4.2 (3.2 - 6.4)	4.1 (3.2 - 6.4)
Lopinavir/Ritonavir once-daily (350/87.5 mg)			
Lopinavir dose (mg/m^2/dose)	562 (514 - 645)	544 (514 - 570)	612 (538 - 645)
$AUC_{0\text{-}24\ hours}$ (µg*h/ml)	167 (95 - 228)	200 (95 - 228)	154 (145 - 182)
Peak concentration (µg/ml)	12.6[b] (8.5 - 15.6)	12.1[b] (8.5 - 15.0)	13.5[b] (11.4 - 15.6)
Tmax (hours)	6.0[b] (2.0 - 12.0)	7.7[b] (2.0 - 12.0)	4.0[b] (2.0 - 8.0)
Trough concentration (µg/ml)	0.38[b] (0.08 - 7.3)	3.9 (0.2 - 7.3)	0.17[b] (0.08 - 0.43)
Trough concentration >1.0 (µg/ml)	12-May	6-May	0/6
TBC (L/h)	4.1 (3.3 - 6.3)	4.0 (3.3 - 6.3)	4.3 (4.0 - 5.1)
Lopinavir/ritonavir once-daily tolopinavir/Ritonavir twice-daily ratio			
$AUC_{0\text{-}24\ hours}$ (µg*h/ml)	1.01 (0.85 - 1.21)	1.05 (0.73 - 1.52)	0.98 (0.81 - 1.17
Peak concentration (µg/ml)	1.31 (1.18 - 1.45)	1.31 (1.18 - 1.45)	1.29 (1.12 - 1.48)
Trough concentration (µg/ml)	0.21 (0.09 - 0.48)	0.63 (0.19 - 2.13)	0.069 (0.040 - 0.12)
TBC (L/h)	1.00 (0.84 - 1.19)	0.98 (0.68 - 1.41)	1.03 (0.85 - 1.12)

EFV = Efavirenz; Trough concentration = 12 or 24 hours post-dose following twice-daily or once-daily dosing-regimen, respectively; Tmax = time to reach the maximum concentration, TBC = total body clearance; [a]Calculated as 2*$\mathbf{AUC}_{0\text{-}12\ hours}$; [b]Level of difference <0.05 between twice-daily and once-daily dosing-regimens assessed by Wilcoxon signed-rank test.

0.155±0.048h^{-1}, respectively. It can be seen that the estimate for K_a was very close to the value of the elimination constant derived from TBC/F and DV/F (i.e., 0.115 h^{-1}). The different values of the influential factor of body-weight on TBC/F and DV/F indicate the non-linear pattern of the lopinavir half-life with respect to body-weight. The mean TBC/F, DV/F, and the half-life values for these subjects are: 1.15 L/h (i.e., 0.35 L/h/kg), 6.7L, and 3.9 hours, respectively. In this subpopulation, the 12 mg/kg of lopinavir dose, that is recommended for children with

Table 4: Standard-dose and low-dose of lopinavir. Figures are the mean, by Puthanakit et al. [5].

Body-weight (kg)	Lopinavir standard-dose (mg)	Number of children	Lopinavir low-dose (mg)	Number of children
8.0 - 16.9	160	2	120	3
17.0 - 19.9	200	0	144	1
20.0 - 24.9	240	5	260	4
25.0 - 29.9	280	5	200	1
30.0 - 34.9	320	0	240	1
>35	400	3	280	2

Table 5: Pharmacokinetic parameters of lopinavir and ritonavir which were obtained in 24 HIV-infected children with median age, body-weight, and body-surface-area of 9.5 years, 24.0 kg, and 0.9 mg/m^2, respectively. Figures are the median and (quartile range), by Puthanakit et al. [5].

	Lopinavir			Ritonavir		
	SD (N = 11)	LD (N = 11)	*P-value	SD (N = 11)	LD (N = 11)	*P-value
$AUC_{0\text{-}12\ hours}$ (mg*h/ml)	118 (74.0 -128)	83.1 (56.0 -113)	0.18	4.3 (3.6 -9.0)	4.7 (3.5 - 7.7)	0.72
%CV	32	35	---	61	54	---
Tmax (hours)	2.0 (2.0 - 4.0)	4.0 (2.0 - 4.0)	0.41	4.0 (0.0 - 4.0)	2.0 (2.0 - 4.0)	0.92
%CV	68	31	---	75	49	---
Peak conc. (µg/ml)	11.9 (10.6 -14.4)	10.1 (7.1 -13.7)	0.16	0.6 (0.5 - 1.1	0.8 (0.4 - 1.0)	0.58
%CV	25	33	---	47	44	---
Half-life (hours)	6.1 (3.9 - 9.6)	4.0 (3.6 - 7.7)	0.41	3.9 (3.4 - 4.7)	4.4 (3.3 - 6.2)	0.49
%CV	54	52	---	57	66	---
TC (µg/ml)	4.9 (2.7 - 8.0)	3.4 (2.7 - 5.4)	0.34	0.1 (0.1 - 0.4)	0.2 (0.1 - 0.4)	0.72
%CV	54	46	---	95	71	---
TBC (L/h)	1.7 (1.0 - 3.5)	1.3 (1.2 - 2.2)	0.97	7.65.4 - 21.0)	7.4 (4.9 - 8.9)	0.37
%CV	79	39	---	86	86	

SD = Standard Dose; LD = Low Dose; %CV = % Coefficient of Variation; Tmax = Time To Reach The Peak Concentration; TC = Trough Concentration; TBC = Total Body Clearance.

body-weights of 7 and 14 kg, would provide the mean $AUC_{0\text{-}12\ hours}$, Peak, and trough concentration values of 38.6 µg*h/ml, 3.68 µg/ml, and 2.16 µg/ml, respectively. If the pharmacokinetic target is the mean $AUC_{0\text{-}12\ hours}$ calculated for this population (i.e., 108 µg*h/ml), a 34 mg/kg dose would be necessary. The corresponding calculated mean of trough concentration would be 6.11 µg/ml. The lopinavir TBC/F was also found to be related to sex in children whose age >12 years.

Table 6: Effect of covariates on the objective function, by Jullien et al. [10].

Covariate	Pharmacokinetic parameter	Ω Fobj 1	Ωɲ1 (%)	Ω Fobj 2	Ωɲ2 (%)
Body-weight	TBC/F	-71	-41	38	100
Body-weight	DV/F	-13	-63	16	165
Age	TBC/F	-42	-16	---	
Age	DV/F	-5	-43	---	
Sex	TBC/F	-33	-17	18	15
Sex	DV/F	---			
Dosage form	F	---			
Nevirapine	TBC/F	---			
Efavirenz	TBC/F	-7	---	11	15
Amprenavir	TBC/F	---			
Lopinavir	TBC/F	---			

TBC = Total Body Clearance; DV = Distribution Volume; Ω Fobj = observed change in the objective function by the corresponding covariate after its distribution to the base model (Ω Fobj 1) or its depletion from the intermediate model (Ω Fobj 2). Ωɲ = percentage change in the interindividual variability of the corresponding pharmacokinetic parameter provided by the addition of the tested covariate in the base model (Ωɲ1) or its deletion from the intermediate model (Ω Fobj 2). --- = no change.

Interaction of lopinavir/ritonavir with drugs which induces adverse-effects in humans

Lopinavir and ritonavir are the drugs of choice to treat coronavirus-and HIV-infections are metabolized by CYP3A4 and interact with drugs at different levels such as the absorption, metabolism, and elimination and induce adverse-effects in patients. Phenytoin induces the clearance of lopinavir *via* CYP3A4 induction and therapy should be individualized for each patient and the dosage adjustment should be necessary [11]. Macías et al. [12] Conducted a review about the interactions of lopinavir/ritonavir with several drugs including antibiotics, drugs acting on the central nervous system, gastrointestinal-tract, β-blockers, corticosteroids, Ca channel blockers, and 36% of patients reported major drug-drug interaction and some patients died. Co-administration of lopinavir/ritonavir with chloroquine, azithromycin, or remdesivir, causes potential drug-drug interactions that induce severe toxicity and death. The co-administration of lopinavir/ritonavir with drugs routinely used

Table 7: Population pharmacokinetic parameters of lopinavir obtained in 157 subjects HIV-infected aged from 3 days to 18 years. The age and body weight were: 9.1 years ± 4.8 years and 29.0 kg+14.9, respectively, and bootstrap. Figures are the mean ± SEM, by Jullien et al. [10].

Parameter	TV TBC/F										
		Total body clearance/F									
Final model, original data set											
---	---	Ω_{BM}	Ω_{Sex}	$\Omega_{nevirapine}$	DV/F (L)	$SV/F\Omega_{BV}$	$W^2_{CL/F}$	$W^2_{V/F}$	$Cov_{TBC,DV}$	∂^2_1	∂^2_2
Mean	2.58	0.46	1.39	1.34	24.6	0.72	0.096	0.18	0.131	0.138	1.83
± SEM	0.12	0.07	0.09	0.14	0.11	0.11	0.021	0.064	0.031	0.014	0.81
Bootstrap value[a]											
Mean	2.59	0.44	1.41	1.39	1.39	0.73	0.092	0.23	0.13	0.137	1.81
± SEM	0.13	0.07	0.13	0.19	0.19	0.17	0.024	0.1	0.04	0.07	0.86

TV = Typical Value of The Corresponding Pharmacokinetic Parameter; TBC = Total Body Clearance; DV = Distribution Volume; $\Omega = {}_{Covariate}$ Influential Factor for the Covariate; W^2 = Interindividual Variability; $COV_{TBC, DV}$ = Covariance between ɲ values of TBC/F and DV/F; [a]Mean of 1,000 bootstrap analysis.157 subjects HIV-infected aged from 3 days to 18 years, the age and body weight were: 9.1 years ± 4.8 years and 29.0 kg ± 14.9 kg, respectively.

for treatment of multidrug-resistant tuberculosis was found to have significant effect on the key pharmacokinetic parameters of lopinavir and ritonavir [13]. Many cardiology, pulmonology, and intensivist physicians have never been exposed to clinical scenarios requiring co-prescription of cardiac and antiviral therapies. Therefore it is essential to consider alternative and safer drugs in order to ensure better patient care [14]. Artemether and lumefantrine are metabolized by CYP3A4 and lopinavir/ritonavir inhibits their metabolism causing clinically important drug-drug interactions [15]. Rosuvastatin AUC and peak concentration were increased 2.1-and 4.7-fold, respectively, when co-administered with lopinavir/ritonavir. Rosuvastatin and lopinavir/ritonavir should be used with caution [16], and rosuvastatin plasma levels was increased 1.6-fold when was co-administered with lopinavir/ritonavir [17]. Co-administration of tenofovir disoproxil fumarate with lopinavir/ritonavir resulted in increased tenofovir exposures at steady-state, possibly through increased absorption [18]. Under lopinavir/ritonavir, cyclosporine a plasma levels showed markedly altered absorption/elimination characteristics with constant blood levels through the dosing interval and prolonged elimination half-life. To obtain equivalent AUC of cyclosporine A, the daily dose was reduced to 5% to 20% [19]. Co-formulated lopinavir/ritonavir with itraconazole lead to a strong increase in itraconazole plasma concentrations and a decrease in concentrations of its metabolite hydroxyitraconazole and the dosage of itraconazole should be reduced when used in combination with lopinavir/ritonavir [20].

Lopinavir/ritonavir induces adverse-effects in infants and children

Adrenal-hormone profiles were compared at weeks 6 and 26 of lopinavir/ritonavir treatment in infants HIV-1 infected. At 26 weeks, the plasma levels of dehydroepiandrosterone and 17-OH-pregnenolonewere higher. There was a significant correlation between lopinavir/ritonavir AUC and trough concentration of dehydroepiandrosterone, thus lopinavir/ritonavir is associated with dose-dependent adrenal dysfunction in infants [21]. Lopinavir/ritonavir causes mitochondrial toxicity in infants, the proposed mechanisms are: (1) impaired of mitochondrial DNA, (2) replication and (3) acquisition of mitochondrial DNA point mutations. Alterations of mitochondrial DNA synthesis reduce the production of mitochondrial DNA-encoded respiratory chain subunits resulting in impaired oxidative phosphorylation and mitochondrial dysfunction [22]. Infants, exposed to mother HIV-infected who was treated with lopinavir/ritonavir, had: (1) thrombocytopenia, (2) hepatic function tests abnormalities, (3) preterm-birth, (4) low-birth-weight and (5) congenital-malformations [23]. Moderate/severe diarrhoea occurred in 1 of 6 patients (16.7%) in a cohort of 1,469 subjects [24]. Lopinavir/ritonavir induced dyslipidaemia in children and hypertriglyceridemia was the most common type of this metabolic disorder [25]. Eight-five children received lopinavir/ritonavir and 71 children (83.5%) were treated with nevirapine. Children treated with lopinavir/ritonavir had: (1) lower high-density lipoprotein, (2) higher total cholesterol, (3) triglycerides concentrations, and (4) body fat. After 4 week treatment with lopinavir/ritonavir to fasting patients (1) triglycerides, (2) free fatty acids, and (3) VDL-cholesterol concentrations increased compared to before therapy [26]. Treatment with lopinavir/ritonavir induced (1) lithiasis, (2) cholangitis, and (3) parotitis [27].Treatment with lopinavir/ritonavir is associated with: (1) insulin resistance, (2) pre-diabetes mellitus, (3) causes increased triglycerides, and (4) total cholesterol plasma levels in HIV-infected children [28]. The most frequent adverse-effects caused by lopinavir/ritonavir treatment in children are: diarrhoea, nausea, and vomiting [29].

Treatment of HIV-infected infants and children

Of 73 HIV-infected infants treated with lopinavir/ritonavir, 52.5% were cured [30]. Infants, in the first month of life, have immature drug elimination process and altered gastrointestinal absorption, extrapolation of lopinavir/ritonavir dose from older children risks different drug-exposure in young infants and incomplete virological suppression and/or potential toxicity. It is thus necessary establish the appropriate dosing-regimen in infants [4]. Therapeutic lopinavir/ritonavir monitoring is essential in infants and children in order to establish the appropriate dosing-regimens [31]. Lopinavir/ritonavir once-daily is a suitable dosing-regimen for antiretroviral-naïve children. However, due to the high interindividual variability and low blood concentrations in some subjects, therapeutic drug monitoring should be necessary to ensure that plasma concentrations are adequate to inhibit viral replication [32]. A large proportion of children preferred lopinavir/ritonavir pellets to other formulations and lopinavir/ritonavir pellets may be suitable in children aged 3 years [33]. Lopinavir exposure with ritonavir super-boosting in a one-to-one ratio during rifampicin-based tuberculosis treatment was non-inferior to the exposure with lopinavir/ritonavir without rifampicin. Safety and efficacy, and field application of super-boosting is limited by poor acceptability. Access to better adapted solid formulations will most likely facilitate public health implementation [34]. Pre-treated children with lopinavir/ritonavir might benefit from a double lopinavir/ritonavir dose to enhance adherence and decrease toxicity whenever possible [35]. Highly active lopinavir/ritonavir therapy can be administered safety and effectively to children in resource-limited settings. Lopinavir/ritonavir-containing highly antiretroviral therapy is a safe, effective, and is a durable treatment option for antiretroviral in drug-experienced older children and adolescents with advanced HIV disease [36].

Treatment of coronavirus-infected infants and children

Infants and children are typically at high risk for admission to hospital after respiratory-tract infection caused by coronavirus 2 (SARS-CoV-2). The case-fatality is 2% in Chinese infants and the risk of death is increased significantly in older children (approximately 15%) and lopinavir/ritonavir is the drug of choice to treat coronavirus infection [37] Song et al. [38] recommend lopinavir/ritonavir as the effective drugs for antiviral-treatment of coronavirus. The management of COVID-19 is mainly a supportive care. In severe pneumonia and critically ill children, trial of lopinavir/ritonavir should be considered [39]. Significant risk factor for requiring intensive care unit admission is infants aged 1 month or younger. The most frequently used drugs to treat COVID-19 are: hydroxychloroquine, remdesivir, lopinavir/ritonavir, and oseltamivir [40]. The most important way to prevent COVID-19 in children is antiviral medications along with the use of muscle relaxants and oxygen therapy [41]. Children with severe COVID-19, clinical symptoms, especially those suffering from pneumonia, must be hospitalized and treatment with antiviral drugs such as lopinavir/ritonavir co-administered with ACE inhibitors, interferon-α 2b, co-therapy with azithromycin, inhaling iNO, and oxygen therapy can be used for treatment [42]. Severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) may be treated with remdesivir, lopinavir/ritonavir, lopinavir/ritonavir plus interferon, and chloroquine or hydroxychloroquine [43]. After administration of lopinavir/ritonavir, β-coronavirus viral loads significantly decreased and no or little coronavirus titers were observed [44]. Clinicians

should not abandon the use of lopinavir/ritonavir for the treatment of COVID-19, possibly using this drug inside a prospective randomized trial [45]. Early initiation of lopinavir/ritonavir plus interferon-α combination therapy may help shortening the duration of SARS-CoV-2 shedding [46]. No statistical significant differences were observed in clinical outcome in patients treated with chloroquine or with lopinavir/ritonavir but patients treated with lopinavir/ritonavir had lower hospital mortality-rate [47].

Prophylaxis with lopinavir/ritonavir in infants and children

Zidovudine plus lamivudine plus lopinavir/ritonavir is the preferred 3-drug regimen for post-exposure prophylaxis [48]. Infant HIV-1 prophylaxis with lopinavir-ritonavir was not superior to lamivudine and both drugs led to very low rates of HIV-1 postnatal transmission for up to 50 weeks of breastfeeding. Infant pre-exposure prophylaxis should be extended until the end of HIV-1 treatment [49]. Antiviral prophylaxis, whether used by the HIV-infected mother or the HIV-exposed newborn infant while breastfeeding, is efficacious in preventing mother-to-child transmission of HIV [50]. Independent of maternal status and delivery type confirmed vertical transmission of HIV-1-infected women who receive zidovudine is 4.2%. Prenatal care with a multidisciplinary team is necessary for good obstetric and newborn outcomes [51].

Use of lopinavir/ritonavir in pregnancy

Lopinavir and ritonavir have limited placental transfer [52]. Following standard-dose of lopinavir/ritonavir no appreciable concentration was observed in the beast-milk [53], and lopinavir migration into the breast-milk was not correlated with the maternal body-mass-index [54]. Infants, born to HIV-infected mothers were treated with lopinavir/ritonavir, reported few adverse-effects [55]. Of 2,058 mothers with HIV who were treated with lopinavir/ritonavir reported only 38 stillbirths (1.8%) suggesting that lopinavir/ritonavir is safe in pregnant women [56]. The use of lopinavir/ritonavir in pregnant women revealed a mother-to-child transmission-rate of 1.1%, preterm-birth-rate of 13.2%, and low-birth-rate of 16.2%. Lovirapin/ritonavir also displays a significant effect in preventing a mother-to-child viral transmission-rate [57]. The proportion of pregnant women with grade 3 or 4 adverse-effects was very low, with no statistically significant differences between groups in severe adverse-effects related to: (1) hepatic transaminases, (2) total bilirubin, cholesterol, or (3) triglycerides concentrations. Lopinavir/ritonavir administration during the third trimester of pregnancy is safe in HIV-infected mothers and their newborn infants [58].

Mechanisms of viral-resistance to lopinavir/ritonavir

Twelve patients with virus L76V positive were compared to 24 patients with virus L76V negative selected at random. In univariate analysis, mutations were found in ≥10% patients, L89M and Q58E mutations were more prevalent in viruses L76V positive than L76V negative. In contrast, I54V, G73S, and L90M mutations were less prevalent in viruses L76V positive than L76V negative (P-value = 0.0006). L90M, I54V, and Q58E mutations were associated with L76V in a multivariate analysis (P-values <0.0001, 0.002, and 0.009, respectively). These results suggest two divergent pathways loading to lopinavir/ritonavir resistance. One contains the L76V and Q58E mutations and the other contains the L90M and 154V mutations [59]. A detailed longitudinal analysis demonstrated the selection of the M46I+L76V protease mutations in all 3 patients. The L76V conferred a solitary 3.5-fold increase in one-half the maximal inhibitory concentration to lopinavir but severely hampered viral replication. Analysis of a large clinical database (>180,000 HIV sequences) demonstrated a significant association between the increased presence of L76V in clinical samples (0.5% in 2000 to 3.4% in 2006) and lopinavir prescription over time. The HIV protease substitution L76V, in combination with M46I, confers clinical relevant levels of lopinavir-resistance and represents a novel resistance-pathway to first-line lopinavir/ritonavir therapy [60]. A positive correlation was found between lovirapin trough concentration and viral load reductions at 3 months under lopinavir/ritonavir (P-value = 0.017). Overall, virological response was seen in 80.8% patients with lopinavir trough concentration >4.8 μg/ml while 52.5% patients with lower lopinavir trough concentration (P-value= 0.002). A Genotype Inhibitor Quotient (GIQ) was estimated for each patient based on the ratio between lopinavir trough concentration and the number of PI-resistance mutations. A positive strong correlation was found between GIQ and viral load reductions (P-value = 0.002). Virological response was seen in 78% of patients with GIQ >0.7 but only in 41.6% of those with lower GIQ (P-value = 0.004). When lopinavir trough concentration was >4.8 μg/ml, PI-resistance mutations ≤ 6, and GIQ >0.7 were all included in a stepwise multivariate analysis, GIQ remains as the main independent predictor of resistance to lopinavir/ritonavir [61]. No evidence of genotypic or phenotypic resistance to lopinavir/ritonavir, defined as any active site or primary mutation in HIV protease, was detected in virus isolates from 51 lopinavir/ritonavir-treated subjects with available genotypes. Primary mutations related to nelfinavir resistance (D30N and/or L90M) were observed in 43 (44.8%) of 96 nelfinavir-treated subjects. Resistance to lamivudine and stavudine was also significantly higher in nelfinavir-treated versus lopinavir/ritonavir-treated subjects. These differences suggest substantially different genetic and pharmacological barriers to resistance for these 2 IPs and may have implications for strategies for initiating antiretroviral therapy [62].

Discussion

Ritonavir is a peptidomimetic Human Immunodeficiency Virus (HIV) Protease Inhibitor (PI) designed to complement the C2 axis of symmetry of the enzyme active site. Ritonavir is active against bot HIV-1 and HIV-2 and is mostly used as an inhibitor of CYP3A4. Lopinavir is structurally similar to ritonavir but is 3- to 10-fold more potent against HIV-1. This agent is active against HIV-1 and HIV-2. Lopinavir/ritonavir is also used to treat coronavirus infection. Lopinavir is available only in combination with low-doses of ritonavir [1]. The dose of lopinavir is 4-fold higher than that of ritonavir and formulations of lopinavir/ritonavir are available as tablets and oral solution and both drugs are rapidly absorbed orally. The dose of lopinavir/ritonavir may be computed on the basis of body-surface-area or body-weight and is 300/75 mg/m^2 twice-daily in infants [2] and it is 200/50 and 400/100 mg twice-daily in children with body-weight <40 and >40 kg, respectively [3]. Lopinavir/ritonavir has been found efficacy and safe in infants and children. Lopinavir half-life is about 4hours [4] and 6 hours [5] in infants and children, respectively. The half-life, TBC, DV, peak and trough concentrations remarkably varied in infants and children. Thus, therapeutic lopinavir/ritonavir monitoring is essential in order to establish the appropriate dosing-regimens and to avoid the large interindividual variability of pharmacokinetic parameters [31]. Lopinavir/ritonavir interacts with drugs at different levels such as the absorption, metabolism, and elimination and induces adverse-effects in patients. Phenytoin induces the clearance of lopinavir *via* CYP3A4 induction [11],

lopinavir/ritonavir interacts with drugs acting on the central nervous system, gastrointestinal-tract, β-blockers, corticosteroids, Ca channel blockers, and many patients reported major drug-drug interaction and some patients died [12]. Co-administration of lopinavir/ritonavir with chloroquine, azithromycin, or remdesivir, causes potential drug-drug interactions that induce severe toxicity and death. Lopinavir/ritonavir also interacts with artemether and lumefantrine which are metabolized by CYP3A4 [15], with rosuvastatin [16], tenofovir disoproxil fumarate [18] and cyclosporine A [19]. Co-administration of lopinavir/ritonavir with itraconazole lead to a strong increase of itraconazole plasma concentrations, a decrease of its metabolite hydroxytraconazole concentrations, and the dosage of itraconazole should be reduced when co-administered with lopinavir/ritonavir [20]. Several drugs induce adverse-effects in infants and children. Infants exposed to mother with HIV-infection were treated with lopinavir/ritonavirhad: (1) thrombocytopenia, (2) hepatic function tests abnormalities, (3) preterm-birth, (4) low-birth-weight and (5) congenital-malformations [23]. Children treated with lopinavir/ritonavir had: (1) lower high-density lipoprotein, (2) higher total cholesterol, (3) triglycerides concentrations, and (4) body fat. After 4 week treatment with lopinavir/ritonavir to fasting patients (1) triglycerides, (2) free fatty acids, and (3) VDL-cholesterol concentrations increased compared to before therapy [26]. Lopinavir/ritonavir causes mitochondrial toxicity in infants, the proposed mechanisms are: (1) impaired of mitochondrial DNA, (2) replication and (3) acquisition of mitochondrial DNA point mutations. Alterations of mitochondrial DNA synthesis reduce the production of mitochondrial DNA-encoded respiratory chain subunits resulting in impaired oxidative phosphorylation and mitochondrial dysfunction [22]. Treatment with lopinavir/ritonavir successfully cured infants and children infected by HIV or coronavirus. The co-administration of lopinavir/ritonavir with ACE inhibitors, interferon-α 2b, azithromycin, inhaling iNO [42] or chloroquine, remdesivir and oseltamivir [40] may short the duration of SARS-CoV-2 shedding [46]. Prophylaxis with lopinavir/ritonavir plus zidovudine and lamivudine has been recommended for naïve or experienced infected in infants and children [48]. Antiviral prophylaxis, whether used by the HIV-infected mother or the HIV-exposed newborn infant while breastfeeding, is efficacious in preventing mother-to-child transmission-rate of HIV [50]. Lopinavir and ritonavir have limited placental transfer [52], following standard-dose of lopinavir/ritonavir, it has no appreciable concentration into the beast-milk [53], and lopinavir migration into the breast-milk is not correlated with the maternal body-mass-index [54]. Lovirapin/ritonavir also displays a significant effect in preventing the viral transmission from the mother-to-child [57]. Some viruses may become resistant to lopinavir/ritonavir and the mechanism of resistance is caused by the HIV protease substitution L76V and in combination with M46I, confers clinical relevant levels of lopinavir-resistance [60]. A Genotype Inhibitor Quotient (GIQ) was estimated for each patient based on the ratio between lopinavir trough concentration and the number of PI-resistance mutations. GIQ remains the main independent predictor of resistance to lopinavir/ritonavir [61].

In conclusion, lopinavir/ritonavir successfully treated infants and children infected by HIV or coronavirus. Ritonavir is an inhibitor of CYP3A4 which is the enzyme that metabolizes lopinavir. Formulations of lopinavir/ritonavir are available as tablets or oral suspension and the dose of lopinavir is 4-fold higher than that of ritonavir and both drugs are rapidly absorbed by the gastrointestinal-tract. This drug combination may be administered on the basis of the body-surface-area and body-weight. Lopinavir/ritonavir dose is 300/75 mg/m^2 in infants and it is 200/50 and 400/100 mg in children with a body-weight < 40 and> 40 kg, respectively. Some authors suggested that the treatment of COVID-19 is facilitated by addition of other drugs such as: chloroquine, remdesivir, oseltamivir or ACE inhibitors, azithromycin, iNO, oxygen or interferon-α. Prophylaxis with lopinavir/ritonavir is recommended in naïve and experienced infant infected by HIV or coronavirus, and is also recommended in newborn infant's breastfeeding from infected mother to prevent the vertical transmission of HIV or coronaviruses. Some viruses may become resistant to lopinavir/ritonavir and the mechanism of resistance is the mutation of protease which impairs is efficacy.

Conflict of Interests

The authors declare no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts, and honoraria.

This article is a review and drugs have not been administered to men or animals.

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References

1. Flexner CW. Antiretroviral Agents and treatment of HIV infection. 13th Ed. McGraw Hill Education. 2018:1137-57.
2. Neonatal Formulary. Lopinavir with ritonavir. Oxford University Press, 8th ed. 2020;463-5.
3. The British National Formulary for Children. Lopinavir with ritonavir. Pharmaceutical Press, 78th ed. 2019-2020:441-2.
4. Chadwick EG, Pointo J, Yogev R, Alvero CG, Hughes MD, Palumbo P, et al. Early initiation of lopinavir/ritonavir in infants less than 6 weeks of age: pharmacokinetics and 24-week safety and efficacy. Pediatr Infect Dis J. 2009;28(3):215-9.
5. Puthanakit T, van der Lugt J, Bunupuradah T, Ananworanich J, Gorowara M, Phasomsap C, et al. Pharmacokinetics and 48 week efficacy of low-dose lopinavir/ritonavir in HIV-infected children. J Antimicrob Chemother. 2009;64(5):1080-6.
6. Verweel G, Burger DM, Sheehan NL, Bergshoeff AS, Warris A, van der Knaap LV, et al. Plasma concentrations of the HIV-protease inhibitor lopinavir are suboptimal in children aged 2 years and below. Antivir Ther. 2007;12(4):453-8.
7. Chadwick EG, Capparelli EV, Yogev R, Pointo JA, Robbins B, Rodman JH, et al. Pharmacokinetics, safety and efficacy of lopinavir/ritonavir in infants less than 6 months of age: 24 week results. AIDS. 2008;22(2):249-55.
8. Best BM, Capparelli EV, Diep H, Rossi SS, Farrell MJ, Williams E, et al. Pharmacokinetics of lopinavir/ritonavir Crushed versus Whole Tablets in Children. J Acquir Immune Defic Syndr. 2011;58(4):385-91.
9. ChokephaibulkitK, Nuntarukchaikul M, Phongsamart W, Wittawatmongkol O, Lapphra K, Vanprapar N, et al. Once- versus twice-daily lopinavir/ritonavir tablets in virologically suppressed, HIV-infected, treatment-experienced children: comparative pharmacokinetics and virological outcome after switching. J Antimicrob Chemother. 2012;67(12):2927-31.
10. Jullien V, Urien S, Hirt D, Delaugerre C, Rey E, Teglas JP, et al. Population Analysis of Weight-, Age-, and Sex-Related Differences in the Pharmacokinetics of Lopinavir in Children from Birth to 18 Years. Antimicrob Agents Chemother. 2006;50(11):3548-55.
11. Lim ML, Sherene SS, Eron JJ, Bertz RJ, Robinson M, Gaedigk A, et al. Coadministration of lopinavir/ritonavir and phenytoin results in two-way drug interaction through cytochrome P-450 induction. J Acquir Immune Defic Syndr. 2004;36(5):1034-40.

12. Macías J, Pinilla A, Lao-Dominguez FA, Corma A, Contreras-Macias E, González-Serna A, et al. High rate of major drug-drug interactions of lopinavir-ritonavir for COVID-19 treatment. Sci Rep. 2020;10:20958.

13. Van der Laan LE, Garcia-Prats AJ, Schaaf HS, Tikiso T, Wiesner L, de Kock M, et al. Pharmacokinetics and Drug-Drug Interactions of Lopinavir-Ritonavir Administered with First- and Second-Line Antituberculosis Drugs in HIV-Infected Children Treated for Multidrug-Resistant Tuberculosis. Antimicrob Agents Chemother. 2018;62(2):e00420-17.

14. Agarwal S, Agarwal SK. Lopinavir-Ritonavir in SARS-CoV-2 Infection and Drug-Drug Interactions with Cardioactive Medications. Cardiovasc Drugs Ther. 2020:1-14.

15. KredoT, MauffK, Workman L, Van der Walt JS, WiesnerL, SmithP J, et al. The interaction between artemether-lumefantrine and lopinavir/ritonavir-based antiretroviral therapy in HIV-1 infected patients. BMC Infect Dis. 2016;16:30.

16. Kiser JJ, G Gerber JG, Predhomme JA, Wolfe P, Flynn DM, Hoody DW. Drug/Drug interaction between lopinavir/ritonavir and rosuvastatin in healthy volunteers. J Acquir Immune Defic Syndr. 2008;47(5):570-8.

17. van der Lee M, Sankatsing R, Schippers E, Vogel M, Fätkenheuer G, van der Ven A, et al. Pharmacokinetics and pharmacodynamics of combined use of lopinavir/ritonavir and rosuvastatin in HIV-infected patients. Antivir Ther. 2007:12(7):1127-32.

18. Kearney BP, Mathias A, Mittan A, Sayre J, Ebrahimi R, Cheng AK. Pharmacokinetics and safety of tenofovir disoproxil fumarate on coadministration with lopinavir/ritonavir. J Acquir Immune Defic Syndr. 2006;43(3):278-83.

19. Vogel M, Voigt E, Michaelis HC, Sudhop T, Wolff M, Türler A, et al. Management of drug-to-drug interactions between cyclosporine A and the protease-inhibitor lopinavir/ritonavir in liver-transplanted HIV-infected patients. Liver Transpl. 2004;10(7):939-44.

20. Crommentuyn KML, Mulder JW, Sparidans RW, Huitema ADR, Schellens JHM, Beijnen JH. Drug-drug interaction between itraconazole and the antiretroviral drug lopinavir/ritonavir in an HIV-1-infected patient with disseminated histoplasmosis. Clin Infect Dis. 2004;38(8):e73-5.

21. Kariyawasam D, Peries M, Foissac F, Eymard-Duvernay S, Tylleskär T, Singata-Madliki M, et al. Lopinavir-Ritonavir Impairs Adrenal Function in Infants. Clin Infect Dis. 2020;71(4):1030-39.

22. Hughes CA, Freitas A, Miedzinski LJ. Interaction between lopinavir/ritonavir and warfarin. CMAJ. 2007;177(4):357-9.

23. Delicio AM, Lajos GJ, Amaral E, Cavichiolli F, Polydoro M, Milanez H. Adverse effects in children exposed to maternal HIV and antiretroviral therapy during pregnancy in Brazil: a cohort study. Reprod Reproductive Health. 2018;15(1):76.

24. Wegzyn CM, Fredrick LM, Stubbs RO, Woodward WC, Norton M. Diarrhea associated with lopinavir/ritonavir-based therapy: results of a meta-analysis of 1469 HIV-1-infected participants. J Int Assoc Physicians AIDS Care (Chic). 2012:11(4):252-9.

25. Santiprabhob J, Tanchaweng S, Maturapat S, Maleesatharn A, Lermankul W, Sricharoenchai S, et al. Metabolic Disorders in HIV-Infected Adolescents Receiving Protease Inhibitors. Biomed Res Int. 2017;2017:7481597.

26. Lee GA, Seneviratne T, Noor MA, Joan CL, Schwarz JM, Aweeka FT, et al. The metabolic effects of lopinavir/ritonavir in HIV-negative men. AIDS. 2004;18(4):641-9.

27. Thanha DL, Annab G, Laurenta T, Philippeb T, Thierrya M, Christiana R. Lopinavir–ritonavir (Kaletra) and lithiasis: seven cases. AIDS. 2004;18(4):705-6.

28. Dejkhamron P, Unachak K, Aurpibul L, Sirisanthana V. Insulin resistance and lipid profiles in HIV-infected Thai children receiving lopinavir/ritonavir-based highly active antiretroviral therapy. J Pediatr Endocrinol Metab. 2014;27(5-6):403-12.

29. Chandwani A, Shuter J. Lopinavir/ritonavir in the treatment of HIV-1 infection: a review. Ther Clin Risk Manag. 2008;4(5):1023-33.

30. Kuhn L, Strehlau R, Shiau S, Patel F, Shen Y, Technau KG, et al. Early antiretroviral treatment of infants to attain HIV remission. EClinicalMedicine. 2020;18:100241.

31. Waalewijn H, Turkova A, Rakhmanina N, Cressey TR, Penazzato M, Colbers A, et al. Optimizing Pediatric Dosing Recommendations and Treatment Management of Antiretroviral Drugs Using Therapeutic Drug Monitoring Data in Children Living With HIV. Ther Drug Monit. 2019;41(4):431-43.

32. Rosso R, Di Biagio A, Dentone C, Gattinara CG, Martino AM, Viganò A, et al. Lopinavir/ritonavir exposure in treatment-naïve HIV-infected children following twice or once-daily administration. J Antimicrob Chemother. 2006;57(6):1168-71.

33. Pasipanodya B, Kuwengwa R, Prust ML, Stewart B, Chakanyuka C, Murimwa T, et al. Assessing the adoption of lopinavir/ritonavir oral pellets for HIV-positive children in Zimbabwe. J Int AIDS Soc. 2018;21(12):e25214.

34. Rabie H, Denti P, Lee J, Masango M, Coovadia A, Pillay S, et al. Lopinavir-ritonavir super-boosting in young HIV-infected children on rifampicin-based tuberculosis therapy compared with lopinavir-ritonavir without rifampicin: a pharmacokinetic modelling and clinical study. Lancet HIV. 2018;S2352-3018(18):30293-5.

35. Martinez BL, Riordan FAI. Novel strategies in the use of lopinavir/ritonavir for the treatment of HIV infection in children. HIV AIDS (Auckl). 2010;2:59-67.

36. Kline MW, Rugina S, Ilie M, Matusa RF, Schweitzer AM, Calles NC, et al. Long-term Follow-up of 414 HIV-Infected Romanian Children and Adolescents Receiving Lopinavir/Ritonavir-Containing Highly Active Antiretroviral Therapy. Pediatrics. 2007;119(5):e1116-20.

37. Kelvin AA, Halperin S. COVID-19 in children: the link in the transmission chain. Lancet Infect Dis. 2020;20(6):633-4.

38. Song Y, Peng W, Tang D, Dai Y. Protease Inhibitor Use in COVID-19. SN Compr Clin Med. 2020:1-8.

39. Sankar J, Dhochak N, Kabra SK, Lodha R. COVID-19 in Children: Clinical Approach and Management. Indian J Pediatr. 2020;87(6):433-42.

40. Götzinger F, Santiago-García B, Noguera-Julián A, Lanaspa M, Lancella L, Calò Carducci FI, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. Lancet Child Adolesc Health. 2020;4(9):653-61.

41. Razavi A. Davoodi L, Shojaei L, Jafarpour H. COVID-19 in Children: A Narrative Review. J Med Sci. 2020;8:23-31.

42. Zare-Zardini H, Soltaninejad H, Ferdosian F, Hamidieh AA, Memarpoor-Yazdi M. Coronavirus Disease 2019 (COVID-19) in Children: Prevalence, Diagnosis, Clinical Symptoms, and Treatment. Int J Gen Med. 2020;13:477-82.

43. Alpern JD, Gertner E. Off-Label Therapies for COVID-19-Are We All In This Together? Clin Pharmacol Ther. 2020;108(2):182-4.

44. Lim J, Jeon S, Shin HY, Kim MJ, Seong YM, Lee WJ, et al. Case of the Index Patient Who Caused Tertiary Transmission of COVID-19 Infection in Korea: the Application of Lopinavir/Ritonavir for the Treatment of COVID-19 Infected Pneumonia Monitored by Quantitative RT-PCR. J Korean Med Sci. 2020;35(6):e79.

45. Meini S, Pagotto A, Longo B, Vendramin I, Pecori D, Tascini C. Role of Lopinavir/Ritonavir in the Treatment of Covid-19: A Review of Current Evidence, Guideline Recommendations, and Perspectives. J Clin Med. 2020;9(7):2050.

46. Zuo Y, Liu Y, Zhong Q, Zhang K, Xu Y, Wang A. Lopinavir/ritonavir and interferon combination therapy may help shorten the duration of viral shedding in patients with COVID-19: A retrospective study in two designated hospitals in Anhui, China. J Med Virol. 2020;92(11):2666-74.

47. Karolyi M, Pawelka E, Mader T, Omid S, Kelani H, Ely S, et al. Hydroxychloroquine versus lopinavir/ritonavir in severe COVID-19 patients: Results from a real-life patient cohort. Wien Klin Wochenschr. 2020:1-8.

48. Penazzato M, Dominguez K, Cotton M, Barlow-Mosha L, Ford N. Choice of antiretroviral drugs for postexposure prophylaxis for children: a systematic review. Clin Infect Dis. 2015;60(Suppl 3):S177-81.

49. Nagot N, Kankasa C, Tumwine JK, Meda N, Hofmeyr GJ, Vallo R, et al. Extended pre-exposure prophylaxis with lopinavir-ritonavir versus lamivudine to prevent HIV-1 transmission through breastfeeding up to 50 weeks in infants in Africa (ANRS 12174): a randomised controlled trial. Lancet. 2016;387(10018):566-73.

50. White AB, Mirjahangir JF, Horvath H, Anglemyer A, Read JS. Antiretroviral interventions for preventing breast milk transmission of HIV. Cochrane Database Syst Rev. 2014;10:CD011323.

51. Carneiro M, Sanchéz A, Maneiro P, Angelosante W, Pérez C, Valleé M. Vertical HIV-1 transmission: prophylaxis and paediatric follow-up. Placenta. 2001;22(Suppl A):S13-8.

52. Louchet M, Sibiude J, Peytavin G, Picone O, Tréluyer JM, Mandelbrot L. Placental transfer and safety in pregnancy of medications under investigation to treat coronavirus disease 2019. Am J Obstet Gynecol MFM. 2020;2(3):100159.

53. Shapiro RL, Rossi S, Ogwu A, Moss M, Leidner J, Moffat C, et al. Therapeutic levels of lopinavir in late pregnancy and abacavir passage into breast milk in the Mma Bana Study, Botswana. Antivir Ther. 2012;18(4):585-90.

54. Somé EN, Engebretsen IMS, Nagot N, Meda NY, Vallo R, Kankasa C, et al. Changes in body mass index and hemoglobin concentration in breastfeeding women living with HIV with a CD4 count over 350: Results from 4 African countries (The ANRS 12174 trial). PLoS One. 2017;12(5):e0177259.

55. Yoon SH, Kang JM, Ahn JG. Clinical outcomes of 201 neonates born to mothers with COVID-19: a systematic review. Eur Rev Med Pharmacol Sci. 2020;24(14):7804-15.

56. Pasley MV, Martinez M, Hermes A, d'Amico R, Nilius A. Safety and efficacy of lopinavir/ritonavir during pregnancy: a systematic review. AIDS Rev. 2013;15(1):38-48.

57. Huang X, Xu Y, Yang Q, Chen J, Zhang T, Li Z, et al. Efficacy and biological safety of lopinavir/ritonavir based anti-retroviral therapy in HIV-1-infected patients: a meta-analysis of randomized controlled trials. Sci Rep. 2015;5:8528.

58. Peixoto MF, Pilotto JH, Stoszek SK, Kreitchmann R, Mussi-Pinhata MM, Melo VH, et al. Lopinavir/ritonavir dosing during pregnancy in Brazil and maternal/infant laboratory abnormalities. Braz J Infect Dis. 2011;15(3):253-61.

59. Champenois K, Baras A, Choisy P, Ajana F, Melliez H, Bocket L, et al. Lopinavir/ritonavir resistance in patients infected with HIV-1: two divergent resistance pathways? J Med Virol. 2011;83(10):1677-81.

60. NijhuisM, Wensing AMJ, Bierman WFW, de Jong D, Kagan R, Fun A, et al. Failure of treatment with first-line lopinavir boosted with ritonavir can be explained by novel resistance pathways with protease mutation 76V. J Infect Dis. 2009;200(5):698-709.

61. de Requena DG, Gallego O, Valer L, Jiménez-Nácher I, Soriano V. Prediction of virological response to lopinavir/ritonavir using the genotypic inhibitory quotient. AIDS Res Hum Retroviruses. 2004;20(3):275-8.

62. Kempf DJ, King MS, Bernstein B, Cernohous P, Bauer E, Moseley J, et al. Incidence of resistance in a double-blind study comparing lopinavir/ritonavir plus stavudine and lamivudine to nelfinavir plus stavudine and lamivudine. J Infect Dis. 2004:189(1):51-60.