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

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Summary

Background Rifampicin reduces lopinavir concentrations in HIV and tuberculosis co-treated patients. We hypothesised that adding ritonavir to co-formulated lopinavir–ritonavir (4:1) to achieve a one-to-one ratio would overcome this drug–drug interaction in young children.

Methods We did a prospective, open-label, one-group, one-sequence study at five sites in three South African provinces. We included HIV-infected children with tuberculosis, a bodyweight of 3–15 kg, and a post-conceptional age of more than 42 weeks. Children received the standard four-to-one ratio of lopinavir–ritonavir in the absence of rifampicin-based anti-tuberculosis treatment, whereas super-boosting of lopinavir–ritonavir with additional ritonavir was given orally twice a day to achieve a one-to-one ratio during rifampicin treatment. The primary outcome was the comparison of the proportion of children with predicted lopinavir morning minimum concentrations (C_{min}) of more than 1·0 mg/L during super-boosting with the proportion of more than 1·0 mg/L during standard lopinavir–ritonavir treatment without rifampicin. Lopinavir concentrations were determined before and at 1, 2, 4, 6, and 10 h after the morning dose during the second and the last month of tuberculosis co-treatment, and 4–6 weeks after stopping rifampicin. A non-linear mixed-effects model was implemented to interpret the data and Monte Carlo simulations were used to compare the percentage of lopinavir with morning C_{min} values of less than 1·0 mg/L for the two dosing schemes. A non-inferiority margin of 10% was used. This study is registered with ClinicalTrials.gov, number NCT02348177.

Findings Between Jan 30, 2013, and Nov 9, 2015, 96 children with a median age of 18·2 months (IQR 9·6–26·8) were enrolled. Of these 96 children, 80 (83%) completed the first three pharmacokinetic evaluations. Tuberculosis therapy was started before antiretrovirals in 70 (73%) children. The model-predicted percentage of morning C_{min} of less than 1·0 mg/L after tuberculosis treatment without super-boosting was 8·8% (95% CI 0·6–19·8) versus 7·6% (0·4–16·2) during super-boosting and tuberculosis treatment. The difference of –1·1% (95% CI –6·9 to 3·2), at a non-inferiority margin of 10%, confirmed the non-inferiority of lopinavir trough concentrations during rifampicin co-treatment. 19 serious adverse events were reported in 12 participants. Three deaths and a temporary treatment interruption due to jaundice were unrelated to study treatment.

Interpretation 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. Safe and effective, field application of super-boosting is limited by poor acceptability. Access to better adapted solid formulations will most likely facilitate public health implementation of this strategy.

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Introduction

In 2016, WHO estimated that 10·4 million people, including one million children, were newly diagnosed with tuberculosis. 40% of HIV-related deaths were from tuberculosis.[1] Sub-Saharan Africa is the epicentre of both tuberculosis and HIV infection. Tuberculosis is common in HIV-infected children.[2] Standard anti-tuberculosis therapy consists of isoniazid, rifampicin, and pyrazinamide with or without either ethambutol or ethionamide for 2 months, followed by isoniazid and rifampicin for 4 months.[3] The WHO guideline recommends the protease inhibitor lopinavir co-formulated with ritonavir (lopinavir–ritonavir) in a four-to-one ratio in first-line combination antiretroviral therapy (cART) for children younger than 3 years, based on its superiority compared with nevirapine, regardless of previous nevirapine exposure to prevent mother-to-child HIV transmission.[4–6] In lopinavir–ritonavir, the low dose of ritonavir inhibits cytochrome CYP3A4-mediated lopinavir metabolism and the P-glycoprotein efflux

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Research in context

Evidence before this study

We searched PubMed for pharmacokinetic studies of lopinavir–ritonavir and rifampicin co-treatment using the search terms "lopinavir/ritonavir" AND "rifampicin", limiting the search to participants younger than 18 years and to papers from Jan 1, 2008, to July 31, 2018. In a prospective study, 12 (60%) of 20 children receiving double-dose lopinavir–ritonavir (4:1) oral solution had lopinavir trough concentrations below the efficacy target of 1·0 mg/L during rifampicin co-treatment. The median age for children receiving double-dose lopinavir–ritonavir was 1·25 years. Modelling suggests that adjusted 8 h dosing is better if seeking to avoid using additional ritonavir, but with no studies yet published. Super-boosting lopinavir–ritonavir with additional ritonavir to achieve a one-to-one parity (ie, lopinavir–ritonavir plus ritonavir) was more successful. In a proof-of-concept pharmacokinetic study, 15 children (median age 16 months) received lopinavir–ritonavir plus ritonavir with rifampicin. They were compared with 15 children (median age 29 months) receiving lopinavir–ritonavir without rifampicin (ie, controls). The median lopinavir dosage was 291·9 mg/m² (range 274·3–308·6) in cases and 265·2 mg/m² (248·8–289·3) in the controls. Only two children on the lopinavir–ritonavir plus ritonavir strategy had lopinavir morning trough concentrations of less than 1·0 mg/L. A modelling study using these data suggested that lopinavir oral clearance was still higher in children on rifampicin than in those without rifampicin. There is no data in older children using lopinavir–ritonavir for either paediatric or adult tablets. Because of the small sample size, an age difference between cases and controls of more than 1 year, excluding children younger than 6 months, and dosing of lopinavir–ritonavir and ritonavir by body surface area rather than weight bands, we decided to evaluate more systematically the safety and pharmacological efficacy of super-boosting in tuberculosis and HIV co-infected infants and young children.

Added value of this study

96 children with HIV and tuberculosis co-infection were prospectively enrolled, of whom 80 completed intensive pharmacokinetic sampling on three occasions. Using a population pharmacokinetic model accounting for the non-linear effects, lopinavir exposure during rifampicin therapy was non-inferior to exposure without rifampicin therapy. This research is one of the largest pharmacokinetic studies of co-infected children. With 27 (29%) of 92 children in our study younger than 12 months at the first pharmacokinetic evaluation, this vulnerable population was well represented. Dosing was pragmatic and used the currently accepted weight bands. We confirmed that this strategy was safe and additional routine laboratory monitoring unnecessary. Short-term HIV viral suppression was comparable to that in routine HIV cohorts without tuberculosis.

Implications of all the available evidence

Super-boosting proved effective and safe; however, with liquid lopinavir–ritonavir and ritonavir formulations, tolerability and logistics remained challenging. Recently approved heat-stable child-adapted solid formulations of lopinavir–ritonavir and ritonavir granules and taste-masked solid-fixed dose combinations are now entering clinical trials, and will likely simplify and improve the acceptability of super-boosting for children co-infected with tuberculosis and HIV.

pump, thereby providing effective lopinavir plasma exposure.[7]

Through the induction of CYP3A4 and P-glycoprotein expression, rifampicin reduces the lopinavir area under the curve by 75% and trough concentration by 99%.[8] The peak rifampicin-associated induction occurs after approximately 1 week of therapy with enzyme activity normalising 2 weeks after stopping rifampicin.[9,10] Double dosing of lopinavir–ritonavir in adults requiring rifampicin is well tolerated and widely used, despite 22% of cases having subtherapeutic lopinavir—ie, the minimum blood plasma concentration reached by lopinavir before administration of the next dose (C_{min}).[11] By contrast, after double dosing in young children co-infected with HIV and tuberculosis, 60% had subtherapeutic lopinavir morning C_{min} values.[12]

A proof-of-concept pharmacokinetic study evaluated super-boosting in South African children. 13 of 15 children (median age 16 months) receiving lopinavir–ritonavir with additional ritonavir to achieve a one-to-one parity during tuberculosis treatment achieved lopinavir morning C_{min} of more than 1·0 mg/L,[13] which is the efficacy threshold in therapeutic drug monitoring guidelines.[14] No safety signals were reported. We decided to further study the optimal adjustment of lopinavir–ritonavir during tuberculosis therapy. We considered that randomisation of participants to a double-dose regimen was not appropriate because the available data were strongly suggestive of inferiority. Therefore, we aimed to systematically assess the safety and pharmacological and clinical effectiveness of super-boosting (ie, lopinavir–ritonavir plus additional ritonavir).

Methods

Study design and participants

We did a prospective, open-label, one-group, one-sequence study at five sites in three South African provinces: the Family Clinical Research Unit in the Western Cape; the Empilweni Services, Shandukani, and the Perinatal HIV Research Units in Gauteng; and the Enhancing Care Foundation in KwaZulu-Natal. This study design included four hospital-based sites and one inner city site. The study protocol and amendments, including change in the primary outcome, were reviewed by the Data Safety and Monitoring Board

(DSMB) and approved by the ethics committees of Stellenbosch University, University of Cape Town, University of the Witwatersrand, and Pharma Ethics in Durban.

We included HIV-infected children with clinician-diagnosed tuberculosis, a bodyweight between 3 kg and 15 kg, and a post-conceptional age of more than 42 weeks. Children could enrol regardless of whether tuberculosis treatment or cART was initiated first (figure 1). We excluded those children who would no longer be on isoniazid, rifampicin, and pyrazinamide (with or without a fourth drug) for the planned first pharmacokinetic visit. We anticipated that children might be sicker in the earlier stages of therapy and therefore at greater risk for adverse events than those enrolled later. Also, because these children acted as their own controls, both for pharmacokinetics and virological response, we sought uniformity of management in all of the study sites. Additionally, we excluded children receiving non-standard dosages of tuberculosis treatment, requiring drugs that substantially induce cytochrome P450 enzymes, or with clinical conditions that would compromise their study participation, a Division of AIDS (DAIDS) grade 3 for alanine aminotransferase (ALT) and renal function abnormalities, or severe comorbidities or contraindications to lopinavir–ritonavir.

Children on double-dose liquid lopinavir–ritonavir at initiation of co-therapy for no more than 7 days could enrol provided that the first pharmacokinetic visit would be at least 14 days after initiation of super-boosting and while still on the intensive phase. We obtained written informed consent from parents or legal guardians. Consent forms were available in English and local languages including Afrikaans, isiXhosa, and isiZulu. Because of the young age of participants, assent was not sought.

Procedures

All drugs, including lopinavir–ritonavir (Kaletra, 80 mg/mL–20 mg/mL solution, respectively) and ritonavir (Norvir 80 mg/mL), were supplied by the South African Department of Health cART programme. Lopinavir–ritonavir and ritonavir were dosed orally twice a day on the basis of the South African weight bands as follows: 1 mL lopinavir–ritonavir with 0·8 mL ritonavir for 3–4·9 kg, 1·5 mL lopinavir–ritonavir with 1·2 mL ritonavir for 5–9·9 kg, 2 mL lopinavir–ritonavir with 1·5 mL ritonavir for 10–13·9 kg, and 2·5 mL lopinavir–ritonavir with 2 mL ritonavir for 14–16·9 kg. The daily oral rifampicin dose was also based on weight bands: 45 mg for 3–3·9 kg, 60 mg for 4–5·9 kg, 90 mg for 6–7·9 kg, 120 mg for 8–11·9 kg, 180 mg for 12–14·9 kg, and 210 mg for 15–19·9 kg.

Children were assessed at enrolment and then monthly until 3 months after completing anti-tuberculosis therapy. The first pharmacokinetic evaluation was done during the second month of tuberculosis and HIV infection co-treatment, and the second pharmacokinetic evaluation during the last month of co-treatment. Standard lopinavir–ritonavir doses were reinstated 2 weeks after stopping rifampicin with the third pharmacokinetic evaluation, which was done 4–6 weeks thereafter. Caregivers were reminded the day before a pharmacokinetic visit to record the evening dose time and to ensure that the child fasted for at least 1 h before arrival at the clinic. Children received cART and tuberculosis drugs at the clinic and remained fasting for a further hour. The pharmacokinetic evaluation was postponed if the participant took an incomplete dose or vomited. Pharmacokinetic samples were drawn before the observed dose and 1, 2, 4, 6, and 10 h later. To assess safety, electrocardiography was done at baseline and week 2; and albumin, full blood count, and ALT were measured at baseline and at each pharmacokinetic

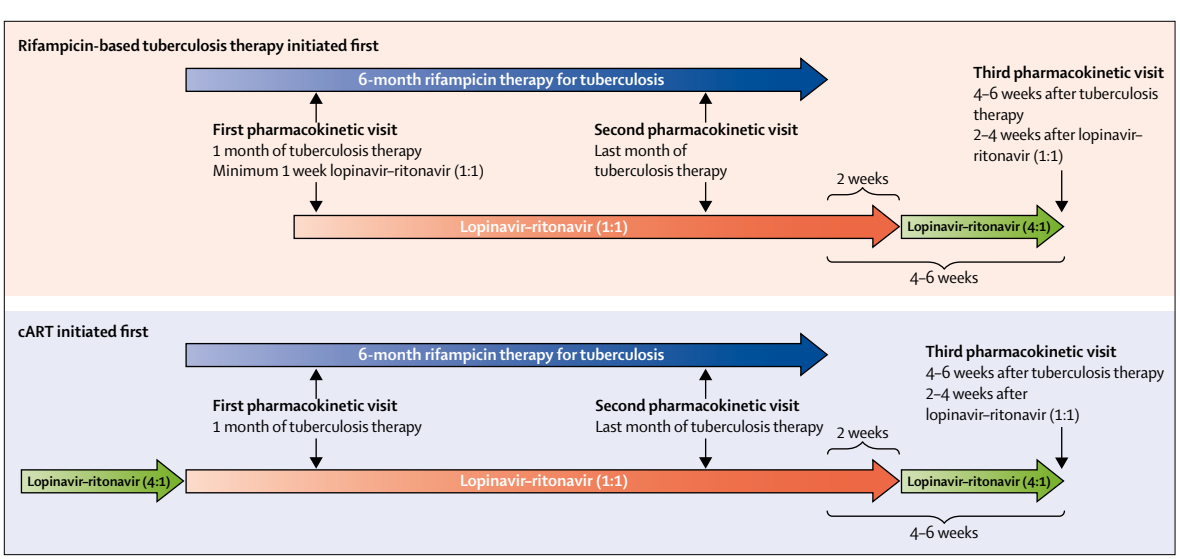

Figure 1: **Study schema**
cART=combination antiretroviral therapy.

	Baseline	First pharmacokinetic visit	Second pharmacokinetic visit	Third pharmacokinetic visit
Number of participants with a pharmacokinetic visit	96	92	82	80
Number of participants included in pharmacokinetic analysis	NA	91*	81†	80
Age (months)	18·2 (9·6 to 26·8)	19·1 (10·4 to 27·6)	23·3 (15·2 to 34·4)	25·0 (16·7 to 34·3)
Number less than 12 months of age	30 (31%)	27 (29%)	15 (18%)	7 (9%)
Girls	52 (54%)	52 (57%)	49 (60%)	48 (60%)
WHO stage 4 HIV infection	60 (63%)	..	..	..
Weight (kg)	8·4 (6·7 to 10·3)	8·8 (7·1 to 11·1)	9·8 (8·5 to 12·2)	10·1 (8·9 to 12·3)
3–4·9 kg	11 (11%)	7 (8%)	0	0
5–9·9 kg	58 (60%)	55 (60%)	43 (52%)	38 (48%)
10–13·9 kg	23 (24%)	26 (28%)	30 (37%)	31 (39%)
≥14 kg	4 (4%)	4 (4%)	9 (11%)	11 (14%)
Weight for age (Z score)	–2·15 (–3·36 to 1·19)	–2·00 (–2·86 to 0·87)	–1·34 (–2·15 to 0·43)	–1·37 (–2·22 to 0·45)
Weight for height (Z score)	–0·64 (–1·6 to –0·3)	..	..	–0·26 (–1·1 to 0·52)
Lopinavir dose (mg/m² per kg)	NA	306·4 (286·5 to 325·6)	297·2 (277·2 to 317·4)	292·9 (273·4 to 316·8)
Ritonavir total dose (mg/m² per kg)	NA	317·7 (296·5 to 337·6)	310·9 (287·4 to 326·3)	73·2 (68·4 to 79·2)
Rifampicin dose (mg/kg)	NA	12·4 (11·2 to 13·4)	12·6 (11·6 to 13·6)	NA

Data are n, n (%), or median (IQR). NA=not applicable. *One pharmacokinetic profile was excluded, as the sequence of levels suggested a specimen labelling error. †One pharmacokinetic profile was excluded, as both lopinavir and ritonavir were below the level of detection; however, at the pharmacokinetic visit, this participant had detectable levels at previous and subsequent visits.

Table 1: **Patient characteristics at enrolment and each pharmacokinetic visit**

visit. Cholesterol and triglycerides were measured at the second pharmacokinetic visit. Laboratory adverse events were graded using the DAIDS grading systems. HIV viral load was assessed at baseline and at the second pharmacokinetic visit.

Through routine care at each site, HIV viral load results were reported with varying non-detectability thresholds. For analysis, HIV viral loads reported below a given threshold were conservatively assigned the specific threshold value; for example, if the value was stated as less than 100 copies per mL, the assigned value was 100 copies per mL. This assignment is conservative but does not overstate viral response.

Additionally, we evaluated the proportion of all drugs returned at each dispensation visit and asked a 7-day recall of missed doses. On the pharmacokinetic visit days, caregivers completed a questionnaire to report issues of preparation, dosing, and refusal of medication.

Outcomes

The primary outcome was the comparison of the proportion of children with predicted lopinavir morning C_{min} of more than 1·0 mg/L during lopinavir–ritonavir plus ritonavir while on rifampicin-based tuberculosis therapy to the proportion of more than 1·0 mg/L during standard lopinavir–ritonavir treatment without rifampicin. Secondary outcomes included safety, tolerability, and acceptability of lopinavir–ritonavir plus ritonavir during super-boosting. An additional secondary outcome was the HIV viral load evolution, documenting HIV resistance mutations in children failing therapy.

Statistical analysis

For the primary outcome, we estimated that 90 evaluable children would provide at least 80% power to determine whether the percentages of children with lopinavir morning C_{min} of less than 1·0 mg/L during super-boosting compared with the percentage after super-boosting were within a clinically acceptable preset non-inferiority margin of 10% (one-sided type I error 0·025). On the basis of scarce paediatric pharmacokinetic data available at the time and knowing that we planned on using weight-banded dosing, we assumed that 8% of children would have a morning C_{min} of less than 1·0 mg/L for lopinavir target when off rifampicin therapy.[15]

After an early DSMB data review showed that some lopinavir morning C_{min} values were inconsistent with the pharmacokinetic curves following observed dose, the DSMB and population pharmacokinetic experts suggested using model-predicted morning C_{min} instead of observed morning C_{min} as the primary endpoint. Pharmacokinetic modelling during and after super-boosting was initially planned as a secondary objective. Model simulations and parameter re-estimations showed no need for sample size adjustment.

The 1·0 mg/L efficacy target was based on morning C_{min}; and because of a 30% decrease of overnight lopinavir clearance, the predicted morning C_{min} values were compared.[14,16] The concentration–time data were interpreted with non-linear mixed-effects modelling.[17]

We first developed a structural model to characterise lopinavir pharmacokinetics for the two dosing scenarios. Pharmacokinetic data from the first visit were fitted to

identify the structural model: one and two compartment dispositions were tested, with first-order absorption (with or without absorption lag time) and first-order elimination. To minimise the effect of uncertainty around the timing and accuracy of dosing on the evening before the pharmacokinetic evaluations, pre-dose concentrations were modelled using the baseline approach by Dansirikul and colleagues.[18] Observed concentrations were used to initialise the model while acknowledging their residual variability. Pharmacokinetic parameters were estimated on the basis of measured concentrations after the supervised dose in the morning of the first pharmacokinetic visit. Between-subject variability was assumed to be log-normally distributed. A combined proportional and additive error model was used to describe the residual unexplained variability. Allometric scaling accounted for the known effect of body size, and the effect of age on clearance (maturation) was tested as a potential covariate.[19] Model development and covariate selection were driven by improvements in the objective function value and inspection of diagnostic plots, including prediction-corrected visual predictive checks.[20]

The selected structural model was then applied to data from the second and third pharmacokinetic visit to characterise and compare the two dosing scenarios. The stochastic model was given flexibility to capture differences between the data from the second and third pharmacokinetic visit with separate estimates of typical clearance, volume of distribution, and absorption rate constant (k_a) values at each visit, and allowed between-subject variability and between-occasion variability on all parameters regardless of their statistical significance, provided that the stability of the model was unaffected.

The uncertainty of the parameter estimates from the second and third pharmacokinetic analyses was obtained through non-parametric bootstrap with reinsertion (n=500). Monte Carlo simulations were then done on 10 000 in-silico patients and repeated 500 times, one for each set of parameter estimates from the bootstrap. In each of the 500 repetitions, the percentage of children with simulated morning C_{min} of less than 1·0 mg/L in the two-dosing scenario was compared, thus obtaining a median difference and confidence interval.

We did descriptive analyses of adverse effects, HIV viral load, resistance, and adherence parameters, and described these analyses with median and IQR.

We interpreted the concentration–time data using NONMEM (version 7.3) and ancillary software, and did all the descriptive analyses using Stata (version 14). This study is registered with ClinicalTrials.gov, number NCT02348177.

Role of the funding source

This study was sponsored by the Drugs for Neglected Diseases initiative (DNDi). DNDi developed the idea, coordinated the protocol development, supported laboratory analysis, data management, and data analysis. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

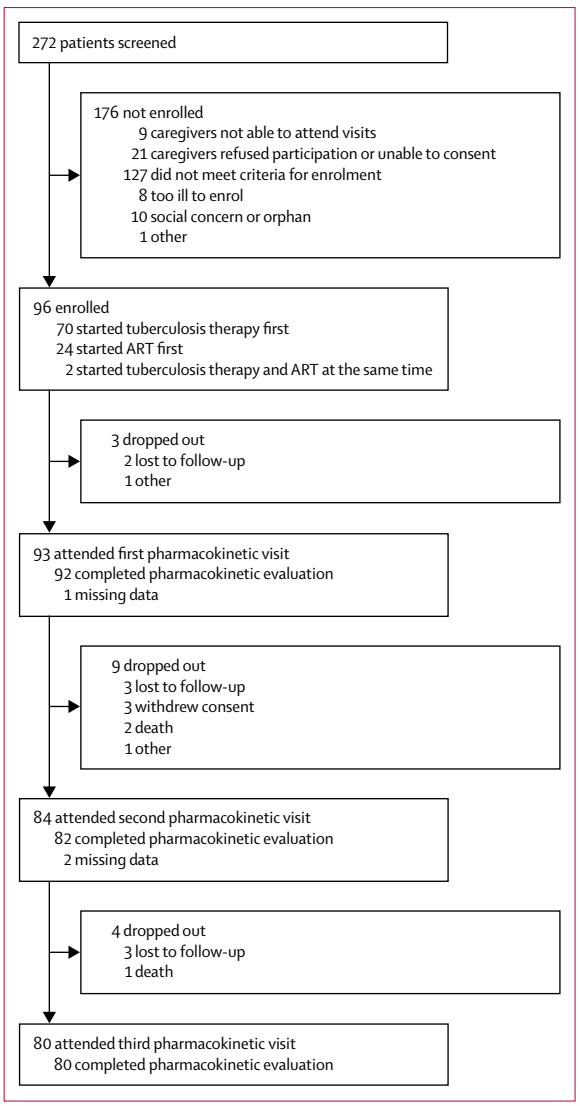

Figure 2: **Trial profile**
ART=antiretroviral therapy.

Results

Between Jan 30, 2013, and Nov 9, 2015, we recruited 96 children. After reviewing the data in November, 2015, given slow enrolment, the DSMB recommended stopping new enrolment because interim modelling suggested an adequate sample size for the study to reach reliable conclusions. The study follow-up concluded on July 26, 2016. Table 1 shows the participant demographics and dosages from each pharmacokinetic visit. At study completion, 80 (83%) of 96 patients had completed the first three pharmacokinetic evaluations (figure 2). Children were young (median age at enrolment was 18·2 months [IQR 9·6–26·8]), and children younger than 12 months were well represented at each

Table 3 citation?

	Typical value* at second pharmacokinetic visit	Typical value* at third pharmacokinetic visit	Between-subject variability†	Between-occasion variability†
Clearance (L/h)	2·48 (2·13–3·01)	2·33 (1·88–2·95)	37·5% (12·7–50·6)	46·6% (17·8–68·7)
Volume of distribution (L)	22·9 (18·1–35·5)	16·1 (12·7–21·6)	NA	NA
K_a (one per h)	0·629 (0·442–1·195)	0·438 (0·358–0·583)	NA	52·8% (31·4–74·8)
Bioavailability	1 (fixed)	1 (fixed)	NA	45·4% (28·3–58·3)
Proportional error	16·5% (9·1–19·2)	16·5% (9·1–19·2)	NA	NA
Additive error (mg/L)	0·174 (0·010–1·035)	0·174 (0·010–1·035)	NA	NA

Data in parentheses are 95% CIs, unless otherwise specified. NA=not applicable. k_a=absorption rate constant. *The typical values of clearance and volume of distribution are reported for a 10 kg child, close to the median weight observed in our cohort. †The between-subject variability and between-occasion variability were assumed to be log-normally distributed, and were reported here as approximate percentage of coefficient of variation.

***Table 2*: Pharmacokinetic parameters estimated by the pharmacokinetic model**

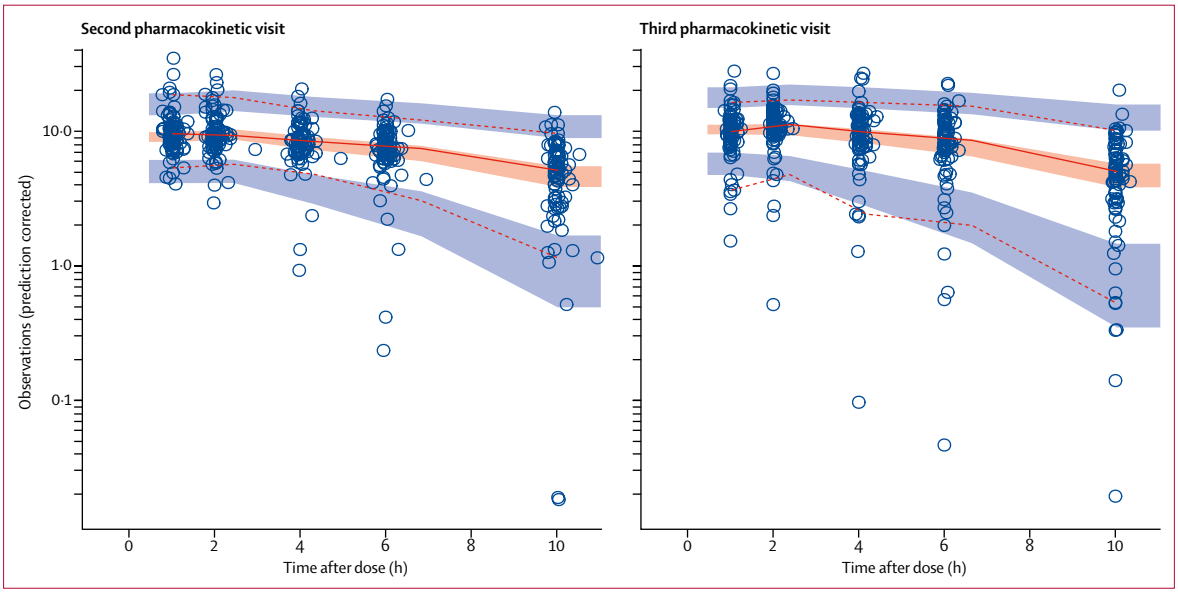

***Figure 3*: Log-scale visual predictive check comparing data from the second pharmacokinetic visit with the third pharmacokinetic visit**
The solid line is the median and the shaded red area represents the model predicted 95%CI for the median. The dashed lines are the 5th and 95th percentiles, respectively and the blue shaded area represents the 95% CI for the same percentiles.

See Online for appendix

pharmacokinetic visit, including the third visit (table 1). Tuberculosis therapy preceded cART IN 70 (73%) of 96 children. Only 12 (13%) of the cohort started cART more than 3 months before initiating tuberculosis therapy. Children who began cART after initiating tuberculosis therapy did so at a median of 14 days (IQR 9–24). Lopinavir, ritonavir, and rifampicin doses at each pharmacokinetic visit are shown in table 1. Most children were in the 5–9·9 kg weight band at all pharmacokinetic visit timepoints. Children had an increase in weight and changed weight bands in the study accordingly, children in the 3–4·9 kg band are only represented in the first pharmacokinetic visit. By the third pharmacokinetic visit, children in the weight band of 14 kg or more are better represented than at the first and second pharmacokinetic visit.

The pharmacokinetic data from the first evaluation were best described by one-compartment model with first-order absorption and elimination. Including an absorption lag time improved the fit marginally, but was excluded as model estimates became unstable. Allometric scaling of clearance and volume of distribution using bodyweight (exponents fixed to 0·75 for clearance and one for volume of distribution) improved the fit, however no significant effect of age on clearance could be detected.

Table 2 shows the parameter estimates under the two dosing scenarios and their uncertainty. The visual predictive check in figure 3 shows the appropriateness of the model fit. For a 10 kg child (the median bodyweight in our cohort), the typical estimated clearance value was similar during super-boosting and after super-boosting (table 2). The predicted exposure for a 10 kg child receiving the 160 mg of lopinavir standard dose twice a day was approximately 50 mg×h/L.

Inclusion of between-subject variability in clearance and between-occasion variability in clearance, k_a, and

bioavailability improved model fit. Random effects on other pharmacokinetic parameters were excluded as they did not significantly improve the fit and caused instability in the parameter estimates.

The percentage of model-predicted lopinavir morning C_{min} of less than 1·0 mg/L was 7·6% (95% CI 0·4–16·2) during super-boosting versus 8·8% (0·6–19·8) during standard lopinavir–ritonavir therapy after tuberculosis therapy discontinuation. The median difference was –1·1% (95% CI –6·9 to 3·2), confirming the non-inferiority of lopinavir exposure during super-boosting lopinavir–ritonavir plus ritonavir compared with standard lopinavir–ritonavir without rifampicin at a non-inferiority margin of 10%.

We detected no cardiac conduction disorders, hepatitis, or ALT elevations requiring therapy interruption. 19 serious adverse events were reported in 12 participants: four neutropenia episodes not requiring study medication interruption, nine children requiring 15 hospitalisations (one diabetic ketoacidosis and 14 infections), and the temporary interruption of super-boosted cART in one child developing obstructive jaundice of unknown cause. Three deaths were reported. One child died in hospital of suspected nosocomial bloodstream infection 411 days after initiating cART and 227 days after start of super-boosting. Tuberculosis treatment was stopped 5 days before death. Review of the two children who died at home concluded that HIV-related causes were most likely, post-mortems were not done. The first of these children died 104 days after starting cART and 102 days after starting anti-tuberculosis treatment, approximately 2 months after completing the first pharmacokinetic visit. For the second child who died outside South Africa, the study team derived information from relatives rather than the parents. This child died approximately 4 months after start of cART and anti-tuberculosis treatment, and had completed the first pharmacokinetic visit. The appendix provides a full list of all adverse events reported, including multiple events listed for one person. Table 3 summarises the laboratory toxic monitoring data.

The caregivers reported lopinavir–ritonavir and ritonavir as the most difficult to administer (table 4). Medication refusal, spitting, or vomiting (asked as a single question) was reported more in the first pharmacokinetic visit than in the second or third visits. Calculated adherence measured through medication dispensed and returned for ritonavir and lopinavir–ritonavir liquid exceeded 100%, confirming the difficulty in determining measured adherence to liquid formulations.

The median HIV viral load at enrolment of 95 children with data was high but by the second pharmacokinetic evaluation children showed good response to therapy, with most achieving suppression of less than 400 copies per mL (table 5). We tested for antiretroviral resistance mutations in 22 of 40 children with detectable HIV viral load at a median of 290 days (IQR 267–383) on cART. Resistance mutations were found in one (13%) of eight children with

	Baseline	First pharmacokinetic visit	Third pharmacokinetic visit
Haemoglobin (g/dL)	9·6 (8·8–10·5)	10·2 (9·4–11·2)	11·2 (10·4–11·9)
Normal (>10·0 g/dL)	34/96 (35%)	40/79 (51%)	66/79 (84%)
Grades 1 and 2 (7·5–10·0 g/dL)	59/96 (61%)	36/79 (45%)	13/79 (16%)
Grades 3 and 4 (<6·5 to 7·4 g/dL)	3/96 (3%)	3/79 (4%)	0
White cell count (×10⁹ per L)	11·3 (8·3–14·6)	10·2 (8·1–13·6)	9·6 (8·3–12·6)
Neutrophil count (×10⁹ per L)	4·1 (2·4–5·8)	2·1 (1·4–4·0)	2·7 (2·1–4·2)
Normal (>1·300×10⁹ per L)	60/66 (91%)	41/54 (76%)	50/55 (91%)
Grades 1 and 2 (0·750–1·300×10⁹ per L)	4/66 (6%)	11/54 (20%)	5/55 (9%)
Grades 3 and 4 (<0·500 to 0·749×10⁹ per L)	2/66 (3%)	2/54 (4%)	0
Platelets (=×10⁹ per L)	377 (276–494)	370 (288–463)	376 (317–449)
ALT (U/L)	25·0 (18·0–40·0)	25·0 (19·0–32·0)	20·0 (19·5–35·5)
Normal	68/95 (72%)	79/92 (86%)	72/78 (91%)
Grades 1 and 2 (elevation ALT 1·5–5×U/L)	27/95 (28%)	13/92 (25%)	6/79* (8%)
Albumin (g/L)	37·0 (32·0–40·0)	41·0 (38·0–44·0)	43·0 (40·0–44·0)
Normal (>30 g/L)	75/93 (81%)	83/90 (92%)	77/80 (96%)
Grades 1 and 2 (20–30 g/L)	16/93 (17%)	6/90 (6%)	3/80 (4%)
Grades 3 and 4 (<20 g/L)	2/93 (2%)	1/90 (1%)	0

Data are median (IQR) or n/N (%). ALT=alanine aminotransferase. *Including missing data for one individual.

Table 3: **Laboratory toxicity monitoring data**

	First pharmacokinetic visit	Second pharmacokinetic visit	Third pharmacokinetic visit
All drugs			
Any refusal, spitting, or vomiting	33/87 (38%)	19/79 (24%)	16/79 (20%)
Abacavir			
Number of children on drug	87	77	74
Median calculated adherence	102·0 (95·0–116·0); n=86	103·0 (97·0–113·0); n=76	104·0 (98·0–113·0); n=74
No doses missed in the past 7 days	45/67 (67%)	41/62 (54%)	43/61 (70%)
Any refusal, spitting, or vomiting	2 (2%)	1 (1%)	1 (1%)
Every dose	1	0	0
Every 2–3 doses	1	1	0
2–3 times per week	0	0	1
Lamivudine			
Number of children on drug	91	82	79
Median calculated adherence	101·9 (93·9–109·7); n=91	103·0 (95·0–110·0); n=80	103·5 (98·0–110·0); n=78
No doses missed in the past 7 days	47/72 (65%)	44/64 (69%)	44/65 (68%)
Any refusal, spitting, or vomiting	2 (2%)	1 (1%)	1 (1%)
Every dose	1	0	0
Every 2–3 doses	1	1	0
2–3 times per week	0	0	1
Lopinavir–ritonavir (4:1)			
Number of children on drug	91	82	79
Median calculated adherence	105·0 (97·6–118·0); n=87	106·3 (101·0–113·0); n=80	108·0 (101·0–114·9); n=78
No doses missed in the past 7 days	56/70 (80%)	56/65 (86%)	58/66 (88%)

(Table 4 continues on next page)

	First pharmacokinetic visit	Second pharmacokinetic visit	Third pharmacokinetic visit
(Continued from previous page)			
Any refusal, spitting, or vomiting	26/70 (37%)	17/65 (26%)	16/66 (24%)
Every dose	7	5	7
Every 2–3 doses	2	0	2
2–3 times per week	17	12	7
Ritonavir			
Number of children on drug	91	82	NA
Median calculated adherence	106·9 (99·0–120·3)	106·0 (99·0–118·0)	NA
No doses missed in the past 7 days	59/73 (81%)	53/65 (82%)	NA
Any refusal, spitting, or vomiting	22/73 (30%)	16/65 (25%)	NA
Every dose	10	4	NA
Every 2–3 doses	0	1	NA
2–3 times per week	12/22 (55%)	11/16 (69%)	NA
Rifampicin–isoniazid (60/60)			
Number of children on drug	91	82	NA
Median calculated adherence	100·0 (95·0–100·0); n=89	100·0 (100·0–104·0); n=81	NA
No doses missed in the past 7 days	57/74 (77%)	57/66 (86%)	NA
Any refusal, spitting, or vomiting	5 (5%)	0	NA
Every dose	1	0	NA
Every 2–3 doses	2	0	NA
2–3 times per week	2	0	NA
Pyrazinamide			
Number of children on drug	91	6	NA
Median calculated adherence	100·0 (97·1–100·0); n=90	100·0 (96·0–100·0); n=6	NA
No doses missed in the past 7 days	56/74 (76%)	4/6 (67%)	NA
Any refusal, spitting, or vomiting	4 (4%)	0	NA
Every dose	1	0	NA
Every 2–3 doses	2	0	NA
2–3 times per week	1	0	NA
Ethambutol			
Number of children on drug	88	6	NA
Calculated adherence	100·0 (95·0–100·0); n=86	100·0 (100·0–100·0); n=6	NA
No doses missed in the past 7 days	54/73 (75%)	5/6 (83%)	NA
Any refusal, spitting, or vomiting	3 (3%)	0	NA
Every dose	0	0	NA
Every 2–3 doses	1	0	NA
2–3 times per week	2	0	NA

Data are n/N (%), n (%), or median (IQR), unless otherwise specified. We did not report on stavudine, zidovudine, and ethionamide as these drugs were infrequently used. NA=not applicable.

Table 4: **Calculated adherence, missed doses, and medication refusal, spitting, or vomiting at each pharmacokinetic visit**

an HIV viral load of more than 10 000 copies per mL, all of three children with an HIV viral load of 1000–10 000 copies per mL, all of two children with an HIV viral load of 400–1000 copies per mL, and six (67%) of nine children with an HIV viral load of 50–400 copies per mL. Only one child had a major protease inhibitor mutation. Of the ten children with non-nucleoside reverse transcriptase inhibitor resistance, six had confirmed exposure to this inhibitor through mother-to-child transmission prevention. Table 5 summarises the mutations detected. No children switched cART regimen.

Discussion

Lopinavir exposure during super-boosting with ritonavir in a one-to-one ratio during rifampicin-based tuberculosis treatment was non-inferior to the exposure with lopinavir–ritonavir without rifampicin. The strategy was safe with only one child requiring therapy interruption for a reason unrelated to super-boosting.

In the initial proof-of-concept paediatric super-boosting study, children treated with rifampicin received lopinavir at a median of 291·9 mg/m² per dose (IQR 274·3–308·6) and those not treated with rifampicin received lopinavir at 265·2 mg/m² per dose (248·8–289·3). Only two of 15 children on rifampicin had a morning C_{min} of less than 1·0 mg/L.[13] The present study is much larger, with children acting as their own controls and with those younger than 12 months being well represented, particularly at the first pharmacokinetic visit. However, most pharmacokinetic data were in the 5–9·9 kg weight band. We used the WHO weight bands targeting a dose of 230–350 mg/m².[6] This approach gives lopinavir exposures above those expected for the US Food and Drug Administration approved dosing.[21] Our study outcomes support WHO's pragmatic dosing approach, confirming that for most children exact dosing by body mass or surface area is unnecessary even during tuberculosis therapy.

For this study, we chose the 1·0 mg/mL morning C_{min} threshold as our efficacy target, which was based on therapeutic drug monitoring recommendations.[14,22] In South African children, a lopinavir level of more than 1·0 mg/L decreased the hazard of an HIV viral load of more than 400 copies per mL (adjusted hazard ratio 0·62, 95% CI 0·40–0·94).[23] Higher lopinavir concentrations reduced the risk of viraemia by 5%, for every 1·0 mg/L increase in lopinavir morning C_{min}.[23] We used modelled morning C_{min} values rather than those observed, using the totality of data collected during a pharmacokinetic visit rather than predose data only. Increasingly, pharmacokinetic studies use modelling as a preferred analysis method.[24]

Care givers reported difficulty with medicine administration. In addition to the lopinavir–ritonavir and ritonavir solutions, they had to give the children liquid nucleoside reverse transcriptase inhibitors and antituberculosis drugs. Despite this complex therapy, more than 80% of children had an HIV viral load of less than 400 copies per mL 6 months into the study. This outcome is comparable with other South African studies where, in the absence of tuberculosis, 74·8% of children achieved this level of suppression at 6 months.[25] These data also compare well with the initial lopinavir–ritonavir pharmacokinetic studies (300 mg/m² per dose of lopinavir and 75 mg/m² per dose of ritonavir), in

	Days on cART	n	Viral load			
			Log value (copies/mL)	<1000 copies per mL	<400 copies per mL	<50 copies per mL
Baseline						
All	NA	95	5·7 (4·6 to 6·3)	8 (8%)	6 (6%)	2 (2%)
On cART for >3 months at the start of tuberculosis therapy	367 (183 to 651)	11	4·7 (1·7 to 5·3)	3 (27%)	3 (27%)	2 (18%)
On cART for <3 months at the start of tuberculosis therapy	40 (22 to 83)	12	5·3 (4·5 to 6·1)	1 (8%)	1 (8%)	0
Initiated cART and tuberculosis therapy at the same time or started cART after tuberculosis therapy	NA	72	5·9 (4·9 to 6·3)	4 (6%)	2 (3%)	0
Second pharmacokinetic visit						
All	161 (141 to 188)	82	2·1 (<1·6 to 2·3)	69 (84%)	67 (82%)	25 (30%)
On cART for >3 months at the start of tuberculosis therapy	522 (337 to 960)	11	2·3 (<1·6 to 4·4)	7 (64%)	7 (64%)	4 (36%)
On cART for <3 months at the start of tuberculosis therapy	191 (165 to 203)	7	2·0 (1·9 to 2·3)	6 (86%)	6 (86%)	1 (14%)
Initiated cART and tuberculosis therapy at the same time or started cART after tuberculosis therapy	154 (137 to 163)	64	2·0 (<1·6 to 2·3)	56 (88%)	54 (84%)	20 (32%)

Data are median (IQR) or n (%), unless otherwise specified. We noted the following resistance mutation combinations: one major protease inhibitor mutation (54Ile/Val) together with 184Val and 70Glu; three 184Val only; four 184Val plus NNRTI resistance mutations; one 184Val, 70Glu, and NNRTI resistance mutations; one 184Val, 74Val, and a minor protease inhibitor resistance mutation; one NNRTI resistance mutation only; and one NNRTI and minor protease inhibitor resistance mutations. We also noted the following NNRTI mutations: seven 103Asn mutations (four alone, one with 190Val, one with 106Met, and one with 138Gln/Gly); one 181Cys mutation, one 181Tyr/Cys with 190Ala; and one 190Ala with 138Ala . NA=not applicable. cART=combination antiretroviral therapy. NNRTI=non-nucleoside reverse transcriptase inhibitor.

Table 5: **Virological response on cART and antiretroviral resistance mutations**

which 79% of naive children older than 6 months achieved an HIV viral load of less than 400 copies per mL by week 48.[26] Of note is the high baseline HIV viral load in children already on therapy; these children managed to suppress with adherence support from health-care providers.

Despite antiretroviral resistance mutations in many children failing therapy, all participants remained fully susceptible to lopinavir and did not require a regimen switch. Children with higher viraemia (>10 000 copies/mL) rarely had documented resistance than those with viraemia below 10 000 copies/mL, also indicating non-adherence.

There are few alternatives to super-boosting in young children. Although efavirenz exposure is relatively unaffected by rifampicin co-treatment, with sufficient data to support its use in children older than 3 years and weighing more than 10 kg, it is not recommended in younger children. To use efavirenz in these children, the CYP2B6 polymorphism must be determined to reduce dosage in slow metabolisers, which is not feasible in most settings.[27] Although there are dose-adaptation guidelines for nevirapine, this drug is already considered suboptimal for non-tuberculosis co-infected infants, so with tuberculosis it is even less of an option.[27] Moreover, we observed high levels of resistance to non-nucleoside reverse transcriptase inhibitors in children failing to suppress, suggesting either maternal transmitted viral resistance or resistance due to nevirapine exposure for prevention of mother-to-child transmission. Nucleoside reverse transcriptase inhibitors have no drug–drug interaction with rifampicin, but the only prospective data using three nucleoside reverse transcriptase inhibitors with rifampicin comes from the AntiRetroviral Research fOr Watoto (ARROW) trial, in which incident tuberculosis was a common reason for changing first-line therapy. HIV viral load testing for monitoring was unavailable in this trial. There is also concern that a triple nucleoside reverse transcriptase inhibitor regimen is not suppressive.[27] Its use in severely ill young children initiating tuberculosis therapy and cART together requires further study.[27]

Integrase inhibitors are becoming first-line treatment options for children but are not exempt from drug–drug interactions. Preliminary data suggest that doubling the raltegravir dose will overcome negative interactions with rifampicin.[28] Dolutegravir dosing for young children is being studied and formulations are under development; in adults, the standard daily dose of twice daily is needed to be given with rifampicin.[29]

Although one can substitute rifampicin with rifabutin in some settings, data for rifabutin dosing during cART in children are scarce. Also, rifabutin is usually unavailable in standard tuberculosis management protocols in most low-income and middle-income settings. Concern about neutropenia in children treated with rifabutin and lopinavir–ritonavir also exists. Such a study was stopped because of frequent severe neutropenia. However, in an observational cohort from Nigeria, haematological abnormalities common at initiation of rifabutin usually resolved.[27]

This study has some limitations. With new fixed-dose combination formulations of 75 mg rifampicin and 50 mg isoniazid per tablet being introduced, children will receive 10·7–18·7 mg/kg rifampicin per day, which is the new WHO recommended dose. There is increasing interest in providing higher doses of rifampicin to optimise tuberculosis therapeutic outcomes in adults and children, with modelling suggesting that higher rifampicin dosing

increases CYP3A4-mediated induction.[30] The effect of rifampicin dose increases on lopinavir drug concentrations during super-boosting might require evaluation. Assessing adherence and tolerability was challenging, and standardised approaches are needed to allow for comparison across studies and study drugs. We were unable to accurately control the timing and completion of the unobserved evening dose before the pharmacokinetic visits. This limitation caused erratic morning C_{min} values and prompted changing the primary outcome from measured to modelled predose concentrations. We were fortunate that in this case we had good pharmacokinetic data to use for modelling and consequently a more powerful comparison of lopinavir exposures during and after super-boosting. However, this situation highlights another limitation of the study in terms of effect. There is a considerable difference between the controlled environment of a clinical trial and real life where treatment must be implemented.

Despite this study being one of the largest pharmacokinetic studies undertaken in co-treated children, its effect is limited by the non-heat-stable unpalatable solutions currently available. Replacement of liquid lopinavir–ritonavir and ritonavir with newer, solid, heat-stable, better child-adapted formulations is expected. Generic lopinavir–ritonavir (40 mg–10 mg) solid formulations consisting of mini-tablets or granules to be sprinkled on food before administration were recently approved. DNDi and Cipla Ltd have developed a taste-masked fixed-dose combination containing lopinavir–ritonavir with lamivudine and abacavir, which is now ready for registration studies. A ritonavir solid formulation is now available in 100 mg sachets that can be dispersed in water that enables exact dosing. Ideally, to serve young children best, ritonavir solid formulation should be formulated in 30 mg capsules to facilitate super-boosting with the 40 mg–10 mg formulations of lopinavir–ritonavir. Data for appropriate strategies to treat older children on tablets are also urgently needed.

In conclusion, this study shows the safety and the efficacy of lopinavir–ritonavir super-boosted with additional ritonavir to achieve a one-to-one ratio during rifampicin coadministration. The data from this study can be used to inform pharmacokinetic modelling for the assessment of super-boosting with the newer solid lopinavir–ritonavir and ritonavir formulations and higher rifampicin doses.

Contributors

HR assisted with the literature search, protocol development, coordinated the study, recruited patients, assisted with data analysis and interpretation, and developed the manuscript. JL, MFC, and ML assisted with the literature review, protocol development, study management, data assessment and interpretation, and manuscript development. HM assisted with the protocol development, data assessment and interpretation, and manuscript development. PD assisted with the protocol development and manuscript development, and did the modelling analysis. MM, AC, SP, and AL recruited patients, collected data, and assisted with the development of the manuscript. FS assisted with the study management and manuscript development.

Declaration of interests

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Data sharing

Drugs for Neglected Diseases initiative (DNDi) will consider data sharing with researchers who provide a methodologically sound proposal that will maximise the value of the research data. Proposals can be directed to the medical director at DNDi. If approved, DNDi will share the following: study protocol, statistical analysis plan, deidentified individual participant data, and the relevant data dictionaries.

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