Physiologically Based pharmacokinetic (PBPK) modeling for optimal dosage prediction of quinine co-administered with ritonavir-boosted lopinavir

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Conflict of Interest

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ABSTRACT

The co-formulated lopinavir/ritonavir significantly reduces quinine concentration in healthy volunteers due to potential drug-drug interactions (DDIs). However, DDIs information in malaria and HIV co-infected patients are lacking. The objective of the study was to apply physiologically-based pharmacokinetic modeling to predict optimal dosage regimens of quinine when co-administered with lopinavir/ritonavir in malaria and HIV co-infected patients with different conditions. The developed model was validated against literature. Model verification was evaluated using the accepted method. The verified PBPK models successfully predicted unbound quinine disposition when co-administered with lopinavir/ritonavir in co-infected patients with different conditions. Suitable dose adjustments to counteract with the DDIs have identified in patients with various situations, *i.e.*, a 7-day course at 1800 mg TID in malaria patients with

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HIV infection, 648 mg BID in chronic renal failure, 648 mg TID in hepatic insufficiency except for severe hepatic insufficiency (324 mg BID), and 648 mg TID in CYP3A4 polymorphism.

Keywords: Physiologically-based pharmacokinetics, malaria, HIV, drug-drug interactions, quinine, ritonavir, lopinavir

INTRODUCTION

Malaria is reported as the third frequent cause of HIV-related morbidity in Africa (human immunodeficiency virus).[1] The estimated number of HIV co-infected with malaria deaths was 65,000 in Africa every year.[2] The prevalence of malaria coinfection with HIV varies from 0.7 to 47.5% worldwide.[2] Additionally, malaria patients co-infected with HIV are prone to have symptomatic parasitemia and high parasitemia.[3] Thus, patients are required to receive both antimalarial and antiretroviral drugs. The incidence and relevance of drug-drug interactions (DDIs) between the antimalarial drugs (victim) and antiretroviral drugs (perpetrators) have been increasing and becoming unavoidable, resulting in impaired efficacy of malaria treatment or increase its adverse effects.[2,4]

Previous two studies of quinine co-administered with ritonavir-boosted lopinavir in healthy volunteers showed that a single oral dose of 600 mg quinine co-administered with Lopinavir/ritonavir resulted in a significant decrease in quinine concentrations.[5,6] A three-fold increase in quinine dosage was suggested to counteract with the effects of lopinavir/ritonavir.[5] In contrast, a study of quinine co-administered with ritonavir alone resulted in a four-fold increase in quinine concentrations.[7] The induction of UDP-glucuronyl transferase (UGT) enzyme by ritonavir and the protein-binding displacement effect of lopinavir may be the critical factors that reduce quinine concentrations.[5,6] These two studies have highlighted a concern when quinine is co-administered with lopinavir/ritonavir for the treatment of HIV patients co-infected with malaria.

Renal failure is a common condition in patients with severe malaria, and the incidence varies from 15% to 48%.[8] This organ impairment has been reported to influence quinine plasma concentrations.[8] Dosage reduction in patients with chronic renal failure without dialysis was suggested based on computer-assisted modeling.[9] However, the optimal dose for quinine co-administered with lopinavir/ritonavir in patients is still lacking. Cytochrome P450 3A4/5 (CYP3A4/5) enzyme has been recognized as a significant human drug-metabolizing enzyme with high inter-individual variations across different ethnicities.[10,11] *In vitro* study demonstrated a reduction of quinine intrinsic clearance in the 23 CYP3A4 variants compared to the wild-type CYP3A4*1.[12] Clinical relevance of this association remains to be clarified.

The traditional dosing strategy for dose adjustment is 'trial and error' to find the optimal dose based on the clinical response. This strategy could result in inappropriate dose regimen and, thus, increase the risk of toxicity and/or treatment failure in patients. Physiologically-based pharmacokinetic (PBPK) modeling has been recognized as a reliable tool to predict drug disposition based on the information from *in vitro* and *in vivo* studies.[13] This model is applied to predict optimal dose regimen in various situations, *e.g.*, concomitant medication (DDIs), renal insufficiency, genetic polymorphism, hepatic insufficiency, as well as multiple diseases including malaria and HIV co-infection.[13-15] The objective of this study was to apply PBPK modeling to predict optimal dose of quinine when co-administered with lopinavir/ritonavir in patients co-infected with malaria and HIV in the following conditions: (i) chronic renal failure, (ii) hepatic insufficiency, and (iii) CYP3A4 polymorphism.

METHODS

Model construction

The whole PBPK model was constructed for three drugs combination (quinine, ritonavir, and lopinavir) based on the previously published information of ritonavir-boosted darunavir (DRV/r)[16] using Simbiology® version 5.8.2, a product of MATLAB® version 2019a (MathWorks, Natick, MA, USA). The physicochemical and biochemical properties of each drug and human physiological parameters were obtained from the published articles.[17-30] The essential parameters for model construction, including physicochemical, physiological, and biochemical properties of each drug are summarized in **Table 1** . Initial model assumptions were blood-flow limited model, immediate dissolution, absence of absorption from the stomach and large intestine, and absence of enterohepatic recirculation. The $f_{m,cyp3A4}$ and $f_{m,\ UGT1A1}$ for quinine were assumed to be 0.44 and 0.56, respectively.[31] There was no effect of CYP3A4 inhibition from 3-hydroxyquinine. The flow charts of single model construction and DDIs model are shown in **Figure 1** and **Figure 2**, respectively.

Virtual population simulation

Plasma concentrations of unbound quinine, ritonavir, and lopinavir were simulated in 100 virtual population aged between 18 and 60 years in the fasting state for malaria and HIV co-infected patients and

CYP3A4 polymorphism. The age range of patients used in renal and hepatic insufficiency conditions were 30-60 years. CYP3A4 variants resulted in the changes in intrinsic metabolism of quinine to 0.226-fold (CYP3A4*3: M44T5), 0.058-fold (CYP3A4*13: P416L), 0.176-fold (CYP3A4*18: L293P), and 0.43-fold (CYP3A4*19: P467S).[12]

Model verification

Eight published clinical articles were used for model validation.[5-7,9,32-35] The simulated results were compared with clinical published data. The details of each simulation are shown in **Table 2.** AAFEs between the predicted and published values were estimated to determine model accuracy. The most common accepted AAFEs are within 2-fold.[36] The mathematical equation for AAFE is as follow:

$$AAFE = 10^{(\Sigma abs(\log(prediction/observation))/n)}$$

Where n is the number of samples. The prediction and observation are simulated and clinically observed data, respectively.

Sensitivity analysis

Sensitivity analysis was performed to determine the effect of the change of the six selected model parameters on the AUC following standard quinine regimen, *i.e.,* 600 mg, every 8 hours (TID) for 7 consecutive days. Besides, additional selected model parameters were applied for the drug combination model to determine their effects on the $AUC_{3\text{-}7days}$ of quinine following the administration of lopinavir/ritonavir (400/100 mg) BID for 21 consecutive days and 600 mg quinine TID administration on day 14 for 7 consecutive days. Six selected parameters included in the model were (i) f_u, (ii) K_a, (iii) liver weight, (iv) R_{bp}, (v) $f_{m,CYP3A4}$, and (vi) $f_{m,\ UGT1A1}$. Furthermore, additional model parameters for the three drugs combination model were (i) E_{max} of ritonavir (for UGT1A1), (ii) EC_{50} of ritonavir (for UGT1A1), (iii) Ind_{50} of ritonavir (for CYP3A4), (iv) Ind_{max} of ritonavir (for CYP3A4), (v) $f_{m,CYP3A4}$, (vi) $f_{m,UGT1A1}$, (vii) f_u of ritonavir, (viii) K_{inact} of ritonavir, and (ix) K_i of ritonavir (for CYP3A4). The effects of these model parameters on $AUC_{3\text{-}7days}$ were evaluated by changing the value of each parameter by +20%. The positive sensitivity was defined as a positive correlation between the model parameters and the $AUC_{3\text{-}7days}$ and vice versa. The equation for sensitivity analysis is as follow:

$$\text{Sensitivity coefficient} = \%\Delta Y/\%\Delta X$$

Where $\%\Delta Y$ is the percent change of the$AUC_{3\text{-}7days}$, and $\%\Delta X$ is the percent change of model parameters.

Renal and hepatic insufficiency

The human physiological changes in hepatic insufficiency were obtained from the published article and applied to the model.[37] The fraction of unbound drug was calculated based on the abundance of albumin in each class of hepatic insufficiency. Blood-to-plasma partition (R_{bp}) ratio was calculated based on the change in hematocrit.[37] The renal clearance was calculated based on the estimated glomerular flow rate (eGFR).

Drug combination model (DDIs model)

Multiple-dose of lopinavir/ritonavir (400/100 mg) given twice a day for 21 consecutive days (with co-administration of a single dose of 600 mg quinine on day 14) were simulated at fasting state. The dose regimens of quinine for model simulations are shown in **Table S1**. The AUC Ratio (AUCR: the ratio of quinine AUC when administered alone and that when co-administered with lopinavir/ritonavir) was calculated to determine the effect of lopinavir/ritonavir on quinine pharmacokinetics. The effect of lopinavir on plasma protein binding displacement and the fraction of unbound quinine was estimated to be 1.45-fold when compared with quinine alone.[6] CYP3A4 inhibitory effect of quinine did not influence lopinavir/ritonavir clearance. The EC_{50} (half-maximal effective concentration) of UGT1A1 activity for ritonavir was assumed to be the same as rifampicin. The E_{max} (maximum effect at high drug concentrations) of UGT1A1 activity for ritonavir was assumed to be 3-fold.[29]

Pharmacokinetic parameters of unbound quinine co-medication with lopinavir/ritonavir were predicted in malaria and HIV co-infected patients, with chronic renal failure, or hepatic insufficiency, or CYP3A4 polymorphism. $AUC_{3\text{-}7days}$ (mg*day/L), C_{max} (mg/L), C_{trough} (mg/L), volume of distribution at steady state (V_{ss}: L/kg), $T_{1/2}$ (h), and CL (L/h) of unbound quinine are presented as mean +(95% Confidence Interval or CI).

Criteria for optimal dose regimen and evaluation

The optimal dose of quinine for curative malaria treatment was determined based on the unbound of quinine concentration reported in the published article, i.e., unbound C_{trough} and unbound $AUC_{3\text{-}7days}$ (unbound $AUC_{3\text{-}7days}$ > 2.18 mg*day/L, and unbound C_{trough} > 0.34 mg/L).[32] The toxic concentration of unbound quinine is > 2.18 mg/L.[38,39] The effects of quinine doses on unbound $AUC_{3\text{-}7days}$ multiple and unbound C_{trough} multiple were evaluated. The unbound $AUC_{3\text{-}7days}$ multiple is the ratio of unbound quinine AUC following new regimens and the required unbound AUC based on the set criteria. The unbound C_{trough} multiple is the ratio of unbound quinine C_{trough} of new regimens and the required unbound C_{trough} based on the set criteria. The dose optimization strategy flow chart is shown in **Figure 2**.

RESULTS

Model verification

The AAFEs (absolute average-folding errors) (ranges) for all model validation was 1.15-fold (1.016 – 1.27) (**Table 2**). The AAFEs (ranges) for all quinine prediction was 1.13-fold. (1.016 – 1.27) Besides, the AAFEs (ranges) of quinine when co-administered with lopinavir/ritonavir was 1.16-fold (1.12 -1.27). The AAFEs (ranges) of lopinavir as given as lopinavir/ritonavir was 1.18-fold (1.18 – 1.23). The developed PBPK model successfully predicted quinine disposition either when quinine was given alone or in combination with lopinavir/ritonavir.

Sensitivity analysis

Sensitivity coefficient analysis for $AUC_{3\text{-}7days}$ (area under the curve) of quinine (a single quinine model) including f_u (fraction of unbound drug), K_a (absorption rate), liver weight, R_{bp} (blood-to-plasma partition), $f_{m,\ CYP3A4}$ (fraction of CYP3A4 on drug metabolism), and $f_{m,\ UGT1A1}$ (fraction of UGT1A1 on drug metabolism) were +0.18, -0.65, +0.66, +0.75, +0.82, and +0.99, respectively. In addition, sensitivity coefficient analysis of $AUC_{3\text{-}7days}$ of quinine (three drugs model), *e.g.*, EC_{50} (half-maximal effective concentration), E_{max} (maximum effect at high drug concentrations), Ind_{50} (concentration causing 50% maximal induction), Ind_{max} (maximal fold induction), Ki3A4 (inhibitor concentration that yields half-maximal inhibition), $K_{inact,\ CYP3A4}$ (inactivation rate of a given enzyme), f_u, $f_{m,\ CYP3A4}$, and $f_{m,\ UGT1A1}$ were -0.038, +0.62, +0.38, +0.20, +0.16, +0.13, +0.23, -0.24, and +0.41, respectively. All sensitivity coefficient values were < 1, indicating no significant impact of these model parameters on $AUC_{3\text{-}7days}$.

Simulation of quinine plasma concentrations in malaria patients with hepatic insufficiency or CYP3A4 polymorphism

For the standard dose regimen of quinine, the average values of unbound $AUC_{3\text{-}7days}$, unbound C_{max} (maximal concentration), and unbound C_{trough} (trough concentration) in patients with hepatic insufficiency and CYP3A4 polymorphism were within therapeutic ranges. In the patients with hepatic insufficiency, $AUC_{3\text{-}7days,}$ and C_{trough} of unbound quinine ranged from 5.148 to 10.25 mg*day/L, and 1.63 to 2.14 mg*day/L, respectively. In patients with Child-Pugh A and B, $t_{1/2}$ values were similar to those reported in healthy subjects (13.63 and 14.58 h, respectively). The half-life in patients with Child-Pugh C was, however, increased to 18.6. The clearance in patients with Child-Pugh A and B ranged from 6.14 to 6.19 L/h, and it decreased to 4.97 in patients with Child-Pugh C. In patients with CYP3A4 polymorphism, the $AUC_{3\text{-}7days}$ of unbound quinine ranged from 5.99 to 6.42 mg*day/L, and C_{trough} of unbound quinine ranged from 1.25 to 1.35 mg/L. In addition, C_{max} of unbound quinine, unbound $AUC_{3\text{-}7days}$, and CL (clearance) ranged from 1.58 to 1.75 mg/L, 2.99 to 3.34 mg*day/L, and 2.84 to 3.07 L/h, respectively.

Simulation of DDIs between quinine and HIV co-infected patients treated with lopinavir/ritonavir

Lopinavir/ritonavir co-administration

The $AUC_{3\text{-}7days}$ and C_{trough} [average (95%CI)] values of unbound quinine administered as standard dose regimen in malaria and HIV co-infected patients treated with lopinavir/ritonavir were 2.15 (2.07 – 2.23 mg*day/L) and 0.43 (0.41 – 0.44 mg/L), respectively. The AUCR was approximately 0.3. Therefore, the suggested dose is about three times higher than the standard dose regimen i.e. 1800 mg TID. Although this regimen resulted in the desired unbound drug concentrations, the average unbound $AUC_{3\text{-}7days}$ was relatively high. Therefore, the dose of quinine was decreased to 1200 mg TID to achieve comparable AUC to no ritonavir/lopinavir patients. Besides, other dose regimens were simulated, *i.e.,* 2400 mg BID and 6000 mg once a day (QD). The pharmacokinetic parameters are summarized in **Table S1.**

Quinine and lopinavir/ritonavir co-administration in patients with chronic renal failure

For the recommended dose regimen of quinine in malaria and HIV co-infected patients with chronic renal failure and treated with lopinavir/ritonavir without dialysis, the average (95%CI) values of unbound $AUC_{3-7days}$, unbound C_{trough}, and AUCR were 2.55 (2.47-2.64), 0.49 (0.48-0.51) and 0.3 respectively. All parameters were within the reported therapeutic targets. But the unbound C_{trough} concentrations were close to the cut-off criteria. To overcome the DDI effect, the suggested dosage was 972 mg BID (3 times higher than the standard dose regimen). However, the quinine 648 mg BID regimen was considered adequate to provide the targeted therapeutic of unbound quinine concentrations.[32] The simulated pharmacokinetic parameters of unbound quinine are summarized in **Table S1.**

Quinine and lopinavir/ritonavir co-administration in patients with hepatic insufficiency

Based on the simulation results of quinine administration alone in hepatic insufficiency, the recommended dosage was considered adequate to provide therapeutic unbound concentrations in malaria patients co-infected with HIV. The average (±95%CI) values of unbound $AUC_{3-7days}$, unbound C_{trough}, and AUCR in patients with mild hepatic insufficiency were 5.02 (4.83-5.20) mg*day/L, 1.06 (1.02-1.10) mg/L, and 0.67, respectively. The corresponding values for patients with moderate and severe hepatic insufficiency ranged from 7.57 to 7.7 mg*day/L, 1.58 to 1.96 mg/L, and 0.65 to 0.79, respectively. The average unbound C_{max} in patients with severe hepatic insufficiency was higher than toxic concentration levels. Therefore, the reduction of dosage administration (324 mg BID for 7 consecutive days) was simulated. The simulated pharmacokinetic parameters are summarized in **Table S1.**

Quinine and lopinavir/ritonavir co-administration in patients with CYP3A4 polymorphism

The $AUC_{3-7days}$ and C_{trough} of unbound quinine for all CYP3A4 polymorphism ranged from 3.78 to 3.95 mg*day/L, and 0.81 to 0.87 mg/L, respectively. The AUCR ranged from 0.42 to 0.44. Based on the AUCR value, the suggested dosage was 1296 mg TID for 7 consecutive days (2 times higher than the standard dose regimen). Furthermore, unbound plasma quinine concentrations were also simulated for the 7-day regimen of 972 mg TID and 1296 mg BID. The simulated pharmacokinetic parameters are summarized in **Table S1**. The predicted unbound $AUC_{3-7days}$, unbound C_{max}, unbound C_{trough}, V_{ss}, CL, and $t_{1/2}$ of quinine for optimal dose regimens in each condition are summarized in **Table 3**.

DISCUSSION

PBPK modeling successfully predicted quinine disposition in various clinical situations, including chronic renal failure without dialysis and impaired liver dysfunction (Child-Pugh A and Child-Pugh C). Some of the recommended dosage regimens of quinine derived from the simulations provided inadequate unbound plasma quinine concentrations for malaria patients when treated with lopinavir/ritonavir due to the metabolic DDI. Simulated regimens of quinine, when co-administered with lopinavir/ritonavir, informed potential dose adjustment strategies to overcome the effects of the DDIs. Furthermore, the potential impact

of various patient conditions was simulated to identify suitable dosing strategies to minimize the risk of side effects or therapeutic failure.

Quinine and lopinavir/ritonavir co-administration

The initially recommended 7-day regimen of 600 mg quinine TID co-administered with lopinavir/ ritonavir resulted in a 3-fold lower quinine exposure compared with quinine alone (**Table S1**). This result was in agreement with quinine pharmacokinetics reported in healthy Thai subjects following a single oral dose of 600 mg quinine given in combination with lopinavir/ritonavir.[5,6] The simulation of dose adjustment of unbound quinine suggested that 1200 mg or 1800 mg TID, or 2400 mg BID, or 6000 mg QD could represent suitable dosing strategies to overcome this DDI. Nevertheless, the 1200 mg TID dose regimen is likely to be too low to account for the large inter-individual variability in quinine clearance and plasma drug concentrations.[9,40]

Apart from dose adjustments, the patient compliance with medication is also an important factor that can influence therapeutic response.[41] Once-daily dose regimen has been shown to improve patient compliance compared with the two times daily and three times daily dose regimens.[42] The simulated unbound exposure for the 2400 mg BID and the 6000 mg QD dose regimens were within therapeutic ranges. Although once-daily dose strategies could support better patient compliance, the 6000 mg QD dose regimen would result in an excessive number of tablets.

Quinine and lopinavir/ritonavir interaction in patients with chronic renal failure

Acute renal failure is one of the most common complications in patients with severe malaria infection.[8] Plasma quinine concentrations in patients with acute renal failure are about 20-30% higher than non-acute renal failure patients.[43] Nevertheless, standard quinine regimen is recommended in patients with acute renal failure[44] as renal excretion of quinine accounts for only 20% of all elimination routes.[9] However, in patients with chronic renal failure without hemodialysis, the recommended dose regimen of quinine was revised from 648 mg TID to 648 mg loading dose followed by 324 mg BID for 7 days.[9] Results from the simulation from our study, however, suggested that the recommended dose regimen resulted in inadequate therapeutic unbound quinine concentrations when quinine was co-administered with lopinavir/ritonavir. This could be due to the shortening in elimination half-life of unbound quinine when co-administered with lopinavir/ritonavir as a consequence of the induction of UGT enzymes and plasma protein-binding displacement of lopinavir. Results of simulation of unbound quinine concentrations when quinine was co-administered with lopinavir/ritonavir in co-infected patients with chronic renal failure suggested inadequate therapeutic unbound quinine concentrations and a higher dose may be required. Subsequent simulation of the 648 mg BID regimen provided sufficient therapeutic unbound quinine concentrations (**Table S1**).

Quinine and lopinavir/ritonavir interaction in patients with hepatic insufficiency

Approximately 80% of quinine is metabolized by hepatic drug-metabolizing enzymes.[9] Even though altered hepatic function could have a significant impact on quinine elimination and systemic drug exposure, when quinine is given alone, the dose adjustment is not recommended.[9] The results from the current simulation of unbound quinine concentrations in malaria and HIV co-infected patients with Child-Pugh C (severe hepatic insufficiency) hepatic impairment suggested the accumulation of unbound plasma quinine concentrations. This could be explained by the reduction in clearance (-24.55 %) and prolongation of elimination half-life (18.6 h vs 13.64 h). Since unbound plasma quinine concentrations remain within the therapeutic range except for patients with severe hepatic insufficiency, dose adjustment may not be required. Our simulated findings supported the recommendation by Orlando and colleges.[33] Furthermore, results are in accordance with the product label of quinine for no requirement of dose adjustment, but with continued monitoring of plasma quinine concentrations.[9] Babalola and colleges, on the other hand, recommended consideration of dose adjustment in this group of patients since quinine disposition was significantly altered.[45] The limitation of the current study is that data from a single-instead of repeat dose administration was used for simulation, and therefore, therapeutic drug concentration was not achieved. The simulation of unbound quinine concentrations, when co-administered with lopinavir/ritonavir in patients with liver impairment, indicates that dose adjustment may not be required except for patients with severe hepatic insufficiency. This could be explained by the decrease in quinine clearance and the prolongation of elimination half-life.

Quinine and lopinavir/ritonavir interaction in patients with CYP3A4 genetic profiles

Pharmacogenetics plays an important role in individualized therapy in modern medicine due to its significant impact on drug disposition, efficacy, and toxicity.[46] CYP3A4/5 is the most common metabolizing enzymes responsible for over 50% of the clinically prescribed drug.[11] With the standard regimen of quinine administration alone, the clearance of quinine by different CYP3A4 variants were 3 to 5-fold lower compared to simulated patients who do not carry any CYP3A4 variants. The allele frequencies of the considered variants varied from 0.01 to 0.27 in Korean, Han Chinese, Japanese, African American, and European/American.[47] The AUCR of quinine following standard regimen when co-administered with lopinavir/ritonavir in patients with the various variant alleles ranged from 0.43 to 0.44. The results of such studies suggested that the higher dose was required. However, simulated uinbound quinine concentrations in patients with most impaired intrinsic clearance (CYP3A4*13) in this study suggested that the unbound $AUC_{3\text{-}7days}$, unbound C_{max}, and unbound C_{trough} parameters were increased (compared to wild-type), but were still within therapeutic ranges. In such a case, quinine dose adjustment may not be required. (**Table 3**). There is no report on the association between ritonavir therapy and CYP3A4 polymorphism. Besides, CYP3A4 mutant allele (CYP3A4*22) which is reported to be associated with variability in lopinavir concentrations is different from that of quinine.[48] Therefore, dose adjustment in the co-formulated lopinavir/ritonavir may not be required in individuals with CYP3A4 polymorphism.[38]

The developed PBPK model did not include the effect of P-glycoprotein transporter (P-gp) on the pharmacokinetics of both quinine, ritonavir, and lopinavir due to lack of information from *in vitro* studies. This is, however, unlikely to have a significant impact on quinine pharmacokinetics as unlike quinidine, quinine is a weak substrate of P-gp.[49] The developed PBPK model did not include the effect of quinine metabolite (3-hydroxyquinine), which can inhibit CYP3A4 enzyme, leading to an increase in quinine plasma concentrations. Nevertheless, considering the relatively high inhibition constant (K_i) of 3-hydroxyquinine (3.74 mg/L)[50] compared to its C_{max} at steady state (1.26 mg/L)[32] the clinical inhibitory effect is unlikely. Subsequent model development should include these factors when the information is available to improve model accuracy.

In summary, the verified PBPK models successfully predicted unbound quinine disposition when co-administered with lopinavir/ritonavir in co-infected patients with different conditions. Suitable dose adjustments to overcome the DDIs were identified (1800 mg TID for 7 days). Dose adjustment strategies are potentially required in patients with chronic renal failure. However, quinine dose adjustment may not be required in co-infected patients with hepatic insufficiency (except for patients with severe hepatic insufficiency) or carrier of CYP3A4 genetic variants. The verified PBPK models can be applied for dose optimization of the existing antimalarial drug when co-administered with lopinavir/ritonavir, supporting the design of future clinical studies.

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STUDY HIGHLIGHTS

What is the current knowledge on the topics?

Ritonavir-boosted lopinavir reduces quinine concentrations in healthy volunteers by 3-fold. The reduction of quinine concentrations when co-administered with lopinavir/ritonavir could lead to malaria treatment failure.

What question did this study address?

What are the optimal dosages of quinine when co-administered with lopinavir/ritonavir in co-infected patients?

What does this study add to our knowledge?

Doses adjustment of quinine in co-infected patients with hepatic insufficiency (except for severe hepatic insufficiency) or with CYP3A4 polymorphisms is potentially not necessary. Dose adjustment is required for HIV co-infected with malaria patients, with renal impairment, and severe hepatic insufficiency.

How might this change clinical pharmacology or translational science?

The co-administration of multiple drugs can cause drug-drug interactions that result in treatment failure or toxicity. PBPK modeling can support the design of future clinical studies for the investigation of drug-drug interactions

AUTHOR CONTRIBUTIONS

T.S., J.K., and K.N. wrote the manuscript; J.K. and K.N. designed the research; T.S. and M.S. performed research; T.S., M.S., and R.K.R.R. analysed the data.

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Figure Legends

Figure1. A schematic workflow of a single model

Figure2. A schematic workflow of the drug interaction model

Supplementary Material

(Simulated unbound quinine exposure pharmacokinetics when quinine was administered alone and co-administered with LPV/r (400/100 mg) in malaria HIV co-infected patients with different conditions.PDF)

Table S1. Simulated unbound quinine exposure pharmacokinetics when quinine was administered alone and co-administered with LPV/r in malaria HIV co-infected patients with different conditions. Set criteria for dose optimization are unbound $AUC_{3\text{-}7days}$ > 2.18 mg*day/L, unbound C_{max} < 2.18 mg/L, and unbound C_{trough} > 0.34 mg/L. Data are presented as mean (±95%CI) values.

Table 1. PBPK model input parameters for quinine, lopinavir, and ritonavir.

Parameters	Quinine	Lopinavir	Ritonavir
Molecular weight (g/moL)	324.42[30]	628.1[22]	721[22]
Log P	3.44[30]	4.2[22]	3.9[22]
pKa	8.5[30]	Neutral[22]	1.8, 2.8[22]
R_{bp} (B:P)	Malaria: 1.13[18] Healthy subjects: 1.11[18]	0.75[37]	0.58[22]
Fraction of unbound drug (f_u)	Asian healthy subjects: 0.17[18] Caucasian healthy subjects: 0.148[18] Malaria: 0.109[18]	0.01[22]	0.015[22]
Absorption rate (K_a) (1/h)	0.68[20]	0.74[22]	2.31[23]
Solubility in fasted state (mg/L)	1300[28]	-	500[27]
Absolute bioavailability (F_{bio})	0.76[9]	-	-
In vivo clearance (l/h)	Malaria and healthy subjects: 12[9] Chronic renal failure (using the lowest reported clearance in clinical trials): 5.6[9]	-	-
Intrinsic clearance (CL_{int}) (µl/min/mg protein)	Back-calculated from in vivo clearance	-	-
CYP3A4	$f_{m,cyp3A4}$=0.44 (assumed)	1.4[24]	20.14[28]
CYP2D6	-	-	0.93[28]
UGT1A1	$f_{m,UGT1A1}$=0.56 (assumed)	-	-
Renal clearance (CL_r) (ml/min/kg)	0.305[44]	-	-
Interaction-inhibition			
CYP3A4	Ki: 17.34 (mg/L)[33]	K_{inact}: 6 (1/h)[25] K_i: 0.257 (mg/L)[25]	K_{inact}: 19.8 (1/h)[29] K_i: 0.18 (mg/L)[29]
Interaction induction			
CYP3A4	-	-	Ind_{50}: 13.9[26] Ind_{max}: 2.45 (mg/L)[26]
UGT1A1	-	-	EC_{50}: 0.281 (mg/L)[29] EC_{max}: 3[29]

Log P: logarithm of octanol-water partition coefficient; pKa: negative decadal logarithm of acid dissociation constant; R_{bp}: blood-to-plasma partition ratio; $f_{m,cyp3A4}$: fraction of CYP3A4 on drug metabolism; $f_{m,UGT1A1}$: fraction of UGT1A1 on drug metabolism; Ki: inhibitor concentration that yields half-maximal inhibition; K_{inact}: inactivation rate of a given enzyme; EC_{50}: half-maximal effective concentration; EC_{max}: maximum effect at high drug concentrations; Ind_{50}: concentration causing 50% maximal induction; Ind_{max}: maximal fold induction

Table 2. Model verification of quinine when administered alone and/or concomitantly with LPV/r in fasting state. Data are presented as mean (±95% CI) values.

Clinical study	PK parameter	Prediction	Observation	Prediction/observation ratios
Quinine				
A single dose of 648 mg quinine QD in healthy volunteers[9]	AUC_{0-12} (mg*h/L)	28.45 (27.27 - 28.46)	28	1.01
	C_{max} (mg/L)	3.13 (3.00 - 3.26)	3.2	0.98
	T_{max} (h)	3 (3-3)	2.8	1.07
	AAFEs			1.03
A single dose of 648 mg quinine QD in malaria patients[9]	AUC_{0-12h} (mg*h/L)	74.2 (71.17 – 77.25)	73	1.016
	C_{max} (mg/L)	8.45 (8.11 - 8.79)	8.4	1.006
	AAFEs			1.016
A single dose of 600 mg quinine QD in Caucasian healthy volunteer[7]	$AUC_{0-48days}$ (mg*h/L)	67.98 (94.91-71.04)	50.06	1.357
	C_{max} (mg/L)	3.07 (2.94-3.19)	2.79	1.099
	Clearance (l/h)	7.62 (7.26-7.99)	9.12	0.835
	Half-life (h)	13.85 (13.48-14.22)	11.15	1.24
	AAFEs			1.18
A single dose of 600 mg quinine QD in Thai healthy volunteer[5]	AUC_{0-48h} (mg*h/L)	135.85 (129.46 - 142.24)	132.4	1.02
	AUC_{0-inf} (mg*h/L)	137.71 (131.08-144.34)	136.83	1.00
	C_{max} (mg/L)	7.39 (7.09-7.70)	7.45	0.99
	Clearance (l/h)	3.80 (3.61-4.00)	3.34	1.13
	V_{ss} (l/kg)	0.79 (0.78-0.80)	0.8	0.98

Clinical study	PK parameter	Prediction	Observation	Prediction/observation ratios
	Half-life (h)	11.36 (10.98-11.74)	10.95	10.
	T_{max} (h)	3 (3-3)	2	1.36
	AAFEs			1.08
A single dose of 600 mg quinine QD in Thai healthy volunteers[35]	AUC_{0-inf} (mg*h/L)	60.10 (57.47-62.72)	61.8	0.97
	C_{max} (mg/L)	2.90 (2.78-3.02)	3.45	0.84
	Clearance (L/h)	8.52 (8.14-8.91)	9.06	0.94
	V_{ss} (l/kg)	1.97 (1.95-2.00)	2.11	0.938
	Half-life (h)	12.78 (12.39-13.18)	9.7	1.31
	AAFEs			1.12
A single dose of 600 mg quinine QD in chronic renal failure patients[35]	AUC_{0-inf} (mg*h/L)	208.61 (198.38-218.83)	181.5	1.149
	C_{max} (mg/L)	4.55 (4.36-4.74)	6.17	0.73
	Clearance (l/h)	3.14 (2.99 – 3.30)	3	1.04
	V_{ss} (L/kg)	1.27 (1.26-1.29)	1.38	0.925
	Half-life (h)	22.22 (21.44-23.00)	26	0.854
	AAFEs			1.18
Multiple dose of 600 mg quinine administration TID for 7 consecutive days in malaria patients[32]	AUC_{0-2} (mg*day/L)	15.51 (14.82-16.20)	17.4	0.89
	AUC_{3-7} (mg*day/L)	46.13 (43.75-48.50)	35.37	1.30

Clinical study	PK parameter	Prediction	Observation	Prediction/observation ratios
	AUC_{0-7} (mg*day/L)	72.21 (69.15-75.25)	54.01	1.33
	C_{max} (mg/L)	12.55 (11.91-13.19)	11.43	1.09
	T_{max} (days)	1.75	1.5	1.16
	AAFEs			1.2
A single dose of 500 mg quinine QD administration in patient with mild hepatic insufficiency (Child-Pugh A)[33]	C_{max} (mg/L)	3.02 (2.90-3.15)	3.23	0.967
	Clearance (l/h)	4.47 (4.26-4.69)	4,788	1.034
	V_{ss} (l/kg)	1.47 (1.45-1.50)	1.368	1.058
	Half-life (h)	18.07 (17.56-18.58)	14	1.11
	T_{max} (h)	4 (4-4)	3.5	1.14
	AAFEs			1.07
A single dose of 500 mg quinine QD administration in patient with severe hepatic insufficiency (Child-Pugh C)[33]	C_{max} (mg/L)	3.14 (3.02-3.28)	2.35	1.34
	Clearance (L/h)	3.79 (3.60 – 3.98)	4.08	0.92
	V_{ss} (L/kg)	1.51 (1.49-1.53)	2	0.756
	Half-life (h)	21.44 (20.7–22.13)	24.52	0.87
	T_{max} (h)	4 (4 – 4)	3.5	1.14
	AAFEs			1.20
A single dose of 648 mg quinine administration in Caucasian healthy volunteers[6]	AUC_{0-inf} (mg*h/L)	56.09 (53.37-58.82)	46.7	1.20
	C_{max} (mg/L)	2.75 (2.65-2.85)	3.2	0.86
	Clearance (L/h)	6.94 (6.59-7.31)	8.74	0.795
	V_{ss} (l/kg)	1.70 (1.68-	1.99	0.855

Clinical study	PK parameter	Prediction	Observation	Prediction/observation ratios
		1.73)		
	Half-life (h)	13.65 (13.20-14.11)	13.7	0.99
	T_{max} (h)	3 (3-3)	3	1
	AAFEs			1.12
A single dose of 648 mg quinine co-administered with LPV/r (400/100) in Caucasian healthy volunteers[7]	AUC_{0-inf} (mg*h/L)	22.35 (21.43-23.28)	24.6	0.908
	C_{max} (mg/L)	1.50 (1.44-1.57)	1.5	1.00
	Clearance (L/h)	17.27 (16.52-18.00)	16.72	1.002
	V_{ss} (L/kg)	3.09 (3.06-3.12)	3.43	1.032
	Half-life (h)	9.80 (9.47-10.14)	10.4	0.900
	AAFEs			1.05
A single dose of 600 mg quinine co-administered with LPV/r (400/100) in Thai healthy subjects[5]	AUC_{0-48} (mg*h/L)	43.63 (42.11 - 4.15)	57.04	0.76
	AUC_{0-inf} (mg*h/L)	46.46 (43.83-47.07)	57.06	0.80
	C_{max} (mg/L)	2.60 (2.51-2.69)	3.78	0.69
	V_{ss} (L/kg)	1.59 (1.58 - 1.61)	1.65	0.97
	Clearance (L/h)	10.72 (10.37-11.07)	8.44	1.34
	T_{max} (h)	3 (3 -3)	2	1.5
	AAFEs			1.27
Quinine	Average AAFEs			1.13
Lopinavir				
A single dose of 600 mg	AUC_{0-12}	97.07 (89.65	93.4	1.04

Clinical study	PK parameter	Prediction	Observation	Prediction/observation ratios
quinine co-administered with LPV/r (400/100) in Caucasian healthy volunteers (LPV)[6]	(mg*h/mL)	- 104.49)		
	C_{max} (mg/L)	10.08 (9.44 - 10.73)	10.2	0.99
	C_{min} (mg/L)	4.42 (3.87 - 4.97)	4.7	0.94
	Half-life (h)	15.27 (14.61 - 15.93)	9.9	1.54
	AAFEs			1.14
Multiple dose of LPV/r (400/100 mg) BID for 14 consecutive days (LPV) in patients with mild hepatic impairment[34]	AUC_{0-12} (mg*h/L)	98.83 (92.95 - 104.71)	109.5	0.90
	C_{max} (mg/L)	10.06 (9.52 - 10.60)	12.22	0.82
	C_{trough} (mg/L)	5.35 (4.94 - 5.76)	8.71	0.61
	Half-life (h)	9.10 (8.74 - 9.45)	9.6	0.95
	AAFEs			1.23
Multiple dose of LPV/r (400/100 mg) BID for 14 consecutive days (LPV) in patients with moderate hepatic impairment[34]	AUC_{0-12} (mg*h/L)	123.37 (115.41 - 131.32)	91.5	1.35
	C_{max} (mg/L)	11.98 (11.28 - 12.67)	10.48	1.14
	C_{trough} (mg/L)	7.71 (7.11 - 8.30)	7.81	0.99
	Half-life (h)	9.92 (9.46 - 10.39)	12.5	0.79
	AAFEs			1.18
Lopinavir	Average AAFEs			1.18
All cases	Average AAFEs			1.15

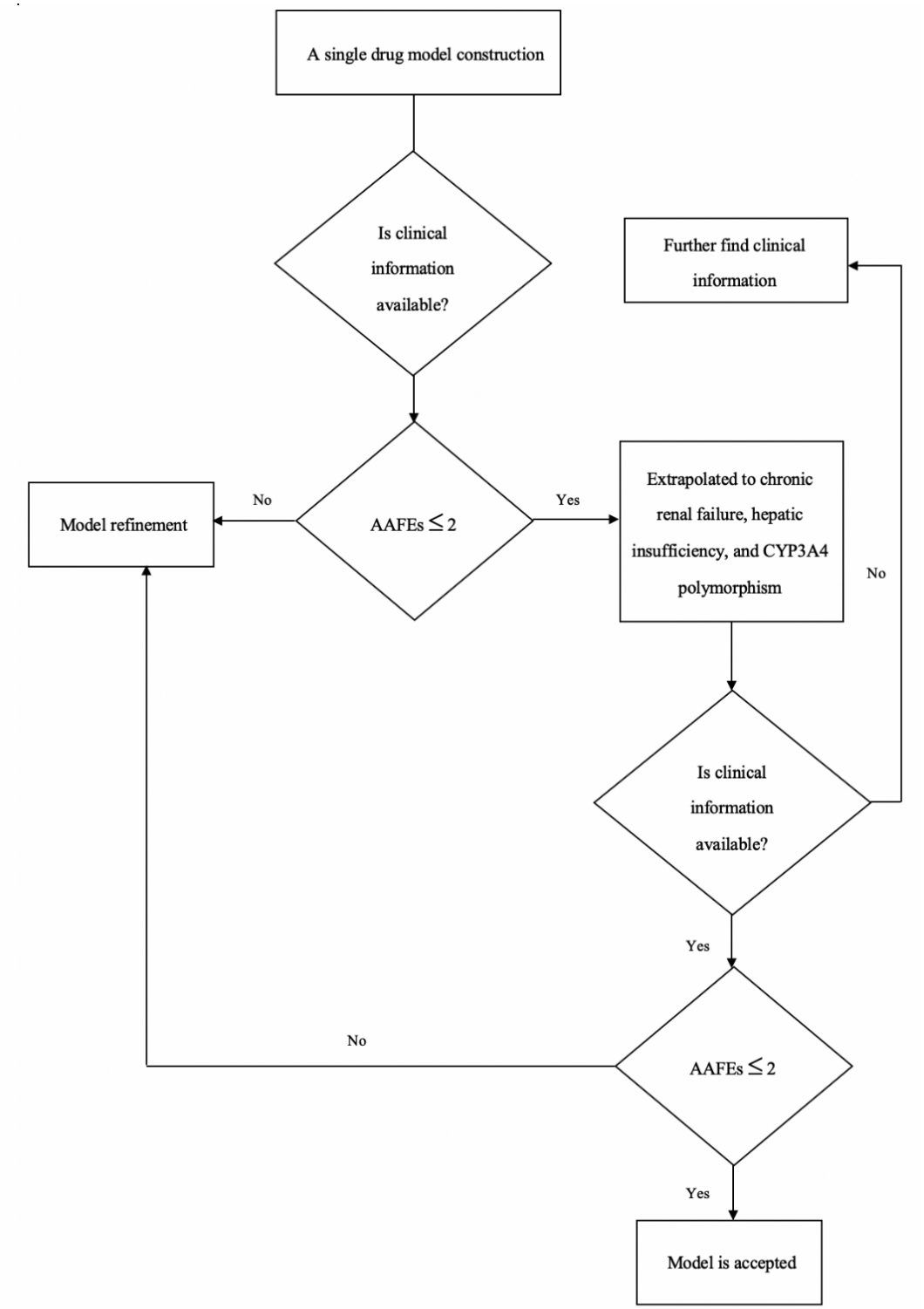
AAFEs: Average-folding errors; RMSE: root mean square errors; AUC: Area Under the curve; C_{max}: maximum concentration; C_{trough}: trough concentration

Table 3. Pharmacokinetic parameters of unbound quinine from simulated optimal dose regimens of quinine when co-administered with LPV/r (400/100 mg) BID in malaria and HIV co-infected patients. Set criteria for dose optimization are unbound $AUC_{3\text{-}7days}$ > 2.18 mg*day/L, unbound C_{max} < 2.18 mg/L, and unbound C_{trough} > 0.34 mg/L. Data are presented as mean (±95% CI) values

Number	**Conditions**	**Regimen**	**Unbound $AUC_{3\text{-}7days}$ (mg*day/L)** (±95%CI)	**Unbound C_{max} (mg /L)** (±95%CI)	**Unbound C_{trough} (mg/L)** (±95%CI)	**V_{ss} (L/kg)** (±95%CI)	**Clearance (L/h)** (±95%CI)	**Half-life (h)** (±95%CI)
1	Malaria co-infection with HIVs	1800 mg TID	5.27 (5.09-5.46)	1.45 (1.40-1.50)	1.07 (1.04-1.12)	2.75 (2.72-2.79)	16.72 (16.12-17.34)	8.70 (8.43-8.98)
2	Malaria co-infection with HIVs with chronic renal failure	648 mg BID	4.71 (4.52-4.87)	1.12 (1.07-1.16)	0.88 (0.85-0.91)	3.37 (3.34 - 3.4)	10.16 (9.75-10.58)	17.95 (17.39-18.50)
3	Malaria co-infection with HIVs with mild hepatic insufficiency	648 mg TID	5.05 (4.85-5.25)	1.34 (1.29-1.40)	1.07 (1.03-1.12)	2.75 (2.71 - 2.79)	7.43 (7.15-7.71)	7.43 (7.15-7.71)
	Malaria co-infection with HIVs with moderate hepatic insufficiency	648 mg TID	7.71 (7.45-7.95)	2.06 (2.00-2.13)	1.62 (1.56-1.71)	2.82 (2.79 - 2.85)	5.56 (5.39-5.74)	27.03 (26.45-27.61)
	Malaria co-infection with HIVs with severe hepatic insufficiency	324 mg BID	5.56 (5.35-5.79)	1.44 (1.39-1.50)	1.00 (0.97-1.05)	2.70 (2.67-2.74)	5.64 (5.50 – 5.83)	28.32 (27.71 – 29.02)
4	Malaria co-infection with HIVs with CYP3A4*3	648 mg TID	3.38 (3.74-4.02)	1.05 (1.02-1.09)	0.84 (0.82-0.88)	2.74 (2.71-2.78)	5.52 (5.30-5.74)	26.46 (25.70-27.23)

Number	Conditions	Regimen	Unbound $AUC_{3\text{-}7days}$ (mg*day/L) (±95%CI)	Unbound C_{max} (mg /L) (±95%CI)	Unbound C_{trough} (mg/L) (±95%CI)	V_{ss} (L/kg) (±95%CI)	Clearance (L/h) (±95%CI)	Half-life (h) (±95%CI)
	Malaria co-infection with HIVs with CYP3A4*13	648 mg TID	3.95 (3.79-4.09)	1.08 (1.04-1.12)	0.87 (0.84-0.90)	2.74 (2.71-2.78)	4.39 (4.22-4.57)	33.47 (32.51-34.44)
	Malaria co-infection with HIVs with CYP3A4*18	648 mg TID	3.90 (3.76-4.04)	1.06 (1.03-1.10)	0.85 (0.82-0.88)	2.75 (2.72-2.79)	5.24 (5.02-5.46)	27.81 (26.95-28.66)
	Malaria co-infection with HIVs with CYP3A4*19	648 mg TID	3.78 (3.64-3.92)	1.02 (0.98-1.06)	0.82 (0.78-0.85)	2.74 (2.71-2.78)	7.03 (6.71-7.36)	20.93 (20.17-21.71)

Unbound $AUC_{3\text{-}7}$: unbound plasma concentration from day 3 to day 7 (mg*day/L); unbound C_{max}: unbound maximum concentration (mg/L); unbound $C_{trough:}$ unbound trough concentration (mg/L) LPV: lopinavir; r: ritonavir; TID: three times a day; BID: Bis In Die; QD: once a day. V_{ss}: volume of distribution at steady state (L/kg).



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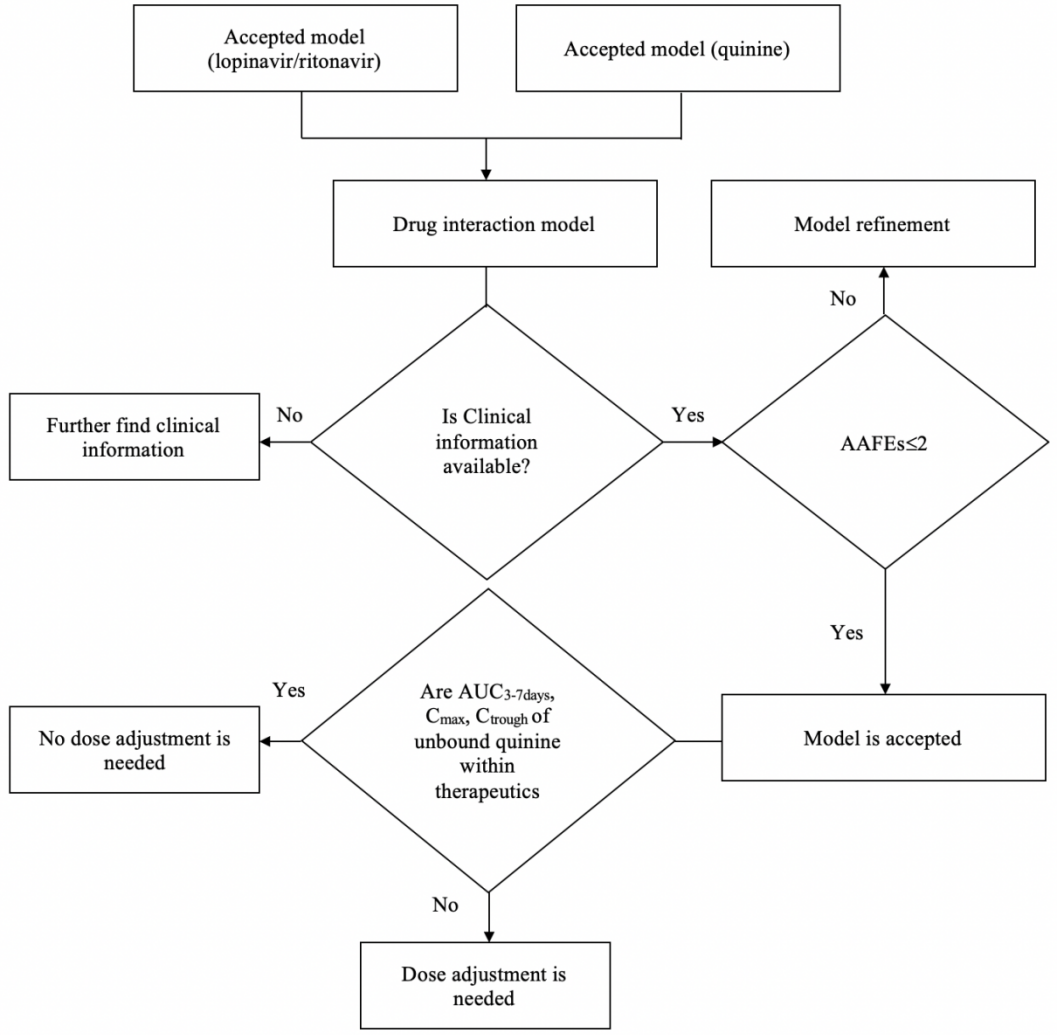

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