Title: Clinical data combined with modelling and simulation indicate unchanged drug-drug interaction magnitudes in the elderly

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Keywords: aging, elderly, drug-drug interaction, modelling and simulation

1 Abstract

Age-related comorbidities and consequently polypharmacy are highly prevalent in the elderly, resulting in an increased risk for drug-drug interactions (DDIs). The effect of aging on DDI magnitudes is mostly uncertain, leading to missing guidance regarding the clinical DDI management in the elderly. Clinical data obtained in aging people living with HIV ≥55 years, who participated in the Swiss HIV Cohort Study, demonstrated unchanged DDI magnitudes with advanced aging for four studied DDI scenarios. These data plus published data for midazolam in the presence of clarithromycin and rifampicin in elderly individuals assessed the predictive potential of the used physiologically based pharmacokinetic (PBPK) model to simulate DDIs in the elderly. All clinically observed data were generally predicted within the 95% confidence interval of the PBPK simulations. The verified model predicted subsequently the magnitude of 50 DDIs across adulthood (20-99 years) with 42 scenarios being only verified in adults aged 20-50 years in the absence of clinically observed data in the elderly. DDI magnitudes were not impacted by aging regardless of the involved drugs, DDI mechanism, mediators of DDIs, or the sex of the investigated individuals. The prediction of unchanged DDI magnitudes with advanced aging were proofed by 17 published, independent DDIs that were investigated in young and elderly subjects. In conclusion, this study demonstrated by combining clinically observed data with modelling and simulation that aging does not impact DDI magnitudes and thus, clinical management of DDIs can *a priori* be similar in aging men and women in the absence of severe comorbidities.

2 Introduction

The number of elderly individuals ≥65 years is estimated to double in the USA and Europe by 2050 (1, 2). The prevalence of age-related comorbidities increases with advanced aging (3, 4), leading to more comedications (5) and consequently, to a higher risk for drug-drug interactions (DDIs) (6). However, clinical studies investigating DDI magnitudes in the elderly are generally not conducted, resulting in a knowledge gap about how to manage DDIs in aging individuals in clinical practice.

Organ functions decline with advanced aging with the potential to alter drug pharmacokinetics and thereby the magnitude of DDIs (7, 8). Significant changes are the reduction in the hepatic and renal blood flow as well as in the glomerular filtration rate affecting drug clearance. Additionally, the age-related reduction in body water and the increase in adipose tissue weight can affect drug distribution in the elderly (9).

The incorporation of age-related physiological changes into physiologically based pharmacokinetic (PBPK) models allows to conduct virtual clinical trials in the elderly to investigate scenarios that cannot easily or ethically be studied (10). The model performance is verified against clinically observed data before extrapolating to unknown scenarios of interest.

There is a particular need to investigate DDI magnitudes in aging people living with HIV (PLWH) (11), because their life expectancy is close to the general population (12), and they have a high prevalence for age-related comorbidities (13), and polypharmacy (14). Furthermore, antiretroviral drugs (ARVs) have a high DDI potential (15). We previously conducted a clinical study in aging PLWH ≥55 years in the framework of the Swiss HIV Cohort Study to analyze DDI magnitudes between ARVs and comedications in the elderly and found similar DDI magnitudes compared with historical data in young adults aged 20-50 years (16). However, the conducted study had limitations regarding the number of studied scenarios and investigated individuals.

The objectives of the present study were to firstly assess the predictive potential of the PBPK approach to simulate DDIs in the elderly and secondly, to investigate comprehensively the impact of aging on DDI magnitudes, involving different drugs and DDI mechanisms, by the verified PBPK model.

3 Methods

We took three different steps to investigate whether aging impacts DDI magnitudes. Firstly, we used the clinically observed data obtained in aging PLWH ≥55 years for four different DDI scenarios (16) to verify the predictive performance of our previously developed PBPK framework (10) to simulate DDI magnitudes in the elderly. Secondly, the verified PBPK model predicted DDI magnitudes across adulthood for 50 different DDI scenarios with different involved drugs and DDI mechanisms. The simulation results were statistically analyzed to determine the general impact of aging on DDI magnitudes. Thirdly, a meta-analysis was undertaken to seek for clinical data investigating DDI magnitudes in young adults aged ≤40 years and elderly adults ≥55 years to proof the general model-based hypothesis of the present study.

3.1 Clinical data to investigate drug-drug interaction magnitudes in aging individuals to verify the physiologically based pharmacokinetic model

In a prospective clinical study, which was conducted at the HIV clinics Lausanne and Basel, PLWH ≥55 years, who participated in the Swiss HIV Cohort Study, were included if they received amlodipine, atorvastatin, and/or rosuvastatin with a dolutegravir (no interaction expected) or a boosted darunavir (high interaction potential) containing ARV regimen. The Ethics Committee of Vaud and Northwest/Central Switzerland approved the study protocol (CER-VD 2018-00369), which is registered at ClinicalTrials.gov (NCT03515772). Written informed consent was collected for each participant. Plasma concentrations were collected over 24 hours. Pharmacokinetic parameters were calculated non-compartmentally. Details on the study design were published previously (16). Historical data from young adults aged 20-50 years, receiving the same drug combination as the elderly PLWH in our conducted study, were gathered from the literature for model verification.

To verify analyzed DDI scenarios, for which clinically observed data exist only in the young, a structured literature search was performed to seek for clinical studies investigating DDIs with drugs, we previously used to analyze the impact of aging on drug pharmacokinetics (7, 17). Observed data were extracted from the literature using GetData Graph digitizer V. 2.26, which has an excellent accuracy (18). Clinical studies used for model verification are detailed in Table S1.

3.2 Physiologically based pharmacokinetic modelling

A whole-body PBPK model was constructed in Matlab® 2017a. The model structure, code, and assumptions were published previously (10). The model was informed by an aging virtual population considering age-related changes of demographical (e.g. body weight), physiological (e.g. organ weight), and biological (e.g. enzyme abundance) parameters with variability (9).

Used drug models for ARVs (i.e. dolutegravir and boosted darunavir) and non-HIV drugs (i.e. amlodipine, atorvastatin, and rosuvastatin) were developed and verified previously (7, 17). To simulate the combination of dolutegravir with boosted darunavir, the possibility to induce uridindiphosphat-glucuronosyltransferases (UGT)1A1 was implemented into the existing PBPK model (10). The turnover rate of UGT1A1 was found to be 0.0693 1/h (19). *In vitro* studies investigating the UGT1A1 induction potential of ARVs are generally missing. It is suggested that cytochrome P-450 (CYP)3A and UGT1A1 are both modulated by the pregnane X receptor (PXR) and thus have a similar half-maximal inducing concentration (20). The maximal inducing potential was also assumed to be similar in the absence of data. The prediction of clinically observed DDIs for raltegravir, a drug purely metabolized by UGT1A1, in the presence of ritonavir, rifampicin, etravirine, and efavirenz served as the verification of the used assumptions regarding UGT1A1 induction.

PBPK models were developed for ketoconazole and nilotinib to analyze the impact of aging on competitive CYP3A inhibition and gemfibrozil and its glucuronide metabolite as inhibitors of the organic anion transporting polypeptide (OATP)1B1. Their input parameters (Table S2) were obtained from published models (21-23), tissue scalars were modified to capture the clinically observed data, and verified with an independent clinical study for our PBPK framework (10). Distribution into the tissues was optimized to match clinically observed data in young adults (Table S3) and verified with at least one independent clinical study. The generation of the gemfibrozil metabolite was implemented in the liver by the UGT2B7 clearance pathway. If compound characteristic of the metabolite were not available from the literature, the same value as for gemfibrozil was assumed. The intrinsic clearance for gemfibrozil and nilotinib were retrogradely calculated from clinically observed data considering the *in vitro* measured fraction metabolized for each enzymatic pathway (21).

DDIs were firstly simulated in young adults aged 20-50 years. Successful predictions were judged by overlaying clinically observed data with the simulation results. We analyzed if pharmacokinetic parameters were predicted within 1.25-fold (bioequivalence criterion), 1.5-fold, and 2.0-fold of clinically observed data, which is considered best practice for modelling by the regulatory agencies (24). Simulations were performed in ten trials containing ten virtual individuals each and were otherwise matched as closely as possible to the conducted and published clinical trials regarding dose and dosing regimen. Drug parameters were not modified when performing simulations in the elderly.

3.3 Analyzing the impact of aging across adulthood by the developed PBPK model

Age-related changes in DDI ratios (in the presence of the perpetrator divided by the absence of the perpetrator) of analyzed pharmacokinetic parameters (Peak concentration: C_{max}, time to C_{max}: t_{max}, area under the curve: AUC, clearance: CLF, apparent volume of distribution: VdF, and elimination half-life: $t_{1/2}$) were estimated across adulthood (20-99 years) in 100 virtual individuals (50% women) per five years using the verified PBPK model. DDI ratios were normalized to the youngest investigated age group (20-24 years).

The normalized DDI ratios were fitted to descriptive linear functions containing age as an independent variable. The analysis was done for men, women, and all virtual subjects to investigate whether sex has an impact on age-related changes of DDI magnitudes. The correlation between age and normalized DDI ratios were compared between non-HIV drugs and ARVs as well as between men and women by a t-test. An ANOVA was performed to investigate whether the impact of aging on DDI magnitudes depends on the mediator of DDIs (CYP enzymes, UGT enzymes, or hepatic transporters) or the DDI mechanism (competitive inhibition – binding of drugs is blocked by the inhibitor binding itself to the active site of the enzyme, mechanism-based inhibition – loss of enzyme by altered transcription/translation caused by the inhibitor, or induction) and an ANCOVA was performed to investigate the combined effects. The statistical analysis was done in R 3.5.

3.4 Proofing the predicted age-related effect on DDI magnitudes by independent clinically observed data

A literature search was performed using the MEDLINE database to screen for clinical studies reporting an AUC-ratio in young and elderly individuals for any DDI. Keywords used were “drug-drug interaction” plus “aging”, “young vs elderly”, or “young vs geriatric”. Inclusion criteria were a direct comparison of the AUC-ratio between young adults with a mean age ≤40 years and aging adults with a mean age ≥55 years to match our own clinical study, and subjects had to be apparently healthy or having no severe disease and medication that could potentially affect the DDI of interest. AUC-ratios were normalized to the youngest age group investigated. Included clinical studies are detailed in Table S4.

4 Results

Results of our conducted clinical study in aging PLWH ≥55 years and the comparison of the obtained DDI magnitudes between amlodipine, atorvastatin, or rosuvastatin and either dolutegravir (no interaction expected) or boosted darunavir (high interaction potential) and historical data in young individuals aged 20-50 years were published previously (16).

4.1 Predictive performance of the PBPK model to simulate DDI magnitudes in the elderly

Firstly, published data in the elderly for midazolam in the presence of clarithromycin and rifampicin (25-27) and clinically observed data from our own clinical study conducted within the framework of the Swiss HIV Cohort Study (16) were used to analyze the predictive performance of our PBPK framework (10) to simulate DDI magnitudes in aging individuals. In all cases, the clinically observed data were generally within the 95% confidence interval of the PBPK model predictions (Figure 1-3) in young (20-50 years) and aging individuals (≥55 years). The AUC-ratio of intravenous midazolam in the presence of rifampicin was overpredicted in young and elderly adults (predicted:observed ratio: 1.69 and 1.64), and the AUC-ratio of midazolam in the presence of clarithromycin and rifampicin was underpredicted in the elderly (predicted:observed ratio: 0.73 and 0.70). All other AUC-ratios were simulated within 1.25-fold of the clinically observed data (Table 1). In both investigated age groups, 73%, 81%, and 100% of C_{max} and $t_{1/2}$ values in the absence and presence of the perpetrator were predicted within 1.25-fold, 1.5-fold, and 2.0-fold of the clinically observed data, respectively.

Secondly, additional drug models were developed for ketoconazole and nilotinib to analyze the impact of aging on competitive CYP3A inhibition and gemfibrozil and its glucuronide metabolite to investigate the age-dependency of DDIs mediated by OATP1B1. Clinically observed data for all drugs were always contained within the 95% confidence interval of the PBPK simulations (Figure S1-S2). Pharmacokinetic parameters in young adults were predicted within 1.25-fold of clinically observed data (Table S5) except for the half-life of ketoconazole, which was overpredicted (predicted:observed ratio: 1.30) and the peak concentration of nilotinib, which was underpredicted (predicted:observed ratio: 0.75). Ketoconazole was the only drug for which clinically observed data in elderly adults with a mean age of 76 years were available (Figure S1) (28). C_{max} for ketoconazole in the elderly was underpredicted with 5,627 ± 4,297 ng/mL being observed and 3,827 ± 1,277 ng/mL being predicted (predicted:observed ratio: 0.68), but all other pharmacokinetic parameters were predicted within 1.25-fold of the clinically observed data in the elderly.

Thirdly, DDIs with drugs we previously used to analyze the impact of aging on drug pharmacokinetics were verified against clinically observed data in young adults aged 20-50 years before extrapolating to elderly individuals using the verified PBPK model. The designs of the used clinical studies are detailed in Table S1. The predictions captured the clinically observed data adequately in individuals aged 20-50 years (Figure

S3-S14). The AUC-ratios were predicted within 1.25-fold, 1.5-fold, and 2.0-fold of clinically observed data in 74%, 95%, and 100% of all investigated DDIs (Table 2). C_{max} and $t_{1/2}$ are detailed in Table S6.

4.2 Analyzing the impact of aging on DDI magnitudes across adulthood

After the successful verification of the PBPK model, all developed DDIs were used to investigate the impact of aging on the C_{max}-, t_{max}-, AUC-, CLF-, VdF-, and $t_{1/2}$-ratio (pharmacokinetic parameter of the victim drug in the presence divided by the scenario in the absence of the perpetrator) across adulthood. The AUC-ratio was not affected by aging (Figure 4). The slope [95% confidence interval] fitted to the mean of the AUC-ratio of all investigated DDI scenarios was close to zero with -9.6E-05 [-2.0E-04; 7.4E-06] (Table S7). The drug class (non-HIV drugs vs ARVS) involved in the DDI (p-value: 0.08), the DDI mechanism (p-value: 0.57), the mediator of the DDI (p-value: 0.77), the combination of DDI mechanism and mediator (p-value: 0.58), and the sex of the studied individual (p-value: 0.61) did not affect the negligible impact of advanced aging on AUC-ratios (Table S7). These results were similar for all investigated DDI ratios (Figure S15-S19), except for t_{max}, which was statistically significant different between DDIs involving ARVs or non-HIV drugs (p-value: 0.03), but the difference in the slope was not judged to be clinically relevant (ARVs: -6.15E-06 [-6.48E-06; -5.83E-06] and non-HIV drugs: -2.90E-04 [-3.09E-04; 2.70E-04]).

4.3 Independent clinically observed data proofed the estimated impact of aging on DDI magnitudes

In a last step, a literature search was performed to seek for studies investigating AUC-ratios in young and elderly individuals to proof the general model-based hypothesis that DDI magnitudes are not affected by advanced aging. Our performed literature search yielded 20 studies that investigated DDI magnitudes in the elderly. Six studies were excluded, because there was no direct comparison between young and elderly individuals and one study was excluded because the age of study participants was not defined. The remaining 13 studies investigated 17 DDIs in elderly compared with young healthy subjects. The DDI mechanism was competitive inhibition in five cases, mechanism-based inhibition in three cases, induction in seven cases, and mechanism-based inhibition combined with induction in two cases. Ten of the investigated DDIs were mediated by CYP1A2, four by CYP3A, and three were not specified to a single enzyme. All included studies demonstrated no changes of DDI magnitudes with advanced aging (Figure 5). The average ratio elderly (n: 274; age: 68.3 years) / young (n = 298; age = 28.4 years) for the AUC-ratio was 1.01 ± 0.64, which confirmed our general PBPK model estimates.

5 Discussion

Clinical data investigating the impact of aging on DDI magnitudes are sparse, leading to uncertainty how to manage DDIs in aging individuals in clinical practice. In this study, we demonstrated based on clinical data in combination with modelling and simulation that DDI magnitudes are not impacted by aging regardless of the drugs being involved in the DDI, the DDI mechanism, the mediator of the DDI, or the sex of the studied individual. Thus, the clinical management of DDIs can *a priori* be similar in the elderly compared with young men and women in the absence of severe comorbidities.

The investigation of age-related changes in DDI magnitudes are especially important for PLWH given the increased life expectancy (12), high prevalence of polypharmacy (14), and the high DDI potential of ARVs (15). We previously conducted a clinical study in aging PLWH ≥55 years, who participated in the Swiss HIV Cohort Study, to investigate for the first time DDI magnitudes between ARVs and comedications in elderly PLWH (16). The comparison with historical data in young individuals, receiving the same drug combination, yielded no age-related changes in the magnitude of the DDIs (16), comparable to studies conducted with midazolam and clarithromycin and rifampicin (25-27). However, we could not include enough participants to adequately power the study and thus, interpretation must be careful. In general, clinical studies in the elderly are ethically difficult to undertake, because necessary treatments (i.e. ARVs in our study) cannot be disrupted to establish a controlled scenario, the medication of interest cannot be added, and participants should not receive any other medication affecting the DDI of interest. Furthermore, it is not feasible or pragmatic to study every single drug combination in elderly individuals.

We used the PBPK approach to overcome all mentioned limitations in the DDI study design in elderly subjects. Before extrapolating to unknown scenarios of interest, it is crucial to verify the PBPK model for the population and the clinical scenario of interest (10). A strength of the present study is the wide range of DDI mechanism (competitive inhibition, mechanism-based inhibition, and induction) and DDI mediators (CYP enzymes, UGT1A1, and OATP1B1) included in the PBPK model verification. All clinically observed data of altered plasma concentrations caused by a DDI were generally within the 95% confidence interval of the PBPK model predictions for young and elderly individuals (Figure 1-3) which demonstrates the predictive power of the used approach to simulate DDIs in aging subjects.

After proofing the predictive potential of the used PBPK model to simulate DDIs in the elderly, we performed sensitivity analyses on age for 50 DDIs with 42 DDIs that could only be verified in adults aged 20-50 years in the absence of clinical data in the elderly. The verified PBPK model estimated that DDI magnitudes are unchanged across adulthood (20-99 years) regardless of the involved drugs, DDI mechanism, the mediator of the DDI, and the sex of the studied individual.

One advantage of the used PBPK approach over traditional clinical studies is that aging can be analyzed as a continuous process through sensitivity analysis. Longitudinal clinical studies are not practical, affordable, and ethically difficult to conduct. Thus, traditional clinical studies compare observed data of an elderly with a young group, ignoring the continuous physiological changes that impact the pharmacokinetics of drugs and the magnitudes of drug interactions throughout adulthood (9).

DDI magnitudes could potentially be affected by advanced aging, because of higher concentration of the inhibitor and inducer and age-related alterations in the regulation of transcription and translation. Drug exposure increases with advanced aging due to a decline of drug clearance that is caused by the age-related decrease in hepatic and renal blood flow as well as in the glomerular filtration rate and is independent of drug characteristics (7). The higher exposure of inhibitors or inducers with advanced aging appears not to lead to an elevated interaction potential in the elderly. Possible explanation could be that higher perpetrator concentrations cannot lead to an increased effect for strong inhibitors and inducers such as clarithromycin, ritonavir, or rifampicin. Strong inhibitors such as ritonavir achieve already a maximal effect in young individuals; therefore, an increased ritonavir concentration in the elderly is not expected to result in greater inhibition. The strong inducer rifampicin binds to PXR, forms a complex with the retinoid X receptor, the complex binds to the DNA response element, and enhances the transcription of metabolizing enzymes such as CYP3A (29). Higher rifampicin concentrations in the elderly might not lead to an increased CYP3A level, because the amount of PXR could be a limiting factor. Even if PXR transcription and translation would be enhanced, a negative feedback loop prevents higher PXR concentrations, and thus, induction of metabolizing enzymes such as CYP3A (30). Other regulations to prevent high induction of metabolizing enzymes might exists but were not studied so far. For moderate perpetrators like niltonib or etravirine, the predicted DDI magnitudes were 10% higher with advanced aging and thus, the effect appears to be marginal.

In contrast to CYP3A4 (31, 32), uncertainty exist whether the transcription and translation of CYP2C9 and CY1A2 are impacted by advanced aging (33-35), which could result in impaired enzyme activity and subsequently lower DDI magnitudes. The majority of DDIs collected in the fourth step of the present study to proof the general PBPK model estimates regarding the impact of aging on DDI magnitudes, were mediated by CYP1A2. CYP1A2 was either induced (smoking, phenytoin) or competitively inhibited (cimetidine, ciprofloxacin). The ratio elderly/young of the AUC-ratio ranged from 0.70 ± 0.57 (36) to 1.14 ± 0.58 (37), demonstrating that drug interactions mediated by CYP1A2 are likely not affected by advanced aging. The results are consistent with our previous work, in which we demonstrated that age-related changes in drug clearance are not determined by the clearance pathway, amongst others CYP3A, CYP2C9, and CYP1A2 (7). However, there are reports in the literature indicating that enzyme inducibility might be different as shown exemplarily for antipyrine with rifampicin (38), where the elderly showed a six-fold lower DDI magnitude than the young group. Differences to other studies investigating age-related changes in DDI magnitudes are not explainable by frailty as all investigated participants were healthy. The

comparison between young and elderly subjects was indirect, because the study in young individuals was conducted earlier, which led to an exclusion in our meta-analysis. The reduced inducibility cannot be assigned to a specific hepatic enzyme, because antipyrine is metabolized by several different hepatic enzymes, which can be induced by rifampicin. In two other studies investigating the effect of smoking and dichloralphenazone on antipyrine with advanced aging, there was no difference in the DDI magnitude between the two investigated age groups (AUC-ratio elderly/young: 1.02 and 0.78 ± 0.62, respectively) (39, 40). Studies using rifampicin as an inducer were in general heterogenic with the found minimal and maximal DDI magnitude ratio elderly/young of 0.67 and 1.86 (Table S4). Both studies showed how variability, which might be explained by the small sample size. These findings indicate no systematic effect of a certain DDI mechanism or involved enzyme. The found heterogeneity of data represents therefore patient variability in clinical practice. Taken together, uncertainty regarding the inducibility of hepatic enzymes exists in the literature probably based on the high variability of enzyme activity (41, 42) and the low number of subjects included in the clinical studies. Overall, the clinically observed data for various DDIs (Table S1, Table S4) proofs our PBPK model estimates of unchanged DDI magnitudes with advanced aging; however, in between patient variability up to twofold might be possible.

As DDI magnitudes are not impacted by aging, static methods can be applied if an elderly patient receives two drugs with an uncharacterized DDI magnitude. Estimates are based on the degree of metabolism by a specific enzyme and the strength of an inhibitor or inducer (43, 44). A PBPK model used in our study is not intendent for the daily management of DDI queries in the clinic, but the static method provides a more straightforward supportive tool to rationalize dose adjustments to overcome a given DDI.

We used a sequential multi-step approach, that might have the risk to propagate assumptions and errors from one step to the next. Using a mathematical model, it is of tremendous importance to clearly mention all underlying assumptions, which we have done previously for our developed aging population and PBPK model (9, 10). The model and its predictive power to simulate pharmacokinetics in elderly individuals was verified against clinically observed data for 20 non-HIV and HIV drugs, which had different drugs characteristics, and clinically observed drug concentrations were generally within the 95% confidence interval of the model predictions (7, 17). Thus, a systematic over- or underprediction based on assumptions or errors in the population and model can be excluded. In the present study, we simulated 50 different DDI scenarios in adults aged 20 to 50 years, involving different DDI mechanisms (competitive inhibition, mechanism-based inhibition, and induction), enzymes (CYP3A, CYP2D6, CYP2B6, CYP2C9, UGT1A1), and active drug transporter (OATP1B1) and 74.5%, 93.6%, and 100% of AUC-ratios were predicted within 1.25-, 1.5-, 2.0-fold of clinically observed data, respectively. The average predicted:observed ratio was 0.99 ± 0.21, indicating no systematic over- or underprediction of AUC-ratios. The predictive power of our model to simulate DDIs in aging individuals was verified against data from our own clinical study and independent, published data (16, 25-27) and all observed data were predicted within the 95% confidence interval. Furthermore, we verified the predicted impact of advance aging on DDI magnitudes against independent

clinically observed data, which verified our general model-based hypothesis. In conclusion, all performed verification with independent data verified the model assumptions and led to the exclusion of systematic errors in the PBPK model.

There are several limitations of our study. Firstly, physiological data to inform the PBPK model are sparse over the age of 85 years and therefore, simulation results in the very old need to be viewed with caution.

Secondly, individuals over the age of 65 years are generally excluded from clinical studies and if included have no major health problems. Thus, results might not be applicable to frail elderly individuals or aging subjects with severe comorbidities such as advanced renal impairment stage 4-5. However, our study delivers a comprehensive overview of conducted DDI studies in the elderly and uses a verified modelling approach to interpret the existing data broadly. Furthermore, the included aging PLWH in our own clinical study are representative of 75% of all elderly PLWH ≥75 years (45), who have mild to moderate renal impairment, hypertension, and receiving combined ARV therapy as well as other comedications. The investigation if severe comorbidities or organ impairment impact age-related changes in DDI magnitudes is the next logical step for future clinical studies.

Thirdly, *in vitro* data regarding the induction of UGT1A1 by ARVs were not available in the literature and based on the same molecular modulation of UGT1A1 and CYP3A (20), the same induction values were assumed for both enzymes. Clinically observed data of DDIs involving UGT1A1 induction were always predicted within the 95% confidence interval of the PBPK model, thus qualifying the used assumption. A last limitation is that the impact of aging on transporter mediated DDIs were only studied for the hepatic uptake transporter OATP1B1, but other hepatic, intestinal or renal transporters were not investigated and hence translation must be careful.

Fourthly, we used the commonly accepted twofold margin (24) to assess the accuracy of predicted pharmacokinetic parameters; however, the twofold limit might be too permissive for the interpretation of AUC-ratios, because it could lead to a misclassification of DDI magnitudes (46). We focused on clinical relevance, when analyzing the successful prediction of DDI magnitudes. The AUC-ratios that were predicted outside of the 1.5-fold margin were midazolam + rifampicin (predicted:observed: 1.69), dolutegravir + atazanavir/ritonavir (predicted:observed: 0.63), and atorvastatin + etravirine (predicted:observed: 1.54). The differences between predictions and clinically observed data were not judged to be of clinical relevance given the safety margin of dolutegravir and atorvastatin. In contrast, an under- or overprediction of the DDI magnitude with the anticoagulant rivaroxaban by twofold could have clinical consequences for the treated patient (47). In the case of rivaroxaban, all AUC-ratios were predicted within the 1.25-fold margin (rivaroxaban + ketoconazole: 0.85, rivaroxaban + clarithromycin: 0.96, and rivaroxaban + ritonavir: 0.99). However, the 1.25-fold margin is still too permissive for narrow therapeutic index drugs for which the 1.11-fold margin is recommended by the health authorities (48).

In conclusion, by combining clinical data with modelling we elucidated that aging does not impact the magnitudes of DDIs regardless of the DDI mechanism, the DDI mediators (enzymes, transporters) or the involved drugs. Thus, the clinical management of DDIs can *a priori* be similar in aging men and women compared to young individuals in the absence of severe comorbidities.

6 Study Highlights

What is the current knowledge on the topic?

Age-related comorbidities are highly prevalent in the elderly leading to polypharmacy and consequently, an increased risk for drug-drug interactions (DDIs). However, clinical studies investigating DDIs are generally not conducted in the elderly resulting in missing guidance regarding the clinical management of DDIs with advanced aging.

What question did this study address?

We combined clinical data with physiologically based pharmacokinetic (PBPK) modelling to investigate the impact of aging on DDI magnitudes across the entire adulthood.

What does the study add to our knowledge?

The PBPK approach has the predictive power to simulate DDIs in the elderly. Predicted DDI magnitudes are not affected by aging regardless of the involved drugs, DDI mechanism or the sex of the investigated individual. This model-based hypothesis was further verified by independent clinically observed AUC-ratios for 17 DDIs being studied in young and elderly individuals.

How might this change clinical pharmacology or translational science?

The clinical management of DDIs can *a priori* be similar in the elderly compared to young men and women in the absence of severe comorbidities.

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8 Authors Contribution

F.S. wrote the manuscript; F.S and C.M. designed the research; F.S., C.P., L.A.D, M.B., and C.M. performed the research; F.S., H.K., M.P., M.S., and C.M analyzed the data.

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10 Figure legends

Figure 1: Predicted vs. observed concentration time profiles for midazolam in the absence (brighter color) and the presence (darker color) of clarithromycin after intravenous administration (a: young; b: elderly) and oral administration (c: young; d: elderly). The design of the simulated DDI scenarios is detailed in Table S1. Red markers show published clinical data. The solid lines, the dashed line, and the shaded area represent the mean of each virtual trial, the mean, and the 95% confidence interval of all virtual individuals, respectively.

Figure 2: Predicted vs. observed concentration time profiles for amlodipine (a: young; b: elderly), atorvastatin (c: young, d: elderly), and rosuvastatin (e: young, f: elderly) in the absence (brighter color) and the presence (darker color) of boosted darunavir. The design of the simulated DDI scenarios is detailed in Table S1. Red markers show published clinical data with different markers indicating different individuals. The solid lines, the dashed line, and the shaded area represent the mean of each virtual trial, the mean, and the 95% confidence interval of all virtual individuals, respectively.

Figure 3: Predicted vs. observed concentration time profiles for dolutegravir (a: young; b: elderly) in the absence (brighter color) and in the presence (darker color) of boosted darunavir. The design of the simulated DDI scenario is detailed in Table S1. Data for young individuals were normalized to 50 mg for comparison with elderly subjects. Red markers show published clinical data. The solid lines, the dashed line, and the shaded area represent the mean of each virtual trial, the mean, and the 95% confidence interval of all virtual individuals, respectively.

Figure 4: Area under the curve (AUC)-ratio normalized to the youngest investigated age group (20-24 years) for all drugs (a), for non-HIV drugs (b), for ARVs (c), for competitive inhibition (d), for mechanism-based inhibition (e), for induction (f), for DDIs mediated by CYP enzymes (g), for DDIs mediated by UGT1A1 (h), and for DDIs mediated by OATP1B1 (i). Black, blue, and red markers represent competitive inhibition, mechanism-based inhibition, and induction. Circles, crosses, and triangles symbolize CYP-, UGT1A1-, and OATP1B1-mediated DDIs. The solid line and the shaded area show the mean ± standard deviation. The dashed lines represent the 1.25-fold interval (bioequivalence criterion).

Figure 5: Impact of aging on area under the curve (AUC) ratios for independent clinically observed data (mean ± standard deviation; Table S4). Black, blue, red, and green markers symbolize competitive inhibition, mechanism-based inhibition, induction, and mechanism-based inhibition combined with induction, respectively. All investigated DDIs were mediated by CYP enzymes. The solid line and the shaded area show the mean ± standard deviation. The dashed lines represent the 1.25-fold interval (bioequivalence criterion).

11 Supplementary Information

Table S1

Table S2

Table S3

Table S4

Table S5

Table S6

Table S7

Figure S1

Figure S2

Figure S3.

Figure S4

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Figure S6

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Figure S9

Figure S10

Figure S1

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Figure S19

Table 1: Observed vs predicted drug pharmacokinetics in the absence and presence of the inhibitor and inducer in young (20-50 years) and aging individuals (≥55 years). Data for dolutegravir are normalized to 50 mg for young individuals to enable comparison with elderly subjects.

	Young adults						**Elderly adults**					
	Victim in the absence of the perpetrator		Victim in the presence of the perpetrator		DDI ratio		Victim in the absence of the perpetrator		Victim in the presence of the perpetrator		DDI ratio	
	Observed	Predicted	Observed	Predicted	Observed	Predicted	Observed	Predicted	Observed	Predicted	Observed	Predicted
Midazolam (iv) + Clarithromycin												
C_{max} [ng/mL]	50.3 ± 34.7	61.9 ± 13.0	64.8 ± 25.4	69.7 ± 14.5	1.29 ± 1.02	1.12 ± 0.33	63.2 ± 22.9	67.8 ± 14.7	65.7 ± 18.2	74.8 ± 16.5	1.04 ± 0.47	1.10 ± 0.34
AUC [ng*h/mL]	125 ± 61	134 ± 64	337 ± 117	379 ± 354	2.69 ± 1.60	2.83 ± 2.98	152 ± 68	176 ± 75	361 ± 155	507 ± 354	2.38 ± 1.48	2.88 ± 2.36
$t_{1/2}$ [h]	3.6 ± 1.8	4.5 ± 1.9	9.2 ± 3.2	9.7 ± 8.4	2.56 ± 1.56	2.15 ± 2.06	5.6 ± 2.5	6.2 ± 2.1	11.9 ± 5.1	13.7 ± 8.2	2.11 ± 1.32	2.21 ± 1.51
Midazolam (po) + Clarithromycin												
C_{max} [ng/mL]	12.5 ± 7.0	16.1 ± 7.4	40.7 ± 25.4	32.0 ± 10.3	3.26 ± 2.73	1.99 ± 1.12	13.0 ± 5.9	14.9 ± 5.5	31.7 ± 13.1	30.5 ± 8.0	2.44 ± 1.50	2.04 ± 0.93
AUC [ng*h/mL]	49.4 ± 25.3	56.7 ± 23.9	304 ± 151	289 ± 194	6.16 ± 4.39	5.10 ± 4.03	49.6 ± 39.8	56.4 ± 20.1	336 ± 136	281 ± 189	6.79 ± 6.10	4.98 ± 3.80
$t_{1/2}$ [h]	3.7 ± 1.9	4.2 ± 1.3	6.9 ± 3.4	8.3 ± 4.6	1.87 ± 1.33	1.99 ± 1.28	3.7 ± 2.9	5.1 ± 1.7	7.1 ± 2.9	8.9 ± 3.8	1.94 ± 1.75	1.74 ± 0.93
Midazolam (iv) + Rifampicin												
C_{max} [ng/mL]		57.5 ± 12.0		52.9 ± 11.4		0.92 ± 0.28		64.1 ± 14.0		60.2 ± 13.0		0.94 ±0.29
AUC [ng*h/mL]	110 ± 34	93.9 ± 28.3	48.6 ± 11.8	70.0 ± 19.4	0.44 ± 0.17	0.75 ± 0.31	127 ± 50	136 ± 48	57.7 ± 17.2	101 ± 27	0.45 ± 0.22	0.75 ±0.33
$t_{1/2}$ [h]	4.0 ± 1.8	3.5 ± 1.3	1.9 ± 0.6	3.1 ± 1.2	0.46 ± 0.25	0.87 ± 0.47	4.3 ± 1.6	5.2 ± 1.7	2.3 ± 0.8	4.3 ± 1.3	0.53 ± 0.27	0.84 ±0.36
Midazolam (po) + Rifampicin												
C_{max} [ng/mL]	18.3 ± 7.1	15.8 ± 7.7	1.8 ± 0.9	1.8 ± 1.7	0.10 ± 0.06	0.12 ± 0.12	23.3 ± 11.4	21.3 ± 9.9	2.5 ± 1.7	2.0 ± 1.6	0.11 ± 0.09	0.09 ±0.09
AUC [ng*h/mL]	41.9 ± 23.4	43.1 ± 18.7	4.1 ± 3.2	3.7 ± 2.4	0.10 ± 0.09	0.09 ± 0.07	40.0 ± 20.6	74.2 ± 36.5	4.3 ± 2.6	5.6 ± 3.2	0.11 ± 0.09	0.08 ±0.06
$t_{1/2}$ [h]		3.7 ± 1.2		3.2 ± 1.1		0.86 ± 0.42		5.1 ± 1.6		4.3 ± 1.3		0.85 ±0.37
Amlodipine + Darunavir/Ritonavir												
C_{max} [ng/mL]	11	12.6 ± 3.4	19.9	21.6 ± 5.8	1.80	1.71 ± 0.65	19.3 ± 4.7	15.0 ± 3.5	32.7 ± 8.8	24.2 ± 5.2	1.69 ± 0.61	1.62 ± 0.52
AUC [ng*h/mL]	777.0	667 ± 233	1,640	1,423 ± 554	2.11	2.13 ± 1.12	1,155 ± 414	884 ± 265	2,425 ± 739	1,773 ± 535	2.10 ± 0.99	2.01 ± 0.85
$t_{1/2}$ [h]	38.0	30.0 ± 2.7	48.4	37.4 ± 5.6	1.27	1.25 ± 0.22	48.1 ± 8.0	34.0 ± 2.8	51.2 ± 0.1	42.9 ± 4.7	1.06 ± 0.18	1.26 ± 0.17
Atorvastatin + Darunavir/Ritonavir												
C_{max} [ng/mL]							4.9 ± 3.6	4.2 ± 2.1	23.9 ± 11.1	20.4 ± 8.7	4.83 ± 4.16	4.89 ± 3.23
AUC [ng*h/mL]							31.4 ± 4.7	25.3 ± 12.9	193 ± 133	153 ± 79	6.16 ± 4.35	6.05 ± 4.40
$t_{1/2}$ [h]							15.3 ± 3.5	9.9 ± 2.4	22.0 ± 12.2	11.2 ± 2.6	1.44 ± 0.87	1.13 ± 0.38
Rosuvastatin + Darunavir/Ritonavir												

C_{max} [ng/mL]	7.3 ± 3.1	7.3 ± 2.5	20.1 ± 16.6	17.4 ± 6.3	2.75 ± 2.56	2.38 ± 1.18	9.9 ± 4.3	7.9 ± 2.5	14.3 ± 6.4	21.2 ± 10.0	1.44 ± 0.89	2.67 ± 1.53
AUC [ng*h/mL]	121 ± 52	97 ± 41	181 ± 97	146 ± 53	1.50 ± 1.03	1.50 ± 0.83	104 ± 33	105 ± 49	167 ± 75	174 ± 91	1.60 ± 0.88	1.66 ± 1.16
$t_{1/2}$ [h]	15.5 ± 6.5	15.4 ± 4.9	18.5 ± 7.6	14.9 ± 4.5	1.19 ± 0.71	0.97 ± 0.42	13.1 ± 3.7	16.5 ± 6.4	33.1 ± 4.9	15.1 ± 5.5	2.52 ± 0.81	0.91 ± 0.49
Dolutegravir + Darunavir/Ritonavir												
C_{max} [ng/mL]	4667 ± 700	3,856 ± 1,263	3,967 ± 793	3,571 ± 1,109	0.85 ± 0.21	0.93 ± 0.42	5,114 ± 1,477	4,194 ± 1,308	3,081 ± 1,333	3,643 ± 1,191	0.60 ± 0.31	0.87 ± 0.39
AUC [ng*h/mL] $\times 10^{-3}$	75.6 ± 14.4	74.6 ± 63.2	52.1 ± 8.3	58.8 ± 48.4	0.69 ± 0.17	0.79 ± 0.93	88.2 ± 34.8	109.3± 95.0	74.9 ± 32.0	79.3 ± 91.8	0.85 ± 0.49	0.72 ± 1.05
$t_{1/2}$ [h]	12.1 ± 1.8	10.7 ± 5.6	9.8 ± 1.7	9.7 ± 4.9	0.81 ± 0.18	0.91 ± 0.66	10.4 ± 4.1	14.8 ± 8.3	13.2 ± 5.6	12.3 ± 8.2	1.27 ± 0.74	0.84 ± 0.72

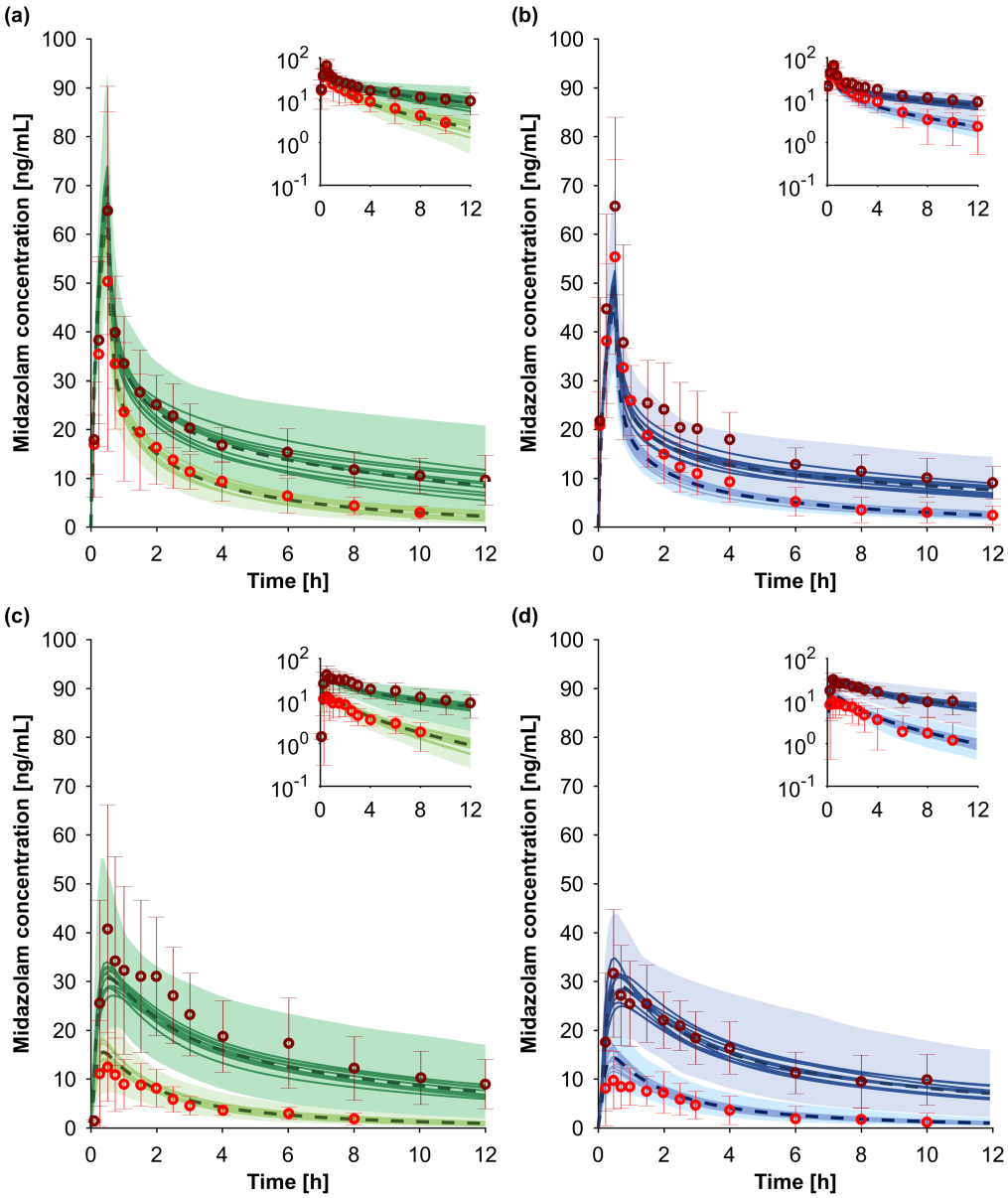
Key Table 1: C_{max} = peak concentration, AUC = area under the curve, $t_{1/2}$ = elimination half-life, iv = intravenous, po = oral, DDI = drug-drug interaction, perpetrator = drug with inhibitory/inducing potential.

Table 2: Predicted vs observed AUC of the control (victim drug in the absence of the perpetrator or extensive metabolizer/transporter phenotype) and DDI (victim drug in the presence of the perpetrator or different phenotype) scenario and the AUC-ratio (DDI scenario / control scenario).

	AUC [ng*h/mL] – control scenario		AUC [ng*h/mL] – DDI scenario		AUC ratio	
	Observed	Predicted	Observed	Predicted	Observed	Predicted
Midazolam + Ketoconazole	123 ± 76	121 ± 73	1,344 ± 648	1,354 ± 1,490	10.89 ± 8.54	11.18 ± 14.01
Rivaroxaban + Ketoconazole	892 ± 241	1,071 ± 314	2,298 ± 597	2,341 ± 894	2.58 ± 0.97	2.19 ± 1.05
Nilotinib + Ketoconazole	9,682 ± 5,686	13,283 ± 13,260	39,314 ± 18,708	56,183 ± 67,376	4.06 ± 3.07	4.23 ± 6.60
Midazolam + Nilotinib	121 ± 73	149 ± 99	157 ± 71	165 ± 119	1.30 ± 0.98	1.10 ± 1.08
Repaglinide + Gemfibrozil in PT of OATP1B1	7.8 ± 1.7	7.6 ± 3.5	50.1 ± 13.4	38.0 ± 19.7	6.42 ± 2.22	5.00 ± 3.45
Rivaroxaban + Clarithromycin	992 ± 249	1,006 ± 289	1,469 ± 360	1,476 ± 456	1.52 ± 0.50	1.47 ± 0.62
Atorvastatin + Clarithromycin	41.9 ± 19.0	32.7 ± 12.6	108 ± 28	84.4 ± 34.0	2.59 ± 1.36	2.58 ± 1.44
Etravirine + Clarithromycin	16,344 ± 4,757	14,161 ± 4,984	27,664 ± 8,156	21,409 ± 12,908	1.69 ± 0.70	1.51 ± 1.06
Midazolam + Ritonavir	30.8	37.8 ± 12.0	169	154 ± 124	5.47	4.07 ± 3.53
Rilpivirine + Darunavir/Ritonavir					2.30	2.27 ± 1.59
Atorvastatin + Rifampicin	64.0 ± 21.3	68.2 ± 28.1	12.6 ± 3.2	17.3 ± 7.7	0.20 ± 0.08	0.25 ± 0.15
Nilotinib + Rifampicin	11,123 ± 4,819	13,411 ± 10,797	2,227 ± 1,122	2,221 ± 615	0.20 ± 0.13	0.17 ± 0.14
Rilpivirine + Rifampicin					0.20 ± 0.11	0.15 ± 0.10
Rilpivirine + Efavirenz	3,012 ± 1,871	3,250 ± 1,760	2,218 ± 1,546	2,369 ± 1,223	0.74 ± 0.69	0.73 ± 0.55
Efavirenz + Rifampicin	200,335 ± 150,433	202,830 ± 127,928	209,062 ± 149,263	166,651 ± 89,725	1.04 ± 1.08	0.82 ± 0.68
Midazolam + Etravirine					0.69 ± 0.21	0.66 ± 0.11
Atorvastatin + Efavirenz					0.65 ± 0.31	0.85 ± 0.48
Atorvastatin + Etravirine	89.1 ± 48.3	59.0 ± 28.8	51.8 ± 31.2	52.7 ± 25.5	0.58 ± 0.47	0.89 ± 0.61
Dolutegravir + Atazanavir	64,559 ± 12,266	80,393 ± 100,190	177,645 ± 30,200	160,250 ± 187,474	2.75 ± 0.70	1.99 ± 3.41
Dolutegravir + Atazanavir/Ritonavir	64,559 ± 12,266	76,471 ± 68,411	149,820 ± 23,971	112,081 ± 125,322	2.32 ± 0.58	1.47 ± 2.10
Dolutegravir + Rifampicin	65,616 ± 46,285	102,641 ± 130,276	32,924 ± 21,428	41,986 ± 53,973	0.50 ± 0.48	0.41 ± 0.74
Dolutegravir + Etravirine	84,151 ± 18,513	105,295 ± 150,624	19,716 ± 43	27,632 ± 34,591	0.23 ± 0.05	0.26 ± 0.50
Raltegravir + Ritonavir	11,139	13,632 ± 6,964	8,905	9,356 ± 3,038	0.80	0.69 ± 0.42
Raltegravir + Rifampicin	12,273	16,349 ± 10,442	7,350	10,007 ± 3,680	0.60	0.61 ± 0.45
Raltegravir + Efavirenz	12,535	13,556 ± 7,627	7,942	10,635 ± 4,240	0.63	0.78 ± 0.54
Raltegravir + Etravirine	10,804 ± 12,153	7,479 ± 4,297	8,201 ± 7,622	5,813 ± 2,568	0.76 ± 1.11	0.78 ± 0.56
Repaglinide + Gemfibrozil	5.8 ± 3.8	4.8 ± 1.5	44.1 ± 24.9	45.5 ± 30.1	7.58 ± 6.57	9.48 ± 6.91

Atorvastatin + Gemfibrozil	35.2 ± 11.8	36.7 ± 14.7	43.6 ± 15.8	50.2 ± 20.3	1.24 ± 0.61	1.37 ± 0.77
Rosuvastatin + Gemfibrozil	464 ± 223	363 ± 134	897 ± 466	674 ± 303	1.93 ± 1.37	1.86 ± 1.08
Rosuvastatin + Atazanavir/Ritonavir	18.8 ± 16.1	20.3 ± 6.2	48.9 ± 34.3	65.7 ± 29.5	2.60 ± 2.88	3.24 ± 1.76
Metoprolol in PM of CYP2D6	668 ± 303	585 ± 472	3,222 ± 137	2,590 ± 2,2276	4.82 ± 2.20	4.43 ± 5.28
Metoprolol in UM of CYP2D6	668 ± 303	585 ± 472	311 ± 117	243 ± 207	0.47 ± 0.27	0.41 ± 0.49
Repaglinide in UM of CYP2C8	106 ± 30.9	72.1 ± 27.1	72.4 ± 37.9	65.2 ± 22.7	0.68 ± 0.41	0.90 ± 0.46
Repaglinide in PT of OATP1B1	4.5 ± 1.6	4.5 ± 1.4	7.8 ± 1.7	7.8 ± 3.1	1.73 ± 0.72	1.74 ± 0.88
Atorvastatin in IT of OATP1B1	24.2 ± 8.6	25.8 ± 11.2	36.2 ± 20.3	33.5 ± 14.9	1.50 ± 0.99	1.30 ± 0.80
Atorvastatin in PT of OATP1B1	24.2 ± 8.6	25.8 ± 11.2	59.3 ± 17.4	60.2 ± 27.3	2.45 ± 1.13	2.33 ± 1.46
Rosuvastatin in IT of OATP1B1	35.0 ± 18.1	42.4 ± 14.1	55.0 ± 22.7	45.4 ± 16.3	1.57 ± 1.04	1.07 ± 0.52
Rosuvastatin in PT of OATP1B1	35.0 ± 18.1	42.4 ± 14.1	56.7 ± 5.1	60.4 ± 27.4	1.62 ± 0.85	1.42 ± 0.80

Key: PM = poor metabolizer, UM = ultrarapid metabolizer, IT = intermediate transporter phenotype, PT = poor transporter phenotype.



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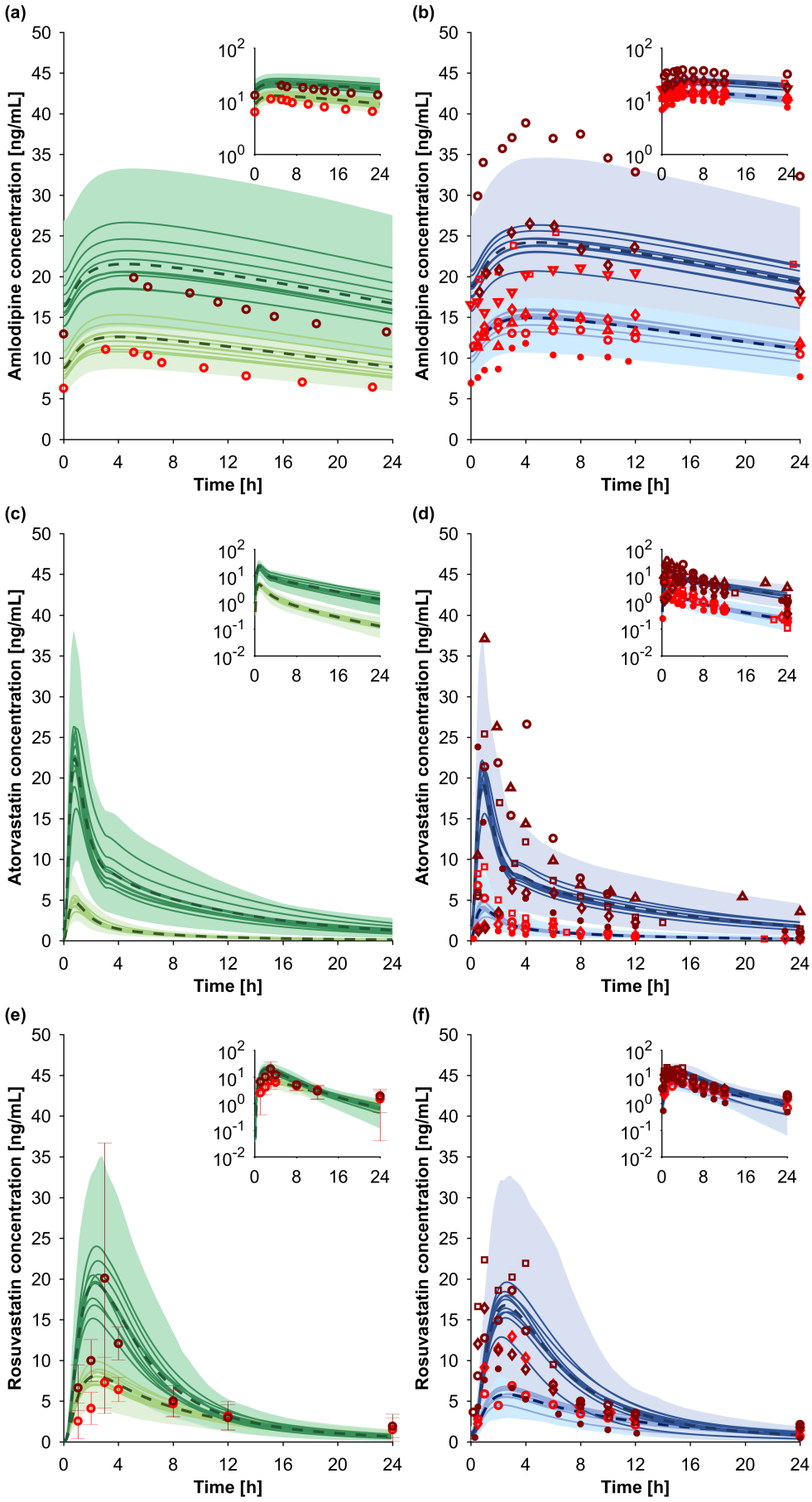

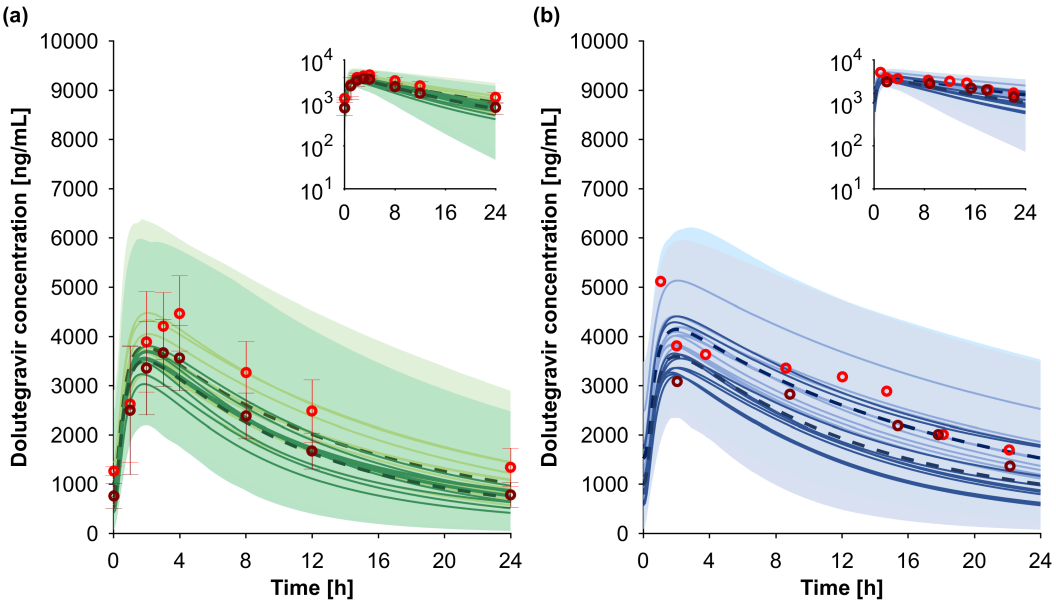

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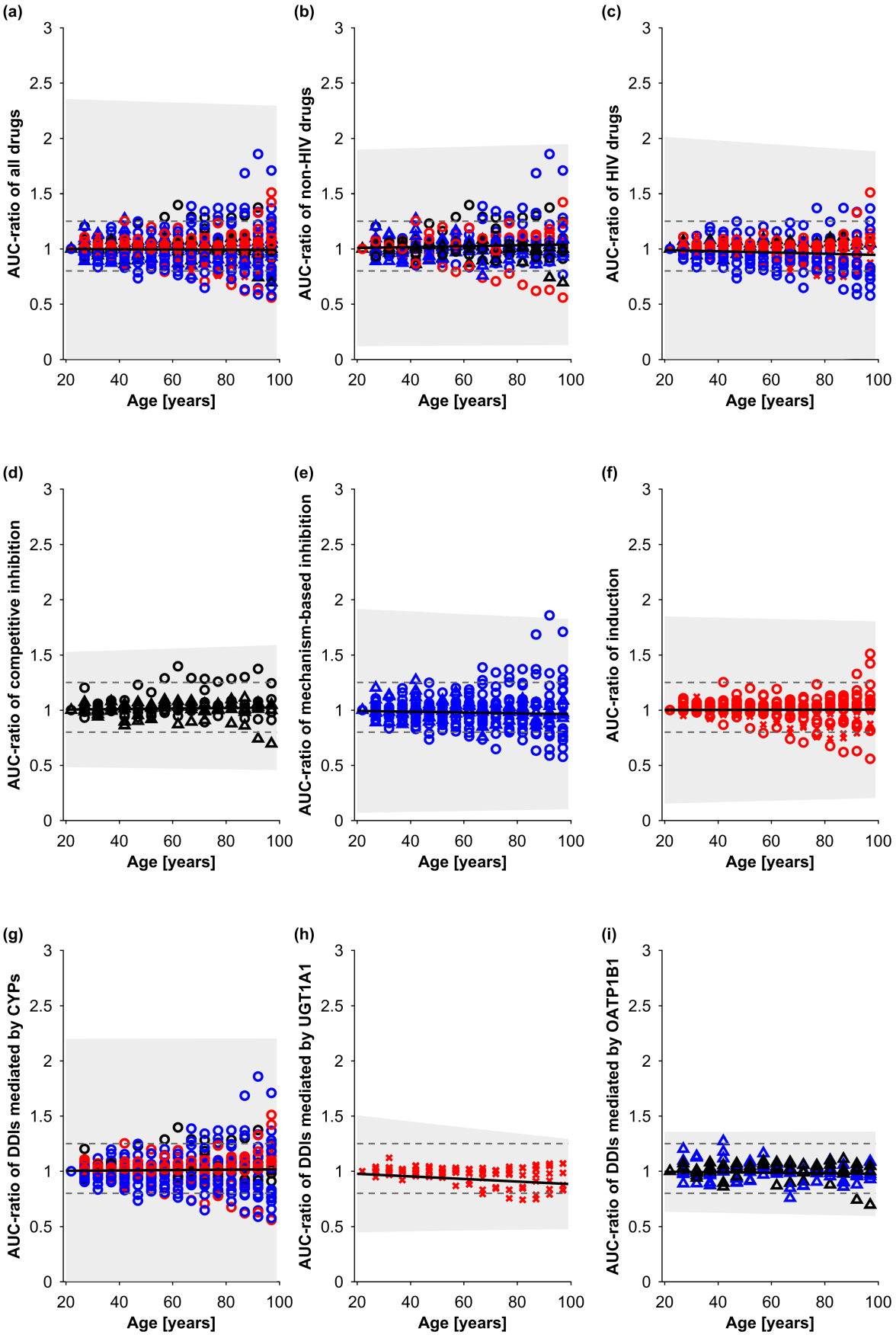

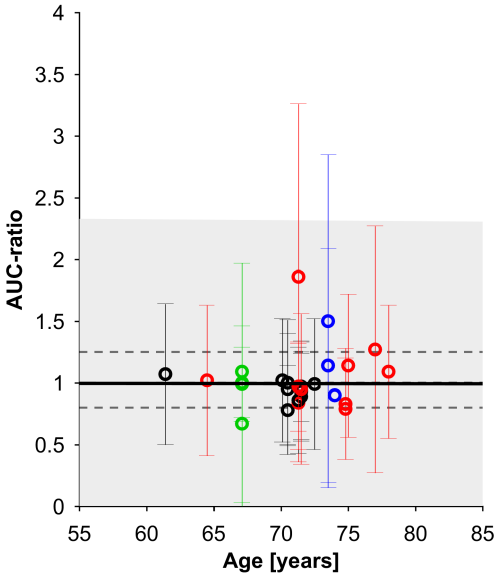

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