Pharmacokinetics of Long-Acting Cabotegravir and Rilpivirine in Elderly Using PBPK Modelling

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BACKGROUND

The quality of life of people with HIV (PWH) has significantly improved thanks to potent antiretroviral regimens characterized by good tolerability. Another milestone has been reached with long-acting (LA) formulations which enable infrequent dosing. Clinical trials of LA agents were mostly conducted in adults aged <50 years leading to a lack of knowledge on the pharmacokinetics in elderly PWH [1]. Physiologically based pharmacokinetic (PBPK) modelling is a mathematical tool approved by the regulatory authorities that can be applied to simulate the pharmacokinetics in special populations [2].

AIM

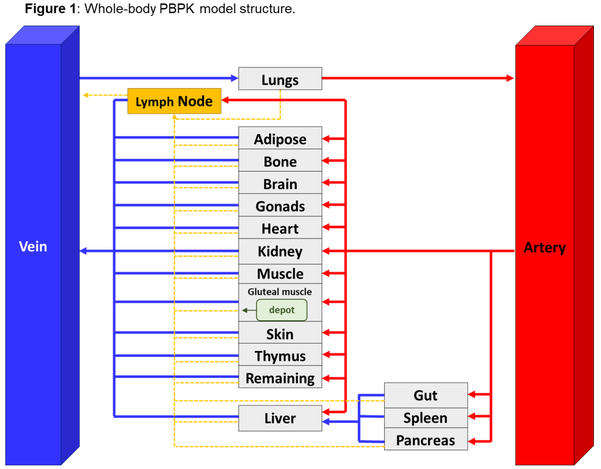
The aim of this study was to determine the impact of ageing on the pharmacokinetics of LA cabotegravir and rilpivirine using PBPK modelling.

METHODS

- Our in-house PBPK model built in Matlab®2020a [3] was implemented with an intramuscular framework (Figure 1) [4].

- The PBPK model was verified against observed data. As per PBPK modelling guidelines, the model was considered verified if the predictions were within 2-fold of clinical data.

Figure 1: Whole-body PBPK model structure.



Elderly people with HIV have higher exposure of ***LA cabotegravir and rilpivirine*** and therefore are *at* ***lower risk for suboptimal drug concentrations*** at the end of the dosing interval.

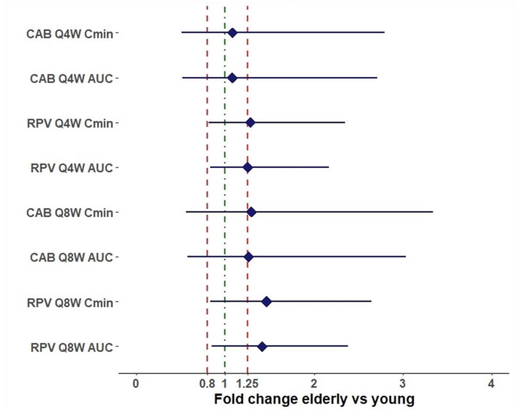
- The effect of ageing was evaluated by reproducing the design of the ATLAS/FLAIR and ATLAS-2M studies in our PBPK model and the fold change in elderly relative to young was determined for the area under the concentration-time curve (AUC) and the trough concentration (C_{min}) at steady state (i.e., 96 weeks).

1. PBPK model informed with physiological parameters of a healthy White population aged 20-99 [5].
2. Drug models verification against clinical observed data for young (<50 years) and elderly (>50 years).
3. Reproducing ATLAS/FLAIR and ATLAS-2M in a cohort of virtual individuals aged 20-50 (50% female).
4. Reproducing ATLAS/FLAIR and ATLAS-2M in a cohort of virtual individuals aged 65-85 (50% female).
5. Calculation fold change in elderly relative to young for AUC and C_{min} at steady state (i.e., 96 weeks).

RESULTS

- The PBPK model was successfully verified as all the predictions were within 2-fold of clinically observed data.
- Age-related physiological changes did not significantly impact the C_{min} and AUC of LA cabotegravir administered every month (Q4W), and the AUC of LA rilpivirine Q4W since the ratios (elderly vs young) were predicted to be within the bioequivalence range (0.8-1.25 fold) (Figure 2).
- The C_{min} of LA rilpivirine administered Q4W was 28% higher in elderly relative to young.
- The C_{min} and AUC of LA cabotegravir administered every other month (Q8W) were predicted to be 29% and 26% higher in elderly relative to young, respectively. Similarly, the C_{min} and AUC of rilpivirine Q8W were 46% and 41% higher in elderly (Figure 2).

Figure 2: Fold change in exposure in elderly relative to young for LA cabotegravir and rilpivirine administered monthly (Q4W) or every other month (Q8W).



Legend: results expressed as geometric mean, 5th/95th percentile. The red dashed lines represent the bioequivalence range. The dashed-dot line represents the unity line.

CONCLUSIONS

Age-related physiological changes are predicted to modestly increase the AUC and C_{min} of LA cabotegravir and rilpivirine. Thus, elderly PWH could possibly be at lower risk for suboptimal drug concentrations at the end of the dosing interval.

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Fundings: this work was supported by Swiss National Science Foundation [grant number 188504].