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Individual level data meta-analysis from HIV pre-exposure prophylaxis (PrEP) clinical trials

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Oral: Drug/Disease modelling

Introduction: Daily tenofovir has proven efficacy in preventing HIV infection in high-risk populations, when patients are compliant. However, effective preventive concentration has not been determined using HIV infection as outcome, due to lack of power in a single clinical trial and large cofounding with non-adherence. Furthermore, infection risk in target populations is poorly defined, making it difficult to properly identify key patients who would benefit the most from PrEP therapy. To address those pertinent questions, we have constructed the largest individual data base up to date from the 5 latest Phase 3 HIV prevention clinical trials.

Our aims were (i) to identify patient subgroups at the highest risk of HIV infection in target populations, (ii) to estimate preventive tenofovir concentrations in target populations based on pharmacokinetic (PK)-HIV outcome modeling and (iii) to evaluate the target site tenofovir diphosphate PK in peripheral blood mononuclear cells (PBMC) vs plasma tenofovir as a marker of HIV prevention.

Methods:(i) Longitudinal PK data of tenofovir in plasma and tenofovir metabolite in PBMC, (ii) HIV outcome and (iii) individual's demographics and risk factors data from 13,727 individuals obtained from 5 phase 3 randomized controlled trials were integrated and analyzed with NONMEM 7.4 using population approaches. Those trials evaluated tenofovir-based PrEP therapy efficacy in different HIV risk groups: injection drug users (Bangkok[1]), men or transgender women who have sex with men (iPrEX[2]), women at high risk of infection (VOICE[3]), HIV serodiscordant heterosexual couples (Partners[4]), and high risk heterosexual men and women (TDF2[5]). The analyses were done sequentially:

- The probability of HIV infection over time was analyzed through parametric survival analysis using data from the placebo arms of the 5 PrEP trials (n=5313). Studies were analyzed separately due to availability of baseline covariates specific for target populations. Baseline survival models were evaluated and covariate analysis was performed by stepwise covariate modelling. Patient-specific risk stratification algorithm was developed.
- The PK analysis of tenofovir (2 compartment model) and its metabolite (effect compartment model) was done sequentially pooling the available data from iPrEX, VOICE and Partners (n=2360). Longitudinal adherence to the treatment was assessed by applying mixture modeling approaches on the relative bioavailability fraction. Data below limit of quantification were handled with the M3 method.
- PK exposure metrics for tenofovir in plasma were linked to the probability of HIV infection in parametric survival analysis. The effect of tenofovir diphosphate in PBMC as predictor of HIV prevention was explored.

Results: Exponential hazard distribution best fitted the time to HIV infection data from the control arms of the PrEP studies. The analysis identified set of risk factors which are common (e.g. female sex, age) or unique to each population (e.g non-condom receptive anal intercourse, and syphilis seroreactivity in iPrEX study). Most surprisingly, women appear to be at greater risk of HIV infection compared to men. In population PK model, 2 patient subpopulations were identified, adherent F=100% and non-adherent F=<1%) through the application of a mixture model on relative bioavailability, with an estimated probability of being in adherent group of 55%. Longitudinal adherence and PK profiles were reconstructed for each patient based on the established mixture model and PK data. These were then linked to HIV infection (characterized by a survival model with Surge hazard distribution) using a sigmoidal Emax model. Underlying individuals risk hazard was found to be important factor in determining accurate PKPD. The EC_{50} identified in high risk group was found to be 10.21 ng/mL. Tenofovir diphosphate, appeared to be a better marker of HIV prevention compared to the plasma tenofovir, with an estimated EC_{50} of 6.91 fmol/10^6cells.

Conclusions: We have quantified tenofovir preventive concentration based on the largest database up to date which includes HIV outcome. We have established patient-specific risk stratification algorithm for HIV infection. These models and tools will further be used for: (i) optimization of novel PrEP clinical trial designs, enrollment and follow up strategies, (ii) the development of novel tenofovir formulations and (iii) implementation of patient management strategies in the clinic.