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Impact of medication adherence measurement on antiretroviral drug pharmacokinetics: A retrospective cohort study in HIV patients followed by therapeutic drug monitoring and taking part in a medication-adherence enhancing program

BACKGROUND

- In our institution, patient at high risk of non-adherence for their antiretroviral therapy are addressed to an adherence-enhancing program combining electronic monitoring (MEMS for medication event monitoring system), pill count and motivational interviewing.
- Therapeutic drug monitoring (TDM) is also proposed for those patients and a Bayesian approach is offered.
- Most population pharmacokinetic (PK) models are developed on TDM data, assuming steady-state condition, but neglects non or partial adherence.

OBJECTIVES

⇨ To evaluate the impact of medication adherence on efavirenz (EFV) and lopinavir (LPV) PK parameters estimation.

⇨ To investigate whether dosing history measured by MEMS compared to patient self-reported last dose intake, modify the interpretation of concentrations measured within the framework of a TDM program.

METHODS

▪ All HIV-patients taking part in the medication-adherence enhancing program from 2004 to 2011 with at least one EFV or LPV concentration were analysed. Fifteen and 10 days (~ 5 $t_{1/2}$) were retrieved for dosing history for EFV and LPV, respectively, from MEMS. Pocket-dose* recovered from interview were also available in the dosing history.

*A misuse of the eletronic system that consists in the removal of more than one dose per opening for a later use

▪ Dosing discrepancies between MEMS and patient self-reporting of last dose intake were investigated by calculating the time difference:

Time difference = Patient self-reported last dosing time – MEMS recorded last dosing time

▪ PK data were fitted with NONMEM® for both methods (self-reporting and MEMS) based on previously published studies[1,2]. Model parameter estimates using steady-state assumption were compared to those using dosing history from MEMS. The worst case scenario, treating the pocket-dose recovered from motivational interview as a non-intake, was also analysed.

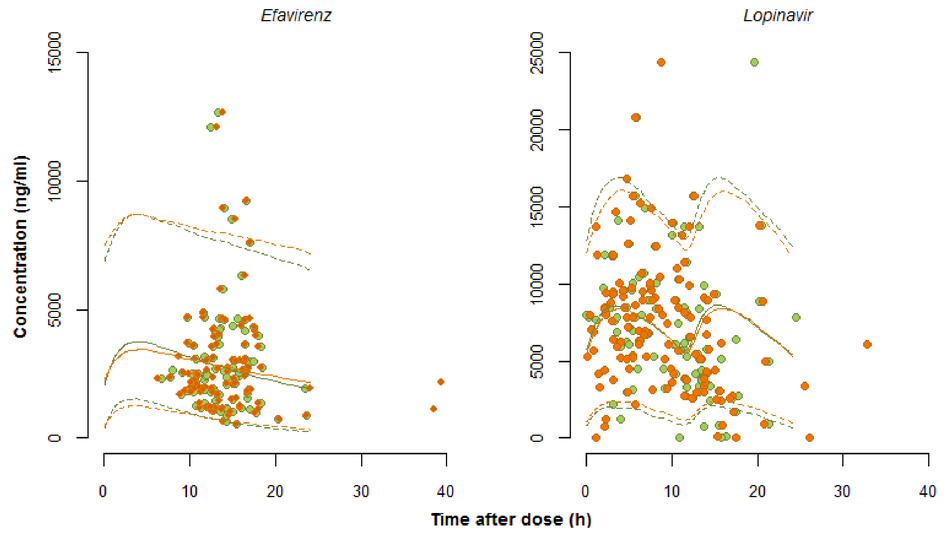
▪ Differences in predicted individual clearance (CL) were evaluated by linear mixed-effect modeling for log transformed CL and Bland-Altman plot for the 3 cases described above (self-reporting, MEMS, MEMS without including the pocket-dose).

▪ Bias and precision characterizing the predictive performance were estimated by mean prediction error (MPE) and root mean squared error (RMSE)[3] for individual predicted concentrations.

RESULTS

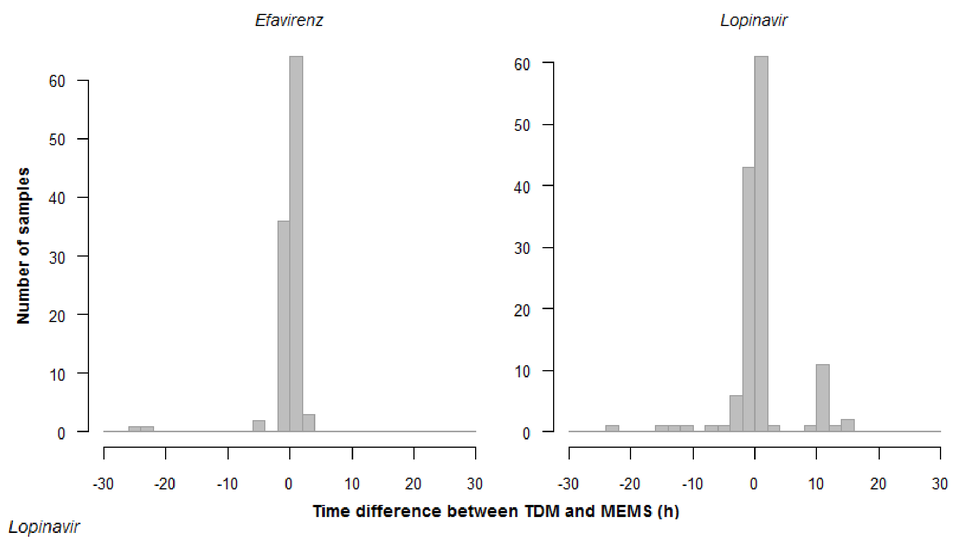
	EFV	LPV
Patients (n)	55	65
Concentrations (n)	107	129
Occasion (median) [range]	1 [1-7]	2 [1-10]
Pocket-dose (n) Patients (n)	44 13	50 11
Standard posology	600 mg 1x/d	400 mg 2x/d
Half-life (h)**	56-72	5-6

***Based on the summary of product*

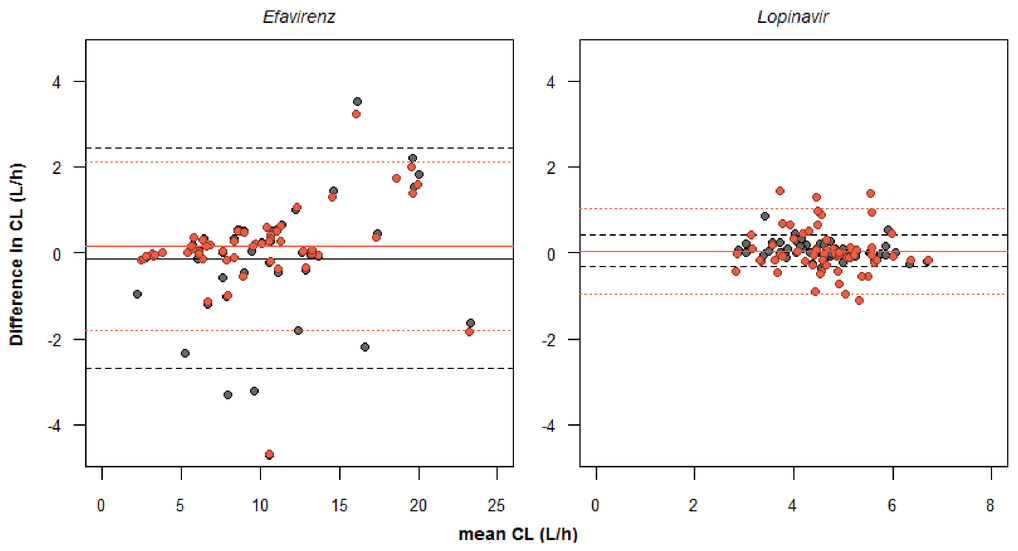


Concentrations vs time for self-reported (green) and MEMS (orange) last drug intake. Solid represents the population prediction with $PI_{95\%}$ based on population PK model using steady-state assumption (green) or MEMS dosing history (orange).

The time difference between self-reporting and MEMS is centered around 0. The mean and standard deviation of the time difference was EFV: 0.41 +/- 3.4 hrs; LPV: -0.07 +/- 4.7 hrs.



Regarding population estimates, the LPV *constant of absorption Ka* estimation was affected by the dosing history method used (Ka was fixed for EFV). For both drugs, the *volume of distribution Vd* seemed also affected, but the *clearance CL* was insensitive to the reporting dosing time method.



The solid line indicates the bias (mean difference in CL) and the dotted lines the precision ($CI_{95\%}$). Individual clearance estimation are similar between self-reporting and MEMS methods (EFV: P=0.74; LPV:P=0.23); The worst case scenario possible (grey points) showed a slight significant difference in CL (EFV: P=0.04; LPV:P=0.02), of little clinical importance.

Relative predictive performance for individual concentrations was similar between self-reported last dose intake and MEMS for both drugs that exhibit a bias of 12.8 ng/mL (EFV) and -33.5 ng/mL (LPV) with a high imprecision for LPV (RMSE: EFV=126.4 ng/mL; LPV=1214.8 ng/mL).

Conclusion

- Self-reporting dosing seems reliable for population pharmacokinetics studies.
- However, HIV adherence program showed successful results with 87% of persistence and 88% of execution[4], thus our data in such context may not be representative for poor adherence behaviour.
- Combination of methods may help to capture complementary aspects of patient's adherence in routine care: longitudinal monitoring of patients' actual behaviour through MEMS and actual quantitative dosing through TDM.

References

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