Development and validation of a multiplex UHPLC-MS/MS assay with stable isotopic internal standards for the monitoring of the plasma concentrations of the antiretroviral drugs bictegravir, cabotegravir, doravirine, and rilpivirine in people living with HI

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Author(s) Courlet, Perrine; Alves Saldanha, Susana; Cavassini, Matthias; Marzolini, Catia; Choong, Eva; Csajka, Chantal; Günthard, Huldrych F.; André, Pascal; Buclin, Thierry; Desfontaine, Vincent; Decosterd, Laurent Arthur

Author(s) at UniBasel Marzolini, Catia ;

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The widespread use of highly active antiretroviral treatments has dramatically changed the prognosis of people living with HIV (PLWH). However, such treatments have to be taken lifelong raising issues regarding the maintenance of both therapeutic effectiveness and long-term tolerability. Recently approved or investigational antiretroviral drugs present considerable advantages, allowing once daily oral dosage along with activity against resistant variants (eg, bictegravir and doravirine) and also parenteral intramuscular administration that facilitates treatment adherence (eg, long-acting injectable formulations such as cabotegravir and rilpivirine). Still, there remains a risk of insufficient or exaggerated circulating exposure due to absorption issues, abnormal elimination, drug-drug interactions, and others. In this context, a multiplex ultra-high performance liquid chromatography coupled to tandem mass spectrometry (UHPLC-MS/MS) bioassay has been developed for the monitoring of plasma levels of bictegravir, cabotegravir, doravirine, and rilpivirine in PLWH. A simple and convenient protein precipitation was performed followed by direct injection of the supernatant into the UHPLC-MS/MS system. The four analytes were eluted in less than 3 minutes using a reversed-phase chromatography method coupled with triple quadrupole mass spectrometry detection. This bioassay was fully validated following international guidelines and achieved good performances in terms of trueness (94.7%-107.5%), repeatability (2.6%-11%), and intermediate precision (3.0%-11.2%) over the clinically relevant concentration ranges (from 30 to 9000 ng/mL for bictegravir, cabotegravir, and doravirine and from 10 to 1800 ng/mL for rilpivirine). This sensitive, accurate, and rapid UHPLC-MS/MS assay is currently applied in our laboratory for routine therapeutic drug monitoring of the oral drugs bictegravir and doravirine and is also intended to be applied for the monitoring of cabotegravir/rilpivirine levels in plasma from PLWH receiving once monthly or every 2-month intramuscular injection of these long-acting antiretroviral drugs.

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