1. Abstract

Title:	A European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC) study assessing the safety and effectiveness of Kaletra® oral solution in children aged 14 days to 2 years with HIV-1 infection in Europe
Keywords:	Lopinavir/ritonavir, safety, HIV, cohort study, paediatrics
Rationale and Background:	Kaletra (LPV/r) was licensed for use in children living with HIV aged ≥14 days in Europe on 26 July 2017. It has high content of ethanol and propylene glycol which can cause toxicity in very young children. Use and safety of LPV/r in children aged <2 years was assessed using data from EPPICC.
Research Question and Objectives:	What is the short and medium term safety profile of LPV/r in children aged <2 years with HIV-1 infection? The study objectives are to: 1. Describe characteristics of children treated with LPV/r oral solution (including off-label use) in the European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC) network in European countries regulated by the European Medicines Agency (EMA) at or after EMA approval date (26 July 2017). 2. Assess appropriateness of LPV/r oral solution dose for weight (or body surface area) at LPV/r initiation using AbbVie Kaletra® oral solution Summary of Product Characteristics (SmPC) as reference. 3. Evaluate safety and tolerability of LPV/r oral solution: a. Describe timing and reasons for discontinuation (especially for toxicity). b. Describe clinical adverse events (AEs) whilst on LPV/r and up to 3 months after discontinuation, especially relating to toxicity due to LPV/r (active ingredient), propylene glycol or ethanol. c. Assess incidence of Division of AIDS (DAIDS) grade 1-4 laboratory results. 4. Assess immunological and virological responses to LPV/r.
Study Design:	Analysis of pseudo-anonymised longitudinal patient data for children initiating LPV/r oral solution aged <2 years at/after the EMA approval date
Setting:	Children with HIV-1 infection in Europe

Subjects and study size, including dropouts:	All children initiating LPV/r aged <2 years at/after the EMA approval date and followed in participating centres.
Variables and Data Sources	Data from 8 cohorts across 7 European countries: demographic factors, HIV medical history, ART history, AIDS events, death, weight, CD4 cell counts, HIV viral loads, laboratory test results, clinical AEs, discontinuations of LPV/r. Children were followed from LPV/r initiation with data censored at earliest of: last visit, death, 3 months after discontinuation of LPV/r oral solution or 2nd birthday.
Results:	42 patients received LPV/r oral solution while aged <2 years at/after EMA approval date, including 9 newly reported this year. Fourteen were on a licensed dose, 14 an unlicensed dose, 1 was off-label use (age <14 days) and 13 were missing weight/dose at LPV/r start. At LPV/r start, median [IQR] age was 6.9 [2.3-14.4] months and 39/42(93%) were treatment naïve. Overall, 12 patients (33% of 36 with laboratory data) experienced ≥1 grade 3/4 events across 10 laboratory markers. Six clinical AEs in three patients (1 in licensed dose group, 2 in unlicensed) were considered causally related to LPV/r (all previously reported). Three of these were serious; none led to discontinuation of LPV/r. At 6(n=23) and 12(n=16) months after start of LPV/r, ≥75% were virally suppressed (≤1000 copies/mL). 5 (12%) patients discontinued LPV/r while aged<2 years, including one due to lack of effectiveness and 1 due to toxicity.
Discussion:	In general, LPV/r, both licensed and unlicensed doses, appears well-tolerated in this population. While some laboratory AEs occurred relatively frequently, safety outcomes reported are consistent with the safety profile specified in the LPV/r SmPC.
Marketing authorisation holder:	AbbVie
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