Title: Safety of darunavir and atazanavir in HIV-infected children in Europe and Thailand

Running Head: Safety of darunavir and atazanavir in children

The European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) study group in EuroCoord

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Short communication for Antiviral Therapy (≤1500 words, ≤20 references, ≤3 display items)

Abstract

Background:

Surveillance for mid- and long-term ART toxicity in children is important for informing treatment guidelines. We assessed the safety of darunavir (DRV) and atazanavir (ATV), commonly used as second-line protease-inhibitors following lopinavir/ritonavir, in Europe and Thailand.

Methods

Cohorts contributed individual patient data on adverse events (AE) in those aged <18 years taking DRV and ATV respectively to 02/2014. Rates of Division of AIDS (DAIDS) grade ≥3 laboratory AEs were calculated.

Results

Of 431 patients on DRV and 372 on ATV, 317 (74%) and 301 (81%) respectively had weight and dose data available of whom 56 (18%) and 33 (9%) took the drugs at a non-approved age or dose. Median age at DRV and ATV start was 14.8 years [IQR 12.8,16.1] and 13.5 years [11.4,15.2]; 43% and 26% had received ≥8 ART drugs previously. Overall rates of grade ≥3 AEs for absolute neutrophils, total cholesterol, triglycerides, pancreatic amylase, lipase and ALT were ≤3/100 person years (PY) on approved doses of both drugs, but 66/100 PY (95% CI 52,84) for bilirubin after <12 months on ATV declining to 32/100 PY (95% CI 23,44) after >24 months. Five serious drug-related clinical AEs were reported in 4 patients on ATV (1 discontinued) and 3 on DRV (all discontinued), and did not substantially differ in those on approved compared to non-approved doses. Proportions on the drugs at last follow-up were 89% (383/431) for DRV and 81% (301/372) for ATV (including 73/92 with grade ≥3 hyperbilirubinemia).

Conclusions

AEs were low and comparable for the two drugs, with the exception of high rates of hyperbilirubinemia for ATV; few patients discontinued due to toxicity.

Introduction

Darunavir (DRV, Prezista®) and atazanavir (ATV, Reyataz®), both protease inhibitors (PI), are approved in Europe for paediatric HIV treatment at ≥3 years and ≥6 years respectively with weight ≥15kg, in combination with other antiretrovirals and low dose ritonavir (/r) (1, 2). Both have commonly been used as a second-line PI following lopinavir/r (LPV/r). European guidelines now recommend ATV/r as a first-line option at ≥6 years and both as first-line from 12 years (3); once daily dosing of these drugs offers considerable advantage over twice-daily LPV/r (4).

Dosing of DRV and ATV is by weight-bands (1)(2). DRV/r safety data from 48 week trials suggest that it is generally well tolerated in children (5-7); a quarter in one trial experienced a severe (Division of AIDS (DAIDS) grade ≥3 (8)) event, but only grade 2 diarrhoea and rash were considered possibly treatment-related (6). For ATV/r, the most common toxicity is elevated bilirubin (9), reported at grade 2-4 in 67% of treated infants and 79% of adolescents in 48-week analyses of a non-randomised study (10). Although this is clinically benign and reversible (11), ATV/r is not recommended at age <3 months due to the potential risk of kernicterus. ATV/r has also been associated with cardiac conduction abnormalities which are generally asymptomatic; all were clinically benign in the AI424-020 study. Compared with other PIs and NNRTIs, ATV/r has minimal impact on lipid parameters in adults (12, 13) as well as children (10).

Pharmacovigilance beyond 48-week licensing trials is critical to ensure long-term patient safety. We investigated the "real life" use and long-term safety of DRV and ATV in children enrolled in observational cohorts participating in the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC), within which a pharmacovigilance programme has been running since 2009 (14).

Methods

Patients receiving DRV (ever) or ATV (on/after 1/1/2011) and aged <18 years at DRV/ ATV start participated. Trial follow-up time for 19 patients starting DRV within a clinical trial was excluded. No ATV patients were in clinical trials. Cumulative data submitted annually from 2011-2014 for DRV and 2012-2014 for ATV were pooled within EPPICC, part of the EuroCoord network (www.eurocoord.net). Individual cohorts gained ethics approval if required. Data collected included demographics, deaths, losses to follow-up, weight, ART, CDC C (AIDS) events, CD4 and HIV-1 RNA viral load (VL), key haematology and biochemistry results, and adverse events, using the HIV Cohorts Data Exchange Protocol (HICDEP) (www.hicdep.org).

Patients were classified into approved and non-approved groups based on age, weight, dose and RTV co-administration at drug start; "approved" doses were within ±20% of the European-approved dose for the patient's weight. "Non-approved" doses were defined as ATV without RTV, non-approved dose/frequency for patient's weight, or DRV use at age <3 years or ATV at age <6 years. In this time period, QD DRV/r dosing was considered non-approved in patients aged <12 years.

DAIDS gradings for paediatric adverse events (AEs) (8) categorised biochemical results, and incidence rates were calculated by drug duration for periods with ≥20 children in follow-up for approved doses. Follow-up time was censored at the first event of each grade in each time period or, for overall rates, at the first event of that grade overall. Clinical AEs were coded according to body system using an in-house system at the MRC Clinical Trials Unit at UCL, and categorised according to whether the clinician considered the AE causally related to the drug. Analyses were undertaken using Stata version 12.0 (Stata Corp, College Station, TX, USA).

Results

Overall 431 patients had ever received DRV (15% of 2950 in 14 cohorts, starting earliest 2004 overall and 2007 in approved dose group) and 372 patients had received ATV since 2011 (14% of 2630 in 11 cohorts). Most were from the UK/Ireland, Spanish and Italian cohorts, around half were black African and almost all were perinatally infected (Table 1). Seven DRV and 4 ATV children were hepatitis C co-infected, and 7 and 5 hepatitis B surface antigen carriers (data not shown).

Median age at DRV and ATV initiation was 14.8 and 13.5 years respectively, around 11 and 9 years after starting ART (Table 1). Up to 2012, 6% (24/381) starting DRV were ART-naïve increasing to 8% (4/50) in 2013-14 (Fisher's exact p=0.549); for ATV these proportions were 8% (27/334) and 18% (7/38) respectively (Fisher's exact, p=0.066). Overall 43% (187/431) starting DRV had previously received ≥8 ART drugs and 26% (96/372) starting ATV. A third (133/431) starting DRV and 29% (107/372) starting ATV were switching from LPV/r. At drug start, 54% (182/336) of DRV patients had VL ≤400 copies/ml vs. 64% (191/247) starting ATV (χ^2=6.70, p=0.010), increasing to 77% (185/241) and 76% (175/230) respectively after 12 (+/-3) continuous months DRV/ATV.

Overall, 82% (261/317) on DRV with weight available were taking the approved dose; of the rest, 3 were aged 0-<3 years, 39 were on a non-approved dose (QD (n=30) or non-approved for weight (n=9)) and 14 took DRV without RTV boosting. Of 301 on ATV with weight available, 89% (n=268) were on the approved dose; of the remainder, 6 were aged <6 years, 7 were on a non-approved dose, 13 lacked RTV boosting, and 7 started on 400mg QD ATV/r (recommended prior to EMA approval (15)). Median follow-up was 17.8

months [IQR 8, 32] on DRV and 22.8 months [10, 42] on ATV (total 743 and 796 person years (PY) of exposure respectively).

Figure 1 shows incidence of DAIDS grade ≥3 events by drug duration for approved dose groups (82% (213/261) DRV and 84% (226/268) ATV patients had laboratory data). Eleven DRV and 8 ATV patients had grade ≥3 neutropenia; all remained on DRV/ ATV at last follow-up and 10/11 and 5/8 subsequently had a normal absolute neutrophil count. Severe hypercholesterolemia and hypertriglyceridemia were uncommon on either drug, and there were no grade ≥3 fasting plasma glucose events. Rates of hyperbilirubinemia were low for DRV but high for ATV patients: 49% (92/188) had a grade ≥3 event, declining from 66/100 PY (95% CI 52-84) at <12 months to 32/100 PY (95% CI 23-44) after >24 months (trend p<0.001). Of the 92, 19 discontinued ATV by last follow-up, 6 due to toxicity. Grade ≥3 events were uncommon for pancreatic amylase, lipase (0/30 patients on DRV and 1/52 patients on ATV) and ALT (1/175 and 4/187 respectively).

Of 43 patients taking non-approved DRV with laboratory data, four had grade 3 neutropenia and two grade 3 hyperbilirubinemia. Thirty of 33 patients taking non-approved ATV had laboratory data, of whom 14 had grade ≥3 hyperbilirubinemia; grade 3 neutropenia, pancreatic amylase and ALT were reported in one patient each.

Among 192 patients on approved and 32 on non-approved DRV with clinical data, there were three DRV-related serious AEs, all in the approved group: hypercholesterolemia/ hypertriglyceridemia (n=2) and hypersensitivity reaction (n=1). Four children on ATV (all approved group) had ATV-related serious AEs: hyperbilirubinemia and rash (same child), proteinuria, lipodystrophy and hepatic disease (in a child without viral hepatitis – the only one to discontinue ATV due to toxicity).

Three patients on approved DRV doses died due to AIDS-defining events, one with hepatitis C on a non-approved DRV dose died from liver transplant complications, and one on an unknown DRV dose died due to invasive bacterial infection. One AIDS-related death occurred in a patient on an unknown ATV dose. Table 2 presents timing of and reasons for the relatively small number of DRV /ATV discontinuations.

Discussion

Rates of AEs among 431 <18 year olds receiving DRV and 372 <18 year olds receiving ATV were generally low and comparable, with the exception of elevated bilirubin among patients taking ATV, declining after longer durations on the drug. Half of patients on an approved ATV dose had grade ≥3 hyperbilirubinemia but only 6 with hyperbilirubinemia stopped ATV due to toxicity. By 2014, 15% of patients had ever taken DRV and 14% had taken ATV since 2011 outside of a clinical trial. Over 90% of patients were ART

experienced at DRV/ATV start, with a trend towards increasing use of ATV among ART-naïve children more recently, reflecting updated guidance for its use first-line (3).

ART and particularly PI-based cART is associated with dyslipidaemia in children and adults (16-19), but DRV and ATV have generally more favourable lipid profiles than other PIs (6, 13) and were associated with modest, comparable elevations in lipids in a recent trial in ART-naïve adults (19). Rates of grade ≥3 hypercholesterolemia and hypertriglyceridemia in our study were very low (≤1/100 PY) for both drugs. Discontinuations for toxicity were infrequent and only three patients on DRV and four on ATV had a serious AE considered to be drug-related.

Our sample size was large although coverage of contributing cohorts varied (20), and so we could not estimate the proportion of HIV-infected children in Europe and Thailand included. Some toxicities may have been due to previous ART regimens (in the first months on ATV /DRV), or other drugs in the ART regimen. Our study demonstrates the importance of ongoing cohort studies in providing long-term pharmacovigilance data which is not usually available from other sources.

Participating cohorts: Hospital St Pierre Cohort, Brussels, Belgium; Copenhagen Cohort, Denmark; KompNet, Germany; Italian Register for HIV infection in children, Italy; Paediatric Cohort, Poland; Centro Hospitalar do Porto, Portugal; "Victor Babes" Hospital Cohort, Romania; The Republican Hospital of Infectious Diseases, St Petersburg, Russia; CoRISpe-cat, Catalonia, Spain; CoRISpeS-Madrid cohort, Spain; Karolinska University Hospital, Stockholm, Sweden; Swiss Mother and Child HIV Cohort Study, Switzerland; Thailand Program for HIV Prevention and Treatment (PHPT) Study Group, Thailand; National Study of HIV in Pregnancy and Childhood, UK and Ireland; Collaborative HIV Paediatric Study, UK and Ireland.

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EuroCoord Appendix

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Table 1: Characteristics of patients taking DRV or ATV

	DRV (n=431)		ATV (n=372)	
	N (%) or median [IQR]			
Country				
Belgium	27	(6)	23	(6)
Denmark	2	(0)	3	(1)
Germany	2	(0)	0	(0)
Italy	60	(14)	41	(11)
Poland	3	(1)	0	(0)
Portugal	4	(1)	2	(1)
Romania	2	(0)	0	(0)
Russia	1	(0)	8	(2)
Spain	91	(21)	52	(14)
Sweden	15	(3)	12	(3)
Switzerland	10	(2)	8	(2)
Thailand	12	(3)	13	(3)
UK/Ireland	202	(47)	210	(56)
Gender				
Male	225	(52)	162	(44)
Ethnic group				
White	94	(22)	57	(15)
Black African	190	(44)	202	(54)
Other	79	(18)	68	(18)
Unknown	68	(16)	45	(12)
Mode of HIV infection				
Perinatal	407	(94)	355	(95)
Other or unknown	24	(6)	17	(5)
Ever AIDS event	164	(38)	108	(29)
Median age at ART start (years) [1]	3.5	[1.1,7.9]	4.3	[1.1,9]
Age at DRV / ATV start (years)				
<6 years	8	(2)	6	(2)
6-8 years	19	(4)	23	(6)
9-11 years	51	(12)	95	(26)
12-14 years	157	(36)	145	(39)
15-<18 years	196	(45)	103	(28)
Median age at DRV / ATV start (years)	14.8	[12.8,16.1]	13.5	[11.4,15.2]
Duration on ART before DRV / ATV start				
ART-naïve	30	(7)	34	(9)
<2 years	16	(4)	27	(7)
2-4 years	51	(12)	53	(14)
5-9 years	111	(26)	121	(33)
≥10 years	220	(51)	137	(37)
Median duration on ART before DRV / ATV start (years)	10.2	[5.5,13.1]	7.9	[3.6,11.4]
Median VL at DRV / ATV start (log_{10} copies/ml) [2]	2.4	[1.7,4]	2	[1.6,3.4]
Median CD4 cell count at DRV / ATV start (cells/mm^3) [3]	501.5	[290,740]	534	[354,799]
Median CD4% at DRV / ATV start [4]	23	[15,32]	25.1	[18,34]
Median time on DRV / ATV (months) [5]	17.8	[8,32]	22.8	[10,42]
NRTIs taken with DRV / ATV				
Lamivudine (3TC) plus abacavir (ABC)	72	(17%)	117	(31%)
Emtricitabine (FTC) plus tenofovir (TDF)	133	(31%)	129	(35%)
Tenofovir (TDF) only	119	(28%)	25	(7%)
Other regimen	107	(25%)	101	(27%)

[1] Excludes ART received as neonatal prophylaxis for prevention of mother-to-child transmission

[2] Viral load at drug start available for 78% (336/431) of DRV group and 80% (297/372) of the ATV group

[3] CD4 cell count at drug start available for 73% (314/431) of the DRV group and 76% (281/372) of the ATV group

[4] CD4% at drug start available for 74% (317/431) of the DRV group and 71% (264/372) of the ATV group

[5] Censored at the last recorded visit date for those still on DRV / ATV at last follow-up. For patients on DRV, time on the drug within a company-sponsored trial is excluded.

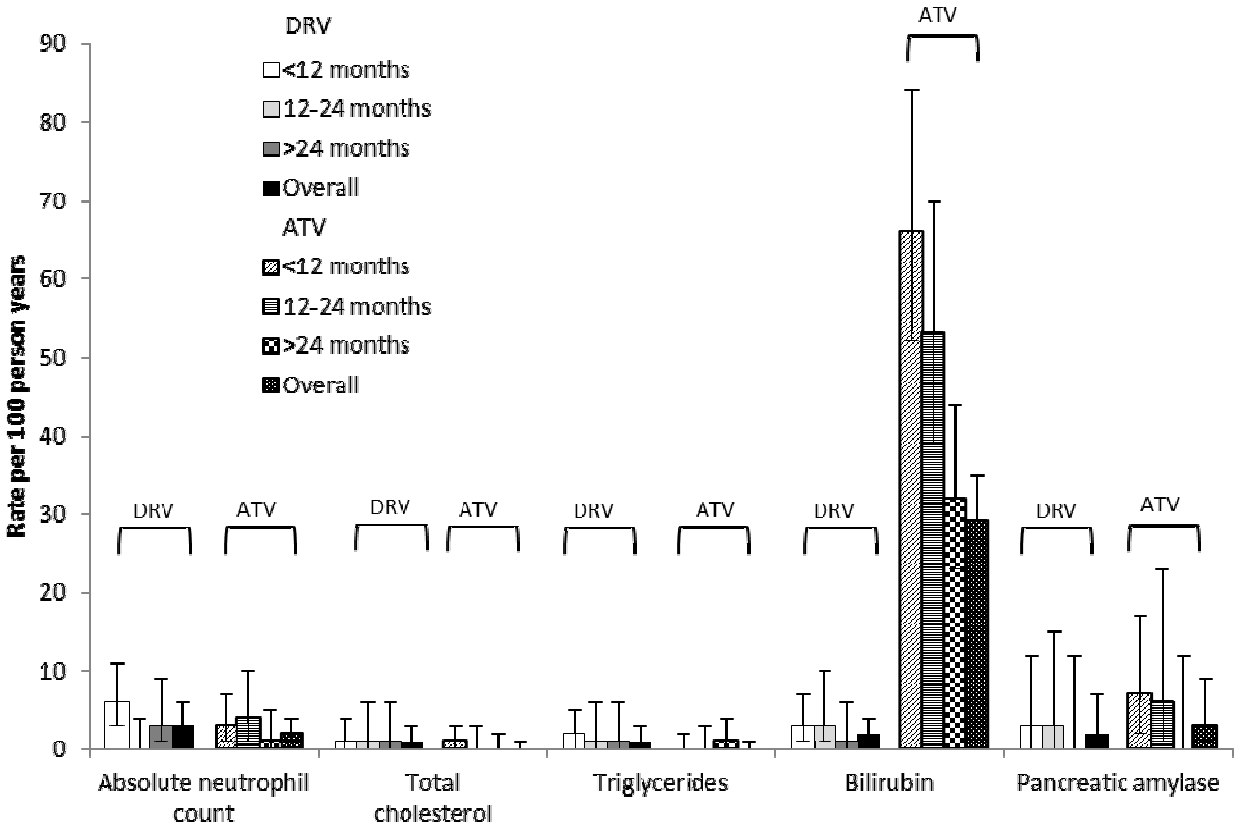

Figure 1: Incidence of grade ≥3 adverse events by duration of DRV / ATV, for 213 children taking the approved dose of DRV and 226 taking an approved dose of ATV with laboratory data available.

Table 2: Timing of and reasons for DRV and ATV drug discontinuations

	DRV (n=431)		ATV (n=372)	
Total not on drug at last follow-up	**48**	**(11)**	**71**	**(19)**
Time to discontinuation:				
<1 month	6	(13)	5	(7)
1 - <6 months	11	(23)	18	(25)
6 - <12 months	10	(21)	12	(17)
≥12 months	20	(42)	36	(51)
Unknown	1	(2)	0	
Reasons for stopping the drug				
Treatment failure[1]	8	(17)	14	(20)
Toxicity / side effects	5[†]	(10)	15[‡]	(21)
Non-compliance	5	(10)	6	(8)
Structured Treatment Interruption	1	(2)	1	(1)
Switch to simpler or more effective regimen	4	(8)	9	(13)
Patient's wish/decision	4	(8)	9	(13)
Physician's decision	1	(2)	1	(1)
Pregnancy – switch to PMTCT regimen	0	(0)	1	(1)
Death	5	(10)	1	(1)
Unknown	15	(31)	14	(20)

[1]Treatment failure includes immunological failure and virological failure

[†]Toxicities / side effects reported among patients stopping DRV were dyslipidaemia (*n*=2), gastrointestinal toxicity (*n*=2) and lipodystrophy (*n*=1)

[‡]Toxicities / side effects reported among patients stopping ATV were renal (*n*=3), gastrointestinal (*n*=2), haematological (*n*=1) or unspecified /other (*n*=9)

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