The prevalence of darunavir associated mutations in HIV-1 infected children in the UK

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ABSTRACT

Background: We examined the prevalence of ritonavir-boosted darunavir (DRV) resistance associated mutations (RAMs) in HIV-infected children in the UK to determine the drug's potential clinical utility as a first or second-line protease inhibitor (PI).

Methods: The prevalence of DRV RAMs, identified from IAS 2010 and Stanford, and the Stanford susceptibility score, were estimated in PI-naive and PI-experienced children in the Collaborative HIV Paediatric Study and the UK HIV Drug Resistance Database 1998-2008. Associations between type/duration of PI exposure and area under the viraemia curve on PI with the number of RAMs were investigated using multivariate Poisson regression.

Results: 17/417(4%) children with a resistance test while PI-naive had one IAS DRV RAM, and one had a Stanford mutation; none had multiple DRV RAMs. 177 PI-treatedexperienced children had a test after a median 2.7(IQR: 1.1-5.2) years on PIs; 19(11%) had one IAS DRV RAM, 7(4%) had 2, 1(0.6%) had 3, and 1(0.6%) had 4. DRV RAMs were independently associated with increased years on a PI, a larger area under the viraemia curve since starting PIs, and any exposure to PIs other than lopinavir (all $p \leq 0.05$). Only 6(3%) PI-experienced children had intermediate-level DRV/r resistance; none had high-level resistance.

Conclusions: DRV resistance was negligible in PI-naive children and those with lopinavir PI exposure alone. However resistance increased with increasing time, and with higher levels of viraemia, on PIs. Once-daily DRV/r would be valuable as a second PI or an alternative first PI, particularly if co-formulated with a booster in an appropriate formulation for children.

INTRODUCTION

The protease inhibitor (PI) darunavir, boosted by ritonavir (DRV/r), has significant activity against both wild-type and multidrug-resistant HIV-1 strains in adults [1-3], and is virologically effective and generally well tolerated in PI-experienced children [4]. Currently, lopinavir (LPV/r) is the preferred first PI in children in Europe [5] and US [6], largely because it is the only co-formulated PI, and is licensed for all ages and weights in tablet and syrup formulations. DRV/r is licensed in children aged ≥6 years as a twice-daily tablet [7] while 24-week data on the safety and efficacy of a DRV/r suspension in 3-6 year olds (ARIEL, NCT0091985) [8] recently found DRV/r to be effective in this group with no additional safety findings. A once-daily dosing study (NCT00915655) is ongoing. In the future, a co-formulation of DRV with a PI booster might increase its clinical utility.

Regarding resistance, the presence of ≥3 DRV resistance-associated mutations (RAMs) at baseline has been associated with diminished virological response to DRV/r in the POWER [9] and DUET [10] trials in adults. However, in another adult study of ~232,000 resistance tests on clinical samples (with unknown ART history) from 2003-2009, only 3% of patients had ≥2 DRV RAMs and 94% harboured none [11], with the prevalence of RAMs having decreased over time. In the ARIEL trial, 2 children with one or two DRV RAMs at baseline had HIV-RNA <50c/ml at 24 weeks [8]. Conversely, the protease mutation V82A has been linked to improved response to DRV/r in adults with multiple DRV RAMs [12].

As DRV/r may be used more frequently in children in the future, as first PI and/or as second PI after previous PI failure (most likely following LPV/r), estimating the prevalence of RAMs in children is important to ascertain its potential clinical utility in this population.

METHODS

Details of the Collaborative HIV Paediatric Study (CHIPS) have been published elsewhere [13]. Briefly, HIV-infected children born in the UK or Ireland or presenting to health services are reported to the National Study of HIV in Pregnancy and Childhood and followed up in CHIPS. CHIPS is linked on an annual basis to the UK HIV Drug Resistance Database, a central repository for resistance tests performed as part of routine care throughout the UK; most of these (~90%) tests are viral gene sequences. Resistance data for this analysis were available to the end December 2008. All three studies have research ethics committee approval.

Mutations associated with resistance to DRV were identified from IAS 2010 [14] (V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, L89V), a list of RAMs updated by the IAS Drug Resistance Mutations Group using published or presented study data. Additional mutations were identified from the Stanford database (I47A, G73S/T/C, I84A/C, V82F), Stanford University, US, which links HIV reverse transcriptase and protease sequences to individual drug-treatment histories and drug susceptibility data. As V82A has been associated with an increased susceptibility to DRV/r [11], it was considered in additional analyses.

The prevalence of DRV RAMs was calculated in PI-naive children (on other combination antiretroviral therapy (ART) or ART-naive) using the first available resistance test for each child prior to PI use to evaluate the extent of transmitted drug resistance and the potential use of DRV as a first PI. In PI-experienced children, cumulative resistance [15] at the last available test on PI, before any use of darunavir, was calculated to evaluate the prevalence of resistance to DRV as a subsequent PI. Multivariate Poisson regression with backwards elimination (exit p=0.10) was used to examine associations between the number of RAMs and years on a PI, area under the log viraemia curve (time-averaged, censoring at <400 copies/ml as <50 copies/ml assays were not always used), and type of PI, adjusting for sex, ethnicity, place of birth, and age and disease parameters at presentation and resistance test. In addition,

susceptibility to DRV was assessed using the Stanford database algorithm which classifies individual drug resistance as susceptible, potential low-level, low-level, intermediate, or high, based on viral gene sequences.

RESULTS

1,485 UK children were followed in CHIPS during 1998-2008. 1,406 were PI-naïve at the start of the study period or at entry into CHIPS if later than 1st January 1998, of whom 417(30%) had a PI-naïve resistance test. 1,154(78%) UK children had taken ART between 1998 and 2008 inclusive. Of these, 620(54%) had taken a PI, most commonly LPV/r (442, 71%) or nelfinavir (NFV 271, 44%), and less frequently DRV/r (15, 2%: 5 once-daily).177 of the 620(29%) had a resistance test whilst on a PI, but before the use of DRV if ever taken.

Demographics and immunological and virological parameters at the time of the first available test for PI-naive children, and last test for PI-experienced children, are presented in Table 1. PI-experienced children were older at their last test than PI-naive children at their first test and a higher proportion had progressed to CDC stage C.

The type and number of DRV RAMs in PI-naïve and PI-experienced (split by LPV/r only vs. other) children are presented in Table 2. No PI-naïve child had more than one DRV RAM. Only 3 (4%) children who had taken LPV/r as their only PI had 1 RAM while 16 (15%) children with other PI exposure had 1 RAM and 7 (6%) had 2 RAMs. Only two PI-experienced children had accumulated ≥3 IAS DRV RAMs. One child with 3 RAMs had been exposed to NFV and amprenavir for 8 months without virological suppression and one child with 4 RAMs had been exposed to NFV, amprenavir, and indinavir for 26 months and suppressed their viral load <400 copies/ml for only 4 months. The majority of IAS DRV RAMs were accumulated by the time of the first test on a PI, when 18 children had one, and one had two, mutations.

PI-experienced children had spent a median (IQR) 2.7 (1.1-5.2) years on PIs, with a median (IQR) time-averaged area under the log viraemia curve on PIs of 3.4 (2.8-3.9) copies/ml. 69/177 (39%) had only ever taken LPV/r: the remainder had taken NFV alone (43, 24%), NFV and LPV/r (29, 16%), or a different combination of PIs (36, 20%). In a multivariate Poisson

model, a higher number of DRV RAMs was independently associated with increased years on PI [rate ratio, RR per year = 1.24 (95% CI: 1.10-1.39), p<0.001], larger area under the viraemia curve on PI [RR per $\log_{10}$ higher = 2.81 (95% CI: 1.88-4.18), p<0.001), and exposure to a PI other than LPV/r [RR vs. LPV/r only = 2.92 (1.00-8.68), p=0.05]. The effects of time-averaged viraemia and exposure to a PI other than LPV/r were independent, suggesting that the effect of non-LPV/r PI is not caused purely by increased low-level viral replication or virological failure on non-LPV/r PIs, and there was no evidence of interaction between these two factors (p=0.94). This independence may be the result of differing viral load patterns between those with exposure only to LPV/r and those with exposure to other PIs but this is difficult to investigate within the scope of this paper. No other factors at presentation or at the resistance test were significantly associated with the number of DRV RAMs (p>0.1). Model results were similar using a zero-inflated Poisson model to account for deviations from model assumptions (results not shown).

Using the Stanford algorithm, only six PI-experienced children had intermediate level resistance to DRV and none had high-level resistance. Five of these had 2 IAS DRV RAMs (1 with an additional Stanford mutation) and one had 4. All six children had prior exposure to LPV/r and NFV with four also having at least two other prior PIs (including amprenavir, indinavir, ritonavir, saquinavir, and tipranavir). None had been virologically suppressed on a PI with PI exposure ranging from 2.5-8 years. A further 12 children had low-level resistance and 10 had possible low-level resistance.

An analysis of predictors of susceptibility, as predicted by Stanford, was consistent with the analysis of predictors of the number of DRV RAMs. Susceptibility reduced with increasing time on PIs (8/96 (8%) children with <3 years PI exposure had possible low-level or higher level resistance vs. 20/81 (25%) with 3+ years, chi^2 p=0.003), a greater area under the viraemia curve (17/141 (12%) children with <4 $\log_{10}$ copies/ml had low or higher-level resistance vs. 11/35 (31%) with 4+ $\log_{10}$ copies/ml, p=0.005), and previous PI limited to LPV/r (0/69 (0%)

children on LPV/r only had potential low-level or higher resistance in comparison to 28/108 (26%) of those with other PI, or multiple PI, experience, $p<0.001$).

DISCUSSION

Ritonavir-boosted darunavir has been shown to be a useful protease inhibitor in HIV-1 infected adults and is increasingly used as first-line PI because of a good tolerability and toxicity profile. Whilst darunavir is virologically effective and well-tolerated in children [4,8], combination ART is a lifelong treatment so it is important to assess how each drug within a class can be used to maximise the overall benefit.

We have shown that resistance to darunavir is extremely rare in PI-naïve children. This finding suggests that with the introduction of paediatric formulations, darunavir could be of potential use as a first-line PI instead of LPV/r in children aged ≥3 years.

DRV/r is increasingly being used first-line in adults, and trials are also evaluating DRV/r in combination with an integrase inhibitor as a nucleoside reverse transcriptase inhibitor (NRTI)-sparing regimen (NEAT-001, NCT01066962). However, currently darunavir and ritonavir are separate formulations, meaning that children either have to take ritonavir as a syrup which has poor palatability, or swallow a large 100mg tablet, which cannot be crushed or split. If tablets are used rather than lower doses of syrup for tolerability reasons, then plasma levels of darunavir may also be higher. Experience to date suggests that major and/or treatment-limiting toxicities for darunavir are rare [1-4].

In our study the prevalence of DRV RAMs was also low in those whose only previous PI exposure was LPV/r, the current first choice PI. It was higher in those with exposure to PIs other than LPV/r and this observed increase is unlikely to have been solely due to virological failure on other PIs, as these effects were observed independently. We also saw more resistance with increasing time, as well as with higher levels of viraemia, on PIs. However, despite these significant effects, only 2 (1%) PI-experienced children had ≥3 IAS DRV RAMs and 6 (3%) had intermediate level resistance using the Stanford algorithm, suggesting that DRV

is likely to also be useful as a second PI after LPV/r (or even other PIs). Indeed all children with ≥3 IAS DRV RAMs or Stanford intermediate level resistance had been on multiple PIs (nelfinavir, amprenavir, indinavir, ritonavir, saquinavir, and tipranavir, now less favoured treatment options) for at least 3 years and none had any significant period of virological suppression on a PI. Therefore, darunavir could also be of use as a second-line PI regimen in children with intolerance to prior PIs even if the viral load has not been continuously suppressed.

In conclusion, we found negligible DRV resistance in PI-naive children, and in those with PI-experience the prevalence of resistance to darunavir was also extremely low. Therefore darunavir/ritonavir should be considered as a first PI treatment option in children and it could also be a very useful PI in a second-line regimen.

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Table 1: Demographics and immunological and virological characteristics of PI-naïve and PI-experienced children with an available resistance test

		First resistance test while PI naïve N = 417		Last resistance test on PI before any use of DRV/r N = 177	
Sex	Female	224	(54)	87	(49)
Ethnicity	Black African	351	(85)	137	(79)
	White	24	(6)	20	(11)
	Other	38	(9)	19	(11)
Born abroad		226	(54)	70	(40)
Median (IQR) age at presentation (years)		3.3	(0.6-7.9)	1.5	(0.2-5.1)
CDC stage C at presentation		31	(7)	22	(12)
Median (IQR) HIV-RNA at presentation (c/ml)		89,000	(21,000-400,000)	181,994	(48,900-573,151)
Median (IQR) CD4% at presentation		20	(14-28)	18	(10-29)
Subtype	C	208	(55)	58	(42)
	A	79	(21)	31	(23)
	B	23	(6)	19	(14)
	Other	66	(18)	30	(22)
Median (IQR) age at resistance test (years)		8.3	(4.2-11.7)	11.4	(7.0-14.1)
CDC stage C at resistance test		74	(18)	80	(45)
Median (IQR) HIV-RNA at resistance test		29,410	(5,550-113,394)	9,500	(2,314-39,180)
Median (IQR) CD4% at resistance test		20	(14-28)	21	(14-30)

Data are no. (%) of patients, unless otherwise indicated. IQR, interquartile range.

Table 2: DRV/r resistance associated mutations (RAMs) in PI-naïve and PI-experienced children with an available resistance test

Mutation	PI-naïve (n=417)		PI-experienced			
			LPV/r only (n=69)		Other PI experience (n=108)	
IAS 2009						
V11I	2	(0.5)	1	(1)	2	(2)
V32I	3	(0.7)	0	(0)	0	(0)
L33F	0	(0)	0	(0)	9	(8)
I47V	0	(0)	1	(1)	1	(1)
I50V	10	(2)	1	(1)	2	(2)
I54L	0	(0)	0	(0)	0	(0)
I54M	0	(0)	0	(0)	0	(0)
T74P	0	(0)	0	(0)	2	(2)
L76V	0	(0)	0	(0)	6	(6)
I84V	1	(0.2)	0	(0)	7	(6)
L89V	1	(0.2)	0	(0)	5	(5)
Any IAS mutation	17	(4)	3	(4)	25	(23)
1 IAS mutation	17	(4)	3	(4)	16	(15)
2 IAS mutations	0	(0)	0	(0)	7	(6)
3 IAS mutations	0	(0)	0	(0)	1	(1)
4 IAS mutations	0	(0)	0	(0)	1	(1)
Stanford						
I47A	1	(0.2)	0	(0)	0	(0)
G73S	0	(0)	0	(0)	4	(4)
G73T	0	(0)	0	(0)	0	(0)
G73C	0	(0)	1	(0.6)	0	(0)
I84A	0	(0)	0	(0)	0	(0)
I84C	0	(0)	0	(0)	1	(1)
V82F	0	(0)	0	(0)	4	(4)
Any Stanford mutation	1	(0.2)	1	(1)	8	(7)
1 Stanford mutation	1	(0.2)	1	(1)	7*	(6)
2 Stanford mutation	0	(0)	0	(0)	1†	(1)
Other						
V82A	1	(0.3)	3**	(5)	5††	(5)

Data are no. (%) of patients.
* Two children had one IAS DRV RAM and one had two
† Had two IAS DRV RAMs
** One child had one DRV RAM
†† 4 patients had two IAS DRV RAMs

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