

## Outcomes in treatment with darunavir/ritonavir in ART-experienced paediatric patients

**To the Editor:** Increasing development of resistant mutations to first- and second-line antiretroviral (ART) regimens among children is a matter of concern, as limited third-line paediatric ART preparations are available in the public sector.<sup>[1,2]</sup> There are various explanations for this increase,<sup>[3]</sup> including drug interactions leading to reduced bioavailability as seen in tuberculosis (TB) co-infection.<sup>[4,5]</sup>

In children <3 years of age, a first-line ART regimen consisting of two nucleoside reverse transcriptase inhibitors (NRTIs) with the protease inhibitor (PI) lopinavir, boosted with ritonavir (LPV/r), is recommended.<sup>[6,7]</sup> Many children may have resistance mutations to the non-nucleoside reverse transcriptase inhibitors (NNRTIs) because of prior exposure to nevirapine during prophylaxis for prevention of mother-to-child transmission.<sup>[8,9]</sup>

In a review of children failing first-line ART in resource-poor countries, at least 54% had major PI mutations.<sup>[2]</sup> It is therefore imperative for paediatric formulations of new antiretrovirals to be developed and be accessible for these children.<sup>[10,11]</sup>

Darunavir, a PI, boosted with ritonavir (DRV/r), has been shown to be effective in viral suppression in PI-experienced patients and has a low side-effect profile.<sup>[12]</sup> The drug has been tested clinically in South Africa (SA) and found to be safe and effective in PI-experienced paediatric participants.<sup>[13,14]</sup> DRV has since been registered for paediatric use in SA in children aged ≥3 years,<sup>[14]</sup> but is available only in the private sector and at the discretion of the paediatric third-line committee in the public sector.

We conducted a retrospective chart analysis of the outcomes of patients receiving DRV/r at Harriet Shezi Clinic (HSC), a paediatric ART clinic based at Chris Hani Baragwanath Hospital, Johannesburg, SA. Five of the 1 128 children currently on follow-up at HSC received DRV/r as part of their antiretroviral regimen from September 2010 to March 2014. DRV was obtained for these children from the manufacturer through a compassionate use programme with the permission of the SA Medicines Control Council (MCC). Permission to study the children was obtained from the bioethics committee of the University of the Witwatersrand (M130760) in 2013. Informed consent was obtained from the caregivers for use of DRV, as it was not registered in the country at the time.

Sociodemographic, laboratory, anthropometric and clinical information for the five patients was extracted from the clinic database. Standard-of-care viral loads and CD4 counts conducted by the National Health Laboratory Service were assessed. Genotype resistance testing was done by the Division of Virology, Stellenbosch University, using the Stanford University HIV Drug Resistance Database for interpretation of the resistance tests.

The median age of initiating first-line PI-based ART in the five children was 3.8 months (range 1.4 - 57.7), and all had World Health Organization stage 3 HIV infection or higher. The median time to virological failure after first-line ART initiation was 30.4 months (range 15.4 - 50.6). All had at least three major PI mutations, V82A, M46L and I54V, which reduced susceptibility to LPV/r. Notably, four of the five patients were on concomitant TB treatment and therefore received double-dose LPV/r; the fifth child was on suboptimal ART for socioeconomic reasons.

The median age at DRV/r initiation was 50.3 months (range 38.5 - 106.7). The baseline median weight-for-age z-score (WAZ) was -0.79 (range -0.65 - -0.94), and the median height-for-age z-score (HAZ) was -0.88 (range -0.82 - -0.97). WAZ and HAZ scores remained constant over 24 months.

Median time to virological suppression on DRV/r was 6 months (range 3 - 12). There were viral rebounds in three of the five patients, but all remained suppressed at 24 months. CD4 counts remained constant. There was no hospitalisation or any significant morbidity on DRV/r.

We found that it was feasible to use DRV/r in a public healthcare setting and achieve virological suppression by 24 weeks. Despite viral rebounds the children managed to resuppress and maintain suppression at 24 months of follow-up, with adequate adherence counselling. These findings are similar to the ARIEL study, which included children with a similar drug resistance profile;<sup>[13]</sup> virological suppression was observed in 56% of the ARIEL participants at 24 weeks and in 81% by week 48.<sup>[14]</sup>

While lipid profiles were not monitored, which is one of our limitations, there were no major safety concerns. We recommend that paediatric preparations of DRV be readily available at tertiary paediatric healthcare facilities so that children failing an LPV/r-based regimen can be treated at the discretion of the treating physician and without resort to a third-line committee. We would like to highlight the importance of adequate super-boosting of LPV/r in children co-treated for TB to ensure that virological suppression is maintained during co-treatment.

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### Gurpreet Kindra

*Wits Reproductive Health and HIV Institute, University of the Witwatersrand, Johannesburg, South Africa*  
gurpreetkindra@gmail.com

### Nosisa Sipambo

*Wits Reproductive Health and HIV Institute, University of the Witwatersrand, Johannesburg, South Africa, and Chris Hani Baragwanath Hospital, Johannesburg*

### Harry Moultrie

*Wits Reproductive Health and HIV Institute, University of the Witwatersrand, Johannesburg, South Africa*

### Lee Fairlie

*Wits Reproductive Health and HIV Institute, University of the Witwatersrand, Johannesburg, South Africa, and Chris Hani Baragwanath Hospital, Johannesburg*

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