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HIV drug resistance in HIV-infected children

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The global roll-out of antiretroviral therapy (ART) in children still lags significantly behind that of adults, and data on treatment outcomes from resource-limited settings have only recently begun to emerge. As a result, while there is a wealth of literature on patterns of drug resistance in adults on ART, there is still limited data on children.

Almeida et al. report, in this issue of the journal, a retrospective study on the prevalence and patterns of antiretroviral drug resistance in 24 treatment-naïve and 23 treatment-experienced children failing therapy between 2000 and 2004 attending a clinic in São Paulo.[1] All children were vertically infected, and the median age of the naïve- and treatment-experienced children was 22 months and 102 months, respectively. In the children failing ART, the median duration of ART exposure was 60 months (range 3-120 months), and the log viral load at treatment failure was 5.04 log copies/mL. The overall distribution of subtypes among both groups of children was 78.3% subtype B, 13% subtype F, 4.4% BF mosaics and 4.3% subtype C, which reflects the distinctive molecular epidemiology of HIV-1 in Brazil, with the low-level but rising prevalence of subtype C infection in the south of the country.[2]

See related article on page 104

There are no surprises in their findings. There was an absence of resistance mutations among vertically infected ART-naïve children, but ART-experienced children had extensive drug resistance. The absence of primary resistance largely reflects the fact that none of the mothers had received ART prior to delivery, and that only two children received zidovudine in the first 6 weeks of life. These findings also highlight the ongoing problem of suboptimal uptake of HIV testing among pregnant women that would enable access to effective prevention of mother-to-child transmission (PMTCT).

Among treated children failing therapy, there was an almost universal presence of nucleoside reverse transcriptase inhibitor (NRTI) resistance mutations, particularly T215Y/F, M184V/I and D67N, M41L and K219Q/E, reflecting the widespread exposure to zidovudine and lamivudine. Overall, 60.8% also had resistance mutations to non-nucleoside reverse transcriptase inhibitors (NNRTIs) (K103N 39.1%) and to Y181C (17.4%), but these were present in all 12 children that were failing on NNRTIs. The most commonly used protease inhibitors (PIs) were unboosted – ritonavir and nelfinavir –, and primary PI resistance mutations were observed in 47.8%, particularly V82A, M46I, and L90M. These findings concur with previous reports from other pediatric cohorts in Brazil.[3-5]

One of the difficulties in the interpretation and generalizability of these findings is the limited information on duration of treatment failure. Although the authors state that the median duration of ART in those failing therapy was 60 months, where failure was defined either as a decrease in viral

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load of less than 1 log after 12 weeks of highly active antiretroviral therapy (HAART), or an increase of greater than 0.5 log, it is not clear how long the children had been failing therapy when the resistance testing was performed.

The most striking difference between resistance patterns in adults failing first-line therapy in resource-poor compared to resource-rich settings has been the much more extensive resistance at treatment switch. This is a result of the lack of routine viral load monitoring, and the use of clinical and immunological criteria to determine treatment failure, such that patients usually have had prolonged virological failure at the time of resistance testing. In a recently published meta-analysis of clinical trial and cohort data of patients failing first-line therapy with two NRTIs and one NNRTI, the prevalence of resistance was substantially higher in the resource-poor settings (NNRTI resistance: 91.1%, M184V: 69%, any thymidine analogue mutations - TAM: 11.2%) compared to the resource-rich settings (NNRTI resistance: 57.3%, M184V: 37.2%, any TAM: 1%).[6] The more ready access to routine viral load monitoring in Brazil should mean a resistance profile more comparable to that observed in Europe and North America. However, the limited availability of various second- and third-line treatment options even in Brazil means that children may remain on a regimen even when persistent virological failure has been demonstrated.

There are also issues with the generalizability of these study findings. The study was conducted more than 5 years ago, when the pediatric roll-out in Brazil was at an early stage, unboosted PIs (ritonavir and nelfinavir) were in common use, and treatment switches with a failing regimen were more likely to be delayed. I would anticipate that the level of resistance at first-line treatment failure would now be lower.

What are the implications of these findings? The high levels of resistance observed in children failing first-line therapy are of particular concern because of the limited future treatment options in the setting of young age, and the longer need for ART compared to adults. There is an urgent need to explore strategies to prevent and minimize the impact of this high level resistance through the use of more frequent viral load monitoring to identify failure early, and identifying second-line regimens for which first-line resistance is not an issue, e.g. boosted PI monotherapy, or PI with an integrase inhibitor. Raltegravir is a potent and selective HIV-1 integrase inhibitor approved for use in adults that achieves good rates of virological suppression in those with extensive drug resistance to NRTIs and NNRTIs. Preliminary data suggest that raltegravir is generally safe and well tolerated in children, but it requires further evaluation in the setting of pediatric treatment failure.

This paper also reinforces the importance of improved standardization in the reporting of resistance data from studies to allow comparisons to be made. A minimum reporting standard for treatment-experienced patients should include baseline CD4 and viral load, type of first- or second-line regimen and use of an unboosted PI, frequency of viral load monitoring, definition of virological or treatment failure, percent of patients who experienced virological or treatment failure, and duration of virological failure and viral load at resistance testing.

The reporting of the genotypic data also needs to be standardized. The authors highlight the variability across studies in the prevalence of mutations to stavudine, due to differences in the mutations reported. In addition to reporting the clinically relevant mutations to each class and drug, it is also helpful to present the number of TAMs and how many had resistance to all three classes.

Periodic surveys to assess the prevalence of drug resistance in ART-naïve children are of value particularly in the setting of an active PMTCT program. For these studies, it is important to specify the time period, use and type of MTCT in the mother and ART in the neonate, as well as age at resistance testing. Such surveys can also serve to monitor the changing local molecular epidemiology and distribution of HIV-1 subtypes among children.

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