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High Prevalence of Abacavir-associated L74V/I Mutations in Kenyan Children Failing Antiretroviral Therapy

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Abstract

A survey of 461 HIV-infected Kenyan children receiving antiretroviral therapy found 143 (31%) failing virologically. Drug resistance mutations were found in 121; 37 had L74V/I mutations, with 95% receiving abacavir (ABC)-containing regimens. L74V/I was associated with current ABC usage ($P = 0.0001$). L74V/I may be more prevalent than previously realized in children failing ABC-containing regimens, even when time on treatment has been short. Ongoing rigorous pediatric drug resistance surveillance is needed.

Keywords

HIV drug-related mutations; abacavir; antiretroviral therapy; pediatrics

In sub-Saharan Africa, where 91% of the world's 3.2 million HIV-1-infected children reside, access to pediatric antiretroviral therapy (ART) has significantly increased, leading to reductions in mortality and morbidity.[1] In Kenya, an estimated 66,070 children were on ART by the end of 2014, accounting for 45% of Kenyan children that are ART-eligible.[2] Over time, some of these children may experience ART failure, which can be associated with the acquisition of HIV-1 drug resistance (HIVDR). This may compromise future treatment options, especially among children, given the limited number of pediatric ART regimens available in resource-limited settings (RLS).[3] It was anticipated that even more children will be initiating ART in Kenya following the expansion of eligibility criteria in 2014.[4]

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Continued success of pediatric ART programs will require understanding of the prevalence and patterns of HIVDR among children failing ART.

Abacavir (ABC) is one of the World Health Organization (WHO)-preferred nucleoside reverse transcriptase (RT) inhibitors for the treatment of HIV infections among children less than 10-year old[5] and has been rapidly incorporated into national guidance documents in RLS, including Kenya.[4] As ABC usage in children has become more widespread, mutations, such as L74V/I, which confer resistance to the drug will become more relevant. However, there are limited data available on L74V/I mutations among children receiving ABC-based ART, especially when routine virologic monitoring is not available. One study in South Africa found high frequency of drug resistance mutations (DRMs) after ABC exposure in children, with virologic failure (VF) referred for resistance testing.[6] Our study describes the prevalence and characteristics associated with RT DRMs at position L74 among children found to be failing ART as part of a national survey in Kenya.

METHODS

A cross-sectional HIVDR survey was conducted in Kenya at 15 ART sites selected using a purposive nonprobability algorithm to identify sentinel sites that represent facilities offering ART in Kenya. On-site sampling size was determined by Lot Quality Assurance Sampling. Children ages 1 through 14 years and retained on ART for 12 to 36 months were enrolled consecutively during routine visits from the 15 ART sites from April to August, 2013. ART program treatment numbers were used to ensure that there were no duplications. Written informed consent was obtained from children's parents or guardians along with assent as per Kenya national policy. Ethics approval was obtained from the Scientific Steering Committee of the Kenya Medical Research Institute and the US Centers for Disease Control and Prevention (CDC). Dried blood spots (DBS) were collected for viral load (VL) quantification and subsequent genotyping in cases of VF, defined as VL ≥1000 copies/mL. DBS were collected on Whatman 903 cards by spotting each of the 5 preprinted circles with 100 μL of whole blood collected by venipuncture. These were dried overnight, then placed separately in glassine envelopes, packaged in sealed bags containing 10 desiccant sacks and 1 humidity indicator and stored at ambient temperature until transported to a processing laboratory via twice-weekly courier and stored at −80°C. Samples were later shipped at ambient temperature to the WHO-designed specialized drug resistance laboratory in the CDC's International Laboratory Branch in Atlanta, GA, for VL and HIVDR testing.

DBS VL was quantified using NucliSENS EasyQ HIV-1 v2.0 kits (Biomerieux, Durham, NC) using one 100 μL spot per participant. Samples with VL ≥1000 copies/mL were genotyped for HIVDR using American Tissue Culture Collection HIV-1 Drug Resistance Genotyping Kits (Manassas, VA) targeting the *pol* gene region encompassing the protease and the 5′ region of RT genes. Sequences were edited with customized RECall software (British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada)[7] and qualified sequences were submitted to the Stanford HIVdb algorithm (found at http://sierra2.stanford.edu/sierra/servlet/JSierra) to identify DRMs. Levels of HIVDR were interpreted following WHO guidelines for acquired HIVDR.[8] Mean, median and interquartile range were used for descriptive analysis of numerical variables as appropriate.

Association of antiretroviral and L74V/I mutations were assessed by the Fisher's exact test. All tests were 2 tailed. $P < 0.05$ was considered statistically significant. Sample sizes for specific mutations were too small for adjustments to be made for clustering. Data analysis was performed using SPSS 21.0 software (SPSS Inc./IBM, Chicago, IL).

RESULTS

Of the 462 HIV-1-infected children enrolled, 461 had VL results available and were included in our analysis. The most common ART regimen components among participating children were nevirapine and lamivudine (3TC) plus either ABC or zidovudine (AZT). Of the 143 (31%) having VF, 136 (95%) were successfully genotyped and 121 (89%) harbored ≥1 DRM.

Overall, 297 (64.4%) children were on ABC-containing regimens, with a median age of 6 years (interquartile range 3–9); 84 (28.3%) had VF. Of the 121 children on any regimens with DRMs, 37 (31%) harbored L74V/I mutations with 35 (95%) being on ABC-containing regimens at the time of sample collection; for 32 of these children, ABC was part of their original ART regimens. Of the 35 children on ABC with L74V/I mutations, 30 had L74V, 4 had L74L/V and 1 had an L74I/V mixture.

The mean duration of ART for children with L74V/I mutations was 750 days (range 140–1127). Detection of L74V/I was associated with ABC use ($P < 0.001$, 2-tailed Fisher's exact test) compared with those not on ABC (Table 1), but was not associated with the concurrent use of nevirapine , efavirenz or lopinavir/ritonavir ($P = 0.34$, $P = 0.24$ and $P = 1.00$, respectively, 2-tailed Fisher's exact test). All 37 children with L74V/I mutations also had M184V and thus high-level resistance to ABC from this combination of mutations. Additionally, 35 (95%) had 1 or more DRMs to non-nucleoside RT inhibitors.

DISCUSSION

This was Kenya's first national survey of HIVDR in children on ART. We found that almost all children on ART with VF and L74V/I mutations were on ABC-containing regimens. L74 mutations alone cause intermediate-level resistance to ABC but when combined with the common mutation M184V as was the case for every child with identified L74V/I in our study, this causes high-level resistance to ABC and likely necessitates a change in the ART regimen to regain virologic suppression. We found high prevalence of these mutations in children with relatively short histories of time of ART.

We were unable to find published reports of DRM for children on modern ABC-containing ART regimens in settings where resistance testing was performed for all cases of VF, as was done in our study. A study conducted in South Africa found a lower probability of viral suppression at 6 and 12 months and a higher probability of virologic rebound for children on ABC-based regimens compared with those treated with stavudine/3TC in both lopinavir/ritonavir- and efavirenz-containing regimens.[9] These findings raised concerns about whether the use of ABC in first-line regimens for children is ideal for achieving long-term virologic suppression in RLS. However, study authors were unable to assess the predicted efficacy of second-line regimens due to the lack of HIVDR data. As L74 mutations have been

associated with continued AZT and tenofovir disoproxil fumarate (TDF) susceptibility[6] and even AZT hypersusceptibility of uncertain clinical significance,[10] there may be benefits to utilize AZT or TDF as second-line choices after failure on ABC-containing regimens rather than the reverse (ABC in the second line after failure on an AZT-containing regimen).

Two children not currently on an ABC-containing regimen had an L74 mutation, and it is unclear if these children had previous exposure to ABC or didanosine (DDI), because the study only collected drug regimen information at ART initiation and at study enrollment. It is possible that other drug changes or substitutions between these 2 time points were not captured. Considering that ABC and DDI are not typically used in HIV-infected pregnant women, it is unlikely that the presence of L74 mutations was secondary to transmission of resistant virus.

Because these results are drawn from a cross-sectional study, we could neither assess the longitudinal association of HIVDR acquisition on all antiretroviral drugs used during the course of follow-up, nor do we have any information on future response to ART in these children. We cannot conclude that accumulation of mutations affecting nucleoside RT inhibitor efficacy would necessarily increase the risk of second-line failure. However, these results are notable for describing HIVDR to ABC among a national sentinel survey of children receiving HIV treatment in a public ART program in RLS. Fortunately, L74 mutations do not interfere with future use of WHO-recommended second-line ART options and the advantages of ABC include good tolerability and ability to co-formulate with other antiretrovirals in pediatric fixed-dose combinations. With such limited choices for children's ART regimens, ABC still carries an important role and further monitoring of HIVDR in these settings is warranted. Routine pediatric surveillance for both acquired and transmitted HIVDR is pivotal for the sustained success of pediatric ART programs, as knowing resistance patterns in children failing treatment will avoid suboptimal regimen switches.

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TABLE 1.

Association Between ABC-containing Regimens and Acquisition of HIV-1 Drug Resistance Mutations at Codon 74 of the Reverse Transcriptase Gene Among Children With Virologic Failure (Defined as Viral Load ≥1000 copies/mL) (n = 137)

Genotype at Codon 74	ABC-containing Regimen (%)	Non ABC-containing Regimen (%)	Total (%)
L (wild type)	45 (45.0) *	55 (55.0)	100 (100.0)
V/I	35 (94.6) †	2 (5.4)	37 (100.0)
Total	80 (58.4)	57 (41.6)	137 (100.0)

* One dried blood spot specimen with invalid viral load result, but successfully genotype was included in the group.

† The difference in prevalence of L74V/I mutations between 2 groups was significant (2-tailed Fisher's exact test, $P < 0.001$).