

Case Report

Development of Dual-class Antiretroviral Drug Resistance in a Child Coinfected with HIV and Tuberculosis: A Case Report from KwaZulu-Natal, South Africa

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Summary

The treatment of concurrent HIV and tuberculosis (TB) in children <3 years of age has not been well-studied and is complicated by potential drug–drug interactions. The recommended antiretroviral therapy (ART) in coinfecting children in South Africa consists of full-strength ritonavir, lamivudine and stavudine. We report on a child initiated on this regimen, during concurrent TB treatment, who promptly developed an adverse reaction, virologic failure and dual-class antiretroviral drug resistance, compromising subsequent salvage ART.

Introduction

In sub-Saharan Africa, tuberculosis (TB) is frequently the initial presentation of HIV infection and, not uncommonly, in severely immunocompromised children, clinicians are compelled to initiate antiretroviral therapy (ART) during concurrent TB treatment. Complicating simultaneous treatment of HIV and TB are important drug interactions,

including the effect of rifampicin in lowering serum levels of both protease inhibitors (PI) and nonnucleoside reverse transcriptase inhibitors (NNRTI). However, there is little evidence-based data to guide clinicians in treating HIV/TB coinfecting children. The World Health Organization recommends—for children under 3 years with HIV/TB coinfection in whom ART cannot be delayed—the use of a triple nucleoside reverse transcriptase inhibitor (NRTI) regimen (i.e. stavudine or zidovudine + lamivudine + abacavir) [1]. However, concerns about the antiviral activity of triple NRTI regimens (and the unavailability of abacavir in some countries) have led to wide variations in the treatment of HIV/TB coinfecting children in sub-Saharan Africa.

In South Africa, which has one of the largest populations of HIV-infected children in the world, national guidelines recommend that when ART cannot be delayed in a HIV/TB coinfecting child below the age of 3 years, that a regimen consisting of stavudine, lamivudine and full-strength ritonavir be initiated [2, 3]. The recommendation rests on pharmacokinetic data showing that when rifampicin is coadministered with a ritonavir, levels of ritonavir—unlike other protease inhibitors—tend to remain therapeutic [4].

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Unfortunately, even in the clinical trial setting, ART regimens that include full-strength ritonavir have not been found to be highly efficacious in young children, possibly because of the unpleasant taste and gastrointestinal toxicity associated with ritonavir [5]. In one US clinical trial, a regimen consisting of full-strength ritonavir plus two nucleoside analogues given to PI-naïve children under 2 years of age (in the absence of concomitant TB treatment) resulted in durable virological suppression in only 36% [6]. We add additional concerns about the use of initial ART consisting of stavudine, lamivudine and ritonavir, as practiced in South Africa, in children under 3 years receiving TB therapy. We present a case of a South African child who developed virologic failure with high level dual-class (PI and NRTI) antiretroviral drug resistance while receiving a ritonavir-based ART regimen, leaving local clinicians few good choices for second-line ART given the limited local formulary.

Case Report

The child was born after a full-term pregnancy to an HIV-infected mother who, prior to the pregnancy, had received stavudine and didanosine dual-therapy intermittently for 2 years (but had never received a PI). During the pregnancy the mother received only single-dose nevirapine. After delivery the infant received short-course AZT and was exclusively formula fed. The mother was initiated on combination ART (stavudine, lamivudine and efavirenz). At 9 months of age—at another hospital—a gastric aspirate from the infant yielded acid-fast bacilli and treatment was initiated for pulmonary TB with rifampicin, isoniazid and pyrazinamide. At 10 months of age, the child and mother presented to our clinic and his initial HIV evaluation revealed a positive DNA PCR, a CD4 cell count of 682 cells/ μ l (14%) and viral load (VL) of 240 000 copies/ml. At this time, he was at the 5th percentile by weight and had generalized lymphadenopathy. A chest X-ray revealed right upper and lower lobe consolidations and an ultrasound showed para-aortic lymphadenopathy. TB therapy was continued with the same agents and ART was delayed to assess a response. At 13 months of age, the child had failed to gain weight and ART was initiated per South African guidelines (for a HIV/TB coinfecting infant) with stavudine, lamivudine and full-strength ritonavir. The child subsequently developed vomiting associated with ritonavir administration and adherence was compromised. After 6 months of ART, there was immunologic and virologic failure with a CD4 cell count of 139 cells/ μ l (7%) and a VL of 2 500 000/ml. A drug resistance test (TRUGENE[®] HIV-1 Genotyping Test on an OpenGene[®] DNA Sequencing System, Bayer Diagnostics, Tarrytown, NY, USA) showed the major reverse transcriptase (RT) mutations K65R

and D67N and the major protease mutation V82A. The mother was referred for adherence counseling.

TB treatment was concluded at 19 months of age. At that time, in line with national guidelines, the child's regimen was changed to zidovudine, lamivudine and lopinavir/ritonavir. There was prompt resolution of the vomiting and 6 months later, the child had improved clinically and immunologically with weight gain to the 10th percentile and a CD4 count of 590 μ l (16%). However, the VL remained elevated at 70 000/ml. At 30 months of age, the VL was still elevated and a second drug resistance testing showed the major RT mutations D67N, K70R and M184V and the major protease mutations M46I, I54V and V82A. At age 3 years, on the same regimen, the CD4 cell percentage declined to 13% (despite a reportedly high level of adherence) and the VL remained elevated at 310 000/ml. There has been associated clinical decline with diarrhea and a 2 kg weight loss.

Discussion

There are no reports describing the development—during simultaneous treatment of HIV and TB in children—of the emergence of clinically significant antiretroviral drug resistance. The existing literature describing HIV/TB coinfection in children does not address this potentially important issue likely because in settings where TB is a common opportunistic infection, access to antiretroviral drug resistance testing has been very limited. However, in the experience at McCord Hospital in Durban, South Africa—where antiretroviral drug resistance assays have been used in children with virologic failure—clinically significant NNRTI and PI resistance has been noted *in particular* among children who have received prior combination ART consisting of two nucleoside analogues and full-strength ritonavir [7]. The major mutations that emerged in this child during the poorly tolerated and nonsuppressive initial regimen (that consisted of stavudine, lamivudine and full-strength ritonavir) created difficult decisions in the design of second-line ART. Predictably, with several major PI mutations, the child had a poor virologic and clinical outcome during lopinavir/ritonavir-based (LPV/r) salvage therapy.

The effect of antiretroviral drug resistance is amplified when the ART formulary is limited. After the development of major PI mutations, the efficacy of a subsequent regimen consisting of lopinavir/ritonavir and two NRTIs (second-line therapy in South Africa) may be compromised. The PI-associated mutations observed in this child after the use of ritonavir, particularly I54V and V82A/F, are known to be associated with poor virologic response to lopinavir/ritonavir [8]. During virologic failure, the child also developed significant NRTI drug resistance, notably the K65R mutation and,

subsequently, several thymidine analogue-associated mutations. It is uncertain if the K65R mutation—which may emerge more readily in subtype C virus—evolved *de novo* in the child or was transmitted from the mother [9]. Regardless, the presence of major NRTI mutations also compromise subsequent triple NRTI or regimens consisting of two NRTIs and a NNRTI.

The preferred initial ART to use in HIV-infected children under 3 years with concurrent TB remains unclear. In this age group, dosing guidelines for efavirenz have not been established and the use of nevirapine-containing regimens during TB therapy have generally been avoided. Triple NRTI regimens, as recommended by the WHO during HIV/TB treatment in young children, are probably less efficacious than NNRTI or boosted PI-based regimens. To address this knowledge gap, clinical studies and more drug formulary options (including rifabutin) are needed in sub-Saharan Africa. Clinical studies of HIV/TB coinfecting children must proceed urgently as TB continues to be the most common presenting opportunistic infection in children with HIV in Southern Africa.

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