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## HIV DRUG RESISTANCE IN A 13 YEAR OLD BOY, A MULTICASUAL PROBLEM

### ABSTRACT

**B**ackground: In 2011, at least 34 million people live with HIV. HIV vertical infected children require close follow-up from all the way through diagnosis to treatment and management of complications.

**Case summary:** This is the case of a 13-year-old male patient with HIV (vertical transmission) diagnosed at 4 months old. His HIV diagnosis was made in the context of opportunistic manifestations of immunodeficiency because his mother did not access prenatal check-ups. He developed AIDS sequelae such as spastic paraparesia derived from HIV myelopathy and CMV retinitis due to immunodeficiency; these diseases presented in first two years of life. After three years from HAART initiation, the patient was exposed to inadequate HAART (ritonavir without another protease inhibitor), and experienced a first change of therapy due to virological failure. Subsequent treatment regimens—a sum of 7—presented failures in their formulation and

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this, along with delays due to administrative issues, led to the patient developing multiresistance to most of antiretrovirals given. The patient died mainly from multiorgan failure due to HIV and wasting syndrome.

**Conclusion:** Congenital HIV is a fundamental issue in public health. It is a preventable disease, and perinatal management, including diagnosis and treatment, is a must. Treatment has demonstrated effectiveness when it is given with proper schemes and adherence. Administrative barriers led to failures in treatment and this affects the prognosis of any patient with HIV. This case is an example that highlights the relationship between virological and clinical failures with health system barriers, in HIV infected children. Managing gaps in diagnosis, antiretroviral administration, and follow up of HIV infected children translates into the prognosis of future adolescents and adults.

**Keywords:** *HIV, children, HIV drug resistance.*

## CLINICAL CASE: DESCRIPTION

The following data was extracted from the complete patient's clinical history, interviews with relatives and the Foundation coordinator.

The patient was the product of third pregnancy of a 27-year-old mother. The patient's mother did not access HIV testing during pregnancy or antenatal care, and we have no information about why she did so. The patient was born at term in a public hospital by vaginal birth. An HIV test was not performed at birth. The patient's parents worked as street vendors and were diagnosed with HIV infection at same time as their son. There is no information about lactation. Mother died by the time the patient was 1 year old due to AIDS related complications (tuberculosis and wasting syndrome). The

father continued to live but had sequelae of neurotoxoplasmosis. The patient's two siblings are not infected. By age of 2, the patient entered a foundation for HIV infected children in Bogotá, where they assumed responsibility for his comprehensive care until death. The patient was affiliated to the contributive health regime, his health care was provided in multiple institutions, but mainly in a third level hospital where he was attended by a pediatric infectologist.

The patient was diagnosed with HIV infection stage C3 by the age of 1 after multiple hospitalizations. His exams showed severe immunodeficiency and multiple opportunistic diseases (pulmonary tuberculosis, myelopathy from HIV with spastic paraparesia and CMV retinitis, malnutrition, *Pneumocystis jirovecii* pneumonia). All this clinical information was validated by specialists through the clinical history. The confirmation test for HIV (western blot) authorization was made with six months of delay. Table 2 shows viral loads and CD4 cell counts over the span of his life as related to ARV regimens.

The first ARV regimen lacked potency (Zidovudine, Didanosine and ritonavir without another protease inhibitor because of a lack of oral solution presentations), leading to incomplete suppression of viral replication, which was interpreted as virological failure. Multiple empirical ARV regimens were given until a necessary viral genotyping was ordered at the age of seven—with a two years delay between when the exam was ordered and when it was actually carried out—. Genotyping showed resistance to all known NRTI's and to PI. Further genotypifications showed new mutations and polymorphisms that confer resistance to almost all ARVs. Table 1 shows the history of antiretroviral resistance mutations and polymorphisms.

Date	Age	Viral Load	Cd4	Art
01/04/2001	17 months	>500.000 copies/mL (Log > 5.70)	185	Zidovudine + didanosine + ritonavir
22/02/2002	2 years, 4 months	800.000 copies/mL	219	Lopinavir/ritonavir + nevirapine + zidovudine
16/06/2004	4 years, 7 months	No data	272	
11/08/2004	4 years, 9 months	210785 copies/mL (Log 5.32)	444	Stavudine + Lopinavir/ritonavir + lamivudine
30/03/2005	5 years, 5 months	>500.000 copies/mL (Log > 5.70)	408	
02/09/2005	5 years, 10 months	423 copies/mL (Log 2.62)	320	
01/02/2006	6 years, 3 months	28934 copies/mL (Log 4.46)	261	
30/11/2006	7 years, 1 month	358.215 copies/mL (Log 5.55)	338	
09/10/2007	7 years, 11 months	>500.000 copies/mL (Log > 5.8)	108	
03/08/2009	9 years, 9 months	405.169 copies/mL (Log 5.61)	15	
02/09/2010	10 years, 10 months	201.177 copies/mL	313	
08/11/2010	11 years	864.917 copies/mL	113	
06/01/2011	11 years, 2 months	646.186 copies/mL (Log 5.81)	165	Raltegravir + Etravirine+Enfuvirtide + Maraviroc
29/06/2011	11 years, 8 months	110.864 copies/mL (Log 5.04)	7	
01/07/2012	11 years, 9 months	185.006 copies/mL (Log 5.27)	4	Raltegravir + Tenofovir/emtricitabine + darunavir
10/01/2013		44.002 copies/mL (Log 4.64)	14	

Table 1. Immunovirologic tests and ARV.

Antiretroviral Group	Mutations And Polymorphisms
Reverse transcriptase inhibitors	M41L, D67N, K70R, Y181C, T215Y, K219E, M184V, T69E, M184, G190A, Y188L, T215F/V
Protease inhibitors	A71V, I54L, I62V, I84V, L10F, L33F, L63P, L90M, M36I, M46L, V82A, K20R, F53L/F, Q58E, K43T, I13V, L89V, V11I, E35D, H69R, G73S

Table 2. Antiretroviral resistance mutations and polymorphisms.

6 months after the genotype results, CD4 had decreased to 66 cell/uL with consequent clinical deterioration that required further hospitalizations. Rescue therapy was initiated, but viral load (VL) continued to rise. A tropism test for the CCR5 co-receptor recommended the use of Maraviroc, a novel therapy that represented an option; however there was a 4 month suspension of ARV because of delay in supply.

The patient received a 5-month treatment with Maraviroc and Enfuvirtide. The VL decreased to 1/8 of the prior count. Nevertheless, the CD4 count continued to decrease from 165 to 7 cells. A new genotypification showed prior resistance plus probable or emergent resistance to NRTI and Non-nucleoside retrotranscriptase inhibitors (NNRTIs). New VL and CD4 cell counts confirmed persistence of virological failure. After one last AR change, the case was presented at a bioethical committee of the last institution where he was attended. They recommended suspension of all ARV drugs because of its lack of effectiveness and administration of analgesia for pain relief in the context of palliative care. The patient died after a complicated respiratory infection 4 months after ARV discontinuation.

## DISCUSSION

This case represents the consequences of the mismanagement of an HIV infected patient at several levels. The first one was the missed opportunity for HIV prenatal diagnosis in his mother while she was pregnant. Poverty due to informal employment affects the access to HIV tests because the economic resources are limited and often they are invested in food and living instead. It is necessary to ensure that all pregnant women access HIV and syphilis tests during antenatal controls, hopefully in first trimester, one way to do this is by rapid point of care tests that do not require administrative authorization or other administrative barriers. Also, HIV tests must be administered during the third trimester and labor.

The second level of failure was directly related to the empiric administration of multiple ARTs to this patient before genotypic evaluation for HIV ART resistance. The elevated viral load and the positive selection induced by multiple empiric antiretrovirals resulted in multi-drug ART resistance, as has been demonstrated in several studies (9 - 11). As in adults, the genotype is an accurate measure for determining the best ART for each patient when virological failure is detected. As such, it must be made as soon as the failure is diagnosed (30).

Drug resistance cases in children may become a public health problem since they behave as regular adolescents and adults, with a high risk of spreading the infection, leading to the consequences that that implies (31, 32).

The delay in health services and the excess of administrative procedures that are present in Colombia's health system affects the clinical course of pathologies such as HIV and AIDS related complications. This leads to cases undertreated sequelae and the loss of life expectancy, especially in children.

Due to the great capacity of the HIV virus to acquire resistance to drugs, it is necessary to provide the best of care to HIV patients, and especially prenatally infected pediatric patients, in terms of early diagnosis, HIV resistance evaluations, and ART treatment (33). This includes the availability of resistance testing to select the best ARV combination for each patient and a multidisciplinary approach to determine the best course of management in cases of reactivation and re-emergence of latent virus when the conditions are favorable.

## CONCLUSION

This case highlights the challenge of middle and low income countries in the diagnosis, evaluation, and treatment of HIV infected children. There is a peremptory need to continue efforts to guarantee antenatal controls and HIV tests for all pregnant women. Women in poverty must be a priority for these programs. Physicians that treat HIV positive children must be trained in this specific issue, Clinical Practice Guidelines must be taken account, especially now that guidelines were published in 2015 with evidence-based recommendations. The adherence to guidelines will lead to fewer undertreated children and a better quality of life for this population.

The access to health system services must be assured in order to apply the guideline's recommendations, especially when diagnostic procedures and antiretrovirals are not included in the health plan. There must be an adequate approach to management including not only the treatment of sequelae and the complications of pathologies but also prevention.

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