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VERTICALLY-TRANSMITTED SECOND GENERATION HIV AND MULTIPLELY TRANSMITTED ANTIRETROVIRAL RESISTANCE

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ABSTRACT

More than 30 years have elapsed from the first reports of children with vertically transmitted HIV (TV) to the present. (1-2-3) This summary intends to share the experience in the complexity of choosing an antiretroviral treatment for a child born with second generation HIV of vertical transmission, assisted in the pediatric hospitalization unit 29 of the FJ Muñiz hospital, who was the first case treated in this hospital.

KEY WORDS : HIV 2nd GENERATION MULTI-RESISTANCE

INTRODUCTION

In Unit 29 of the Muñiz Hospital, a few years after the start of the HIV pandemic, we began to assist the first cases of children who acquired the infection through vertical transmission. This form of contagion includes pregnancy, childbirth, the moment of greatest transmission of the infection, and breastfeeding. (3-4) (9) (12) In the eighties there were the first births of children infected by vertical transmission. (9) Mortality in pediatric patients was higher than in adults due to the lack of antiretroviral treatment, the immunological immaturity of the pediatric patient and the immunodeficiency itself caused by HIV, with a mortality rate higher than that of adults, mainly in the first 5 years of children's lives. (12) The majority of children who died from infection during the eighties and nineties died due to a lack of pediatric treatment and due to the little knowledge there was about the behavior of this virus in pediatrics. (9) (12) Of these children, those who managed to survive and reach adolescence or adulthood did so due in part to carrying a low-virulence virus and the possibility of starting treatment when drugs adapted to pediatric patients became available. , which happened at the end of the nineties, and also to the adherence that many families had at that time. (13-14) With time and learning about the behavior of the virus in this age group, interdisciplinary work was essential, adapting the work of health teams to family needs, such as accompanying children during the death process of family members, parents, siblings, interpret the new scenario of AIDS orphans, escort or guide grandparents, relatives, neighbors, or strangers, who were in charge of these children and would be in charge of administering daily treatment and for life with little hope. (10) Starting in the year 2000, many infants had pediatric formulation medication available and grew up in families affected by this disease, but with the possibility of treatment. (15) At the time, the biggest problem was adherence to antiretroviral treatments, and it still is today. (15)

Over the years we have gained experience and we can say that many of the children who grew up with the example of poor adherence, upon reaching adolescence and adulthood, had poor adherence. There are exceptions, but they are the least. Most of the women who became pregnant after acquiring the infection through vertical transmission with a history of poor adherence in their childhood, improved between 90 to 100% their adherence to ARV treatment until the birth of their children, the aim was to avoid transmission vertical since they knew their carrier status from the beginning of the pregnancy.

MATERIAL AND METHODS

There are very few reported cases of second generation infected children of vertical transmission.

The case of this second-generation child with vertical transmission and its evolution up to the present, occurred in a context of poor adherence, first from his grandmother to the patient's mother, which the young woman later maintained in her adolescence and during pregnancy. The boy is currently 11 years old, the son of a young woman who gave birth to him at the age of 19, she was born in 1991 and died a year after the birth of her son.

Family background

Child's mother: 19-year-old, HIV+ (TV) with poor adherence to antiretroviral (ARV) medication. Diagnosed for HIV at the age of 6, due to the death of the father due to an Isoniazid TB-R that he also infected his daughter. During childhood, adolescence, and pregnancy, she had poor adherence to all indicated ARV treatments. It should be noted that poor adherence to ARV treatments in children is always the responsibility of their adult guardians, even when they achieve their own autonomy.

DATE	CD4	%	CV	LOG-10	TT	NOTE
04/1998	290		128,000	5.1	AZT/DDI/RTV	TT. P/ TBC R/E/P/PIR
05/1999			165,000	5.2	AZT/DDI/IDV	intoleranceRTV
10/1999	364	17	157,000	5.2	AZT/DDI/IDV	
03/2000	214		>750,000	>5.7	DDI/d4T/NVP DDI/d4T/ABC	NVP allergy
07/2000	429		8,200	3.92		
10/2000			31,900	4.51	3TC/d4T/ABC	
02/2001	397	16%				poor adherence
06/2001	260	17%	213,000	5.33		
12/2007	637		2,710	3.64	d4T/DDI/ rTV /NFV	
04/2002			5,280	3.73		
08/2002	420	twenty-one%	11,700	4.07		poor adherence
02/2003	473		66,800	4.83	d4T/DDI/ rTV /IND	
07/2003	517		16,500	4.22		
03/2004	206		>100,000	>5		poor adherence
07/2004	146		495,000	5.7	AZT/DDI/IND/ rTV /EFV	poor adherence
12/2004			>750,000	>5.7		poor adherence
01/2005	251	eleven%	149,000	5.18		
07/2005	173	9%	213,000	5.33		poor adherence
11/2005	163	10%				
12/2005	103	10%	334,000	5.5	ABC/d4T/DDI/EFV	poor adherence
01/2006	357	eleven%	150,000	5.3		
05/2006	202	eleven%	57,000	4.57		
08/2006	177	12%	59,000	4.7		
11/2006	125	9%	590,000	5.7		poor adherence
01/2007	121	10%	390,000	5.6		Test R.
10/2007	107	6%			RESISTANCE TEST	AIDS C3
08/2008	107	6%				TBCMR
09/2008	113	6.3%	94,000	4.92	ABC/3TC/AZT/LPV/ rTV	AIDS C3
01/2009	47	4%	134,000	5.1		
03/2009	63	7%			T20/AZT/3tc RESCUE	MNG/TBCMR
05/2009	Four. Five	4%	549	2.74	RALTEGRA/AZT/3TC	
12/2009	79	8.2%	<400	<2.2		pass adult
08/2010	Four. Five					Pregnancy/AIDS
01/2011	66	4%	89,000	4.8		Pregnancy
03/2011					RESISTANCE TEST	birth son
01/2012	twenty-one	2%				AIDS C3
03/2012	27	3%				
04/2012	24	3%				
06/2012					DRV/RTV/RALT/FTC	
08/2012	19	2%			DRT/ Rtv /T20/MARAV	
12/2012						DEATH

The experience documented in the bibliography, and the recommendations of the WHO, PAHO, and the national Ministry of Health, report that correct compliance with ARV treatment during pregnancy, administering IV zidovudine during delivery or cesarean section to the mother, and administering for 45 days zidovudine syrup orally to the baby, decreases vertical transmission to 1%.(9-11) Not taking ARV medication during pregnancy or childbirth, or not stopping breastfeeding, increases the possibility of vertical transmission to more than 30%. , with a higher risk of transmission at the time of delivery 80%, during pregnancy 20% and during lactation from 15 to 20%.

Viral loads (CV) in the mother of the last trimester, greater than 1000 to 10,000 copies increase the possibility of vertical transmission from 1% to 12%, and viral loads (CV) greater than 10,000 copies increase the possibility of transmission of 9% at 29%. (9-11)

The case of this young mother was an *UNSCHEDULED PREGNANCY, with POOR ARV ADHERENCE.*

At the time of the child's birth, an emergency caesarean section was performed due to ruptured membranes.

At the time of the child's birth (March 2011), the young woman had CV 116,000 log 5. The mother's clinical condition was very delicate, AIDS C3, disseminated CNS Tuberculosis (MR-TB) (peñasco meningoencephalitis and osteomyelitis) and sequelae of facio - brachio -crural hemiplegia . *RESISTANCE TEST (TR) ONLY SENSITIVE PROTEASE INHIBITORS (PI).*

The mother dies a year after the birth of her son (2012) due to maintaining a lack of adherence to ARV treatment, with the consequence of severe immunodeficiency and the presence of opportunistic infections that ended the life of the patient at the age of 21.

PATIENT ("MAVI")

Child born in March 2011, preterm , in a public hospital, due to ruptured membranes, an emergency caesarean section was performed.

The child presented a PCR from the month of birth, March 2011, and another from 1 (one) month of life, April of the same year, POSITIVE for HIV.

At 50 days of life, he was admitted to our unit, room 29 of the FJ Muñiz Infectious Diseases Hospital, the reason for hospitalization was HIV AIDS stage, second generation of vertical transmission (HIV/AIDS) TV, febrile syndrome, sepsis, poor progress growth, 2 PCR positive for HIV.

Studies carried out from birth until obtaining the result of the resistance test (RT) requested in April 2011:

03/2011 PCR positive
04/08/2011 PCR positive
04/12/2011 CV 182,000 log10 5.27 (endurance test)
05/10/2011 CV > 750,000 log10 > 5.7 CD4 2062 (27%)

Resistance test (RT) result of the child and comparison with the mother's TR:
Transmission of ARV resistance to the child from the mother is observed.

RESULTS OF THE CHILD'S RESISTANCE TEST April 2011

Resistance and possible Resistance All NRTIs and all NRTIs
Sensitivity All IP

For this child, the possible alternatives of pediatric antiretroviral treatments were thoroughly evaluated, because due to the ARV resistance transmitted by his mother, he had no therapeutic possibilities with the available pediatric ARVs . In addition, the child presented poor clinical, immunological, and virological progress, with the urgency of a HAART rescue.

PEDIATRIC ARV AVAILABILITY FOR THE YEAR 2011:
Pediatric Antiretroviral Medication
Presentation and doses available for pediatrics in 2011

INRT SYRUP INNRT SYRUP IP SYRUP
(NUCLETOTIDE INHIBITORS OF (NON-NUCLETOTIDE INHIBITORS OF REVERSE TR.) (PROTEASE INHIBITORS)
Zidovudine (AZT) Nevirapine (NVP) Lopinavir / Ritonavir (LPV/ rtv)
Lamivudine (3tc) Fosamprenavir (FPV)
Abacavir (ABC)
Stavudina (d4t)

SITUATION
50-day-old patient
Weight 3.5 Kg (Pc 3-10 -2DS -1DS)) (low weight)
Virological and clinical failure
CV > 750,000 log > 5.7

POSSIBLE TREATMENTS (16-17-18-19)
2IP: Lopinavir / Rtv (Kaletra) + Fosamprenavir (FVR)
Not recommended 2 PI in pediatrics
Not recommended as a first outline
No experience in infants

It is decided due to the impossibility of other therapeutic presentations to start ARV treatment with:
IP 2 (two) pediatric presentations.
FOSAMPRENAVIR (sol.).
LOPINAVIR/ ritonavir (sol.).

Ritonavir- boosted protease inhibitors was available in relation to RT (treatment not recommended).

EVALUATION OF POSSIBLE THIRD DRUG

First problem, age, body surface and weight of the child, (50 days) and weight (3.5 Kg).
Third drug with another Protease Inhibitor (PI):
There were no other pediatric presentations.
Difficult to achieve a safe pediatric dose with adult tablets
Increased toxicity with a third PI.
Not recommended three IP.

Third drug fusion inhibitor **Enfuvirtide** (IF) (T20)
Injectable ampoule every 12 hours.
A dose adapted to the patient's body surface was agreed upon by the medical team.
No dose for infants.
No experience in infants.
Complication: Risk of infection at the application site.

Third drug integrase inhibitors (II) **Raltegravir**:
No pediatric presentation (year 2011).
Difficulty in obtaining a safe dose with adult tablets.
No dose for infants.
No experience in infants.
Not recommended in infants.
Possibility of resistance due to misuse of this drug during the mother's pregnancy.

Third drug **Maraviroc** (CC5R antigen)
No pediatric presentations.
Difficulty in obtaining a safe dose with adult tablet presentations.
No dose for infants.
No experience in infants.
Not recommended for use in patients with undetectable viral loads.

IT IS DECIDED TO START TTO. ARV ACCORDING TO TR AND THE CHILD'S CLINIC 05/13/11
Drugs:
• LOPINAVIR/RITONAVIR syrup 16/4 mg/kg/0.4ml dose every 12 hours . PO (1 ml syringe)

Difficulty in adherence: Extremely unpleasant taste
Rejected by most children.
Main cause of ARV switching.
Main cause of poor adherence and resistance to IP
Main cause of abandonment of pediatric treatments

• FOSAMPRENAVIR syrup arabic
30 mg/kg/dose 2 ml every 12 hours. VO

Difficulty in adherence: large volumes of syrup in each dose of treatment

• THIRD DRUG: T20 (ENFUVIRTIDE)
This ARV was chosen as the third drug because it was the only one with which an exact dose could be made, homogeneously distributed and adapted to the child's body surface.

A dose of 0.1 ml every 12 was decided, subcutaneous application (1 ml syringe).

Difficulty in adherence:
Subcutaneous injectable administration.
Main cause of ARV change.
Rejected by most patients of all ages.
Chosen for the rescue of patients with severe immunocompromised.
Complication, painful subcutaneous nodules at the application site.
Possibility of superinfection of the application site.
Personnel trained in the preparation and application of the ARV.

EVALUATION OF THE CHOSEN TREATMENT

An ARV treatment never previously administered was indicated in children and less so in infants under 3 months of age due to vertically transmitted resistance
The evaluation of the SOCIAL situation presented by this family, made up only of the father and the child, was HIGH RISK, father with epileptic disease, without his own home, illiterate, without stable work and in charge of a one-year-old child with a ARV treatment that is very specific and difficult to administer. Because of this antiretroviral treatment, the child had to remain hospitalized for a year and the father was trained for many months in the preparation and application of this medication.
The child -thanks to his father and the health team that trained and accompanied him- from 9 months after the start of ART and up to the present time, he maintained non-detectable CV.
He was in treatment with T20 for 2 years.
For the previously described reasons, when the conditions for changing ARV treatment improved due to weight-height growth , the good evolution of the child , the body surface according to its development and the availability of another ARV of pediatric presentation, it was possible to rotate the medication.

DATE	CD4	%	CV	LOG	ARV TREATMENT
05/2011	2062	27%	750,000	log 5.88	
06/2011	3842	32%	20,800	Log. 4.32	
09/2011	3491	40%	967	log 2.99	T20/LPV/ rTV /FPV
12/2011			461	Log. 2.67	
03/2012	934	28%	400	Log. 2.67	
06/2012			<34	Log. < 1.53	
10/2012	2611	39%	<34	Log. <1.53	
01/2013	1776	36%	<34	Log. < 1.53	
04/2013			<34	Log. <1.53	
07/2013	1945	3. 4%	<34	Log. <1.53	
11/2013			<20	Log. <1.3	Raltegravir /LPV/ rTV /FPV
01/2014	1338	36%	<20	Log. <1.3	
05/2014	1132	31%	<20	Log. <1.3	
09/2014	2124	27%	<20	Log. <1.3	
02/2015	1415	29%	<20	Log. <1.3	
05/2015	919	32%	<20	Log. <1.3	
10/2015	1018	30%	<20	Log. <1.3	
02/2016	931	32%	<20	Log. <1.3	
07/2016	733	31%	<20	Log. <1.3	
01/2017	913	35%	<20	Log. <1.3	
04/2017			<20	Log. <1.3	
09/2017	1307	30%	<20	Log. <1.3	
01/2018	963	3. 4%			
04/2018	1402	31%	<40	Log. <1.6	
08/2018			<20	Log. <1.3	
11/2018	1231	30%			Pediatric DRV/ rTV / Raltegravir
03/2019			<20	Log. <1.3	
07/2019	856	40%	<20	Log. <1.3	
11/2019	1033	38%			
10/2020	824	3. 4%	<40	Log. <1.6	
02/2021	884	3. 4%	<20	Log.<1.3	
06/2021			<40	Log. <1.6	
08/2021	741	33%			
12/2021	710	33%	<40	Log. < 1.6	
03/2022	708	36%	<40	Log<1.6	
06/2022	634	36%	<40	Log<1.6	
09/2022	666	32%	<40	Log<1.6	

IMMUNOVIROLOGICAL EVOLUTION OF THE CHILD DURING THESE YEARS

Complications of treatment during its evolution.
During the administration of the chosen ARV treatment, laboratory controls were carried out to evaluate possible manifestations of toxicity. In the first year of the child's life, abnormal laboratory values, serum lactate, and liver enzymes were higher than the maximum values considered normal on multiple occasions.
Normal lactate dosage <= 20 08/11 Lactate 49 TGO 41 TGP 59
It was necessary to adjust the doses of the drugs that, due to experience in the treatment of other patients, modified these values in the laboratories.
Fosamprenavir dose was changed to 18mg/k/dose

DATE	AGE	BLOOD LACTATE	TRIGLYCERIDES	ARV TREATMENT
11/08	05 MONTHS	22.5		T20/LPV/ rTV /FPV
09/11	06 MONTHS	25		
09/11	06 MONTHS	29	228	
09/11	06 MONTHS	27		
10/11	07 MONTHS	24		
11/12	08 MONTHS	38		
11/12	08 MONTHS	39		
04/12	12 MONTHS	29		

Assessment of the chosen treatment in the growth and development of the patient
Growth and development:
11/05 45 days, Reflexes and Stimuli for age: Negative or diminished
06/11 - CI Pediatric Neurology (Patient 3 months- 12 days) Diagnostic printout "PROGRESSIVE ENCEPHALOPATHY SECOND TO HIV+ INFECTION"
Marker disease: AIDS patient C3.

Meets two of three points of the Symptomatic Triad:
DELAYED MATURATION maturational age approx. 2 months
EMS. PIRAMIDAL presents spastic quadriparesis .
MICROCEPHALUS It was necessary to complete the evolution of the fall of PC to define.

07/11- CT CNS widening of cortical and bitemporal subarachnoid spaces . Rest s/p.

Since 05/2011, together with the ARV treatment, work has been done on early stimulation of the child with Psychopedagogy, Speech Therapy, Kinesiology rehabilitation, psychology, hospitalization unit nursing, social service, nutrition, with the improvement of the evaluation parameters.

DATE	AGE	WEIGHT		pc		SIZE	
06/16/11	3m	4400	pc<3	39	Pc10	52.5	pc<3
06/30/11	3m20d			40	PC25		
07/08/11	4m	5300	Pc10	40.5	PC25		
08/02/11	4m15d	5930	Pc3	41.5	25-50 pc	62	Pc3-10
08/10/11	4m 23d	6050	Pc3	42	PC25-50	62	Pc3-10
08/19/11	5m	6200	Pc3-10	43	pc50	65	pc50
09/13/11	5m25d	6750	Pc3-10	44.5	pc75-90		
10/11	6m	7120	Pc3-10	44.5	PC>50		

GROWTH CONTROLS TO HIGHLIGHT FROM THE FIRST YEAR

First year after start of treatment

05/2012 TAC SNC Normal report

I present during its growth maturation patterns according to age

Second year after start of treatment

July 2013

CV <34 lg10 <1.53

The child presented maturational patterns according to age.
Good adherence to antiretroviral treatment (by the patient's father).
Complication: painful subcutaneous nodules from T20 applicatio.n
Risk of superinfection in application sites.
Risk of abandoning treatment due to difficulty in adherence to T20.
The medical team proposed the change of treatment to preserve adherence in addition to relieving the father of the preparation, conservation and artisanal application of the T20 to his 2-year-old son and also with a greater degree of importance, to improve the quality of life of the child and his social relationship, affected by constant pain in the places of application of the T20.

2013 antiretroviral change (17)
Replacement of T20 (ENFUVIRTIDE)
Causes: painful administration of the antiretroviral and complications of the application site. Appearance of painful inflammatory subcutaneous nodules with risk of colonization, or subcutaneous cellulitis

THERAPEUTIC POSSIBILITIES

RALTEGRAVIR Pediatric Chewable Tablets
OTHER Protease Inhibitors
MARAVIROC

- T20 was replaced by pediatric Raltegravir
- LPV/ rTV -very unpleasant tasting syrup + (FPV) syrups.

After this change, I still have undetectable CVs

Year 2018; Seven years after antiretroviral modification
It was decided to change both protease inhibitors to a single PI co-formulated with ritonavir , a single daily tablet, a treatment that he continues to this day.

- LPV/ rTV + FPV were replaced by Darunavir 600/ rTV 100
- Continued with pediatric raltegravir

2022 present
Eleven years after starting ARV treatment and modifications to improve adherence (19-20)

2022 CV <20 log <1.3 Cd4 856 (40%)
Schooled, attending primary school according to chronological age.
Age-appropriate growth and development pc 50
The patient did not present opportunistic diseases during his growth
Never stop your antiretroviral treatment
I never submit detectable CVs.

CONCLUSIONS

The implementation of an early ARV treatment adapted to its resistance test guaranteed a good clinical evolution in this patient and reversed the poor prognosis of the first months of life.
The IAP (abbreviated programmed admission) as a form of interdisciplinary follow-up ensured that this was possible.
This child, thanks to his father's adherence to ARV treatment, presented a very different clinical evolution from his mother's, even though he had the same viral resistance. The possibility of maintaining this evolution will depend on the future behavior of the child in his adolescence, who, unlike his mother's experience, had an example of good adherence throughout his childhood. The patient's father was exposed to this retrovirus without protection and did not become infected.

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