Arch Argent Pediatr 2024;122(1):e202302992

# Resistance to integrase inhibitors in children with vertically-transmitted human immunodeficiency virus: First cases in Uruguay

*Ana V. González Castro*[a], *Verónica Sande*[a], *Lorena V. Pardo Casaretto*[a,b], *Stella I. Gutiérrez Rodríguez*[a]

## ABSTRACT

Antiretroviral (ARV) drug resistance is a public health issue. Resistance has also been observed in the case of integrase strand transfer inhibitors (INSTIs) used in pediatrics.

The objective of this article is to describe 3 cases of INSTI resistance. These are the cases of 3 children with vertically-transmitted human immunodeficiency virus (HIV). They were started on ARVs as infants and preschoolers, with poor treatment adherence, and had different management plans due to associated comorbidities and virological failure due to resistance.

In the 3 cases, resistance developed rapidly as a result of virological failure and INSTI involvement. Treatment adherence should be monitored so that any increase in viremia can be detected early. Virological failure in a patient treated with raltegravir forces to a rapid change in ARV therapy because its continued use may favor new mutations and resistance to second-generation INSTIs.

***Keywords:*** *human immunodeficiency virus; antiviral drug resistance.*

doi: http://dx.doi.org/10.5546/aap.2023-02992.eng

**To cite:** González Castro AV, Sande V, Pardo Casaretto LV, Gutiérrez Rodríguez SI. Resistance to integrase inhibitors in children with vertically-transmitted human immunodeficiency virus: First cases in Uruguay. *Arch Argent Pediatr* 2024;122(1):e202302992.

[a] *Clínica Pediátrica;* [b] *Departamento de Bacteriología y Virología; Facultad de Medicina, Universidad de la República, Uruguay.*

***Correspondence to*** *Ana V. González Castro: vickygc21@gmail.com*

***Funding****: None.*

***Conflict of interest****: None.*

***Received****: 1-2-2023*
***Accepted****: 2-22-2023*

## INTRODUCTION

Currently, combination antiretroviral therapy (ART) for the treatment of human immunodeficiency virus (HIV) infection has fewer adverse effects and greater efficacy. However, chronic medication may be a threat to adequate treatment adherence and predisposes to virological failure associated with resistance to antiretrovirals (ARVs). Both adherence and the characteristics of the different ARVs are related to resistance and become a public health issue.[1]

New effective drugs, a better safety profile, and fewer tablets taken per day are attempts to improve the development of resistance. Integrase strand transfer inhibitors (INSTIs) raltegravir (RAL) and, more recently, dolutegravir (DTG), are in this group.[2,3]

In Uruguay, the prevalence of resistance in children under 18 years of age is 28.6%; non-nucleoside reverse transcriptase inhibitors (NNRTIs) are involved most frequently.[4]

INSTIs in pediatric formulation have become recently available in Uruguay and were included in preferred plans. In this setting, our objective was to describe 3 clinical cases of children/adolescents with HIV who developed resistance to INSTIs.

## CASE REPORT 1

This was a 12-year-old male patient with vertically-transmitted HIV who had been diagnosed at 2 months old. His mother was treated with zidovudine (AZT), lamivudine (3TC), and saquinavir/ritonavir during pregnancy. The child developed learning difficulties and moderate persistent asthma.

He started antiretroviral therapy (ART) at the time of diagnosis; it included AZT, 3TC, and lopinavir/ritonavir (LPV/r). Adherence was average due to intolerance to protease inhibitors (PIs). *Table 1* describes the treatments, the changes in ART, and the resistance tests performed. Since he was 21 months old, he developed bronchial obstruction episodes and was admitted several times to the medium care unit, so montelukast was started due to the interaction of inhaled fluticasone with ritonavir.

Asthma attacks persisted and the number of hospitalizations increased; treatment was changed from LPV/r to efavirenz (NFV) plus inhaled fluticasone. His asthma was subsequently controlled, but he developed virological failure and his ART was changed to RAL, tenofovir (TDF), and FTC, with an adequate response. His viral load (VL) was undetectable until 11 years of age; at that time, difficulties in the timing of administration led to virological failure. Resistance to RAL and elvitegravir (EVG) and a possible resistance to bictegravir (BIC) and DTG were observed. Due to asthma improvement, fluticasone was discontinued and montelukast was maintained. Protease inhibitors (TDF + FTC + LPV/r) were restarted and his response to date has been adequate.

## CASE REPORT 2

This was a 15-year-old female patient who had been diagnosed at 2 months old. Her mother was diagnosed after giving birth. The baby was started on ART at 4 months old, with poor adherence and multiple drug discontinuations. She developed pulmonary tuberculosis at 7 years of age, with an adequate clinical course and 2 prolonged hospitalizations due to cryptococcal meningitis that was difficult to manage, until achieving negativization at the age of 12–13 years. She developed chronic malnutrition and learning difficulties, and dropped out of school. *Table 2* describes the treatment and the resistance tests performed on this patient. During the hospitalization due to cryptococcal meningitis, her VL became undetectable. At the age of 14, she discontinued her medications in a setting of high social vulnerability and failure to attend her scheduled follow-ups. A sustained increased VL was confirmed; a resistance test was performed and treatment with TDF + FTC + LPV/r was restarted, with poor adherence. She resumed her follow-up visits at 15 years of age, while pregnant with her first baby. The pregnancy was adequately monitored and she had an uncomplicated C-section, VL: 34 copies/mL and CD4: 183 cells/uL.

## CASE REPORT 3

This was a 4-year-old girl with HIV infection diagnosed at 1.5 years old due to her mother's diagnosis during an episode of pneumonia. HIV was probably transmitted through breast milk (negative serology during pregnancy and delivery). Her initial VL was 11 300 copies/mL and her CD4 count was 1179 (15%). She was treated with AZT + 3TC + LPV/r, with no resistance test. Due to pulmonary tuberculosis, her ART was changed to AZT, 3TC, and NFV. She developed virological failure and the following was confirmed: resistance to 3TC, possible resistance to abacavir (ABC), resistance to NFV and nevirapine (NVP),

**Table 1. Main clinical and laboratory variables of case 1**

| Age | Viral load copies/mL (log) | CD4 cells/uL (%) | ART | Adherence | Concurrent conditions | Action |
|---|---|---|---|---|---|---|
| 2 months | 2 400 000 (6.4) | 1990 (39) | AZT + 3TC + LPV/r | Intolerance of LPV/r | | |
| 14 months | 42 000 (4.6) | 1157 (31) | = | | | RT = M184V resistance to 3TC/FTC |
| 21 months | Undetectable | 1496 (38) | | | 1st asthma attack | Montelukast |
| 2 years and 8 months | 29 000 (4.5) | 1325 (30) | = | | Several asthma attacks | |
| 3 years and 5 months | 38 000 (4.6) | 1128 (30) | = | Inconsistent | Allergic rhinitis Monthly asthma attacks | |
| 6 years and 3 months | 1500 (3.2) | 999 (29) | AZT + 3TC + NFV + NFV | | Hospitalized due to asthma attack with respiratory failure | ART changed Fluticasone + montelukast |
| 6 years and 6 months | 950 (3) | 1189 (27) | AZT + 3TC | Adequate | Improvement in asthma attacks | Fluticasone + montelukast |
| 6 years and 9 months | Undetectable | 1372 (30) | = | | Held back in school due to absenteeism | No montelukast |
| 7 years | 902 (2.9) | 935 (26) | = | | No attacks | |
| 8 years | 1380 (3.2) | 852 (30) | | Adequate | | RT = M184V K103N G190A Initiation of RAL procurement |
| 9 years | 2070 (3.32) | 567 (27) | TDF + FTC + RAL | | | |
| 9 years | 2240 (3.35) | 702 (26) | = | | | |
| 9 years | Undetectable | 843 (31) | = | | | |
| 10 years | Undetectable | 419 (30) | = | | | |
| 11 years | 27 (1.43) | 675 (28) | = | | | |
| 11 years | 445 (2.65) | 790 (31) | | | | |
| 12 years | 1140 (3.06) | 680 (32) | TDF + FTC + LPV/r | | | RT = M184/ T215F/K103N/ G190A Y143H N155H |
| 12 years | 3390 (3.53) | 605 (29) | = | | | |
| 12 years | 51 (1.71) | 505 (27) | | | | |
| 12 years | Undetectable | 710 (32) | = | | | |
| 12 years | Undetectable | 763 (34) | = | | | |

*ART: antiretroviral therapy; RT: resistance test; AZT: zidovudine; 3TC: lamivudine; LPV/r: lopinavir/ritonavir; FTC: emtricitabine; TDF: tenofovir; NFV: efavirenz; RAL: raltegravir.*

possible resistance to etravirine (ETV) and rilpivirine (RPV), sensitivity to PIs. Her ART was changed to AZT, 3TC, and RAL. Her initial response was adequate, but an undetectable VL was not achieved. She often missed follow-up visits, which led to an increased VL and reduced CD4 count. The resistance test showed resistance to RAL and her ART was changed to AZT + 3TC + LPV/r, with an adequate response (*Table 3*).

**Table 2. Main clinical and laboratory variables of case 2**

| Age | Viral load copies/mL (log) | CD4 cells/uL (%) | ART | Adherence | Concurrent conditions | Action |
|---|---|---|---|---|---|---|
| 2 months | 9 900 000 (6.99) | 4600 (65) | AZT + 3TC + NVF | Started at 4 months | | |
| 2 years and 4 months | 110 000 (4.04) | 2150 (47) | | = | | NVF changed to LPV/r |
| 3 years and 7 months | 5700 (3.8) | 944 (26) | AZT + 3TC + LPV/r | | | |
| 4 years and 7 months | 43 000 (4.63) | 1035 (23) | | = | | |
| 7 years | 2000 (3.3) | 550 (33) | | | Pulmonary tuberculosis | ART changed AZT + 3TC + NFV |
| 8 years and 7 months | 410 000 (5.6) | 76 (4) | AZT + 3TC + NFV | | | |
| 9 years | 52 800 (4.7) | 144 (7) | | | Resistance test: D67N/K70R/V75M/ K103N/M184V/ G190A/K219Q L10V/ M36I | ART changed 3TC + TDF + LPV/r |
| 9 years | 79 600 (4.9) | No data | 3TC + TDF + LPV/r | | Resistance test | |
| 12 years | 21 200 (4.3) | 48 (2) | RAL + TDF + FTC + ATV/r | | K103N/G190A K219Q | |
| 12 years and 6 months | 44 600 (4.6) | 25 (1) | = | | | |
| 13 years and 2 months | 30 (1.48) | 132 (7) | = | | | |
| 13 years and 7 months | Undetectable | 225 (15) | = | | | |
| 14 years and 6 months | Undetectable | 624 (21) | RAL + TDF + FTC | Discontinued ART | | |
| 14 years and 9 months | 161 000 (5.2) | 277 (9) | = | Reinitiation of ART | | |
| 15 years | 46 800 (4.6) | | 364 (14) | | Resistance test: M184V/T215I/ K219Q/ K103S/G190A N155H | |
| 15 years | 47 (1.67) | 183 (9) | | | | C-section at 38 weeks of gestation |

*ART: antiretroviral therapy; AZT: zidovudine; 3TC: lamivudine; LPV/r: lopinavir/ritonavir; FTC: emtricitabine; TDF: tenofovir; NFV: efavirenz; ATV/r: atazanavir/ritonavir; NVF: nelvinafir.*

## DISCUSSION

INSTIs are the most recently approved family of antiretrovirals for the treatment of people with HIV. They include RAL and EVG (both first-generations INSTIs) and DTG; BIC and cabotegravir (CAB) (second-generations INSTIs). The latter are not available in Uruguay at the time of this article.[5,6]

RAL is well tolerated in children, with few interactions and adverse effects. It achieves a rapid decrease in VL and undetectable levels after a few weeks, but it has a low genetic barrier that may lead to the development of resistance in cases of average adherence.

Three pathways of resistance have been described: Y143R/C, N155H, and Q148H/K/R mutations, considered primary for resistance to RAL.[7] A single resistance mutation to RAL causes a high level of resistance and possibilities of resistance to other INSTIs, such as EVG. The presence of some isolated mutations or combinations may result in cross-resistance to

**Table 3. Main clinical and laboratory variables of case 3**

| Age | Viral load copies/mL (log) | CD4 cells/uL (%) | ART | Adherence | Concurrent conditions | Action |
|---|---|---|---|---|---|---|
| 08/2018<br>1 year and 8 months | 11 300 (4.05) | 1179 (15) | None | | Resistance test sensitive, and to NRTIs, NNRTIs PIs | Initiation of AZT + 3TC + LPV/r |
| 10/2018<br>1 year and 10 months | 552 (2.74) | 1654 (30) | AZT + 3TC + LPV/r | | Pulmonary tuberculosis | LPV/r changed to NFV |
| 03/2019<br>2 years and 3 months | 100 (2) | 1365 (25) | AZT + 3TC + NFV | | | |
| 09/2019<br>2 years and 9 months | 540 000 (5.73) | 716 (21) | = | | | |
| 09/2020<br>3 years and 9 months | 202 000 (5.3) | 2538 (23) | = | | Resistance test: M184V/K103N/V106Y/ G190A/H221Y/ | NFV changed to RAL |
| 10/2020<br>3 years and 10 months | 7000 (3.85) | 764 (42) | AZT + 3TC + RAL | | | |
| 01/2021<br>4 years and 1 month | 125 000 (5.1) | 112 (21) | = | | | |
| 02/2021<br>4 years and 2 months | 82 500 (4.92) | 422 (28) | = | | Resistance test: M184V/K103N/V106I/ G190A/H221Y/G140S/Q148H | RAL changed to LPV/r |
| 06/2021<br>4 years and 6 months | 144 (2.16) | 658 (26) | AZT + 3TC+ LPV/r | | | |

*ART: antiretroviral therapy; AZT: zidovudine; 3TC: lamivudine; LPV/r: lopinavir/ritonavir; NFV: efavirenz; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor.*

second-generation INSTIs.[3,7]

In France, adults with virological failure treated with INSTIs had an overall resistance of 42%; most of them had been treated with first-generation INSTIs (EVG and RAL). The most common mutations included N155H/S/T (16.6%), L74F/I/M (12.1%), Q148H/K/R (8%), and T97A (7.9%). As in the cases analyzed here, the most common mutation combination was G140S + Q148H.[7]

Sánchez et al., described 30 patients with virological failure treated with RAL; 14 were children or adolescents with vertical HIV transmission. Similar to what was observed in these cases, most had a high level of resistance to RAL and showed resistance to other ARV families.[5]

The 3 patients described here who received RAL did so after the development of resistance to NNRTIs. In the first case, persistent low viral loads were decisive. Persistent low-grade viremias (20–200 copies/mL) and below 1000 copies/mL are associated with resistance mutations.[8,9] In Uruguay, the available genotypic resistance testing requires a viremia level greater than 1000 copies/mL, which may lead to diagnostic delays and also new mutations.

The second case described here achieved an undetectable VL 6 months after starting RAL. She discontinued her medications and developed high viremia levels with resistance to RAL and EVG, without involvement of second-generation INSTIs.

On the other hand, the third case described here did not achieve a sustained reduction in VL, and resistance to RAL and EVG developed, with involvement of second-generation INSTIs.

The development of resistance to INSTIs in these 3 patients is in addition to mutations in other ARV families, such as nucleoside reverse transcriptase inhibitors (NRTIs) and NNRTIs. No mutations to PIs were found in any of our cases, probably due to their high genetic barrier

and the short time of their administration due to rejection, intolerance, and adverse effects, which are the most common problems that interfere with patient adherence. Due to limited pediatric options and pharmaceutical forms of other ARVs, the M184V mutation present in all 3 patients led to maintaining their second- and third-line plans with 2 active drugs. Virological resistance may occur both due to poor adherence and suboptimal treatment regimens. This should be taken into account when choosing a drug for rescue with a low genetic barrier, such as RAL.[10,11] Virological failure in a patient treated with RAL forces to a rapid change in ARV therapy because its continued use may favor new mutations and resistance to second-generation INSTIs.[5,9]

Periodic monitoring of treatment adherence is relevant to seek strategies that improve adherence, to monitor viremia, and to detect early failure.

Monitoring frequency and modality will be adjusted to each patient, their networks, their beliefs, and the characteristics of the drugs they receive (pharmaceutical forms, effectiveness, and genetic barrier).[12,13]

## CONCLUSIONS

Here we described the first 3 cases of children with HIV who developed resistance to INSTIs after receiving RAL.

These drugs were administered as part of a follow-up or rescue ARV regimen, with rapid development of resistance as a result of virological failure and second-generation INSTI involvement when RAL was maintained in the ART.

The failure of an ARV regimen that includes RAL should be considered early in order to change ARVs in a timely manner and thus avoid secondary mutations.

It is important to assess patient's adherence individually prior to initiation of low-genetic-barrier INSTIs. ■

## REFERENCES


1. Anstett K, Brenner B, Mesplede T, Wainberg MA. HIV drug resistance against strand transfer integrase inhibitors. *Retrovirology*. 2017; 14(1):36.
2. FDA US FOOD & DRUG. Drug Approval Package: Isentress (raltegravir) NDA #022145 [Internet]. [Accessed on: January 2nd, 2023]. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022145_Isentress.cfm
3. Fun A, Leitner T, Vandekerckhove L, Däumer M, et al. Impact of the HIV-1 genetic background and HIV-1 population size on the evolution of raltegravir resistance. *Retrovirology*. 2018; 15(1):1.
4. González V, Gutiérrez S. Prevalencia de resistencia a los anti-retrovirales en niños y adolescentes uruguayos infectados con el virus de la inmunodeficiencia humana en el Centro de Referencia VIH-SIDA. Centro Hospitalario Pereira Rossell. Montevideo-Uruguay. *Rev Chil Infectol*. 2018; 35(5):509-17.
5. Sánchez D, Arazi Caillaud S, Zapiola I, Fernandez Giuliano S, et al. Impact of genotypic diversity on selection of subtype-specific drug resistance profiles during raltegravir-based therapy in individuals infected with B and BF recombinant HIV-1 strains. *J Antimicrob Chemother*. 2020; 75(6):1567-74.
6. República Oriental del Uruguay. Ministerio de Salud. Recomendaciones de tratamiento antirretroviral. [Internet]. 2018 [Accessed on: January 2nd, 2023]. Available at: https://www.gub.uy/ministerio-salud-publica/sites/ministerio-salud-publica/files/documentos/noticias/Recomendaciones Tratamiento Antirretroviral.pdf
7. Marcelin A-G, Grude M, Charpentier C, Bellecave P, et al. Resistance to integrase inhibitors: a national study in HIV-1-infected treatment-naive and-experienced patients. *J Antimicrob Chemother*. 2019; 74(5):1368-75.
8. Antiretroviral Therapy Cohort Collaboration (ART-CC), Vandenhende MA, Ingle S, May M, et al. Impact of low-level viremia on clinical and virological outcomes in treated HIV-1-infected patients. *AIDS*. 2015; 29(3):373-83.
9. Boillat-Blanco N, Darling KEA, Schoni-Affolter F, Vuichard D, et al. Virological outcome and management of persistent low-level viraemia in HIV-1-infected patients: 11 years of the Swiss HIV cohort study. *Antivir Ther*. 2015; 20(2):165-75.
10. Fitzgerald F, Penazzato M, Gibb D. Development of antiretroviral resistance in children with HIV in low- and middle-income countries. *J Infect Dis*. 2013; 207(Suppl 2):S85-92.
11. Vignoles M, Barboni G, Agosti MR, Quarleri J, et al. Evaluation of minority populations of HIV type-1 with K103N and M184V drug resistance mutations among children in Argentina. *Antivir Ther*. 2009; 14(8):1175-81.
12. Loveday M, Furin J, Hlangu S, Mthethwa T, Naidoo T. 'If I am playing football, I forget that I have this virus': the challenges and coping strategies of adolescents with perinatally acquired HIV in KwaZulu-Natal, South Africa. *BMC Infect Dis*. 2022; 22(1):796.
13. Adams C, Kiruki M, Karuga R, Otiso L, et al. "Your status cannot hinder you": the importance of resilience among adolescents engaged in HIV care in Kenya. *BMC Public Health*. 2022; 22(1):1272.