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CASE REPORT

Lamivudine plus dolutegravir as a switch strategy in children: three case reports

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SUMMARY

Lamivudine (3TC)/dolutegravir (DTG) single tablet regimen (STR) has shown long-term efficacy and tolerability in people living with HIV (PLWH). Dolutegravir has been approved for use in children, while data on the efficacy of 3TC plus DTG in maintaining virological suppression in this population are still under evaluation. In this case series, we describe three children with perinatally acquired HIV who maintained virological suppression after switching antiretroviral therapy to DTG/3TC.
We present three case reports of three children enrolled in the Italian Register for HIV Infection in Children: a 9-year-old boy, a 10-year-old girl, and a 2-year-old girl with perinatally acquired HIV who immediately started antiretroviral therapy with a three-drug regimen upon diagnosis, which occurred at delivery, after 6 months of life, and after 2 years of life, respectively. They achieved and maintain virological suppression after 1, 6, and 7 months of therapy, respectively; then a switch strategy was performed with a two-drug regimen with DTG/3TC STR at the age of 7 years for the first child and at the age of 9 years for the second, while the third was switched to a DTG plus 3TC not STR, owing to weight requirements, at the age of 2 years and 10 months. All children maintained virological suppression at last follow-up visit (January 2024), showing an excellent growth curve and maintaining good adherence and tolerability to DTG plus 3TC.
A two-drug regimen with DTG/3TC demonstrated efficacy in maintaining virological suppression in a switch strategy in these children, with important advantages such as better tolerability and comfort of taking a single tablet once daily.

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INTRODUCTION

Lamivudine (3TC) plus dolutegravir (DTG) has demonstrated high efficacy and good tolerability in people living with HIV (PLWH) (Patel R *et al.*, 2021). Its efficacy in treatment-naïve PLWH has been demonstrated in two randomized clinical trials, GEMINI-1 and GEMINI-2 (Cahn P *et al.*, 2020), and TANGO and SALSA confirmed the non-inferior efficacy in switching strategies (van Wyk J *et al.*, 2020; Llibre JM *et al.*, 2023). There are also promising real-life data showing the long-term efficacy and tolerability of this two-drug regimen in virologically suppressed PLWH (Ciccullo A *et al.*, 2021).
Dolutegravir was recently approved by the Food and Drug Administration (FDA) for use in infants and children aged ≥4 weeks and weighing ≥3 kg, and was introduced in the Department of Health and Human Services (DHHS) guidelines; however, the use of DTG combined with 3TC has not been well studied for inclusion in DHHS or other HIV guidelines including children with HIV (DHHS Pediatric Guidelines, 2022).
This recommendation was based on pharmacokinetic and safety data from ODYSSEY trial in which DTG was superior to standard of care therapy based on virological and clinical failure by 96 weeks in children, also in "under 14 kg" cohort (Moore CL *et al.*, 2021) and on the results of IMPAACT P1093 study, a phase I/II multicenter open-label study of DTG in combination regimens in age-defined pediatric cohorts that demonstrated safety, good tolerance and efficacy in treatment-experienced adolescents living with HIV (Viani RM *et al.*, 2020).
There are currently no data on the use of DTG/3TC STR in children, either in treatment-naïve or in switch studies in treatment-experienced PLWH. Two ongoing studies are evaluating efficacy in maintaining virological suppression in children aged 2 to <15 years and the safety of DTG/3TC in treatment-naïve adolescents with HIV (NCT03682848; NCT04337450).

Key words:
Dolutegravir; lamivudine; two-drug regimen; perinatally acquired HIV; children living with HIV.

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As demonstrated in adults, DTG/3TC STR could ensure efficacy and promising advantages in children and adolescents living with HIV, such as a reduction in side effects, pill burden, and frequency of administration, which are particularly relevant issues in this population.

In this case series, we present a real-life experience of a switch strategy based on DTG plus 3TC treatment in three children living with HIV who were enrolled in the Italian Register for HIV Infection in Children, a nationwide multicenter study on children perinatally exposed to HIV-1 instituted by the Italian Association of Pediatrics in 1985 (De Martino M *et al.*, 2000).

DESCRIPTION OF CASES

Case 1

A 9-year-old Caucasian boy, born by cesarean section from a mother who tested HIV positive 24 hours after delivery, acquired HIV infection with HIV-RNA>10,000,000 copies/ml and CD4+ T cell count of 4462/mm^3 (46.7%, CD4+/CD8+ ratio 2.2), thus revealing as a CDC pediatric stage 1.

After a genotypic resistance test (GRT) on NRTI, NNRTI and PI classes mutation showing V118l mutation he immediately started antiretroviral therapy (ART) with zidovudine (AZT) 4 mg/kg twice daily, lamivudine (3TC) 2 mg/kg twice daily, and lopinavir/ritonavir (LPV/r) 16 mg/4 mg twice daily, all in syrup formulations.

On day 4 of life, antiretroviral therapy (ART) was intensified by adding 4 mg daily raltegravir (RAL), which contributed to rapid HIV-RNA load decay and immunological recovery (Taramasso L *et al.*, 2019). He changed five different ART regimens for lack of adherence and side effects such as anemia with AZT, nausea, and vomiting with LPV/r, and at the age of 7 months, 3TC 5 mg/kg twice daily plus abacavir (ABC) 16 mg/kg once daily plus RAL 40 mg twice daily, after a negative HLA-B57-01 screening. With RAL-based ART, he achieved HIV-RNA suppression at one year of age.

In December 2020, at the age of 7 years, the boy weighed 25 kg with a body mass index (BMI) of 13.4 kg/m^2 and his ART was simplified: he stopped the triple-drug regimen and started a two-drug regimen with DTG/3TC STR, with high adherence. At the time of switch, he had HIV-RNA <50 copies/mL and CD4+ were 1940/mm^3 (35.9%, CD4+/CD8+ ratio 1.3), and HIV-RNA remained undetectable after 4 years of follow-up.

At the time of writing, the boy was healthy, with a BMI of 18 kg/m^2, the HIV-RNA remained undetectable, and since 2021, he has continued DTG/3TC as a single tablet regimen, maintaining good tolerability and excellent compliance.

Case 2

A 10-year-old Caucasian girl, born by natural section, tested HIV-positive at 6 months of age. At diagnosis, she had HIV-RNA >1,000,000 copies/ml and a CD4+ T cell count of 1602/mm^3 (46.3%, CD4+/CD8+ ratio 2.3) with CDC pediatric stage 1. GRT on NRTI, NNRTI and PI classes showed a wild-type HIV virus. Immediately after diagnosis she started ART with AZT 12 mg/kg twice daily, 3TC 5 mg/kg twice daily, and nevirapine (NVP) 7 mg/kg twice daily. Under this treatment, she developed anemia with the need for blood transfusions; thus, she stopped AZT and NVP, continued 3TC, and introduced RAL 60 mg twice daily plus ABC 16 mg/kg once daily after a negative HLA-B57-01 screening. HIV-RNA <50 copies/mL was achieved with this regimen in 2012, when she was 2 years old and CD4+ T cell count was 3932/mm^3 (46%, CD4+/CD8+ ratio 2.2).

In August 2019, at the age of 10 years, we simplified the ART, and she started a two-drug regimen with DTG 50 mg once daily plus 3TC 300 mg once daily with high adherence; at age of 12 years, she switched to DTG/3TC STR. At the time of switch, she weighed 30 kg (BMI 16.9 kg/m^2), HIV-RNA was <50 copies/mL and CD4+ were 1212/mm^3 (42.5%, CD4+/CD8+ ratio 1.8). The HIV-RNA remained undetectable 4 weeks after the switch and at 3 years of follow-up.

Currently, the child is growing up with a current BMI of 20 kg/m^2, and she maintains excellent compliance with the two-drug regimen.

Case 3

A 2-year-old girl of African origin, born by cesarean section from a mother who tested HIV positive 2 years after delivery because of AIDS defining condition, tested HIV positive when she presented with recurrent diarrhea (at least 2 episodes per month) and chronic dermatitis. At diagnosis HIV-RNA was 2,500,000 copies/ml, CD4+ T cell count was 242 cells/mm3 (4.1%, CD4+/CD8+ 0.1), with CDC pediatric stage 3. GRT on NRTI, NNRTI and PI classes showed a wild-type HIV virus. Prior to negative HLA-B57.01 screening, she immediately started ART with 3TC 5 mg/kg twice daily plus ABC 16 mg/kg once daily and RAL 100 mg twice daily with lack of adherence, related to scarce palatability of the syrups and because of her mother's fear of disclosure, which made it difficult to take the therapy daily. Adherence became optimal when social support improved, with achievement of virological suppression after 7 months of therapy and CD4+ T cell count of 871/mm^3 (42%, CD4+/CD8+ ratio 0.4). Therefore, it was feasible to simplify the strategy by starting a two-drug regimen with DTG 25 mg plus 3TC 150 mg in September 2022, based on her weight, at the age of 2 years and 10 months with good adherence. At time of switch, she weighed 14 kg (BMI 19 kg/m^2), HIV-RNA was <30 copies/ml and remained undetectable at 6 months of follow-up, and she had CD4+ T cell count of 1738/mm3 (18%, CD4+/CD8+ ratio 0.4). At this time, the girl weighed 18 kg (BMI 20.37 kg/m^2), with an op-

Table 1 - *Clinical and immunovirological characteristics of the three children.*

Case	*Trans-mission*	*Sub-type*	*GRT*	*Age at start ART (month)*	*Age at start DTG+3TC (years)*	*Year of switch*	*HIV-RNA zenit (cp/ml)*	*HIV-RNA at start DTG+3TC (copies/ml)*	*CD4+ zenit (cell/mm³, %)*	*CD4+ at start DTG+3TC (cell/mm³, %)*	*HIV-RNA at 4 weeks from DTG+3TC (copies/ml)*	*Date of last follow-up visit*	*HIV-RNA at last follow-up visit (copies/ml)*
1	vertical	B	V118l	At birth	7	2020	>10.000.000	TND	872 (37,4)	1940 (35,9)	TND	29/1/2024	TND
2	vertical	B	Wild type	18	10	2021	>1.000.000	TND	806 (46,4)	1212 (42,5)	TND	03/01/2024	TND
3	vertical	B	Wild type	24	2	2022	2.500.000	TND	242 (69)	1738 (18)	TND	05/01/2024	TND

GRT: genotypic resistance testing; DTG: dolutegravir; 3TC: lamivudine; TND: target not detected.

timal growth curve and we are now waiting for her weight to exceed 25 kg so that we can also start STR therapy with DTG/3TC.

Clinical and immunovirological characteristics of the three children are summarized in *Table 1*.

DISCUSSION

Treatment of HIV infection in children and adolescents remains a challenge for clinicians. A recent study showed that patients with perinatally acquired HIV develop a high prevalence of drug related mutation (DRM) at long-term follow-up due to biological and behavioral reasons such as adherence; therefore, it is crucial to find new treatment regimens and strategies to preserve drug susceptibility for current and future antiretroviral classes and optimize adherence to therapy (Chen TK *et al.*, 2008; Ungaro R *et al.*, 2019).

In this case series, despite differences in the three children (based on ethnicity, age, and time of observation), the two-drug regimen of 3TC plus DTG has so far been effective in maintaining HIV-RNA suppression as a switch strategy in these children, with good tolerability and adherence. This regimen also presents some important advantages over classical three-drug antiretroviral regimens, such as reduced side effects, lower pill burden, and high genetic barrier.

All three children were switched to dolutegravir and lamivudine from a three-drug regimen based on ABC+3TC+RAL. The advantage of switching from a RAL-based regimen to a DTG-based one is that the latter provides a higher genetic barrier, greater compliance due to once-daily (QD) dosing regimens, and better tolerability (DHHS Pediatric Guidelines, 2022; Jiménez-Montero B *et al.*, 2014). On the other hand, the disadvantage is the risk of stored resistance.

Tolerability and good adherence are even more important in children and adolescents, for whom switching to a single-tablet regimen before school age may improve adherence, reduce social stigma, and lead to a more sustainable routine.

Recent studies have demonstrated DTG's high durability and low virological failure rates, even in two-drug regimens, with prevention of adverse events, and could be considered a suitable option to minimize drug interactions and improve tolerability (Cahn P *et al.*, 2020; Maggiolo F *et al.*, 2017; Galizzi N *et al.*, 2020).

Several key factors must be considered when choosing the best antiretroviral regimen for children. Among these, side effects play an important role. As demonstrated by the EPHIC study, it is crucial to optimize antiretroviral therapy for children from the perspective of the safety profile, which is essential to ensure adherence to treatment and decrease the risk of opportunistic infections and ART failure rates (Taramasso L *et al.*, 2021).

Furthermore, another important feature of DTG can be its high genetic barrier. In fact, while in our cohort, in a country with high socioeconomic development, it was possible to perform GRT at time of diagnosis, in many countries, such as sub-Saharan Africa, where HIV remains an endemic disease with high mortality and morbidity, it is not possible to access genotypic testing in either the child or the mother (Taramasso L *et al.*, 2021).

In low-income countries, guaranteeing universal access to antiretroviral therapy is mandatory, and a possible advantage of DTG based therapy can be its lower cost per person with viral suppression compared to other regimens (Jamieson L *et al.*, 2021).

Randomized clinical trials play a key role in evaluating the effectiveness of this regimen, especially in underdeveloped countries. To date, a trial is recruiting children and adolescents with HIV-1 aged 2 to <15 years to determine whether DTG plus 3TC is safe and as effective as a three-drug regimen currently used in routine practice (NCT04337450).

In this scenario, DTG/3TC, especially in a single-tablet regimen, emerges as the therapy of choice precisely because of the many advantages mentioned.

CONCLUSIONS

Further studies are needed to evaluate the efficacy, safety, and durability of a two-drug regimen based

on DTG/3TC in large cohorts of children and adolescents with HIV infection. Our cases support the possible clinical use of the two-drug regimen as in adult PLWH, also showing good maintenance of virological suppression in children with perinatally acquired HIV infection, with important advantages, such as better adherence, fewer side effects, and greater tolerability than older antiretroviral regimens.

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Author Contributions
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Laura Labate, Claudia Bartalucci, Lucia Taramasso and Antonio Di Biagio. The first draft of the manuscript was written by Laura Labate and Claudia Bartalucci and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript."

Conflict of Interest Disclosures (includes financial disclosures)
Outside the submitted work, Lucia Taramasso received grants for consultancies by ViiV Healthcare, Janssen and Gilead Sciences; Matteo Bassetti has received funding for scientific advisory boards, travel, and speaker honoraria from Angelini, Astellas, Bayer, BioMérieux, Cidara, Cipla, Gilead, Menarini, MSD, Pfizer, Shionogi, Tetraphase, Nabriva; Antonio Di Biagio has received funding for scientific advisory boards, travel, and speaker honoraria from ViiV Healthcare, Gilead, Janssen, Abbvie, MSD. The other authors declare no conflicts of interest.

Ethics/Ethical Approval
The planning, conduct, and reporting of human research reported in this manuscript are in accordance with the Helsinki Declaration as revised in 2013.
Informed consent was obtained from the legally authorized representatives and assent was obtained from minor children whose images or cases are included.
The children presented in this case study are enrolled in the Italian Register for HIV Infection in Children, a nationwide multicenter study on children perinatally exposed to HIV-1 that was instituted in 1985 by the Italian Association of Pediatrics. Data collection started on 1 June 1985. The Register's data source is a network of 106 pediatric clinical centers located throughout Italy. These centers, which participate voluntarily, aim to enroll all children born to HIV- 1-infected mothers and forward data to two coordinating centers located at the Departments of Pediatrics of the Universities of Florence and Turin. Data are collected through specific individual forms for registration and follow-up every 6 months by a pediatrician. Children are examined at least every 2 months, and any clinical or immunological changes are reported on the follow-up form (de Martino, M et al., "Reduction in mortality with availability of antiretroviral therapy for children with perinatal HIV-1 infection. Italian Register for HIV Infection in Children and the Italian National AIDS Registry." JAMA vol. 284,2 (2000): 190-7. doi:10.1001/jama.284.2.190).

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