Dolutegravir-based antiretroviral therapy in a severely overweight child with a multidrug-resistant human immunodeficiency virus infection. A case report and review

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Abstract

The management of multidrug-resistant human immunodeficiency virus (MDR HIV) infections in children is particularly challenging due to the lack of experience with new drugs. Dolutegravir, combined with an optimized antiretroviral background therapy, is promising for the treatment of MDR HIV and has been approved recently for adults and adolescents. Data for children are extremely limited. We describe the efficacy, safety and plasmatic levels of a dolutegravir-based, complex active antiretroviral treatment regimen in a severely overweight 11-year-old child infected with an MDR HIV strain.

Keywords: Children, dolutegravir, multidrug-resistant human immunodeficiency virus, rescue therapy, T-20
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Case report

Vertically infected children may have significant human immunodeficiency virus (HIV) drug resistance due to non-suppressive regimens and/or inadequate adherence [1]. As a result of the lack of experience with newer drugs, these cases are extremely challenging for clinicians. We describe a case of a successful treatment based on dolutegravir in a patient with multidrug class resistance.

An 11-year-old boy has been treated at our clinic for a vertical HIV infection since 2009. Due to either viral failure or intolerance, he was exposed successively to several antiretroviral regimens between 2009 and May 2013, including zidovudine, stavudine, tenofovir, lamivudine, efavirenz, lopinavir/ritonavir, darunavir/ritonavir, fosamprenavir/ritonavir and raltegravir. Following chronically poor compliance with care and antiretroviral therapy, he presented multiple virological failures, resulting in the development of a multidrug-resistant (MDR) HIV strain (Table 1). The highest viral load was 6.8×10^5 copies/mL (April 2013) and the CD4 nadir was 53 cells/μL (5%) (December 2010). He was also significantly overweight with a weight of 56.5 kg (>90th centile) and a body mass index of 26.1 kg/m^2 (>90th centile).

After a multidisciplinary discussion, the following regimen was introduced in May 2013: enfuvirtide 90 mg twice a day subcutaneously; dolutegravir 50 mg once a day; tenofovir 300 mg once a day, emtricitabine 200 mg once a day (co-formulated as Truvada®, Gilead, Foster City, CA, USA) and abacavir 300 mg twice a day with excellent initial virological and immunological responses (Fig. 1). However, despite the daily home visit of a nurse for enfuvirtide injections, adherence to oral treatment was poor, resulting in an increase in viraemia in July 2013.

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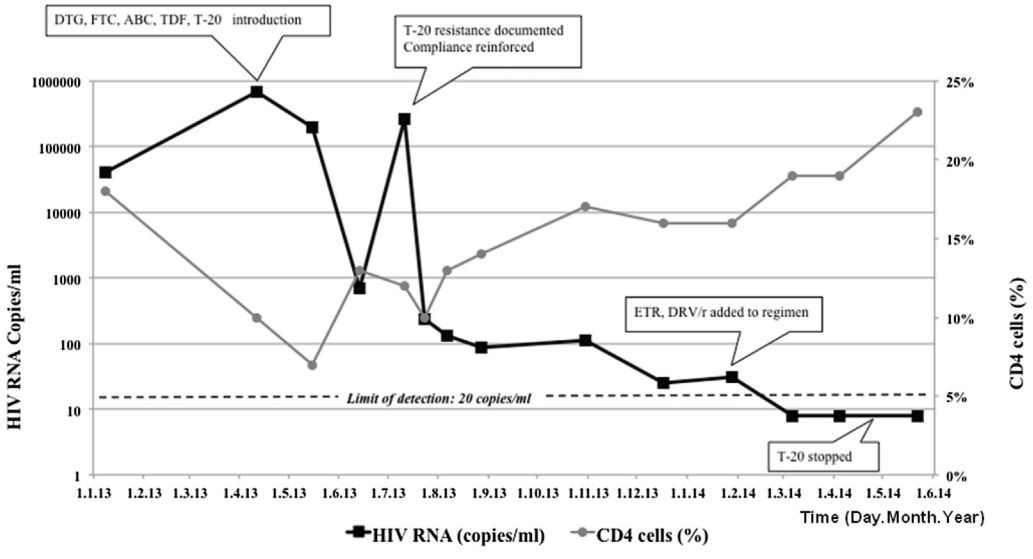
TABLE 1. Genotypic drug resistance interpretation according to the French National Agency for AIDS Research (ANRS)

		8 January 2013		11 July 2013		Cumulative genotype (six samples) 29 June 2010 to 11 July 2013	
	Drug	Mutations/Interpretation[a]		Mutations/Interpretation[a]		Mutations/Interpretation[a]	
NRTI	Lamivudine/Emtricitabine (3TC/FTC)		S		S	184V	R
	Abacavir (ABC)		S	215Y	S	184V, 215Y, 219Q	I
	Stavudine (D4T)	219Q	S	215Y	R	215N, 215S, 215Y, 219Q	R
	Didanosine (DDI)	219Q	S	215Y	S	184V, 215Y, 219Q	I
	Tenofovir (TDF)		S	215Y	S	215Y	S
	Zidovudine (AZT)	219Q	S	215Y	R	215N, 215S, 215Y, 219Q	R
NNRTI	Efavirenz (EFV)	188L, 190S	R	188L, 190S	R	188L, 190S	R
	Etravirine (ETR)	98G, 190S	S	98G, 179M, 190S	I	98G, 179M, 190S	I
	Nevirapine (NVP)	188L, 190S	R	188L, 190S	R	188H, 188L, 190S	R
	Rilpivirine (RPV)	188L	R	188L	R	188L	R
PI	Atazanavir (ATV)	10I, 16E, 33F, 46I, 84V	R	10I, 16E, 33F, 46I, 84V	R	10I, 10V, 16E, 33F, 46I, 84V, 85V	R
	Darunavir (DRV)	11I, 33F, 76V, 84V	R	33F, 76V, 84V	I	11I, 33F, 76V, 84V	R
	Indinavir (IDV)	36I, 46I, 84V	R	36I, 46I, 84V	R	36I, 46I, 84V	R
	Lopinavir (LPVr)	10I, 33F, 46I, 76V, 84V	R	10I, 33F, 46I, 76V, 84V	R	10I, 10V, 33F, 46I, 76V, 84V	R
	Nelfinavir (NFV)	10I, 36I, 46I, 84V	R	10I, 36I, 46I, 84V	R	10I, 36I, 46I, 84V	R
	Saquinavir (SQV)	10I, 15V, 20I, 84V	R	10I, 15V, 20I, 84V	R	10I, 10V, 15V, 20I, 84V	R
	Tipranavir/(TPV)	36I, 58E, 69K, 89M	R	36I, 58E, 69K, 89M	R	36I, 58E, 69K, 89M	R
	Fosamprenavir (FOS)	10I, 10V, 33F, 36I, 84V	R	10I, 33F, 36I, 84V	R	10I, 10V, 33F, 36I, 84V	R
INSTI	Dolutegravir (DTG)	74I, 155H	S	74I, 155H	S	74I, 155H	S
	Elvitegravir (EVG)	155H	R		R	155H	R
	Raltegravir (RAL)	155H	R		R	155H	R
FI	Enfuvirtide (T20)		S	36D, 38M	R	36D, 38M	R

HIV-1 strain: X-4 tropic

FI, fusion inhibitor; INSTI, integrase strand transfer inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitors; PI, protease inhibitor.
[a]Interpretation: S, susceptible; I, intermediate; R, resistant.

Resistance to enfuvirtide was detected at this time, but the drug was kept for a potential residual activity and fitness effect [2]. A directly observed therapeutic strategy was implemented to improve adherence. However, viraemia remained detectable (between 30 and 130 copies/mL) during the following 6 months (Fig. 1), presumably because of insufficient activity of the other drugs associated with dolutegravir. In February 2014, the decision was made to add etravirine 400 mg once a day and darunavir/ritonavir 600/100 mg twice daily to the regimen. Etravirine was considered to retain some antiretroviral activity against the MDR HIV strain, but it is known to decrease dolutegravir plasma levels [3]. For this reason, ritonavir-



DTG: dolutegravir FTC: emtricitabine ABC: abacavir TDF: tenofovir T-20: enfuvirtide ETR: etravirine DRV/r: darunavir/ritonavir

FIG. 1. CD4 cell count and human immunodeficiency virus (HIV) viral load evolution during follow up.

boosted darunavir was chosen for its compensatory effect on the dolutegravir level [4]. We assumed also a residual activity of darunavir/ritonavir. Two weeks after this change of therapy, under a twice-daily regimen of enfuvirtide, abacavir, darunavir/ritonavir, dolutegravir and once daily tenofovir, emtricitabine and etravirine, viraemia became undetectable (<20 copies/mL). Administration of enfuvirtide was stopped 2 months later, and the patient maintained undetectable levels at the following viraemia determinations.

Despite the previous exposure to an integrase strand transfer inhibitor, dolutegravir treatment was first started with a dose of 50 mg once a day, because of lack of data in children, and dosage was adjusted according to plasma levels as a main pharmacokinetics parameter. The first dolutegravir steady-state plasma level (1487 ng/mL)—determined 3 h after dosing using liquid chromatography combined with mass spectrometry according to a previously published, modified method and extrapolated to 24 h after the last drug intake—was considered to be below the supposed threshold of virological response [5,6]. The dolutegravir daily dose was then increased to 50 mg twice a day with more satisfying levels (peak level measured 2.5 h after intake, 6757 ng/mL; trough level, measured 12 h after intake, 3327 ng/mL), according to the available information for adults. Dolutegravir plasma levels were checked monthly after the addition of etravirine and darunavir/ritonavir. Peak levels of approximately 6000 ng/mL and trough levels between 2500 and 3000 ng/mL were systematically observed.

Despite excellent efficacy and tolerability in adults, dolutegravir use in children is poorly documented [7–9]. Indeed, the drug is approved for adolescents, but not for children in the age range of our patient. In the IMPAACT study (children ART-experienced, II naive), 70% of adolescents (12 to <18 years old) achieved HIV RNA values <50 copies/mL [10]. Results are pending for the other age groups. The dolutegravir daily dose in children still has to be defined. In the IMPAACT study, the administration of 1 mg/kg once daily achieved dolutegravir levels comparable to those achieved with 50 mg once a day in adults [10]. The study used 35 mg once a day for patients between 30 and 39 kg and 50 mg once a day for patients weighing 40 kg.

To our knowledge, the use of dolutegravir in treatment-experienced children with raltegravir-resistant or elvitegravir-resistant HIV infection has not been documented. With its higher genetic barrier, dolutegravir maintains an activity in the presence of some raltegravir- and elvitegravir-associated mutations, including N155H [3]. The results of the VIKING study showed a better viral response with twice-daily dosing in treatment-experienced adults with RAL-resistant HIV infection [11]. These data were an additional incentive to treat our 56-kg patient with a double dose of dolutegravir (50 mg twice daily). Dolutegravir is known to be highly bound (98.9%) to human plasma proteins [12]. Distribution does not appear to be affected in the context of obesity, but literature is lacking. A decrease in dolutegravir plasma levels after etravirine exposure is well known. However, it has been demonstrated that this can be counteracted by adding a boosted protease inhibitor (lopinavir/ritonavir or darunavir/ritonavir), presumably via inhibition of CYP3A [4]. In our patient, the etravirine effect was counterbalanced by darunavir/ritonavir with similar minimal dolutegravir levels before and after the addition of both drugs. This level has remained stable over the last 3 months. Although dolutegravir was probably the most active drug in the antiretroviral regimen, its individual weight in the combined therapy cannot be established.

Importantly, the potential side-effects of this complex regimen, which contains eight different drugs, require close monitoring for drug toxicity. Although the regimens now in use for naive patients are extremely well tolerated and can be monitored even up to every 6 months, complex regimens require very frequent assessment of liver and kidney functions, haematological parameters, and adherence (monitoring of pill number and drug levels, when available). In our case, this has been performed every 30 to 60 days. Despite MDR, our patient's strain appears to have a high capacity for replication, as shown by the high viral load observed when treatment was stopped and the rapid decrease of CD4 cells. In this context, the risk of toxicity was lower than the risk of an unsuccessful regimen and the risk of development of resistance to dolutegravir. Although it is controversial, we decided to maintain enfuvirtide treatment until obtaining undetectable viraemia, despite resistance, for a possible action on viral fitness [2,13].

To our knowledge, the use of high-dose dolutegravir in the context of virological failure in a child has never been documented. Our case provides information on the use of dolutegravir in a child in the particular setting of an MDR HIV strain, weight issues, a complex regimen and multiple drug–drug interactions. In our case, dolutegravir has demonstrated efficacy and safety and the addition of darunavir/ritonavir counterbalanced the negative effect of etravirine on dolutegravir plasma levels. Close monitoring and a multidisciplinary approach are recommended for an optimal management of these challenging cases.

Conflicts of interest

The authors have no funding or conflicts of interest to disclose.

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