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Dolutegravir Based cART in Vertically-HIV-1-Infected Adolescents in Real-Life Setting

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BACKGROUND

Attaining long-term good therapeutic adherence and viral suppression remains a challenge in perinatally-infected adolescents. Dolutegravir (DTG)-based cART are now approved for use in HIV⁺ adolescents aged ≥12 years in many countries worldwide. However, published data about efficacy of DTG in this population with high risk of virological failure (VF) are scarce. This multicenter study provides the first data about safety and efficacy of DTG in adolescents in real-life setting.

METHODS

Clinical and biological data from 50 adolescents, who initiated DTG-based cART between January 2014 and December 2015, were retrospectively analyzed. The primary endpoint was the proportion of patients who reached virological suppression (i.e. plasma viral load (PVL) <50 copies/mL obtained ≤ 3 months after DTG initiation) for viremic patients, and remained controlled until the last follow-up visit for all patients. The secondary endpoint was safety.

RESULTS

Patients were mainly male (68%), born in Sub-Saharan Africa (66%). All but one were ART-experienced. 9/50 patients were previously exposed to raltegravir (RAL), of whom 3 experienced virological failure (VF) on RAL.
At baseline, virological suppression was observed for ≥ 6 months in 17/50 patients (Figure).

Cumulative GSS was determined at baseline in 44 patients. Major NRTI, NNRTI and PI resistance mutations were observed in 68%, 43% and 28% of cases, respectively. The most frequent RAMs were M184V/I (61%), Y181C (20%) and TAMs (30%).
The *integrase* gene was sequenced in all 9 RAL-experienced patients and in 21/41 INI-naive patients. INI RAMs were detected in 4 patients : an isolated L74I mutation in 3 cases, and an isolated N155H in the remaining case.

Efficacy

Overall, sustained virological success and undetectable PVL at the last visit were obtained in 66% and 78% of patients (Figure).
The subjects with VF were more likely than those with virological success to have been born in Sub-Saharan Africa (94% versus 52%; *p*=0.004), and to have more frequently detectable PVL on ART during the six months preceding DTG initiation (82% versus 58%; *p*=0.03) (Table). The two groups were similar in terms of sex, age and characteristics of the DTG-based regimen (number of pills/day, dosing frequency, cumulative GSS).

ARV drug resistance

Genotypic resistance was assessed in samples from all 17 subjects presenting VF during follow-up. Median peak viraemia at VF was 3.8 log_{10} copies/mL (IQR: 2.9-4.8). No selection of new RAMs in the RT, *protease* or *integrase* gene was observed in these 17 patients during exposure to dolutegravir (median follow-up = 6 months).

Tolerance

Two patients (4%) experienced neurological side effects during follow-up: moderate headache and dizziness not necessitating DTG cessation in one case, and severe dizziness, sleeping disorders and anxiety, which resolved after DTG interruption, in the other. No other grade 3 or 4 clinical or biological side effects were reported. No AIDS-related events or deaths occurred.

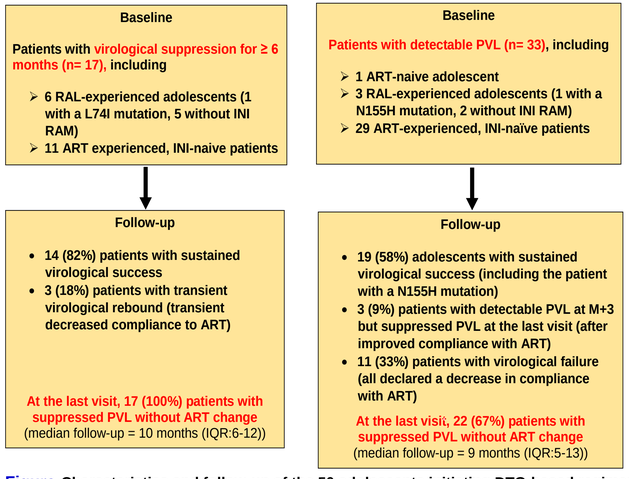

Figure Characteristics and follow-up of the 50 adolescents initiating DTG-based regimen
PVL = plasma viral load; RAL = raltegravir; INI = integrase inhibitor; RAM= resistance associated mutation

DISCUSSION

•In virologically-suppressed patients, DTG was generally introduced as a simplification strategy, to decrease the number of pills taken daily (≤2 pills/day in 70% of adolescents versus 35% previously) and/or the daily dosing frequency (once daily in 94% of patients versus 71% previously). All patients had suppressed viraemia at the last visit
•In patients with detectable PVL at baseline, the efficacy of DTG-based regimen was similar to that reported in the IMPAACT P1093 study (58% versus 61%),[1] but lower than that obtained in the SAILING study (71%).[2] This difference reflects the characteristically poor compliance with ART of perinatally infected adolescents.
•The low rate of severe drug-related adverse events is similar to those reported in previous trials in adults [2,3,4] and adolescents[1] but lower than that described in a recent study in a real-life setting, in which 15,3% of adults stopped taking DTG due to intolerance.[5]
•No emergence of RAMs were observed in the patients with VF on DTG. A recent *in vitro* study suggested that the M184I/V and K65R RAMs could prevent the emergence of DTG RAMs.[6] This may help to explain the very low rate of INI RAMs selected in perinatally-infected, highly ART experienced adolescents, in whom the M184I/V and K65R mutations are frequently observed (59% and 6%, respectively, in our patients experiencing VF on DTG).

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	Total (*n*=50)	Patients with virological success (*n*=33)	Patients with virological failure (*n*=17)	*P*-value
Male	34 (68%)	22 (67%)	12 (71%)	0.780
Place of birth of the child				0.004
Sub-Saharan Africa	33 (66%)	17 (52%)	16 (94%)	
France	12 (24%)	12 (36%)	0 (0%)	
Another country	5 (10%)	4 (12%)	1 (6%)	
Place of birth of the mother [a]				0.342
Sub-Saharan Africa	36 (81.8%)	21 (75.0)	15 (93.7%)	
France	3 (6.8%)	3 (10.7)	0 (0%)	
Another country	5 (11.4%)	4 (14.3)	1 (6.2%)	
ART history				
Cumulative duration of ART (years) (median, IQR)	12.7 (7.6 – 17.2)	14.6 (11.9 – 19.0)	11.0 (7.1 – 14.7)	0.038
Number of different ART combinations (median, IQR) [a]	4 (3 – 7)	4 (4 – 7)	3 (3 – 5)	0.094
Number of drugs (median, IQR) [a]	8 (5 – 10)	8.0 (5.5 – 10.0)	7 (5 – 9)	0.302
PVL during the 6 months before dolutegravir initiation				
Sustained control of viraemia on ART	17 (34%)	14 (42%)	3 (18%)	0.08
Detectable viraemia on ART	30 (60%)	16 (58%)	14 (82%)	0.03
Detectable viraemia without ART	3 (6%)	3 (9%)	0 (0%)	0.513
Characteristics at the time of dolutegravir initiation				
Age (years) (median, IQR)	18.0 (15.5 – 20.2)	18.4 (15.7 – 20.3)	16.6 (15.5 – 18.3)	0.129
PVL (log_{10}copies/mL) (median, IQR) [a]	1.8 (0.0 – 4.0)	0.0 (0.0 – 3.1)	3.9 (0.0 – 4.8)	0.03
CD4 count (/mm³) (median, IQR) [a]	633 (360 – 798)	644 (418 – 850)	462 (312 – 793)	0.350
CD4 count (%) (median, IQR) [a]	28 (15 – 38)	30 (22 – 39)	17 (13 – 36)	0.128
Number of pills per day (including dolutegravir)				0.463
1	9 (18%)	6 (18%)	3 (18%)	
2	27 (54%)	19 (58%)	8 (47%)	
3	10 (20%)	7 (21%)	3 (18%)	
4	3 (6%)	1 (3%)	2 (12%)	
6	1 (2%)	0 (0%)	1 (6%)	
Dosing frequency of dolutegravir-based regimen				0.321
Once daily	45 (90%)	31 (94%)	14 (82%)	
Twice daily	5 (10%)	2 (6%)	3 (18%)	
Cumulative GSS of dolutegravir-based regimen				0.881
1	2 (5%)	2 (7%)	0 (0%)	
> 1 to 2	26 (59%)	17 (59%)	9 (60%)	
> 2	16 (36%)	10 (34%)	6 (40%)	
Duration of follow-up (months) (median, IQR)	9 (5 – 13)	10 (6 – 14)	6 (5 – 11)	0.089

Table Comparison of the characteristics of patients attaining/maintaining virological success versus those with VF (i.e. detectable PVL ≥ 3 months after DTG initiation) on a DTG-based regimen
[a] The total number of patients for individual variables may not necessarily be equal to the total number of patients studied, due to missing values.

CONCLUSION

DTG was safe and provided good virological efficacy. Because of its high genetic barrier to resistance and small pill burden, DTG could be especially useful in ART-experienced adolescents with dramatically high risk of poor treatment adherence.

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