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EFFICACY AND SAFETY OF DOLUTEGRAVIR-BASED REGIMENS IN ADVANCED HIV-INFECTED NAÏVE PATIENTS: RESULTS FROM A MULTICENTER COHORT STUDY

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Background and objectives

Dolutegravir (DTG) is a second-generation unboosted-integrase inhibitor (INSTI), given once daily with limited cross resistance and a high barrier to resistance, recommended as first-line in most guidelines. However, limited data are available about DTG use in advanced naïve HIV-1 infected patients in clinical practice.

The aims of the study were:

- ✓to evaluate the viroimmunological efficacy and tolerability of DTG-including regimens and regimens without DTG in ART-naïve late and AIDS presenters in real life settings
- ✓to describe IRIS defining events in DTG-including regimens and in regimens without DTG

Methods

Multicenter cohort of advanced naïve HIV-1 infected patients starting first-line antiretroviral regimens (ART) between 01/01/2014 and 30/12/2017 in 9 clinical centers.

All patients presenting for care with a CD4 count below 350 cells/mm^3 (late presenter) or presenting with an AIDS-defining event, regardless of the CD4 cell (AIDS-presenter), starting their first ART were retrospectively included.

Unmasking and paradoxical Immune Reconstitution Inflammatory Syndrome (IRIS) events were defined by clinicians as symptoms consistent with an infectious or inflammatory condition associated with a drop of > 2 $\log_{10}$ copies/mL of HIV-RNA, not explained by a newly acquired infection, the expected clinical course of a previous infection, or side-effects.

Statistical analysis

Continuous variables were described using median and interquartile range (IQR).

Rate of first-line ART discontinuation for any reason was analised by survival analysis; virological suppression (defined as HIV-1 RNA<50 copies/mL) was evaluated after 1, 3, 6, 12 and 24 months.

Mean CD4 cells count and CD4/CD8 ratio changes from baseline at 1, 3, 6, 12 and 24 months were assessed using Student's t-test for paired samples.

Results

Table 1. Baseline characteristics of patients

	Overall (n=272)	ART with DTG (n=132)	ART without DTG (n=140)
Age (years)*	44 (36-51)	44 (37-52)	43 (38-51)
Female gender, n (%)	85/272 (31)	28/132 (21)	57/140 (41)
Caucasian ethnicity, n (%)	217/272 (80)	106/132 (80)	111/140 (79)
AIDS-presenters	120/272 (44)	58/132 (44)	62/140 (44)
Late-presenters	152/272 (56)	74/132 (56)	78/140 (56)
Risk factor			
Heterosexual contacts	147/272 (54)	56/132 (42)	91/140 (65)
MSM	59/272 (22)	50/132 (38)	9/140 (6)
Injecting drug user	14/272 (5)	6/132 (4)	8/140 (6)
Other/unknown	52/272 (19)	20/132 (16)	32/140 (24)
Baseline CD4 count (cell/μL)*	114 (40-241)	93 (30-192)	154 (50-270)
Baseline CD4<200 cell/μL	180/259 (66)	100/129 (77)	80/130 (61)
Viral subtype B	89/126 (71)	45/62 (73)	44/64 (69)
HIV-1 RNA $\log_{10}$ (copies/mL)* (on 114 available)	5.2 (4.8-5.7)	5.2 (4.8-5.8)	5.2 (4.8-5.7)
HIV-RNA >100,000 (cps/mL)	201/250 (74)	84/124 (68)	117/126 (93)
HIV-RNA >500,000 (cps/mL)	60/250 (22)	32/124 (26)	28/126 (22)

Values are expressed as n (%) except for *median (interquartile range, IQR)

Table 2. Antiretroviral regimens

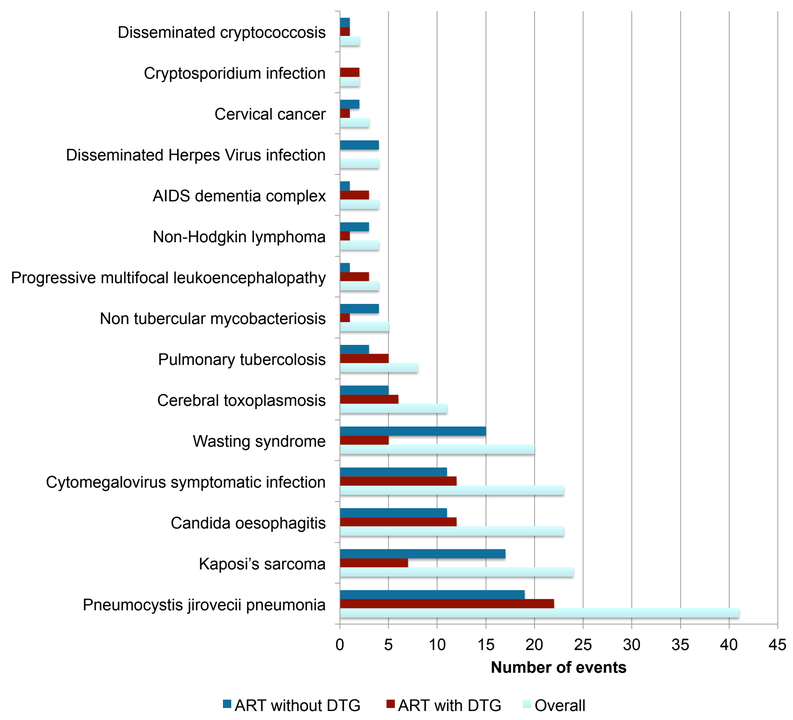
	Overall (n=272)	ART with DTG (n=132)	ART without DTG (n=140)
3-drugs ART	246/272 (90)	121/132 (92)	125/140 (89)
>3-drugs ART	23/272 (8)	8/132 (5)	15/140 (11)
2-drugs ART	3/272 (1)	3/132 (2)	0
INSTI-based 3-drugs ART*	189/272 (70)	121/132 (92)	68/140 (48)
PI-based 3-drugs ART*	56/272 (21)	0	56/140 (40)
TDF/TAF+FCT backbone	210/272 (77)	78/132 (59)	132/140 (94)
ABC+3TC backbone	55/272 (18)	49/132 (37)	6/140 (4)

* 1 patient on treatment with 3TC+RAL+DRV/r

Values are expressed as n (%) except for *median (interquartile range, IQR)

Results of 2

Figure 1. AIDS-defining events according to ART-regimens (n= 178 in 120 patients)



IRIS was reported in 13/272 (5%) AIDS-presenters: 5/132 (4%) among patients on treatment with regimens including DTG and 8/140 (6%) among those treated with regimens without DTG.

Among patients on ART with DTG IRIS was related to:

- •Kaposi's sarcoma in 2 patients
- •*Pneumocystis jirovecii* pneumonia associated to Candida oesophagitis and Wasting syndrome or Kaposi's sarcoma in 2 patients
- •Progressive multifocal leukoencephalopathy in 1 patient

Among patients on ART without DTG IRIS was related to:

- •Kaposi's sarcoma in 3 patients
- •Wasting syndrome associated to Cytomegalovirus symptomatic infection and Candida oesophagitis in 2 patients
- •Disseminated Herpes Virus infection in 1 patient
- •*Pneumocystis jirovecii* pneumonia associated to Wasting syndrome in 1 patient
- •Non-Hodgkin lymphoma associated to Kaposi's sarcoma and disseminated Herpes Virus infection in 1 patient.

No correlation was found between IRIS and baseline HIV-RNA >100,000 copies/mL or >500,000 copies/mL.

One hundred-eighty-two (67%) patients changed their first-line regimen

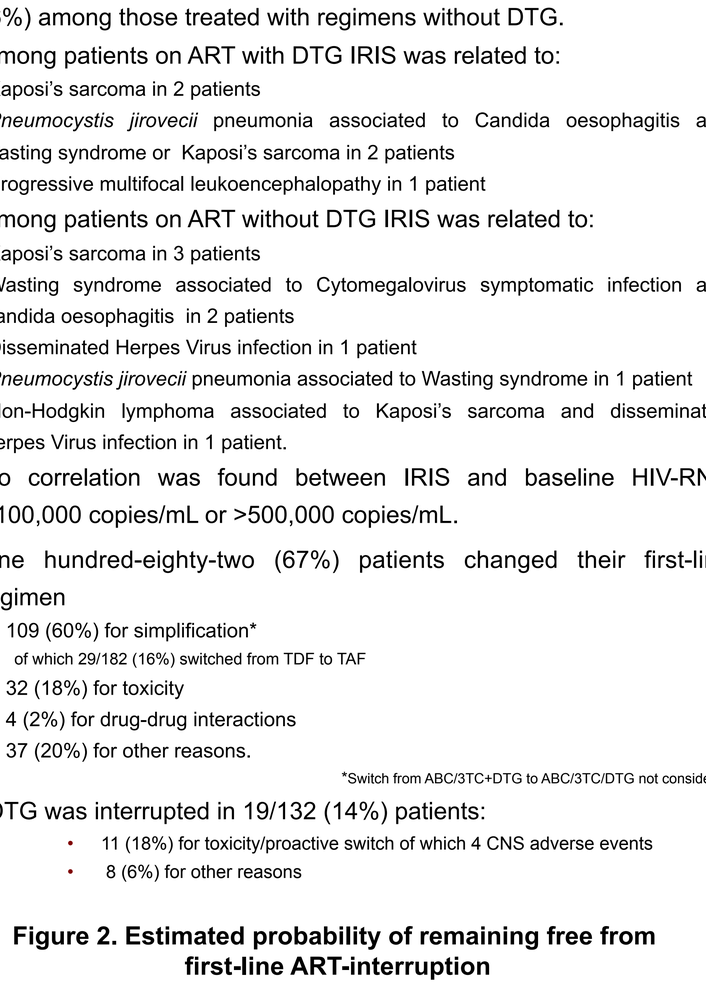
- 109 (60%) for simplification*
  of which 29/182 (16%) switched from TDF to TAF
- 32 (18%) for toxicity
- 4 (2%) for drug-drug interactions
- 37 (20%) for other reasons.

*Switch from ABC/3TC+DTG to ABC/3TC/DTG not considered

DTG was interrupted in 19/132 (14%) patients:

- 11 (18%) for toxicity/proactive switch of which 4 CNS adverse events
- 8 (6%) for other reasons

Figure 2. Estimated probability of remaining free from first-line ART-interruption

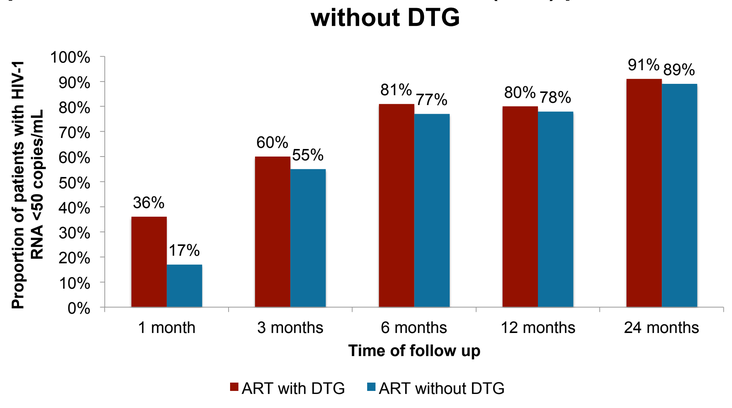


The 12-month estimated probability of first-line interruption was 40% (CI 95% 36-44) for any drug in regimens without DTG and 44% (CI 95% 40-48) in regimens with DTG.

The 12-month estimated probability of DTG interruption was 14% (CI 95% 11-17).

Results of 3

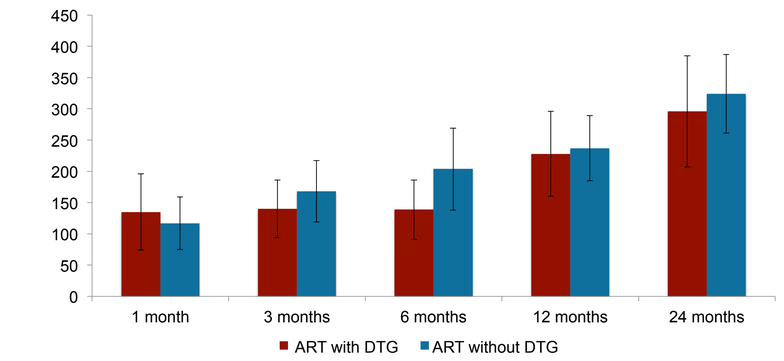
Figure 3. HIV-1 RNA<50 cps/mL had been achieved in 95/132 (72%) patients on ART with DTG and in 92/140 (66%) patients on ART without DTG



with DTG	36/100	59/98	68/84	56/69	31/34
without DTG	18/107	55/100	76/98	75/96	51/57

The median observation time was 16 months (IQR 5-24). Among 38 patients with HIV-RNA> 50 copies/ml after 6 months of treatment, 14/16 in ART with DTG and 21/22 in ART without DTG presented HIV-RNA>100,000 copies/mL at baseline.

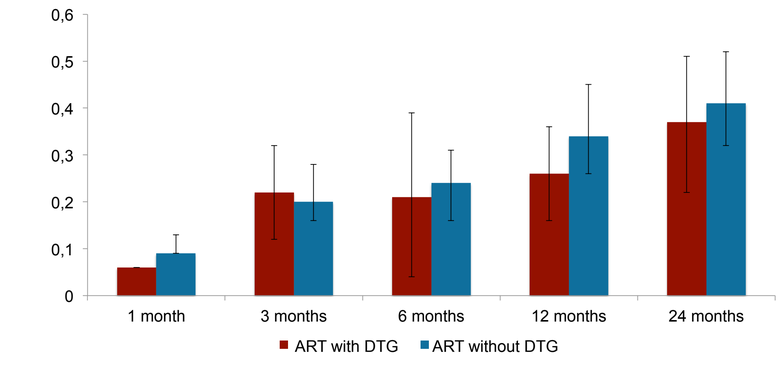
Figure 4. Mean CD4 change from baseline



with DTG	123	139	122	106	53
without DTG	40	42	47	47	37

P<0.005 for all comparisons intragroup

Figure 5. Mean CD4/CD8 ratio change from baseline



with DTG	84	101	88	73	42
without DTG	31	33	36	37	31

P<0.005 for all comparisons intragroup

Ten patients died within 24 months after ART initiation:

5 patients on ART with DTG

- •2 for Kaposi's sarcoma complications
- •1 for progressive multifocal leukoencephalopathy
- •1 for *Pneumocystis jirovecii* pneumonia
- •1 for non-AIDS related event

5 patients on ART without DTG

- •2 for Pneumocystis jirovecii pneumonia
- •2 for non-AIDS related event
- •1 for Non-Hodgkin lymphoma

Limitations

- ✓ Retrospective design
- ✓ Clinical definition of IRIS

Conclusion

Although preliminary, our results confirm the high potency, good tolerability and safety of DTG-containing regimens as first-line treatment of advanced-naive patients. Patients treated with DTG exhibited a frequency of IRIS which was comparable to those who did not receive DTG.

Reference

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