VIROLOGIC FAILURE AND RESISTANCE IN DOLUTEGRAVIR-BASED MAINTENANCE DUAL REGIMENS

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BACKGROUND

- Dolutegravir (DTG)-based dual regimens (2DR) as maintenance have proved their efficacy in large randomized trials (SWORD 1-2, TANGO).
- We evaluated virologic failure (VF) and resistance-associated mutations (RAM) on 2DR of DTG with rilpivirine (RPV) or 3TC/FTC (xTC) in a large cohort and analyzed the factors associated with VF.

METHODS

- The Dat'AIDS cohort is a French prospective cohort of more than 65 000 PLWH attending clinical care at 23 HIV reference centres in France (NCT 02898987). All patients provided written consent.
- Between 2014 and 2018, all HIV-1 adults starting DTG/RPV or DTG/xTC as a first maintenance 2DR (with HIV RNA < 50 c/mL prior switch) were enrolled.
- The primary outcome was VF, defined as 2 consecutive HIV RNA > 50 c/mL or a single value > 400 c/mL. Cumulative historical genotypes prior to 2DR were compared with genotype at VF, when available.
- The secondary outcomes were associated factors with VF and reasons for treatment discontinuation.
- Cox proportional hazards models were used to analyze factors associated with VF. Patients were right-censored when discontinuing 2DR for other causes of virologic failure.

RESULTS

- 1374 patients were included: 799 on DTG/RPV and 575 on DTG/xTC with a median follow-up of 587 days [IQR 334-934] and 562 days [IQR 326-938] respectively.
- Baseline characteristics of patients are presented in ***Table1***.

Virologic failure during follow-up: (*Figure 1 and Table 2*)

- **DTG/RPV group**

30/799 (3.8%), at median time of 232 days [IQR 100–507], leading to 2DR discontinuation in 17/30 (60%).

- **DTG/xTC group**

15/575 (2.6%), at median time of 301 days [IQR 188-428], leading to 2DR discontinuation in 6/15 (40%).

Resistance associated mutations at VF (*Table 3*)

- **At DTG/RPV VF**: 13/30 genotypes were missing or not amplified. Among the 17 amplified genotypes, 6 harbored RAMs: 6/6 NNRTI RAMs and 2/6 INSTI RAMs.
- **At DTG/xTC VF**: 9/15 genotypes were missing or not amplified. Among the 6 amplified genotypes 1 harbored RAM: M184V already detected on historical genotype.

RESULTS

Table 1 *- Baseline characteristics of patients (n=1374)*

median [IQR] or n (%)	DTG/RPV n= 799	DTG/xTC n = 575	p
Age, years	54.5 [48.7, 62.4]	52.5 [44.8, 60.8]	<0.001
Male	552 (69.1)	402 (69.9)	0.788
MSM	295 (36.9)	241 (41.9)	0.069
CDC stage C	231 (28.9)	109 (19.0)	<0.001
Nadir CD4, cell/mm^3	199 [90, 315]	288 [169, 415]	<0.001
Nadir CD4 ≤ 200/mm^3	401 (50.2)	177 (30.8)	<0.001
Zenith HIV RNA > 5 log$_{10}$ c/mL	388 (48.6)	248 (43.1)	0.053
Duration of undetectable HIV RNA , years	7.5 [3.8, 11.4]	6.2 [3.4, 10.4]	0.011
History of VF			
Regardless of ART	350 (43.8)	114 (19.8)	<0.001
on NRTI	333 (41.7)	108 (18.8)	<0.001
on NNRTI	90 (11.3)	38 (6.6)	0.005
on INSTI	38 (4.8)	10 (1.7)	0.004

Table 2 *- Virologic failures according to the 2DR used*

n (%)	DTG/RPV n= 799	DTG/xTC n = 575
Virologic failure	**30 (3.8)**	**15 (2.6)**
One HIV RNA > 400 c/ml	18 (2.3)	12 (2.1)
followed with 2DR discontinuation	*8 (1.0)*	*5 (0.8)*
Two consecutive HIV RNA >50 c/ml	12 (1.5)	3 (0.5)
followed with 2DR discontinuation	*9 (1.1)*	*1 (0.2)*

Table 4 *- Adverse events leading to 2DR discontinuation*

n (%)	DTG/RPV n= 799	DTG/xTC n = 575
Adverse event	**80 (10)**	**47 (8.2)**
CNS symptom	*31 (3.9)*	*19 (3.3)*
GI disturbance	*7 (0.9)*	*8 (1.4)*
Cutaneous event	*5 (0.6)*	*2 (0.3)*
Arthralgia	*3 (0.4)*	*3 (0.5)*
Renal impairment	*3 (0.4)*	*2 (0.3)*
Dyslipidemia	*1 (0.1)*	*0 (0)*
Other AE	*30 (3.8)*	*13 (2.3)*

Factors associated to VF

- In multivariate analysis, factors associated with VF included age, CDC stage C, CD4 nadir (cut-off: 200 cells/mm^3), HIV RNA zenith (cut-off: 5 log$_{10}$ c/ml), duration of undetectable HIV RNA before 2DR initiation (cut-off: 12 months), history of virologic failure on NRTIs or NNRTIs, and introduction of first ART prior to 1996.
- The only predictive factor of VF on DTG/RPV was history of VF to NNRTI-based ART (HR 2.82, 95%CI 1.04-7.6)
- No factor was associated with VF on DTG/xTC

Discontinuation during follow-up *(Table 4)*

- DTG/RPV group, n = 183 (22.9%) after a median time of 9.6 months [4.2, 19]
- DTG/xTC group, n = 113 (18.7%), after a median time of 9.6 months [3.6, 18.7]
- Reasons : **Virologic failure**, n = 23 (1.7%), **adverse events**, n=127 (9.2%), **miscellaneous**, n = 94 (6.8%) including drug-drug interactions and death in 7 cases (0.9%) and 12 cases (1.5%) in DTG/RPV, and 2 (0.3%) and 9 cases (1.6%) in DTG/xTC.
- CNS symptoms were the main adverse event leading to discontinuation in both groups.

Table 3 *- Resistance mutations associated to VF on DTG-2DR*

n	2nd drug	Time of VF	History of VF	HIV RNA at VF (c/mL)	2DR discontinuation	Resistance mutations			
						historical genotype		genotype at VF	
						NRTI or NNRTI	INSTI	NRTI or NNRTI	INSTI
1	RPV	W75	NNRTI	68;133	Yes	K103H/N/S/T	*none*	K103H/N/S/T	*none*
2	RPV	W6	No	531	Yes	*none*	*none*	E138K	*none*
3	RPV	W32	No	142;189[a]	Yes	*none*	*none*	K101E, E138K	N155H
4	RPV	W86	No	474	Yes	*NA*	*none*	E138A	*none*
5	RPV	W34	No	52310	Yes	E138K	*none*	E138A,L100I	L74I[c]
6	RPV	W5	No	109;109	Yes	K103H/N/S/T	*none*	K103H/N/S/T	*none*
7	xTC	W29	NRTI	66;59[b]	No	M184V	*none*	M184V	*none*

a: *HIV RNA at 2DR discontinuation was 787 c/mL,* ***b:*** *All HIV RNA following VF were < 50 c/mL,* ***c:*** *L74I alone does not confer genotypic resistance to DTG*

➢ Very low rate of virologic failure on real-life 2DR maintenance strategies
➢ RAM emergence at VF
- none on DTG/xTC
- 4 on DTG/RPV including 1 case with NNRTI and INSTI RAM

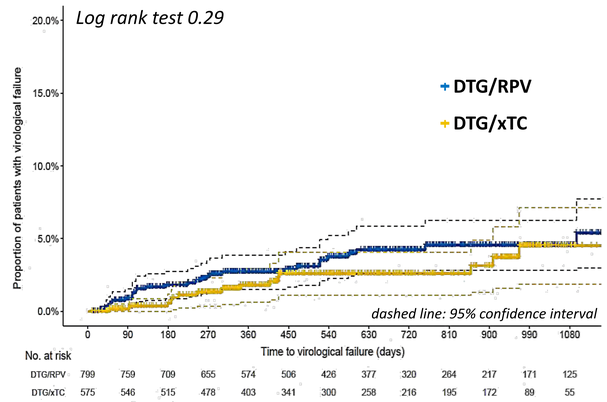

Figure 1 *– Kaplan-Meier plot of the time to VF*

DISCUSSION / CONCLUSION

- **In this large real-life cohort, DTG-based 2DR maintained sustained virologic suppression, and were associated with low rate of VF.**
- **On DTG/xTC, no resistance associated mutation emergence at VF.**
- **On DTG/RPV, the only associated factor with VF was a previous VF on a NNRTI-including regimen.**
- **DTG confirms its virologic robustness even in 2DR.**
- **These findings add further support to the use of DTG-based 2DR as an alternative maintenance strategy to 3DR for virologically suppressed ART-experienced individuals, as long as ART history and absence of active HBV infection are verified.**

Dat'AIDS group . Drobacheff-Thiébaut, A. Foltzer, K. Bouiller, L. Hustache- Mathieu, C. Chirouze, Q. Lepiller, F. Bozon, O Babre, A.S. Brunel, P. Muret (***Besançon***) ; H. Laurichesse, O. Lesens, M. Vidal, N. Mrozek, C. Aumeran, O. Baud, V. Corbin, P. Letertre-Gibert, S. Casanova, J. Prouteau, C. Jacomet (***Clermont Ferrand***) ; I. Lamaury, I. Fabre, E. Curlier, R. Ouissa, C. Herrmann-Storck, ,B. Tressieres, T. Bonijoly,M.C. Receveur, F. Boulard, C.Daniel, C.Clavel (***Guadeloupe***) ; D. Merrien, P. Perré, T. Guimard, O. Bollangier, S. Leautez, M. Morrier, L. Laine (***La Roche sur Yon***) ; F. Ader, A. Becker, F. Biron, A. Boibieux, L. Cotte, T. Ferry, P Miailhes, T. Perpoint, S. Roux, C. Triffault-Fillit, S. Degroodt, C. Brochier, F Valour, C. Chidiac (***Lyon***) ; A. Ménard, A.Y. Belkhir, P.Colson, C. Dhiver, A.Madrid, M.Martin-Degiovani, L. Meddeb, M. Mokhtari, A.Motte, A.Raoux, I. Ravaux, C.Tamalet, C. Toméi, H. Tissot Dupont (***Marseille IHU Méditerranée***) ; S. Brégigeon, O. Zaegel-Faucher, V. Obry-Roguet, H Laroche, M. Orticoni, M.J. Soavi, P Geneau de Lamarlière, E Ressiot, M.J. Ducassou, I. Jaquet, S. Galie, A Galinier, P. Martinet, M. Landon, A.S. Ritleng, A. Ivanova, C. Debreux, C. Lions, I. Poizot-Martin (***Marseille Ste Marguerite***) ; S. Abel, O. Cabras, L. Cuzin, K. Guitteaud, M. Illiaquer, S. Pierre-François, L. Osei, J. Pasquier, K. Rome, E. Sidani, JM Turmel, C. Varache, A. Cabié (***Martinique***) ; N. Atoui, M. Bistoquet, E Delaporte, V. Le Moing, A. Makinson, N. Meftah, C. Merle de Boever, B. Montes, A. Montoya Ferrer, E. Tuaillon, J. Reynes (***Montpellier***) ; M. André, L. Boyer, MP. Bouillon, M. Delestan, C. Rabaud, T. May, B. Hoen (***Nancy***) ; C. Allavena, C. Bernaud, E. Billaud, C. Biron, B. Bonnet, S. Bouchez, D. Boutoille, C. Brunet-Cartier, C. Deschanvres, N. Hall, T. Jovelin, P. Morineau, V. Reliquet, S. Sécher, M. Cavellec, A. Soria, V. Ferré, E. André-Garnier, A. Rodallec, M. Lefebvre, O. Grossi, O. Aubry, F. Raffi (***Nantes***) ; P. Pugliese, S. Breaud, C. Ceppi, D. Chirio, E. Cua, P. Dellamonica, E. Demonchy, A. De Monte, J. Durant, C. Etienne, S. Ferrando, R. Garraffo, C. Michelangeli, V. Mondain, A. Naqvi, N. Oran, I. Perbost, S. Pillet, C. Pradier, B. Prouvost-Keller, K. Risso, V. Rio, PM. Roger, E. Rosenthal, S. Sausse I. Touitou, S. Wehrlen-Pugliese, G. Zouzou (**Nice**) ; L. Hocqueloux, T. Prazuck, C. Gubavu, A. Sève, A. Maka, C. Boulard, G. Thomas (***Orléans***) ; A. Cheret, C.Goujard, Y.Quertainmont, E.Teicher, N. Lerolle, O.Deradji, A.Barrail-Tran (***Paris Hop. Bicêtre***) ; R. Landman, V. Joly, J Ghosn, C. Rioux, S. Lariven, A. Gervais, F.X. Lescure, S. Matheron, F. Louni, , Z. Julia, C. Mackoumbou-Nkouka, S Le Gac C. Charpentier, D. Descamps, G. Peytavin, Y. Yazdanpanah (***Paris Hop. Bichat***) ; K. Amazzough, G. Benabdelmoumen, P. Bossi, G. Cessot, C. Charlier, P.H. Consigny, F. Danion, A. Dureault, C. Duvivier, J. Goesch, R. Guery, B. Henry, K. Jidar, F. Lanternier, P. Loubet, O. Lortholary, C. Louisin, J. Lourenco, P. Parize, B. Pilmis, F Touam. (***Paris Hop. Necker Pasteur***) ; M.A. Valantin, R. Tubiana, R Agher, S.Seang, L.Schneider, R.PaLich, C. Blanc, C. Katlama (***Paris Hop. Pitié Salpétrière***) ; J.L. Berger, Y. N'Guyen, D. Lambert, I. Kmiec, M. Hentzien, A. Brunet, V. Brodard, F. Bani-Sadr (***Reims***) P. Tattevin, M. Revest, F. Souala, M. Baldeyrou, S. Patrat-Delon, J.M. Chapplain, F. Benezit, M. Dupont, M. Poinot, A. Maillard, C. Pronier, F. Lemaitre, C. Guennoun, M. Poisson-Vanier, T. Jovelin, J.P. Sinteff, C. Arvieux (***Rennes***) ; E. Botelho-Nevers, A. Gagneux-Brunon, A. Frésard, V. Ronat, F. Lucht (***St Etienne***) ; P. Fischer, M. Partisani, C Cheneau, M Priester, ML Batard, C Bernard-Henry, E de Mautort, S. Fafi-Kremer, D. Rey (***Strasbourg***) ; M. Alvarez , N. Biezunski, A. Debard, C. Delpierre, P. Lansalot, L. Lelièvre, G. Martin-Blondel, M. Piffaut, L. Porte, K. Saune, P. Delobel (***Toulouse***) ; F. Ajana, E. Aïssi, I. Alcaraz, V. Baclet, L. Bocket, A. Boucher, P. Choisy, T. Huleux, B. Lafon-Desmurs, A. Meybeck, M. Pradier, O. Robineau, N. Viget, M. Valette (***Tourcoing***)