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Long-Term Experience with Dual Therapy in Multi-Experienced Patients. COMBINE Study

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Abstract

Introduction: Dual Antiretroviral Therapy (DT) has been evaluated as a successful treatment approach in various patient populations, including treatment-naïve and suppressed individuals. However, its effectiveness in experienced patients who become nonadherent due to pill burden, dosing frequency, and/or associated toxicities and develop resistance to it is uncertain.

Objectives and Methods: This study aimed to assess the therapeutic efficacy of DT involving dolutegravir (DTG), doravirine (DOR), and darunavir/cobicistat (DRV/c) or darunavir/ritonavir (DRV/r 600/100 bid) in multi-experienced patients, both suppressed and unsuppressed. For patients experiencing treatment failure, genotypic resistance testing was conducted to evaluate drug efficacy. In cases without treatment failure, regimen selection was based on considerations such as previous toxicities, drug interactions, and clinical history.

Results: A total of 72 multi-experienced patients were studied (one with more than one treatment) between 2015 and 2023, mostly men (64%), with ages between 37 and 73 (average 54 ± 9) and a time of infection between 4 and 24 years (median or mean 16 ± 5). The major risk for infection was heterosexual (63%), followed by intravenous drug users (23%). All of them presented with more than one therapeutic drug class resistance, and the most previously used regime was RAL+LPV/R in 18 patients (24%). The most frequent reason for switching was the development of resistance in 30 (41%) of the patients, followed by simplification of the number of doses or tablets in 31 (42%) patients. At the switch, DTG+DRV/c were used in 46 (62%) patients, followed by DTG+DRV/R 600 in 19 (26%) patients. At the end of follow-up, 82% had a viral load of less than 200 cps/mL, 79% less than 100 cps/mL, and 67% had complete viral suppression. Twelve patients were lost for follow-up; seven patients were off medications; and of these, three died with AIDS-defining illnesses. Four additional patients died of non-HIV-related causes, all virally suppressed.

Conclusion: The extended evaluation period (6 years) demonstrated that the simplification for dual therapy in patients who were treatment experienced with prior adherence failure with consequent multi-resistant drug patterns is associated with a high degree of efficacy (82%). Many (18%) still dropped out, consistent with findings from other studies. The reduction of pill burden and toxicities are factors that, by promoting a higher adherence rate to treatment, may have contributed to this success.

Keywords: Dual Therapy (DT); Single-Tablet Regimen (STR); Dolutegravir (DTG); Darunavir/boosted (DRV/b); Low-Level Viremia (LLV)

Introduction

Since the early days of HIV treatment, patients with poor adherence have often been lost to follow-up and experienced multiple drug resistance patterns. Once reintroduced into treatment, the complexity of subsequent treatment regimens has been a major obstacle, with a delicate decision-making process for further treatment, follow-up, and survival. The need for simplification of therapies becomes apparent, yet the use of Dual Therapy (DT), while successful in treatment-naïve and suppressed patients, lacks extensive validation in experienced patients with prior resistance and suboptimal treatment histories. Many remain challenged by pill burden and drug-induced toxicities. Novel and simplified therapeutic regimens, including dual therapy, are an option.

While DT has been explored and accepted in certain scenarios in therapy guidelines, its effectiveness and tolerability have varied across studies, such as PROGRESS [1], exploring the combinations of RAL+DRV/r [2], DRV/r+3TC [3], and LPV/r+3TC [4,5]. However, recent advancements have changed this. High-potency DT, such as dolutegravir/rilpivirine (DTG/RPV) [6] and lamivudine/dolutegravir (3TC/DTG) [7], have shown promising outcomes for both naive and experienced patients. These treatments have been particularly successful when patients switch to simplified regimens (e.g., reducing pill burden and/or minimizing toxicities).

Since the introduction of DTG and DOR, treatment patterns have shifted, benefiting from accumulated experience with both drugs. Additionally, the co-formulation of DRV with cobicistat (DRV/c) in a Single-Tablet Regimen (STR) has enabled the use of high-genetic-

barrier therapeutics in simplified regimens, often comprising only two drugs when cobicistat functions solely as a booster. Further studies focusing on multi-experienced patients, such as those seen in BenchmrK [8], Resist [9], Power [10], and more recently Capella [11] and Brighte [12], are essential for evaluating these new combinations and their efficacy in challenging patient populations.

Objectives

This study aims to evaluate the response to DT comprising Dolutegravir (DTG), either doravirine (DOR), or darunavir boosted by ritonavir or cobicistat (DRV/b) in multidrug-experienced patients with resistance to more than two therapeutic classes, often nucleoside (tide) reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors. The evaluation will be based on achieving a negative or decreased viral load (quantitative HIV RNA), with a criterion of at least a $2_{log}10$ decrease at the end of 8 weeks of therapy.

Additionally, secondary analysis will assess the degree of recovery of the immune response measured by variations in total CD4+ T lymphocyte count (TCD4+), as well as the recovery of the immune system through analyzing variations in the percentage of CD4+ T lymphocytes and the CD4+/CD8+ ratio.

Furthermore, the study will assess the reasons for discontinuation or modification of therapy.

Methods

Seventy-two patients were studied between 2015 and 2023, drawn from the database of the Infectious Diseases Service (IDS) of the Local Health Unit of Matosinhos, EPE-Pedro Hispano Hospital in Matosinhos, Portugal. The service closely monitors approximately 1200 patients with HIV/AIDS infection, 1141 of whom is undergoing treatment with various therapeutic regimens-first, second, or third line. These 72 patients were all multi-experienced individuals, exhibiting resistance to at least two therapeutic drug classes. They were receiving suboptimal regimens (characterized by a high number of pills and toxicities) based on genotypic tests and had been maintaining therapy due to the lack of robust solutions allowing simplification.

The choice for the switch based on combinations with dolutegravir (DTG), doravirine (DOR), and darunavir/cobicistat (DRV/c) or darunavir/ritonavir (600/100 bid) was made after a re-analysis of the patient's history (past ART regimens and their clinical status), and in patients in failure, the choice of drugs was made according to the results of the genotyping test.

A close follow-up was maintained with quantitative HIV RNA, total T-CD4+ counts, and TCD4+/CD8+ ratio, initially every 3 months and then extended to every 6 months from the second year of follow-up.

The efficacy of ART was determined by the variation in the percentage of patients with suppressed HIV RNA <200 copies/mL (cps/mL) or the decrease of $2_{log}10$ at the end of 8 weeks of therapy in patients with previous treatment failure, according to the FDA's Snapchat algorithm [13,14] where missing = failure.

The immune response analysis was made by the variation of the TCD4+ and TCD8+ counts, their percentages, and the CD4+/CD8+ ratio before and at the end of follow-up. Microsoft Excel® 365 was used for correlation statistical analysis.

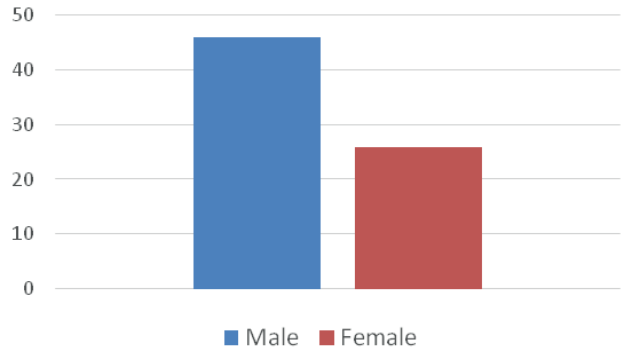
Results

Out of 1250 patients, 72 were undergoing complex and suboptimal therapies due to either a high pill burden or toxicity issues, prescribed based on genotypic resistance tests. Among these, 46 (64%) were males, aged between 37 and 73 years (mean age 54 ± 9 years), with 96% being of Portuguese nationality (Graph 1).

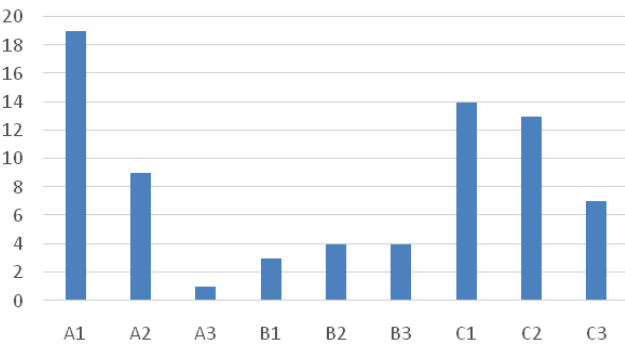
The risk for HIV infection was heterosexual intercourse in 63%, followed by intravenous drug addiction in 32%, and men who have sex with men (MSM) in 7%. In this group of patients, the duration of infection ranged from a minimum of 4 years to a maximum of 24 years (mean 16 ± 5 years). Analyzing the immunological status according to the criteria of the Centers for Disease Control and Prevention (CDC), 46% were in stage C (Graph 2).

The 72 patients had different ART regimens (one had two different regimens due to resistance), some in monotherapy, with the most represented regimen being RAL+LPV/r, in 18 patients (24%), followed by DTG+DRV/c, in 5 patients (7%) (Table 1).

The most frequent reason for switching was resistance in 30 (41%) patients, followed by simplification of pill burden in 31 (42%), and Low-Level Viremia (LLV) (persistence of HIV RNA between 100 and 200 cps/mL) in 9 (12%). Toxicity was the reason for change in 4 (5%) patients, although it is conceivable that in some cases of simplification, there were also concerns to prevent future toxicities. In one case, DT was changed due to gastrointestinal effects-the patient was on DTG+DRV/c and changed to DTG+DOR with the resolution of the effects. Regarding regimens, the most used regimen was DTG+DRV/c 800/100mg in 45 (62%) patients, followed by DTG+DRV/r 600/100mg twice daily in 19 (26%). The remaining is shown in graph 3.



Graph 1: Distribution of the 72 patients by gender.



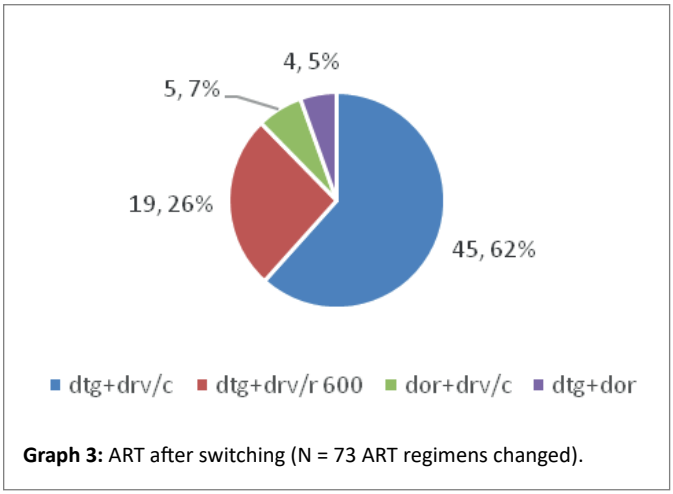
Graph 2: Distribution of the 72 patients according to the CDC Staging at the beginning of the study.

Table 1: ART Regimens previously to switch.

ART Regimes prior to switch	Patients	%
ral+lpv/r	18	24%
dtg+drv/c	5	7%
abc/3tc/dtg	5	7%
tdf/ftc/efv	4	5%
ral+etr	4	5%
lpv/r	3	4%
tdf/ftc+drv/r	3	4%
ral+drv/c	2	3%
taf/ftc/drv/c	2	3%
abc/3tc+drv/r	1	1%
taf/ftc+dor	1	1%
abc/3tc+drv/c	1	1%
ral+etr+drv/r	1	1%
tdf+ral+drv/r	1	1%
etr+dtg+drv/r+mrv	1	1%
mvc+drv/r 600	1	1%
tdf/ftc+etr	1	1%
ral+lpv/r+3tc	1	1%
tdf+ral+etr	1	1%
dtg+etr+drv/r	1	1%
tdf/ftc+lpv/r	1	1%
drv/r+etr	1	1%
abc/3tc+ral+etr	1	1%
drv/r+etr+dtg	1	1%
tdf+etr+drv/c	1	1%
azt/3tc+ral+etr	1	1%
azt+ral+drv/r	1	1%
ral+drv/r	1	1%
tdf+etr+drv/r	1	1%
abc/3tc+atz/r	1	1%
abc/3tc+ral	1	1%
abc/3tc/azt+ral	1	1%
tdf/ftc+ral	1	1%
ral+drv/r+azt	1	1%
azt/3tc+efv	1	1%
dtg/rpv	1	1%

(NOTE: the total is 73- as one patient was on two regimens prior due to side effects).

ral – raltegravir; lpv/r-lopinavir/ritonavir; dtg-dolutegravir; drv/c-darunavir/cobicistat 800/100mg; abc-abacavir; 3tc- lamivudine; efv-efavirenz; etr-etravirine; tdf-tenofovir DF; taf-tenofovir alafenamide; drv/r-darunavir/ritonavir 600/100mg; dor-doravirine; ftc-emtricitabine; mrv-maraviroc; azt-zidovudine; rpv-rilpivirine; atz/r- atazanavir/ritonavir.



Graph 3: ART after switching (N = 73 ART regimens changed).

These regimens were used for a minimum of 4 weeks up to 443 weeks, with average treatment duration of 175 weeks.

At the beginning of the new treatment, HIV RNA varied from <200 cps/mL to 787,973 cps/mL, with 30 (36%) patients negative and 12 (16%) with levels compatible with LLV. At the end of the evaluation, 82% were suppressed with HIV RNA <200 cps/mL, and 79% had levels <100 cps/mL, with 49 (67%) patients testing negative. Regarding immune status, 32 (43%) patients had TCD4+ counts <350 cells/µL, and of these, 8 (25%) had counts <100 cells/µL. However, there was substantial recovery of immunity at the end of the evaluation, as presented in table 2.

At the end of the evaluation period, 12 patients were lost to follow-up, all abandoning treatment after periods of poor adherence. Among these, 3 died from AIDS-defining illnesses. Additionally, 4 patients died, but they were negative at the time of death and their deaths were not related to HIV/AIDS.

Discussion and Conclusion

This study underscores the complexity of managing HIV patients with diverse treatment histories. Despite facing challenges such as resistance and medication toxicity, the implementation of dual therapy regimens has shown promising results in improving treatment outcomes. The observed reduction in viral loads and improvement in immune status reflect the efficacy of these regimens in suppressing HIV replication and restoring immune function.

However, the study also highlights the persistent issue of treatment adherence, as evidenced by the loss of follow-up of 12 patients, as presented in other studies. This underscores the ongoing need for interventions to support patient adherence and retention in care.

Furthermore, the occurrence of AIDS-related deaths among the lost-to-follow-up patients emphasizes the critical importance of continuous monitoring and support for HIV-positive individuals, particularly those with advanced disease stages. While dual therapy offers a valuable treatment option, comprehensive care strategies addressing both medical and psychosocial needs remain essential for optimizing patient outcomes.

Overall, this study contributes valuable insights into the real-world application of dual therapy regimens and emphasizes the importance of individualized treatment approaches and holistic patient care in the management of HIV/AIDS.

Table 2: Data regarding the Virological and Immune status of the 73 cases before and after switching to dual therapy.

At switch								After switch									Reasons	Var % CD4	Var % CD8	Var CD4	Var CD8
DATA i	RNA HIV	log HIV	% CD4	% CD8	CD4/CD8	CD4	CD8	DATA f	RNA HIV	log HIV	% CD4	% CD8	CD4/CD8	CD4	CD8	T ARV					
12/01/2016	4717	3,67	15,3	61,1	0, 25	501	1999	27/03/2023	0		22,2	54,3	0,41	605	1482	376		45%	-11%	21%	-26%
15/10/2019	40		23,5	37,7	0,62	1227	1968	22/07/2021	0		24,1	35,7	0,68	1203	1777	92		3%	-5%	-2%	-10%
17/03/2021	0		45,4	41,1	1,1	313	284	10/01/2023	21	1,32	32,3	46,3	0,7	501	717	95		-29%	13%	60%	152%
20/05/2019	11916	4,08	12,6	45,9	0,27	339	1238	23/03/2023	4939	3,69	18	47	0,38	417	1089	200	Bad Adhesion	43%	2%	23%	-12%
04/07/2019	40		28,2	43,6	0,65	712	1102	13/06/2023	0		34	33,8	1,01	941	934	206		21%	-22%	32%	-15%
01/08/2019	0		22,6	54,4	0,41	432	1041	09/05/2023	0		29,7	53,4	0,56	410	738	197		31%	-2%	-5%	-29%
08/10/2018	0		27,8	49	0,57	645	1138	03/05/2023	0		26	49,4	0,53	873	1658	238		-6%	1%	35%	46%
27/09/2017	2130	3,33	10,9	74,7	0,15	248	1695	19/07/2021	8946	3,95	11,8	76,6	0,15	155	1002	199	Bad Adhesion	8%	3%	-38%	-41%
23/06/2016	7553	3,88	21,5	66,5	0,32	623	1923	21/03/2023	0		33,9	47,6	0,71	1278	1797	352		58%	-28%	105%	-7%
24/02/2016	0		4,4	57	0,08	91	1169	11/05/2023	0		7	65,3	0,11	232	2170	376		59%	15%	155%	86%
14/04/2021	64	1,81	41	31,3	1,31	605	462	23/05/2023	0		42	30,8	1,36	571	419	110		2%	-2%	-6%	-9%
12/01/2016	2186	3,34	10,9	75,8	0,14	282	1965	02/03/2023	0		28	47,2	0,59	507	855	372		157%	-38%	80%	-56%
29/05/2019	104	2,02	18,6	52,1	0,36	264	740	15/05/2023	0		19,8	51,1	0,39	312	807	207		6%	-2%	18%	9%
29/09/2020	0		41,5	37,4	1,11	1054	950	05/01/2023	0		42,3	35,7	1,18	980	828	118		2%	-5%	-7%	-13%
05/07/2018	0		32,4	33,1	0,98	438	447	21/06/2023	0		32,1	33,9	0,95	459	485	259		-1%	2%	5%	9%
26/10/2017	146	2,16	18,7	51,6	0,36	275	758	22/05/2019	40		25,8	34,8	0,74	380	511	82		38%	-33%	38%	-33%
17/04/2017	17562	4,24	12,4	60,5	0,2	308	1506	05/06/2023	0		18,9	52,3	0,36	484	1341	320		52%	-14%	57%	-11%
26/12/2019	3896	3,59	22,2	41,6	0,53	204	382	17/05/2023	8149	3,91	17,2	67,3	0,26	229	895	177	Bad Adhesion	-23%	62%	12%	134%
07/10/2019	0		34	39,9	0,85	568	666	02/01/2023	0		27,4	33,3	0,82	753	918	169		-19%	-17%	33%	38%
18/08/2020	0		40,3	40,4	1	805	806	17/03/2021	0		40,9	39,6	1,03	718	696	30		1%	-2%	-11%	-14%
19/09/2018	197643	5,3	7,8	86,4	0,09	96	1072	09/08/2023	0		10,6	74,5	0,14	281	1978	255		36%	-14%	193%	85%
13/06/2017	0		36	33,4	1,08	940	871	28/12/2022	0		40,5	32,9	1,23	1264	1025	289		13%	-1%	34%	18%
15/05/2019	0		32,2	33,9	0,95	619	651	22/03/2023	0		30,6	38,6	0,79	668	843	201		-5%	14%	8%	29%
02/01/2019	0		21,4	53,2	0,4	504	1254	06/02/2023	0		21,2	47,7	0,44	439	988	214		-1%	-10%	-13%	-21%
30/03/2016	2264	3,35	44,3	46	0,96	1115	1158	27/03/2023	0		46,2	39,5	1,17	1074	920	365		4%	-14%	-4%	-21%
11/04/2019	264	2,42	17,4	53,3	0,33	466	1434	10/04/2023	0		24	39,7	0,61	818	1352	209		38%	-26%	76%	-6%
14/06/2021	0		20,9	32,1	0,65	541	830	20/03/2023	0		20,9	29,4	0,71	306	429	92		0%	-8%	-43%	-48%
18/06/2018	20708	4,32	23	61,4	0,37	281	749	10/03/2022	71811	4,86	8,1	82,6	0,1	55	561	194	Bad Adhesion	-65%	35%	-80%	-25%
03/06/2015	40		15,4	53,7	0,29	329	1148	26/10/2015	0		18,8	60,4	0,31	250	804	21		22%	12%	-24%	-30%
03/03/2015	0		15,5	43,8	0,35	302	851	16/02/2022	46	1,66	7	71,8	0,1	109	1121	363		-55%	64%	-64%	32%
16/02/2022	46	1,66	7	71,8	0,1	109	1121	04/01/2023	2483100	6,39	8,2	64,3	0,13	88	687	46	Bad Adhesion	17%	-10%	-19%	-39%
06/07/2021	20213	4,31	10,9	49,4	0,22	31	143	26/06/2023	105	2,02	21,3	49,3	0,43	145	335	103		95%	0%	368%	134%
17/03/2022	12550	4,1	16,1	56,7	0,28	73	256	27/09/2023	0		16,7	53,1	0,3	123	391	80		4%	-6%	68%	53%
03/04/2023	0		33,5	40,6	0,83	691	837	16/10/2023	0		36,2	44,1	0,8	652	795	28		8%	9%	-6%	-5%
19/05/2016	88338	4,95	18,4	63,3	0,29	386	1330	20/04/2023	0		35,7	46	0,78	892	1148	361		94%	-27%	131%	-14%
23/04/2019	0		0,3	39,1	0,51	532	1037	19/04/2022	0		18,3	45,9	0,4	486	1220	156		6000%	17%	-9%	18%
06/11/2018	0		0,38	44,1	0,71	679	956	11/10/2023	0		30,3	39,3	0,8	677	876	257		7874%	-11%	0%	-8%
20/10/2022	23	1,36	40,4	38,6	1,05	1424	1362	23/08/2023	0		41,7	35,9	1,2	1609	1385	44		3%	-7%	13%	2%
29/05/2019	0		36,9	39,5	0,93	795	852	07/02/2023	0		39,4	39,4	1	970	970	193		7%	0%	22%	14%
20/08/2018	787973	5,9	11,9	49,1	0,24	63	260	20/08/2018	787973	5,9	11,9	49,1	0,24	63	260	0	Bad Adhesion	0%	0%	0%	0%
11/05/2023	0		14,9	51,9	0,29	338	1172	11/05/2023	0		14,9	51,9	0,3	338	1172	0		0%	0%	0%	0%
08/11/2018	103	2,01	19,6	42,5	0,46	211	458	16/09/2019	0		18,9	47,3	0,4	230	577	45		-4%	11%	9%	26%
09/02/2017	220765	5,34	12,8	70	0,18	261	1428	22/05/2019	870964	5,94	5,7	71,4	0,08	98	1244	119	Bad Adhesion	-55%	2%	-62%	-13%
03/07/2018	84	1,92	21,2	35,9	0,59	528	895	22/06/2023	0		20,4	31,7	0,64	542	844	259		-4%	-12%	3%	-6%
13/04/2016	0		9,7	67,2	0,14	380	2632	08/05/2023	0		11,4	59,4	0,19	559	2924	369		18%	-12%	47%	11%
24/10/2018	246	2,39	35,9	41,9	0,86	959	1119	27/12/2022	0		44,1	31,3	1,41	1552	1103	218		23%	-25%	62%	-1%
21/12/2020	0		17,7	42,6	0,42	485	1166	24/05/2023	0		21,4	44,2	0,48	397	821	126		21%	4%	-18%	-30%
14/01/2019	0		46,1	26,9	1,72	1168	680	08/05/2023	0		47,5	26,4	1,8	908	506	225		3%	-2%	-22%	-26%
05/12/2019	129587	5,11	18,4	60,3	0,31	291	953	01/02/2023	154360	5,19	8,6	70,7	0,12	108	890	165	Bad Adhesion	-53%	17%	-63%	-7%
01/03/2018	104	2,02	19,2	43	0,45	613	1373	13/02/2023	0		24,8	37,2	0,67	862	1292	259		29%	-13%	41%	-6%
29/05/2019	875	2,94	24,6	48,5	0,51	596	1173	16/03/2023	0		14,9	67	0,22	607	2734	198		-39%	38%	2%	133%
05/12/2019	185017	5,27	24,5	44,7	0,55	336	612	03/07/2023	0		30,6	37,2	0,8	615	747	187		25%	-17%		
17/04/2023	0		32,1	27,7	1,16	1432	1238	07/11/2023	0		33,2	28,3	1,2	1476	1259	29		3%	2%		
21/10/2015	124867	5,1	3,6	70,9	0,05	89	1774	31/07/2017	21293	4,33	8,5	69,3	0,12	177	1436	93	Bad Adhesion	136%	-2%	99%	-19%
21/11/2018	0		20,5	24,8	0,83	307	371	20/03/2023	0		20,2	33,3	0,61	379	617	226		-2%	34%	23%	66%
05/03/2018	458284	5,66	6,3	37,5	0,17	31	184	28/06/2023	28	1,45	20,1	51,9	0,39	445	1151	277		219%	38%	1335%	526%
18/12/2019	6391	3,81	29,1	46,1	0,63	332	525	04/03/2020	300681	5,48	25,4	35,8	0,71	289	408	11	Bad Adhesion	-13%	-22%	-13%	-22%
26/07/2016	718208	5,86	32,2	56,6	0,57	462	811	13/09/2022	199	2,3	36,6	48	0,76	1206	1581	320	Side Effects	14%	-15%	161%	95%
15/03/2023	511	2,71	28,9	55,8	0,52	707	1362	26/10/2023	97	1,99	37,1	46,6	0,8	730	919	32		28%	-16%	3%	-33%
20/07/2022	3886	3,59	17,6	35,8	0,49	366	748	11/04/2023	58	1,76	16,2	33,5	0,48	453	937	38		-8%	-6%	24%	25%
30/03/2022	514643	5,71	5,6	78,3	0,07	83	1158	03/01/2023	291	2,46	13,3	72,5	0,18	289	1580	40		138%	-7%	248%	36%
17/02/2015	4408	3,64	22,3	44,1	0,5	298	590	27/02/2023	0		35,6	35,1	1,01	541	533	419		60%	-20%	82%	-10%
13/05/2021	638	2,8	19,1	56,4	0,34	536	1586	25/01/2022	0		22,3	51,3	0,44	572	1313	37		17%	-9%	7%	-17%
25/01/2022	0		22,3	51,3	0,44	572	1313	27/02/2023	490	2,69	19,8	53	0,37	505	1351	57	Bad Adhesion	-11%	3%	-12%	3%
09/05/2023	0		33,4	56,5	0,59	976	1650	07/11/2023	34	1,53	32,6	56,8	0,6	956	1668	26		-2%	1%	-2%	1%
05/04/2016	0		33	39,4	0,84	722	863	29/06/2023	0							377		-100%	-100%	-100%	-100%
11/10/2018	0		20,4	58,9	0,35	390	1124	23/02/2022	0		21	59,5	0,35	118	334	176		3%	1%	-70%	-70%
07/03/2019	10127	4,01	13,2	57	0,23	265	1142	11/04/2023	0		21,4	44,1	0,48	605	1249	214		62%	-23%	128%	9%
17/10/2018	72	1,86	19,4	62,7	0,31	429	1385	28/03/2023	0		29,3	5,29	0,55	583	1054	232		51%	-92%	36%	-24%
13/01/2022	136859	5,14	11,5	51,4	0,22	123	551	26/06/2023	1001	3.00	10,2	57,4	0,18	148	838	76	Bad Adhesion	-11%	12%	20%	52%
06/06/2019	50063	4,7	7,2	52,2	0,14	116	836	11/04/2023	31	1,49	21,7	39	0,56	516	929	201		201%	-25%	345%	11%
06/02/2020	17779	4,25	11,4	66,2	0,17	357	2065	26/04/2023	22	1,34	18,1	33,7	0,54	337	628	168		59%	-49%	-6%	-70%
25/08/2021	105	2,02	20,8	58,3	0,36	133	373	12/04/2023	0		22,2	44,9	0,49	302	611	85		7%	-23%	127%	64%

Data i: DATA initial; DATA f: DATA final; Var: variation; T ART: Time after switch.

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