Switching to DTG+3TC vs 3-Drug Regimens in Routine Clinical Care: Long-term Swedish Data

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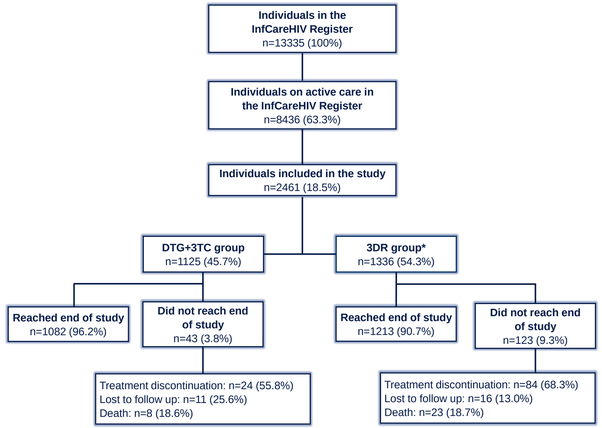
Introduction

- Swedish HIV treatment guidelines recommend that switching to the 2-drug regimen dolutegravir (DTG) + lamivudine (3TC) for maintaining virologic suppression should be considered in people living with HIV (PLHIV) in routine clinical care - provided there is no history of virologic failure, chronic hepatitis B, or resistance to 3TC, emtricitabine, or integrase inhibitors.
- We conducted a retrospective, observational, multi-center, comparative cohort study evaluating long-term outcomes of switching to DTG+3TC versus 3-drug standard of care regimens (3DR) in routine clinical care in Sweden.

Methods

- Retrospective data (patient demographic, virus-related, and clinical predictors including patient-reported outcomes such as self-reported adherence) of all ART-experienced individuals with HIV RNA <50 copies/mL and switching to either DTG+3TC or a 3DR (July 2019 - May 2023) were obtained from the Swedish National Quality Registry for HIV (InfCareHIV).
- The primary endpoint was the proportion of participants in the intent-to-treat (ITT) and on-treatment (OT) population with virological failure (VF, two consecutive HIV RNA levels ≥200 copies/mL prior to/by assessment timepoint) at months M6, M12, M24, M36, and M42 post-switch to DTG+3TC or 3DR.
- A logistic generalized estimating equations (GEE) model was used to find associations between patient demographic and clinical predictors on VF, assuming an exchangeable correlation structure.

Figure 1. A Flowchart Summarizing the Population Analyzed in This Study



*The most common 3-drug regimens were, among others: bictegravir/emtricitabine/tenofovir alafenamide (n=544, 40.7%), dolutegravir/emtricitabine/tenofovir disoproxil fumarate (n=296, 22.2%), dolutegravir/abacavir/lamivudine (n=210, 15.7%), dolutegravir/emtricitabine/tenofovir alafenamide (n=130, 9.7%), and doravirine/emtricitabine/tenofovir disoproxil fumarate (n=56, 4.2%).

Switching to DTG+3TC is an effective strategy for maintaining virologic suppression in routine clinical practice

Table 1. Baseline Characteristics

Characteristic	DTG+3TC (n=1125)	3DR (n=1336)	Total (n=2461)	*P* value
Age at baseline (years), mean (SD)	50.1 (13.0)	47.5 (15.0)	48.7 (14.0)	2.53E-06
Age at diagnosis (years), mean (SD)	36.1 (12.0)	33.0 (13.0)	34.4 (13.0)	8.26E-10
Weight at baseline (kg), mean (SD)	79.0 (15.0)	76.4 (18.0)	77.4 (17.0)	0.195
Sex at birth, n (%)				3.44E-08
Male	737 (66%)	723 (54%)	1460 (59%)	
Female	387 (34%)	613 (46%)	1000 (41%)	
Missing	1 (0.09%)	0 (0.0%)	1 (0.04%)	
Time on ART (years), mean (SD)	12.8 (6.9)	13.7 (7.8)	13.3 (7.4)	0.001
Baseline VL, median (range)	0 (0-49)	0 (0-49)	0 (0-49)	
Mode of transmission, n (%)				1.14E-13
Heterosexual	541 (48%)	729 (55%)	1270 (52%)	
MSM	436 (39%)	376 (28%)	812 (33%)	
PWID	34 (3%)	59 (4%)	93 (4%)	
Perinatal	11 (1%)	77 (6%)	88 (4%)	
Other/missing	103 (9%)	95 (7%)	198 (8%)	
Geographical origin, n (%)				2.13E-14
Europe and North America	577 (51%)	488 (37%)	1056 (43%)	
Sub Saharan Africa	267 (24%)	520 (39%)	787 (32%)	
Asia and the Pacific	140 (12%)	151 (11%)	291 (12%)	
Other/missing	150 (13%)	177 (13%)	318 (13%)	
CD4 count at baseline, n (%)				4.43E-06
<500	248 (22%)	422 (32%)	670 (27%)	
≥500	696 (62%)	761 (57%)	1457 (59%)	
Missing	181 (16%)	153 (11%)	334 (14%)	
[a]Pre-switch self-reported adherence, n (%)				0.404
Optimal	815 (72%)	832 (62%)	1647 (70%)	
Sub-optimal	56 (5%)	68 (5%)	124 (5%)	
Missing	254 (23%)	436 (33%)	690 (28%)	
[b]Pre-switch low-level viraemia, n (%)				4.32E-06
No	734 (65%)	749 (56%)	1483 (60%)	
Yes	391 (35%)	587 (44%)	978 (40%)	
Pre-switch M184V RAMs[c], n (%)	10 (0.9%)	86 (6.4%)	96 (3.9%)	<0.001

ART, antiretroviral therapy; MSM, men having sex with men; PWID, people who inject drugs; RAM, resistance associated mutation.

[a]Patients were classified as having sub-optimal adherence if they self-reported not having taken any HIV medication or if they had missed any doses during the week preceding filling the HRQOL questionnaire. Otherwise, their self-reported adherence was classified as optimal. [b]Low-level viraemia was defined as the incidence of HIV-1 RNA measures of >50 c/mL and <200 c/mL after suppression to <50 c/mL at any timepoint. [c]The most common pre-switch RAMs for the DTG+3TC group were: M36I (n=202, 18%), L89M (n=181, 16%), I93L (n=155, 14%), L63P (n=102, 9%), and H69K (n=89, 8%). The most common pre-switch RAMs for the 3DR group were: M36I (n=229, 17%), L89M (n=215, 16%), I93L (n=175, 13%), L63P (n=148, 11%), and H69K (n=110, 8%).

Table 2. Sample Sizes (n) at Each Time-Point in Intent-to-Treat and On-Treatment Analysis Sets

	BL	6 months		12 months		24 months		36 months		42 months	
		ITT	OT	ITT	OT	ITT	OT	ITT	OT	ITT	OT
DTG+3TC	1125	773	773	558	551	308	304	112	107	35	32
3DR	1336	1005	1005	860	835	677	644	332	312	139	132
Total	2461	1778	1778	1418	1386	985	948	444	419	174	164

BL, baseline; ITT, intent-to-treat; OT, on-treatment.

Results

- 2461 individuals switched regimen between July 2019 – May 2023; 1125 (46%) to DTG+3TC and 1336 (54%) to a 3DR (**Figure 1** and **Table 1**).
- 1778 individuals had data for the period between baseline and month 6 (M6), M6-M12 (n=1418), M12-M24 (n=985), M24-M36 (n=444), and M36-M42 (n=174, **Table 2**).
- The absolute virologic failure counts were lower in the DTG+3TC group at all timepoints in both the intent-to-treat (ITT) and on-treatment (OT) analyses (**Table 3** and **Table 4**).
- In the adjusted OT analysis:
  - VF rates were lower in the DTG+3TC compared with 3DR at M24, M36, and M42 (**Table 5**).
  - In the DTG+3TC group, the odds of VF were statistically significantly lower at M24, M36, and M42 compared with M6 (p<0.001), whilst in the 3DR group the odds of VF were significantly higher at M36 and M42 timepoints compared with M6 (p=0.014, and p=0.041, respectively).
- Treatment discontinuation rates were 3.8% for the DTG+3TC group and 9.2% for the 3DR group.
- Incidence of treatment-emergent resistance[#] post-switch was low in the study population:
  - The DTG+3TC group; NRTI resistance, 0.061 (95% CI 0.009, 0.436) per 100 person years (PY).
  - The 3DR group; NRTI and PI resistance were 0.531 (0.315, 0.895) and 0.114 (0.037, 0.352) per 100 PY, respectively.
  - No emergent INSTI resistance was observed post-switch in either group.
- In the adjusted ITT analysis (GEE model[a]):
  - A unit increase in age and CD4 count ≥500 at baseline were statistically significantly associated with decreased odds of VF (adjusted odds ratio [aOR], 0.96 [0.93 – 0.99], p=0.005, and 0.27 [0.12 – 0.58], p=0.001, respectively).
  - Having low-level viraemia post-switch (4.84 [2.39 – 9.80], p<0.001), sub-optimal self-reported adherence post-switch (3.87 [1.12 –13.40], p=0.033), documented ART resistance pre-switch (1.5*10e-18 [6.84*10e-19 – 3.28*10e-18], p<0.001) and documented ART resistance post-switch (21.79 [4.32 – 109.86], p<0.001) were statistically significantly associated with increased odds of VF.
- In the adjusted OT analysis:
  - A unit increase in age was associated with lower odds of VF (aOR, 0.94 [0.90 – 0.97], p=0.005).
  - Viral blips post-switch (8.45 [3.70 – 19.31], p<0.001), sub-optimal self-reported adherence post-switch (5.02 [1.29 –19.47], p=0.020), documented ART resistance pre-switch (1.3*10e-18 [3.27*10e-19 – 4.77*10e-18], p<0.001) and documented ART resistance post-switch (46.63 [7.76 – 280.09], p<0.001) were statistically significantly associated with increased odds of VF.

[a]Overall, the top 3 treatment-emergent mutations in the DTG+3TC group were: V179I (n=3), A98G (n=3), and G198A (n=2); and for the 3DR group: M50I (n=6), A71T (n=2), and K20R (n=2).

[c]Covariates in the GEE model included: Treatment group, ART self-reported adherence, sex at birth, age, baseline CD4, HIV subtype, baseline drug resistance mutations, HBV, and HCV serostatus, viral blips before baseline and during the study.

Table 3. Absolute Virologic Failure Counts Occurring in Different Time-Points in the Intent-to-Treat Analysis Set

ART group	M0-M6 (n=1778)	M6-M12 (n=1418)	M12-M24 (n=985)	M24-M36 (n=444)	M36-M42 (n=174)
DTG+3TC	1	2	1	2	1
3DR	3	12	12	7	3
Total	4	14	13	9	4

Baseline study population: DTG+3TC group (n=1125), 3DR group (n=1336), total study group (n=2461). Overall, in the intent-to-treat analysis, seven patients on DTG+3TC and 37 patients on 3DR had VF.

Table 4. Absolute Virologic Failure Counts Occurring in Different Time-Points in the On-Treatment Analysis Set

ART group	M0-M6 (n=1778)	M6-M12 (n=1418)	M12-M24 (n=985)	M24-M36 (n=444)	M36-M42 (n=174)
DTG+3TC	1	2	0	0	0
3DR	3	9	7	6	3
Total	4	11	7	6	3

Baseline study population: DTG+3TC group (n=1125), 3DR group (n=1336), total study group (n=2461). Overall, in the on-treatment analysis, three patients on DTG+3TC and 28 patients on 3DR had VF.

Table 5. Adjusted Virologic Failure Rates (per 10000 PLHIV, 95% CI) Occurring in Different Time-Points in the On-Treatment Analysis Set

ART group	M0-M6 (n=1778)	M6-M12 (n=1418)	M12-M24 (n=985)	M24-M36 (n=444)	M36-M42 (n=174)
DTG+3TC	13 (1.8, 91.5)	36 (9.1, 145)	0 (0.0-0.0)	0 (0.0-0.0)	0 (0.0-0.0)
3DR	30 (9.7, 92.6)	108 (56.4, 207)	109 (52.2, 228)	192 (86.9, 424)	227 (74.2, 695)
Total	23 (8.5, 59.9)	79 (44.1, 143)	74 (35.3, 154)	143 (64.6, 316)	183 (59.6, 562)

Within-group estimates of precision for virologic failure rates following switch to DTG+3TC or 3DR therapy and corresponding 95% confidence intervals (CIs). Baseline figures: DTG+3TC group (n=1125), 3DR group (n=1336), total study group (n=2461).

Limitations

- In routine clinical care, patients self-reporting optimal adherence are more likely to be switched to DTG+3TC than those reporting sub-optimal adherence. Interpretation of between group differences should be made with caution due to selection bias.
- The observational study design could generate bias and undetected confounding variables.

Conclusions

- The study presents long-term real-world data on DTG+3TC effectiveness in clinical practice.
- We report low rates of VF, low levels of ART resistance post switch, and low treatment discontinuation for individuals treated with DTG+3TC, supporting data from randomized controlled trials[1,2].
- These findings strengthen switching to DTG+3TC as an effective strategy for maintaining virologic suppression in routine clinical practice.

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References: 1. Llibre et al. *Clin Infect Dis*. 2023;76:720-729. **2.** Osiyemi et al. *Clin Infect Dis*. 2022;75:975-986.

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