Rare Outcome Analysis in Longitudinal Real-World Data: Methodological Insights from a Study Assessing the Switch of HIV Treatment to 2 Versus 3-Drug Regimens in Sweden

MSR80

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Key Takeaways

- The study supports DTG+3TC as an effective strategy for virologically suppressed HIV patients in routine clinical care, results aligning with other real-world studies and randomized clinical trials.
- Over 3.5 years, 1,125 individuals switched to DTG+3TC and 1,336 to 3-drug regimens (3DR). The number of virologic failures was low with the highest incidence at any one time being 2 in DTG+3TC and 12 in 3DR across all timepoints.
- Methodological strategies successfully addressed challenges associated with rare outcome analysis, yielding consistent results across various analyses.
- No significant difference in virologic failures between DTG+3TC and 3DR was found. Older age and higher baseline CD4 count were associated with decreased odds of virologic failure, while viral blips post-switch and suboptimal adherence increased the odds of failure.
- Controlling for unmeasured factors affecting treatment selection remains a limitation.

Introduction

- Analyzing longitudinal HIV outcomes in patients who switch treatment poses an extra challenge to real-world data (RWD) analysis due to selection bias and the rarity of the outcomes, in addition to common issues like missing data and small patient numbers in long-term follow-up.
  - Selection bias may make matching insufficient to fully address group differences. In addition, given the rarity of the outcome, matching treatment groups could result in information loss and difficulties in achieving balance.
  - To mitigate these biases, we employed multivariable regression to adjust for potential confounders, supplemented by sensitivity and subgroup analyses.
- This retrospective, national cohort study used a combination of statistical methods to assess the long-term outcomes of switching to the 2-drug regimen dolutegravir and lamivudine (DTG+3TC) versus various 3-drug regimens (3DR), in Sweden.
  - DTG+3TC was approved as a treatment option in 2019 based on clinical trials showing non-inferior efficacy and favourable safety and tolerability compared to 3-drug regimens.
  - Swedish guidelines were updated in 2019 to include DTG+3TC as an option for maintaining viral suppression in individuals with no history of virologic failure or resistance to 3TC or INSTIs.

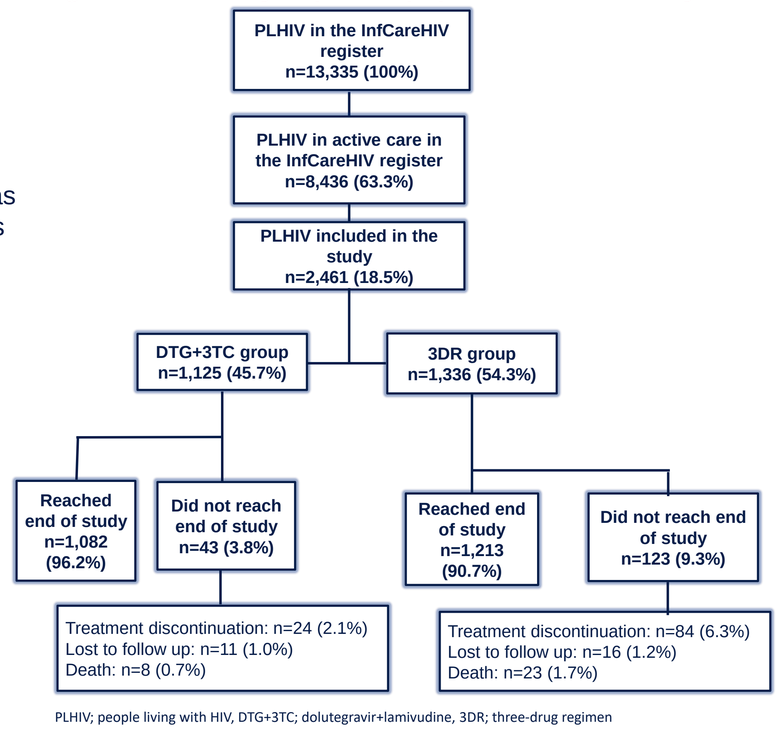
Methods

- All ART-experienced individuals with undetectable viral load (HIV RNA <50 copies/mL) who switched to DTG+3TC or a 3DR included in Swedish guidelines between 7/2019-05/2023 were collected from the Swedish National Quality Register for HIV (InfCareHIV).
- The primary endpoint was the proportion of study participants with virologic failure (VF) at 6, 12, 24, 36 and 42 months post-switch. VF was defined as having either two consecutive tests showing HIV RNA levels ≥200 copies/mL prior to or at the time of assessment, or one test showing HIV RNA levels ≥200 copies/mL followed by core agent discontinuation.

Statistical Methods

- Logistic generalized estimating equations (GEE) modelling was used to investigate the effects of clinical and demographic variables on VF and to adjust for confounders for intent-to-treat (ITT) and on-treatment (OT) analysis sets.
- Overall time to VF was analyzed using univariable and multivariable methods (Kaplan-Meier curves and Cox regression models).
- Sensitivity analyses included penalization for rare outcomes in GEE modelling for patients who were followed at least 6 months.
- Missing data patterns were assessed for collected variables and missing indicator method was used to capture the patterns associated with the absence of data.

Figure 1. Summary of patient population in this study.



PLHIV; people living with HIV, DTG+3TC; dolutegravir+lamivudine, 3DR; three-drug regimen

Results

- Out of 2,461 individuals, 1,125 (46%) switched to DTG+3TC and 1,336 (54%) 3DR between July 2019 and May 2023 (Figure 1).
- The number of individuals in the ITT and OT analysis sets at each timepoint are shown in Table 1.
- The counts and rates of virologic failure were low (Table 2).
  - In the ITT analysis, 7 individuals on DTG+3TC met VF and 37 on 3DR.
  - In the OT analysis, 3 and 28 individuals met VF in DTG+3TC and 3DR groups respectively.

Table 1. Number of individuals in the ITT and OT 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

- GEE modelling enabled the estimation of population-averaged effects for longitudinal, multivariable, and repeated measures data, as well as the assessment of potential differences in VF between the ART groups at each timepoint.
- In the ITT analysis, no difference between ART groups at any timepoints was found.
  - One year increase in age and CD4 count ≥500 at baseline were significantly associated with a decreased odds of VF (aOR, 0.96 [0.93 – 0.99], p=0.005, and 0.27 [0.12 – 0.58], p=0.001, respectively).
  - Having viral blips post-switch (4.84 [2.39 – 9.80], p<0.001), suboptimal 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 significantly associated with increased odds of VF.
- In the OT analysis, the odds of having VF were significantly lower on DTG+3TC compared with 3DR at 24, 36 and 42 months (p<0.001 for all).
  - Otherwise, the same effects were observed as for the ITT, except no association between CD4 count ≥500 at baseline and VF was found.
- Missing pre-switch RAM information and adherence data were associated with increased odds of VF.

Table 2. Virologic failure rates per 10,000 individuals (95% CI) in the ITT and OT analysis sets.

ART group	M6 (n=1778)	M12 (n=1418)	M24 (n=985)	M36 (n=444)	M42 (n=174)
ITT					
DTG+3TC	12.9 (1.8, 91.5)	35.8 (9.0, 143)	32.5 (4.6, 230)	179 (45.3, 707)	286 (41.4, 1970)
3DR	29.9 (9.7, 92.6)	140 (79.8, 246)	177 (101, 310)	211 (101, 439)	216 (70.5, 662)
Total	22.5 (8.5, 59.9)	98.7 (58.6, 166)	132 (76.9, 227)	203 (106, 388)	230 (87.3, 606)
OT					
DTG+3TC	12.9 (1.8, 91.5)	36.3 (9.1, 145)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
3DR	29.9 (9.7, 92.6)	108 (56.4, 207)	109 (52.2, 228)	192 (86.9, 424)	227 (74.2, 695)
Total	22.5 (8.5, 59.9)	79.4 (44.1, 143)	73.8 (35.3, 154)	143 (64.6, 316)	183 (59.6, 562)

Table 3. Baseline characteristics.

Characteristic	DTG+3TC (n=1125)	3DR (n=1336)	Total (n=2461)
Age at baseline, mean (SD)	50.1 (13%)	47.5 (15%)	48.7 (14%)
Age at diagnosis, mean (SD)	36.1 (12%)	33.0 (13%)	34.4 (13%)
Weight at baseline, mean (SD)	79.0 (15%)	76.4 (18%)	77.4 (17%)
Sex at birth, n (%)			
Male	737 (66%)	723 (54%)	1460 (59%)
Female	387 (34%)	613 (46%)	1000 (41%)
Missing	1 (0.09%)	0 (0.0%)	1 (0.04%)
Mode of transmission, n (%)			
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 (%)			
Europe & N. 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 (%)			
<500	248 (22%)	422 (32%)	670 (27%)
≥500	696 (62%)	761 (57%)	1457 (59%)
Missing	181 (16%)	153 (11%)	334 (14%)
CD8 count at baseline, n (%)			
<150	4 (1%)	4 (1%)	8 (0%)
≥150	780 (69%)	983 (73%)	1763 (72%)
Missing	341 (30%)	349 (26%)	690 (28%)
Pre-existing RAMs, n (%)			
No	549 (49%)	689 (52%)	1238 (50%)
Yes	571 (51%)	626 (47%)	1197 (49%)
Missing	5 (0%)	21 (1%)	26 (1%)

Overall time to virologic failure

- Time-to-event analysis allowed assessing the individual time-based risk of a VF happening while adjusting for confounding.
- Estimated probabilities of time-to-VF are shown in Figures 2 and 3 for the ITT and OT analysis sets.
- No significant difference was found in the time to VF between the DTG+3TC and 3DR groups in the univariable ITT analysis.
- In a multivariable Cox proportional hazard model, a significant difference observed in the univariate OT analysis disappeared when the analysis was adjusted for confounding variables
  - Older age and male sex were significant predictors of longer time to VF in both the ITT and OT analyses, whereas missing resistance information at baseline was predictive of shorter time to VF.
  - CD4 count ≥500 at baseline was also a significant predictor of longer time to VF in the ITT, but not in the OT analysis.

Sensitivity analysis

- Analyses validated the findings by comparing results across different model specifications.
- In the OTT analysis, older age, CD4 count ≥500 at baseline and documented ART resistance pre-switch were associated with decreased odds of VF.
- Suboptimal study adherence, viral blips post-switch and treatment emergent resistance increased the odds of VF.
- At M6, 3DR group had increased odds of VF compared to DTG+3TC.
- Similar results were achieved for the OT analysis set.

Figure 2. Time to virologic failure in the ITT analysis set.

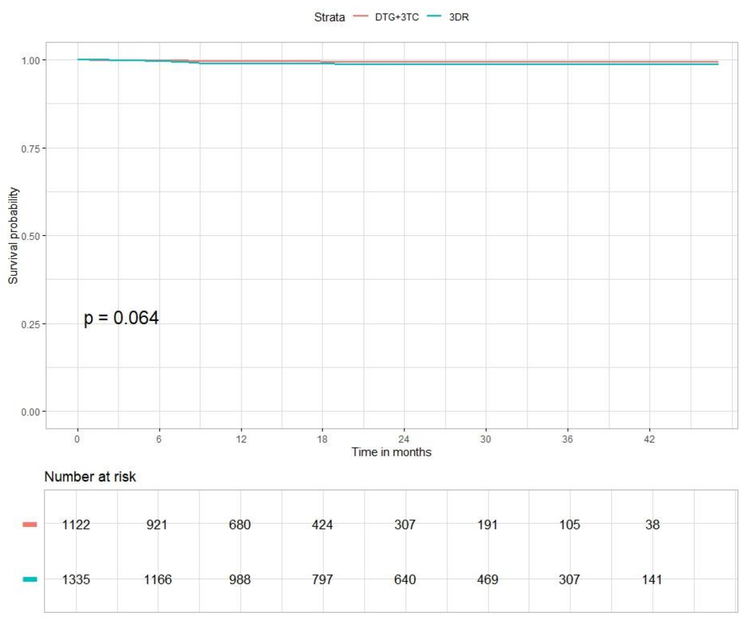
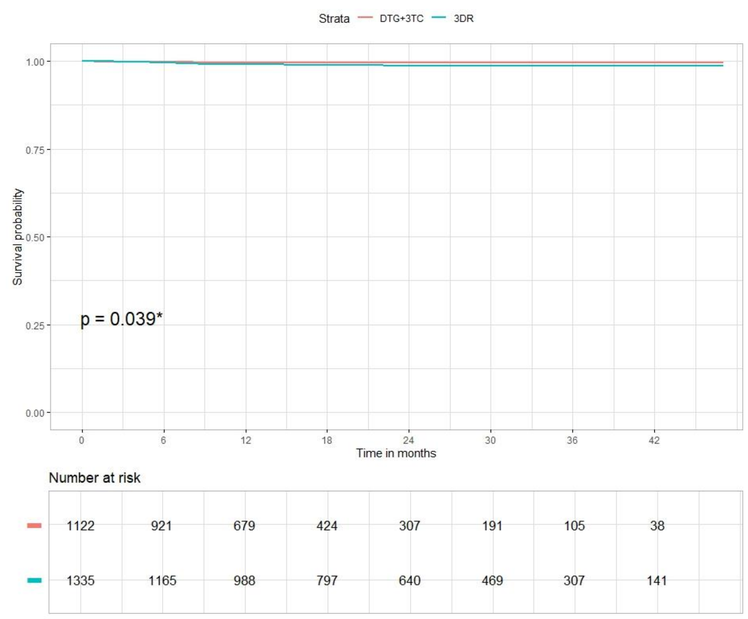


Figure 3. Time to virologic failure in the OT analysis set.



* Not a statistically significant difference after adjustment.

Conclusions

- The findings support the growing evidence of DTG+3TC as a viable simplification strategy for virologically suppressed people living with HIV in routine clinical care.
- The results are consistent with other real-world evidence studies[1] and RCTs[2].
- Methodological strategies effectively addressed the challenges of rare outcome analysis and comparable results were achieved from different analyses.
- Sensitivity analyses confirmed the robustness of the primary analysis by showing consistency in results.
- However, controlling for unmeasured variables affecting treatment selection remains a challenge.

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