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Comparison of the Risk of Resistance Accumulation According to ART Switching Strategies after Virological Failure >200 Copies/mL to First cART Using the g-computation Procedure

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BACKGROUND: No large randomized trials comparing switching strategies after virological failure of first ART exist. Despite this lack of clinical evidence, many clinical guidelines provide recommendations regarding the best time of switching after virological failure of ART. The World Health Organization (WHO) guidelines have been recently updated and the recommended viral load threshold for when to switch has been moved from >5,000 copies/mL to >1000 copies/mL. Consequences of a delayed switch compared to the prompt switch at viral load >200 copies/mL typically occurring in the resource rich settings are unknown.

OBJECTIVES: To use g-computation to mimic a switch strategy trial with endpoint the accumulation of drug resistance mutations (DRM) using observational data and compare 4 possible strategies: switch within 3 months of a viral load (VL) i) >200 copies/mL ii) >1,000 copies/mL iii) >5,000 copies/mL and then continue new treatment or iv) no switch (people kept on virological failing regimen).

METHODS: Participants in EuroSIDA who started their first cART regimen, achieved a VL≤50 copies/mL and subsequently experienced viral rebound (VR-two consecutive VL>200 copies/mL) and had ≥1 genotypic test (GT) either before starting ART or while failing but before the estimated date of VR and ≥1 after VR were included. Repeated GTs are available in the cohort because of extensive prior work in the area of accumulation of resistance using stored samples. A therapy switch was defined at the date at which ≥1 new drug was started for the first time with a VL>200 copies/mL after the date of VR. The outcome was the accumulation of ≥1 IAS-USA listed DRM (yes/no, **Figure 1** for an example of an included participant). DRM accumulation rates (AR) for the four strategies was compared using g-computation procedure. Results were loosely compared to those of a standard Cox regression analysis.

G-computation

1. Use parametric models to capture the relationships between the time-varying covariates and between these and the outcome. Baseline covariates were not included- (**Table 1**)
2. Estimate the parameters linking these variables
3 Use the estimates from the parametric models to simulate the time-varying covariates and the outcome which would have been observed if each study participant had followed the pre-specified switching strategies rather than being allowed to evolve naturally as in the collected data
4. The time-varying confounders and the outcome are simulated under each intervention
5. Perform inference by comparing the outcomes under different interventions as if these had been generated from a randomized experiment
6. 95% CI around the cumulative rate ratios (RR) were calculated using bootstrapping over 1,000 simulations.

RESULTS: We included 289 participants who experienced VR and had two resistance test results; main characteristics of the participants are shown in **Table 2**. One hundred and fifty-three (53%) of these accumulated ≥1 DRM between the two tests. Actual observed data and the simulated data under the observational regime were very similar (0.522 vs. 0.529) indicating that modelling assumptions are unlikely to be violated. **Table 3** shows the unadjusted estimates of the cumulative DRM-AR and DRM-RR adjusted for time-varying CD4 count and viral load. Results suggest comparable effect of either of the three switch strategies on risk of DRM accumulation, but all had a more favourable outcome compared with no switch. When comparing these with the results from the Cox regression analysis, the unadjusted analysis paradoxically suggested a beneficial effect of delaying treatment. Adjusting for time-varying CD4 count and viral load resulted in the delay to appear even more beneficial because conditioning on future viral load and CD4 count masks most of the beneficial effect of switching treatment promptly, and collider-stratification bias is induced, exaggerating the bias further.

MAIN LIMITATIONS:

- People with viral failure and no genotypic test data are excluded – this might generate bias
- G-computation does not control for unmeasured confounding
- Although the parametric models for time-varying CD4 count and viral load provided a good fit for the data (the factuals), we cannot rule out that there is incorrect specification for the counterfactuals
- Endpoint was defined as accumulation of any DRM (i.e. not specific to failing regimen)
- Applicability to the setting of people using first line with TDF+NNRTI-based regimens and non-B subtype is limited

CONCLUSIONS: ***The applied statistical approach has potential to inform clinical decisions as there is paucity of data from randomized clinical trials. A larger dataset and an improved model for imputing missing genotypic resistance data is required to validate this observation.***

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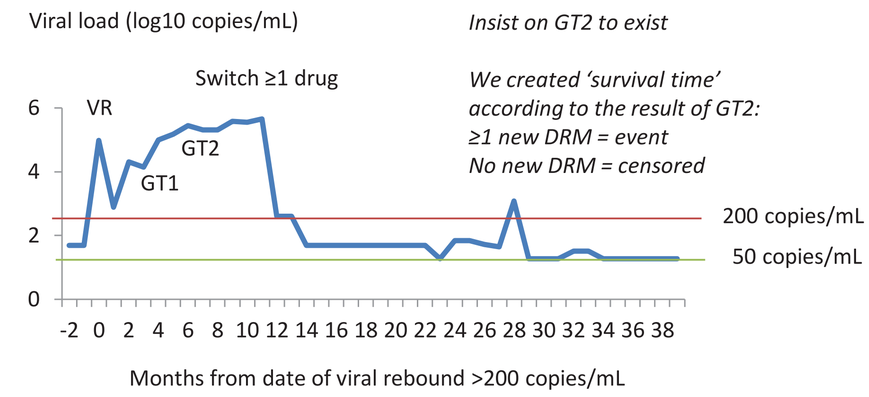
Figure 1. Example of one person contributing to the analysis



VR = viral rebound; GT = genotypic test; DRM=drug resistance mutations

Table 1. Modelling of post-VR outcome and confounders

Response variable	Predictors	Statistical Model
DRM[t]	VL[t-1] Months since ART switch[t-1]	Cox regression
Log10 VL[t]	VL[t-1] ART switch[t-1]	Linear regression
CD4[t]	CD4[t-1] VL[t-1] ART switch[-1]	Linear regression
ART switch[t]	VL[t] CD4[t]	Cox regression

VL=viral load; ART=antiretroviral therapy [t] month t; [t-1] = one month before month t
The modelling and simulation is carried out forward in time: model the month t data given the month t-1 data; then t+1 given t and t-1, so on…
Thus for example the risk of accumulating DRM depends on previous viral load and cumulative duration of exposure o high viral load up to the previous month, etc.

Table 2. Mains characteristics of patients

Characteristics	
Female, n%	66 (23%)
MSM, n%	141 (49%)
Age years, median (IQR)	32 (27-39)
First genotypic test, n(%)	
Before cART initiation	36 (12%)
Within 3 months of estimated date of VR	175 (61%)
Between VR and ART switch	78 (27%)
Subsequent genotypic test, n(%)	
Before ART switch	150 (52%)
After ART switch	139 (48%)
Drug class of failing regimen	
PI-based	150 (52%)
NNRTI-based	139 (48%)
VL at VR, log10 copies, median (IQR)	3.5 (2.8-4.5)
CD4 count at VR cells/mm3, median (IQR)	371 (232-530)

Table 3. Modelling of post-VR outcome and confounders

Response variable	Predictors	RH/β estimates
DRM[t]	VL[t-1] Months since ART switch[t-1]	1.26 per log10 higher 0.96 per month longer
Log10 VL[t]	VL[t-1] ART switch[t-1]	+0.51 per log10 higher -0.56 vs. no ART switch
CD4[t]	CD4[t-1] VL[t-1] ART switch[-1]	+114 per doubling -10 per log10 higher -1 vs. no ART siwtch
ART switch[t]	VL[t] CD4[t]	0.43 per log10 higher 0.67 per doubling

Table 4. Results from standard Cox regression and g-computation

	Cox regression analysis			
ART switch	Crude RH	95% CI	Adjusted RH	95% CI
Per 3 months delay in switching	0.51	0.47-0.56	0.48	0.42-0.53
	G-computation			
ART switch strategy	Adjusted 3-monthy IR	95% CI	Adjusted RR	95% CI
If VL>200 cps/mL	0.41	0.32-0.49	0.82	0.73-0.91
If VL>1,000 cps/mL	0.50	0.40-0.60	**1.00**	
If VL>5,000 cps/mL	0.53	0.43-0.63	1.06	0.96-1.16
No Switch	0.93	0.87-0.99	1.88	1.82-1.94

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