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FULL TITLE: Increased Mortality with Delayed and Missed Switch to Second-Line Antiretroviral Therapy in South Africa

RUNNING TITLE: Mortality after Delayed or Missed ART Switch in South Africa

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Abstract

Background. After failure of first-line antiretroviral therapy (ART) in the public sector, delayed or missed second-line ART switch is linked with poor outcomes in patients with advanced HIV.

Setting: We investigated delayed or missed second-line ART switch following confirmed virologic failure in the largest private sector HIV cohort in Africa.

Methods. We included HIV-infected adults with confirmed virologic failure after six months of non-nucleoside reverse-transcriptase inhibitor-based ART. We estimated the effect of timing of switch on the hazard of death using inverse probability of treatment weighting of marginal structural models. We adjusted for time-dependent confounding of CD4 count, viral load, and visit frequency.

Results. 5748 patients (53% female) with confirmed virologic failure met inclusion criteria; the median age was 40 (interquartile range [IQR]: 35 - 47), advanced HIV was present in 48% and the prior duration of NNRTI-based ART was 1083 days (IQR: 665-1770). Median time to confirmation of virologic failure and to second-line switch was 196 (IQR: 136-316) and 220 days (IQR: 65-542), respectively. Switching to second-line ART after confirmed failure compared to remaining on first-line ART reduced risk of subsequent death [aHR: 0.47 (95% CI: 0.36-0.63)]. Compared to patients who experienced delayed switch, those switched immediately had a lower risk of death, regardless of CD4 cell count.

Conclusions. Delayed or missed switch to second-line ART after confirmed first-line ART failure is common in the South African private sector and associated with mortality. Novel interventions to minimize switch delay should be tested and not limited to those with advanced disease at treatment failure.

Key Words: second-line antiretroviral therapy, antiretroviral therapy failure, virologic failure, HIV, AIDS, South Africa

Introduction

With the expansion of routine VL monitoring and earlier identification of antiretroviral therapy (ART) failure, the demand for second-line ART in sub-Saharan Africa has increased. By 2020 the number of patients who will require second-line ART is estimated to be 500,000 to 3 million.[1] Unfortunately in sub-Saharan Africa the delay between first-line ART virologic failure – HIV viral load >1000 copies/mL for two consecutive measurements – and the initiation of effective second-line ART can be prolonged.[2,3]

Significant delay before switch to second-line ART may result from multiple factors including clinician reluctance to switch when prior adherence is uncertain, concerns about the increased toxicity of second-line ART and because patients with virologic failure are more likely to cycle in and out of care.[4,5] Also contributing to switch delay are algorithms embedded in World Health Organization (WHO) and other HIV treatment guidelines. For example, national treatment guidelines in South Africa recommend a routine two month delay prior to second-line switch in order to accommodate additional adherence support and laboratory confirmation of virologic failure.[6,7] Switch delay has important clinical consequences including placing patients with ongoing virologic failure at increased risk for OI and mortality as reported in Ugandan and South African public sector.[8,9,10,11,12,13,14,19]

One reason delayed switch has proven hazardous is because, at the time of virologic failure, advanced HIV infection is already present in about half of patients. However, not all patients in high-prevalence regions are managed in the public sector. Patients in the private sector account for 8.5% of persons with HIV in South Africa. These patients experience a higher doctor to patient ratio and shorter waiting times with better access to care, including clinicians, pharmacies and phlebotomy facilities for laboratory

monitoring. However, whether these factors translate into improved management of first-line treatment failure is uncertain.

We investigated the prevalence and consequences of delayed and missed switch following confirmed virologic failure among patients receiving first-line ART in South Africa within the Aid for AIDS cohort – a private sector managed care program using the same switch threshold (two consecutive plasma viral loads >1000 c/mL) as the public sector – with the hypothesis that delayed or missed switch is also common in the private sector and associated with increased patient mortality, particularly in patients with advanced HIV disease.[15]

Methods

Ethics Statement

The study was approved by the Human Research Ethics Committee of the University of Cape Town (HREC R007/2015) and the Institutional Review Board of the Los Angeles Biomedical Research Institute (31123-01).

Study Design and Setting

In the absence of a randomised trial, we designed a "target trial" from observational data and applied causal inference methods to adjust for time-dependent confounding affected by prior treatment decisions with two aims.[16,17,18] The first was to estimate among patients with first-line ART virologic failure the impact of a switch to second-line treatment, compared to not switching, on subsequent mortality, defining time zero as the time of confirmed virological failure (time of

second viral load > 1000 c/mL). The second was to estimate the impact on mortality of a delay in switch to second-line ART.

We identified adult patients who experienced confirmed virologic failure on first-line ART within the AfA cohort, regardless of whether or not a second-line ART regimen was initiated. AfA is a unique cohort of HIV-infected patients in the private sector in South Africa; AfA collects demographic, clinical, medication and laboratory data relating to patients receiving HIV care through this scheme. AfA treatment protocols conform to the WHO HIV treatment guidelines with first-line ART consisting of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus one non-nucleoside reverse-transcriptase inhibitors (NNRTI) and second-line ART consisting of two NRTIs plus one boosted protease inhibitor (PI). The first-line ART initiation threshold changed over time reflecting the evolution of WHO and South African recommendations. Virologic monitoring was recommended at 6 month intervals until 2015, and subsequently every 12 months.

The study population included adult patients (over 18 years of age) who received first-line ART treatment for at least 6 months and who failed first-line ART between 1st January 2012 and database closure on 31st August 2017. Patients were excluded if (1) initial ART did not consist of a standard first-line regimen (2 NRTIs + 1 NNRTI), or (2) if virologic failure occurred less than 6 months after initiation of first-line ART.

Definitions

First-line virologic failure was defined as two consecutive VL measures greater than 1000 RNA copies per mL at least 4 weeks apart after a minimum of 6 months of first-line NNRTI-based ART. We defined advanced HIV as a CD4 <200 cells/uL at the time of first-line ART virologic failure and defined second-line as a regimen that replaced a first-line regimen and contained at a ritonavir-boosted protease inhibitor (bPI).

Statistical analysis

We censored patients when they were lost to follow-up (LTFU) which we defined as 9 months without visit after a patient has last been seen at a health care facility. Thus, follow-up ended at time of LTFU, which is last visit plus 9 months. Censoring also occurred due to patients leaving the scheme and at time of database closure.

To estimate the effect of second-line switch versus no switch, we applied inverse probability of treatment weighting (IPTW) of marginal structural models.[20] Censoring weights were also applied to adjust for bias from LTFU, leaving the scheme and administrative censoring, Both treatment and censoring weighting models included baseline covariates in the denominator and included baseline and time dependent covariates in the numerator as described previously.[17,19] Measured baseline characteristics at time of confirmed virologic failure were age, sex, highest and lowest CD4 count prior to failure, highest and lowest log VL measure prior to failure, a binary indicator of VL suppression prior to failure, WHO clinical stage and year of ART initiation. Time-varying confounders that were assumed to be affected by prior treatment decisions included CD4 count, VL and treatment frequency measured as number of visits within

the past 6 months. Stabilized weights were estimated using pooled logistic models, truncated at the 99th percentile and applied within a marginal structural pooled logistic model.

To estimate the impact of the timing of the switch on mortality, we defined five switching strategies as follows; no switch, less than 30 days from VL failure to switch, greater than or equal to 30 days and less than 60 days from VL failure to switch, greater than or equal to 60 days and less than 90 days from VL failure to switch, and greater than or equal to 90 days from VL failure to switch. The dataset was replicated five times, each replicate corresponding to one of the five strategies. Patient time was censored at the time point that the patient ceased to adhere to the corresponding strategy. The probabilities for the numerator and denominator of the treatment and censoring weights were estimated using pooled logistic models, which included the above-mentioned variables and were truncated at the 99th percentile. To create the weights, probabilities from treatment and censoring denominator and numerator models were assigned to each person-time point, and cumulative probabilities were calculated overtime. The weights applied in the marginal structural outcome model were calculated by dividing numerator by denominator cumulative probabilities, and multiplying treatment and censoring weight together. See Rohr *et. al.* and Bell-Gorrod *et al* for more details of the method.[10,19]

Results

Study Population

We identified 5748 patients (53% female) with confirmed first-line ART virologic failure eligible for study inclusion. The median age was 40 (interquartile range (IQR): 35 - 47) and the median prior duration of first-line NNRTI-based ART was 35.6 months (IQR: 21.9-58.2). At the

time of confirmed virologic failure the median CD4 cell count was 208 cells/uL and advanced HIV (CD4 cell count < 200 cells/uL) was present in 48%. The median time between initial viral load >1000 copies/mL and confirmation of virologic failure was 6.4 months (IQR: 4.5-10.4). Additional patient characteristics are shown in Table 1.

Second-Line ART Switch

At 6, 12, and 24 months after confirmed virologic failure the cumulative number of cases (proportion) of second-line switch was 964 (17%), 1343 (23%), and 1590 (28%), respectively. Overall, 1768 (31%) of 5748 patients with confirmed virologic failure were switched. The median time from confirmation of virologic failure to second-line switch was 12.8 months (IQR: 7.6-21.8). We found that compared to men with confirmed virologic failure women with confirmed failure were more likely to be switched (OR 1.18, 95% CI=1.07-1.31). Moreover, patients who had elevated viral loads and low CD4 counts at their last visit, and patients with many follow-up visits, were also more likely to be switched (Table 2).For example, compared to patients with a CD4 of $\geq$200 cells/uL, the odds of switch was increased in patients with a CD4 cell count <200 cells/uL for a given follow-up time point (OR 1.60, 95% CI= 1.32-1.95). There is greater statistical significance of the ORs on the time dependent variables than the baseline variables, indicating that decisions to switch were more strongly based on the health of the patient at the time of switch than health at the time of confirmed failure. The time delay between first elevated viral load and confirmed failure also has predictive power on the probability of switch. The probability of switch for patients with at least 60 days and less than 120 days between first elevated viral load and confirmed failure is greater than the probability of switch for those with less than 60 days between these viral load measures (OR 1.42, 95% CI= 1.11-

1.81). Conversely, the probability of switch for patients with more than a 360 day gap between first elevated viral load and confirmed failure is lower than for those with less than 60 days between measures (OR 0.75, 95% CI= 0.58-0.96).

Overall, 3980 patients (69%) did not switch to second-line ART after confirmed virologic failure. In this group, only 491 (12%) were observed to achieve virologic suppression (<200 RNA copies/ml) without switch within 12 months of confirmed failure, 3489 (88%) did not achieve suppression within 12 months of confirmed failure, 172 (4%) were observed to achieve virologic suppression after 12 months and before database closure and 155 (4%) did not have an additional VL measurement beyond 30 days after confirmed virologic failure.

Mortality

Overall, 421 (7%) of 5748 patients died after confirmed first-line ART virologic failure. Among those who died, the median time from confirmed failure to death was 7.2 months (interquartile range (IQR): 2.1-18.2). Mortality was evaluated according to CD4 cell count at failure. The majority of mortality after failure was observed among patients with advanced HIV at failure, with 330 (78%) of 421 deaths in this subgroup. Relatively little mortality was observed in patients with a CD4 cell count of ≥350 cells/uL at failure, with 32 (8%) of 421 deaths in this subgroup.

Switching to second-line ART after confirmed virologic failure compared to remaining on first-line ART reduced the risk of subsequent death [aHR: 0.47 (95% CI: 0.36-0.63)]. Among patients with advanced HIV at failure, a switch to second-line ART also reduced the risk of death [aHR:

188 0.40 (95% CI: 0. 29-0.56)]. The impact of second-line switch on mortality was further
189 investigated according to timing of switch. Compared to patients who experienced delayed
190 switch after failure, those switched immediately had a lower risk of death, regardless of CD4 cell
191 count. The hazard of mortality was lowest in those that switched within 30 days which,
192 compared to those that did not switch, was 0.11 (95% CI: 0.09-0.14). Slightly more pronounced
193 results were found for the subgroup with advanced HIV at failure. Figure 1 shows results for
194 each of the delay categories in our analysis.
195
196 It was examined whether the prevalence of advanced HIV at the time of confirmed virologic
197 failure has declined since 2012. The proportion with advanced disease in 2012 was 1118 (50%
198 with advanced HIV) of 2233, 2013: 368 (53%) of 689, 2014: 307 (45%) of 677, 2015: 319 (46%)
199 of 688, 2016: 582 (46%) of 1263, and 2017; 85 (43%) of 198 (*p* value for time trend= 0.041).
200 These proportions were consistent with a small decline in advanced HIV at failure since 2012.
201

202 ## Discussions

203 Delayed or missed switch to second-line ART after virological failure increases mortality in
204 patients with HIV infection, including in the South African private sector. In the private sector,
205 40% of patients with confirmed virologic failure during first-line ART had advanced HIV
206 disease, yet delayed (and missed) switch to second-line ART was very common.
207
208 The median time from first-line ART virologic failure to confirmation of viremia in this private
209 sector cohort was 6.4 months, and the median time before second-line ART switch in patients
210 with persistent failure was 12.8 months. A large group of patients who appeared eligible for

second-line ART were not switched at all. The majority of mortality after virologic failure (78% of deaths) was observed among patients with advanced HIV with 78% of deaths in this subgroup. However, a reduction in mortality was observed in all patients with virologic failure when second-line ART switch occurred; patients with the most rapid switch after confirmed failure experienced the lowest hazard of death both in the overall cohort and in the subgroup with advanced HIV disease. This suggests that broad efforts to more rapidly identify with ART failure in clinics in South Africa and, if necessary, to switch them to active second-line ART may avert deaths.

Switch delay is multifactorial but a major contributor in the South African private sector is a prolonged time-period prior to confirmation of virologic failure. Significant lags before confirmatory VL testing have also been reported in the public sector in southern Africa.[20] This lengthy delay complicates the identification and management of patients with ongoing treatment failure and has been the subject of quality improvement interventions, an example of which has been the introduction of VL "champions" in KwaZulu-Natal, South Africa.[4] Another proposed approach to shorten switch delay after virologic failure is to reduce the second-line switch threshold from two elevated VL measurements, to a single elevated VL above 1000 copies/mL. Under a reduced switch threshold approach, which could be applied generally or targeted at high-risk patients, a switch would take place immediately after the first elevated VL. Under such an algorithm, instead of delaying switch for adherence training, patients triaged to rapid switch would receive enhanced adherence simultaneous to or shortly after the switch takes place. This strategy was modelled in a recent publication which demonstrated that by reducing second-line switch delay, approximately 10,215 deaths could be averted annually in a country the size of

South Africa.[11] Another tool that could potentially reduce switch delay is the wider introduction of point-of-care viral load testing. Although not yet shown in a clinical trial, point-of-care viral load monitoring could provide earlier information regarding the need to switch (or not) at the time of the second (confirmatory) viral load measurement allowing for more rapid treatment decisions.

When outcomes among patients with virologic failure in the Aid for AIDS (AfA) cohort are compared to outcomes in patients with virologic failure in the largest public sector cohort reported from South Africa, some differences are apparent.[10] Notably, compared to patients described by Rohr *et. al.* in the South African public sector, in whom the median time to confirmation of virologic failure and time to switch was 3.4 months and ~6 months, respectively, patients in the private AfA cohort experienced a longer time to confirmation of failure and longer time to switch of 6.4 months and 12.8 months, respectively. Delayed identification of treatment failure and delayed switch may be – compared to the public sector – more common in the South African private sector. A possible reason for the longer time to second-line switch we observed could be explained by delays incurred by the treating clinicians with varying experience in the management of patients with virologic failure.

However, in important respects, published patient outcomes in the public and private cohorts are similar. First, in both cohorts it is evident that a significant proportion of patients with confirmed virologic failure were never switched to second-line ART. Rohr *et. al.* found that 37% of patients with confirmed failure never switched to second-line ART and they describe that, following confirmed failure without switch, that only 28% failing to switch had evidence of virologic

suppression. In the AfA private cohort, 69% did not switch to second-line ART after confirmed virologic failure and only 12% of this patient group subsequently had evidence of virologic suppression without switch. Second, in public and private cohorts it was observed that – in the absence of switch after virologic failure – rates of loss to follow-up were high. For example, in the AfA cohort, 42% of patients not switched only had one recorded visit after virologic failure, compared to 12% of patients who switched to second-line ART. In both sectors, virologic failure may be an important early warning sign of potential loss to follow-up, highlighting the importance of virologic failure as a potentially critical event in the HIV care continuum. Third, in line results from public settings, we found that predictors of second-line switch include a higher viral load, a CD4 count below 200 cells/microL and increased clinic visit frequency.[21,22] The latter may relate to engagement in care and clinicians' perception of adherence, and suggests that switch decisions may not be based purely on guideline algorithms. We also found that female patients were more likely to be switched than males. Although the mechanism by which gender affects treatment decisions is unclear, the finding suggests an additional gender-related differences in HIV management and outcomes in southern Africa.[23]

Our study has several strengths. This cohort study represents patients cared for within private practice settings in South Africa and as a result provides novel evidence that delayed identification and management of first-line ART virologic failure is not strictly a public sector issue of limited resources or overwhelming patient numbers.[4] Our sample size was very large, with more than 5000 patients with confirmed virologic failure included given us considerable power to look at critical subgroups, including patients with advanced disease. Another strength of our study is the use of marginal structural modelling; this allowed us to adjust for potentially

confounding variables – namely, CD4 cell count, VL and treatment frequency – that change over time and are affected by prior treatment decisions. Several potential limitations should be considered. Ours was a cohort study and the potential for unmeasured confounding exists. For example, unmeasured factors such as treatment adherence could potentially affect both the likelihood of switch to second-line ART and the likelihood of mortality after treatment failure. Unfortunately we did not have access to direct measures of adherence. Further, we only included patients who had confirmed virologic failure with two VL measurements > 1000 copies/ml. By definition, our study excludes patients who had a single VL indicating initial virologic failure but were subsequently lost to follow-up or died. This may be a substantial patient subgroup with particularly poor outcomes but is a difficult group to study as they are – by definition – out of care and often with no recorded outcomes.

Despite better access to care and monitoring, delayed or missed switch to second-line ART after first-line ART virologic failure is common in the South African private sector. Our findings suggest the need to both strengthen the management of virologic failure and to test novel interventions to reduce switch delay to less than 30 days in patients with first-line regimen failure. Although these could be targeted at patients with advanced HIV, who continue to make up 40-50% of patients in South Africa with treatment failure, we found benefit of rapid switch in all patients with treatment failure. Another approach worth considering, based on a modelling exercise showing potential net public health benefit, is reducing the second-line ART switch threshold to a single VL > 1000 c/ml.[11] This would, albeit at the cost of some unnecessary switching, hasten switch tempo considerable and, based on modelling, save thousands of lives otherwise lost resulting from unnecessary delays. Additional research in this domain will be

303 critical – as virologic monitoring is expanded and more patients with virologic failure are
304 identified – in strengthening the management of ART virologic failure and optimizing long-term
305 on-treatment patient survival.
306
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410 **Table 1. Characteristics of patients in South African private sector with first-line ART virologic failure**

Variables		Total (N=5748)[a]	CD4 <200 at failure (N=2779)	CD4 ≥200 at failure (N=2958)
Age at virologic failure (yrs.) [median, IQR]		40 (35-47)	41 (35-47)	40 (34-46)
Female gender [number, %]		3038 (53)	1295 (47)	1734 (59)
Achieved VL suppression prior to failure, [number, %]		2687 (47)	1028 (37)	1659 (56)
CD4 count at failure (cells/uL), [median, IQR]		213 (108-336)	98 (47-150)	328 (257-444)
CD4 count (cells/uL) at failure [number, %]				
	0-99	1419 (25)	1419 (51)	-
	100-199	1360 (24)	1360 (49)	-
	200-349	1676 (29)	-	1676 (56)
	350-499	730 (13)	-	730 (25)
	≥500	563 (10)	-	563 (19)
HIV-1 RNA (c/ml) at failure [median, IQR]		27614 (6800-99937)	71700 (20239-210787)	12398 (3827-39084)
HIV-1 RNA (c/ml) at failure [number, %]				
	<10,000	1,745 (30)	429 (16)	1316 (44)
	10,000-99,999	2,523 (44)	1202 (43)	1321 (44)
	≥100,000	1,480 (26)	1148 (41)	332 (11)
Time from confirmed failure to last contact [median, IQR]		368 (214-824)	326 (196-593)	442 (244-993)
Type of last contact [number, %]				
	Administrative censoring	1713 (30)	600 (25)	1113 (33)
	Lost to follow-up	3614 (63)	1446 (61)	2168 (64)
	Death	421 (7)	338 (14)	83 (2)
Time to loss to follow-up [median, IQR]		309 (206-587)	279 (186-427)	331 (210-757)

411 **Table 2: Predictors of switch from first-line to second-line ART**

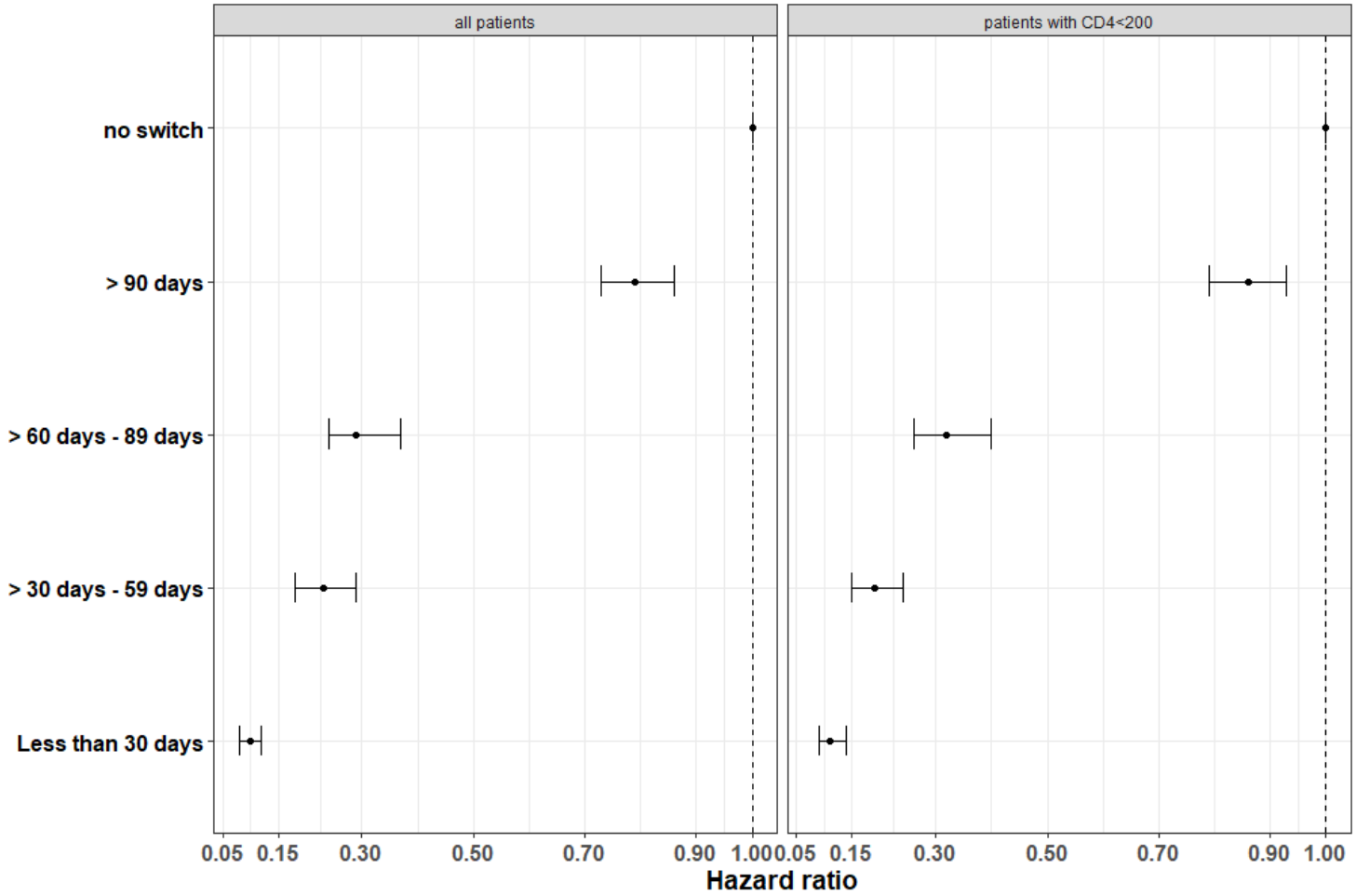
	Odds ratio (OR) of switch to second-line ART		
	OR	P- value	(95% CI)
Time-dependent			
CD4 cell count, per mm^3 <200	1.60	0.000	(1.32-1.95)
RNA, copies/ml (reference-category >=0 and <250)			
>=250 and <500	2.00	0.043	(1.02-3.90)
>=500 and <1000	1.28	0.548	(0.57-2.88)
>=1000 and <10000	6.24	0.000	(4.26-9.14)
>=10000 and <100000	10.61	0.000	(7.15-15.75)
>=100000	12.89	0.000	(8.40-19.79)
Time-CD4 interaction	1.00	0.000	(1.00-1.00)
Time-RNA interaction	0.99	0.000	(0.99-0.99)
Number of visits within the past 6 months	1.05	0.000	(1.04-1.06)
Baseline			
CD4 cell count, per mm^3 <200	0.90	0.263	(0.74-1.09)
RNA, copies/ml (reference-category >=1000 and <5000)			
>=5000 and <10000	1.24	0.031	(1.02-1.51)
>=10000 and <50000	0.98	0.827	(0.80-1.19)
>=50000 and <100000	0.96	0.691	(0.77-1.19)
>=100000	0.88	0.290	(0.70-1.11)
Time from first elevated VL to confirmed failure (reference-category <60)			
>=60 and <120 days	1.42	0.005	(1.11-1.81)
>=120 and <240 days	1.04	0.699	(0.83-1.32)
>=240 and <360 days	0.83	0.142	(0.65-1.07)
<360 days	0.75	0.023	(0.58-0.96)
Pre-failure VL suppression	1.04	0.876	(0.64-1.70)
Age	1.00	0.269	(1.00-1.01)
Female gender	1.18	0.001	(1.07-1.31)

This analysis was performed using a logistic model with a binary switch dependent variable, and adjusted for follow-up time using restricted cubic splines.

Other controls include pre-failure highest and pre-failure lowest CD4 and RNA, binary indicator of year of failure. This model was used to estimate the denominator probabilities for the switching weights, which were used to adjust for time-dependent confounding in the survival analysis shown in figure 1. The time-dependent variables change over time from baseline to switch. The time-

dependent variables have larger ORs and tend to be more statistically significant than the baseline variables, because the decision to switch depends more heavily on the patient characteristics at the time of switch. ORs for RNA categories should be interpreted relative to the reference-category, where each reference category represents an OR=1.00.

Figure 1. Hazard rations for death in patients with confirmed virologic failure by timing of second-line ART switch



*Adjusted for time-dependent confounding of CD4 count, VL, and visit frequency.