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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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1 **Abstract**

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

4

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

7

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

13

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

22

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

27

28

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

31 **Introduction**

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

37  
38 Significant delay before switch to second-line ART may result from multiple factors including clinician  
39 reluctance to switch when prior adherence is uncertain, concerns about the increased toxicity of second-  
40 line ART and because patients with virologic failure are more likely to cycle in and out of care.<sup>4,5</sup> Also  
41 contributing to switch delay are algorithms embedded in World Health Organization (WHO) and other  
42 HIV treatment guidelines. For example, national treatment guidelines in South Africa recommend a  
43 routine two month delay prior to second-line switch in order to accommodate additional adherence  
44 support and laboratory confirmation of virologic failure.<sup>6,7</sup> Switch delay has important clinical  
45 consequences including placing patients with ongoing virologic failure at increased risk for OI and  
46 mortality as reported in Ugandan and South African public sector.<sup>8,9,10,11,12,13,14,19</sup>

47  
48 One reason delayed switch has proven hazardous is because, at the time of virologic failure, advanced  
49 HIV infection is already present in about half of patients. However, not all patients in high-prevalence  
50 regions are managed in the public sector. Patients in the private sector account for 8.5% of persons with  
51 HIV in South Africa. These patients experience a higher doctor to patient ratio and shorter waiting times  
52 with better access to care, including clinicians, pharmacies and phlebotomy facilities for laboratory

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

55  
56 We investigated the prevalence and consequences of delayed and missed switch following confirmed  
57 virologic failure among patients receiving first-line ART in South Africa within the Aid for AIDS cohort  
58 – a private sector managed care program using the same switch threshold (two consecutive plasma viral  
59 loads >1000 c/mL) as the public sector – with the hypothesis that delayed or missed switch is also  
60 common in the private sector and associated with increased patient mortality, particularly in patients  
61 with advanced HIV disease.<sup>15</sup>

## 63 **Methods**

### 64 **Ethics Statement**

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

### 69 **Study Design and Setting**

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

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

77

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

89

90 The study population included adult patients (over 18 years of age) who received first-line ART  
91 treatment for at least 6 months and who failed first-line ART between 1<sup>st</sup> January 2012 and  
92 database closure on 31<sup>st</sup> August 2017. Patients were excluded if (1) initial ART did not consist of  
93 a standard first-line regimen (2 NRTIs + 1 NNRTI), or (2) if virologic failure occurred less than  
94 6 months after initiation of first-line ART.

95

96 **Definitions**

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

102

### 103 **Statistical analysis**

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

108

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

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

121

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

136

## 137 **Results**

### 138 *Study Population*

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

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

146

#### 147 *Second-Line ART Switch*

148 At 6, 12, and 24 months after confirmed virologic failure the cumulative number of cases  
149 (proportion) of second-line switch was 964 (17%), 1343 (23%), and 1590 (28%), respectively.  
150 Overall, 1768 (31%) of 5748 patients with confirmed virologic failure were switched. The  
151 median time from confirmation of virologic failure to second-line switch was 12.8 months (IQR:  
152 7.6-21.8). We found that compared to men with confirmed virologic failure women with  
153 confirmed failure were more likely to be switched (OR 1.18, 95% CI=1.07-1.31). Moreover,  
154 patients who had elevated viral loads and low CD4 counts at their last visit, and patients with  
155 many follow-up visits, were also more likely to be switched (Table 2).For example, compared to  
156 patients with a CD4 of  $\geq 200$  cells/uL, the odds of switch was increased in patients with a CD4  
157 cell count <200 cells/uL for a given follow-up time point (OR 1.60, 95% CI= 1.32-1.95). There  
158 is greater statistical significance of the ORs on the time dependent variables than the baseline  
159 variables, indicating that decisions to switch were more strongly based on the health of the  
160 patient at the time of switch than health at the time of confirmed failure. The time delay between  
161 first elevated viral load and confirmed failure also has predictive power on the probability of  
162 switch. The probability of switch for patients with at least 60 days and less than 120 days  
163 between first elevated viral load and confirmed failure is greater than the probability of switch  
164 for those with less than 60 days between these viral load measures (OR 1.42, 95% CI= 1.11-

165 1.81). Conversely, the probability of switch for patients with more than a 360 day gap between  
166 first elevated viral load and confirmed failure is lower than for those with less than 60 days  
167 between measures (OR 0.75, 95% CI= 0.58-0.96).

168

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

175

#### 176 *Mortality*

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

184

185 Switching to second-line ART after confirmed virologic failure compared to remaining on first-  
186 line ART reduced the risk of subsequent death [aHR: 0.47 (95% CI: 0.36-0.63)]. Among patients  
187 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

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

219

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

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

239

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

251

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

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

272

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

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

291

292 Despite better access to care and monitoring, delayed or missed switch to second-line ART after  
293 first-line ART virologic failure is common in the South African private sector. Our findings  
294 suggest the need to both strengthen the management of virologic failure and to test novel  
295 interventions to reduce switch delay to less than 30 days in patients with first-line regimen  
296 failure. Although these could be targeted at patients with advanced HIV, who continue to make  
297 up 40-50% of patients in South Africa with treatment failure, we found benefit of rapid switch in  
298 all patients with treatment failure. Another approach worth considering, based on a modelling  
299 exercise showing potential net public health benefit, is reducing the second-line ART switch  
300 threshold to a single VL > 1000 c/ml.<sup>11</sup> This would, albeit at the cost of some unnecessary  
301 switching, hasten switch tempo considerable and, based on modelling, save thousands of lives  
302 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

307 **Acknowledgments**

308 We thank the patients in the Aid for AIDS cohort for generously allowing their health  
309 information to be utilized to improve the recognition and response to ART virologic failure in  
310 South Africa.

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410 **Table 1. Characteristics of patients in South African private sector with first-line ART virologic failure**

| Variables   |                          | Total<br>(N=5748) <sup>a</sup> | CD4 <200 at failure<br>(N=2779) | CD4 ≥200 at failure<br>(N=2958) |
|---|--------------------------|--------------------------------|---------------------------------|---------------------------------|
| Age at virologic failure (yrs.) [median, IQR]             |                          | 40<br>(35-47)                  | 41<br>(35-47)                   | 40<br>(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<br>(108-336)               | 98<br>(47-150)                  | 328<br>(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<br>(6800-99937)          | 71700<br>(20239-210787)         | 12398<br>(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**

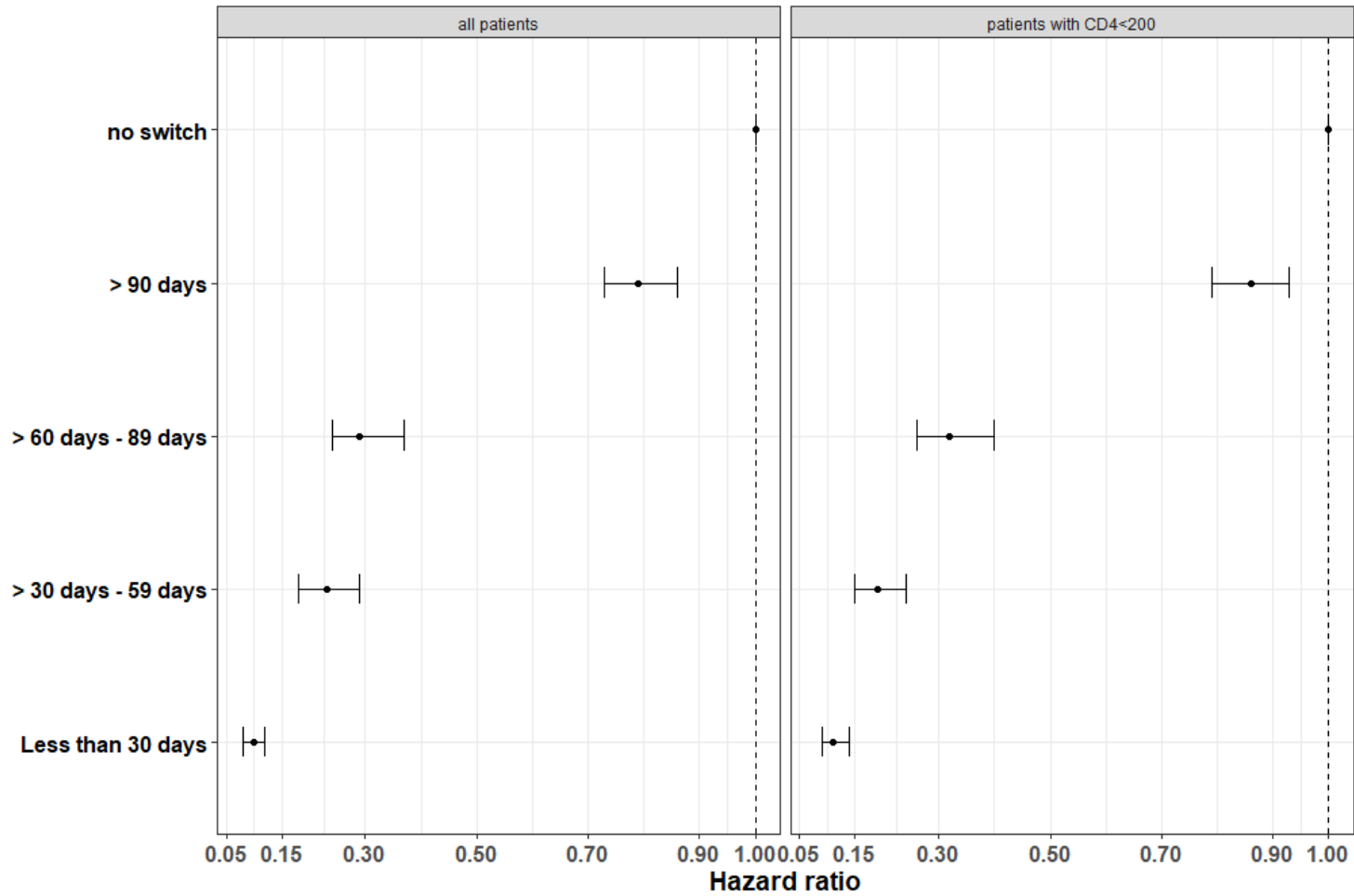
|   | Odds ratio (OR) of switch to second-line ART |          |              |
|---|--|----------|--------------|
|   | OR   | P- value | (95% CI)     |
| <u>Time-dependent</u>   |  |          |              |
| CD4 cell count, per mm <sup>3</sup> <200                                  | 1.60   | 0.000    | (1.32-1.95)  |
| RNA, copies/ml (reference-category $\geq 0$ and <250)                     |  |          |              |
| $\geq 250$ and <500   | 2.00   | 0.043    | (1.02-3.90)  |
| $\geq 500$ and <1000  | 1.28   | 0.548    | (0.57-2.88)  |
| $\geq 1000$ and <10000  | 6.24   | 0.000    | (4.26-9.14)  |
| $\geq 10000$ and <100000  | 10.61  | 0.000    | (7.15-15.75) |
| $\geq 100000$   | 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)  |
| <u>Baseline</u>   |  |          |              |
| CD4 cell count, per mm <sup>3</sup> <200                                  | 0.90   | 0.263    | (0.74-1.09)  |
| RNA, copies/ml (reference-category $\geq 1000$ and <5000)                 |  |          |              |
| $\geq 5000$ and <10000  | 1.24   | 0.031    | (1.02-1.51)  |
| $\geq 10000$ and <50000   | 0.98   | 0.827    | (0.80-1.19)  |
| $\geq 50000$ and <100000  | 0.96   | 0.691    | (0.77-1.19)  |
| $\geq 100000$   | 0.88   | 0.290    | (0.70-1.11)  |
| Time from first elevated VL to confirmed failure (reference-category <60) |  |          |              |
| $\geq 60$ and <120 days   | 1.42   | 0.005    | (1.11-1.81)  |
| $\geq 120$ and <240 days  | 1.04   | 0.699    | (0.83-1.32)  |
| $\geq 240$ 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)  |

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

413 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  
414 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-

415 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  
416 time of switch. ORs for RNA categories should be interpreted relative to the reference-category, where each reference category represents an OR=1.00.

417 **Figure 1. Hazard ratios 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.

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