

The Effect of Switching to Second-Line Antiretroviral Therapy on the Risk of Opportunistic Infections Among Patients Infected With Human Immunodeficiency Virus in Northern Tanzania

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Background. Due to the unintended potential misclassifications of the World Health Organization (WHO) immunological failure criteria in predicting virological failure, limited availability of treatment options, poor laboratory infrastructure, and healthcare providers' confidence in making switches, physicians delay switching patients to second-line antiretroviral therapy (ART). Evaluating whether timely switching and delayed switching are associated with the risk of opportunistic infections (OI) among patients with unrecognized treatment failure is critical to improve patient outcomes.

Methods. A retrospective review of 637 adolescents and adults meeting WHO immunological failure criteria was conducted. Timely and delayed switching to second-line ART were defined when switching happened at <3 and ≥3 months, respectively, after failure diagnosis was made. Cox proportional hazard marginal structural models were used to assess the effect of switching to second-line ART on the risk of developing OI.

Results. Of 637 patients meeting WHO immunological failure criteria, 396 (62.2%) switched to second-line ART. Of those switched, 230 (58.1%) were delayed. Switching to second-line ART reduced the risk of OI (adjusted hazards ratio [AHR], 0.4; 95% CI, .2–.6). Compared with patients who received timely switch after failure diagnosis was made, those who delayed switching were more likely to develop OI (AHR, 2.2; 95% CI, 1.1–4.3).

Conclusions. Delayed switching to second-line ART after failure diagnosis may increase the risk of OI. Serial immunological assessment for switching patients to second-line ART is critical to improve their outcomes.

Keywords. HIV; immunological failure; opportunistic infection; second-line ART; switching.

Diagnosis and treatment of patients failing first-line antiretroviral therapy (ART) in low- and middle-income countries (LMIC) remains challenging [1, 2]. Because of the lack of routine viral load monitoring, the definition of treatment failure to a large extent depends entirely on World Health Organization (WHO) clinical and immunological failure criteria [3–5]. Due to the potential misclassification of treatment failure resulting from using these failure criteria [6–9] as well as limited availability of treatment options, poor laboratory infrastructure, low healthcare provider confidence in making switches, and high costs of second-line ART, physicians are often reluctant [3, 4, 10, 11] to switch. One consequence of

unrecognized treatment failures and/or delayed switches may be an increased risk of opportunistic infections (OI).

Delayed switching to second-line ART in programs without routine viral load monitoring is common. A higher proportion of patients remain on a failed first-line regimen in programs without routine viral load monitoring, compared with those in programs with routine viral load monitoring [8]. Of patients meeting WHO immunological and clinical failure criteria, <45% are switched to second-line ART [12, 13]. The rate of switch is higher in eastern Europe than in sub-Saharan Africa [14], and the difference in the rates of switch is attributed to the lack of routine viral load monitoring in African programs. A delay in switching is also indicated by the variation in switching times from diagnosis of failure [2, 14]. In addition, in resource-limited settings, switching happens earlier in programs with routine viral load monitoring than in those without [15].

Despite treatment success for many patients on second-line ART, mortality and virological failure rates are high [14, 16–19]. Virological failure is defined as increasing levels of detectable human immunodeficiency virus (HIV) RNA and is associated with multiple nucleoside/nucleotide resistance mutations

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[20, 21]. Higher levels of HIV RNA pose the risk of OI. Other than medication nonadherence, high mortality and treatment failure may also be due to delayed switching among patients with unrecognized treatment failure. Compared with patients meeting clinical/immunological failure criteria and switched into second-line ART, those who met criteria and did not switch had poor survival [13].

Reports about the frequency of OI among patients failing first-line ART in LMIC are limited. Whether disproportionately higher OI are observed in patients remaining on failed first-line regimen compared with those who switched to second-line ART is not understood. We sought to evaluate the influence of switching and delayed switching to second-line ART on the risk of OI among patients meeting immunological failure criteria.

METHODS

Study Design and Population

We used a retrospective cohort study design to evaluate the effect of switching to second-line ART on the incidence of OI among patients infected with HIV in Northern Tanzania. Records of patients attending the Kilimanjaro Christian Medical Centre (KCMC), Mawenzi Regional Hospital (MRH), and Kibosho, Kilema, and Machame Hospitals between January 2004 and August 2013 were reviewed. Patients who were <13 years old were excluded. According to the hierarchy of the health system in Tanzania, KCMC is a tertiary referral hospital, MRH is a regional hospital, and Kibosho, Kilema, and Machame are district hospitals. These care and treatment centers (CTCs) offer treatment according to the Tanzanian Ministry of Health treatment guidelines for the provision of ART. According to these guidelines, patients receive a fixed-dose combination of stavudine (D4T), lamivudine (3TC), and nevirapine (NVP) as first-line ART. Zidovudine (AZT) and efavirenz are used in place of D4T and NVP, respectively, depending upon toxicities and concurrent medications. Each patient is typically seen on a monthly basis and their prescriptions are refilled. At the time of this study, routine viral load monitoring was not available in these CTCs; therefore, patients were switched to second-line ART based on clinical and immunological criteria according to the WHO guidelines (www.who.int/hiv/pub/arv/adult2010) of a decline in CD4⁺ cell count to the pretreatment value or below $\geq 50\%$ decline from the peak value CD4⁺ cell count value while on treatment or persistent low CD4⁺ cell count <100 c/mm³. The drugs used for second-line ART included tenofovir, abacavir (ABC), and lopinavir/ritonavir (LPV/r); atazanavir/ritonavir was substituted for LPV/r as needed. The second-line nucleoside reverse-transcriptase inhibitor choice for adolescents and adults depended on the first-line ART. For patients on AZT or D4T in first-line ART, the default second-line option was tenofovir disoproxil fumarate (TDF) combined with 3TC or FTC and LPV/r. For those who had

received TDF in first-line, the second-line option was an AZT-based regimen. For those who were on TDF during first-line because of intolerance to AZT or D4T, an alternative second-line option was ABC combined with 3TC or FTC and LPV/r.

Data Collection

As part of routine HIV clinical care, all patient data including demographics, medication use, OI, adherence indicators (adherent = fewer than 2 missed days per month/nonadherent = 2 or more missed days per month), and laboratory values were collected on standardized forms and entered into a database designed and funded by the Tanzanian National AIDS Control Program in collaboration with Elizabeth Glaser Pediatric AIDS Foundation. This database was searched for clinical data, and when information was missing, it was abstracted from their respective medical files. Treatment monitoring included clinical and immunological criteria; CD4⁺ cell counts were checked at 4- to 6-month intervals using flow cytometry.

Definition of Variables

The primary end point was the time from immunological failure to the first occurrence of OI (pulmonary tuberculosis [TB], pneumonia, Kaposi's sarcoma [KS], cryptococcal meningitis [CM], and herpes zoster [HZ]). All TB, KS, CM, and some pneumonia infections were confirmed by the laboratory, histopathology, or x-ray, whereas HZ infections were diagnosed clinically. We defined loss to follow-up as the absence of a documented clinic visit 6 months from date of the previous clinic visit.

The exposure of interest was time until switching to second-line ART. We defined switching to second-line as initiation of a boosted protease inhibitor-based regimen; otherwise, the patient was considered not switched. Furthermore, among those switched to second-line, we defined timely switching and delayed switching as switching occurring at <3 months vs ≥ 3 months after the diagnosis of immunological failure was made, respectively. A cutoff of 3 months was chosen because after a failure diagnosis, patients received 1 to 2 months of intensive adherence counseling before making the switch. Institutional review board approval was obtained from the University of North Carolina and KCMC.

Statistical Analyses

Statistical analyses were conducted using Statistical Analysis Software (SAS), version 9.3 (SAS Institute Inc., Cary, NC). The distribution of continuous variables was explored to guide categorization. Frequencies and distributions of sociodemographic and clinical characteristics were computed.

Because switching to second-line ART is influenced by CD4⁺ cell counts, confounding by indication is a potential problem such that patients with low CD4⁺ cell are more likely to be switched to second-line than those without low CD4⁺ cell. Time-varying covariate (CD4 cell) affects both time-varying exposure (time to switching) and outcome (OI or death). In addition, switching history predicts future CD4 cell count. Because

of the existence of such scenarios, the use of marginal structural models (MSMs) is recommended. We assessed the effect of switching to second-line ART on the risk of OI using Cox proportional hazards MSMs, which address confounding by indication. CD4⁺ cell count was considered as a time-varying confounder. To ensure switching to second-line ART happened after a time-varying confounder, CD4⁺ cell count values at failure diagnosis were assigned to the preceding month. Other covariates included age, gender, adherence to first-line ART, adherence to second-line ART, treatment sites, and duration spent on first-line ART. Patients began accumulating person time from the moment failure diagnosis was made, and they were observed until first occurrence of an opportunistic infection, death, lost to follow-up, or end of the study, whichever came first. All patients who died, were loss to follow-up, and did not experience OI were censored in the primary analysis.

Marginal structural model analyses use inverse probability of exposure weights to control confounding by time-varying covariates that are also on the causal pathway from exposure to outcome. In this case, the persons were assigned weights inversely proportional to their probability of having the exposure, given their exposure and covariate histories. We used logistic regression models to compute the weights, and all weights were stabilized. After computation of the stabilized weights, we used Cox proportional hazards MSMs to estimate the associations. All associations were presented as adjusted hazard ratios (AHRs) with 95% confidence intervals (CIs). Estimates whose CIs excluded 1 were regarded as statistically significant.

Kaplan–Meier curves were used to assess the survival distributions among those who were switched and those who were not switched to second-line ART. We used log-rank tests to compare the hazard functions for those switched against those not switched to second-line ART. Poisson regression models were used to compute the incidence rate of OI. Two sensitivity analyses were performed: the first defined time from failure diagnosis to death or first occurrence of OI used as the outcome, and the second used propensity scores weighting to assess the effect of switching to second-line ART on the risk of OI. In the second case, the main exposure switching to second-line ART was considered as time fixed mimicking the design of a randomized controlled trial where every eligible patient would be assigned either to be switched or not at baseline. A regression model to generate the scores included the following variables: age (<30, 30–55, >55), gender, months patient spent on first-line ART (<36, 36–60, >60), CD4 cell count (<100, 100–200, >200), sites (tertiary hospital, regional hospital, district hospital), percentage adherence to first-line ART (<90, ≥90), and percentage adherence to second-line ART (<90, ≥90).

RESULTS

From January 2004 through August 2013, we identified 637 adolescent and adult patients at the 5 sites who met WHO

immunological failure criteria. Three hundred ninety-four (61.8%) patients were female, and the majority (454, 71.3%) of patients were aged between 30 and 55 years (Table 1). Most patients (476, 74.7%) had suboptimal adherence to first-line ART, 360 (56.5%) patients spent <36 months on first-line ART, and 174 (43.9%) patients had CD4⁺ cell count of <100/mm³ at the time of switching to second-line ART. Three hundred ninety-six (62.2%) patients switched to second-line ART, whereas 241 (37.8%) patients did not. Among those switched, 233 (58.8%) switched within the first 3 months from the time failure diagnosis was made.

Approximately one fifth (n = 115; 18.1%) experienced an opportunistic infection. The most common infections were pneumonia (n = 46; 7.2%) and TB (n = 35; 5.5%). Other OI included CM, KS, or HZ (n = 34; 5.3%).

Table 1. Demographic and Clinical Characteristics of HIV-Infected Adolescents and Adults Meeting WHO Immunologic Failure Criteria at 5 Infectious Disease Clinics in Kilimanjaro Region, Tanzania, 2004–2013

Variable	Overall (n = 637)	Switched to Second-Line (n = 396)	Did not Switch to Second-Line (n = 241)
Gender			
Male	243 (38.2)	146 (36.9)	97 (40.2)
Female	394 (61.8)	250 (63.1)	144 (59.8)
Age			
<30 y	134 (21.0)	97 (24.5)	37 (15.3)
30–55 y	454 (71.3)	221 (68.4)	123 (75.9)
>55 y	49 (7.7)	28 (7.1)	21 (8.7)
Duration on first-line ART			
<36 mo	360 (56.5)	222 (56.1)	138 (57.3)
36–60 mo	187 (29.4)	146 (31.8)	61 (25.3)
>60 mo	90 (14.1)	28 (12.1)	32 (17.4)
First-line adherence			
Optimal	161 (25.3)	98 (24.8)	63 (26.1)
Suboptimal	476 (74.7)	298 (75.2)	178 (73.9)
Second-line adherence^a			
Optimal	N/A	260 (65.7)	N/A
Suboptimal	N/A	136 (34.3)	N/A
CD4 cells at time of switch^a			
<100 c/mm ³	N/A	174 (43.9)	N/A
100–200 c/mm ³	N/A	166 (41.9)	N/A
>200 c/mm ³	N/A	56 (14.1)	N/A
Sites			
Tertiary hospital	327 (51.3)	244 (61.6)	83 (34.5)
Regional Hospital	167 (26.2)	92 (23.2)	75 (31.1)
District Hospital	143 (22.5)	60 (15.2)	83 (34.4)
Infections^a			
Tuberculosis	35 (5.5)	14 (3.5)	21 (8.7)
Pneumonias	46 (7.2)	12 (3.0)	34 (14.1)
Meningitis	1 (0.2)	0 (0.0)	1 (0.4)
Kaposi sarcoma	8 (1.3)	3 (0.8)	5 (2.1)
Herpes zoster	25 (3.9)	9 (2.3)	16 (6.6)

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; N/A, not applicable; WHO, World Health Organization.

^a Not measured in full 637.

Survival Distributions Among Those Switched and Those not Switched to Second-Line Antiretroviral Therapy

During the follow-up, 637 patients contributed 1181 person-years with overall median of follow up of 1.4 (interquartile range [IQR], 0.7–2.7) years. Those who switched had a median follow up of 2.3 (IQR, 1.2–3.9) years, the corresponding median follow up among those who did not switch was 1.0 (IQR, 0.5–1.4) years. Among those who switched, 38 experienced an opportunistic infection (incidence rate = 5.4 per 100 person-years [95% CI, 4.0–7.5]), compared with 77 among those who did not switch (incidence rate = 15.9 per 100 person-years [95% CI, 12.7–19.9]) The difference in probabilities of developing OI among those switched and those who did not switch is apparent from the start of follow up (Figure 1). Kaplan–Meier curves showed a steep decline of OI free-survival during the first 16 months among patients not switched to second-line. The 6- and 12-month probabilities of having OI among those switched to second-line ART were 0.03 and 0.07, respectively, compared with 0.13 and 0.36 among those who did not switch ($P < .001$, log-rank test).

Compared with patients who met immunological failure criteria and did not switch to second-line ART, those who met and switched were less likely to acquire OI (AHR, 0.4; 95% CI, .2–.6; Table 2). The models were adjusted for age, gender, duration on first-line ART, site of care, and adherence.

Among those switched to second line ART, compared with patients who were timely switched after their failure diagnosis was made, those who were delayed to switch were more likely to acquire OI (AHR, 2.2; 95% CI, 1.1–4.3; Table 3).

When the primary end point was defined as death or occurrence of the first opportunistic infection, compared with patients who met immunological failure criteria and did not switch to second-line ART, those who met and switched were less likely to die or acquire OI (AHR, 0.4; 95% CI, .2–.7; Table 4).

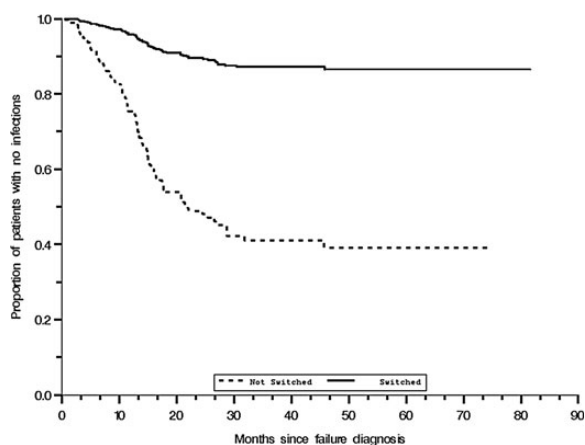


Figure 1. Kaplan–Meier curves for 637 human immunodeficiency virus-infected adolescent and adult patients according to switching status.

The logistic regression model used to estimate the propensity score yielded a c-statistic of 0.8. The mean propensity to receive second-line ART was 0.7 (standard deviation, 0.2) compared with 0.4 (standard deviation, 0.2) for those who did not receive second-line ART. The distribution of the propensity score for those switched to second-line ART was somewhat higher than those who did not switch to second-line; however, approximately 97.7% of the propensity scores overlapped between the 2 groups. Using propensity scores analyses, compared with patients who met immunological failure criteria and did not switch to second-line ART, those who met and switched were less likely to acquire OI (AHR, 0.2; 95% CI, .1–.2; Table 5).

DISCUSSION

The study attempted to assess the association between switching to second-line ART and the risk of OI among HIV-infected patients meeting immunologic failure criteria from 5 CTCs in northern Tanzania. We demonstrated that switching to second-line ART reduced the incidence of OI among patients meeting immunological failure criteria infections (AHR, 0.4;

Table 2. Risk Factors of Opportunistic Infections Among HIV-Infected Adolescents and Adults Switched and Those not Switched Into Second-Line Antiretroviral Therapy at 5 Infectious Disease Clinics in Kilimanjaro Region, Moshi, Tanzania, 2004–2013^a

Variable	Number of Infections	Person Years	Rate/100 py	Adjusted HR (95% CI)
Switched				
No	77	483.3	15.9	1
Yes	38	697.3	5.4	0.4 (.2–.6) ^b
Gender				
Male	43	489.1	8.8	1
Female	72	691.5	10.4	1.2 (.8–1.7)
Age				
<30 y	27	270.4	10.0	1
30–55 y	80	827.0	9.7	0.9 (.5–1.5)
>55 y	8	83.2	9.6	0.6 (.3–1.5)
Duration on first-line ART				
<36 mo	76	647.4	11.7	1
36–60 mo	29	371.2	7.8	0.5 (.3–.8) ^b
>60 mo	10	161.9	6.2	0.3 (.1–.6) ^b
First-line adherence				
Optimal	20	357.2	5.6	1
Suboptimal	95	823.4	11.5	1.5 (.9–2.4)
Second-line adherence				
Optimal	43	686.3	6.2	1
Suboptimal	72	494.3	14.6	1.3 (.8–1.9)
Sites				
Tertiary Hospital	54	738.3	7.3	1
Regional Hospital	30	251.8	11.9	1.1 (.7–1.8)
District Hospital	31	190.4	16.3	1.3 (.8–2.1)

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazards ratio; py, person years.

^a Hazards ratios are based on analysis of Cox proportional marginal structural models on 636 patients.

^b Statistically significant.

Table 3. Risk Factors of Opportunistic Infections Among HIV-Infected Adolescents and Adults Switched Into Second-Line Antiretroviral Therapy at 5 Infectious Disease Clinics in Kilimanjaro Region, Moshi, Tanzania 2004–2013^a

Variable	Number of Infections	Person Years	Rate/100 py	Adjusted HR (95% CI)
Timely switched				
Yes	11	323.1	3.4	1
No	27	374.2	7.2	2.2 (1.1–4.3) ^b
Gender				
Male	15	277.6	5.4	1
Female	23	419.6	5.5	1.1 (.5–2.1)
Age				
<30 y	12	177.3	6.8	1
30–55 y	22	486.2	4.5	0.5 (.2–1.3)
>55 y	4	33.8	11.8	1.6 (.2–4.8)
Duration on first-line ART				
<36 mo	22	445.7	4.9	1
36–60 mo	11	211.7	5.2	1.0 (.3–3.6)
>60 mo	5	39.9	12.5	1.5 (.5–4.3)
First-line adherence				
Optimal	4	219.4	1.8	1
Suboptimal	34	477.9	7.1	4.1 (1.4–12.6) ^b
Second-line adherence				
Optimal	23	510.7	4.5	1
Suboptimal	15	186.6	8.0	1.7 (.6–5.2)
Sites				
Tertiary Hospital	22	516.7	4.3	1
Regional Hospital	11	120.2	9.2	1.5 (.7–3.6)
District Hospital	5	60.4	8.3	1.5 (.5–4.5)

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazards ratio; py, person years.

^a Hazards ratios are based on analysis of Cox proportional marginal structural models on 396 switched to second line ART.

^b Statistically significant.

95% CI, .2–.6). Furthermore, time of switching impacted the risk of OI with longer delays associated with approximately 2-fold increase in risk relative to timely switching.

In the absence of routine viral load testing for determining treatment failure, delayed switching is common in many low- and middle-income countries [2, 14, 19]. In this study, only 62% of those meeting immunological failure criteria switched at all, and the median time to switch from the time of immunological failure diagnosis was 5.1 months. Limited availability of the second-line medications, low sensitivity of the WHO immunologic failure criteria in predicting virological failure, and low confidence of healthcare providers in making switches may have contributed to the delays in switching. In addition to these factors, delays in switching in this cohort could as also be explained by the low levels of adherence. Approximately 75% of the patients had adherence levels below 90% before switch. Those with low levels of adherence may have been less likely to be switched. Similar delays in switching were documented in Haiti where the median time to switching to second-line ART was 7 months and patients with adherence

Table 4. Analyses of the Effect of Switching to Second Line Antiretroviral Therapy on Risk of Opportunistic Infections or Deaths Among HIV-Infected Adolescents and Adults at 5 Infectious Disease Clinics in Kilimanjaro Region, Moshi, Tanzania 2004–2013^a

Variable	Number of Infections/Deaths	Person Years	Rate/100 py	Adjusted HR (95% CI)
Switched				
No	77	697.3	4.6	1
Yes	48	483.3	3.3	0.4 (.2–.7) ^b

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; HR, hazards ratio; py, person years.

^a Hazards ratios are based on analysis of Cox proportional marginal structural models on 396 patients.

^b Statistically significant.

below 90% were less likely to be switched [13]. Substantial proportions of patients who met immunological failure criteria in a study from Mali [3] did not switch to second-line ART, and the median duration of follow up from failure diagnosis was 5 months. These observations suggest that delays in switching to second-line ART are a serious management concern across low- and middle-income countries.

Among patients meeting immunological failure criteria, switching to second-line ART is associated with a 60% reduction in the risk of OI compared with those who remained on a failed first-line regimen. The association between immunological failure and the incidence of HZ has been reported previously [22], in which the incidence of HZ was 6.2 episodes per 100 person years. We observed a slightly lower incidence rate of 2.1 episodes per 100 person years. The high incidence of OI is likely attributable to unrecognized treatment failure and relatively severe immunosuppression. Among those who switched, approximately half of the patients in our study had CD4⁺ cell count <100 c/mm³ at the time of switch. Severe immunosuppression defined by CD4⁺ cell <100 c/mm³ is a clear risk factor for OI such as TB and pneumonia [23, 24].

Our sensitivity analyses results were robust with the results from the main analysis. Using propensity scores, switching to second-line ART is associated with an 80% reduction in the risk of OI compared with those who remained on a failed

Table 5. Propensity Score Analyses of the Effect of Switching to Second-Line Antiretroviral Therapy on Risk of Opportunistic Infections Among HIV-Infected Adolescents and Adults at 5 Infectious Disease Clinics in Kilimanjaro Region, Moshi, Tanzania 2004–2013

Variable	Categories	AHR	95% CI
Switched	No	1	
	Yes	0.2	(.1–.2) ^a

Abbreviations: AHR, adjusted hazard ratio; CI, confidence interval; HIV, human immunodeficiency virus.

^a Statistically significant.

first-line regimen. The mean propensity among those switched to second line ART was higher than that of those who did not switch, indicating that those switched were at a greater need to receive second-line ART than those who did not.

Combining deaths and OI as the end point, the effect of switching to second-line persisted; the risk of death or OI was less among those switched compared with those continued on the failed first-line regimen. Among those who died, 31% had OI before death. Others have previously shown that delayed switching is associated with an increased risk of mortality [13, 25]. Although the causes of death were not ascertained in these studies, it is likely patients had life-threatening OI before their deaths.

Many of the OI in this study were clinically diagnosed. Misdiagnosis might have overestimated the incidence of OI. Although it is possible to misdiagnose pneumonia infections clinically, the dermatological manifestations of HZ are obvious and unlikely to be misdiagnosed in patients infected with HIV. Moreover, clinical diagnosis of HZ is common in many studies [22, 26, 27]. Although TB infections were confirmed by sputum examination, the presence of smear negative does not rule out TB, especially in patients infected with HIV. The timing of sputum collection and processing can also impact the diagnosis of TB. Variations in timing and processing from different laboratories might have underestimated the incidence of TB infections.

The timing of diagnosis of OI could be measured with some errors in this study. Due to the factors related to patients, access to care, and healthcare systems in LMIC, diagnoses of TB and KS and other acquired immune deficiency syndrome-defining cancers are likely to be made late [28, 29]. All patients in this study were screened for TB at ART initiation, and patients were periodically evaluated for TB as they attended their CTCs. In addition, with monthly clinic visits and periodic evaluation, errors in the timing of diagnosis of OI are likely to be minimal.

Because CD4⁺ cell counts were measured at intervals of 4–6 months, the diagnosis of treatment failure was made late in most patients, especially those whose CD4⁺ cells were measured at 6-month intervals. In our analyses, the most current CD4⁺ cell measurements were assigned to the previous month to account for possible late treatment failure diagnosis.

We did not have HIV-RNA results for the patients, and therefore CD4 cell count were used to make failure diagnosis. It is likely that some patients considered failed might not have failed and those with virological failure might have not been included into the study. Such misclassification of the failure diagnosis might have introduced selection bias. Moreover, practically, HIV RNA is known to influence both OI and physicians' decision in making switches. However, because physicians did not have the knowledge of the HIV-RNA results, it is unlikely that their decisions were directly influenced by the HIV RNA. High plasma

HIV-RNA leads to suppression of the patient's immunity, which is being reflected by the low CD4 cell count that was controlled for in this study.

We compared switched versus not switched and timely switched versus delayed switched separately; however, comparison of not switched versus timely switched and delayed switched in a single model is another alternative. Moreover, death could be a competing risk in a model assessing effects of switching and risk of OI or death, and therefore the resultant effect size could be biased. Furthermore, because patients who failed in 2004 would be much less likely to access second-line treatment than those in 2013, inclusion of the year of immunological failure in the estimation of the propensity score probabilities would have slightly changed propensity score effects size.

CONCLUSIONS

The risk of OI and death is reduced among patients switched to second-line ART after a diagnosis of immunological failure is made. Furthermore, the risk of opportunistic infection is higher when the delay to switch is 3 months or longer from the time of failure. Delay in switching could mainly be due to uncertainties physicians have due to the relatively poor ability of the WHO immunological failure criteria to predict virological failure. If this theory is true, efforts should be made to invest in viral load testing equipment to improve the timing of failure diagnosis and manage patients accordingly. This process could be made possible by placing a central testing laboratory where patients' dry blood spots from different care and treatment centers could be evaluated. Dry blood spot is known to reduce logistic difficulties and the cost that is associated with the use of plasma.

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