Similar Mortality and Reduced Loss to Follow-Up in Integrated Compared With Vertical Programs Providing Antiretroviral Treatment in Sub-Saharan Africa

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Background: Vertical HIV programs have achieved good results but may not be feasible or appropriate in many resource-limited settings. Médecins sans Frontières has treated HIV in vertical programs since 2000 and over time integrated HIV treatment into general health care services using simplified protocols. We analyzed the survival probability among patients receiving antiretroviral therapy (ART) from 2003 to 2010 in integrated versus vertical programs in 9 countries in sub-Saharan Africa.

Methods and Findings: Cox regression assessed mortality and program design association, adjusting for baseline age, body mass index, clinical WHO stage, tuberculosis, program age and setting. The analysis included 15,403 HIV-positive adults on ART in 7 vertical (14,124 patients) and 10 integrated (1279 patients) programs. Cox regression including 14,523 patients followed for up to 30 months ART showed similar outcomes for mortality (adjusted hazard ratio (aHR) 1.02; 95% confidence interval (CI): 0.83 to 1.24) and lower risk of loss to follow-up (aHR: 0.71; 95% CI: 0.61 to 0.83) in integrated compared with vertical programs. The greatest risk of death was from initiating ART at WHO stage 4 (aHR 1.99, 95% CI: 1.74 to 2.29), although greater program experience was protective (aHR: 0.77, 95% CI: 0.66 to 0.89). Risk of loss to follow-up was greater in experienced programs (aHR: 3.33; 95% CI: 2.92 to 3.79) and rural settings (aHR: 3.82; 95% CI: 3.49 to 4.20).

Conclusions: ART delivery in integrated general health care programs results in good outcomes. Compared with vertical HIV programs, patients initiated ART in integrated programs at more advanced stages of clinical immunosuppression yet had similar risk of death and lower risk of loss to follow-up.

Key Words: antiretroviral therapy, HIV, integrated healthcare, resource-limited settings

(*J Acquir Immune Defic Syndr* 2012;59:e92–e98)

INTRODUCTION

Rapid progress has been made in scaling-up access to antiretroviral therapy (ART) in resource-limited settings and early outcomes on treatment are comparable to Western settings.[1] These early results were predominantly achieved via large-scale, vertical treatment programs, mainly in urban areas. Due to substantial resource requirements, vertical programs may not be feasible or appropriate in rural areas or in low HIV prevalence areas where other important health priorities place competing demands on health services. Programs which integrate HIV care into other medical activities offer a potentially feasible alternative model of introducing HIV care that can utilize HIV resources and staff to provide both HIV and non-HIV services.[2,3]

Integrated HIV programs have a number of potential advantages which include the following: increasing the access of patients to HIV care in areas where vertical HIV programs may not be feasible; supporting retention in care by bringing services closer to patients and distributing the burden of HIV care provision across services[4]; strengthening other parts of health programs by utilizing the increased resources that HIV usually brings such as clinical training for health staff, improved laboratory services, and procurement supply management systems[5]; normalizing HIV as one illness among many, with potential stigma reduction; allowing the treatment of patients for multiple conditions in the same facility by the same staff[6]; increasing program cohesiveness; and increasing staff morale by enabling the treatment of patients dying of HIV.

Despite these potential benefits, integrating HIV care could come at the expense of the quality of care that can be

Received for publication July 11, 2011; accepted October 28, 2011.

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Presented at the International AIDS Conference, July 18–23, 2010, Vienna, Austria.

Author contributions: DOB conceived the study. JG, DOB, NF, TS and KS contributed to the analysis of the data. DOB, LS and JG wrote the first draft of the paper. NF, TS and KS contributed to the writing and review of the paper. All authors read and approved the final manuscript.

The authors have no funding or conflicts of interest to disclose.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jaids.com).

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achieved in vertical programs that provided dedicated services and specialized staff. In this study, we assessed outcomes of patients treated with ART in Médecins sans Frontières (MSF) integrated and vertical HIV programs.

METHODS

Study Setting

We analyzed retrospective observational cohort data from 17 programs in 9 countries in sub-Saharan Africa (see **Map, Supplemental Digital Content 1**, http://links.lww.com/QAI/A240). All sites in sub-Saharan Africa where MSF-Holland commenced HIV care from 2003 until 2007 and which maintained electronic medical records were included. Vertical programs were defined as those programs designed to specifically treat HIV in a population and thus focused only or predominantly on HIV. Integrated programs aimed to provide comprehensive health care, with inclusion of HIV care as part of the general health care services provided. Hence there were some differences in program design and activities between these models (Table 1). Despite the differences, HIV and opportunistic infection testing, diagnosis and treatment protocols, adherence counseling and patient follow-up, data collection and monitoring, laboratory protocols, and drug procurement and supply mechanisms were standardized across MSF vertical and integrated programs. In addition, out-of-program training and advisory staff were the same for integrated and vertical programs. All programs were integrated within the local Ministry of Health facilities, although drugs and materials were procured and supplied through MSF channels.

Vertical programs were implemented in all projects opened before 2005. Using the experience gained in these early vertical programs, MSF began to integrate HIV care into the general package of services provided in its health programs. HIV vertical programs were reserved for settings where HIV was judged to be the major morbidity and an unmet medical need, but where other basic health needs were already met by others.

Data Management and Analysis

Data were routinely collected by clinical staff at each consultation using standardized forms and entered into a standardized electronic database (Follow-Up and Care of HIV Infection and AIDS, Epicentre, Paris) maintained at each program site. Data were included only for the period that MSF staff were active in the clinics, with ART commencement dates ranging from 2003 until early 2010. Only patients aged 15 years or older at the time of commencing ART who had at least 6 months of potential follow-up time were included in the 12 month analysis. Loss to follow-up was defined as missing a scheduled appointment by 2 months or more. Data were censored at time of analysis, death, or at the last appointment for patients who transferred out of a program or were lost to follow-up.

Patient data were exported from Follow-Up and Care of HIV Infection and AIDS according to time on ART cohorts and analyzed using Microsoft Office Excel 2007 and STATA 10.0 and 11.0 (StataCorp, College Station, TX). Patients were categorized according to the program design (integrated or vertical). Baseline characteristics were described using medians and interquartile range for continuous variables

TABLE 1. Comparison of Program Design

Design and Activities	Integrated	Vertical
Staff responsibilities	HIV component only part of an individual's workload. Doctors caring for patients with HIV would also work in other areas including general inpatient wards, maternity, and TB services; HIV counselors often worked in psychosocial counseling or had other professional backgrounds such as nursing where they spent the majority of their time; and nurses worked on general medical wards	Activities involved management of HIV-positive patients only
Provision of clinical care	Doctors, nurses. Task shifting utilized	Doctors, nurses. Task shifting utilized
IEC activities	Minor component—focus on health staff, patients and their families	Large component—attempt to reach the entire community or target population
HIV testing and counselling	Focused on patients presenting to health facilities in 'patient-initiated' model	Included additional community outreach component in a 'client-initiated' model
Treatment of Opportunistic infections (OIs)	Treatment for basic OIs and more basic regimens (eg, cotrimoxazole for toxoplasmosis, fluconazole for cryptococcal meningitis)	Increased availability of OI treatment (eg, pyrimethamine for toxoplasmosis, amphotericin B for cryptococcal meningitis, bleomycin for Kaposi sarcoma)
TB	Care provided by staff involved in HIV activities	Patients referred to TB staff for care*
ART	Limited availability of second-line ARVs	Increased availability second-line ARVs
Diagnostics	Limited availability of CD4, viral load, X-ray and ALT	Increased availability of CD4, viral load, X-ray, and ALT
Socioeconomic support programs	Not included	Included

*Except for Bukavu, Epworth, and Gweru.
ALT, Alanine aminotransferase; ARV, antiretroviral.

and counts and percentages for categorical variables. Characteristics were compared between program designs on univariate analysis using Wilcoxon rank sum test for medians of continuous variables and risk ratios with 95% confidence intervals (CIs) for binomial variables.

A multivariate Cox proportional hazards model was used to estimate hazard ratios for the outcome of death, adjusting for the following potential confounders identified a priori: sex (male or female), age at baseline, body mass index at baseline, WHO stage at baseline (stage 4, stage 1–3), tuberculosis (TB) at initiation, age of program at the time the patient commenced ART (providing ART 12 months or more, providing ART less than 12 months), and setting (rural, urban). CD4 at initiation, although important, was not included due to relatively large amounts (30%) of missing data because not all programs were able to provide CD4 testing at all times. Only patients with all data available were included in the multivariable model. ART experience before initiation with MSF (experienced, naive) was not included in the model as equally high proportions of patients were ART naive. Follow-up time was greater in vertical programs as these started earlier (2003) than integrated programs (2005). The final model included follow-up data censored at 30 months on ART.

Hazard proportionality was assessed by analysis of scaled Schoenfeld residuals. The potential effect of misclassification of mortality among patients lost to follow-up was assessed in a sensitivity analysis using a competing risks framework.[7] All reported *P* values are exact and 2-tailed, and for each analysis, *P* less than 0.05 was considered significant.

Ethics Statement

Ethical review and Individual patient consent were not sought because the analysis was based on routine clinical data. All patient information was entered into the database using coded identification numbers, and no information that could reveal patient identity was included.

RESULTS

Baseline Characteristics

A total of 17,561 adult patients commenced ART in the 17 programs; 15,876 (90%) received treatment in 7 vertical HIV programs, and 1685 (10%) in 10 integrated programs (Table 2). Of these, 15,403 (88%) had at least 6 months of follow-up time in the database and were included for analysis of 12-month treatment outcomes, and 14,523 patients had complete data for inclusion in the Cox proportional hazards model. The number of patients per program ranged from 17 to 5029 (351 to 5029 for vertical, 17 to 480 for integrated).

Baseline characteristics differed by program design (Table 3). Vertical programs had fewer female patients (64% vs. 71%), and patients had an older median age (36.1 vs. 35.0), a higher body mass index (20.0 vs. 18.0), a lower proportion of patients were classified clinical WHO stage 4 (18% vs. 36%), and fewer patients had a current TB diagnosis (7% vs. 13%) at ART initiation (all $P < 0.001$). The proportion of patients without prior exposure to ART at initiation with MSF was the same (94% vs. 94%).

Median CD4 was higher in integrated programs (150 vs. 132 for vertical programs), but CD4 measurement was not administered uniformly: fewer patients overall had a CD4 measurement in integrated programs [61% (n = 781) vs. 70% (n = 9833)], including a smaller proportion of patients in WHO stage 4 [54% (n = 249) vs. 65% (n = 1606), $P = 0.041$].

Comparison of Outcomes With Program Design

Median time on ART for all patients was 12.7 months (interquartile range: 4.5–24.0) for vertical programs and 6.8 months (2.3–15.0) for integrated programs. After 12 months on ART, the proportion of patients lost to follow-up was similar for both program designs [11.8% (n = 1383) vs. 13.6% (n = 115) for vertical versus integrated programs respectively, $P = 0.12$]; however, the proportion of patients who had died was lower in vertical programs (7.9%, 929 patients vs. 11.9%, 101 patients in integrated programs; $P < 0.001$). In 6 vertical and 4 integrated programs, CD4 counts were measured as follows: median gain in CD4 was not different between program design after ART for either 6 months (median CD4 gain 130 for vertical programs vs. 138 for vertical for integrated programs; $P = 0.11$) or 12 months (165 vs. 155; $P = 0.83$).

Multivariate risk analysis indicated that, converse to a higher proportion of deaths at 12 months on univariate analysis, the adjusted hazard of death was similar with both program designs [Fig. 1, Table 4 adjusted hazard ratio (aHR): 1.02; 95% CI: 0.83 to 1.24]. Factors that were statistically significantly associated with mortality in the multivariable model were increasing age, decreasing body mass index, clinical WHO stage 4, and the age of the program at the time the patient started ART. Having been diagnosed with clinical WHO stage 4 gave the greatest risk for death (aHR: 1.99, 95% CI: 1.74 to 2.29), although being treated in a more established program seemed to be protective (aHR: 0.77, 95% CI: 0.66 to 0.89). The integrated program design had a significantly lower risk for loss to follow-up (aHR: 0.71; 95% CI: 0.61 to 0.83), and most other significant factors were different to the outcome of death as follows: being treated in a more experienced program was a risk for loss to follow-up (aHR: 3.33; 95% CI: 2.92 to 3.79) and the greatest risk was being in a rural setting (aHR: 3.83; 95% CI: 3.49 to 4.20).

The models did not display proportional hazards, so we applied a range of statistical contingencies. Our mortality estimate was unchanged in a competing risk regression (sub hazard ratio: 1.03, 95% CI: 0.84 to 1.25), but the effect of program design was somewhat sensitive to segmenting follow-up time, with integrated programs being protective for mortality in some 6 month periods.

DISCUSSION

Our study has demonstrated that patients managed in integrated programs have similar or better outcomes when compared with those managed in vertical HIV programs with

TABLE 2. Location and Details of HIV Treatment Programs

Country	Program	Program Design	Rural or Urban Setting	Year ART First Provided	Estimated Adult HIV Prevalence*[14]	Number Adults Started ART
Central African Republic	Boguila	Integrated	Rural	2006	6.1%	184
Cote d'Ivoire	Danane	Integrated	Rural	2005	4.8%	613
Democratic Republic of Congo	Dubie	Integrated	Rural	2007	1.6%	95
	Kilwa	Integrated	Rural	2007	1.6%	41
	Walikale	Integrated	Rural	2006	1.6%	29
Dem. Rep. Congo (South Kivu)	Baraka	Integrated	Rural	2006	1.6%	173
	Bukavu	Vertical	Urban	2003	1.6%	1576
Ethiopia	Abdurafi	Vertical	Rural	2007	—	396
	Humera	Vertical	Rural	2004	—	894
Nigeria	Lagos	Vertical	Urban	2004	3.7%	1918
Republic of Congo	Kindamba	Integrated	Rural	2006	3.6%	23
	Kinkala	Integrated	Rural	2005	3.6%	51
	Mindouli	Integrated	Rural	2005	3.6%	222
Uganda	Kitgum	Integrated	Rural	2007	6.3%	254
Zambia	Nchelenge	Vertical	Rural	2003	14.1%	1250
Zimbabwe	Epworth	Vertical	Urban	2006	17.2%	4336
	Gweru	Vertical	Rural	2006	17.2%	5476

*HIV prevalence in year program first provided ART.

comparable levels of baseline immunosuppression. This validates the program design of integration and its associated benefits.

Although unadjusted estimates show a higher proportion of deaths in integrated compared with vertical programs, this is likely to be due to the fact that patients were more clinically immunosuppressed at baseline in integrated programs. Our Cox proportional hazards model showed that with adjustment of other factors, the risk of death up to 30 months after ART initiation was similar in integrated compared with vertical programs and most significantly influenced by clinical WHO stage at ART initiation. The risk of loss to follow-up in integrated programs was 29% less than in vertical programs. These results may be explained by better integration of services allowing more optimal treatment of coexistent illness including TB (ie, treating the patient holistically rather than treating an individual disease), lower patient numbers allowing more individualized care and follow-up, proximity of services allowing easier access for patients, and a normalization of HIV reducing stigma and increasing adherence to the program.

ART outcomes in both vertical and integrated programs are comparable to other published outcomes in resource-limited settings. The Antiretroviral Therapy in Lower Income Countries cohort of 18 programs in low-income settings across Africa, Asia, and Latin America reported 12-month combined mortality and lost-to follow-up rates of 21% compared with 19% in MSF vertical and 24% integrated programs in our study.[1] Furthermore, while not measured in all patients, median immunological gains after 6 months of treatment seem slightly better in integrated and vertical MSF programs compared with the Antiretroviral Therapy in Lower Income Countries cohorts (138, 130, and 106 cells/mm^3, respectively).

TABLE 3. Baseline Characteristics at ART Initiation of Patients With at Least 6 Months of Follow-Up Time After Commencing ART, by Program Design

	Vertical (n = 14,124)	Integrated (n = 1279)	*P*
Female, n (%)	9056 (64%)	905 (71%)	<0.001
Age, median years (IQR)	36.1 (30.2–43.1)	35.0 (28.2–41.1)	<0.001
Body mass index, median (IQR)	20.0 (17.9–22.4)	18.0 (16.0–20.2)	<0.001
ART naive at ART initiation with MSF, n (%)	13267 (94%)	1202 (94%)	0.503
CD4*, median (IQR)	132 (63–199)	150 (66–224)	0.0009
Clinical WHO stage 4, n (%)	2489 (18%)	459 (36%)	<0.001
Clinical WHO stage 1–3, n (%)	11302 (82%)	818 (64%)	
Current tuberculosis diagnosis, n (%)	997 (7%)	162 (13%)	<0.001
Program providing ART <12 months when patient initiated ART, n (%)	2095 (15%)	535 (42%)	<0.001
Program in an urban setting, n (%)	6983 (49%)	0 (0%)	<0.001

*CD4 from up to 3 months before up until ART initiation available for 70% patients (n = 9833) in vertical programs and 61% (n = 781) in integrated.
IQR, interquartile range.

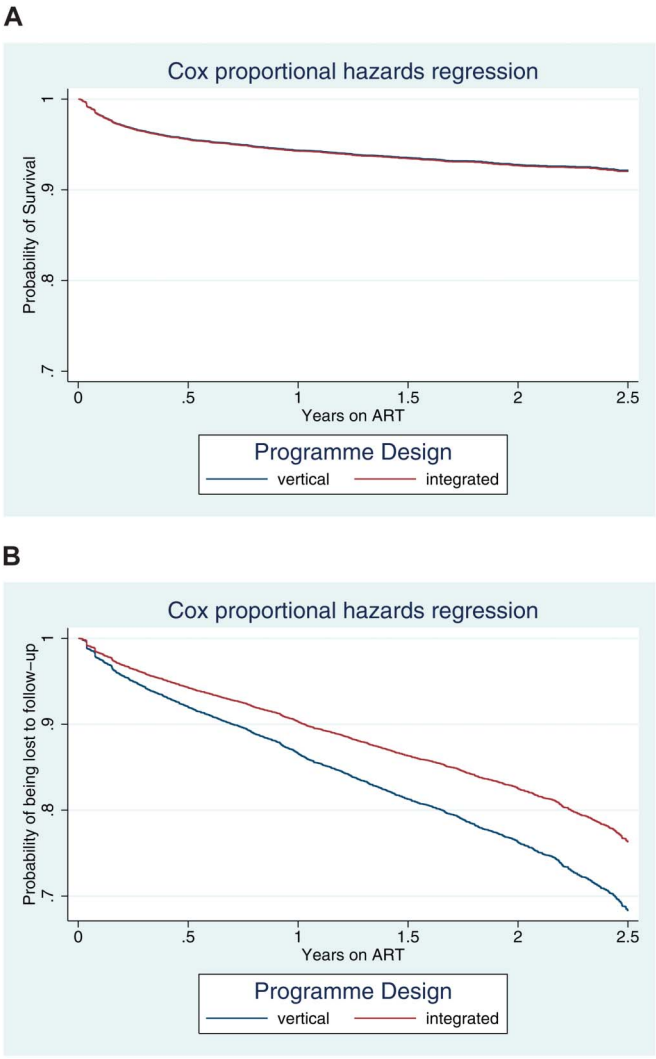

FIGURE 1. Cox proportional hazards regression plots of the adjusted risk of (A) death and (B) loss to follow-up after initiation of ART.

There are a number of important differences in patients in integrated compared with vertical programs at ART initiation. Notably, a higher proportion of patients were severely clinically immunosuppressed (WHO clinical stage 4) in integrated programs. This finding is similar to other reports[8] and likely resulted from the fact that many of these programs targeted people presenting to health facilities when they were already sick, whereas vertical programs devoted specific resources to large-scale community counseling and testing which attracts more asymptomatic patients. The median CD4 count at ART initiation was higher in integrated programs, but this was likely due to the fact that a higher proportion of those in WHO stage 4 did not have a baseline CD4 count in integrated programs. This may have occurred if CD4 count measurement was not done when patients already qualified for ART based on clinical status[9,10] and CD4 counts were instead reserved for those with better clinical condition to guide ART initiation decisions.

Both program designs used similar inclusion criteria and protocols for ART. The main difference was that in integrated programs health staff tended to be less specialized and often had a range of additional clinical and surgical duties (Table 1). Simplification of protocols took place mainly in terms of less sophisticated laboratory monitoring and a more limited drug formulary, in that some integrated programs had no access to CD4 or biochemistry, and less choice of drugs for management of opportunistic infections.[2,3] Integration of TB diagnosis and treatment was the ambition for both program designs. Implementation of HIV care was taxing on the teams who were busy with regular activities; however, we found that a standard package of protocols and training material helped staff, as did the engagement of an experienced HIV clinician to help start the program and train staff.[2] After adjusting for other factors in our Cox hazards model, so irrespective of program design, the longer time programs had been treating patients with ART and thus the experience staff could have been expected to gain was protective against death. On the other hand, program age was a hazard for loss to follow-up, which we hypothesize might indicate less time spent on patient selection, preparation, and counselling for adherence to ART as the programs grow in size. The substantially increased risk for loss amongst patients treated in programs in rural settings is not surprising where travel distances and transport options will be far more challenging than in urban settings.

Our study results demonstrate that integration of HIV care into general medical services can be beneficial in rural and relatively low HIV prevalence settings. In a time of intense debate regarding the merits of specific funding to HIV services,[11] our data provides evidence in these settings that resources dedicated to HIV through integrated programs can benefit the individual patient, and as we have previously described, this can also strengthen the health system as a whole.[2,3]

Our study is subject to several potential limitations. First, it is important to note that the Cox hazards models did not adhere to the assumption of proportional hazards, primarily because of the body mass index variable which was resistant to attempts to obtain proportionality through categorization, transformation, removal of data outliers, and assessment of possible interactions. Nonetheless, it was retained in the model as a clinically important factor related to our outcomes of interest. The likely effect of a nonproportional predictor is that the power of the test for this variable is reduced, such that any association may be missed, and the concurrent model predictors that do satisfy proportionality also suffer from decreased power associated with a poorer overall model fit.[12] A second potential limitation of the study is the misclassification of mortality among patients who were lost to follow-up, as tracing has found that a proportion of patients who are lost to care will have died.[13] However, the results of our competing risks analysis suggested that such misclassification is not an important source of bias. Third, there are substantially more patients in vertical than integrated programs due to the focus and the timing of commencement of programs; nonetheless, we were able to assess large numbers of patients treated in integrated programs. Furthermore, vertical programs tended to be in larger and more urban facilities, which may have had an unmeasured impact on outcomes. Fourth, these data comes from a range of programs across different countries and over a number of years, and

TABLE 4. Unadjusted and Adjusted Risk of Death or Loss to Follow-Up Comparing Program Design for Patients Followed for up to 30 Months on ART

	Mortality				Loss to follow-up			
	HR (95% CI)	*P*	aHR (95% CI)	*P*	HR (95% CI)	*P*	aHR (95% CI)	*P*
Program design								
Vertical	1	—	1	—	1	—	1	—
Integrated	1.62 (1.37 to 1.92)	<0.001	1.02 (0.83 to 1.24)	0.876	0.92 (0.81 to 1.07)	0.32	0.71 (0.61 to 0.83)	<0.001
Sex								
Female	1	—	1	—	1	—	1	—
Male	1.40 (1.24 to 1.56)	<0.001	1.12 (0.98 to 1.27)	0.09	1.01 (0.94 to 1.08)	0.85	0.96 (0.89 to 1.04)	0.32
Age at ART initiation	1.01 (1.01 to 1.02)	<0.001	1.02 (1.01 to 1.02)	<0.001	0.99 (0.99 to 1.00)	0.007	0.99 (0.99 to 1.00)	0.001
Body mass index at ART initiation	0.82 (0.80 to 0.84)	<0.001	0.84 (0.82 to 0.86)	<0.001	0.97 (0.96 to 0.98)	<0.001	0.98 (0.97 to 0.99)	0.002
Clinical WHO stage at ART initiation								
Stage 1–3	1	—	1	—	1	—	1	—
Stage 4	2.62 (2.33 to 2.95)	<0.001	1.99 (1.74 to 2.29)	<0.001	0.86 (0.78 to 0.95)	0.002	0.95 (0.86 to 1.06)	0.35
Current TB diagnosis at ART initiation								
No	1	—	1	—	1	—	1	—
Yes	1.40 (1.17 to 1.68)	<0.001	1.14 (0.94 to 1.39)	0.18	0.70 (0.60 to 0.82)	<0.001	0.92 (0.78 to 1.09)	0.35
Age of program providing ART								
<12 Months	1	—	1	—	1	—	1	—
≥12 Months	0.61 (0.53 to 0.69)	<0.001	0.77 (0.66 to 0.89)	0.001	2.47 (2.20 to 2.78)	<0.001	3.33 (2.92 to 3.79)	<0.001
Setting								
Urban	1	—	1	—	1	—	1	—
Rural	1.49 (1.33 to 1.67)	<0.001	1.10 (0.95 to 1.26)	0.19	3.20 (2.94 to 3.47)	<0.001	3.83 (3.49 to 4.20)	<0.001
Schoenfelds *P*	—	—	—	<0.001	—	—	—	<0.001

aHR, adjusted hazards ratio; HR, unadjusted hazards ratio.

although this supports the generalizability of our findings, data quality may have varied between projects despite the use of a standardized database. Although program protocols were generally standardized and used the same drugs, training, and advisors, there may be slight differences between programs in different contexts, and staff/patient ratios and clinical workload were not measured. Thus, it is possible that any unmeasured differences were not uniform between integrated and vertical programs. However, after statistical assessment, it was determined that clustering by program was not justified, and in sensitivity analysis, it was found to negatively affect hazard proportionality. Fifth, access to CD4 testing was limited in some programs, and thus CD4 could not be included in the Cox hazards model without losing too much data and potentially biasing results. As there were significant differences in the groups between median CD4 at baseline, we are unable to exclude this as having a significant effect on the outcome. Finally, the study will have had the expected limitations of missing data and unmeasured confounders. However, our main findings were unchanged by sensitivity analyses.

CONCLUSIONS

Integrated programs had good HIV treatment outcomes, which are as good as or better than vertical programs, particularly in terms of patient retention in care. This validates the model of integrating HIV care into general medical services to increase access to HIV services for populations living in rural or lower HIV prevalence settings.

ACKNOWLEDGMENTS

We thank Robin Meldrum for assistance in designing the map, and Stephanie Bartlett for editing assistance.

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