Noninferiority of a Task-Shifting HIV Care and Treatment Model Using Peer Counselors and Nurses Among Ugandan Women Initiated on ART: Evidence From a Randomized Trial

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Objective: To assess the noninferiority of a task-shifting HIV treatment model relying on peer counselors and nurses compared with a physician-centered model among HIV-1-positive women initiated on antiretroviral therapy (ART) at a prevention of mother-to-child transmission clinic in Mulago Hospital, Uganda.

Methods: HIV-1-infected ART eligible naive women were randomized to either nurse–peer (intervention) or doctor–counselor (standard model) arm. The primary endpoint was virologic success defined attaining a viral load < 400 RNA copies per milliliter 6–12 months after ART initiation. Noninferiority was defined as the lower 95% confidence limit for the difference in proportions with virologic success being less than 10%. Secondary outcomes included immunologic success (mean CD4 count increase from baseline) and pill count.

Results: Data on 85 participants were analyzed (n = 45 in the intervention and n = 40 in the standard model). The proportion of participants with virologic success was similar in the standard and intervention models [91% versus 88% respectively; difference, 3%; 95% confidence interval (CI): −11% to 12%]. Probability of viral detection at 6–12 months' time point was similar in the 2 models (log-rank test $P = 0.73$). Immunologic and pill count indicators were also similar in the intervention and standard models, with mean CD4 increase of 217 versus 206 cells per microliter (difference, 11; 95% CI: −60 to 82 cells/μL) and pill counts of 99.8% versus 99.7% (difference, 0.0; 95% CI: −5% to 5%) respectively.

Conclusions: Nurses and peer counselors were not inferior in providing ART follow-up care to postpartum women, an approach that may help deliver treatment to many more HIV-infected people.

Key Words: HIV, adherence, task-shifting, antiretroviral therapy, nurses, peers, intervention

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INTRODUCTION

Sub-Saharan Africa is home to more than 60% of the 40 million people infected with HIV-1 worldwide.[1] In Uganda, the HIV/AIDS epidemic has claimed tens of thousands of lives and continues to be one of the primary causes of both child and adult mortality.[2] An estimated 64,000 deaths occurred in Uganda in 2009 because of HIV/AIDS,[1] and the cumulative number of AIDS-related deaths by the end of 2010 is approximated at 1.8 million.[3] Antiretroviral treatment (ART) can reduce morbidity and mortality by delaying HIV disease progression and producing clinical improvements in symptomatic HIV/AIDS patients when used optimally.[4] Based on the findings of a recent clinical trial (HIV Prevention Trials Network 052), early treatment also provides the benefit of reducing the risk of transmission among discordant couples.[5]

Drug adherence to ART is the most critical determinant of achieving and maintaining maximum immunologic and virologic success.[6–8] Although current ART regimens are forgiving at moderate levels of ART adherence, patients should be advised to maintain maximum levels of ART adherence to optimize treatment response and minimize the risk of drug resistance,[7,9–13] which leads to disease complications, poor survival, and increased need of switching to expensive second-line therapy. Unsuppressed viral load (VL) is also linked to increased risk of onward HIV transmission, including the risk of transmitting drug-resistant HIV.[14–19]

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In addition, human resource limitations in the health sector mitigate the potential to rapidly scale up access to HIV care and treatment services using physician-centered models of care.[20–22] Research has suggested that more cost-effective HIV service delivery models involving task-shifting are promising.[23,24] Task-shifting from doctors to nurses has not been shown to have a negative effect on the quality of care or health outcomes among HIV patients.[17,19,25] Another response to human resource limitations, in addition to the social and structural barriers, is the trend toward engaging lay health workers, often people living with HIV (PLHIV), to provide psychosocial support to patients in care, defaulter tracing or home visiting, and to facilitate patient flow, referrals and assist with administrative tasks.[23,24,26–29]

This study aims to assess the noninferiority of a task-shifting model involving PLHIV peer counselors compared with a physician-centered model, using a randomized-controlled design and biological (VL and CD4) endpoints. We compared 2 HIV/AIDS care program models: the intervention model used nurses and PLHIV peer counselors to help support delivery of ART on a reduced visit schedule, and the standard model relied on doctors and certified counselors on a monthly visit schedule for delivery of ART services.

METHODS

Study Design

The intervention model evaluated the effect of a task-shifting model where ART nurses managed most follow-up visits at longer intervals between visits, and patients were supported by peer counselors and home visiting, if indicated. The standard clinic-based model relied on doctors to provide monthly ART care, supported by routine counseling at each scheduled visit provided by a certified nurse counselor. Although formal costing analysis of the 2 models was not part of this study, the literature suggests that the intervention model has lower cost to the system and to patients, compared with the standard model, because (1) nurses are more available compared with doctors and at lower salary costs, (2) PLHIV peer counselors can be trained, supervised, and engaged at lower cost compared with medical professionals, and (3) patients save on transportation and opportunity costs (social and financial) from a reduced visit schedule. The study was designed to investigate whether virologic, immunologic, and clinical measures of adherence in the intervention arm were not significantly worse than those in the standard arm with a hypothesized adherence rate of about 85% compared with the standard model's expected adherence rate of about 95% over a 6- to 12-month follow-up period.

Study Setting and Participants

The study was based at a comprehensive ART follow-up clinic attached to the prevention of mother-to-child transmission (PMTCT) unit within the reproductive child health clinic of Mulago National Referral Hospital, Kampala-Uganda. Patients referred from the PMTCT program for antiretroviral initiation either before or after delivery were evaluated for study participation. Study eligibility criteria included ≥18 years of age, provision of written informed consent, residence in a stable home within 15 km of Mulago hospital, willingness to be home visited, and commitment to start ART for life. Participants did not receive any transport reimbursement or any other compensation for visit attendance. Eligibility for ART was determined in accordance with the Ugandan Ministry of Health guidelines at that time (WHO stage III/IV or CD4 cell counts less than 200 cells/μL). Patients who were not eligible to start ART were excluded from the study and referred for standard HIV pre-ART care at Mulago hospital.

Procedures

Randomization

All eligible participants were randomly allocated to either of 2 comprehensive HIV/AIDS care models, an intervention model and a standard clinic-based model, using a table of random numbers. The allocation codes were sealed in sequentially numbered envelopes, reflecting their order on the randomization list. The study coordinator randomized participants by opening the envelope to reveal the randomization code (study arm) and participant randomization number and writing the participant's study identification number, study arm, and date of enrollment on the next available line on the randomization log. Because of the nature of the intervention, both study staff and participants could not be blinded.

HIV Care Models

All participants were started on ART provided through support from the US President's Emergency Plan for AIDS Relief by a hospital doctor. After the baseline visit conducted by a doctor and certified nurse counselor, participants in the intervention arm were given follow-up appointments at week 2 and months 1, 2, 3, 6, 9, and 12. These participants were scheduled to see a doctor and certified counselor at 2 and 12 months, and otherwise, they were seen by nurses trained in ART management and peer counselors. Clinic patients who were HIV positive and currently on ART served as peer counselors in the intervention model and received 10 days training in basic counseling on issues related to adherence, managing side effects, and psychosocial support. Peer counselors also performed home visits to patients randomized to the intervention model who missed visits, counseling them to reengage in care.

Participants in the standard model had a monthly interval between visits and received all care from doctors and certified counselors, as per Ministry of Health guidelines. They were seen at baseline, weeks 2 and 4, and monthly thereafter. Patients in both care models were asked to come to the clinic for medical care each time they felt unwell. Standard model patients did not receive home visits in case of missed visits.

Clinical Assessments

Standardized questionnaires assessing HIV testing history, background, and psychosocial characteristics were administered at enrollment. Data on adherence were collected using pill counts at clinic visits. Biological outcomes (CD4

count and VL) were measured at baseline and again at 12 months. However, because of limited funding, participants enrolled after November 2008 had an abbreviated 6 months follow-up and endpoint laboratory testing was at approximately 6 months instead of 12 months.

All questionnaires and patient's records were reviewed for completeness, accuracy, and consistency by quality control reviewers before double-data entry.

Laboratory Methods

CD4 cell count and VL testing on mothers were performed with the FACS Calibur (Becton Dickinson Biosciences, San Jose, CA) and Roche Amplicor MONITOR 1.5 assay (Roche Diagnostics, Branchburg, NJ), respectively. The upper limit for the VL assay was 750,000 copies per milliliter, and levels below 400 copies per milliliter were not detectable. Both VL and CD4 cell counts were performed at the College of American Pathologists-certified MU-JHU Core Research Laboratory and the Joint Clinical Research Center (JCRC) in Kampala, Uganda, respectively.

Outcomes

The primary outcome was virologic success, defined as the proportion of patients with VL $<$ 400 HIV-1 RNA copies per milliliter 6–12 months after initiation of ART. Secondary outcomes included immunologic success (mean increase in CD4 cell count from baseline) and drug adherence assessed through pill counts, at the 6–12 months' time point after initiation of ART.

Ethical Considerations

The study was approved by Institutional Review Boards at the National HIV/AIDS Research Committee in Uganda, and the Johns Hopkins School of Medicine, MD. Written informed consent for study participation was obtained from all participants.

Statistical Analysis

All variables were checked for missing data and inconsistencies. Distribution of the data using summary distributions, summary measures, and graphical displays was examined to identify outliers and verified against source documentation. Baseline characteristics were compared between arms to assess success of randomization using Pearson χ^2 test for categorical and Student t test for continuous variables. Mean (SD) and medians (interquartile ranges) were used to summarize continuous data.

As a noninferiority study, we hypothesized a priori that adherence to ART among patients in the nurse–peer arm is not significantly lower than those in the standard doctor–counselor arm considering a difference of less than 10% of the absolute values for continuous variables and a difference in proportions of less than 0.1 for categorical variables as being of no clinical importance.

Noninferiority was defined as the lower 95% confidence interval (CI) for the difference in proportions with undetectable VL at the endpoint (6–12 months) follow-up measure being no greater than 0.1. Probability of virologic success over time was described by Kaplan–Meier estimates and compared between groups using a log-rank test.

Secondary outcome measures included immunologic success and pill counts. Immunologic success was defined as the mean increase in CD4 cell count from baseline to the study endpoint at 6–12 months after initiation of ART. The differences in the mean increase in CD4 cell count between the 2 groups and corresponding lower confidence limit were obtained.

A summary adherence percent was calculated using pill counts (number of pills taken over the study period by the sum of pills expected to be taken over the study period). The adherence percent in the 2 groups was compared, and the difference in percent adherence with the corresponding lower confidence limit obtained.

Sample Size Calculation

If we consider a difference between the standard and intervention arms of $\leq$10% as having no clinical importance, then the noninferiority margin we selected is $\delta = 0.1$. If the true percent with undetectable VL at follow-up is 95% for the doctor–counselor arm and 85% for the nurse–peer arm, then we would have 93.4% power ($\beta = 0.06$) at $\alpha = 0.05$ with 85 participants.[30]

RESULTS

Participants were recruited between May 2007 and March 2009 and follow-up continued until September 2009. A total of 143 participants were screened late in pregnancy or postpartum and 92 enrolled. Reasons for exclusion included lack of willingness to be home visited (n = 20), working/staying upcountry (n = 7), and lack of interest or busy working schedule (n = 24). A total of 92 participants were enrolled into the study (Fig. 1), but the final analytic sample was n = 85 (40 in the standard arm and 45 in the intervention arm) after the exclusion of data from 7 participants because of incomplete documentation of study records. A high retention rate (99%) was achieved with 84 participants attending all scheduled visits. Overall, 57% (n = 48) were followed up the full 12 months after ART initiation and the remaining followed up only 6 months. Mean duration of follow-up was similar in both study arms (Table 1).

Participant Sociodemographic and Clinical Characteristics

There were no statistically significant imbalances among participant baseline characteristics for the 2 study groups (Table 1). All participants were taking a nonnucleoside reverse transcriptase inhibitor-based regimen, majority on zidovudine/lamivudine/nevirapine (90.6%), and a smaller proportion were on stavudine/lamivudine/nevirapine (3.5%) and zidovudine/lamivudine/efavirenz (5.9%). Demographic and clinical baseline data of study participants are presented in Table 1.

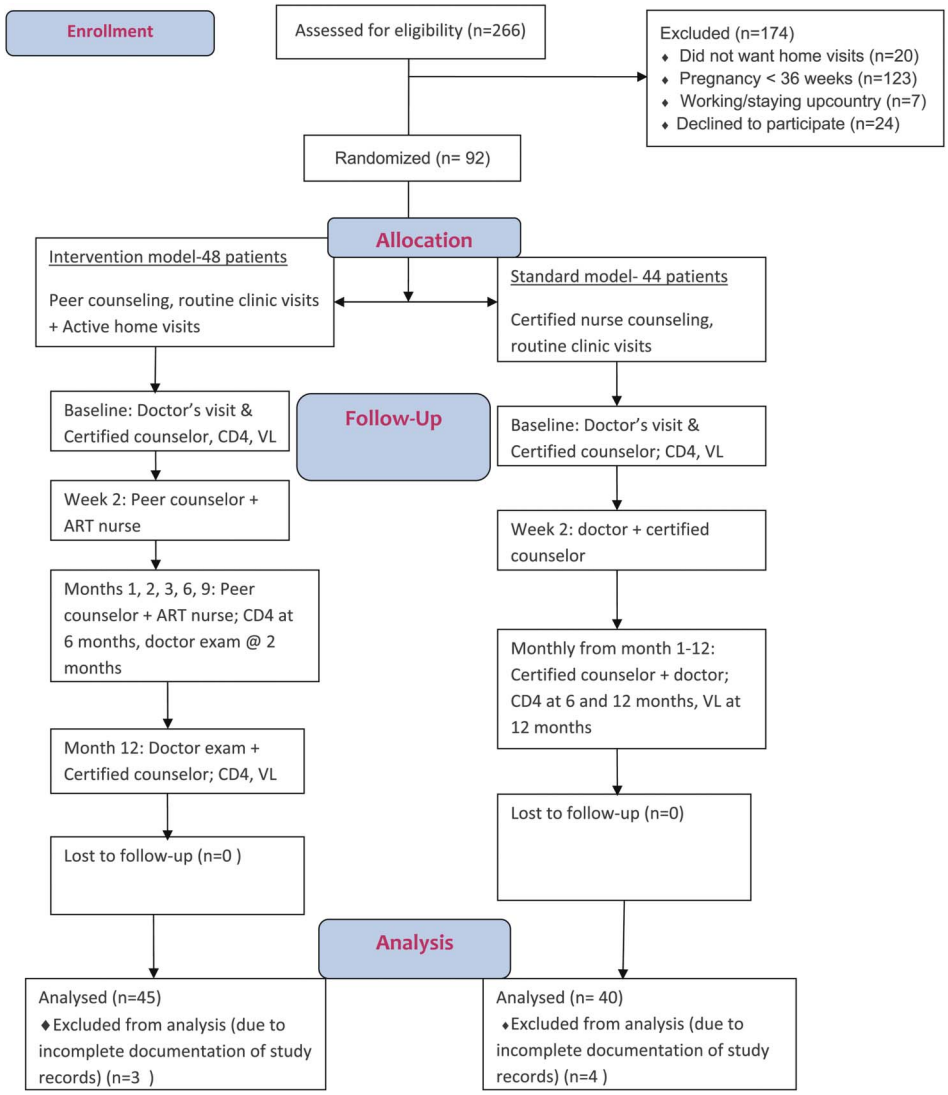

FIGURE 1. Flow chart for the HIV/AIDS care program randomized study arms: an intervention model arm and a standard clinic-based model arm.

Virologic Response

A total of 67 out of 75 (89%) participants with VL outcomes achieved virologic success (Table 2). The proportion of participants with virologic success was similar in the 2 HIV care models. Twenty nine out of 32 (91%) participants in the standard model achieved virologic success versus 38 out of 43 (88%) in the intervention model with an absolute difference of 3% (95% CI:-12% to 11%)(Fig. 2). Figure 3 shows the cumulative probability of VL detection over time by HIV care model. Time to virologic success was similar in the 2 HIV care models; *P* value for the log-rank test = 0.733.

Immunologic Response

The mean CD4 increase from baseline for all participants was 212 cells per microliter (SD, 161 cells/μL; Table 2). This increase was slightly higher in the intervention (mean, 217 cells/μL) compared with the standard model (206 cells/μL), but the absolute difference of 11 cells per microliter between the 2 arms was less than 10% (95% CI: −60 to 82 cells/μL).

Drug Adherence

There was a very high pill count adherence in the study with an overall mean adherence of 99.7%. Drug adherence based on pill count was similar in both study arms, mean drug adherence 99.8% (interquartile ratio, 95%–100%) and 99.7 (IQR, 91%–100%) in the nurse–peer and doctor–counselor arms, respectively, absolute difference of 0.0 (95% CI: −5% to 5%).

DISCUSSION

Findings from this prospective randomized intervention trial in an ART clinic for women in PMTCT postpartum follow-up demonstrate that a task-shifting intervention model using nurses and counselors to deliver a substantial part of the ART follow-up care was not categorically inferior to the standard model that used doctors and certified counselors

TABLE 1. Baseline Characteristics of Study Participants by Intervention Group

Characteristic	Total (N = 85)	Doctor–Counselor (N = 40)	Nurse–Peer (N = 45)	*P*
Age (yr), mean (SD)	27.3 (5.2)	27.8 (4.9)	27.0 (5.4)	0.239
Follow-up period (mo)	10.4 (2.9)	10.5 (2.4)	10.3 (3.3)	0.625
Married	66 (77.6)	27 (67.5)	39 (86.7)	0.161
Type of marriage				
Monogamous	48 (56.5)	19 (47.5)	29 (64.4)	0.100
Polygamous	18 (21.2)	8 (20.0)	10 (22.3)	
Not applicable	19 (22.3)	13 (32.5)	6 (13.3)	
Primary education or less	41 (48.2)	18 (45.0)	23 (51.1)	0.927
Occupation				
Employed	44 (51.8)	12 (55.0)	22 (48.9)	0.925
House wife	25 (29.4)	12 (30.0)	13 (28.9)	
Not employed	16 (18.8)	6 (15.0)	10 (22.2)	
Monthly income*				
>200,000	4 (5.2)	2 (5.6)	2 (4.9)	0.816
50,000–200,000	21 (27.2)	10 (27.8)	11 (26.8)	
<50,000	17 (22.1)	8 (22.2)	9 (21.9)	
Refused/NA	35 (45.5)	16 (44.4)	19 (46.3)	
Missing	8	4	4	
No. children				
0–1	48 (57.8)	25 (62.5)	23 (53.5)	0.508
2–3	23 (27.7)	11 (27.5)	12 (27.9)	
4+	12 (14.5)	4 (10.0)	8 (18.6)	
Missing	2	0	2	
Prior ART				
None	64 (75.3)	30 (75.0)	34 (75.6)	0.601
PMTCT	17 (20.0)	9 (22.5)	8 (17.8)	
Transfer without records	4 (4.7)	1 (2.5)	3 (6.7)	
Weight (kg), mean (SD)	58.6 (10.1)	59.8 (10.7)	57.4 (9.6)	
WHO stage				
Stage I	27 (31.8)	17 (42.5)	10 (22.3)	0.167
Stage II	53 (62.4)	20 (50.0)	33 (73.3)	
Stage III	3 (3.5)	2 (5.0)	1 (2.2)	
Stage IV	2 (2.5)	1 (2.5)	1 (2.2)	
ART regimen				
Zidovudine/lamivudine/nevirapine	77 (90.6)	37 (92.5)	40 (89.0)	0.836
Stavudine/lamivudine/nevirapine	3 (3.5)	1 (2.5)	2 (4.4)	
Zidovudine/lamivudine/efavirenz	5 (5.9)	2 (5.0)	3 (6.6)	
Baseline CD4 cell count, cells/μL				
Median (IQR)	203 (136–240)	204 (121–231)	201 (139–241)	—
Mean (SD)	186 (72)	185 (70)	187 (74)	0.623
<100	14 (16.5)	5 (12.5)	9 (20.0)	0.548
101–250	59 (69.4)	30 (75.0)	29 (64.4)	
>250	12 (14.11)	5 (12.5)	7 (15.6)	
Baseline VL, copies/mL				
Median (IQR)	40,137 (10,867–197,715)	32,195 (11,470–160,973)	61,791 (10,595–223,076)	—
Mean (SD)	143,854 (207,746)	122,452 (196,164)	162,125 (217,878)	0.829
<10,000	17 (22.4)	8 (22.8)	9 (22.0)	0.523
10,000–99,000	33 (43.4)	17 (48.6)	16 (39.0)	
>100,000	26 (34.2)	10 (28.6)	16 (39.0)	
Baseline VL, log copies/mL				
Median (IQR)	4.6 (4.0–5.3)	4.5 (4.1–5.2)	4.8 (4.0–5.3)	—
Mean (SD)	4.6 (0.9)	4.5 (0.9)	4.6 (0.9)	0.605

*USh 2600 = 1 USD.
IQR, interquartile ratio; NA, not applicable; WHO, World Health Organization.

TABLE 2. Drug Adherence and Biological (Immunologic/Virologic/Clinical) Response to ART of Nurse-Peer Compared With Doctor/Counselor HIV Care Models by Study Arm at 6–12 months Following ART Initiation

Characteristic	Total (N = 85)	Doctor–Counselor (N = 40)	Nurse–Peer (N = 45)	Difference (95% CI)
Proportion VL < 400 copies/mL	0.89	0.91	0.88	−0.03 (95% CI:−12% to 11%)
Change in CD4 cell count from baseline, cells/μL				
Mean increase (SD)	212 (161)	206 (163)	217 (152)	11 (95% CI: −60 to 82)
Median increase (IQR)	187 (91–284)	178 (101–279)	203 (77–295)	—
Mean % drug adherence/(pill count) (IQR)	99.7 (100–100)	99.7 (95–100)	99.8 (91–100)	0.0 (95% CI: −5% to 5%)
Proportion with ≥95% drug adherence (pill count)	0.98	0.97	0.99	0.02 (95% CI: −0.01 to 0.05)
Change in weight from baseline, kg				
Mean increase (SD)	1.7 (5.4)	1.3 (5.8)	2.1 (5.0)	0.8 (95% CI: −1.5 to 3.1)
Median increase (IQR)	2 (−1 to 5)	2 (−2 to 4)	2 (−1 to 5)	—

based on a predefined noninferiority margin of 10%. For all outcomes, only small and clinically insignificant differences between the 2 models were observed. Although the clinical measure of adherence based on pill count met the noninferiority criteria, the biological outcomes of VL and CD4 count did not reach the statistical cutoff for noninferiority, probably because of our small sample size.

The intervention HIV care model included fewer scheduled visits, 8 compared with 12 visits in the standard, and relied on nurses and peers counselors. This strategy is likely to be more cost saving[23,24] than the standard of care because the fewer clinic visits translate to time savings for the health care professionals, freeing them up for other work and patient care. In addition, nurses and peer counselors are available in larger numbers within human resource deprived health systems and are not as highly paid as doctors. Doctors tend to be based in urban areas whereas nurses are the backbone of the primary health care system, which tends to be decentralized in most developing country settings. In higher-level clinical settings where doctors are available, they tend to be overwhelmed by the large number of patients seeking HIV care and treatment, which makes the current model of monthly visits less tenable. As a result, nurses are increasingly playing an important role in providing quality health care including HIV/AIDS care, and HIV clinical care systems are often supported by lay health workers (often persons living with HIV) who provide logistical support to clinic flow, patient escort for referrals, counseling, and defaulter tracing in the community. Utilization of lower level health cadres such as nurses and peers can help to more rapidly scale up of HIV care and treatment services in other resource constrained settings in a sustainable manner.[31]

Our findings are consistent with a body of emerging research findings on task shifting, suggesting that task shifting may be effectively implemented into ART programs without adversely affecting treatment outcomes.[25–27,29,32–36] A retrospective study in Uganda by Chang et al[27] that heavily used peer health workers and nurses to help support adult HIV treatment showed that 86% patients remaining in the ART program at 2 years had VLs which were undetectable (less than 400 copies). However, similar to most previous studies, this study had no "standard care arm" using doctors and counselors as a comparison, which limited the strength of the findings.[37] Emerging data from randomized trials have given consistent results.[26,29,38] Most recently, findings from a cluster randomized equivalence trial in a rural Ugandan setting found that a home-based HIV care strategy using trained paramedical or nonmedical field officers to deliver ART drugs to individuals in their homes and family members to help support clients to take their antiretroviral drugs was as effective as a standard clinic-based strategy that used medical officers and certified counselors in delivering ART,[20] when comparing virologic, immunologic, and clinical outcomes. These studies enrolled adult populations; hence, application

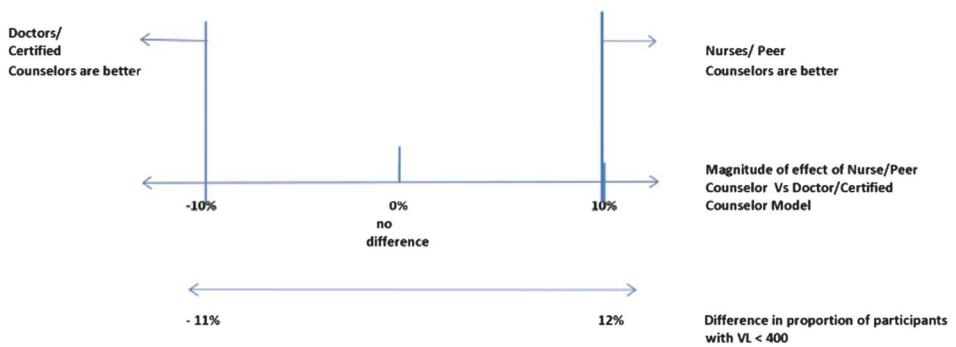

FIGURE 2. Confidence intervals for the nurse/peer counselor versus doctor/certified counselor HIV care models.

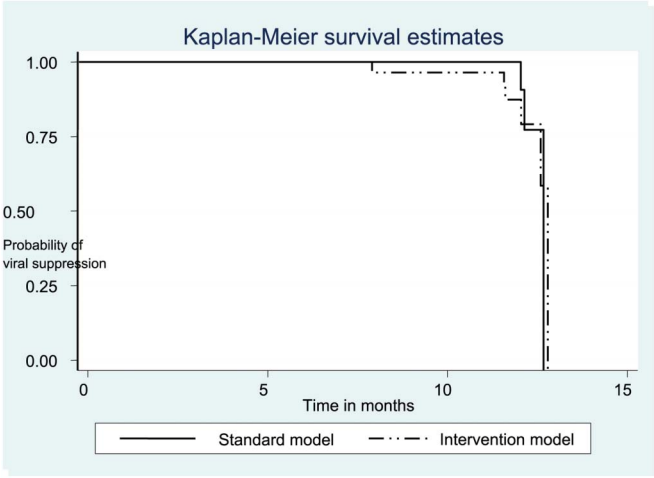

FIGURE 3. Kaplan-Meier curve of probability of HIV-1 RNA VL suppression over time

of the results to special groups such as postpartum women and children could be questionable.

Our study assessed the effect of task shifting among postpartum women in a PMTCT setting of a busy National Referral Hospital. One of the strengths of our study was its randomized intervention design and the use of virologic, immunologic, and clinical endpoints. This study had some limitations including the unavoidable unblinded nature of randomization. Blinding of participants or the personnel delivering the intervention was not possible because of the nature of the interventions. In addition, because of limited funding, follow-up was abbreviated to as early as 6 months for some participants. It would have been useful to explore the long-term benefit of this model on the different endpoints including virologic outcomes. Finally, fluctuations in maternal weight during the postpartum period make this measure an unreliable secondary endpoint. However, given the well-balanced distribution of the baseline characteristics between the 2 care models, randomization is believed to have been effective in this study. Hence, all confounding factors such as weight fluctuations during the postpartum period were taken care of.

In conclusion, nurses and peer counselors were not inferior to doctors and certified counselors in providing ART follow-up care to postpartum women in a PMTCT setting. Further studies evaluating ART treatment in special groups in desperate need of increased access to care such as postpartum women and children are needed to further validate this promising cost saving HIV care model in developing countries with physician staffing shortages.

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