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Authors

Amanyire, Gideon
Semitala, Fred C
Namusobya, Jennifer
et al.

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Effects of a multicomponent intervention to streamline initiation of antiretroviral therapy in Africa: a stepped-wedge cluster-randomised trial

Gideon Amanyire, MbChB,
Makerere University, Kampala, Uganda

Fred C Semitala, MMed,
Makerere University, Kampala, Uganda

Jennifer Namusobya, MbChB,
Makerere University, Kampala, Uganda

Richard Katuramu, MbChB,
Makerere University, Kampala, Uganda

Leatitia Kampiire, MbChB,
Makerere University, Kampala, Uganda

Jeanna Wallenta, MPH,
University of California San Francisco, San Francisco, CA, USA

Prof Edwin Charlebois, PhD,
University of California San Francisco, San Francisco, CA, USA

Prof Carol Camlin, PhD,
University of California San Francisco, San Francisco, CA, USA

Prof James Kahn, MD,
University of California San Francisco, San Francisco, CA, USA

Wei Chang, MPH,
University of California San Francisco, San Francisco, CA, USA

Prof David Glidden, PhD,
University of California San Francisco, San Francisco, CA, USA

Prof Moses Kamya, MMed,
Makerere University, Kampala, Uganda

Correspondence to: Dr Elvin Geng, University of California San Francisco, San Francisco, CA 94110, USA elvin.geng@ucsf.edu.

Contributors

GA, FCS, JN, MK, RK, LK, JW, DH, and EG oversaw the implementation of the study. GA and EG wrote the first draft of the report, which was revised by all authors. GA, FCS, JN, MK, RK, LK, JW, DG, DH, and EG contributed to design of the study. All authors contributed to interpretation of the results. JW, EG, and DG did the statistical analysis. All authors approved the final version of the report for submission.

Declaration of interests

We declare no competing interests.

Prof Diane Havlir, MD, and
University of California San Francisco, San Francisco, CA, USA

Elvin Geng, MD
University of California San Francisco, San Francisco, CA, USA

Summary

Background—In Africa, up to 30% of HIV-infected patients who are clinically eligible for antiretroviral therapy (ART) do not start timely treatment. We assessed the effects of an intervention targeting prevalent health systems barriers to ART initiation on timing and completeness of treatment initiation.

Methods—In this stepped-wedge, non-blinded, cluster-randomised controlled trial, 20 clinics in southwestern Uganda were randomly assigned in groups of five clinics every 6 months to the intervention by a computerised random number generator. This procedure continued until all clinics had crossed over from control (standard of care) to the intervention, which consisted of opinion-leader-led training and coaching of front-line health workers, a point-of-care CD4 cell count testing platform, a revised counselling approach without mandatory multiple pre-initiation sessions, and feedback to the facilities on their ART initiation rates and how they compared with other facilities. Treatment-naive, HIV-infected adults (aged ≥18 years) who were clinically eligible for ART during the study period were included in the study population. The primary outcome was ART initiation 14 days after first clinical eligibility for ART. This study is registered with ClinicalTrials.gov, number NCT01810289.

Findings—Between April 11, 2013, and Feb 2, 2015, 12 024 eligible patients visited one of the 20 participating clinics. Median CD4 count was 310 cells per μL (IQR 179–424). 3753 of 4747 patients (weighted proportion 80%) in the intervention group had started ART by 2 weeks after eligibility compared with 2585 of 7066 patients (38%) in the control group (risk difference 41·9%, 95% CI 40·1–43·8). Vital status was ascertained in a random sample of 208 patients in the intervention group and 199 patients in the control group. Four deaths (2%) occurred in the intervention group and five (3%) occurred in the control group.

Interpretation—A multicomponent intervention targeting health-care worker behaviour increased the probability of ART initiation 14 days after eligibility. This intervention consists of widely accessible components and has been tested in a real-world setting, and is therefore well positioned for use at scale.

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Introduction

Although antiretroviral therapy (ART) for HIV-infected patients substantially reduces morbidity, mortality, and transmission of HIV in low-income and middle-income countries,[1–3] systematic reviews suggest that up to 20–30% of patients identified as clinically eligible for ART either do not start treatment or encounter delays to treatment initiation.[4,5] Slow ART uptake results in large part from three systems-based barriers. First, the consequences of delay are not always apparent to providers; although clinical studies

show that delays in ART initiation in patients with serious infections, even for a few weeks, contribute to AIDS progression,[6,7] this information has not reached all front-line health workers. Additionally, even in patients with higher CD4 cell counts for whom the clinical effects of delays are less clear, loss to follow-up during the ART preparation period can be high.[5] Second, overnight CD4 cell count processing means that establishing ART eligibility[8] requires multiple patient visits to the clinic, thus creating a period of uncertainty about treatment. Third, patient preparation through multiple adherence counselling sessions and requirements for treatment supporters are the norm,[9–11] but can represent barriers to treatment for some patients.

Existing studies of the HIV treatment cascade have not identified an approach to enhance ART initiation after linkage in treatment-eligible patients. Interventions on the HIV cascade have overwhelmingly targeted HIV testing on the one hand (eg, testing campaigns, self-testing[12,13]), and retention and adherence on the other (eg, text messages, peer support[14–17]). Several studies have shown that point-of-care CD4 cell count measurement at the time of HIV testing can increase the rate of ART initiation, but this effect is mostly mediated by more rapid linkage to care after testing or more rapid staging, and not faster initiation once linked to care or once eligibility for treatment is known; a meta-analysis reported no association between point-of-care CD4 cell count testing and ART initiation in eligible patients after linkage.[18] Results of a randomised trial suggested feasibility and potential clinical effect of same-day ART compared with standard initiation,[19] but this trial did not target health-care worker behaviour, and therefore implications with regard to how to change health-care worker behaviour are unclear. As a result, a strategic approach for accelerating uptake of ART in treatment-eligible patients in high-burden settings in Africa remains unclear. We therefore designed an intervention targeting prevalent health systems barriers to ART initiation and assessed its effects on timing and completeness of ART initiation, HIV RNA suppression, and retention in care.

Methods

Study design and participants

Between April 11, 2013, and Aug 2, 2015, we did a stepped-wedge, non-blinded, cluster-randomised trial in a network of health facilities providing HIV treatment in Uganda operated by the Ministry of Health and supported by the Makerere University Joint AIDS Program (MJAP), a programme supported by the President's Emergency Plan for AIDS Relief. We used a stepped-wedge design because all components of the intervention were existing (but not fully implemented) elements of the Ugandan health system, including the use of point-of-care diagnostics in rural settings, the use of data for feedback to clinic sites, and dissemination of clinical and epidemiological information to improve care. MJAP supports ART provision in Kampala, the capital city, as well as Mbarara District, a rural district in western Uganda. All HIV-infected adults (aged ≥18 years) clinically eligible for ART (by clinical or CD4 cell count criteria) during the study period were included in the study population. This population includes patients who were eligible for ART before the study period began but ART naive at the beginning of the study, as well as individuals who became newly ART eligible after the study began. At the conception of the trial, ART

eligibility criteria were CD4 count of 350 cells per μL or less, any WHO stage 3 or 4 condition, and pregnancy. On Jan 3, 2014, about a third of the way through the trial, Ugandan national guidelines[20] revised the CD4 threshold for ART eligibility from 350 cells per μL to 500 cells per μL and also included seronegative partners in discordant couples and key populations (eg, sex workers, men who have sex with men, fisherfolk).

The intervention targeted the health system and health-care workers and as such individual-level informed consent was not obtained apart from patients who provided HIV RNA measurements, since this procedure was not a part of routine care at the time of the study. This approach was approved by institutional review boards of the University of California, and by ethics boards at the Makerere University in Kampala and the Uganda National Council for Science and Technology.

Randomisation and masking

Health facilities (clinics) were the unit of randomisation. Four groups of five clinics were randomly assigned to receive the intervention in one of four steps at intervals of about 6 months. The five calendar periods were April 11 to June 18, 2013 (period 1), June 19 to Dec 4, 2013 (period 2), Dec 5, 2013, to March 30, 2014 (period 3), March 31 to Oct 1, 2014 (period 4), and Oct 2, 2014, to Feb 2, 2015 (period 5). This procedure continued until all clinics had crossed over from control (standard of care) to the intervention group. Patients eligible for ART before the clinics crossed over from the control to the intervention group were not exposed to the intervention, whereas those who became eligible for ART after crossover were considered exposed. Randomisation was stratified by four facility levels defined by size and time offering HIV care and treatment services. Randomisation was done with a random number generator in Stata (version 13). Random allocation of clinics was done by a statistician who was not otherwise involved with the study planning or analysis. This trial was non-blinded.

Procedures

To influence health systems to provide ART more efficiently and effectively, we developed the Streamlined ART START-ART Strategy (START-ART) based on insights from health promotion literature.[21,22] Specifically, work by Green and Krueter[22] suggests that interventions to change health-care worker behaviour are most effective when they combine three factors: predisposing factors consisting of knowledge, attitudes, or beliefs that affect behaviour; enabling factors consisting of skills or materials that make the desired behaviour easier; and reinforcing factors consisting of anticipated con sequences following a behaviour. In our assessment, barriers to ART are the widespread belief that delays to ART initiation are not harmful; overnight CD4 cell count processing and therefore multiple visits by patients to the clinic before ART eligibility is known; and standard practices demanding up to three adherence counselling visits before ART initiation and the need for treatment supporters. Our intervention therefore included opinion-leader-led training about the evidence regarding clinical and behavioural consequences of waiting to offer ART to recalibrate the balance of risks and benefits of offering ART made by doctors, nurses, clinical officers, and counsellors. This training included one on-site, face-to-face, lecture-style didactic session, subsequent coaching visits on the clinical considerations, and

introduction of a revised counselling approach that relaxed strict requirements for treatment supporters and emphasised that individual patients should be assessed for ART readiness rather than the application of one-size-fits-all multiple adherence counselling sessions. We also introduced PIMA (Alere, Waltham, MA, USA; appendix p 3) CD4 assay machines at the sites to enable health-care workers to offer real-time results. Finally, we provided biannual feedback to the facilities, which involved presentation of the clinic ART initiation rates compared with other clinics. The feedback meetings were held with the facility manager as well as all staffat the site. Although standard-of-care practices at the participating facilities were diverse, three pretreatment counselling sessions, requirement for treatment supporter, and overnight CD4 cell count processing were the usual practice at these facilities before introduction of the intervention.

Sociodemographic, clinical, and laboratory data were retrieved from a Microsoft Access database used by the clinics to document clinical care. Data management for this study was embedded within the programme data system: the research team offered support for data entry, programming, and data transfer but did not create a parallel research database. The study team adjudicated a random sample of charts to verify the outcomes. The study team also analysed charts of all ART-eligible patients for whom ART initiation was not documented and all patients for whom ART eligibility criteria could not be discerned in the database. We found the electronic medical record to be 99% accurate for visits and ART initiation—ie, the data elements used to define outcomes in this study. HIV RNA assay was done with COBAS TaqMan Platform HIV-1 test, version 2 (Roche, Basel, Switzerland), with a lower limit of detection of 200 copies per mL.

Outcomes

The primary endpoint was ART initiation within 14 days after the first date of clinical eligibility for ART during the study period. Secondary outcomes were the probability of ART initiation on the same day of eligibility as well as 30 days and 90 days after clinical eligibility for ART; HIV RNA suppression and survival 1 year after ART eligibility, assessed in a random sample of patients; retention in care after eligibility; vertical transmission; and cost and cost-effectiveness. The intervention acted on health workers and clinical organisations; therefore, we did not systematically collect data for adverse events. These analyses of vertical transmission and cost and cost-effectiveness are ongoing and will be reported elsewhere.

Statistical analysis

In power calculations, we anticipated the number of patients clinically eligible for ART in the clinic sites supported by the MJAP organisation during the study period to be around 12 000. On the basis of assumptions that 25% of patients in the control group and 50% of patients in the intervention group would achieve the primary outcome, and with five clinics randomly assigned to the intervention in each of four steps, a harmonic mean of 50 individuals in each clinic during each period, and a coefficient of variation of 0.2, we calculated that the study had 99% power. HIV RNA levels were assessed 1 year after ART eligibility in a random sample of patients from clinics randomised in step 1 (intervention) and step 4 (control) in whom a year of observation in the same treatment condition was

possible. With the assumptions of a coefficient of variation of 0.10, 80% of patients achieving HIV RNA suppression in the control group, 92% of patients achieving HIV suppression in the intervention group (a 12% absolute risk difference), and a harmonic mean of 50 patients per clinic, we calculated a power of 77%.

We treated the primary outcome as a binary variable: patients were deemed either to have started ART or not to have started ART by 14 days. Patients with less than 14 days of observation time before crossover to intervention or end of study database closure were not included in the analysis of the primary outcome. Deaths before ART initiation were considered non-initiations. We used a mixed effects logistic regression model (meglm in Stata version 14.0) with a normal random effect for site and a fixed effect for intervention to estimate the primary outcome. The primary analysis was unadjusted. In additional analyses, we adjusted for calendar time (specified as a restricted cubic spline) and ART regimen. We did a subgroup analysis (and examined interactions) on the basis of patients' characteristics at the time of ART eligibility including CD4 count (<50 cells per μL or ≥50 cells per μL), pregnancy, WHO stage, and tuberculosis.

In secondary analyses, we examined HIV RNA suppression and survival 1 year after eligibility in a randomly selected subset of patients from step 1 and step 4 using mixed effects logistic regression. We analysed patients in step 1 and step 4 because these groups were exposed to either the intervention or control for 1 year. Additionally, we took a random sample to minimise costs associated with both tracing to obtain outcomes and HIV RNA testing. In the analysis of HIV RNA suppression, patients who died or from whom we did not obtain an HIV RNA measurement were deemed not to have achieved HIV RNA suppression. We also did a prespecified analysis using inverse probability weighting to account for missing outcomes. In additional secondary analyses, we examined retention in care using visit adherence,[23–25] which was defined as the fraction of appointments made within 7 days. All secondary analyses were adjusted for patients' characteristics including clinical eligibility for ART before the study period (ie, incident or prevalent ART eligible), sex, age (three knot cubic spline), CD4 cell count (three knot cubic spline), time since eligibility, and calendar period of eligibility. Stata version 14.0 was used for all statistical analyses.

This study is registered with ClinicalTrials.gov, number NCT01810289.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We approached 22 clinics operated by the Ugandan Ministry of Health. Two facilities declined to participate. In the remaining 20 facilities, exactly 15 000 treatment-naive patients newly entered care during the study period from April 11, 2013, to Feb 2, 2015. After excluding 2976 patients who never completed assessment for ART eligibility, our study

population included 12 024 patients eligible for ART according to criteria outlined in the Ugandan national guidelines (figure 1).[20] 7545 (63%) were women. Median CD4 count at eligibility was 310 cells per μL (IQR 179–424; tables 1 and 2). Patients in the intervention group had slightly higher CD4 counts at baseline (median 320 cells per μL [IQR 183–419]) than patients in the control group (median 304 cells per μL [175–430]). The intraclass correlation coefficient for the primary outcome was 0.069 (95% CI 0.034–0.140) for the intervention group and 0.050 (0.024–0.101) for the control group.

3753 of 4747 patients (weighted proportion 80%) in the intervention group had started ART by 2 weeks after eligibility compared with 2585 of 7066 patients (38%) in the control group: risk ratio (RR) 2.11 (95% CI 2.03–2.20); risk difference 41.9% (95% CI 40.1–43.8; figure 2). Findings were similar after adjustment for calendar time and ART regimen: RR 1.86 (95% CI 1.72–2.02); risk difference 35.7% (95% CI 32.4–38.9). 3358 (71%) of 4747 patients in the intervention group started ART on the same day of eligibility compared with 1313 (18%) of 7277 patients in the control group: RR 3.87 (95% CI 3.64–4.11); risk difference 52.5% (95% CI 50.7–54.3). 3716 of 6731 patients (weighted proportion 57%) in the control group started ART within 30 days compared with 3999 of 4747 (85%) in the intervention group (RR 1.49 [95% CI 1.46–1.53]; risk difference 28.1% [95% CI 26.5–29.7]). At 90 days after eligibility, 4349 of 4747 patients (weighted proportion 90%) had started ART in the intervention group compared with 4004 of 5580 patients (70%) in the control group: RR 1·27 (95% CI 1.25–1.30); risk difference (19.3%, 95% CI 17.6–21.0). Results were consistent across predefined subgroups based on sex, age, clinic size, CD4 cell count at eligibility, WHO stage, pregnancy, and tuberculosis at eligibility (figure 3).

We randomly sampled 437 patients for enhanced outcome ascertainment of HIV RNA viral load and vital status 1 year after eligibility. The patients randomly sampled were similar to patients in the study population of individuals who were exposed either to the intervention or control for 1 year in step 1 and step 4, respectively (appendix p 1). We successfully obtained HIV RNA measurements for 335 (77%) of 437 of these randomly sampled patients, 164 (75%) of 220 in the intervention group and 171 (79%) of 217 in the control group. When patients with missing data were treated as failures, 138 of 206 individuals (weighted proportion 66%) in the intervention group achieved HIV RNA suppression compared with 128 of 208 (58%) in the control group (RR 1.14, 95% CI 0.93–1.38; p=0.20). Use of inverse probability weighting based on clinic, sex, age, and CD4 cell count to address missing outcomes yielded an estimate of 85% virological suppression in the intervention group and 75% virological suppression in the control group (RR 1.13, 95% CI 1.02–1.27; p=0.024). Vital status was ascertained for 407 (93%) of the 437 patients who were randomly selected for enhanced outcome ascertainment, 208 (95%) of 220 in the intervention group and 199 (92%) of 217 in the control group. Four deaths (2%) in 208 individuals occurred in the intervention group and five (3%) in 199 individuals occurred in the control group (risk ratio 0.65, 95% CI 0.14–3.0; p=0.58; inverse probability weighting based on clinic, sex, age, and CD4 cell count to address missing vital status outcomes).

In the analysis of retention in care, visit adherence or the proportion of appointments made within 7 days was not changed by the intervention. After controlling for age, sex, CD4 cell count at eligibility, incident or prevalent eligibility, time since eligibility, and period of

eligibility, patients attended 84% (95% CI 83–85) of appointments in the control group and 84% (83–85) of appointments in the intervention group (RR 1.00, 95% CI 0.99–1.01; p=0.93). The effect of the intervention on retention in care as measured through visit adherence was consistent across subgroups (figure 4). The distribution of visit adherence was similar in the intervention and control groups (appendix p 2). Patients in the control group made a mean of 1.44 visits per 90 days (95% CI 1.42–1.46) whereas patients in the intervention group made 1.39 visits per 90 days (1.37–1.41), yielding a rate ratio of 0.96 (95% CI 0.94–0.99; p=0.0024).

An examination of the probability of ART initiation at 14 days over calendar time suggests that the slightly diminishing effect of the intervention over time was caused by accelerations in ART initiation in the control group whereas the probability of ART initiation in the intervention sites remained constant and sustained over the intervention period (figure 5).

Discussion

Our study shows that a theory-based intervention targeting the health system increased the probability of ART initiation 14 days after eligibility compared with standard care. The proportion of patients starting ART on the same day as eligibility and the total proportion of patients on ART 90 days after eligibility were higher in the intervention group than in the control group, suggesting both increasing rapidity and completeness of ART initiation. The intervention was also associated with greater HIV RNA suppression 1 year after ART eligibility when inverse probability weights were used to address missing outcomes. Mortality was low and did not differ between intervention and control groups in a subset of individuals randomly selected for intensive vital status assessments. No change in retention in care was seen after accelerating ART initiation with the package of training, point-of-care technology, and incentivisation. Effects on ART initiation, HIV RNA viral load, and retention were consistent among subgroups and with adjustment.

This study identifies a widely usable strategy to improve the cascade of HIV care by influencing health-care worker behaviour. Studies in which research protocols take control of the ART initiation process (perhaps through visits staffed by a study physician) have shown the clinical value of rapid initiation,[10,19] but do not offer directly applicable information about how to change clinical practice in the real world. The START-ART intervention consists of replicable components (ie, opinion-leader-led training, point-of-care devices, and reputational incentives). The intervention successfully influenced front-line health workers employed by the Ugandan Ministry of Health and accelerated ART initiation in a completely unselected population of patients (all patients eligible for ART at these facilities were included in the analysis). Our study therefore not only shows that accelerated initiation of ART is possible, but also offers a strategic approach for achieving this acceleration under real-world programme conditions.

Our study focuses attention on the importance of ART initiation as a target for health systems interventions. Current modelling efforts suggest that increasing HIV testing will yield the greatest reductions in morbidity and mortality. Strategies to enhance testing such as door-to-door approaches, health fairs, and self-testing have paved the way to greater uptake

of testing.[13] Likewise, a diverse set of interventions targeting retention in care such as text messages, microclinics, and others have shown the ability to improve retention and adherence.[14,26–28] Enhanced testing and retention interventions, however, will achieve maximal effects on public health only if these steps in the cascade are efficiently linked by ART initiation.

The large change in provider practice also underscores the usefulness of a health promotion model (PRECEDE) in global health,[22] a framework that suggests that combining mechanisms (ie, predisposing, enabling, and reinforcing factors) can yield larger effects. In global health, interventions that use only one mechanism to change health behaviour often yield small[29] or no effects because sufficient causes for change consist of many com ponents.[30] The introduction of technology alone, for example, by making Pima machines available at health facilities in South Africa had no effect on the rate of ART initiation among eligible patients in a retrospective study[31] and in a meta-analysis.[32] A supply-side intervention to task-shift ART services to nurses and improve the care cascade likewise did not change rates of ART initiation.[30] Although an all-encompassing intervention is likely to achieve impact, complex interventions can be impractical to scale up. PRECEDE offers something in the middle: a framework to assemble sufficient cause for change that maintains parsimony through the identification of a generic framework that conceptualises component causes.

Our study has limitations. First, we did the study in a real-world context and therefore used clinical electronic records systems as the research database. We did, however, carry out extensive manual chart reviews to verify the accuracy of data in the electronic data systems. Second, the use of point-of-care CD4 cell count testing has most relevance for settings in which treatment is based on this measure, which could change in the future in many countries. However, our intervention also includes provider training and incentivisation components that will remain relevant even in settings where CD4 cell count thresholds are eliminated. Third, we do not know the relative contribution of each of the intervention components. Fourth, the stepped-wedge design itself has shortcomings.[33–35] The design is susceptible to trends over calendar time. The stepped-wedge trial design has also been criticised because outcomes (eg, clinic visits) are measured multiple times,[33] thus creating a potential burden for patients and staff. Because our study measurements were embedded within existing clinical data systems, however, no additional burden was incurred in the study. Contamination of non-intervention groups might occur over time. In this study, evidence consistent with spillover was present—ie, the probability of rapid ART initiation in the control group increased over calendar time. Finally, we placed less emphasis on measuring clinical outcomes (ie, assessing mortality and viral load in a sample rather than in all patients), which is less robust than assessing outcomes in all patients. Implementation science, however, is motivated by the recognition that testing interventions to promote evidence-based practices constitutes a scientific objective in its own right.

There is a large gap in public health practice in the ability of health systems to efficiently initiate people infected with HIV and known to be eligible on life-saving ART. We tested an intervention targeting known barriers to ART initiation and showed its effectiveness using a pragmatic design in a real-world setting. The intervention components are widely accessible

—when adequate investments are available—to improve the efficiency and effectiveness of the global treatment response to HIV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in context

Evidence before this study

We searched PubMed for implementation science studies of interventions to increase antiretroviral therapy (ART) initiation in HIV-infected people in Africa published between Jan 1, 2005, and Feb 1, 2016. We used the search terms “antiretroviral therapy” AND “initiation” AND “Africa” AND “intervention”. The search resulted in 97 citations, including two systematic reviews. The proportion of treatment-eligible patients who begin ART after presenting to a treatment facility is estimated to be around 68% in systematic reviews. Studies suggest that point-of-care CD4 cell count determination increases ART initiation in patients who newly test HIV positive, but also show that this effect is largely explained by enhanced linkage between testing and treatment facilities. Point-of-care CD4 cell count determination has little or no effects on ART initiation in eligible patients after presentation to a treatment facility. Other interventions to enhance ART initiation that have been tested with mixed results include lay counsellor follow-up for newly diagnosed patients and task shifting of ART from doctors to primary care nurses on treatment initiation. One recent randomised study showed same-day ART initiation was feasible and improved ART virological outcomes at 6 months compared with standard of care.

Added value of this study

By use of perspectives from implementation science and pragmatic study designs, our study extends existing literature by offering a strategy for increasing ART initiation that is well positioned for translation into routine practice. The START-ART intervention led to a substantial rise in ART initiation on the same day as eligibility, 14 days after eligibility, and 90 days after eligibility. These effects were seen in an unselected population of treatment-eligible patients presenting to care in southwestern Uganda, which suggests that our findings are likely to be generalisable to real-world populations. The intervention targeted health-care workers, but ultimately left the decision to offer ART in the hands of front-line doctors and nurses working under programme conditions (rather than research staff), which shows that the intervention is well positioned to be acceptable and adoptable in routine care. We used a pragmatic design (a cluster-randomised, stepped-wedge trial) that balances internal and external validity.

Implications of all the available evidence

The available evidence suggests that speed and completeness of ART initiation in eligible patients is suboptimal, but that use of point-of-care CD4 cell count testing, nested within a behavioural intervention targeting health-care worker practice, can accelerate ART initiation. One-size-fits-all practices that systematically delay ART initiation, such as mandatory multiple pretreatment adherence counselling sessions, can introduce unnecessary delays and increased loss to follow-up. Accelerating ART initiation through evidence-based interventions such as the START-ART intervention, which targets health-care workers while preserving provider discretion and patient preference, can

simultaneously accelerate ART initiation and minimise the potential for negative consequences of hasty initiation.

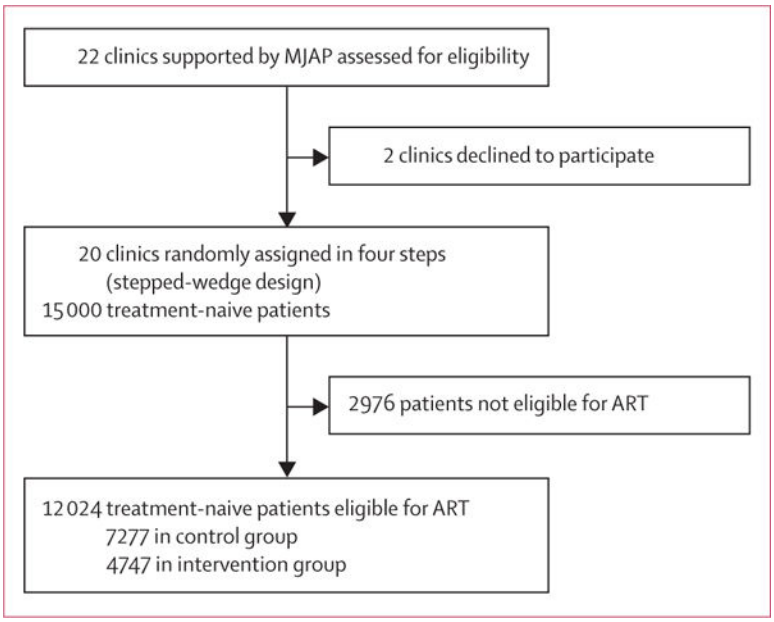

Figure 1. Trial profile

MJAP=Makerere University Joint AIDS Program.

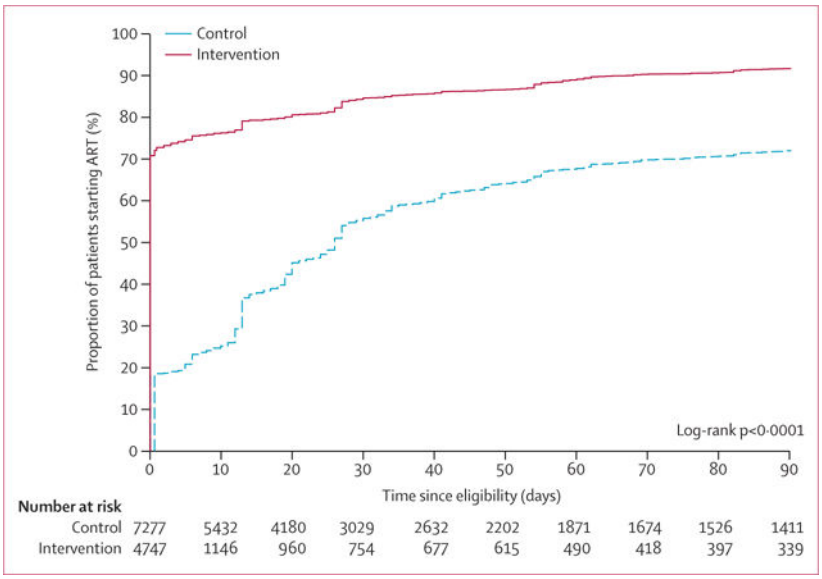

Figure 2. Cumulative incidence of ART initiation

ART=antiretroviral therapy.

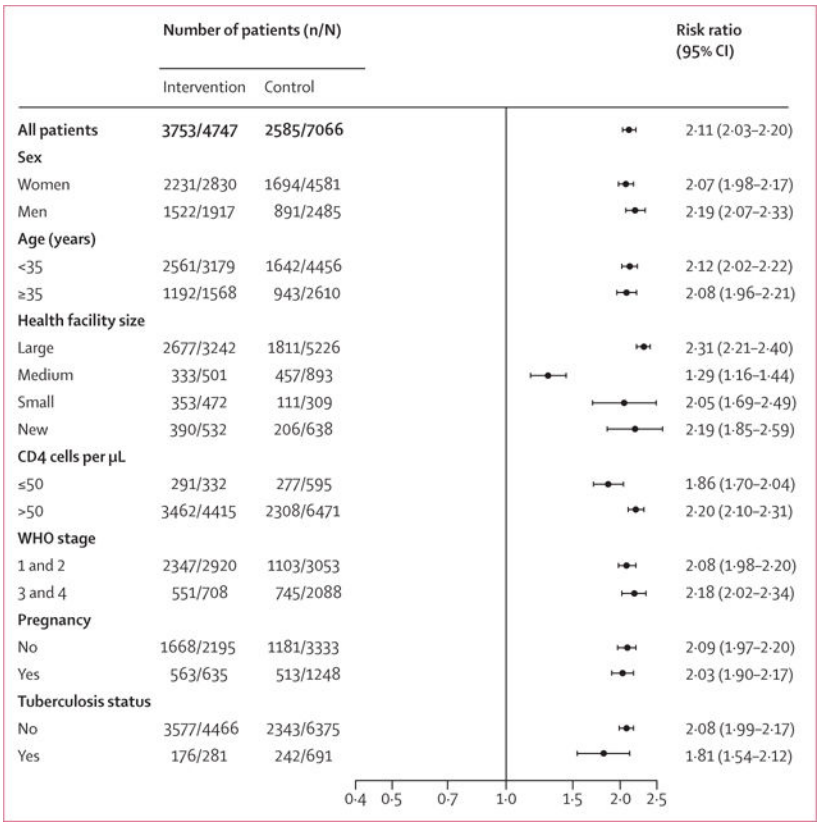

Figure 3. Subgroup analyses of ART initiation by 14 days after eligibility

Patients were censored if they did not contribute enough observation time (14 days) to be able to have an outcome, hence why there are 7066 patients in the control group rather than 7277. ART=antiretroviral therapy.

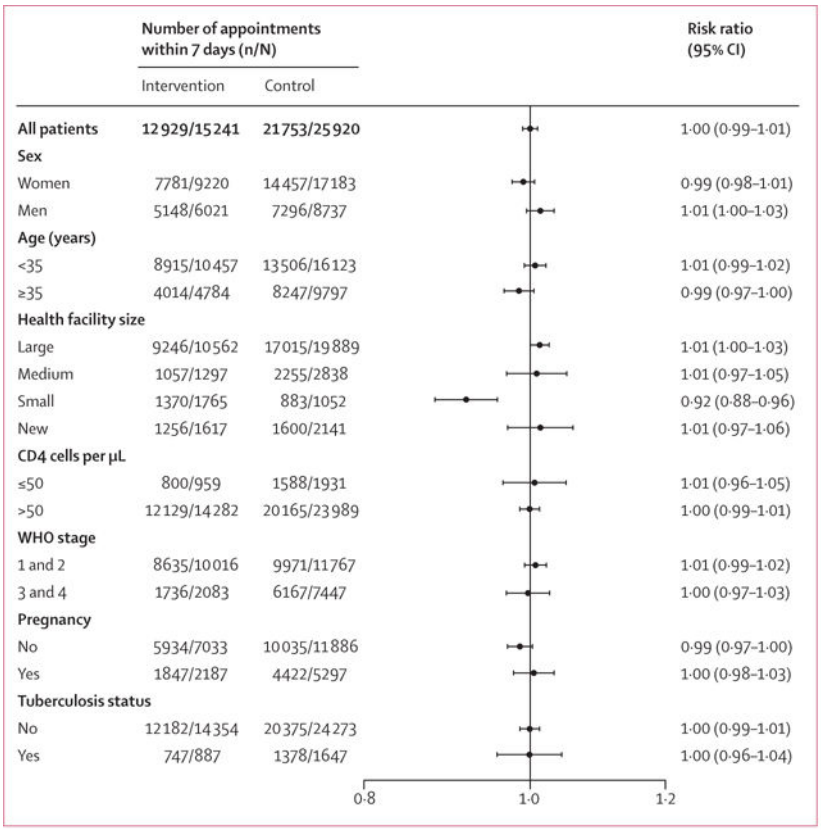

Figure 4. Subgroup analyses of retention in care as measured through visit adherence

Data are number of appointments made within 7 days (n) out of total number of appointments (N).

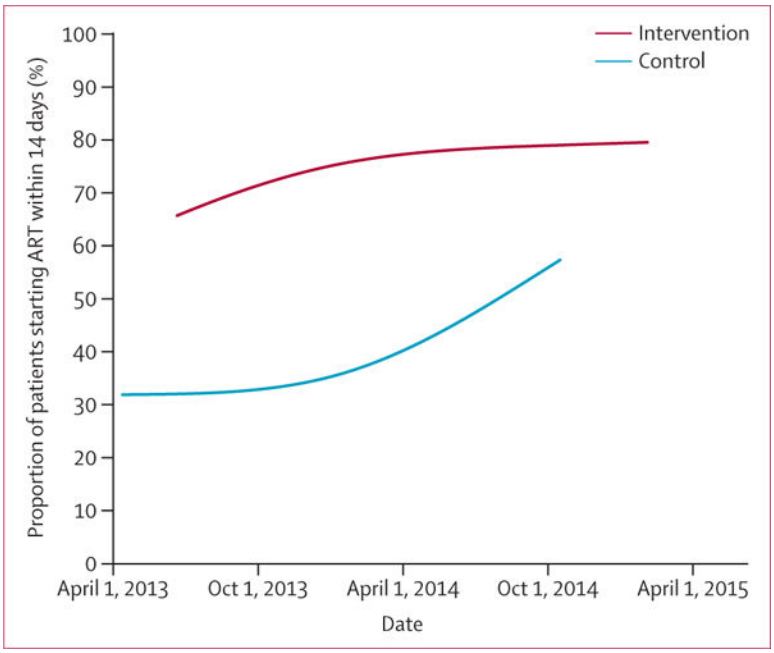

Figure 5. The adjusted probability of ART initiation 14 days after eligibility by date
ART=antiretroviral therapy.

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Table 1

Patient characteristics by step of intervention roll-out

	Step 1 clinics		Step 2 clinics		Step 3 clinics		Step 4 clinics		Total intervention	Total Control
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control		
Patients eligible for ART	2072 (76%)	647 (24%)	1346 (50%)	1337 (50%)	879 (37%)	1501 (63%)	450 (11%)	3792 (89%)	4747 (39%)	7277 (61%)
Sex										
Men	828 (40%)	221 (34%)	516 (38%)	456 (34%)	408 (46%)	641 (43%)	165 (37%)	1244 (33%)	1917 (40%)	2562 (35%)
Women	1244 (60%)	426 (66%)	830 (62%)	881 (66%)	471 (54%)	860 (57%)	285 (63%)	2548 (67%)	2830 (60%)	4715 (65%)
Age at eligibility (years)	29 (24–36)	30 (26–36)	30 (25–38)	30 (25–38)	31 (26–39)	32 (27–40)	31 (26–38)	32 (27–38)	30 (25–37)	31 (26–38)
Health facility size *										
Large	1601 (77%)	555 (86%)	904 (67%)	1052 (79%)	394 (45%)	560 (37%)	343 (76%)	3207 (85%)	3242 (68%)	5374 (74%)
Medium	139 (7%)	33 (5%)	0	0	315 (36%)	625 (42%)	47 (10%)	261 (7%)	501 (11%)	919 (13%)
Small	233 (11%)	47 (7%)	157 (12%)	106 (8%)	61 (7%)	81 (5%)	21 (5%)	88 (2%)	472 (10%)	322 (4%)
New	99 (5%)	12 (2%)	285 (21%)	179 (13%)	109 (12%)	235 (16%)	39 (9%)	236 (6%)	532 (11%)	662 (9%)
ART eligibility										
Incident	1979 (96%)	235 (36%)	1321 (98%)	922 (69%)	840 (96%)	1214 (81%)	443 (98%)	2964 (78%)	4583 (97%)	5335 (73%)
Prevalent	93 (4%)	412 (64%)	25 (2%)	415 (31%)	39 (4%)	287 (19%)	7 (2%)	828 (22%)	164 (3%)	1942 (27%)
ART eligibility date (dd/mm/yy)	25/03/14 (25/10/13–22/07/14)	08/05/13 (16/04/13–04/06/13)	16/05/14 (10/03/14–26/09/14)	10/06/13 (12/03/13–16/09/13)	19/07/14 (22/05/14–15/10/14)	30/08/13 (28/05/13–13/12/13)	03/12/14 12/11/14–08/01/15)	13/11/13 (13/06/13–28/03/14)	02/06/14 (25/02/14–16/10/14)	14/08/13 (13/05/13–27/01/14)
Eligibility CD4 cells per μL	315 (188–417)	322 (228–457)	318.5 (191–417)	271 (159–338)	334 (159–419)	246 (126–338)	337 (186–430)	340 (198–460)	320 (183–419)	304 (175–430)
Missing data	61 (3%)	30 (5%)	82 (6%)	109 (8%)	89 (10%)	139 (9%)	64 (14%)	198 (5%)	296 (6%)	476 (7%)
Pregnancy status at eligibility										
Pregnant	373 (30%)	142 (33%)	110 (13%)	85 (10%)	78 (17%)	183 (21%)	74 (26%)	862 (34%)	635 (22%)	1272 (27%)
Not pregnant	871 (70%)	284 (67%)	720 (87%)	796 (90%)	393 (83%)	677 (79%)	211 (74%)	1686 (66%)	2195 (78%)	3443 (73%)
Eligibility WHO stage										
Stage 1 and 2	1686 (81%)	404 (62%)	367 (27%)	187 (14%)	534 (61%)	586 (39%)	333 (74%)	1993 (53%)	2920 (62%)	3170 (44%)
Stage 3 and 4	256 (12%)	111 (17%)	133 (10%)	352 (26%)	225 (26%)	584 (39%)	94 (21%)	1086 (29%)	708 (15%)	2133 (29%)
Missing data	130 (6%)	132 (20%)	846 (63%)	798 (60%)	120 (14%)	331 (22%)	23 (5%)	713 (19%)	1119 (24%)	1974 (27%)
Tuberculosis at ART eligibility	103 (5%)	205 (32%)	18 (1%)	69 (5%)	130 (15%)	247 (16%)	30 (7%)	194 (5%)	281 (6%)	715 (10%)
Tuberculosis and CD4 count ≤50 cells per μL	13 (1%)	11 (2%)	0	10 (1%)	29 (3%)	64 (4%)	10 (2%)	59 (2%)	52 (1%)	144 (2%)
Tuberculosis and CD4 count >50 cells per μL	87 (4%)	190 (29%)	13 (1%)	46 (3%)	58 (7%)	137 (9%)	17 (4%)	126 (3%)	175 (4%)	499 (7%)
Missing data	3 (<1%)	4 (1%)	5 (<1%)	13 (1%)	43 (5%)	46 (3%)	3 (1%)	9 (<1%)	54 (1%)	72 (1%)
No tuberculosis	1969 (95%)	442 (68%)	1328 (99%)	1268 (95%)	749 (85%)	1254 (84%)	420 (93%)	3598 (95%)	4466 (94%)	6562 (90%)
Ever initiated ART	2006 (97%)	256 (40%)	1280 (95%)	899 (67%)	837 (95%)	1217 (81%)	428 (95%)	3236 (85%)	4551 (96%)	5608 (77%)

	Step 1 clinics		Step 2 clinics		Step 3 clinics		Step 4 clinics		Total intervention	Total Control
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control		
ART initiation date (dd/mm/yy)	08/04/14 (21/11/13–06/08/14)	02/07/13 (27/05/13–14/01/14)	29/05/14 (21/03/14–19/10/14)	13/09/13 (21/06/13–10/12/13)	07/08/14 (05/06/14–04/11/14)	24/10/13 (11/07/13–14/02/14)	10/12/14 (20/11/14–19/01/15)	05/03/14 (13/09/13–10/06/14)	16/06/14 (11/03/14–31/10/14)	30/11/13 (17/07/13–11/04/14)
ART regimen										
Regimen contained efavirenz	1856 (92%)	433 (80%)	1208 (94%)	1027 (87%)	755 (90%)	1017 (73%)	397 (92%)	2993 (86%)	4216 (92%)	5470 (83%)
Regimen contained tenofovir	1933 (96%)	492 (91%)	1187 (92%)	968 (82%)	765 (91%)	1106 (80%)	400 (93%)	2904 (83%)	4285 (94%)	5470 (83%)
Missing	57 (3%)	106 (16%)	59 (4%)	154 (12%)	39 (4%)	115 (8%)	18 (4%)	310 (8%)	173 (4%)	685 (9%)

Data are n (%) or median (IQR). Step 1 is composed of five facilities in which the intervention was rolled out earliest in calendar time. Therefore, most patients who became eligible for ART in the step 1 clinic sites did so during the intervention phase. ART=antiretroviral therapy.

* Facilities were defined as large if they had ≥100 patients per day, medium if they had 20–99 patients per day, small if they had <20 patients per day, and new if they had <20 patients per day and were also newly providing ART.

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Table 2

Patient characteristics by calendar period of ART eligibility

	Period 1	Period 2		Period 3		Period 4		Period 5	Total intervention	Total control
	Control *	Intervention	Control	Intervention	Control	Intervention	Control	Intervention †		
Patients	2741 (38%)	644 (14%)	2337 (32%)	836 (18%)	1259 (17%)	1901 (40%)	940 (13%)	1366 (29%)	4747 (39%)	7277 (61%)
Sex										
Men	893 (33%)	232 (36%)	853 (36%)	327 (39%)	496 (39%)	802 (42%)	320 (34%)	556 (41%)	1917 (40%)	2562 (35%)
Women	1848 (67%)	412 (64%)	1484 (64%)	509 (61%)	763 (61%)	1099 (58%)	620 (66%)	810 (59%)	2830 (60%)	4715 (65%)
Age at eligibility (years)	31 (26–38)	29 (24–36)	31 (26–39)	29 (25–36)	32 (27–39)	30 (25–37)	32 (27–38)	30 (25–38)	30 (25–37)	31 (26–38)
Health facility size ≠										
Large	2145 (78%)	470 (73%)	1634 (670%)	608 (73%)	859 (68%)	1172 (62%)	736 (78%)	992 (73%)	3242 (68%)	5374 (74%)
Medium	265 (10%)	53 (8%)	321 (14%)	13 (2%)	243 (19%)	302 (16%)	90 (10%)	133 (10%)	501 (11%)	919 (13%)
Small	120 (4%)	93 (14%)	131 (6%)	102 (12%)	43 (3%)	178 (9%)	28 (3%)	99 (7%)	472 (10%)	322 (4%)
New	211 (8%)	28 (4%)	251 (11%)	113 (14%)	114 (9%)	249 (13%)	86 (9%)	142 (10%)	532 (11%)	662 (9%)
ART eligibility										
Incident	1137 (41%)	572 (89%)	2041 (87%)	821 (98%)	1231 (98%)	1856 (98%)	926 (99%)	1334 (98%)	4583 (97%)	5335 (73%)
Prevalent	1604 (59%)	72 (11%)	296 (13%)	15 (2%)	28 (2%)	45 (2%)	14 (1%)	32 (2%)	164 (3%)	1942 (27%)
ART eligibility date (dd/mm/yy)	08/05/13 (23/04/13–29/05/13)	30/08/13 (22/07/13–18/10/13)	06/09/13 (23/07/13–21/10/13)	14/02/14 (15/01/14–07/03/14)	14/02/14 (21/01/14–07/03/14)	07/06/14 (02/05/14–22/07/14)	18/06/14 (02/05/14–12/08/14)	28/11/14 (30/10/14–06/01/15)	02/06/14 (25/02/14–16/10/14)	14/08/13 (13/05/13–27/01/14)
Eligibility CD4 cells per μL	310 (199–442)	274 (162–344)	264 (131–348)	330 (187–384)	340 (188–438)	342 (194–426)	362 (190–455)	331 (180–433)	320 (183–419)	304 (175–430)
Missing data	133 (5%)	34 (5%)	199 (9%)	33 (4%)	76 (6%)	93 (5%)	68 (7%)	136 (10%)	296 (6%)	476 (7%)
Pregnancy status at eligibility										
Pregnant	604 (33%)	142 (34%)	405 (27%)	101 (20%)	141 (18%)	206 (19%)	122 (20%)	186 (23%)	635 (22%)	1272 (27%)
Not pregnant	1244 (67%)	270 (66%)	1079 (73%)	408 (80%)	622 (82%)	893 (81%)	498 (80%)	624 (77%)	2195 (78%)	3443 (73%)
Eligibility WHO stage										
Stage 1 and 2	1019 (37%)	482 (75%)	764 (33%)	456 (55%)	724 (58%)	1121 (59%)	663 (71%)	861 (63%)	2920 (62%)	3170 (44%)
Stage 3 and 4	900 (33%)	105 (16%)	759 (32%)	109 (13%)	293 (23%)	272 (14%)	181 (19%)	222 (16%)	708 (15%)	2133 (29%)
Missing data	822 (30%)	57 (9%)	814 (35%)	271 (32%)	242 (19%)	508 (27%)	96 (10%)	283 (21%)	1119 (24%)	1974 (27%)
Tuberculosis at ART eligibility	339 (12%)	61 (9%)	192 (8%)	25 (3%)	117 (9%)	97 (5%)	67 (7%)	98 (7%)	281 (6%)	715 (10%)
Tuberculosis and CD4 count ≤50 cells per μL	33 (1%)	5 (1%)	59 (3%)	2 (<1%)	34 (3%)	21 (1%)	18 (2%)	24 (2%)	52 (1%)	144 (2%)
Tuberculosis and CD4 count >50 cells per μL	289 (11%)	53 (8%)	102 (6%)	22 (3%)	64 (5%)	48 (3%)	44 (5%)	52 (4%)	175 (4%)	499 (7%)
Missing data	17 (1%)	3 (<1%)	31 (1%)	1 (<1%)	19 (2%)	28 (1%)	5 (1%)	22 (2%)	54 (1%)	72 (1%)
No tuberculosis	2402 (87.6%)	583 (91%)	2145 (92%)	811 (97%)	1142 (91%)	1804 (95%)	873 (93%)	1268 (93%)	4466 (94%)	6562 (90%)
Ever initiated ART	1874 (68%)	608 (94 %)	1892 (81%)	815 (97%)	1060 (84%)	1824 (96%)	782 (83%)	1304 (95%)	4551 (96%)	5608 (77%)

	Period 1	Period 2		Period 3		Period 4		Period 5	Total intervention	Total control
	Control*	Intervention	Control	Intervention	Control	Intervention	Control	Intervention†		
ART initiation date (dd/mm/yy)	20/06/13 (16/05/13–29/11/13)	17/09/13 (02/08/13–08/11/13)	21/10/13 (23/08/13–10/12/13)	21/02/14 (21/01/14–18/03/14)	13/03/14 (18/02/14–08/04/14)	17/06/14 (08/05/14–07/08/14)	21/07/14 (29/05/14–09/09/14)	08/12/14 (11/11/14–13/01/15)	16/06/14 (11/03/14–31/10/14)	30/11/13 (17/07/13–11/04/14)
ART regimen										
Regimen contained efavirenz	1878 (79%)	530 (87%)	1706 (80%)	753 (92%)	1064 (89%)	1682 (92%)	822 (92%)	1251 (95%)	4216 (92%)	5470 (83%)
Regimen contained tenofovir	1924 (81%)	568 (93%)	1652 (78%)	768 (94%)	1067 (89%)	1701 (93%)	827 (93%)	1248 (95%)	4285 (94%)	5470 (83%)
Missing	364 (13%)	31 (5%)	212 (9%)	20 (2%)	60 (5%)	69 (4%)	49 (5%)	53 (4%)	173 (4%)	685 (9%)

Data are n (%) or median (IQR). ART=antiretroviral therapy.

*All clinics in period 1 received control; no clinics had received the intervention.

†All clinics in period 5 are assigned to intervention; no clinics were left in the control group during this period.

‡Facilities were defined as large if they had ≥100 patients per day, medium if they had 20–99 patients per day, small if they had <20 patients per day, and new if they had <20 patients per day and were also newly providing ART.