# Evaluation of impact of long-lasting insecticide-treated bed nets and point-of-use water filters on HIV-1 disease progression in Kenya

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**Objectives:** Among HIV-1-infected individuals in Africa, coinfection with malaria and diarrhoeal disease may be associated with more rapid HIV-1 disease progression. We sought to determine whether the use of long-lasting insecticide-treated bed nets and simple point-of-use water filters can delay HIV-1 disease progression.

**Design:** A prospective cohort study.

**Setting:** Two HIV care sites in Kenya.

**Participants:** HIV-1-infected adults not yet meeting criteria for antiretroviral therapy.

**Interventions:** One group received the standard of care, whereas the other received long-lasting insecticide-treated bed nets and water filters. Individuals were followed for up to 24 months.

**Main outcome measures:** The primary outcome measures were time to CD4 cell count less than 350 cells/μl and a composite endpoint of time to CD4 cell count less than 350 cells/μl and nontraumatic death. Time to disease progression was compared using Cox proportional hazards regression.

**Results:** Of 589 individuals included, 361 received the intervention and 228 served as controls. Median baseline CD4 cell counts were similar ($P = 0.36$). After controlling for baseline CD4 cell count, individuals receiving the intervention were 27% less likely to reach the endpoint of a CD4 cell count less than 350 cells/μl (hazard ratio 0.73; 95% confidence interval 0.57–0.95). CD4 cell count decline was also significantly less in the intervention group (−54 vs. −70 cells/μl per year, $P = 0.03$). In addition, the incidence of malaria and diarrhoea were significantly lower in the intervention group.

**Conclusion:** Provision of a long-lasting insecticide-treated bed net and water filter was associated with a delay in CD4 cell count decline and may be a simple, practical and cost-effective strategy to delay HIV-1 progression in many resource-limited settings.



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## Introduction

Less than half of all individuals in low and middle-income countries who need antiretroviral therapy (ART) are currently receiving it [1]. In addition, the majority of HIV-1-infected individuals in sub-Saharan Africa (SSA) are not aware of their HIV status, representing a huge population of individuals at risk of HIV-related complications and death [2].

In parts of SSA, HIV-1, malaria and diarrhoeal illnesses are prevalent. Several studies [3–9] have shown that HIV-1-infected individuals have an increased susceptibility to malaria and diarrhoeal diseases. Coinfection with HIV-1 and other endemic diseases is associated with increased HIV-1 viral load and may impact HIV disease progression [10–16]. Bed nets and water filtration devices can prevent malaria and waterborne diseases. In addition to reducing these diseases among HIV-1-infected individuals, they may also delay HIV-1 disease progression.

Using a prospective observational study design, we evaluated whether the provision of a long-lasting insecticide-treated bed net (LLIN) and a point-of-care water filtration device to HIV-1-infected ART-naive adults in Kenya delays HIV-1 disease progression, as measured by time to CD4 cell count less than 350 cells/μl and/or death.

## Materials and methods

### Ethics statement

The study was approved by both the University of Washington Human Subjects Review Committee and the Kenya Medical Research Institute Ethical Review Committee. The trial was registered with ClinicalTrials.gov identifier NCT00914225.

### Setting and participants

ART-naive HIV-1-infected adults were enrolled from HIV care and treatment clinics at two sites in Western Kenya (Kisii Provincial and Kisumu District Hospitals) with differing malaria endemicities (Entomological inoculation rate - # of infectious bites/person per year is 0.4 in Kisii and 31.1 in Kisumu) [17].

The study arms consisted of cohorts from two studies conducted at the same care and treatment clinics utilizing identical eligibility criteria and enrolment and follow-up procedures (Fig. 1). Eligible individuals were 18 years of age or older, seropositive for HIV-1, ART naive, had a screening CD4 cell count of more than 350 cells/μl within the previous 3 months, and were WHO clinical stage I or II. Both studies also excluded individuals if they were pregnant at enrolment (by urine human chorionic gonadotropin testing), or reported taking ART previously.

Information about the study was provided to individuals attending voluntary counselling and testing facilities in Nyanza province and to community members through existing groups of people living with HIV/AIDS (PLWHA). In addition, in September 2009, a large public health campaign was held in six communities surrounding the care and treatment sites of Kisii and Kisumu. The 10 000 individuals participating in the campaign were provided with an LLIN (Permanet) and a point-of-care water filtration device (LifeStraw) as an incentive for receiving information about voluntary counselling and testing for HIV. The LifeStraw family device used in this study exceeds WHO criteria for 'High Protective' microbial water purifiers [18,19]. Individuals found to be HIV-positive were offered point-of-care CD4 cell count testing and those meeting inclusion criteria for the study were referred to the study clinics for screening.

Participants in the control cohort did not receive an LLIN or a water filter and consisted of the standard-of-care arm from a concurrent trial described elsewhere [20]. These individuals were enrolled between February 2008 and June 2010, whereas individuals in the intervention cohort were enrolled and randomized between September 2009 and July 2010 (9 months of overlapping enrolment into

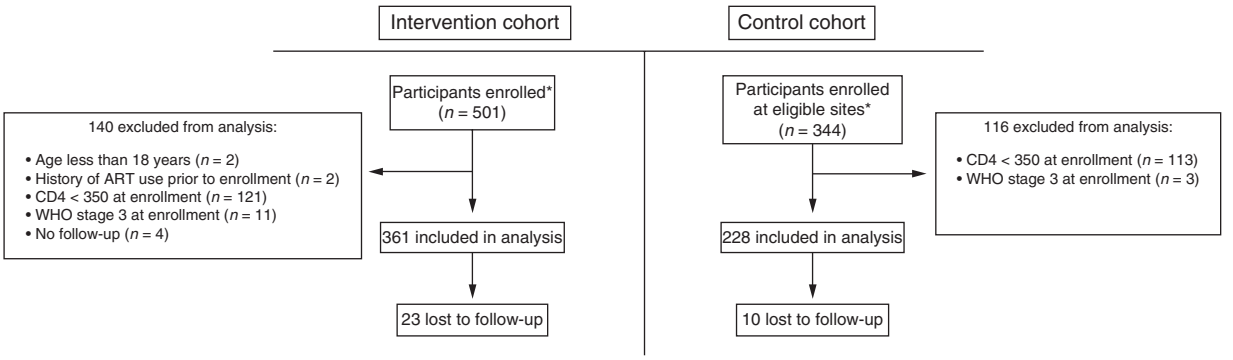


**Fig. 1. Flowchart of study enrolment.**

the cohorts). Individuals who had participated in the public health campaign were enrolled into the intervention cohort, whereas individuals who did not participate were enrolled into the control cohort, until June 2010 (after which time all participants were enrolled in the intervention cohort). The intervention cohort received an LLIN and a point-of-use water filtration device if they did not previously receive one during the public health campaign upon enrolment.

## Procedures

Study procedures were the same in both cohorts. At the screening visit, each participant was provided information regarding the aims and procedures of the study and assessed for eligibility. Interested individuals were consented for possible enrolment in the language of their choice (Kiswahili, Kisii, Luo, Giriama or English). Individuals provided written consent unless illiterate, in which case oral consent was documented in the presence of a witness and confirmed by thumbprint. Participants were only eligible to be enrolled into one study. Baseline demographic and medical history was obtained from participants following consent. As per the eligibility criteria, all participants had a screening CD4 cell count of at least 350 cells/μl within the previous 3 months. Upon enrolment, a baseline clinical examination was performed and blood was collected for repeat HIV-1 serologic testing, complete blood count and measurement of CD4 lymphocyte count.

Participants were followed every 3 months for up to 24 months after enrolment. All participants received cotrimoxazole during the study. At each follow-up visit, study staff assessed changes in health, ART initiation and WHO stage. Complete blood counts and CD4 cell counts were measured every 6 months. Participants meeting criteria for ART (as determined by Kenyan National Guidelines) were referred to the local care and treatment clinic. Participants who missed scheduled visits were called or visited and encouraged to reschedule. Cause of death was determined by interviewing family members (verbal autopsy) or by evaluating available medical records. All individuals were followed until completion of the study including those who had a baseline CD4 cell count less than 350 cells/μl or initiated ART.

## Laboratory analysis

All randomized participants underwent repeat HIV-1 serologic testing using Determine rapid test qualitative immunoassay (Abbot, Japan). The CD4 lymphocyte counts were determined using Multiset software on a FACSCalibur machine (Becton Dickinson, Franklin Lakes, New Jersey, USA) at the University of Washington/Kenya Medical Research Institute laboratory. External quality assurance and quality control was conducted in accordance with the NHLS Proficiency Testing Programme, South Africa. All patients presenting to any study visit (scheduled or unscheduled) with fever (>38°C) had blood tested for malaria using rapid diagnostic tests and/or malaria thin and thick smear.

## Study endpoints

The primary study endpoints were time to CD4 cell count less than 350 cells/μl and a composite endpoint of time to CD4 cell count less than 350 cells/μl and nontraumatic death, controlling for baseline CD4 cell count. Similar composite measures have been used as outcomes among studies assessing HIV disease progression [21–23]. Secondary study endpoints included incidence of self-reported diarrhoea (three or more episodes of watery stools in a day), self-reported malaria and whether malaria was confirmed by laboratory testing.

## Statistical analysis

Participants who started ART were censored from the risk set at the time of ART initiation. Initiation of ART was not included as a study endpoint due to differences in the timing of ART initiation between the cohorts. Kenya National ART Guidelines changed in July 2008, increasing the criteria for ART initiation from 200 to 350 cells/μl. As a result, in both cohorts, only individuals who had a baseline CD4 cell count of at least 350 cells/μl at enrolment were included in the final analyses.

Baseline characteristics were compared using chi-square tests for categorical data and Wilcoxon rank-sum tests or *t*-tests for continuous data. To identify covariates associated with both the exposure of interest and the outcome, we also evaluated the unadjusted associations between baseline characteristics and the primary study endpoints using Cox proportional hazards regression.

Time to disease progression was compared using Cox proportional hazards regression. Treatment hazard ratios and 95% confidence intervals (CIs) were estimated unadjusted, adjusted for enrolment CD4 cell count and adjusted for enrolment CD4 cell count as well as potential confounders.

Primary analyses used continuous time survival methods, as the exact timing of CD4 cell count measurements was variable. Discrete time survival models were used to assess the sensitivity of the results to choice of continuous vs. discrete time methods. The proportional hazards assumption was assessed in the fully adjusted continuous time models with plots and tests of Schoenfeld residuals vs. log time. Missing CD4 cell count measurements were handled by assuming that no failure had occurred at the time of missingness.

The survival function within each treatment arm was estimated using the Kaplan–Meier method. Linear mixed effects models, with a time–treatment arm interaction, were used to compare the yearly rate of decline in mean CD4 cell count between the two cohorts, adjusting for

enrolment CD4 cell count and censoring participant's follow-up at the time of ART initiation. Relative risk (RR) regression models were used to assess differences in usage of water filters, bed nets and cotrimoxazole, and also to assess differences in the incidence of self-reported malaria and diarrhoea between groups. These were Poisson models with log link and robust variance estimate, using generalized estimating equations with working independence correlation structure to handle correlation among repeated measurements on patients.

All tests were two-sided, with a significance level of 0.05. All statistical analyses were performed using Stata v12 (Stata Corp, College Station, Texas, USA).

## Results

Between October 2009 and January 2012, 501 HIV-1-infected, ART-naive adults with a screening CD4 cell count of more than 350 cells/μl in the previous 3 months were enrolled into the intervention cohort and provided with an LLIN and water filter. Of these, 361 (72.0%) had an enrolment CD4 cell count of more than 350 cells/μl and were included in the analyses. Participants in the control cohort were enrolled and followed as previously described. Among 979 individuals screened, 948 were enrolled and randomized. Among those studied at eligible sites (Kisumu and Kisii), 344 were allocated to the standard of care arm. Of these, 228 (47.6%) individuals had an enrolment CD4 cell coutn of more than 350 cells/μl and were included in the analyses (Fig. 1).

Baseline demographic data are presented in Table 1. Most participants were female (80.6%) and married (62.3%). The majority of participants had completed primary school (70.6%), came from households with incomes less than US$2 per day (77.4%) and used either pit latrines or no latrine (94.4%). A higher proportion of those in the intervention group were married, and individuals in the intervention cohort were more likely to live in households with less infrastructure (Table 1).

Health status at baseline was similar between the groups (Table 1). Fewer individuals in the intervention cohort reported taking cotrimoxazole at enrolment. However, all participants were provided cotrimoxazole, and following enrolment, there was no difference in the use of cotrimoxazole between the cohorts (intervention cohort: 99.7%, control cohort: 99.8%; $P = 0.8$).

Use of water purification methods and bed nets varied between the groups when ascertained at 12 months of follow-up (Table 2). In the intervention cohort, 99.5% of participants reported using some form of water purification during follow-up compared with 76.0% in the control cohort ($P < 0.001$). Individuals in the intervention

**Table 1. Characteristics of the study participants at baseline.**

| Variable | Intervention cohort ($N = 361$) *N* (%) | Control cohort ($N = 228$) *N* (%) | *P* |
|---|---|---|---|
| Female sex | 294 (81.4) | 181 (79.4) | 0.54 |
| Median age (IQR) | 31 (25–39) | 32 (26–38) | 0.59 |
| Clinic location | | | |
| Kisii | 168 (46.5) | 108 (47.4) | 0.84 |
| Kisumu | 193 (53.5) | 120 (52.6) | 0.84 |
| Marital status | | | |
| Married | 236 (65.4) | 131 (57.5) | 0.02 |
| Divorced/separated/widowed | 96 (26.6) | 62 (27.2) | 0.02 |
| Single | 29 (8.0) | 35 (15.4) | 0.02 |
| Education (highest completed) | | | |
| Less than primary | 108 (29.9) | 65 (28.5) | 0.72 |
| Primary or greater | 253 (70.1) | 163 (71.5) | 0.72 |
| Estimated monthly income (Kenyan shillings) | | | |
| <5000 (US$2/day) | 285 (79.8) | 171 (76.0) | 0.27 |
| ≥5000 (US$2/day) | 72 (20.2) | 54 (24.0) | 0.27 |
| Number of residents per room in household; mean (SD) | 2.2 (1.3) | 2.1 (1.3) | 0.22 |
| Water source | | | |
| Piped or well water | 275 (76.4) | 197 (86.4) | <0.01 |
| Environmental water source | 85 (23.6) | 31 (13.6) | <0.01 |
| Toilet type | | | |
| Flush toilet | 10 (2.8) | 23 (10.1) | <0.01 |
| Pit latrine or bush | 351 (97.2) | 205 (89.9) | <0.01 |
| Drug use at enrolment | | | |
| Cotrimoxazole | 262 (72.8) | 218 (97.3) | <0.01 |
| Multivitamins supplement | 260 (72.2) | 219 (97.8) | <0.01 |
| Clinical measurements | | | |
| CD4 cell count at enrolment; median (IQR) | 531 (446–666) | 552 (441–690) | 0.36 |
| Haemoglobin (g/dl); mean (SD) | 12.9 (3.0) | 12.8 (2.1) | 0.60 |
| Weight (kg); mean (SD) | 62.1 (12.0) | 63.1 (13.7) | 0.40 |
| BMI (kg/m$^2$); mean (SD) | 22.9 (4.2) | 22.8 (4.2) | 0.63 |

**Table 2. Water purification methods and use of bed nets during study follow-up between cohorts.**

| | Intervention ($N=361$) Est. %[a] | Control ($N=127$[c]) Est. %[a] | $P$[a] |
|---|---|---|---|
| Water purification methods | | | |
| % who drink purified water | 99.5 | 76.0 | <0.001 |
| Purification system[b] | | | |
| % who boil | 9.0 | 29.9 | <0.001 |
| % who use chlorine | 5.7 | 45.4 | <0.001 |
| % who use filter | 93.0 | 0.4 | <0.001 |
| Use of bed nets | | | |
| % who have a net | 97.7 | 83.1 | <0.001 |
| % who both have a net and sleep under it | 97.3 | 82.4 | <0.001 |

[a]Estimates and $P$ values are from GEE relative risk regression models (Poisson family, log link, working independence correlation structure, robust variance estimate) from follow-up visits at months 3, 6, 9, 12, 15, 18, 21 and 24.
[b]Percentage add up to more than total percentage of who drink purified water, as some participants used more than one system to purify water.
[c]A subset of individuals in the control cohort had data related to water purification and bed net use ($n=127/228$).

cohort were more likely to report using a water filter (93.0%), compared with those in the control cohort (0.4%) ($P<0.001$). Use of bed nets during the follow-up period was also more common in the intervention cohort compared with the control cohort (97.3 vs. 82.4%, respectively) ($P<0.001$).

Mean follow-up time was 1.85 years in the control cohort and 1.67 years in the intervention cohort. In the control cohort, 107 of 228 (46.9%) of participants reached a CD4 cell count of 350 cells/μl or less, compared with 135 of 361 (37.4%) in the intervention cohort. When controlling for baseline CD4 cell count between the cohorts, there was a significant difference in time to CD4 cell count of less than 350 cells/μl (hazard ratio 0.73; 95% CI 0.57–0.95) (Table 3; Fig. 2a), with individuals in the intervention cohort at a lower risk of reaching a CD4 cell count of 350 cells/μl or less compared with participants in the control cohort. This difference remained significant after adjusting for either toilet type or water source in a stratified Cox model (hazard ratio 0.75; 95% CI 0.58–0.97). There was a significant difference in time to the composite endpoint of disease progression (reaching a CD4 cell count of 350 cells/μl or death) between the two cohorts when controlling for baseline CD4 cell count (hazard ratio 0.74; 95% CI 0.58–0.95) (Table 3; Fig. 2b). This difference remained significant after stratifying by toilet type (hazard ratio 0.75; 95% CI 0.59–0.97) or water source. The treatment effect did not differ significantly between study sites for either of the primary endpoints.

In tests based on Schoenfeld residuals, the hypothesis of nonproportional hazards for the treatment effect was not rejected. Discrete time survival models for both endpoints yielded results very similar to the continuous time models (results not shown) with regard to both estimates and statistical significance. The proportion of missing CD4 cell count measurements was low (0.6%), with only nine of 1541 expected CD4 cell count measurements missing in nine participants. Of these nine participants, seven had not reached the study endpoint at their last follow-up time.

Differences were also observed in the mean annual change in CD4 cell count after controlling for baseline CD4, with individuals in the intervention cohort experiencing a smaller decrease in CD4 cell count, (−53.7 cells/μl per year; 95% CI −63.8 to −43.7) compared with individuals in the control cohort (−70.4 cells/μl per year; 95% CI −81.5 to −59.4; $P=0.03$).

Secondary analyses suggested that participants in the intervention cohort were less likely to self-report a history

**Table 3. Time to primary endpoint, censoring at antiretroviral therapy initiation.**

| | Time to CD4 cell count <350 cells/μl | | Time to CD4 cell count <350 cells/μl or death | |
|---|---|---|---|---|
| Variable | Intervention | Control | Intervention | Control |
| Number included in analysis | 361 | 228 | 361 | 228 |
| Number of events | 135 | 107 | 140 | 110 |
| Incidence per 100 person-years | 27.8 | 34.7 | 28.8 | 35.7 |
| HR (95% CI); $P$ | 0.79 (0.61–1.02); $P=0.08$ | | 0.80 (0.62–1.03); $P=0.08$ | |
| aHR[a] (95% CI); $P$ | 0.73 (0.57–0.95); $P=0.02$ | | 0.74 (0.58–0.95); $P=0.02$ | |
| aHR[b] (95% CI); $P$ | 0.75 (0.58–0.97); $P=0.03$ | | 0.75 (0.59–0.97); $P=0.03$ | |

CI, confidence interval; HR, hazard ratio.
[a]Adjusted for enrolment CD4.
[b]Adjusted for enrolment CD4 and toilet type.

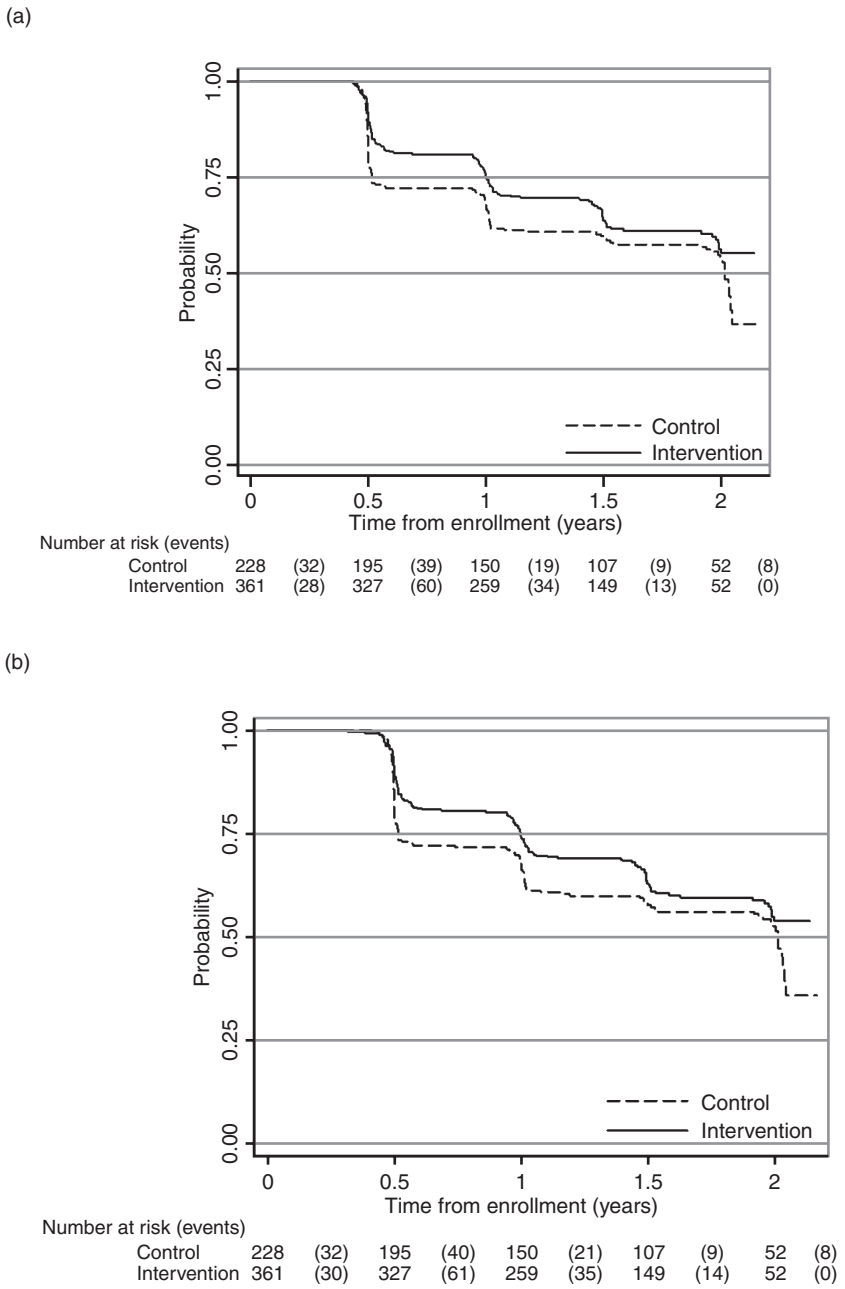


**Fig. 2. Kaplan–Meier plot of time to disease progression by cohort.** (a) Time to CD4 cell count <350 cells/μl; (b) time to CD4 cell count <350 cells/μl or death.

of diarrhoea within the previous 3 months compared with individuals in the control cohort (RR 0.65; 95% CI 0.45–0.93) and less likely to self-report malaria (RR 0.75; 95% CI 0.60–0.93). Self-reported diarrhoea among household members within the prior 3 months did not differ between the cohorts (RR 0.91; 95% CI 0.61–1.36). The incidence of clinically diagnosed malaria within the previous 3 months was also significantly lower in the intervention group than in the control group (RR 0.66; 95% CI 0.49–0.88). There were no significant differences in these secondary outcomes between the study sites.

During the 24-month follow-up period, 58 individuals initiated ART (44 individuals in the intervention arm and 14 in the control arm) and 15 individuals died (nine in the intervention cohort and six in the control cohort). Thirteen deaths occurred prior to initiation of ART. There was no difference in the incidence of death

between the cohorts (intervention cohort: 1.5 per 100 person-years, control cohort: 1.4 per 100 person-years).

## Discussion

The results of this large prospective observational study suggest that the addition of an LLIN and a point-of-use water filtration device to the existing package of care provided to ART-naive HIV-1-infected adults in Africa delays HIV-1 disease progression. The combined intervention resulted in a 27% risk reduction in HIV disease progression and a 24% decrease in CD4 cell count decline among HIV-1-infected adults already receiving cotrimoxazole and multivitamins (MVI).

In many areas of SSA, HIV-1-infected individuals are at an increased risk of malaria and diarrhoeal disease compared with HIV-uninfected individuals [3–9]. The use of insecticide-treated bed nets in HIV-1-infected adults and children significantly reduces malaria incidence above the benefit observed with the use of cotrimoxazole alone, and the use of point-of-use water treatments significantly reduces the risk of diarrhoeal illnesses in HIV-1-infected individuals [24–28]. In addition, malaria episodes are associated with transient increases in HIV-1 RNA and with CD4 cell count decline [13–16].

Although the two study sites included in this analysis differed in malaria endemicity, no significant differences were observed in the impact of the intervention between these sites. This may suggest that the benefit of the intervention is related to the use of a point-of-use water filtration device or may simply reflect limited power to detect potential differences when stratified by site.

Compared with other available interventions, the use of an LLIN and a water filter may be a more feasible and generalizable intervention to delay HIV-1 disease progression, as they can be delivered at one time with a fixed cost. In addition, these interventions confer additional benefit in reducing morbidity and mortality due to malaria and diarrhoeal disease and may provide multidimensional health benefit to pre-ART HIV-1-infected individuals and public health programmes. However, it is important to consider that deferral of ART initiation may place individuals at a risk of HIV transmission and the potential impact of such an intervention on HIV-1 transmission should be considered in light of this possibility.

Among the 22.5 million individuals living with HIV-1 in SSA, at least half do not yet meet criteria for ART, representing a large population engaged in care who are able to benefit from the intervention [1]. Deferral of ART has important individual implications, including delaying the time to ART-associated toxicity, pill burden and risk of drug resistance [29]. In addition, the programmatic benefits of such a delay may also be considerable. As global programmes aspire for wider and earlier ART provision, there continue to be HIV-1-infected individuals who do not yet qualify for ART, for whom other interventions may be useful. Of the 15 million individuals in low and middle-income countries who qualify for ART, only 36% have initiated treatment due to lack of infrastructure, human resources and drug supply [1]. In addition, less than half of the individuals living with HIV-1 in Africa are aware of their serostatus and this intervention could have a broader impact in areas of moderate to high HIV-1 prevalence [30].

Strengths of this study include prospective enrolment of individuals into both cohorts from identical care and treatment sites using similar inclusion criteria, the high retention observed in both cohorts, the use of objective measures of HIV disease progression and the inclusion of two study sites with differing malaria endemicity. However, the study also had potential limitations. The study was an industry-sponsored trial (Vestergaard-Frandsen manufactures both LLIN and the LifeStraw Family water filters). However, the funder did not play a role in the study design, implementation, analysis or interpretation of these data. The observational design may also have introduced bias during the allocation of cohorts. Although the cohorts were enrolled from the same sites and using identical inclusion criteria, there are several important factors that may have led to differences between the cohorts that should be mentioned. First, enrolment initially started with recruitment into the control arm in February 2008 and enrolment into the intervention arm did not begin until September 2009. As a result, many of the participants enrolled in the control arm were identified from existing patients at the care and treatment sites (already receiving care). Most of the patients enrolled in the intervention arm were new patients to the clinics. This explains the discrepancy in the use of cotrimoxazole and MVI at baseline, as participants recruited from ongoing care would have already been on cotrimoxazole and MVI, whereas new patients would not. However, it is important to note that all participants received cotrimoxazole and MVI at study entry and continued throughout the follow-up. We speculate that prior cotrimoxazole and MVI use in the control group, would, if anything, have decreased HIV-1 disease progression compared with the intervention group, which was opposite to our findings. In addition, as participants from the public health campaign were referred into the intervention cohort, there may have been some differences in the patient population recruited in this way. Although we attempted to control for confounding in the analysis, residual confounding may have remained. We did not routinely assess LLIN or water filter usage and therefore were unable to perform a sensitivity analysis to see whether the impact of the intervention was greater among the most adherent

participants. Secondary data analyses included self-reported malaria and diarrhoea; these data could have been influenced by reporting bias. In addition, a large proportion of individuals in the control cohort reported using bed nets and water purification methods, which may have resulted in a bias towards the null. Lastly, due to the nature of providing a combined intervention, we were unable to differentiate the relative impact of LLINs as compared with water filtration on markers of HIV-1 disease progression.

HIV-1-infected individuals in many parts of the world are at a risk of infection with multiple endemic pathogens. The provision of an LLIN and a simple point-of-use water filtration device was associated with a delay in HIV-1 disease progression, as measured by CD4 cell count. This combined intervention has the potential to impact the lives of millions of individuals living with HIV-1, particularly in resource-limited settings where malaria and diarrhoeal disease are prevalent.

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J.W. was principal investigator and was primarily responsible for designing, coordinating and analysing the study. L.S. helped develop the statistical plan, manage data and performed the statistical analysis. B.S. assisted in the design and implementation of the study and was involved in the analysis. J.N. coordinated field study activities. B.P. was responsible for supervising field activities. K.Y. was responsible for data management and statistical analysis. F.O. assisted with data collection, cleaning and analysis. P.O. contributed to the design of the study and provided assistance with study supervision. J.M. contributed to the design of the study. C.Z. contributed to the design of the study and the laboratory analysis. B.R. conducted statistical analysis. G.J.S. contributed to the design of the study and assisted with the data analysis. J.W. and L.S. were responsible for manuscript preparation. All authors saw and approved the final draft. All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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### Conflicts of interest

There are no conflicts of interest.

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