Multimonth dispensing of up to 6 months of antiretroviral therapy in Malawi and Zambia (INTERVAL): a cluster-randomised, non-blinded, non-inferiority trial

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Summary

Background Facility-based, multimonth dispensing of antiretroviral therapy (ART) for HIV could reduce burdens on patients and providers and improve retention in care. We assessed whether 6-monthly ART dispensing was non-inferior to standard of care and 3-monthly ART dispensing.

Methods We did a pragmatic, cluster-randomised, unblinded, non-inferiority trial (INTERVAL) at 30 health facilities in Malawi and Zambia. Eligible participants were aged 18 years or older, HIV-positive, and were clinically stable on ART. Before randomisation, health facilities (clusters) were matched on the basis of country, ART cohort size, facility type (ie, hospital *vs* health centre), and region or province. Matched clusters were randomly allocated (1:1:1) to standard of care, 3-monthly ART dispensing, or 6-monthly ART dispensing using a simple random allocation sequence. The primary outcome was retention in care at 12 months, defined as the proportion of patients with less than 60 consecutive days without ART during study follow-up, analysed by intention to treat. A 2·5% margin was used to assess non-inferiority. This study is registered with ClinicalTrials.gov, NCT03101592.

Findings Between May 15, 2017, and April 30, 2018, 9118 participants were randomly assigned, of whom 8719 participants (n=3012, standard of care group; n=2726, 3-monthly ART dispensing group; n=2981, 6-monthly ART dispensing group) had primary outcome data available at 12 months and were included in the primary analysis. The median age of participants was 42·7 years (IQR 36·1–49·9) and 5774 (66·2%) of 8719 were women. The primary outcome was met by 2478 (82·3%) of 3012 participants in the standard of care group, 2356 (86·4%) of 2726 participants in the 3-monthly ART dispensing group, and 2729 (91·5%) of 2981 participants in the 6-monthly ART dispensing group. After adjusting for clustering, for retention in care at 12 months, the 6-monthly ART dispensing group was non-inferior to the standard of care group (percentage-point increase 9·1 [95% CI 0·9–17·2]) and to the 3-monthly ART dispensing group (5·0% [1·0–9·1]).

Interpretation Clinical visits with ART dispensing every 6 months was non-inferior to standard of care and 3-monthly ART dispensing. 6-monthly ART dispensing is a promising strategy for the expansion of ART provision and achievement of HIV treatment targets in resource-constrained settings.

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Introduction

Long-term adherence to antiretroviral therapy (ART) for HIV can result in near-normal life expectancy for individuals who are able to remain on treatment and achieve viral suppression.[1] However, in settings where there is a high prevalence of HIV, such as sub-Saharan Africa, there are major barriers to achieving optimal ART retention and viral suppression at the patient level and health system level. Common barriers for patients include the need for frequent clinic visits for clinical evaluations and medication refills, long wait times in ART clinics, long travel times to and from ART clinics, high costs for travel to clinics, and missed wages as a result of time away from work.[2–4] Frequent clinical visits might not be beneficial for patients who are clinically stable and impose strain and unnecessary costs on busy providers and ART clinics with high patient numbers.

Multimonth dispensing of ART is one strategy to reduce the frequency of medication refill visits, which can reduce barriers to care at both the patient level and health-system level. 3-monthly dispensing has become common for patients who are clinically stable in many settings.[5] There is now increasing interest in extending dispensing intervals to up to 6 months, driven by the US President's Emergency Plan for AIDS Relief (PEPFAR) to have fully implemented 6-monthly ART dispensing by the end of the fiscal year 2020 in all supported countries.[6] In three cluster-randomised studies from Africa, retention in care

Research in context

Evidence before this study

Previous randomised studies from Africa found retention with 6-monthly dispensing to be non-inferior to 3-monthly dispensing when delivered as part of differentiated models of care, including community antiretroviral therapy (ART) refill groups, adherence clubs, and community-based drop-off points. These studies did not evaluate 6-monthly facility-based dispensing and did not report on the cost of 6-monthly dispensing relative to standard of care. We searched PubMed for studies up to June 30, 2020, using the search terms "HIV" and "antiretroviral therapy" and "multi-month dispensing" or "six-month dispensing" and "differentiated models of care" or "health facility", with no language or date restrictions. This search did not identify any randomised trials of facility-based 6-monthly dispensing.

Added value of this study

6-monthly ART dispensing in Malawi and Zambia was associated with a 9·1 (95% CI 0·9–17·2) percentage-point increase in retention at 1 year compared with standard of care, and a 5·0 (1·0–9·1) percentage-point increase in retention compared with 3-monthly dispensing. 6-monthly dispensing was non-inferior to both standard of care and 3-monthly dispensing. Compared with standard of care, 6-monthly dispensing was modestly cost saving for providers as well as for patients through less time spent accessing care and lost potential income. Our study adds to the literature on 6-monthly ART dispensing and is the first randomised trial to evaluate facility-based 6-monthly dispensing and the cost of different dispensing intervals in resource-limited settings.

Implications of all the available evidence

6-monthly dispensing of ART for patients who are clinically stable could provide benefits for retention in care and cost at both the provider and patient levels. Further study is needed to confirm the benefits of 6-monthly dispensing beyond 1 year and evaluate viral suppression rates and the role of multimonth dispensing in different populations, including among participants who do not meet commonly used definitions of clinical stability in sub-Saharan Africa.

among patients enrolled in the 6-monthly dispensing group was non-inferior to 3-monthly dispensing when delivered as part of out-of-facility models of care, including community ART refill groups in Zimbabwe,[7] adherence clubs in South Africa,[8] and community pick-up points in Lesotho.[9] However, these studies did not evaluate 6-monthly facility-based dispensing, nor did they report on the costs of 6-monthly dispensing for either patients or providers.

We did the Varying Intervals of Antiretroviral Medication Dispensing to Improve Outcomes for HIV (INTERVAL) study to assess whether 6-monthly ART dispensing was non-inferior to standard of care and 3-monthly ART dispensing. In this paper, we aimed to report on the effects of varying dispensing interval on retention in care and on cost.

Methods

Study design and participants

We did a pragmatic, cluster-randomised, non-blinded, non-inferiority trial at 30 health facilities in Malawi and Zambia. At the time of study implementation, ART guidelines in Malawi and Zambia recommended 3-monthly dispensing for patients who were clinically stable, but adherence to guidelines was variable, with most patients receiving between 1 and 3 months' supply of antiretrovirals per refill. Study sites in Malawi were located in the central and southern regions and study sites in Zambia were in the central and Copperbelt provinces (appendix 1 p 2).

Eligible individuals were aged 18 years or older, HIV-positive, and were considered clinically stable on ART (ie, on ART for at least 6 months). Full inclusion criteria are summarised in appendix 2 (p 1). These inclusion criteria were developed using the Malawi Clinical Management of HIV guidelines,[10] Zambia Consolidated Guidelines for Treatment and Prevention of HIV infection,[11] and WHO guidelines,[12] with additional input from HIV clinicians in Malawi, Zambia, and the USA. Exclusion criteria included patients who were clinically unstable, women who were pregnant or breastfeeding, patients with non-communicable diseases, patients on an ART regimen other than first-line ART, and having an increased viral load within 6 months of screening. The study protocol was approved by the institutional review board of the University of California, Los Angeles, the National Health Sciences Research Committee in Malawi, the Zambia Excellence in Research Ethics and Science Converge, Zambia National Health Research Ethics Board, and Zambia Medicines Regulatory Authority. The study was approved for use of anonymised data analysis by the institutional review board of Boston University. All participants provided written informed consent. The study protocol has been published elsewhere.[13]

Randomisation and masking

A cluster was defined as a health facility providing outpatient ART care. 15 clusters per country were selected on the basis of ART cohort size, completeness of medical records, and willingness to participate in the study. Before randomisation, clusters were matched on the basis of known characteristics that might be associated with our outcomes of interest, including country, ART cohort size, facility type (ie, hospital *vs* health centre), and region or province. Matched clusters were randomly assigned (1:1:1) to receive standard of care ART dispensing (ART typically

See Online for appendix 2

See Online for appendix 1

given every 1–3 months, depending on provider judgment), 3-monthly (ie, 90-day) ART dispensing, or 6-monthly (ie, 180-day) ART dispensing. For all groups, clinical service delivery occurred simultaneously with the dispensing visits. Thus, the only differences between the study groups were the frequency of clinical consultations and the amount of ART given at these visits. Randomisation was done by the study coordinator (AB) using a simple random allocation sequence generated by the study epidemiologist (MPF). Masking of the participants and investigators was not possible because allocated groups were obvious due to the amount of medication dispensed and the timing between appointments.

Procedures

Patients were offered general information about the study in ART clinic waiting areas and those who were interested in participation were taken to a private space for written informed consent. Patients who consented were administered a questionnaire by study staff and returned to the clinic queue to complete a routine clinical consultation with a site provider and received ART, to be administered orally, dispensed as per the facility's intervention allocation. Provision of oxazole preventive therapy and isoniazid preventive therapy followed country-specific guidelines for the use of these therapies as part of routine HIV care, and was provided in the same amount as ART, unless there were concerns about toxicity. Participants in the 6-monthly dispensing group were offered opaque plastic bags to assist with carrying and concealing the large supply of medications.

After the enrolment visit, the study staff had no further interaction with participants until the completion of study follow-up. There were no financial incentives to participate in the study. Ongoing support was provided to facility staff to promote consistent compliance with multimonth dispensing. Study participants who missed scheduled refill visits or were lost from care were followed up by the clinics using routine tracing procedures, not by the study staff. All other aspects of care (including adherence counselling and adherence interventions) were done according to the standard of care at the facility.

Participants' medical records were reviewed to collect clinical information, including date of ART initiation, history of ART clinic visits, and ART dispensing intervals in the previous year. Study staff members also administered a brief questionnaire to obtain sociodemographic information, and travel and opportunity costs associated with the participant's ART clinic visits.

Participants were followed up for 14 months to enable assessment of retention at 1 year. At 14 months after study entry (12 months plus 60 days to allow for the 12-month retention endpoint to be reached), study staff abstracted data from participants' medical records, including dates of ART refill visits over the year, number of pills dispensed per visit, and reason for loss from care, if relevant.

Site-level cost data were abstracted from a representative subsample of sites' performance reports (eg, for number of patients served) and finance and procurement records (for unit costs). Cost data for items and services procured above the level of the facility were obtained from national sources (eg, Ministry of Health salary scales) and commercial price lists in Malawi and Zambia (eg, cost of antiretroviral medications).

If patients frequently visit health-care facilities for reasons other than ART dispensing, the benefits to the patient of multimonth dispensing might be diminished. To assess the effect of additional visits, medical records of each participant in Zambia were reviewed to determine the number of non-ART dispensing visits during the 12-month follow-up period. In Malawi, additional health visits that were not associated with ART dispensing were only recorded in the patient's health passport (a small book carried by the patient). Study staff scanned the health passports for a random subset of participants from each group to estimate the number and types of non-ART additional visits.

Outcomes

The primary outcome was retention in care at 12 months, defined as the proportion of patients with less than 60 consecutive days without ART at any point during follow-up. Primary outcome data were centrally assessed. Secondary outcomes were viral suppression (defined as <1000 copies per mL in Malawi and <20 copies per mL in Zambia), feasibility and acceptability of dispensing intervals to participants and providers, and cost (per patient achieving the primary outcome in each group). Data were not available to assess the virological suppression outcome due to delays in viral load scale-up in both Malawi and Zambia. Feasibility and acceptability outcomes have been reported elsewhere, including qualitative interviews with a subset of study providers in Zambia[14] and a subset of providers and patients in Malawi.[15] We did several post-hoc analyses to further evaluate the primary outcome of retention, including a per-protocol analysis, and analyses by country, sex, urban versus rural facility, and duration on ART (6–12 months *vs* >12 months).

Cost analysis

Cost was assessed as the average cost per participant and the average cost per participant who met the primary outcome in each group. We excluded participants whose visit dates were unclear. Provider costs were estimated using widely published microcosting methods developed by the investigators.[16–18] Costs and resource utilisation are reported as means with 95% CIs and medians with IQRs. To calculate provider costs, we estimated ART dispensed, outpatient clinic visits attended, and the fixed costs of ART care, including study purchases to establish site capacity for multimonth dispensing. Outpatient clinic visit costs, which were allocated per visit made, included all ART clinical staff salaries and 50% of other HIV-related

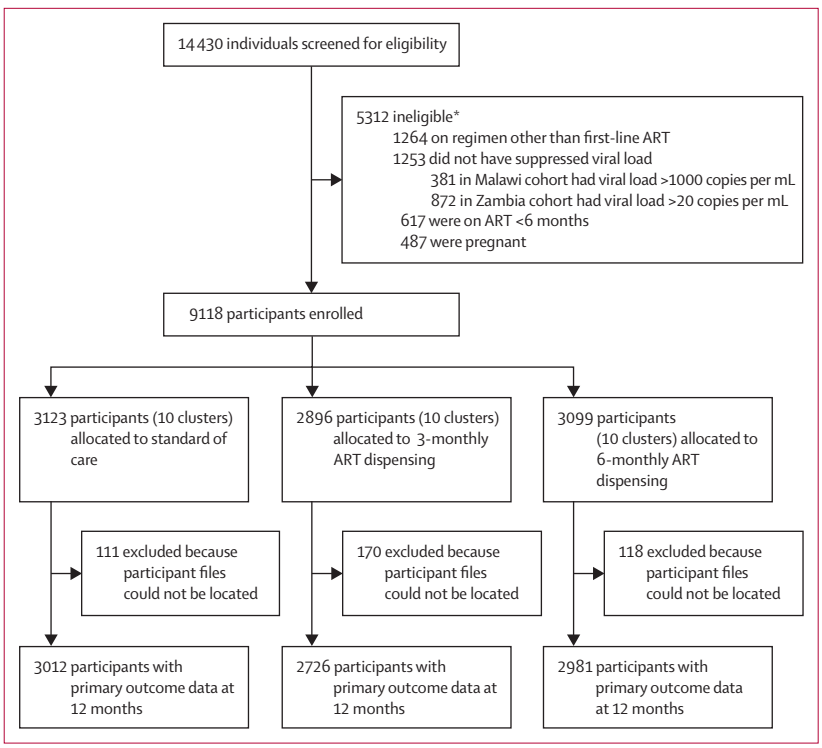

Figure: **Trial profile**
ART=antiretroviral therapy. *Full list of reasons for ineligibility in appendix 2 (p 3)

clinic costs, such as building space and equipment. The remaining 50% of these costs were defined as fixed costs and allocated per patient month in care. Because of the absence of data, we excluded the costs of all laboratory tests, clinic visits not associated with ART refills, and any other services provided to patients. We estimated the average cost per primary outcome achieved by group and the production cost per participant, for which we divided total costs for the study group by the number of participants who met the primary outcome, and thus provided a cost comparison between the groups. Full details of the cost analysis are provided in appendix 1 (pp 1–3).

To estimate the costs to participants of obtaining ART, we used baseline survey data to calculate an average cost per clinic visit, including time, transport, and lost wages. For each participant, the number of clinic visits made per year for any reason was multiplied by that participant's cost per visit. The value of lost wages was estimated by multiplying the published national mean minimum wage in each country,[19,20] in 4 h increments, by the approximate number of 4 h periods spent seeking care per participant per year based on total time spent on clinic visits during the year.

Statistical analysis

Our sample size was estimated for a cluster-randomised non-inferiority trial. We had 30 clusters available for random assignment and assumed a fixed number of clusters (k), an equal number of clusters per group, and an equal number of participants per cluster. Assuming approximately 5% of participants would not be retained in care in the standard of care group, and a retention rate of less than 7·5% to be non-inferior in the 3-monthly or 6-monthly dispensing groups, we estimated that a sample size of 271 participants per cluster (2710 participants per group; 8130 participants overall) would have 90% power, with a one-sided α of 5%, and an intracluster correlation coefficient of 0·004,[21] with non-inferiority defined as a difference of 2·5%.

The primary outcome was analysed by intention to treat. We used generalised estimating equations to estimate risk differences and their associated 95% CIs for the effect of 6-monthly ART dispensing and 3-monthly ART dispensing compared with standard of care and the effect of 6-monthly ART dispensing versus 3-monthly ART dispensing on retention in care. We specified facility-level clustering using generalised estimating equations to account for the study design and estimated robust standard errors.

To determine fidelity to the randomised dispensing interval during the follow-up period, we calculated the percentage of person-months covered by each of six possible dispensing intervals (ranging from once-monthly to 6-monthly). Considering that not all individuals remained on their assigned dispensing interval, we did a post-hoc per-protocol analysis including only participants who received the intended interval up until the point they reached an outcome or reached 1 year of follow-up. A 2·5% margin was used to assess non-inferiority. Additionally, we did several post-hoc analyses, including summarising uncovered ART days (as a proxy for ART adherence), and assessing modification of the effect of 6-monthly dispensing on retention by country, sex, urban versus rural facility, and duration on ART (6–12 months *vs* >12 months). We also did analyses adjusted for parameters that were not well balanced at baseline. For the uncovered days analysis, results were estimated on the basis of total days without ART during the study period for each participant and calculated as mean and SD with a 95% CI. This calculation assumed that participants had no remaining pills at the time of a scheduled ART refill. This trial is registered with ClinicalTrials.gov, NCT03101592.

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.

Results

Between May 15, 2017, and April 30, 2018, 14430 individuals were screened for eligibility, of whom, 5312 were ineligible for inclusion (figure). The most common reasons for exclusion were being on an ART regimen other than first-line ART (8·8%) and having an

increased viral load within 6 months of screening (8·7%). Low levels of viral suppression were more frequent in Zambia due to the national viral suppression threshold of less than 20 copies per mL compared with Malawi, where the threshold was defined as less than 1000 copies per mL during the period of the study. Other common reasons for ineligibility are described in appendix 2 (p 3).

9118 participants were randomly assigned to groups: 3123 participants (from ten clusters) to standard of care, 2896 participants (ten clusters) to 3-monthly ART dispensing, and 3099 participants (ten clusters) to 6-monthly ART dispensing. 8719 participants (n=3012, standard of care group; n=2726, 3-monthly ART dispensing group; n=2981, 6-monthly ART dispensing group) had primary outcome data available at 12 months and thus were included in the primary analysis (figure). No notable sociodemographic or clinical differences in characteristics were identified between participants with and without medical records available for review (appendix 2 p 4).

Baseline sociodemographic and clinical characteristics are summarised in table 1 and are stratified by country in appendix 2 (pp 5–6). Median age of participants was 42·7 years (IQR 36·1–49·9), 5774 (66·2%) of 8719 participants were women, and the median duration on ART at the time of enrolment was 5·0 years (2·7–8·2); these characteristics were similar by group. 5516 (63·3%) of 8719 participants were married, and of those with partners, self-reported disclosure was common (91·6%) and similar by group. In the year before enrolment, the median ART dispensing interval was 60 days (IQR 43·0–90·0) in the standard of care group, 80 days (60·0–90·0) in the 3-monthly ART dispensing group, and 78 days (60·0–90·0) in the 6-monthly ART dispensing group. Participants in Zambia had higher levels of educational attainment and higher mean monthly income compared with participants in Malawi (US$182 per month in Zambia *vs* $27 per month in Malawi). Significant differences were identified between countries in the number of participants receiving co-trimoxazole and isoniazid prophylaxis due to differences in country-specific guidelines.[10,11]

Of the participants who were randomly assigned to the two intervention groups, 1714 (62·9%) of 2726 in the 3-monthly ART dispensing group and 2535 (85·0%) of 2981 in the 6-monthly ART dispensing group received the intervention per protocol for the entire year of study follow-up. The most common dispensing interval in the standard of care group was 3 months (1777 participants; 59·0%), followed by 2 months (373 participants; 12·4%), and 6 months (331 participants; 11·0%). ART dispensing data by group during follow-up are summarised in appendix 2 (p 7). Participants in the 6-monthly ART dispensing group had the fewest mean days without ART (17·6 days [IQR 16·1–19·2]) compared with the 3-monthly ART dispensing group (30·6 days [28·5–32·7]) and standard of care group (36·1 days [33·8–38·4]), and findings were consistent for Malawi and Zambia (appendix 2 p 8).

	Standard of care (n=3012)	3-monthly dispensing (n=2726)	6-monthly dispensing (n=2981)
Age, years	42·9 (35·9–50·3)	42·7 (36·1–49·6)	42·6 (36·2–49·7)
Missing or not answered	47 (1·6%)	57 (2·1%)	25 (0·8%)
Sex			
Women	2020 (67·1%)	1841 (67·5%)	1913 (64·2%)
Men	991 (32·9%)	885 (32·5%)	1068 (35·8%)
Missing or not answered	1 (<0·1%)	0	0
Disclosure of HIV status to primary partner*			
Yes	2054/2218 (92·7%)	1819/2046 (88·9%)	2100/2267 (92·7%)
No	161/2218 (7·3%)	224/2046 (11·0%)	166/2267 (7·3%)
Missing or not answered	3/2218 (0·1%)	3/2046 (0·1%)	1/ 2267 (<0·1%)
Time receiving ART, years	4·9 (2·6–8·4)	5·4 (2·8–8·2)	4·9 (2·6–7·9)
Missing or not answered	982 (32·6%)	1060 (38·8)	1096 (36·8%)
Marital status			
Married or long-term partner	1889 (62·7%)	1650 (60·6%)	1977 (66·3%)
Single or no long-term partner	247 (8·2%)	248 (9·1%)	267 (9·0%)
Widowed, divorced, or separated	876 (29·1%)	827 (30·3%)	736 (24·7%)
Missing or not answered	0	1 (<0·1%)	1 (<0·1%)
Household size	4 (3–6)	5 (3–6)	5 (3–6)
Missing or not answered	0	0	0
Education (highest level completed)			
No education or less than primary school	574 (19·1%)	480 (17·6%)	347 (11·6%)
Primary school	1453 (48·2%)	1293 (47·4%)	1372 (46·0%)
Secondary school	841 (27·9%)	811 (29·8%)	978 (32·8%)
University graduate	137 (4·5%)	138 (5·1%)	267 (9·0%)
Missing or not answered	7 (0·2%)	4 (0·1%)	17 (0·6%)
Employment status			
Formal employment	450 (14·9%)	398 (14·6%)	629 (21·1%)
Informal employment	1435 (47·6%)	1027 (37·7%)	1545 (51·8%)
Not working	1121 (37·2%)	1297 (47·6%)	803 (26·9%)
Missing or not answered	6 (0·2%)	4 (0·1%)	4 (0·1%)
Missed work to attend current ART clinic visit	1490 (49·6%)	1101 (40·5%)	1600 (53·7%)
Missing or not answered	8 (0·3%)	6 (0·2%)	4 (0·1%)
Mean monthly earnings, US$†	48·02 (13·8–138·0)	66·24 (19·3–198·8)	72·45 (27·6–198·8)
Missing or not answered	24/3012 (0·8%)	7/2726 (0·3%)	16/2981 (0·5%)
Transport method to ART clinic			
Walk	1786 (59·3%)	1618 (59·4%)	1306 (43·8%)
Bicycle	339 (11·3%)	304 (11·2%)	385 (12·9%)
Bus or minibus	770 (25·6%)	634 (23·3%)	925 (31·0%)
Bicycle taxi	65 (2·2%)	96 (3·5%)	237 (8·0%)
Personal or friend's vehicle	42 (1·4%)	55 (2·0%)	119 (4·0%)
Other	10 (0·3%)	19 (0·7%)	9 (0·3%)
Missing or not answered	0	0	0
One-way travel time to ART clinic, min	40·2 (19·8–66·5)	45·0 (25·2–90·0)	40·2 (19·8–60·0)
Missing or not answered	0	0	0

(Table 1 continues on next page)

In Malawi, additional non-ART visit data were collected for 254 participants (64·6% women) from all 15 sites

	Standard of care (n=3012)	3-monthly dispensing (n=2726)	6-monthly dispensing (n=2981)
(Continued from previous page)			
Patients incurring transport costs to clinic	917 (30·4%)	812 (29·8%)	1265 (42·4%)
Missing or not answered	0	0	0
Cost of one way transport to ART clinic, US$‡	0·69 (0·30–1·0)	0·55 (0·40–0·97)	0·69 (0·41–1·38)
Missing or not answered	0	0	0
Time spent at ART clinic, min	120·0 (60·0–180·0)	180·0 (120·0–240·0)	180·0 (120·0–240·0)
Missing or not answered	0	0	0
ART dispensing interval in previous year, days	60·0 (43·0–90·0)	80·0 (60·0–90·0)	78·0 (60·0–90·0)
Missing or not answered	804 (26·7%)	642 (23·6%)	784 (26·3%)
Lost any ART bottles in past 12 months	19 (0·6%)	14 (0·5%)	13 (0·4%)
Missing or not answered	0	0	0
Any ART bottles stolen in past 12 months	16 (0·5%)	17 (0·6%)	19 (0·6%)
Missing or not answered	1 (<0·1%)	0	0
Location of ART storage			
Home	2144 (71·2%)	2130 (78·1%)	2474 (83·0%)
Friend's home	2 (0·1%)	6 (0·2%)	2 (0·1%)
Family member's home	25 (0·9%)	8 (0·3%)	9 (0·3%)
"I keep it with me"	811 (26·9%)	577 (21·2%)	493 (16·5%)
Other	30 (1·0%)	5 (0·2%)	3 (0·1%)
Missing or not answered	0	0	0
Keep ART bottles hidden from others	707 (23·5%)	501 (18·4%)	599 (20·1%)
Missing or not answered	0	3 (0·1%)	0
Receiving co-trimoxazole at baseline	1814 (70·2%)	1611 (65·1%)	1713 (68·6%)
Missing or not answered	427 (14·2%)	250 (9·2%)	483 (16·2%)
Receiving isoniazid preventive therapy at baseline	46 (1·9%)	0 (0·0)	23 (1·0%)
Missing or not answered	538 (17·9%)	574 (21·1%)	741 (24·9%)
Received contraception in past 3 months§	139/1001 (13·9%)	155/962 (16·1%)	214/1035 (20·7%)
Missing or not answered	204/1001 (20·4%)	212/962 (22·0%)	220/1035 (21·3%)

Data are median (IQR), n (%), or n/N (%). ART=antiretroviral therapy. *Among patients who reported a primary partner (6524 patients [3565 patients in Malawi; 2959 patients in Zambia]). †Among patients who reported earnings (5451 patients [3111 patients in Malawi; 2340 patients in Zambia]). ‡Among patients who reported incurred costs for transport to clinic (2994 patients [1394 patients in Malawi; 1600 patients in Zambia]). §Among women of reproductive age.

Table 1: **Baseline demographic and clinical characteristics of participants (n=8719)**

(median 17 health passports per site [IQR 13–21]). Most individuals had zero (157 [61·8%]) or one (46 [18·1%]) non-ART facility visits and there were small differences in visit pattern by group (appendix 2 p 12). Men were more likely than women to have no additional visits (70·0% *vs* 57·3%). Acute illnesses were the cause of most visits (85·8% for febrile illnesses, viral syndromes, and injuries) followed by visits for non-communicable diseases, such as hypertension and asthma (10·8%). Only four (2·4%) women had documentation of family planning visits (data not shown).

In Zambia, data for additional clinic visits not linked to ART pharmacy dispensing were collected for all participants with primary endpoint data at 12 months (n=4169). Of the 4169 participants, 3556 (85·3%) had no additional non-ART clinic visits and 496 (11·9%) had one visit. Visit patterns were similar by group (appendix 2 p 12) and no major differences by sex were identified (data not shown). No data were collected regarding the reasons for additional visits in Zambia due to limitations in the information available in medical records.

The primary outcome was met by 2478 (82·3%) of 3012 participants in the standard of care group, 2356 (86·4%) of 2726 participants in the 3-monthly ART dispensing group, and 2729 (91·5%) of 2981 participants in the 6-monthly ART dispensing group (table 2). The differences were largely driven by Zambia, where lower rates of retention overall and larger differences between groups were identified (74·6% standard of care, 82·3% 3-monthly ART dispensing, and 89·7% 6-monthly ART dispensing) compared with Malawi (89·7% for standard of care, 90·2% in the 3-monthly ART dispensing group, and 93·2% in the 6-monthly ART dispensing group). After adjusting for clustering, for retention in care at 12 months, the 6-monthly ART dispensing group was non-inferior to the standard of care group (percentage-point increase 9·1 [95% CI 0·9–17·2]) and to the 3-monthly ART dispensing group (5·0 percentage point increase [1·0–9·1]).

For the cost analysis, we excluded 179 participants with unclear visit data, thus 8540 patients were included (4400 patients from Malawi and 4140 patients from Zambia). In both countries, for study participants who were retained at 1 year, those in the 6-monthly ART dispensing group made an average of one (in Zambia) or two (in Malawi) fewer clinic visits per year than did participants in the other groups. For retained participants in Malawi, the provider incurred a mean cost of $89·00 per participant in the standard of care group, $88·40 in the 3-monthly ART dispensing group, and $85·92 in the 6-monthly ART dispensing group, with a similar pattern observed in Zambia, but at larger overall costs ($143·60 in the standard of care group, $141·60 in the 3-monthly ART dispensing group, and $131·13 in the 6-monthly ART dispensing group). Antiretroviral medications accounted for a large proportion of overall costs in both countries and all groups. Clinic visits and fixed costs accounted for a small proportion of overall costs in all groups, with the lowest costs in the 6-monthly ART dispensing group (table 3). Unit costs and infrastructure costs were variable by country (appendix 1 pp 2–3).

Average annual costs to participants for time losses were lowest in the 6-monthly ART dispensing group compared with the standard of care group (reduction in time accessing care of 45% in Malawi and 33% in Zambia). Similarly, lost potential income was lowest in the 6-monthly ART dispensing group compared with the standard of care group (reduction of 25% in Malawi

	Standard of care	3-monthly dispensing	6-monthly dispensing	3-monthly dispensing *vs* standard of care, RD (95% CI)	6-monthly dispensing *vs* standard of care, RD (95% CI)	6-monthly dispensing *vs* 3-monthly dispensing, RD (95% CI)
Overall (n=8719)						
Retention	2478/3012 (82·3%)	2356/2726 (86·4%)	2729/2981 (91·5%)	4·0% (–4·3 to 12·3)	9·1% (0·9 to 17·2)	5·0% (1·0 to 9·1)
Lost to follow-up	479/3012 (15·9%)	315/2726 (11·6%)	195/2981 (6·5%)	–4·3% (–14·0 to 5·3)	–9·4 % (–18·3 to –0·4)	–5·0% (–9·7 to –0·3)
Transfer	60/3012 (2·0%)	66/2726 (2·4%)	58/2981 (2·0%)	0·4% (–0·8 to 1·6)	–0·1% (–0·9 to 0·8)	–0·5% (–1·7 to 0·7)
Death	11/3012 (0·4%)	8/2726 (0·3%)	8/2981 (0·3%)	–0·1% (–0·4 to 0·2)	–0·1% (–0·4 to 0·2)	0·0 (–0·3 to 0·3)
Malawi (n=4550)						
Retention	1374/1532 (89·7%)	1290/1430 (90·2%)	1480/1588 (93·2%)	0·5% (–6·5 to 7·6)	3·5% (–2·5 to 9·5)	3·0% (–1·8 to 7·8)
Lost to follow-up	131/1532 (8·6%)	109/1430 (7·6%)	75/1588 (4·7%)	–0·9% (–8·1 to 6·2)	–3·8% (–9·7 to 7·2)	–2·9% (–7·6 to 1·8)
Transfer	29/1532 (1·9%)	38/1430 (2·7%)	35/1588 (2·2%)	0·8% (–0·7 to 2·2)	0·3% (–1·0 to 1·6)	–0·5% (–1·9 to 1·0)
Death	9/1532 (0·6%)	6/1430 (0·4%)	4/1588 (0·3%)	–0·2% (–0·7 to 0·4)	–0·3% (–0·7 to 0·1)	–0·2% (–0·6 to 0·3)
Zambia (n=4169)						
Retention	1104/1480 (74·6%)	1066/1296 (82·3%)	1249/1393 (89·7%)	7·7% (–7·2 to 22·5)	15·1% (0·4 to 29·8)	7·4% (1·7 to 13·1)
Lost to follow-up	348/1480 (23·5%)	206/1296 (15·9%)	120/1393 (8·6%)	–7·6% (–22·4 to 7·2)	–14·9% (–29·2 to –0·6)	–7·3% (–13·4 to –1·2)
Transfer	31/1480 (2·1%)	28/1296 (2·2%)	23/1393 (1·7%)	0·1% (–1·9 to 2·0)	–0·4% (–1·4 to 0·5)	–0·5% (–2·4 to 1·4)
Death	2/1480 (0·1%)	2/1296 (0·2%)	4 (0·3%)	0 (–0·2 to 0·2)	0·2% (–0·2 to 0·5)	0·1% (–0·3 to 0·5)

Data are n/N (%), unless otherwise indicated. RD=risk difference. All data were cluster-adjusted using a generalised estimating equation analysis. Participants who died or were transferred could also be considered to be retained or lost-to-follow up depending on their ART supply when the outcome occurred: these categories are non-exclusive; therefore the total percentage for all outcomes can be greater than 100%.

Table 2: **Outcomes at 12 months**

and 33% in Zambia). Among individuals who incurred costs for transportation to clinics (approximately a third of individuals), costs were lowest in the 6-monthly ART dispensing group in both countries by more than 25%, relative to the costs in the standard of care group (table 3). The full cost analysis is included in appendix 1 (pp 4–5).

The retention results did not significantly change in the per-protocol analysis (data not shown). Analyses adjusted for average monthly wages, proportion of participants paying for transportation, and whether the facility was a hospital or health centre did not significantly change the results for the primary outcome (data not shown). The intracluster correlation coefficient estimate for retention was 0·077. Transfers and deaths were similar by group and low overall (table 2).

In a post-hoc analysis of retention by country, in Zambia, the 6-monthly ART dispensing group was associated with a 15·1 (95% CI 0·4 to 29·8) percentage-point increase in retention relative to the standard of care group, and a 7·4 (1·7 to 13·1) percentage-point increase relative to the 3-monthly ART dispensing group. In Malawi, 6-month dispensing benefits were less notable, although the non-inferiority criterion was met for both the 6-monthly ART dispensing group versus the 3-monthly ART dispensing group (risk difference 3·0% [95% CI –1·8 to 7·8]) and 6-monthly ART dispensing group versus standard of care comparisons (3·5% [–2·5 to 9·5]; table 2). Additional post-hoc analyses of urban versus rural sites suggested more benefit of 6-monthly ART dispensing versus standard of care for individuals receiving care in urban facilities in both Malawi (risk difference 9·0% [2·1 to 15·9]) and Zambia (15·1% [0·4 to 29·8]) compared with rural facilities in Malawi (–3·8% [–7·4 to –0·2]), with similar results for 6-monthly ART dispensing versus 3-monthly ART dispensing (appendix 2 p 9).

In a post-hoc effect modification analysis, retention of men was similar to retention of women in the 6-monthly ART dispensing versus 3-monthly ART dispensing groups (risk difference 5·3% for men *vs* 5·1% for women); however, in the 6-monthly ART dispensing versus standard of care comparison, the retention effect was slightly larger for men than for women (10·7% *vs* 8·6%; appendix 2 p 10). In another post-hoc analysis of patients who were on ART for more than 12 months at entry, those in the 6-monthly ART dispensing group had a 10·4 (95% CI 0·4–20·4) percentage-point increase in retention compared with the standard of care group and a 5·9 (0·9–11·0) percentage-point increase compared with the 3-monthly ART dispensing group. For patients on ART between 6 and 12 months at entry, the proportion of patients retained in care was similar by group (80·6% for standard of care, 86·3% in the 3-monthly ART dispensing group, and 84·8% in the 6-monthly ART dispensing group), and the 6-monthly ART dispensing group did not meet the non-inferiority criterion for the 3-monthly ART dispensing or standard of care comparisons, with analyses limited by small sample size (n=534; appendix 2 p 11).

Discussion

In this cluster-randomised, non-inferiority trial, 6-monthly clinical consultations with ART dispensing was non-inferior to 3-monthly ART dispensing and standard of care ART dispensing and reduced the

	Malawi			Zambia		
	Standard of care (n=1477)	3-monthly dispensing (n=1351)	6-monthly dispensing (n=1572)	Standard of care (n=1472)	3-monthly dispensing (n=1283)	6-monthly dispensing (n=1385)
Resource utilisation per patient who met the primary outcome						
Clinic visits, median (IQR)	5·0 (5·0–6·0)	5·0 (5·0–5·0)	3·0 (3·0–3·0)	4·0 (4·0–5·0)	5·0 (4·0–5·0)	3·0 (2·0–3·0)
Clinic visits, mean (95% CI)	5·4 (3·4–7·4)	4·9 (2·9–6·9)	2·9 (0·9–4·9)	4·6 (2·6–6·6)	4·7 (2·7–6·7)	2·8 (0·8–4·8)
Days of ART dispensed, mean (95% CI)	364·2 (362·2–366·2)	365·4 (363·5–367·4)	368·0 (366·0–370·0)	368·3 (366·4–370·3)	358·4 (356·5–360·4)	367·6 (365·7–370·3)
Mean provider cost per patient by outcome (95% CI), US$						
Achieved primary outcome	$89·00 (87·90–91·90)	$88·40 (86·44–90·36)	$85·92 (83·97–87·89)	$143·60 (141·68–145·60)	$141·60 (139·64–143·56)	$131·13 (129·20, 133·12)
Did not achieve primary outcome	$63·40 (61·42–65·37)	$62·30 (60·35–64·30)	$66·10 (64·12–68·09)	$99·00 (97·04–100·98)	$99·00 (96·98–100·92)	$96·90 (94·96–98·91)
All patients	$86·50 (84·50–88·42)	$86·00 (83·99–87·91)	$84·60 (82·62–86·54)	$132·00 (130·43–134·35)	$134·00 (132·09–136·02)	$128·00 (125·64–129·57)
Provider cost breakdown for patients who met the primary outcome						
ART medications	$77·54 (87% [77·32–77·75])	$77·65 (88% [77·31–77·99])	$78·18 (91% [78·01–78·37])	$109·65 (76% [109·12–110·18])	$106·71 (75% [106·71–107·21])	$109·45 (83% [109·11–109·79])
Clinic visits (staff and infrastructure costs allocated per visit)	$8·19 (9% [8·09–8·30])	$7·43 (8% [7·37–7·49])	$4·42 (5% [4·37–4·47])	$31·75 (22% [31·27–32·23])	$32·69 (23% [32·42–32·96])	$19·48 (15% [19·26–19·70])
Fixed costs (infrastructure costs allocated per patient month in care)	$3·32 (4% [3·32–3·32])	$3·32 (4% [3·32–3·32])	$3·32 (4% [3·32–3·32])	$2·20 (2% [2·20–2·20])	$2·20 (2% [2·20–2·20])	$2·20 (2% [2·20–2·20])
Percentage change in total cost per patient (excluding medications) compared with standard of care	NA	–6·6%	–32·8%	NA	2·8%	–36·1%
Production cost						
Proportion of patients achieving the primary outcome	1328 (89·9%)	1224 (90·6%)	1465 (93·2%)	1101 (74·8%)	1056 (82·3%)	1241 (89·6%)
Production cost per patient achieving the primary outcome	$96·15	$94·87	$90·76	$177·00	$162·87	$142·41
Patient cost of obtaining ART (IQR)						
Median time spent accessing care per year, min (IQR)	1200 (750–1700)	1500 (1050–2100)	780 (510–1080)	990 (500–1500)	1150 (800–1580)	660 (420–930)
Median work value lost per year (IQR), US$	$5·30 (3·31–6·63)	$6·63 (3·31–6·63)	$3·98 (1·99–3·98)	$15·00 (9·98–20·00)	$20·00 (12·50–25·00)	$9·98 (7·49–15·00)
Patients incurring travel costs, n (%)	341 (23·1%)	288 (23·1%)	719 (45·7%)	564 (38·3%)	487 (38·0%)	532 (38·4%)
Median cost per year for patients who incurred travel costs (IQR), US$	$6·89 (3·31–11·0)	$6·89 (4·13–11·0)	$4·96 (2·76–8·27)	$4·36 (3·11–9·34)	$4·15 (3·11–7·26)	$3·11 (1·87–5·60)

Data are mean (SD), n (%), or median (IQR). ART=antiretroviral therapy. NA=not applicable.

Table 3: **Resource utilisation and cost per participant by country and study group**

number of days participants were without ART during the 1-year intervention period. Differences were driven largely by the lower baseline retention rates in Zambia, which offered more opportunity to show improvements over the 1 year. Additional data are needed to better understand populations for whom longer dispensing intervals have the most benefit.

This study adds to the growing literature on 6-monthly dispensing for patients on ART who are clinically stable. A randomised study from Zimbabwe[7] evaluated 6-monthly dispensing in community ART refill groups and found retention was non-inferior to 3-monthly community ART refill groups and 3-monthly facility-based dispensing. Similarly, a randomised trial from Lesotho[8] showed that 6-monthly dispensing at community drop-off points was non-inferior to 3-monthly dispensing in adherence clubs and 3-monthly facility-based dispensing, and a randomised study from South Africa showed that extending ART refills in adherence clubs from 2 to 6 months was associated with non-inferior retention and viral suppression.[9] These studies involved integrating 6-monthly dispensing into off-site, community-based models of care, making results difficult to generalise to routine facility-based care. To the best of our knowledge, INTERVAL is the first randomised study of facility-based 6-monthly dispensing, which is likely to be a highly feasible and cost-effective model of dispensing for large-scale implementation in resource-limited settings.

The inclusion criteria for INTERVAL were limited to patients on ART who were clinically stable. Although there is no universally accepted definition of stability on ART, our definition is similar to that used by WHO,[12] with

the exception of requiring 6 months rather than 1 year of ART before enrolment. We compared the effect of 6-monthly dispensing with 3-monthly dispensing in participants on ART for 6–12 months and found that 6-monthly dispensing caused no significant detriment to retention. However, our analysis was limited by small sample size, and further work should be done to understand the optimum timing for implementation of 6-monthly dispensing in patients who are newly initiating ART. Our study excluded patients who were clinically unstable, women who were pregnant or breastfeeding, and those with non-communicable diseases, and further work should be done to characterise the benefits and risks of 6-monthly dispensing for individuals other than those considered stable by commonly used definitions of clinical stability in sub-Saharan Africa.

During the study period, both Malawi and Zambia implemented national guidelines that recommended 3-monthly dispensing for patients who were clinically stable on ART. Despite these guidelines, the amount of ART dispensed varied across the sites randomly assigned to the standard of care group in our study. These findings might reflect provider apprehension with regard to 3-monthly dispensing (regardless of clinical stability) or other constraints at the site, such as ART supply. Our study provided support to the 3-monthly ART dispensing and 6-monthly ART dispensing facilities, including frequent clinical mentoring and job aids to remind providers to dispense at the appropriate intervention allocation, and support for the ART supply chain. This type of support is provided by the Ministry of Health in both Malawi and Zambia (commonly through implementing partners that support HIV care); however, the quality of support in our study might have been higher than typically delivered through routine programming. These findings show that in real-world conditions, providers might require consistent mentoring and strong support for supply chain to maximise opportunities for multimonth dispensing.

In both Malawi and Zambia, 6-monthly dispensing was slightly less expensive for providers than 3-monthly dispensing and standard of care. Although visit costs and clinic fixed costs decreased by about a third in the 6-monthly ART dispensing group, the absolute difference in the cost per patient was modest, primarily reflecting the large proportion of total costs due to antiretroviral medications. However, considering the large number of patients being treated for HIV in the national programmes in these countries, cost reduction of a few dollars per patient could ultimately allow more patients to be treated with a fixed budget, or for higher quality of care to be offered to patients with more complex needs. 6-monthly dispensing also offered substantial cost savings for patients, with reductions in the total time spent accessing ART equal to roughly 1 working day. Other cost analyses of differentiated models of care have also suggested cost savings of 6-month dispensing relative to standard of care,[22,23] but to our knowledge, our study is the first randomised trial to directly compare cost for different strategies of multimonth dispensing.

Additional clinic visits for purposes other than ART dispensing can reduce the benefits of adopting 6-monthly dispensing, which result primarily, if not entirely, from a reduction in visit numbers. We found that most participants in both countries had no additional clinic visits in the year of follow-up. Additional visits were less common in Zambia than Malawi, although this difference might reflect data limitations in Zambia because only ART records were used to determine whether additional visits had occurred in Zambia. In Malawi, health passport data include visits that would have occurred outside of those to the ART clinic and thus such data might provide a more accurate depiction of care-seeking.

Our study had several limitations, many of which are common to implementation studies of service delivery interventions. Funding limitations restricted the follow-up period to 1 year; we cannot assume that the improvements in retention that we observed will persist over time for all participants. Although we had prespecified viral suppression as a secondary study endpoint, approximately 75% of participants did not have routine viral load tests during the follow-up period because of the early state of viral load scale-up in Malawi and Zambia. Although we did not have data for virological suppression, we did analyse uncovered ART days, which were low overall and lowest in the 6-monthly ART dispensing group. Previous research suggests that this finding is a good proxy for adherence to treatment.[24,25] We excluded patients who were clinically unstable and other patients who did not meet study inclusion criteria. The risks and benefits of 6-monthly dispensing are likely to be different in these populations and require further study. For the subset of patients who were retained in care but had their dispensing interval shortened from either 6-monthly ART dispensing or 3-monthly ART dispensing, we were unable to determine the reason for this change because of limitations in medical record documentation. A more nuanced understanding of reasons for transition away from multimonth dispensing will be important to optimise patient selection for this model of care. We only assessed health passports in a small number of participants in Malawi, and similar data were not available in Zambia, limiting the representativeness of this sample for non-ART health facility visits. Additionally, we were unable to determine, from the insufficient detail of health records available, whether women in the 6-monthly dispensing group had extra visits for contraception. For the costing analyses, unit cost data were collected for only a subset of study sites and we did not have data for laboratory tests or other HIV services provided that were unrelated to ART dispensing. Adding one viral load test per year, which is the current laboratory requirement for patients who are stable on ART in both countries, would possibly add approximately $19 to the provider cost.[26] Future studies of 6-monthly dispensing

should account for laboratory costs and non-ART services that are considered as standard of care for the setting to provide a more comprehensive view of costs. We did not do a probabilistic sensitivity analysis, which limits the generalisability of our cost results.

The INTERVAL study showed that 6-monthly clinical visits with ART dispensing was non-inferior to 3-monthly dispensing and standard of care dispensing and could improve retention in care for patients in Malawi and Zambia on ART who are stable, while reducing costs to providers and patients. 6-monthly dispensing also decreased the burden of care-seeking on patients, achieving the goal of greater patient-centred care. The importance of continuing to expand ART provision in resource-constrained settings makes 6-monthly dispensing a promising intervention for many countries. Future research should address longer-term follow-up and viral suppression rates, and explore the benefits of 6-monthly dispensing for additional patient groups, such as individuals newly initiating treatment, those struggling with engagement in care, pregnant and breastfeeding women, and individuals living with chronic non-communicable diseases.

Contributors

RMH designed the study, was the main principal investigator responsible for implementation, participated in data analyses, and was the lead manuscript author. CM was the Zambia principal investigator responsible for implementation and participated in writing and editing the paper. KTB was the overall project data manager and supported implementation, analysis, and editing of the manuscript. ZS was the project manager in Zambia and supported implementation as well as helped with manuscript writing and editing. JH was the project coordinator in Malawi, supported implementation in Malawi, contributed to data analysis, as well as writing and editing of the manuscript. AB was the overall project manager and contributed to study design, implementation in both Malawi and Zambia, and manuscript editing. MPF helped design the study and supported data analyses, manuscript writing, and editing. GK supported project implementation in Malawi and participated in editing the manuscript. TK supported project implementation in Malawi and participated in editing the manuscript. MN-H supported implementation of the project in Zambia and contributed to manuscript editing. KD supported implementation in Malawi and contributed to manuscript editing. PMC supported implementation of the project in Malawi and Zambia and contributed to data analyses, and manuscript writing and editing. C-HT was the study biostatistician, did the primary data analyses, and assisted with manuscript editing. PTP supported project implementation in Zambia and contributed to manuscript editing. RC supported the collection of cost data in Malawi and Zambia, contributed to the cost analyses, and manuscript editing. SG supported implementation in Malawi and contributed to manuscript editing. MB contributed to the cost analyses and manuscript editing. LL contributed to cost analyses and manuscript editing. TX helped with study design and participated in manuscript editing. IS designed the study and participated in manuscript editing. SR designed the study, supported the implementation of costing, and worked closely with RMH throughout the development and editing of the manuscript. All authors had full access to all of the data and had the final responsibility for the decision to submit for publication. RMH, MPF, and C-HT accessed and verified the data.

Declaration of interests

We declare no competing interests.

Data sharing

De-identified data from the study can be made available to other investigators after all secondary analyses for the study have been completed from March, 2021, onwards. Data can be shared after a signed agreement has been completed with the INTERVAL investigators.

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References

1 The Antiretroviral Therapy Cohort Collaboration. Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies. *Lancet HIV* 2017; **4:** e349–56.

2 Nhassengo P, Cataldo F, Magaço A, et al. Barriers and facilitators to the uptake of Test and Treat in Mozambique: a qualitative study on patient and provider perceptions. *PLoS One* 2018; **13:** e0205919.

3 Ayieko J, Brown L, Anthierens S, et al. "Hurdles on the path to 90-90-90 and beyond": qualitative analysis of barriers to engagement in HIV care among individuals in rural East Africa in the context of test-and-treat. *PLoS One* 2018; **13:** e0202990.

4 Roy M, Holmes C, Sikazwe I, et al. Application of a multistate model to evaluate visit burden and patient stability to improve sustainability of human immunodeficiency virus treatment in Zambia. *Clin Infect Dis* 2018; **67:** 1269–77.

5 Georgetown University HIV Policy Lab. Access during COVID-19: national policies on multi-month supplies of HIV medications. https://www.hivpolicylab.org/documents/PolicyLab-Multi-Month%20ARVs_4.15.20.pdf (accessed May 31, 2020).

6 US President's Emergency Plan for AIDS Relief. PEPFAR 2019 country operational plan guidance for all PEPFAR countries. 2019. https://www.state.gov/wp-content/uploads/2019/08/PEPFAR-Fiscal-Year-2019-Country-Operational-Plan-Guidance.pdf (accessed April 15, 2020).

7 Fatti G, Ngorima-Mabhena N, Mothibi E, et al. Outcomes of three-versus six-monthly dispensing of antiretroviral treatment (ART) for stable HIV patients in community ART refill groups: a cluster-randomized trial in Zimbabwe. *J Acquir Immune Defic Syndr* 2020; **84:** 162–72.

8 Tukei BB, Fatti G, Tiam A, et al. Community-based multimonth dispensing of art: a cluster randomised trial in Lesotho. Conference on Retroviruses and Opportunistic Infections; Boston, MA, USA; March 8–11, 2020 (abstr 43).

9 Lebelo K, Cassidy T, Grimsrud A, et al. Twelve-month retention and viral load outcomes from a non-inferiority cluster randomized trial extending adherence club ART refill dispensing intervals to 6-monthly. International AIDS Conference; July 6–10, 2020, virtual meeting (abstr OAELB01).

10 Malawi Ministry of Health. Malawi Guidelines for Clinical Management of HIV in Children and Adults. 3rd edn. 2016. https://www.childrenandaids.org/sites/default/files/2017-04/Malawi_Clinical-HIV-Guidelines_2016.pdf (accessed March 14, 2020).

11 Zambia Ministry of Health. Zambia consolidated guidelines for the prevention and treatment of HIV infection. 2016. http://www.differentiatedservicedelivery.org/Portals/0/adam/Content/fLl-2LVqM0izU06VDY6DqQ/File/Zambia_Consolidated_2016_Guidelines.pdf (accessed March 14, 2020).

12 WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach. 2nd edn. 2016. https://www.who.int/hiv/pub/arv/arv-2016/en/ (accessed April 1, 2020).

13 Hoffman R, Bardon A, Rosen S, et al. Varying intervals of antiretroviral medication dispensing to improve outcomes for HIV patients (The INTERVAL Study): study protocol for a randomized controlled trial. *Trials* 2017; **18:** 476.

14 Phiri K, McBride K, Siwale Z, et al. Provider experiences with three- and six-month antiretroviral therapy dispensing for stable clients in Zambia. *AIDS Care* 2020; published online Oct 8, 2019. https://doi.org/10.1080/09540121.2020.1755010.

15 Hubbard J, Phiri K, Moucheraud C, et al. A qualitative assessment of provider and client experiences with 3- and 6-month dispensing intervals of antiretroviral therapy in Malawi. *Glob Health Sci Pract* 2020; **8:** 18–27.

16 Long L, Brennan A, Fox MP, et al. Treatment outcomes and cost-effectiveness of shifting management of stable ART patients to nurses in South Africa: an observational cohort. *PLoS Med* 2011; **8:** e1001055.

17 Rosen S, Long L, Sanne I. The outcomes and outpatient costs of different models of antiretroviral treatment delivery in South Africa. *Trop Med Int Health* 2008; **13:** 1005–15.

18 Scott CA, Iyer H, Bwalya DL, et al. Retention in care and outpatient costs for children receiving antiretroviral therapy in Zambia: a retrospective cohort analysis. *PLoS One* 2013; **8:** e67910.

19 WageIndicator Foundation. Minimum wage—Malawi. https://wageindicator.org/salary/minimum-wage/malawi (accessed July 17, 2020).

20 WageIndicator Foundation. Minimum Wage—Zambia. https://wageindicator.org/salary/minimum-wage/zambia (accessed July 17, 2020).

21 Pagel C, Prost A, Lewycka S, et al. Intracluster correlation coefficients and coefficients of variation for perinatal outcomes from five cluster-randomised controlled trials in low and middle-income countries: results and methodological implications. *Trials* 2011; **12:** 151.

22 Barker C, Dutta A, Klein K. Can differentiated care models solve the crisis in HIV treatment financing? Analysis of prospects for 38 countries in sub-Saharan Africa. *J Int AIDS Soc* 2017; **20** (suppl 4)**:** 21648.

23 Roberts DA, Limaye N, Barnabas RV. The cost of differentiated service delivery: a systematic review. 2018. http://cquin.icap.columbia.edu/wp-content/uploads/2018/08/ICAP_CQUIN-satellite_Costs_Barnabas_FINAL.pdf (accessed Dec 29, 2019).

24 Orrell C, Cohen K, Leisegang R, Bangsberg DR, Wood R, Maartens G. Comparison of six methods to estimate adherence in an ART-naïve cohort in a resource-poor setting: which best predicts virological and resistance outcomes? *AIDS Res Ther* 2017; **14:** 20.

25 Sangeda RZ, Mosha F, Prosperi M, et al. Pharmacy refill adherence outperforms self-reported methods in predicting HIV therapy outcome in resource-limited settings. *BMC Public Health* 2014; **14:** 1035.

26 Nichols BE, Girdwood SJ, Crompton T, et al. Impact of a borderless sample transport network for scaling up viral load monitoring: results of a geospatial optimization model for Zambia. *J Int AIDS Soc* 2018; **21:** e25206.