



Effectiveness and cost-effectiveness of a nurse-delivered intervention to improve adherence to treatment for HIV: a pragmatic, multicentre, open-label, randomised clinical trial

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Summary

Background No high-quality trials have provided evidence of effectiveness and cost-effectiveness of HIV treatment adherence intervention strategies. We therefore examined the effectiveness and cost-effectiveness of the Adherence Improving self-Management Strategy (AIMS) compared with treatment as usual.

Methods We did a pragmatic, multicentre, open-label, randomised controlled trial in seven HIV clinics at academic and non-academic hospitals in the Netherlands. Eligible participants were patients with HIV who were either treatment experienced (ie, with ≥ 9 months on combination antiretroviral therapy [ART] and at risk of viral rebound) or treatment-naïve patients initiating their first combination ART regimen. We randomly assigned participants (1:1) to either AIMS or treatment as usual (ie, containing a range of common adherence intervention strategies) using a computer-generated randomisation table. Randomisation was stratified by treatment experience (experienced vs naïve) and included block randomisation at nurse level with randomly ordered blocks of size four, six, and eight. 21 HIV nurses from the participating clinics received three training sessions of 6 h each (18 h in total) on AIMS and a 1.5 h booster training session at the clinic (two to three nurses per session) after each nurse had seen two to three patients. AIMS was delivered by nurses during routine clinic visits. We did mixed-effects, intent-to-treat analyses to examine treatment effects on the primary outcome of \log_{10} viral load collected at months 5, 10, and 15. The viral load results were exponentiated (with base 10) for easier interpretation. Using cohort data from 7347 Dutch patients with HIV to calculate the natural course of illness, we developed a lifetime Markov model to estimate the primary economic outcome of lifetime societal costs per quality-adjusted life-years (QALYs) gained. This trial is registered at ClinicalTrials.gov (number NCT01429142).

Findings We recruited participants between Sept 1, 2011, and April 2, 2013; the last patient completed the study on June 16, 2014. The intent-to-treat sample comprised 221 patients; 109 assigned to AIMS and 112 to treatment as usual. Across the three timepoints (months 5, 10, and 15), log viral load was 1.26 times higher (95% CI 1.04–1.52) in the treatment-as-usual group (estimated marginal mean 44.5 copies per mL [95% CI 35.5–55.9]) than in the AIMS group (estimated marginal mean 35.4 copies per mL [29.9–42.0]). Additionally, AIMS was cost-effective (ie, dominant: cheaper and more effective) since it reduced lifetime societal costs by €592 per patient and increased QALYs by 0.034 per patient.

Interpretation Findings from preparatory studies have shown that AIMS is acceptable, feasible to deliver in routine care, and has reproducible effects on medication adherence. In this study, AIMS reduced viral load, increased QALYs, and saved resources. Implementation of AIMS in routine clinical HIV care is therefore recommended.

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Introduction

Efficacious drugs for the treatment of HIV/AIDS have been widely available in high-income countries since 1996, and are becoming increasingly available in low-income countries. The life expectancy of people with HIV using antiretroviral therapy (ART) is now almost identical to that of people without HIV.¹ Moreover, the risk of HIV transmission is reduced considerably for successfully treated patients.² However, despite a marked reduction in side-effects and complexity of combination ART regimens over the past two decades, suboptimum intake of drugs (faulty execution) and premature discontinuation (non-persistence) of combination ART continue to compromise treatment effectiveness.³ Non-adherence can lead to poor

patient outcomes, the development of drug-resistant virus, fewer treatment options because of drug resistance, and increased transmission risks of viral strains, including resistant ones.^{4–9} Hence, supporting patients' adherence is an important objective from a patient and public health perspective, and essential for achieving the UNAIDS 90-90-90 targets.¹⁰

For the long-term success of combination ART and its consequent effect on the spread of HIV, suboptimal adherence has to be addressed before virological failure occurs. Although results from meta-regression analyses suggest that the quality of adherence support provided to patients has a large influence on viral suppression rates,^{11,12} little direct experimental evidence shows that

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Research in context

Evidence before this study

We searched for effectiveness and cost-effectiveness evidence from trials done in high-income countries, with at least 12 months follow-up including a clinical outcome that focused on adult HIV-infected patients. Interventions had to promote autonomous behaviour (ie, directly observed therapy interventions were excluded) and treatment simplification studies (eg, once-daily versus twice-daily medication) were excluded. For evidence on effectiveness of the interventions we searched MEDLINE, PsycINFO, and Embase with no language restrictions for articles published between January, 2013, and October, 2016, using the terms (“HIV” or “HAART” or “cART” or “Antiretroviral”) and (“adherence” or “compliance” or “persistence” or “concordance”) and (“viral load” or “virologic failure” or “CD4”) in the title or abstract, and (“random*” or “clinical trial”) in all text, and (“2013” or “2014” or “2015” or “2016”) in the year. We identified 529 unique titles, of which 27 assessed an adherence intervention. Only one was an eligible trial, assessing the Managed Problem Solving (MaPS) intervention, which noted that MaPS improved adherence. A particular strength of the trial was the high consent rate; possible weaknesses were differential attrition and a missing data imputation method that deemed missing data to equal treatment failure. No cost-effectiveness analysis was reported. For evidence on cost-effectiveness of adherence interventions, we searched the same databases and date range as above with the terms (“HIV” or “HAART” or “cART” or “Antiretroviral”) and (“adherence” or “compliance” or “persistence” or “concordance”) and (“Cost Analysis” or “Cost Effectiveness” or “Cost Benefit” or “Cost Utility” or “Cost Minimisation” or “Economic Evaluation”) in the title or abstract, and (“2013” or “2014” or “2015” or “2016”) in the year. We identified 137 unique titles and abstracts, of which only one was an eligible study that reported the cost-effectiveness of a

computer-delivered intervention to promote adherence to HIV medication (FL, USA). This assessment was, however, based on effectiveness data from a subgroup analysis in a short-term intervention feasibility study. Further limitations were that the effectiveness data was derived from self-reported adherence and did not line up with the effectiveness input in the economic model. Thus, these searches did not identify any adherence interventions from high-quality, long-term trials, and economic assessment that provided evidence of effectiveness and cost-effectiveness.

Added value of this study

To our knowledge, this multicentre, randomised controlled trial and economic model is the first to show that our adherence intervention Adherence Improving self-Management Strategy (AIMS) produced meaningful effects on viral load and was cost-effective in a high-resource setting, compared with treatment as usual. The findings from the study showed that HIV treatment adherence interventions can increase quality-adjusted life-years (QALYs) while saving resources, even when compared with medium-to-high-quality treatment-as-usual adherence support. Moreover, AIMS required few resources because it has been adapted to fit in routine HIV clinic services, which should facilitate implementation in routine care.

Implications of all the available evidence

HIV treatment adherence interventions, such as AIMS, can benefit patients, even in high-resource settings, and lead to gains in QALYs while saving resources. AIMS seems at present to be the only adherence intervention for which the effects have been replicated in consecutive trials. The economic evaluation also provided robust evidence on cost-effectiveness. Implementation of AIMS in routine clinical care is therefore recommended.

adherence interventions have a sustained effect on adherence and—more importantly—on viral loads and CD4 cell counts.^{13,14} A Cochrane review did not identify any low risk of bias trials of HIV adherence interventions in high-income countries that provided evidence of intervention effects on adherence and clinical outcomes such as viral load. Two trials were identified in low-income countries, the results from which showed promising effects on viral load.¹⁵ Moreover, no evidence is available that shows effective HIV treatment adherence interventions yield benefits for society in terms of cost-effectiveness.¹⁶ Our updated search of the scientific literature did not yield additional evidence.

In 2003, we developed the Adherence Improving self-Management Strategy (AIMS), based on empirical literature, behavioural theories, and input from health-care professionals and patients.¹⁷ AIMS is a nurse-delivered, one-on-one behavioural intervention that

incorporates adherence feedback from electronic medication monitors (Medication Event Monitoring System [MEMS]-caps; an electronic pill-bottle cap that registers date and time of bottle opening) and is designed to fit into routine clinic visits. After a successful pilot study¹⁷ that highlighted its acceptability, feasibility, and effects on adherence, we did a single-centre randomised controlled trial with treatment-experienced patients.¹⁸ Although powered to detect an effect on adherence (the primary outcome), this trial also provided tentative evidence of improved viral suppression rates (a secondary outcome). However, this trial had a homogeneous patient group and a short follow-up of 7 months. Showing clinically relevant effects on viral load in a high-quality pragmatic trial with a long follow-up, and a heterogeneous group of patients and HIV clinics, could provide conclusive evidence that AIMS is effective. Moreover, showing that AIMS is also cost-effective would be

important for policy makers, as well as for adherence intervention research generally, given the scant evidence of the economic benefits of adherence interventions.

Effective HIV treatment adherence interventions should benefit patient and public health, and reduce health-care expenditures; yet, experimental evidence of these benefits is scarce. This report describes findings from our study that assessed the effectiveness of AIMS, and the results of a Markov model assessing the cost-effectiveness of AIMS over a lifetime horizon.

Methods

Study design and participants

The protocol for this study has been published¹⁹ and a separate article has been published on the strategies used for reducing the risk of bias in this trial²⁰ (the appendix includes a table summarising the risk of bias rationale in this article). We did a pragmatic, multicentre, open-label, randomised controlled trial in seven HIV clinics at academic and non-academic hospitals in the Netherlands.

Eligible participants were patients with HIV who were either treatment-experienced (≥ 9 months on combination ART and at risk of viral rebound), or treatment-naïve patients initiating their first combination ART regimen. At risk of viral rebound was determined on the basis of having at least one detectable viral load during the previous 3 years and suboptimal adherence during 2 months baseline MEMS monitoring ($< 100\%$ adherence for once-daily and $\leq 95\%$ for twice-daily regimens). These criteria were based on analyses of data from a large HIV cohort including all registered HIV patients in the Netherlands,²¹ and from our previous trial.¹⁸ Exclusion criteria were: age less than 18 years, severe psychiatric disorders or other comorbidities precluding compliance with study procedures, pregnancy, plans to interrupt treatment in the next 14 months, life expectancy less than 1 year, not able to communicate in English or Dutch, viral resistance to three or more antiretroviral drug classes, and about to initiate hepatitis C treatment. Eligible patients were approached by their treating physician or HIV nurse, and given information about the study verbally and in writing. All patients gave written informed consent. The trial was approved by the medical ethics committees of all participating hospitals. Given the absence of any patient safety risks according to the medical ethics committee that approved the trial, there was no data and safety monitoring board.

Randomisation and masking

We randomly assigned consenting participants (1:1) to either AIMS or treatment as usual (ie, containing a range of common adherence intervention strategies) using a computer-generated randomisation table. The resulting risk of contamination was kept low because key intervention elements, such as MEMS feedback and all other intervention materials (panel) could only be accessed when a MEMS-cap of a patient in the intervention group

was downloaded.²⁰ Randomisation was stratified by treatment experience (experienced *vs* naïve) and we used block randomisation (with randomly ordered blocks of size four, six, and eight to avoid predictability of assignment) to balance intervention and control patients over nurses. The randomisation table was computer-generated by a statistician and treatment assignment was done automatically by software after nurses entered the details of consenting patients on a study website. Because masking to treatment assignment was not possible given the nature of the intervention, we developed a distraction strategy for drawing the attention of patients and health-care providers away from the primary study aims. Specifically, we included a second research objective in the study (ie, to examine the content of, and patient satisfaction with, nursing care provided to patients treated for HIV), and the regular questionnaires that nurses and patients completed during the trial focused on this study aim, rather than on the comparison of AIMS versus treatment as usual.²⁰ The statistician (WV) who did the analyses was masked to group assignment.

Procedures

21 HIV nurses from the seven participating clinics received three training sessions (6 h each, 18 h in total) on AIMS and on how to use the MEMS-caps and software. A 1.5-h booster session was delivered at each HIV clinic (two to three nurses per session) after each nurse had seen two to three patients. The first author (MdB) delivered the training and booster sessions. There was no additional support or advice in relation to the delivery of the intervention.

Details of patient demographic characteristics and treatment were obtained at baseline. Plasma viral load and CD4 cell counts were assessed at baseline and at approximately 5 months, 10 months, and 15 months as part of routine care. For treatment-initiating patients, the first follow-up measurement was planned slightly later at 6 months, to allow their viral load to become undetectable. Treatment-experienced patients followed the usual 4–5 months visit interval. The viral load assays used were COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, v2.0 (Roche), Abbott m2000 RealTime HIV-1, and NucliSENS Easy Q HIV-1 v2.0 (Biomérieux), with lower detection limits varying from 20 to 75 copies per mL. The study was overpowered for detecting an effect on adherence. To avoid unnecessary study burden, we measured MEMS adherence in a randomly selected 50% of the control group patients. Since a subset of patients preferred using their own medication bottles over the MEMS-caps bottles (especially if MEMS-caps were used for monitoring only, as in the treatment-as-usual group),^{18,22} and because adherence was a secondary outcome, if randomised patients preferred further trial participation without MEMS monitoring, they were allowed to do so (appendix).

The quality and quantity of treatment as usual adherence support provided to control groups in

See Online for appendix

Panel: Treatment-as-usual strategy versus the Adherence Improving self-Management Strategy (AIMS)**Materials used***Treatment as usual*

- Patient information leaflet

AIMS

- Simple graph explaining how drug concentrations vary with adherence patterns, and affect treatment outcomes
- Seven example adherence reports from electronic monitors ranging from excellent to poor adherence
- A list with common reasons that other patients have given for achieving high adherence
- MEMS-cap to monitor own adherence and obtain printed personal adherence reports
- Templates for action plans and coping plans
- Drop-down lists with common reasons for non-adherence and effective solutions for dealing with these problems
- Ruler (1–10 scale) to score own confidence in improving adherence
- For treatment-initiating patients only: score sheet of five reasons for, and five concerns about, initiating treatment

Procedures*Treatment as usual*

When the physician, nurse, and patient agreed that treatment should be initiated, typically the following activities were done to support adherence:

- Patients were given a verbal explanation of how the medication works and what the relation is between adherence, viral replication, and treatment outcomes. This explanation included risks (eg, viral resistance) and benefits (eg, a healthy immune system and being less infectious) of adherence and non-adherence. An information leaflet was provided.
- Patients were given an explanation of how to take the medication, how often, and at what dose.
- The nurse and patient discussed when it was best for each individual patient to take their medication (at what time and where, linking intake to daily routines or using reminder devices that can serve as cues)
- Patient were given a telephone number to call in case of difficulties (eg, occurrence of side-effects or difficulties with adherence)
- During follow-up visits:
 - Patient and nurse discussed self-reported adherence (and any problems) and tried to identify solutions that would work for that patient
 - The nurse or physician asked the patient about any side-effects and discussed how to deal with them (if severe, a change of regimen is considered)
 - Nurses provided feedback on viral load and CD4 cell counts. If results were positive, this finding served to reinforce adherence. If results were negative, adherence problems or other causes (eg, drug resistance or drug interactions) were explored (appendix)

Management of side effects, feedback of clinical outcomes, and receiving a telephone number in case of difficulties was also part of the routine care for AIMS patients.

AIMS

Here we explained AIMS for treatment-experienced patients. The intervention at the first visit was slightly different for treatment-naive patients (appendix).

Before the first AIMS intervention visit, patients used an electronic medication monitor for 4–8 weeks. Data were downloaded and a website guided patients and nurses through the steps below. Tailoring of the intervention to the needs and abilities of each individual patient was a core component of each step.

- Similar to step 1 for treatment as usual, except that material 1 was used to aid discussion and storage of information in long-term memory.
- Nurse explained seven exemplar MEMS-reports using material 2 while linking patterns of adherence and non-adherence to the adherence-outcome information discussed in step 1. The patient selected one adherence report reflecting how they would like to take their medication (desired adherence level) and the nurse asked the patient to explain why this is important to them personally and in the long run (material 3).
- Patients' own MEMS-report was printed (actual adherence level; material 4) and compared with their desired adherence level. The nurse reinforced periods of good adherence and highlighted discrepancies (ie, where actual adherence was lower than desired).
- Patient MEMS-report was used to identify any non-adherence patterns, causes, and solutions. These were written down in coping plans (using an if..., then... format; materials 5 and 6).
- Patient selected an adherence goal for the next visit using material 2 and scored their confidence in their ability to accomplish that goal (material 7). If confidence was low, the nurse explored whether important adherence barriers had been unaddressed or if their adherence goal should be approached incrementally.
- The patient was offered a MEMS-view cap with a display showing how often the bottle had been opened that day (to facilitate adherence self-monitoring; material 4). Patient was given their printed adherence report and coping plan.
- Subsequent intervention sessions were mainly repetitions of steps 3, 4, and 5. The aim was that patients reached their desired level of adherence during the first 5 months of the intervention, strived for behavioural maintenance during the next 5 months, followed by a follow-up of another 5 months. Patients with many adherence difficulties could be seen more frequently.

Both the treatment-as-usual strategy and AIMS were delivered as part of routine care by trained HIV/AIDS nurses. The panel summarises the materials used and procedures for both strategies. A more comprehensive table including the behavioural-change objectives and techniques is in the appendix. MEMS=electronic medication monitors. AIMS=Adherence Improving self-Management Strategy.

adherence trials varies between trials and impacts on effect sizes.^{11,12} We developed a minimally intrusive method for collecting treatment as usual data from participating nurses,²³ and noted that treatment as usual in participating clinics ranged from medium to high quality when compared with meta-analyses on this topic.^{11,12} Treatment as usual was not standardised between clinics for the purpose of this trial, and reflected what patients receive in routine clinical care in the Netherlands. The panel shows details of the AIMS intervention and treatment as usual.

Outcomes

The primary effectiveness outcome was defined as \log_{10} -transformed plasma viral load (copies per mL) across the three follow-up timepoints (5, 10, and 15 months). The secondary effectiveness outcome was percentage adherence. Post-hoc outcomes were (1) treatment failure, defined as having a detectable viral load on two consecutive follow-up measurements; (2) CD4 cell counts (cells per μ L); and (3) detectable versus undetectable viral loads, which was to be used as the primary outcome instead of \log_{10} viral load if the skewed distribution of \log_{10} viral load data would lead to violation of statistical model assumptions. Because model assumptions were not violated, this analysis was reported as post hoc.

Using cohort data from 7347 Dutch patients with HIV to calculate the natural course of illness, we developed a lifetime Markov model to estimate the primary economic outcome of lifetime societal costs (including health-care costs, productivity loss, HIV transmission costs, and intervention cost) per quality-adjusted life-years (QALYs) of AIMS versus treatment as usual.¹⁹ A trial-based economic assessment, which examined the short-term economic outcomes observed during the follow-up of the trial and therefore has another primary outcome (same trial number as this study), will be published separately.

Statistical analysis

The study was powered to detect an effect on plasma viral load, measured at three consecutive timepoints, while controlling for baseline viral load. A sample of 230 randomised patients was required to obtain 80% power to detect a significant intervention effect on viral load for at least one of three timepoints with $\alpha=0.05$ (two-sided), using a Bonferroni correction and assuming a maximum dropout of 10%.

The primary intent-to-treat analysis for \log_{10} viral load used a mixed-effects (multilevel) model.^{24,25} A factor for timepoint (three levels, one for each follow-up measurement at months 5, 10, and 15), group (two levels), and their interaction (testing for a between-group change during follow-up) were the primary variables of interest. In the absence of a time-by-group interaction, the overall intervention effect can be estimated by a between-group (marginal) contrast across the three follow-up timepoints. Baseline viral load and the stratification variable

(treatment-experienced *vs* treatment-naïve) were added to the model as covariates; as well as a four-level factor for ethnic group (white, sub-Saharan African, Caribbean, and others), as this is an important prognostic covariate.^{11,20} The viral load results were exponentiated (with base 10) for easier interpretation. Undetectable viral loads (eg, <40 copies per mL) were replaced by the corresponding detection limit.

We also did: (1) a mixed-effects logistic regression model,²⁵ using detectable versus undetectable viral load (based on the detection limit of each respective clinic). The detection limit value of each viral load test was added as an additional covariate; (2) a mixed-effects logistic regression model examining treatment failure, using the same covariates; and (3) a mixed-effects model examining the effects of the intervention on CD4 cell count, using the same model as for the primary viral load analysis, but with viral load replaced by CD4 values. No statistical analyses were done for adherence, because of substantial differences in the uptake of the MEMS monitoring between the study arms (eg, 52 [91%] of 57 treatment-naïve patients assigned to AIMS *vs* 15 [54%] of 28 assigned to treatment as usual started the use of MEMS after randomisation).

Based on the fitted models, we also obtained marginal estimates of the specific means for the AIMS and treatment-as-usual groups (viral load and CD4 cell count analyses) and risks (detectable viral load and treatment failure analyses), using the median value at baseline for continuous covariates (ie, baseline viral load and detection limit) and the observed proportions at baseline for categorical covariates (ie, treatment-experienced *vs* treatment-naïve, ethnic group, and detection status at baseline).

Analyses were done in R (version 3.1.2) using the nlme package,²⁴ and Stata (version 13.1) using functions mixed and meqrlogit. The appendix shows additional details on the sample size calculation and statistical analyses.

Our Markov model was based on the Dutch guideline for health economic evaluations and international guidelines for modelling (ISPOR-SMDM guidelines).²⁶ In a Markov model, a cohort of patients is assumed to transit between health states. Based on the scientific literature^{8,27,28} and input from clinicians in the participating clinics, 13 health states were identified: three CD4-cell count categories (0–200, 201–500, and >500 cells per μ L) combined with four viral load categories (0–50, 51–200, 201–1000, and >1000 copies per mL), and death. These health states capture the key changes in viral load and CD4 cell count associated with changes in costs, HIV transmission risk, and quality of life. Patients could change between health states every 6 months. All transitions between health states are possible except when a patient died. Hence, the Markov model was a matrix of 13 rows (current health status) and 13 columns (the health state patients move to; appendix).

Next, we calculated the 6-month transition probabilities of patients on treatment as usual moving between these

health states (the natural course of illness), and the health-care consumption in each health state over a 6-month period. For this, we obtained a longitudinal dataset (2008–15) from the HIV Monitoring Foundation in the Netherlands. We used data from all registered Dutch HIV patients ($n=7347$) who were on treatment for

at least 12 months, and had at least one detectable RNA viral load measurement (>50 copies per mL) in the past 3 years (excluding the first 12 months of treatment), to approximate the inclusion criteria for treatment-experienced patients in the trial. Excess mortality per health state was also derived from this cohort. Utility data (ie, quality of life) per health state were based on CD4 cell count and obtained from another cohort study.²⁷ HIV transmission probabilities per health state based on viral load data were estimated by the lead author of an HIV transmission modelling study,⁸ and multiplied by the lifetime treatment costs for an HIV-infected patient.²⁸ For the societal perspective, the model also included productivity losses per health state based on 600 questionnaires completed by 195 patients during the current trial. The appendix shows these transition probabilities, costs (health-care costs, HIV transmission costs, and productivity loss), and utilities per health state.

To assess the cost-effectiveness of AIMS, data were required on the intervention cost, as well as on the effects of AIMS on the transition probabilities during and after the intervention period. These effects were calculated from the trial data and expressed in relative risks (AIMS vs treatment as usual; appendix). For the AIMS intervention, these relative risks were then applied to the natural course of illness (appendix) over three 6-month cycles, which was the approximate duration of the trial. The cohort of patients receiving AIMS therefore had different probabilities of moving between health states than patients receiving treatment as usual, and therefore costs and outcomes were different.

To define the relative risks of AIMS, we did a base case and two additional scenarios. The base case (scenario 1) included all relative risks (AIMS vs treatment as usual) when at least five transitions occurred in the trial (appendix). Scenario 2 included all available relative risks irrespective of the number of transitions, whereas the more conservative scenario 3 included only relative risks with at least ten transitions. Within these three scenarios, we varied our assumptions about how long the effects of AIMS would last if delivery would be discontinued after the initial 18 months: (1) a linear decrease of the effects of AIMS to zero 18 months after intervention discontinuation; (2) no effect after AIMS discontinuation; and (3) AIMS effects fully sustained for another 18 months, and then to zero. A total of nine scenarios were therefore tested. We also did sensitivity analyses for a health-care perspective (ie, excluding productivity losses) and a time horizon of 10 years instead of lifetime.

For each scenario and sensitivity analysis, we estimated the societal costs and QALYs of AIMS compared with treatment as usual, and calculated the incremental cost-effectiveness ratio (ICER) between AIMS and treatment as usual. The ICER expresses the additional cost of AIMS compared with treatment as usual to obtain one additional QALY. When an intervention is more effective and less costly, the intervention is said to be cost-saving.

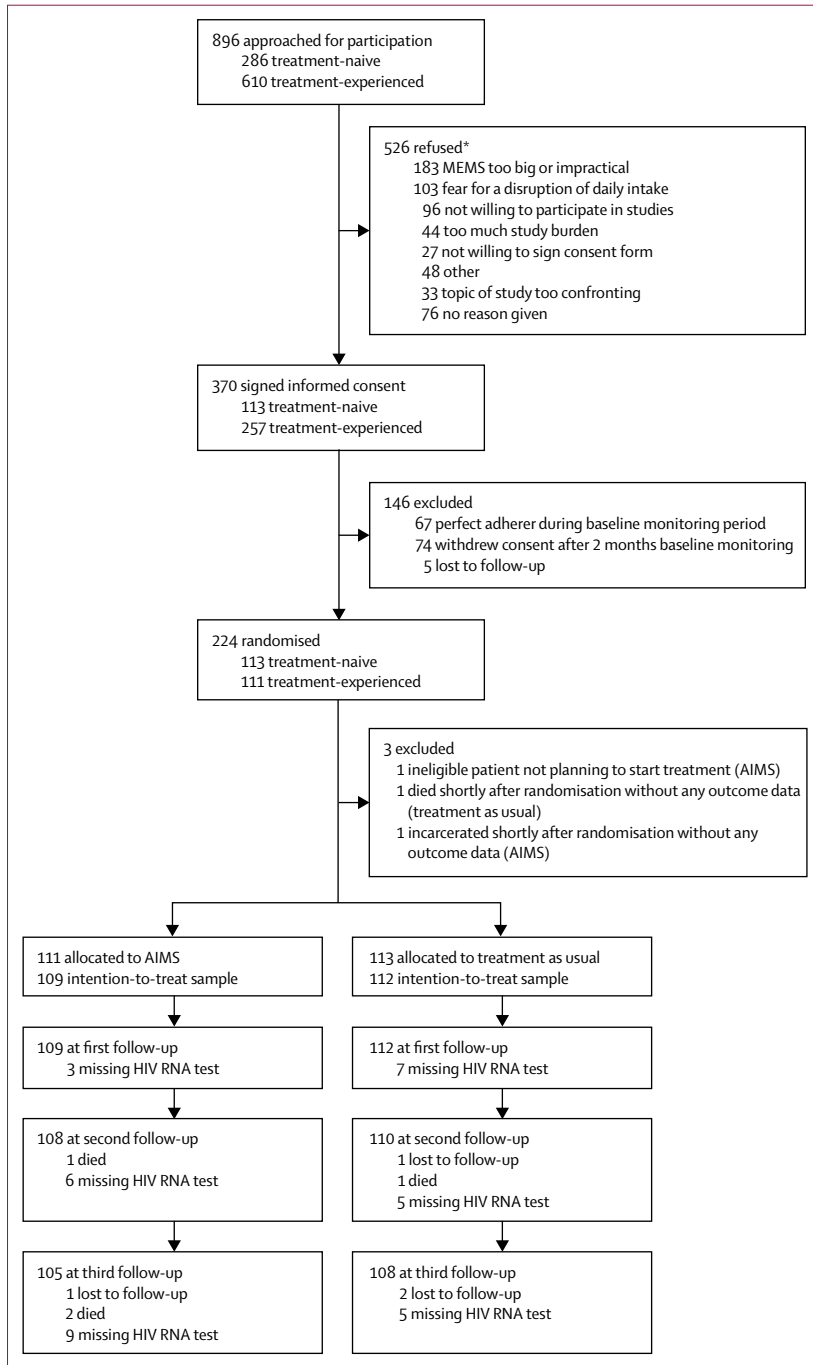


Figure: Trial profile

* Not all patients were willing to disclose a reason for refusal and patients could provide more than one reason for refusing participation.

This trial is registered at ClinicalTrials.gov (number NCT01429142).

Data sharing

The data for the effectiveness analyses are available online (<https://osf.io/wk8vm/>). The data for the cost-effectiveness analyses are in the appendix.

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 to submit for publication.

Results

Patient recruitment started on Sept 1, 2011, and was completed on April 2, 2013. The last patient completed the study on June 16, 2014. 224 patients were randomly assigned to treatment, which was slightly below the target of 230 but dropout was lower than anticipated (ten [4.5%] of 224 instead of 10%). The intent-to-treat sample was comprised of 221 patients, 109 assigned to AIMS and 112 to treatment as usual (figure). One patient who was not planning to start with combination ART was accidentally randomly assigned, and two eligible patients (one in each arm) did not provide any outcome data, because soon after randomisation one died of a cardiovascular event, and the other was incarcerated in another country. Because these reasons were unrelated to group assignment or the dependent variable, team members (MdB, WV, and JMP) masked to group assignment concluded these were valid reasons for exclusion (Cochrane handbook 8.13 and 16.2).²⁹

Most of the intent-to-treat sample was male and white, with a mean age of 44 years (SD 10.9) and a low to medium educational level (table 1). About half the participants were treatment-experienced and of those, 37 (34%) of 109 had a detectable viral load at baseline, confirming that the at-risk selection criteria were useful (viral suppression rate in the general treatment-experienced population in the Netherlands is 91%).³⁰ In a logistic regression analysis, study participation was associated with being treatment-naive ($p < 0.0001$), but study participation could not be predicted by sex, age, ethnic group, CD4 cell count, or viral load ($p > 0.5$ for all).

Mean follow-up was 14.6 months (SD 2.7). The mean number of visits were 3.2 (SD 1.6) for treatment as usual and 3.2 (1.7) for AIMS. The mean number of days between randomisation and follow-up assessments for treatment-experienced versus treatment-naive patients were 125 days (SD 44) versus 177 days (54) for the first follow-up, 270 days (76) versus 306 days (69) for the second, and 447 days (87) versus 454 days (83) for the third visit.

The delivery of treatment as usual took on average 18.8 min; AIMS delivery took on average 29.1 min

	AIMS group (n=109)	Treatment-as-usual group (n=112)
Female	14 (13%)	22 (20%)
Age (years; mean [SD])	45.4 (11.0)	43.3 (10.8)
Ethnic origin		
White	81 (74%)	62 (55%)
Sub-Saharan African	16 (15%)	21 (19%)
Caribbean*	9 (8%)	21 (19%)
Other	3 (3%)	8 (7%)
Education†		
Less than or equivalent of primary education, lower secondary education	47 (43%)	45 (40%)
Higher secondary education, lower vocational education	40 (37%)	39 (35%)
Higher vocational education, university	22 (20%)	28 (25%)
Sexual orientation		
Homosexual	56 (51%)	63 (56%)
Bisexual	11 (10%)	11 (10%)
Heterosexual	42 (39%)	38 (34%)
Treatment status		
Treatment-experienced	52 (48%)	57 (51%)
Treatment-naive	57 (53%)	55 (49%)
CD4 cell count (cells per µL)		
Treatment-experienced patients	520.6 (212.9)	535.1 (226.4)
Treatment-naive patients	379.1 (239.5)	431.8 (200.5)
Plasma HIV-RNA (copies per mL; mean _{log} [SD])		
Treatment-experienced patients	1.74 (0.61)	1.83 (0.83)
Treatment-naive patients	4.83 (0.71)	4.30 (1.01)

Data are n (%) unless otherwise specified. AIMS=Adherence Improving self-Management Strategy. *Surinamese, Latin American, and Antillean. †Categorisation based on the Dutch education system.

Table 1: Baseline characteristics of the intention-to-treat population

(a difference of 10.3 min per visit, with a total of 35 min during the entire follow-up), during which adherence support and also other treatment-as-usual activities were delivered.

AIMS patients received on average 85% of all planned intervention visits, during which 65% of all the intervention elements were delivered (recorded on the intervention website). The main reason recorded for not delivering all intervention elements was adherence having improved during follow-up sessions, without additional issues to address, or because the action or coping plans made during the previous intervention session remained relevant and did not need to be completed again.

There were 634 (95.6%) of 663 completed follow-up viral load measurements and 29 (4.4%) of 663 missing values, which were not associated with group assignment or viral load values at other timepoints in logistic regression models. Missing data were assumed to be missing at random, except for two patients who dropped out of care, discontinued medication after the second follow-up visit, and did not provide a viral load at the third visit. Because AIMS should reduce such non-persistence,³ and non-persistence affects the dependent variable, these

	AIMS	Treatment as usual
Viral load (copies per mL)	35.4 (29.9–42.0)	44.5 (35.5–55.9)
Viral load (% detectable)	9.6 (3.8–15.4)	16.7 (8.2–25.3)
Treatment failure (%)	9.0 (2.4–15.7)	22.8 (11.7–34.0)
CD4 cell count at first follow-up (cells per μ L)	550.9 (520.4–581.4)	519.9 (489.3–550.5)
CD4 cell count at second follow-up (cells per μ L)	562.5 (531.7–593.3)	569.0 (538.7–599.4)
CD4 cell count at third follow-up (cells per μ L)	597.8 (567.1–628.5)	558.4 (528.2–588.6)

Data are marginal risk (95% CI) for detectable viral load and treatment failure, and marginal means (95% CI) for all other variables. For CD4 cell counts, analysis was done per timepoint given the significant time-by-group interaction during the three follow-up measures (ie, effects were different at different follow-up timepoints). AIMS=Adherence Improving self-Management Strategy.

Table 2: Estimated marginal means and risks for viral load and CD4 cell count values

	Lifetime costs	Lifetime QALYs	ICERs
Offset: linear decrease of AIMS effect over 18 months			
Scenario 1 (base case)	€-592	0.034	AIMS dominant
Scenario 2	€-843	0.036	AIMS dominant
Scenario 3	€-412	0.025	AIMS dominant
Offset: effect of AIMS maintained over another 18 months			
Scenario 1	€-793	0.046	AIMS dominant
Scenario 2	€-1117	0.049	AIMS dominant
Scenario 3	€-599	0.035	AIMS dominant
Offset: no effect after stopping AIMS			
Scenario 1	€-375	0.023	AIMS dominant
Scenario 2	€-546	0.024	AIMS dominant
Scenario 3	€-221	0.016	AIMS dominant
Sensitivity analyses (base case)			
Healthcare perspective	€-597	0.034	AIMS dominant
10-year time horizon	€-643	0.028	AIMS dominant

Data from base case analyses and sensitivity analyses. Scenario 1: all relative risks where at least five transitions occurred. Scenario 2: all available transition probabilities irrespective of the number of transitions. Scenario 3: only relative risks with at least ten transitions in total. QALY=costs per quality-adjusted life-years. AIMS=Adherence Improving self-Management Strategy. ICER=incremental cost-effectiveness ratio.

Table 3: Lifetime costs per patient, QALYS, and incremental cost-effectiveness ratios of AIMS compared with treatment as usual

data cannot be treated as missing at random. Based on clinical advice, the two missing values were replaced by the median baseline viral load (50123 copies per mL) and CD4 cell count (400 cells per μ L) of the treatment-naive patients participating in the study. These decisions were based on consensus between team members (MdB, WV, and JMP) masked to group assignment.

Since all 221 patients provided data for at least one follow-up measure, the mixed-effects analyses include the full intent-to-treat sample. The main treatment effects are described here (the results on the covariates and

exploratory subgroup analyses are in the appendix). The three-level mixed-effects regression model showed that there was no indication of a change in the intervention effect across the three follow-up timepoints (time-by-group interaction $F[2409]=0.75$, $p=0.47$). We could therefore examine the between-group contrast across the three follow-up time points, which showed that the intervention was effective ($F[1196]=6.40$, $p=0.012$), while controlling for baseline viral load, treatment experience, and ethnic group. Across the three timepoints (months 5, 10, and 15), log viral load was 1.26 times higher (95% CI 1.04–1.52) in the treatment-as-usual group (estimated marginal mean 44.5 copies per mL [95% CI 35.5–55.9]) than in the AIMS group (estimated marginal mean 35.4 copies per mL [29.9–42.0]). There was no significant variability of the treatment effect across nurses ($p=0.14$). The three-level mixed-effects logistic regression model with detectable versus undetectable viral loads showed the same pattern (χ^2 [df=1] 3.66, $p=0.056$). Overall, patients in the treatment-as-usual group had a 1.89 times higher odds of a detectable viral load across the three timepoints, although this was not significant (95% CI 0.98–3.65). The two-level logistic regression model of treatment failure indicated a significant group difference (χ^2 [df=1] 5.61, $p=0.012$). The odds of treatment failure were 2.99 times higher in treatment as usual (95% CI 1.21–7.38).

The model examining the effects on CD4 cell count revealed a significant time-by-group interaction ($F[2398]=3.09$, $p=0.047$). We therefore examined the group difference for each follow-up timepoint separately. At the first follow-up visit, there was a non-significant increase in CD4 cell count in AIMS compared with treatment as usual (31 cells per μ L, 95% CI -8.37 to 70.37); at the second follow-up visit the treatment-as-usual group caught up (-6.55 cells per μ L, 95% CI -46.03 to 32.92); and at the third follow-up visit CD4 cell counts continued to rise in AIMS but not in treatment as usual, with a significant difference (39.39 cells per μ L, 95% CI 0.10–78.67). Marginal group means and risks for these analyses are in table 2.

In the base-case cost-effectiveness analysis, the Markov model estimated that AIMS reduced lifetime societal costs by €592 per patient and increased QALYs by 0.034 per patient. AIMS was therefore cost-saving (ie, more QALYs and less costs) in the base case. Results were similar for the other scenarios and for the sensitivity analyses with a health-care perspective, and a 10-year time horizon (table 3).

Discussion

To our knowledge, this is the first randomised controlled trial of an HIV treatment adherence intervention that showed a clinically meaningful effect on viral load as well as cost-effectiveness. The economic model showed that AIMS is dominant to treatment as usual, both cheaper and more effective, regardless of the time

horizon (lifetime or 10 years) and perspective (health care or societal). These results were obtained in a heterogeneous sample of HIV-infected patients and HIV clinics, where AIMS was delivered by nurses as part of routine care.

A Cochrane review¹⁵ did not identify trials with a low risk of bias that showed an effect of HIV treatment adherence interventions on adherence and clinical outcomes in high-income settings. Short follow-up periods (<6 months) and a high risk of bias were important reasons for excluding many trials from these analyses. In the design of the current study, we tried to overcome these and other challenges by designing a study with a long follow-up (15 months), extensive efforts to minimise the risk of bias (which is particularly challenging in behavioural trials because masking to treatment assignment is typically not possible), and the detailed reporting of treatment as usual provided to participants.^{11,12,20,23} Although one limitation of our study was the low uptake of MEMS monitoring in the treatment-as-usual group, precluding meaningful secondary adherence analyses, the effects of AIMS on adherence had already been shown in two previous studies.^{17,18} Moreover, because there was no other plausible pathway to improved viral loads in the AIMS group than through improved adherence, this limitation did not influence the overall study conclusions. Second, although dropout rates were low, a 60% study refusal rate could have restricted the generalisability of the findings. We did not, however, find demographic or clinical differences between participants and patients who refused to participate in the study. Most reasons for study refusal (figure) are unlikely to be a barrier to the uptake of AIMS in routine care. Specifically with regard to patients' willingness to use an electronic adherence monitor, we expect substantially fewer issues when AIMS is implemented in routine care, since patients know they will receive AIMS and the feedback, AIMS can be presented as evidence-based care, and ongoing technological developments will make more user-friendly devices available shortly. Indeed, in a pharmacy-based HIV treatment adherence clinic in Lausanne (Switzerland) that uses MEMS monitoring in routine care, refusal of MEMS monitoring is rare in patients in need of adherence support (personal communication with M P Schneider, University of Geneva and University of Lausanne).

Similarly, findings from a recent systematic review identified an absence of evidence on the cost-effectiveness of HIV treatment adherence interventions, because it identified only one cost-effective HIV treatment adherence intervention assessed in a randomised clinical trial and subjected to a high-quality economic assessment.¹⁶ However, the study did not report evidence of intervention effectiveness, or the content of the control and experimental interventions, so generalisability, replicability, and scalability of the intervention were unclear.¹⁶ In our study,

the aim was to obtain and report this information, and do a similarly high-quality economic evaluation. Given the absence of a suitable and up-to-date Markov model for that purpose, we developed a new model using ISPOR-SMDM guidelines.²⁶ Up-to-date cohort data (2008–15) from all registered HIV patients in the Netherlands meeting our inclusion criteria were used to describe the natural course of illness. Besides effects on costs (health care and productivity) and quality of life, the model also incorporated HIV transmissions avoided, given the evidence that lower viral loads reduce transmission risk.^{2,8} Although a limitation of the current model was the absence of trial data to populate the full health state transition matrix, the finding that AIMS was more effective and saves resources was robust because all scenarios and sensitivity analyses produced the same result.

The cumulative results of our multicentre trial and the previous pilot study and single-centre trial show that AIMS requires few resources, is feasible to deliver in routine care, and is acceptable to health-care providers and patients (although more patient-friendly electronic monitoring devices are desirable). Moreover, they showed relevant and replicable effects of AIMS on adherence (in the pilot study and single-centre trial) and viral load (in the single-centre and multicentre trials).^{17,18} On average patients receiving treatment as usual had a 1.26 higher log viral load than AIMS patients, and AIMS reduced the risk of treatment failure (two consecutive detectable viral loads) by 61% (22.8% vs 9.0%). These effects were similar for treatment-naive and treatment-experienced patients at-risk for viral rebound (appendix), and despite some risk of contamination and the medium-to-high-quality treatment-as-usual adherence support provided to the control group. The economic analysis showed that AIMS is dominant and that when the intervention is provided to 10 000 patients over a period of 18 months, the approximate savings would be €5 920 000 while 340 QALYs would be gained. Because these results have been obtained in a heterogeneous sample of patients and clinics, we would expect at least similar effects if AIMS was rolled out nationally in the Netherlands, and in other countries where HIV care is organised in a similar manner (ie, western Europe). Nationwide training of health-care professionals, reimbursement of electronic monitors, and adoption of AIMS in national HIV-treatment guidelines in the Netherlands is currently being negotiated as a first step.

In conclusion, our pragmatic, randomised controlled trial and economic model showed that AIMS was feasible to deliver in routine care, reduced viral load, increased QALYs, and saved resources. To our knowledge, this is the first HIV treatment adherence intervention for which such an evidence base has been established. The AIMS intervention should be scalable and the results generalisable to the wider population of patients and HIV clinics—at least in high-income settings. Implementation of AIMS in routine HIV clinical care is therefore strongly recommended.

Contributors

MdB, JMP, SMAAE, and WV designed the study and obtained project funding. All authors were involved in defining inclusion or exclusion criteria, measures to protect against bias, and data collection procedures. All authors except WV and SMAAE were involved in data collection for the effectiveness or cost-effectiveness analyses. MdB, EJMO, JMP, and WV were mainly responsible for the effectiveness analyses. MH, EJMO, and MdB were mainly responsible for the cost-effectiveness analyses. All other authors critically examined the analyses and findings. MdB, EJMO, JMP, and MH drafted the report. All other authors critically read and commented on draft versions of the report, and approved the final version.

Declaration of interests

We declare no competing interests.

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