Cost-Effectiveness and Cost-Utility of the Adherence Improving self-Management Strategy (AIMS) in HIV-Care: A Trial-Based Economic Evaluation

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Abstract

Objectives: Several promising HIV-treatment adherence interventions have been identified, but data about their cost-effectiveness is lacking. This study examines the trial-based cost-effectiveness and cost-utility of the proven-effective Adherence Improving self-Management Strategy (AIMS), from a societal perspective, with 15 months' time horizon.

Methods: Treatment-naïve, and treatment-experienced patients at-risk for viral rebound were randomized to treatment-as-usual (TAU) or AIMS in a multi-center randomized controlled trial, in the Netherlands. AIMS is a nurse-led, 1-on-1 self-management intervention incorporating feedback from electronic medication monitors, delivered during routine clinical visits. Main outcomes were costs per reduction in $\log_{10}$ viral load, treatment failure (two consecutive detectable viral loads), and quality-adjusted life years.

Results: 223 patients were randomized. From a societal perspective, AIMS was slightly more expensive than TAU but also more effective, resulting in an ICER of €549 per reduction in $\log_{10}$ viral load and €1,659 per percentage decrease in treatment failure. In terms of QALYs, AIMS resulted in higher costs but more QALYs compared to TAU, which resulted in an ICER of €27,759 per QALY gained. From a healthcare perspective, AIMS dominated TAU. Additional sensitivity analyses addressing key limitations of the base case analyses also suggested that AIMS dominates TAU.

Conclusions: The base case analyses suggests that over a period of 15 months, AIMS may be costlier, but also more effective than TAU. All additional analyses suggest that AIMS is cheaper and more effective than TAU. This trial-based economic evaluation confirms and complements a model-based economic evaluation with a life-time horizon showing that AIMS is cost-effective.

INTRODUCTION

Adherence to combination Antiretroviral Therapy (cART) is crucial for successful treatment of HIV.[1] However, non-adherence to cART is common,[2,3] can lead to viral rebound and resistance,[4-8] and an increased risk of forward transmission.[9,10] Moreover, non-adherence has been associated with a substantial economic burden, as it can lead to more health care consumption and productivity losses.[11-16] Interventions that successfully increase adherence and viral control may therefore yield benefits for both patient and public health, and reduce the societal burden of non-adherence to cART. However, despite the large number of adherence interventions that have been evaluated, there is no robust evidence that effective adherence interventions are also cost-effective.[17-26] The objective of the current study is to examine the cost-effectiveness of the Adherence Improving self-Management Strategy (AIMS): a face-to-face intervention using MEMS data delivered by trained HIV-nurses during routine clinical visits. AIMS requires minimal resources, yet, as one of the few adherence interventions in HIV, with robust evidence on improving adherence and viral load.[2,27,28]

A pilot-study and a single-center randomized controlled trial demonstrated the acceptability and feasibility of AIMS, and positive effects on adherence and viral load.[2,27] Next, a multi-center pragmatic randomized controlled trial showed that AIMS was effective in reducing viral load and treatment failure.[28,29] A Markov model evaluating the cost-effectiveness of AIMS with a 10 year and life-time horizon, suggested that AIMS is cost-effective, and even cost-saving.[28] It is important, however, to combine results from model-based economic evaluations with trial-based economic evaluations, which maintain the integrity of randomization and make no assumptions about data beyond the observation period. The present study reports on the trial-based economic evaluation, piggy-bagged on the multi-center trial, examining the cost-effectiveness and cost-utility of AIMS compared to treatment-as-usual (TAU) over the 15-month trial follow-up period.

METHODS

The study protocol has been published,[30] and registered online on clinicaltrials.gov (Identifier: NCT01429142). The RATIONALE Table has been used to describe in detail the strategies utilized for

reducing the risk of bias.[31] The effectiveness paper including a Markov economic model is published elsewhere.[29]

Study Design and Patient Recruitment

Patients were recruited by 21 HIV-nurses from seven Dutch HIV-clinics from June 2011 to March 2013, with an average follow-up of 14.5 months. Treatment-naïve and treatment-experienced patients at risk for viral rebound (i.e., a recent detectable viral load and suboptimal adherence) were eligible for participation.[30] Patients were randomized to AIMS or TAU, using block randomization to balance intervention and control patients within nurses. The randomization procedure was stratified for treatment experience. Please see above-mentioned sources for further details.

Treatment-As-Usual

TAU adherence support was comprised of 1-on-1 nurse-support of medium to high standard compared with meta-analyses on this topic [26,32,33] Nurses routinely delivered tailored information and medication intake instructions, feedback on clinical outcomes, encouraged adherence, developed individually-tailored medication plans with reminders, offered dose organizers and reminder devices/SMS services, explored social support, and discussed adherence problems and solutions.

Intervention

AIMS is a nurse-delivered intervention designed to fit in routine clinical care, and employs educational, motivational, action planning, and self-management techniques. An important element is the measurement of medication intake with an electronic medication monitor (Medication Event Monitoring System, AARDEX). These data are discussed with patients to identify causes of and tailored solutions for suboptimal adherence (see [2,27,30]). Nurses were trained in AIMS for approximately 18 hours. In this trial, patients were expected to receive the intervention at least three times: at baseline, and around month 5 and 10.

Sample Size

A sample of 230 randomized patients was required to obtain 80% power to detect a significant intervention effect on viral load for at least one of three time points with alpha = .05 (two-sided)), using a Bonferroni correction and assuming a maximum dropout of 10%.[30]

Identification, Measurement, and Valuation of Costs

The cost-effectiveness and cost-utility analyses were conducted from a societal perspective.[34] The following cost components were measured: (a) direct costs (e.g, intervention costs and other health care costs), and (b) indirect costs (e.g, informal care costs, productivity losses).

Medical records were used to collect information on all health care consumed in the hospital where patients also attended the HIV clinic. Paper-and-pencil questionnaires were used to assess all other health care consumption (e.g., visits to the general practitioner) and the indirect costs.

Treatment-experienced patients were asked to complete the questionnaires during four planned study visits: at baseline, around month 5, 10, and 15. Treatment-naïve patients completed five questionnaires, as they visit the clinic more frequently during the initial stages of treatment (at baseline, and around month 3, 6, 10 and 15). The recall period was standardized at 4 months for the baseline and last follow-up questionnaires. The recall period for the intermediate questionnaires was allowed to vary, as questionnaires were handed over during clinic visits and inter-visit intervals can vary between patients. For the baseline and follow-up questionnaires, HIV-nurses reminded patients to complete the questionnaire if it was not returned within one week. This was not done for the intermediate questionnaires purposely, as additional nurse-patient contacts were deemed to possibly interfere with adherence behavior.

Analyses were performed according to the Dutch manual for cost analysis in health care research.[35] Medication costs were calculated using prices based on Daily Defined Dosage (see: www.medicijnkosten.nl). Prices of informal care, absence of school, and domestic activities were based on the Dutch minimum wage.[35] Productivity losses were calculated according to the friction cost method, based on the mean income of the Dutch population by age and gender.[35] Costs were expressed in Euros and converted to the price year 2013. Discounting was considered unnecessary given the 15-month follow-up period.

Identification, Measurement, and Valuation of Effects

The primary outcome measure for the cost-effectiveness analysis was the $\log_{10}$ plasma viral load. An additional and clinically more meaningful outcome measure was treatment failure, defined as a detectable viral load at 2 consecutive measures (±5 month intervals).

The outcome measure for the cost-utility analysis were utilities converted to quality-adjusted life years (QALYs). Utilities were measured using the Short Form Health Survey version 2 (SF-12v2) [36], to allow for comparison of our results with economic evaluations conducted in other conditions [34]. QALYs were calculated by means of the "under the curve method," in which the time in a certain health state was multiplied by the utility of this health state.[31]

Analyses

All analyses were performed based on intention-to-treat. Missing questionnaire data met missing at random assumptions, as missing values were unrelated to demographics, plasma viral load, utilities, health care consumption components, or group assignment. Missing data were imputed using expectation maximization (for details on data imputation, see Appendix S1).

As in the effectiveness analyses,[29] it was planned a-priori to control for baseline values of the dependent variables, for which we used regression-based adjustments.[38,39] The base case analysis considers the costs and benefits over the full trial period.

Both the incremental costs and incremental effects were used to calculate the incremental cost-effectiveness ratio (ICER). The ICER was calculated as $(C^{intervention}–C^{control\ group})/(E^{intervention}–E^{control\ group})$, where 'C' reflects the average participant costs and 'E' are the effects or the utilities in the AIMS and TAU arms. The ICER represents the additional costs that AIMS imposes over TAU, with respect to the effects it delivers. To handle stochastic uncertainty in the cost and effect data, seemingly unrelated regression equations (SURE) were bootstrapped (5000 times) to allow for correlated residuals of the cost and utility equations. The regression also adjusted for baseline $\log_{10}$ viral load and patients' treatment experience (i.e., treatment naïve or experienced). The ICERs were plotted on a cost-effectiveness plane to capture the uncertainty in the ICER estimate.

The choice for a treatment depends on what society is prepared to pay for a gain in one QALY, the so-called ceiling ratio. In the present study, we used an accepted Dutch threshold (for preventive interventions) of €18,000 per QALY.[40] The AIMS-intervention was deemed to be cost-effective, if the ICER of AIMS fell below this threshold. Cost-Effectiveness Acceptability Curves (CEACs) were constructed to show the probability that AIMS is cost-effective given different ceiling ratios. One patient

reported an unrealistically high number of GP (home) visits at baseline (z =111.7), hence this item was set to missing and imputed in the same way as all the other missing values.

The syntaxes and raw data are available at [the link I provided you].

Sensitivity Analyses

We conducted several sensitivity analyses. Two to address key limitations of the base-case analyses, i.e., a high percentage of missing questionnaire data (i.e., 50%) and variable recall periods for questionnaires at intermediate time points. A first sensitivity analysis used only the baseline and follow-up data (25% missing data and standardized recall period). A second sensitivity analysis examined whether individual means imputation provided similar results to expectation maximization.[43] This was done only for the cost-utility analyses as the viral load data were available for nearly all patients. Additionally, we ran a sensitivity analyses that also considered the costs saved through reduced risk of HIV transmission. HIV transmission probabilities based on viral load data were provided by the lead author of an HIV transmission modeling study,[10] and multiplied by the lifetime costs for an HIV-infected patient.[44] Lastly, a sensitivity analysis adopting a healthcare perspective was performed (using direct costs only). This is the preferred perspective in some countries, utilizes mostly objective and complete data from medical databases, and is not influenced by a small number of patients in this trial reporting very high productivity losses.

RESULTS

Baseline Sample Characteristics

In total, 223 patients were randomized (intervention, *N*=110; control group, *N*=113; see Table 1). Their mean age was 44 years (*SD* = 10.89), most participants were male (84%), and Caucasian (65%). Treatment-naïve patients had high viral loads (M_{log} copies/ml=4.57, *SD*=0.90) and an average CD4+ cell count of 395/ul (*SD*=226.7). Of the treatment-experienced patients, 34% had a detectable viral load at baseline (M_{log}=1.79, *SD*=0.73) and they had a higher CD4+ cell count than treatment-naïve patients (*M*=537/ul, *SD*=228.1). The mean number of visits during follow-up were 3.2 (SD=1.6) for TAU and 3.2 (1.7) for AIMS. See Figure 1 for the CONSORT flow-chart.

The total baseline costs were similar for the intervention (mean[sd] €4,743[€5,760]) and control participants (mean[sd] = €4,554[€1517]). The baseline quality of life scores were similar for intervention and control participants (mean[sd] 0.705[0.113] and mean[sd] 0.698[0.119], respectively).

Costs

The total intervention costs were €82.61 per patient (see Table 1 for a breakdown and Appendix S2 for additional information).

During follow-up, direct costs were slightly higher in the control versus intervention group (mean[sd] €13,284[5026] and €12,741[5495], respectively). Indirect costs on the other hand were slightly higher for the intervention versus the control group (mean[sd] €5,476[8646**]** and €4576[6894] respectively). The total costs were almost identical between groups (intervention versus control mean[sd] €18,217[11617] and €17,861[9027], respectively).

---Table_1---

---Table_2---

---Figure_1---

Cost-Effectiveness Analyses

During follow-up, the intervention and control group had a reduction of plasma $\log_{10}$ viral load of 1.74 (SD=1.75) and 1.34 (SD=1.67) respectively. In terms of QALYs, the intervention group had an average utility of 0.908 (SD= 0.12) compared to 0.898 (SD=0.12) in the control group. Lastly, fewer intervention patients failed on treatment (8 of 110 (7.3%) versus 19 of 113 (16.8%) control patients). ICERs were generated for $\log_{10}$ viral load and treatment failure. Both ICERs showed that AIMS was slightly more expensive than TAU but also more effective, resulting in an ICER of €549 per reduction in $\log_{10}$ viral load and €1,659 per percentage decrease in treatment failure (see Figure 2a & 2b). The CEAC for $\log_{10}$ viral load is shown in Figure 3a. If we are willing to pay €5000 or more for (on average) a point decrease in $\log_{10}$ viral load, the probability that AIMS is cost-effective is 82%. The CEAC for treatment failure shows that the probability that AIMS is cost-effective from a societal perspective is 75% at a ceiling ratio of €10,000 or higher per percentage decrease in treatment failure (see Figure 3b).

Cost-Utility Analysis

An ICER was generated for the cost-utility base-case analysis (i.e., including all time points), which showed that that AIMS resulted in higher costs compared to TAU but also in more QALYs, giving an ICER of €27,759 per QALY gained (see Figure 2c). The CEAC showed a 46% to 55% probability that AIMS is cost-effective from a societal perspective for ceiling ratios ranging from €0 per QALY to €75,000 per QALY.

Sensitivity Analyses

The first sensitivity analysis using only baseline and follow-up data, resulted in a dominant ICER (i.e. AIMS was more effective and is cheaper than TAU). The CEAC showed an 74% to 72% probability that AIMS is cost-effective regardless of the ceiling ratios. The second sensitivity analysis using individual mean imputation showed similar results. The CE-plane and CEACs for these analyses can be found in Appendix S3.

The third sensitivity analysis including the reduced risk of HIV transmission, showed lower costs and higher effects (i.e. AIMS dominated TAU) for all outcomes (see Figure 2d-f). Likewise, the analyses from a healthcare perspective produced dominant ICERs (see Figure 2g-i).

The percentage of bootstrapped ICERs which are covered for each quadrant of the cost-effectiveness plane are displayed in Figure 2d-i. The CEACs corresponding to each sensitivity analyses are provided in Figure 3d-i.

---Figure_2---

---Figure_3---

DISCUSSION

This multi-center randomized controlled trial investigated the cost-effectiveness and cost-utility of the Adherence Improving self-Management Strategy compared to TAU. AIMS resulted in a small gain in QALYs over the 15 months follow-up, a decrease in viral load, and fewer patients with treatment failure. The probability that AIMS is cost-effective using plasma viral load as outcome parameter ultimately depends on the willingness-to-pay for a point decrease in plasma $\log_{10}$ viral load or a treatment failure prevented. For cost-utility, the the base case analysis produced an ICER above the willingness-to-pay threshold for preventive interventions in the Netherlands. This is unsurprising given the restricted

follow-up period of 15 months. All sensitivity analyses, however, revealed considerably more favorable probabilities of AIMS being cost-effective. In particular, when using only baseline and follow-up data (less missing data and with standardized recall periods), adopting a healthcare perspective, or when accounting for HIV transmissions prevented, the analyses all suggest that AIMS is more effective and cheaper than TAU.

The current study is complementary to a recently published Markov model evaluating the cost-effectiveness of AIMS.[28] The Markov was conducted to estimate the costs per QALY over longer follow-up periods (i.e., 10 years and lifetime), and suggested that AIMS was dominant. The complementary value of the current trial-based economic evaluation is that it retains the integrity of randomization, does not make assumptions about long-term effects as it utilizes observed data, and that it includes short-term outcome measures (costs per viral load gain), which may be more directly relevant to clinicians. Combined, the trial-based and model-based analyses suggest that AIMS is likely cost-effective and potentially even cost-saving, regardless of the perspective.

It is challenging to compare the results of this trial with other proven cost-effective HIV treatment adherence interventions, as to our knowledge there has only been one previous cost-effectiveness analysis.[45] The authors of that study compared twice-weekly home visits with standard care, and concluded that this intervention was cost-effective using a model-based cost-effectiveness analysis. The quality of their economic evaluation was judged to be high in a systematic review.[30] Limitations were that the authors did not describe the content of the intervention, the comparator, and that no evidence of effectiveness was provided. Our aim was to also conduct a high-quality evaluation by following the Drummond checklist[34] and guidelines for cost-effectiveness evaluations.[46] The AIMS intervention has been described in detail in previous publications and demonstrated reproducible effects on adherence and plasma viral load (see Appendix S4).[2,27,30] Moreover, the study was designed with a minimal risk of bias,[31] and the comparator arm receiving TAU was described in detail.[2,29,33]

Another strength of the current trial and economic evaluation is the heterogeneity of the study sample in terms of treatment experience, physical and mental comorbidities, educational level, and ethnicity; and that the intervention was delivered by HIV-nurses working in academic and non-academic settings, and with variable quality of TAU and nursing experience.[33] These characteristics suggest

that the results may be generalizable to other settings in a similar (publically funded) health care context. Transferability of costs to other health care systems cannot be guaranteed without careful consideration.[47]

This study also had several limitations. First, part of our costs data relied on self-reports and although the questionnaire response rates (75%) were acceptable at baseline and follow-up, the non-response was a concern for the intermediate questionnaires (approximately 50%). the various sensitivity analyses suggest that this has resulted in a conservative estimate of cost-effectiveness in the base-case analysis. Second, the pre-planned base case analyses did not incorporate the assumed reduction in forward transmission risk, but studies have now convincingly proven the societal impact (both in clinical and economic terms) of preventing onward transmission of HIV.[10,29] It must be noted that the sensitivity analysis in which HIV transmission was included, employs a relatively crude method for calculating transmission risk (i.e, a cumulative probability rather than a dynamic transmission model). Finally, we used the observed viral loads as input in this study. These are slightly different from those used in the Markov model, which used relative risks estimated from a model that adjusted for additional covariates.[29]

In conclusion, the primary analysis suggests that AIMS is more costly but also more effective, and may possess a favorable profile in terms of cost-effectiveness (costs per viral load gain) and cost-utility (costs per QALY). Sensitivity analyses designed to address missing data limitations in the base case produced more favorable cost-utility probabilities for AIMS. Additional sensitivity analyses showed that when onward viral transmission is considered or a healthcare perspective is adopted, AIMS is cheaper and more effective than TAU (i.e., dominant) in all scenarios. The current trial-based economic evaluation complements the model-based economic evaluation with a longer horizon, showing that AIMS is cost-effective. Combined these studies suggests that incorporating AIMS in routine HIV-care could lead to relevant benefits for only a modest investment.

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Written informed consent was obtained from each patient. The study has been approved by the ethics committee of each participating center.

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Tables

Table 1: Baseline Characteristics

Characteristic	*Intervention group (N = 110)*	*Control group (N = 113)*
Female, *n* (%)	14 (12.8%)	22 (19.6%)
Age, years, mean (*SD*)	45.4 (11.0)	43.4 (10.8)
Ethnicity, *n* (%)		
Caucasian	81 (73.7%)	63 (55.7%)
African	16 (14.5%)	21 (18.6%)
Caribbean [a]	10 (9.1%)	21 (18.6%)
Other	3 (2.7%)	8 (7.1%)
Education,[b] *n* (%)		
Low	48 (43.6%)	46 (40.7%)
Medium	40 (36.4%)	39 (34.5%)
High	22 (20.0%)	28 (24.8%)
Sexual orientation, *n* (%)		
Homosexual	57 (51.8%)	64 (56.6%)
Bisexual	11 (10.0%)	11 (9.7%)
Heterosexual	42 (38.2%)	38 (36.7%)
Treatment-experienced, *n* (%)	52 (47.3%)	58 (51.3%)
CD4+ cell count, cells/mm^3, mean (*SD*)		
Treatment-experienced	520.6 (212.9)	530.1 (205.8)
Treatment-naïve	381.2 (239.9)	431.8 (200.5)
Plasma HIV-RNA, $mean_{log}$ (*SD*)		
Treatment-experienced	1.74 (0.61)	1.83 (0.82)
Treatment-naïve	4.83 (0.70)	4.30 (1.01)

Study outcome	*Costs per unit*	*Mean (SD)*	*Mean (SD)*
Total direct costs[c]		**€2361.11 (1998.43)**	**€2573.32 (2171.75)**
GP consultation			
Visit	€28.00/consultation	€36.95 (37.79)	€39.33 (45.51)
Home visit	€43.00/consultation	€1.58 (9.92)	€0.65 (4.42)
Telephone consultation	€14.00/consultation	€3.50 (8.87)	€3.06 (8.26)
Practice nurse			
Visit	€14.00/consultation	€4.92 (10.60)	€5.85 (10.8)
Home visit	€9.00/consultation	€0.00 (0.00)	€0.00 (0.00)
Telephone consultation	€4.50/consultation	€0.53 (1.89)	€0.44 (1.82)
ID Physician	€72.00/consultation	€86.92 (47.88)	€87.39 (59.01)
Other medical specialist	€72.00/consultation	€33.49 (77.62)	€26.35 (40.89)
Physiotherapist	€36.00/consultation	€25.41 (6.88)	€41.34 (144.66)
Acupuncture	€36.00/consultation	€1.27 (7.55)	€2.48 (22.12)
Homeopathy	€36.00/consultation	€0.87 (5.25)	€0.10 (0.28)
Psychologist	€80.00/consultation	€59.67 (170.24)	€38.64 (97.13)
Psychiatrist	€103.00/consultation	€10.47 (49.81)	€17.22 (90.24)
Psychotherapist	€77.00/consultation	€6.95 (19.95)	€17.93 (127.08)
Social worker	€65.00/consultation	€6.57 (30.96)	€14.13 (43.14)
Medication	Price/drug	€1515.31 (1936.50)	€1838.81 (2083)
Hospitalization	€457.00/night	€252.03 (841.34)	€148.14 (554.34)
Home care	€70.00/hour	€45.76 (184.39)	€102.89 (527.55)
Plasma HIV-RNA test	€150.00/test	€160.91 (52.63)	€163.27 (55.10)
CD4+ cell count test	€5.21/test	€5.77 (2.64)	€6.02 (2.85)
Drug level test	€25.00/test	€0.23 (2.38)	€0.66 (4.04)

Total indirect costs		**€2382.10 (5458.71)**	**€1980.63 (5254.14)**
Informal care	€12.50/hour	€102.03 (382.73)	€60.16 (220.00
Productivity losses[h]	Costs/hour[h]	€1979.87 (5005.84)	€1410.75 (4120.89)
School absence	€12.50/hour	€22.93 (70.50)	€80.88 (716.54)
Unable to do domestic activities	€12.50/hour	€306.33 (802.63)	€451.46 (1517.17)
Total costs		**€4743.21 (5760.15)**	**€4553.95 (5640.36)**
Utilities	N/A	0.705 (0.113)	0.698 (0.119)
Plasma HIV-RNA_{log}	N/A	3.37 (1.68)	3.03 (1.54)

[a] Surinamese, Latin American, and Antillean.

[b] Categorization was based on the Dutch education system, ranging from (a) low: (less than) primary education, lower secondary education; (b) medium: higher secondary education, lower vocational education; (c) high: higher vocational education, university.

[c] The recall period was 4 months.

[d] €38.33 per monitor per year is based on a price of €115 per MEMS-cap (when ordering 1,000 MEMS-caps) with a battery life of three years. The software required to read MEMS-monitors and to run the intervention is included in this price.

[e] Total training costs were €7.52 (based on the tariff of a motivational interview trainer and productivity losses of HIV-nurses for attending the training). The total costs were spread over all eligible patients in the seven participating clinics (N = 1826).

[f] Total costs for booster sessions in pairs of two nurses were €5940 (based on the tariff of a motivational interview trainer and productivity losses of HIV-nurses for attending the booster session). The total costs were spread over all eligible patients in the seven participating clinics (N = 1826).

[g] The average additional time for an intervention visit was 10.3 minutes.

[h] Based on the mean income in the Netherlands, corrected for age and gender.

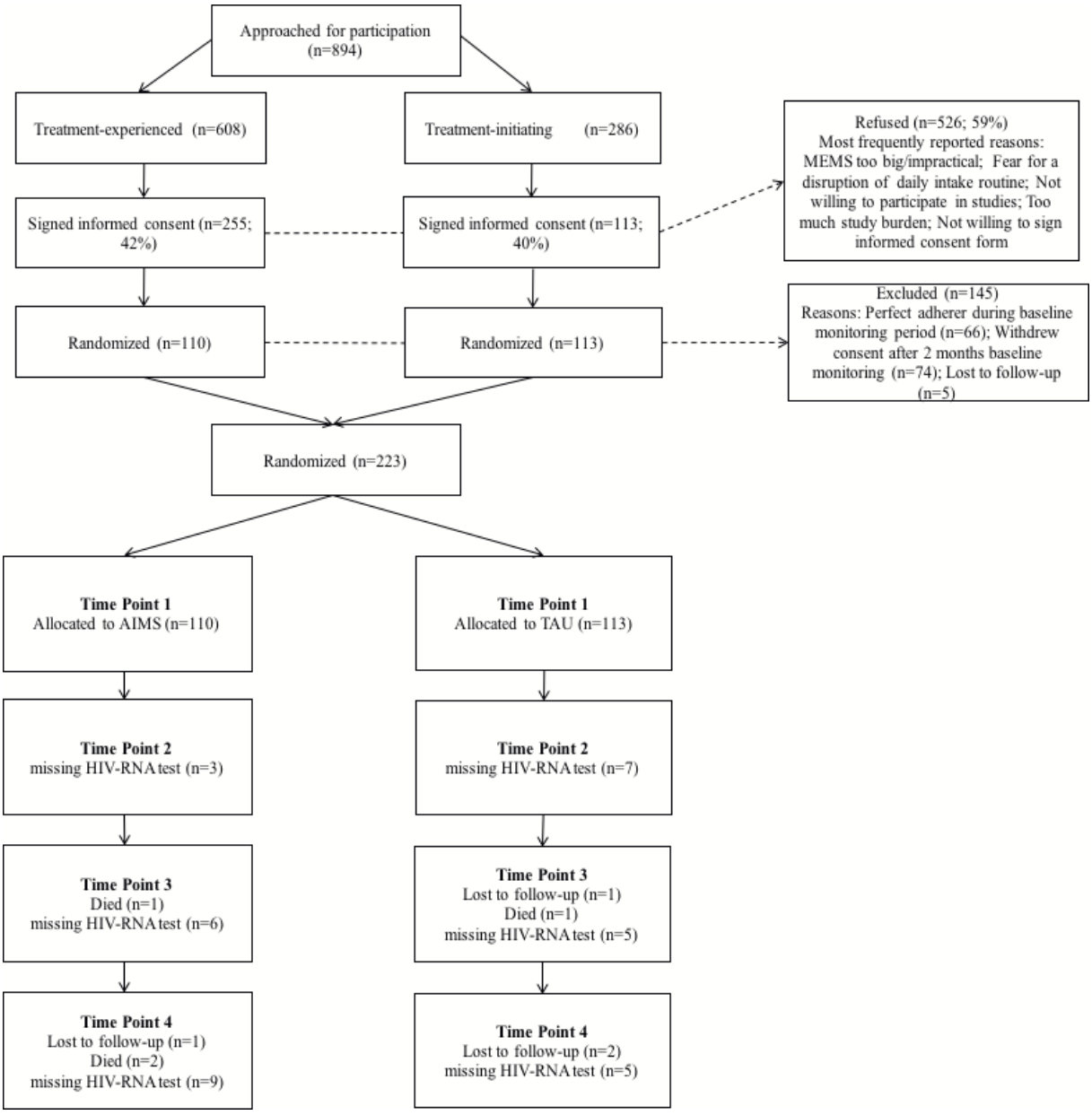
Table 2: Mean Per-Participant Costs, Effects, and Utilities by Condition during the Follow-Up Period (raw costs without baseline correction)

	Follow-up costs and effects (12 months), Mean (SD)	
	Intervention group (N = 110)	*Control group (N = 113)*
Per-participant direct costs	**€12740.81 (5495.21)**	**€ 13284.38 (5025,55)**
Electronic monitors	€38.33 (0.00)	€0.00 (0.00)
Training costs AIMS	€7.52 (0.00)	€0.00 (0.00)
Booster training sessions AIMS	€3.25 (0.00)	€0.00 (0.00)
Average additional minutes intervention visit	€33.65 (0.00)	€0.00 (0.00)
GP consultation		
Visit	€66.96 (87.58)	€79.75 (109.12)
Home visit	€0.84 (2.16)	€2.98 (22.04)
Telephone consultation	€6.16 (12.35)	€4.11 (6.98)
Practice nurse		
Visit	€8.32 (11.03)	€11.04 (14.93)
Home visit	€0.00 (0.00)	€0.00 (0.00)
Telephone consultation	€2.10 (3.95)	€0.95 (1.09)
ID Physician	€271.45 (148.88)	€268.40 (145.79)
Other medical specialist	€109.72 (150.95)	€114.43 (213.87)
Physiotherapist	€57.88 (152.33)	€75.38 (190.01)
Acupuncture	€9.01 (37.71)	€7.26 (27.14)
Homeopathy	€1.56 (5.05)	€4.97 (29.70)
Psychologist	€320.17 (1146.54)	€262.57 (1255.37)
Psychiatrist	€371.80 (2692.56)	€296.14 (1664.89)
Psychotherapist	€27.84 (95.49)	€25.57 (76.86)
Social worker	€42.91 (118.08)	€48.46 (103.79)

Medication	€10460.87 (3974.37)	€11171.27 (3916.38)
Hospitalization	€247.25 (1107.08)	€216.19 (630.38)
Home care	€11.33 (33.47)	€75.15 (424.99)
Plasma HIV-RNA test	€556.36 (172.82)	€541.59 (180.88)
CD4+ cell count test	€16.95 (6.98)	€16.06 (6.76)
Drug level test	€9.55 (16.58)	€6.64 (12.51)
Per-participant indirect costs	**€5476.23 (8646.39)**	**€4576.36 (6893.69)**
Informal care	€253.46 (741.85)	€247.84 (643.32)
Productivity losses	€3313.83 (5596.09)	€2615.11 (3884.49)
School absence	€291.10 (810.63)	€506.43 (2599.29)
Unable to do domestic activities	€1617.85 (4268.08)	€1206.97 (2757.30)
Per-participant total costs	**€18217.04 (11616.57)**	**€17860.74 (9026.77)**
Outcomes		
Utilities[a]	0.908 (0.12)	0.898 (0.12)
Plasma HIV-RNA		
Reduction in plasma HIV-RNA_{log} during follow-up	1.74 (1.75)	1.34 (1.67)
Number of patients failed on treatment	8 of 110 patients (7.3%)	19 of 113 patients (16.8%)

[a] Maximum QALY over 15 months is 15/12 = 1.25

Figure 1: CONSORT Diagram Summarizing the Progress of Patients throughout the Trial



N.B. The intention-to-treat sample comprised two patients who were excluded in the effectiveness analysis.[28] These two patients did not deliver any viral load data (and therefore excluded in the effectiveness analysis), but they did complete questionnaires on health care consumption and utilities (and therefore included in the cost-effectiveness analyses).

Figure 2: Cost-Effectiveness and Cost-Utility Planes for the Base Cases (row 1; a-c) and two Sensitivity Analyses (row 2; d-f: including onward transmission, row 3;g-i: healthcare perspective); for Log_{10} viral load (column 1), treatment failure (column 2), and QALYs (column 3). Costs are in Euros, based on the bootstrapped ICERs (5000 times).

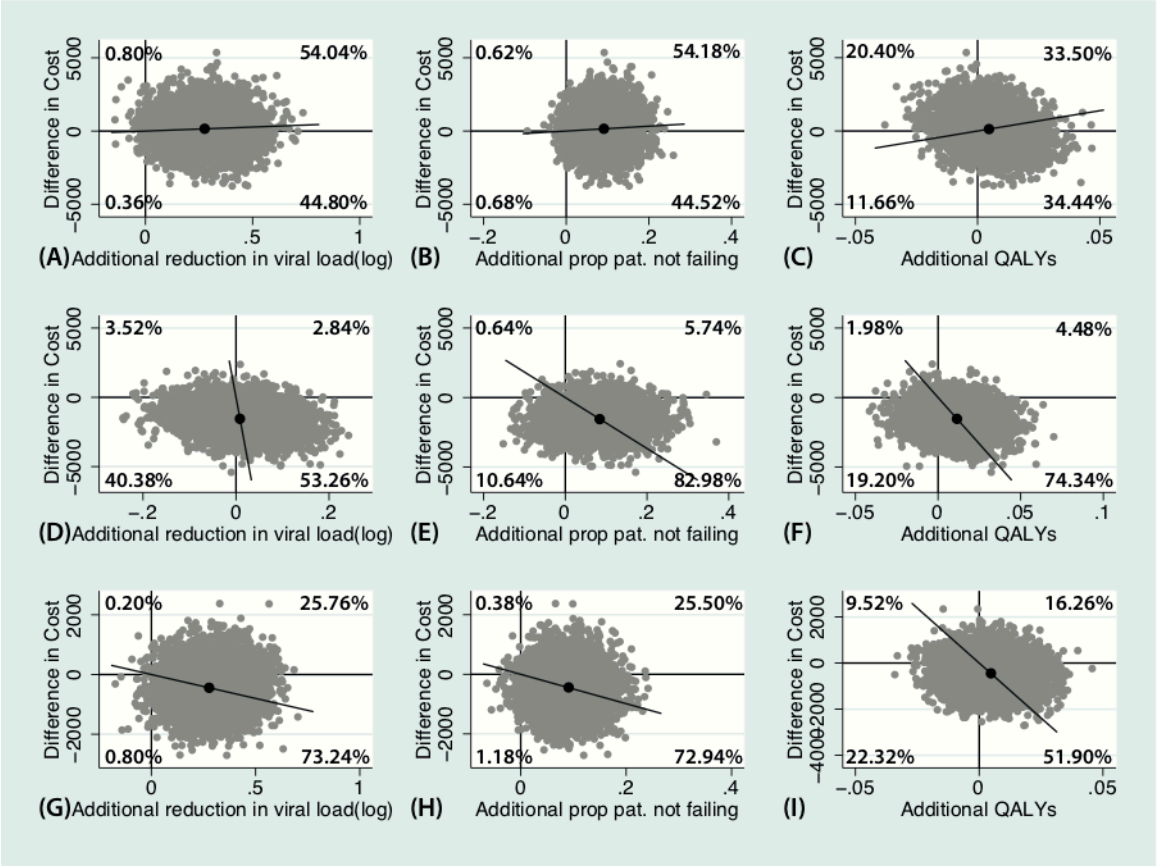
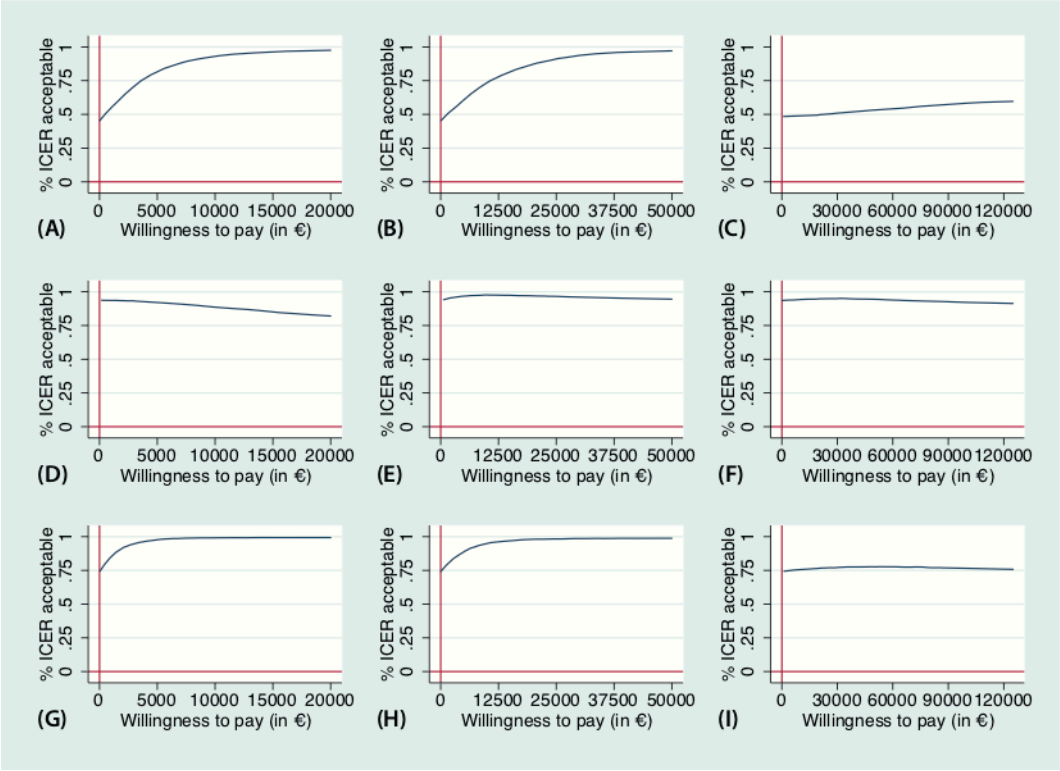


Figure 3 Cost-effectiveness acceptability curves for cost-effectiveness and cost-utility analyses, for the Base Cases (row 1; a-c) and two Sensitivity Analyses (row 2; d-f: including onward transmission, row 3; g-i: healthcare perspective); for Log_{10} viral load (column 1), treatment failure (column 2), and QALYs (column 3). Costs are in Euros, based on the bootstrapped ICERs (5000 times).



Online supplementary material S1: Details regarding imputation

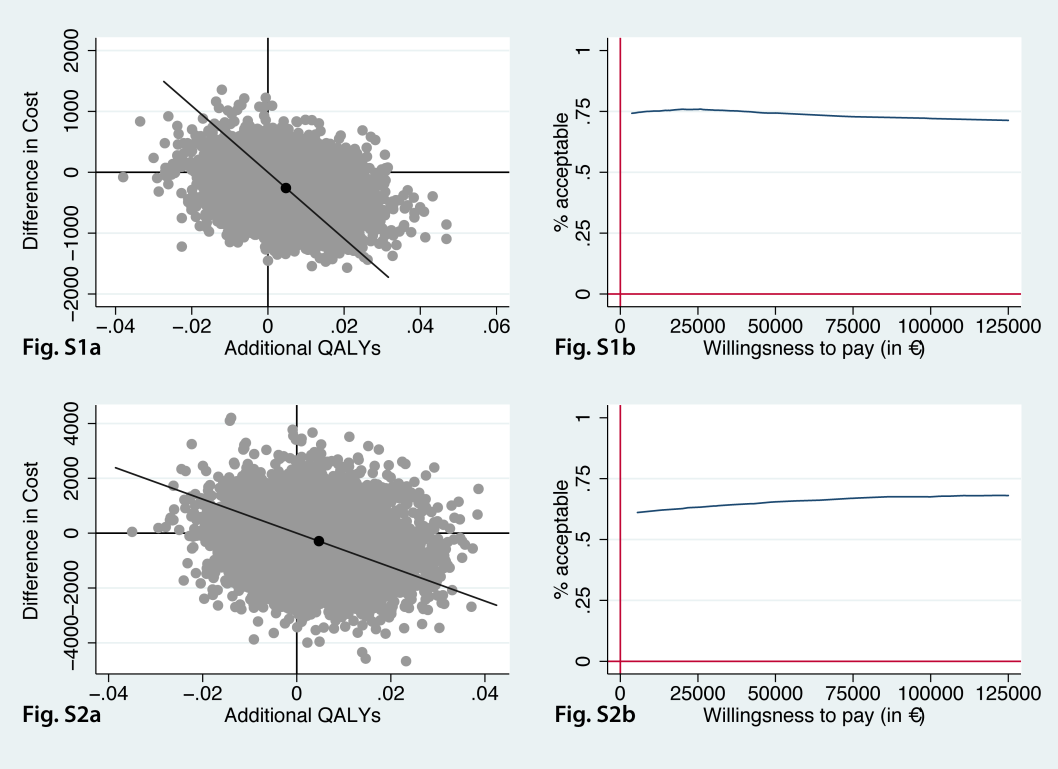
Missing data were imputed using expectation maximization, using costs and utilities on the other time points, educational level, ethnicity, gender, age, treatment experienced or naïve, and years since diagnosis as predictor variables. Values for patients without *any* completed questionnaire (N = 29, 13.0%) were replaced by the sample mean of their group (treatment-naïve versus experienced; intervention versus control) at that time point. All baseline plasma viral loads were available, and missing data on the other points was low (3.5%). We employed interpolation (i.e., the average of the viral load before and after) or – if that was not possible – the last observation carried forward method. If last observation carried forward was not meaningful (e.g., if treatment-naïve patients only had a baseline viral load), a sample mean imputation (again of their group at that time point) procedure was applied.

Online supplementary material S2: Details regarding intervention costs

Costs for the monitors were €38.33 per year which was based on a price of €115 per MEMS-cap (when ordering 1,000 MEMS-caps) with a battery life of three years. The total training costs were €13,740 (based on the tariff of a motivational interview trainer and productivity losses of HIV-nurses for attending the training), which is €7.52 per patient when spread over all eligible patients (N= 1826) in participating centers during the 18-months inclusion period. Total costs for booster sessions in pairs of two nurses were €5,940 (based on the tariff of a trainer and HIV-nurse productivity losses. The total costs were spread over all eligible patients attending the seven participating clinics during the trial recruitment period (N = 1826), resulting in €3.25 per patient. As clinical visits in the intervention group were on average 10.3 minutes longer compared to the TAU, additional patient costs were €33.51 per patient in the intervention group. Overhead costs are already included in the reference prices provided in the Dutch guidelines [35], hence, the total intervention costs were €82.61 per patient.

Online supplementary material S3: Base case analyses with alternative imputations

Figure S1&S2: Cost-Effectiveness and Cost-Utility Planes for All Base Cases with alternative imputations



[S1.a] Cost-utility analysis: costs per QALY gained, only baseline and follow-up time points

[S1.b] Cost-effectiveness acceptability curve for costs per QALY gained, only baseline and follow-up time points

[S2.b] Cost-utility analysis: costs per QALY gained, individual mean imputation

[S1.c] Cost-utility analysis: cost-effectiveness acceptability curve for costs per QALY gained, individual mean imputation

Online supplementary material S4: Information on previously published studies of AIMS

Markov health economic model

The current study is complementary to a recently published Markov model evaluating the cost-effectiveness of AIMS. The Markov model had a longer time horizon (10 years and life time perspective, as opposed to 15 months in this study), and was therefore more appropriate for estimating cost-utility (i.e. any effects of an adherence intervention on quality of life were unlikely expected to manifest themselves within 15 months). The cost-utility analyses in the Markov model showed that AIMS was cost-effective and in fact cost-saving in all scenarios on the long run.

The full paper is published as:

- de Bruin, M., Oberjé, E., Evers, S., Nobel, H., Prins, J. M., & Hiligsmann, M. (2016). The cost-effectiveness of the adherence improving self-management strategy (AIMS) in HIV-care: a Markov model. European Health Psychologist, 18(S), 476.

(Clinical) effectiveness paper on the results of this RCT including a lifetime Markov model to estimate the primary economic outcome of lifetime societal costs per quality-adjusted life-years (QALYs) gained

Across the three time points (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]). The cost-effectiveness was modeled using a Markov model which demonstrated that AIMS was cost-effective (i.e., dominant: cheaper and more effective) since it reduced lifetime societal costs per patient and increased QALYs.

This study differs from the current study as result of the cost-effectiveness analyses were based on a Markov model, whereas the results of the current study are solely based on the trial results without any extrapolation.

The full paper is published as:

- de Bruin, M., Oberjé, E. J., Viechtbauer, W., Nobel, H. E., Hiligsmann, M., van Nieuwkoop, C., ... & Groeneveld, P. H. (2017). Effectiveness and cost-effectiveness of a nurse-delivered intervention to improve adherence to treatment for HIV: a pragmatic, multicentre, open-label, randomised clinical trial. The Lancet Infectious Diseases, 17(6), 595-604.