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Extended Research Article

Supporting antiretroviral therapy uptake and adherence: the SUPA research programme and RCT

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Disclaimer: This manuscript contains transcripts of interviews conducted in the course of the research, or similar, and contains language which may offend some readers.

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This article

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Abstract

Background: Antiretroviral therapy has transformed human immunodeficiency virus infection intoa chronic condition associated with normal life expectancy. In the United Kingdom, the uptake of antiretroviral therapy is generally high, but a delay in starting antiretroviral therapy and non-adherence compromise the health and well-being of people living with human immunodeficiency virus, increase the risk of transmission of human immunodeficiency virus and increase National Health Service costs.

Objectives: The overall aim was to improve antiretroviral therapy uptake and adherence by addressing perceptual and practical barriers. The objectives were to (1) identify culturally specific beliefs and other factors influencing uptake of and adherence to antiretroviral therapy that have not emerged in previous research; (2) refine existing methods for assessing perceptual and practical barriers to antiretroviral therapy uptake and adherence; (3) develop an intervention to increase antiretroviral therapy uptakeand adherence; (4) determine intervention feasibility and acceptability; (5) evaluate intervention efficacy;(6) assess the short- and long-term costs and cost-effectiveness of the interventions and (7) prepare for implementation within the National Health Service.

Design: Objective 1 – in-depth interviews with Black African and Black Caribbean people living with human immunodeficiency virus (n = 52); objective 2 – adaptation of the Beliefs about Medicines Questionnaire; objective 3 – development of the Supporting UPtake and Adherence to antiretroviral therapy service intervention; objective 4 – feasibility study (n = 213) and acceptability/process interviews (n = 24); objective 5 – observational study (n = 484) and randomised controlled trial (n = 143); objective 6 – systematic review, cost-effectiveness analysis (n = 210) and economic modelling; and objective 7 – preparatory implementation work with people living with human immunodeficiency virus and human immunodeficiency virus clinic staff.

Setting: National Health Service human immunodeficiency virus clinics in England with a high proportion of ethnic minority populations.

Participants: People living with human immunodeficiency virus.

Interventions: Adherence support – cognitive–behavioural therapy plus care as usual.

Main outcome measures: Workstream 1 – adapted Beliefs about Medicines Questionnaire–antiretroviral therapy. Workstream 2 – feasibility study: participant recruitment and withdrawal rates. Workstream 3 – randomised controlled trial – primary outcome: medication event monitoring system adherence. Workstream 4 – incremental cost-effectiveness ratio.

Results: Workstream 1 – qualitative studies were used to refine the Beliefs about Medicines Questionnaire – antiretroviral therapy and, together with our preparatory research, to inform the cognitive–behavioural therapy-based intervention. Workstream 2 – recruitment to the randomised controlled trial and observational study was deemed feasible. Thematic analysis of exit interviews with recipients of the SUPA intervention demonstrated that the intervention was acceptable and addressed perceptual and practical barriers to antiretroviral therapy. In Workstream 3, we did not meet the recruitment targets and our trial was underpowered for the primary outcome: 143 participants met the inclusion criteria and were randomised (care as usual, n = 72; care as usual plus cognitive–behavioural therapy, n = 71). There was no significant effect of cognitive–behavioural therapy on the primary end point. Of the 112 participants (care as usual, n = 55; cognitive–behavioural therapy, n = 57) for whom sufficient data for primary end-point analysis were available, 17 (15.2%) met the primary end point (> 80% of months with an average monthly adherence of ≥ 90%) [9 (16.4%) in the care-as-usual group and 8 (14.0%) in the cognitive–behavioural therapy group (p = 0.94)]. Secondary end points: median Medication Event Monitoring System adherence at 12 months was 61.9% in the care-as-usual group and 66.5% in the cognitive–behavioural therapy group (p = 0.40), representing a 7.5% uplift in adherence. Participants who were randomised to receive the intervention, based on perceptions of antiretroviral therapy at baseline (low antiretroviral therapy necessity beliefs, and/or high antiretroviral therapy concerns), experienced a greater decrease in antiretroviral therapy concerns [care as usual −0.9 (95% confidence interval −1.4 to −0.5) vs.

cognitive–behavioural therapy −0.6 (95% confidence interval −0.8 to −0.3); $p = 0.03$], treatment intrusiveness [median change in highly active antiretroviral treatment (antiretroviral therapy) Intrusiveness Scale scores: care as usual −0.5 (95% confidence interval −5.6 to 18.0) vs. cognitive–behavioural therapy −5.6 (95% confidence interval −20.4 to 1.2); $p = 0.03$] and depression scores [median change in depression score: care as usual 0 (95% confidence interval −1.5 to 2.0) vs. cognitive–behavioural therapy −1 (95% confidence interval −3 to 0); $p = 0.02$] between baseline and 12 months. Workstream 4 – cognitive–behavioural therapy resulted in 0.056 more quality-adjusted life-years than care as usual (95% confidence interval 0.0029 to 0.083). The incremental cost-effectiveness ratio was £11,189 per quality-adjusted life-year. At a threshold of £20,000 per quality-adjusted life-year, there was > 90% likelihood that the intervention would be more cost-effective than care as usual. There was a 13% likelihood that the intervention would produce more quality-adjusted life-years and result in lower health and social care costs than care as usual. A Markov model showed that, over the longer term, cognitive–behavioural therapy results in fewer quality-adjusted life-years and higher costs and, therefore, care as usual would be the more cost-effective option.

Limitations: Our primary outcome of full Medication Event Monitoring System adherence was problematic, our randomised controlled trial was underpowered and we were unable to demonstrate a significant difference in our primary outcome.

Conclusions: Patients who received the Supporting UPtake and Adherence to antiretroviral therapy service intervention benefited from a reduction in antiretroviral therapy concerns, a reduction in antiretroviral therapy intrusiveness and reduced depressive symptoms, and from improved quality of life. The intervention was likely to be cost-effective for the National Health Service within 12 months.

Future work: Given the difficulty in recruiting people at a high risk of non-engagement with human immunodeficiency virus care, future work assessing the effectiveness of adherence interventions may require alternative, non-standard randomised controlled trial designs. Further studies are necessary to recalibrate our understanding of the levels of antiretroviral therapy adherence necessary to achieve viral load suppression.

Study registration: The trial is registered as ISRCTN35514212 and the study is registered as CRD42019072431.

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List of abbreviations

3TC	lamivudine
AAF	Africa Advocacy Foundation
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
BHIVA	British HIV Association
BIPQ	Brief Illness Perception Questionnaire
BMQ	Beliefs about Medicines Questionnaire
BMQ-ART	Beliefs about Medicines Questionnaire – antiretroviral therapy
CAU	care as usual
CBT	cognitive–behavioural therapy
CD4	cluster of differentiation 4
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
FTC	emtricitabine
GP	general practitioner
HAART	highly active antiretroviral therapy
HADS	Hospital Anxiety and Depression Scale
HIS	Highly Active Antiretroviral Treatment (Antiretroviral Therapy) Intrusiveness Scale
HIV	human immunodeficiency virus
ICER	incremental cost-effectiveness ratio
IDG	Intervention Development Group
IDMC	Independent Data Monitoring Committee
IPA	interpretative phenomenological analysis
MARS	Medication Adherence Report Scale
MARS-5	Medication Report Scale-5 item version
MEMS	Medication Event Monitoring System
MI	motivational interviewing
MRC	Medical Research Council
MSM	men who have sex with men
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
PLWH	people living with human immunodeficiency virus
PMG	Programme Management Group
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSC	Programme Steering Committee
QALY	quality-adjusted life-year
R&D	research and development
RCT	randomised controlled trial
SAQ	Symptoms Associated with human immunodeficiency virus and antiretroviral therapy Questionnaire
SCPQ	Standard Care Perceptions Questionnaire
SMS	short message service
START	Strategic Timing of AntiRetroviral Treatment
SUPA	Supporting UPtake and Adherence to antiretroviral therapy
TIDieR	Template for Intervention Description and Replication
UCL	University College London
UNAIDS	Joint United Nations Programme on human immunodeficiency virus/ acquired immunodeficiency syndrome
WS	workstream

Plain language summary

Human immunodeficiency virus treatment (known as antiretroviral therapy) is very effective, but some patients do not get the full benefit because they delay treatment or miss doses. This increases the chances of getting ill and the risk of passing human immunodeficiency virus on to others. There are many reasons why people delay treatment or take less than has been prescribed, including beliefs and concerns about treatment and practical difficulties.

People from United Kingdom Black African and Caribbean communities often experience difficulties with human immunodeficiency virus treatment, but few studies have focused on this group. We interviewed 52 people from Black African and Caribbean communities about their views and experiences of human immunodeficiency virus and its treatment, and designed questionnaires to measure these. After consulting with people living with human immunodeficiency virus, we developed a new service to help people get the best from human immunodeficiency virus treatment (i.e. Supporting UPtake and Adherence to antiretroviral therapy).

The Supporting UPtake and Adherence to antiretroviral therapy service included a video and booklet about human immunodeficiency virus and antiretroviral therapy and up to four meetings or telephone calls with a nurse to address questions and concerns. We compared the Supporting UPtake and Adherence to antiretroviral therapy service with usual National Health Service care to test whether or not patients who received the Supporting UPtake and Adherence to antiretroviral therapy intervention were more likely to take antiretroviral therapy as prescribed by their doctor (known as adherence). We also tested whether or not the Supporting UPtake and Adherence to antiretroviral therapy programme benefited patients by reducing antiretroviral therapy concerns and practical difficulties, and if it improved depression and provided value for money for the National Health Service.

It was more difficult than we expected to recruit people to the trial. Because of this, and difficulties in measuring the amount of antiretroviral therapy taken, we did not show that people who received the Supporting UPtake and Adherence to antiretroviral therapy intervention took more antiretroviral therapy over 12 months than those who received normal care. People who received the Supporting UPtake and Adherence to antiretroviral therapy intervention benefited from reduced concerns about antiretroviral therapy and antiretroviral therapy interfered less in their lives. People who received the Supporting UPtake and Adherence to antiretroviral therapy intervention were also less depressed and used fewer extra National Health Service services. The Supporting UPtake and Adherence to antiretroviral therapy service represented value for money in the short term.

Scientific summary

Background

Antiretroviral therapy (ART) is highly effective and the majority of people living with human immunodeficiency virus (PLWH) in the UK now have an undetectable viral load and a near-normal life expectancy and pose a low risk of onward human immunodeficiency virus (HIV) transmission. However, adherence to ART is necessary to suppress and maintain an undetectable HIV viral load. Substantial numbers of PLWH in the UK are not prescribed ART or have a detectable viral load when prescribed ART. This is a problem because both delays to start ART and non-adherence compromise the health and well-being of PLWH, increase the risk of HIV transmission and increase NHS costs.

There is a need for a pragmatic, evidence-based approach to increase uptake and adherence to ART. Interventions to increase adherence across long-term conditions have had limited success, and it is not yet clear which strategies are most effective. To optimise engagement with ART, there is a need to understand why people with HIV may not want to, or be unable to, initiate and take ART. Our preparatory research was conducted across multiple chronic illnesses, including HIV infection, and in different cultural contexts and showed that adherence was consistently related to both perceptions of their treatment [i.e. how patients judged their personal necessity for treatment (necessity beliefs) relative to their concerns about potential adverse effects] and practical difficulties with taking treatment, such as limitations in capability and opportunity. This work influenced the National Institute for Health and Care Excellence (NICE) guidelines for adherence that recommend tailoring adherence support to address the specific perceptual and practical barriers that are salient for the individual.

Aim

The aim of this programme was to improve engagement with ART (uptake and adherence) by addressing perceptual and practical barriers, providing the evidence base for HIV care and informing the implementation of NHS policy. *Figure a* shows an overview of the programme and highlights the various components of each workstream (WS).

Objectives

- Identify culturally specific beliefs and other factors influencing uptake of and adherence to ART that have not emerged in previous research.
- Refine our existing methods for eliciting and measuring the salient perceptual and practical factors influencing uptake of and adherence to ART.
- Develop an intervention (including intervention manuals, materials and therapeutic intervention) to increase uptake of and adherence to ART.
- Determine the feasibility and acceptability of the intervention.
- Evaluate the efficacy of the intervention for increasing ART uptake and adherence.
- Assess the costs and cost-effectiveness of providing the intervention in the short and long term.
- Prepare for implementation within the NHS.

Methods and results

Workstream 1: intervention development

Workstream 1 addressed objectives 1–3 in three studies from discussions with our patient and public involvement group, clinical advisors and our analysis of gaps in the published literature on adherence to antiretrovirals, it became apparent that people from UK Black African and Caribbean communities often experience difficulties with HIV

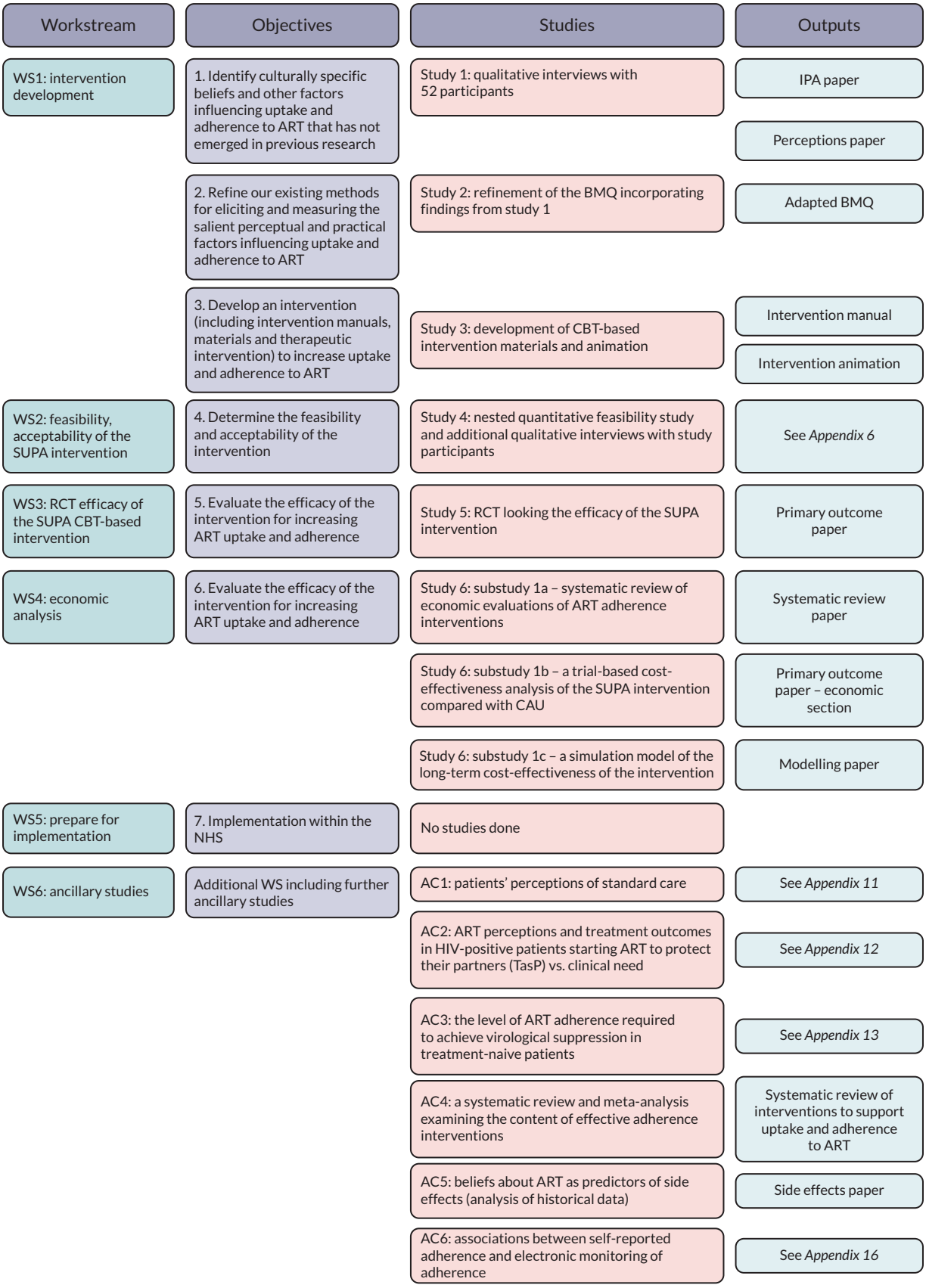

FIGURE a Programme overview. AC, ancillary study; BMQ, Beliefs about Medicines Questionnaire; CAU, care as usual; CBT, cognitive–behavioural therapy; IPA, interpretative phenomenological analysis; RCT, randomised controlled trial; SUPA, Supporting UPtake and Adherence to ART.

treatment, but few studies have focused on this group. We therefore paid particular attention to this group in our intervention development studies.

Study 1 identified culturally specific beliefs and other factors influencing the uptake of and adherence to ART in Black African and Caribbean communities that have not emerged in previous research. We interviewed 52 men and women from Black African and Caribbean communities in London who had been identified as having previous or current problems adhering to their medication. Two separate analyses were conducted. The first used interpretative phenomenological analysis to understand the lived experiences of taking ART among a group of women from West Africa (n = 10), which was a previously under-represented community in HIV adherence research. The analysis identified issues and challenges that the women experienced with adherence to ART. The following three overarching themes were identified: (1) negative experiences of medication, (2) temporal improvement and (3) spurs to adherence.

The second analysis used framework analysis to identify perceptual and practical barriers to adherence (n = 52). This analysis of in-depth interviews with people with demonstrated suboptimal adherence showed that perceptual barriers to ART could be grouped into two overarching themes: doubts about the need for ART and concerns about potential harm and stigma. The findings of our preparative research were discussed with patient representatives and practising clinicians from centres with a large proportion of men who have sex with men (MSM). The consistent view was that our preparative research findings remained relevant for MSM and that further research in this group to inform our measures of perceptual and practical barriers to ART was unnecessary.

Study 2 refined existing methods to measure patients' perceptions of ART. The study 1 findings were used to refine our measures of perceptual and practical barriers to ART uptake and adherence with four items added to the Beliefs about Medicines Questionnaire (BMQ)-ART.

Study 3 developed an intervention to address barriers and facilitate ART uptake and adherence. Medical Research Council guidance was applied to develop a cognitive–behavioural therapy (CBT)-based intervention to support uptake and adherence to ART. The intervention, intervention manual and animations were developed by an Intervention Development Group, including experts in adherence, behaviour change theory, CBT, HIV medicine, nursing, pharmacy and HIV patient advocacy. It was informed by our preparatory research and the findings of study 1, incorporating:

1. standardised information about HIV and its treatment, designed to address common, adherence-related misconceptions and concerns and signpost patients to further support to help overcome practical difficulties with taking ART and reduce the degree to which ART interfered with daily living (ART intrusiveness), delivered through an animated video and a booklet
2. personalised discussion with a HIV nurse to introduce the Supporting UPtake and Adherence to ART (SUPA) video and booklet and address barriers to adherence, applying CBT techniques in up to four sessions – the first was face to face, with further sessions in clinic or by telephone follow-up, determined by patient preference.

The intervention manual and animation were reviewed by the SUPA management group and members of the target population. User testing and further development of materials were conducted with PLWH, who were recruited through the Africa Advocacy Foundation (AAF).

Workstream 2: feasibility and acceptability of the Supporting UPtake and Adherence to antiretroviral therapy (cognitive–behavioural therapy) intervention

Study 4 determined the feasibility and acceptability of the SUPA (CBT) intervention. Study 4 included the following two components.

Quantitative feasibility study nested within the randomised controlled trial to determine the feasibility of the Supporting UPtake and Adherence to antiretroviral therapy intervention

Over an initial period of 14 months, 213 PLWH were recruited to an observational study, of whom 86 were eligible for the randomised controlled trial (RCT) and 46 were successfully randomised [23 to the care as usual (CAU) group and 23

to the CBT group]. Rates of attrition were low: of the 213 patients enrolled in the observational study, only 5 were not reached for follow-up appointments. Of the 46 patients randomised, 2 withdrew.

Qualitative feasibility study

The qualitative feasibility study was a thematic analysis of qualitative interviews conducted with people randomised to receive the SUPA intervention. This analysis determined the acceptability of the SUPA intervention and explored the process of change. Twenty-four people from the PLWH community in the UK were interviewed about their experiences of taking part in the trial and receiving the SUPA intervention. Participants reported various reasons for enrolling in the trial, including the desire to learn about HIV and its treatment, play an active role in their health care, and give something back to other PLWH. Intervention sessions gave participants the opportunity to discuss their concerns about ART and to receive confidential advice and support. Participants indicated that the intervention materials were relevant and accessible. The findings indicated that the intervention addressed misconceptions about HIV, provided a rationale for taking ART, reduced concerns about ART and provided practical strategies for adherence and emotional support.

Workstream 3: randomised controlled trial efficacy of the Supporting UPtake and Adherence to antiretroviral therapy cognitive–behavioural therapy-based intervention to support antiretroviral therapy uptake and adherence

The efficacy of the SUPA intervention was examined in a RCT. A two-step consent process was followed. ART-naive PLWH who had received a treatment offer were recruited from eight HIV clinics in England to take part in an observational study. Participants completed the BMQ-ART, and those who had perceptual barriers to ART (doubts about personal need for ART and/or concerns about ART), and were therefore deemed at risk of non-adherence, were invited to take part in the RCT. Those who consented to take part in the RCT were randomised to receive CAU or CBT (*Figure b*). Those who were not eligible for the RCT or who declined to take part remained in the observational study and completed the BMQ-ART at the 3-, 6- and 12-month follow-ups.

The primary end point was designed to capture both a delay to initiate treatment and non-adherence, and was developed in discussion with NIHR. In the months prior to ART initiation, adherence was set to 0%. After starting ART, the proportion of days within the month with full adherence was assessed using Medication Event Monitoring System (MEMS®) (AARDEX Group, Seraing, Belgium). Adherence within each patient-month was then classified as being good (≥ 90%) or poor (< 90%), and the prespecified primary outcome was met if individuals achieved good adherence in > 80% of the months during which they were under follow-up.

The secondary outcomes were percentage MEMS adherence, self-reported adherence, changes in beliefs about ART, ART intrusiveness and practical difficulties with ART, perceptions of HIV, depression and anxiety, viral load suppression, regimen switches, treatment failure, and disengagement from care.

Between March 2014 and July 2017, 1575 patients were assessed for eligibility, of whom 143 were randomised (CAU, n = 72; CBT, n = 71). Recruitment was challenging, and our target of 372 was not reached. The observational study included 484 individuals who were not eligible or chose not to take part in the RCT (RCT-eligible decliners at high non-adherence risk, n = 27; not eligible for RCT at low non-adherence risk, n = 457).

Owing to the challenges in using MEMS, the number of participants with sufficient data for primary end-point analysis was 112 (CAU, n = 55; CBT, n = 57). Of those, 17 participants (15.2%) met the primary end point (> 80% of months, with an average monthly adherence of ≥ 90%) [9 (16.4%) in the CAU group and 8 (14.0%) in the CBT group (p = 0.94)]. There was no significant difference in the primary outcome (i.e. MEMS adherence) between the CBT and CAU groups at 12 months. There was a 7% improvement in median percentage adherence by MEMS in the CBT group relative to the CAU group (61.9% CAU and 66.5% CBT; p = 0.40). There was a significant increase in the proportion of people with high adherence (by self-reported Medication Adherence Report Scale) at 3 months' follow-up (75% CAU and 81% CBT; p = 0.02).

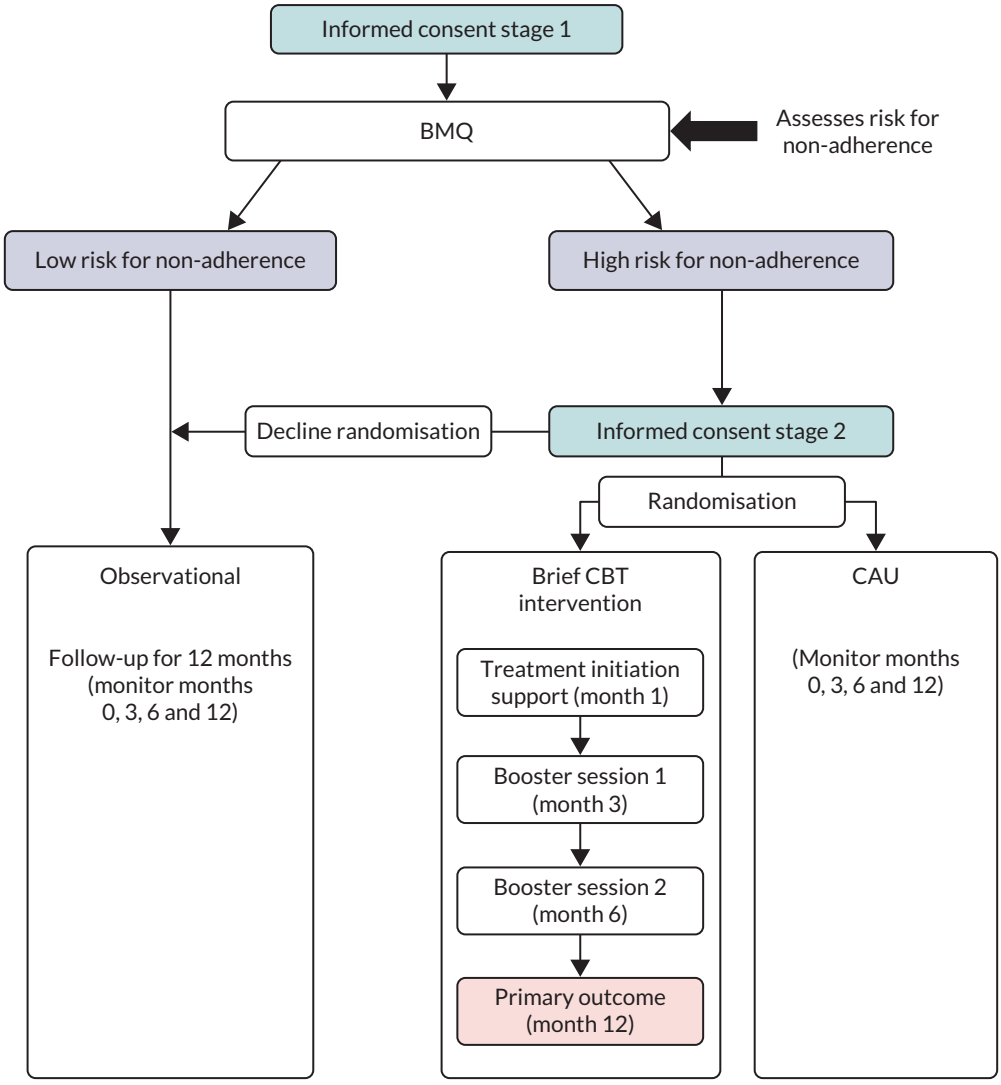

FIGURE b The SUPA study trial design.

Participants randomised to receive CAU plus CBT benefited from a significantly greater reduction in ART concerns, ART intrusiveness and depression between baseline and 12 months than those randomised to receive CAU. There were no significant differences between the randomised groups in ART necessity beliefs (which were high in both groups), anxiety, illness perceptions, viral load, cluster of differentiation 4 (CD4) T-cell count, rates of treatment failure or treatment switches.

Workstream 4: economic studies

Workstream 4, study 6, addressed objective 6: assessing the costs and cost-effectiveness of the SUPA intervention in the short and long term. It comprised three substudies, as follows.

Systematic review of economic evaluations of antiretroviral therapy adherence interventions

A systematic literature search identified 20 studies reporting costs or cost-effectiveness of interventions to increase adherence to ART in PLWH. The quality of the economic evaluations was assessed. There was evidence of improved adherence and favourable cost-effectiveness ratios in people receiving adherence interventions compared with the control conditions. However, these effects tended to be short term.

Trial-based cost-effectiveness analysis of the Supporting UPtake and Adherence to antiretroviral therapy intervention

Use of the intervention and other health and social care services and HIV-specific medications were measured in the RCT (i.e. study 5) and costs were calculated. Quality-adjusted life-years (QALYs) were generated from the EuroQol-5 Dimensions, five-level version (EQ-5D-5L). Costs were compared at baseline and each follow-up time point. QALYs were compared, controlling for baseline EQ-5D-5L tariffs. Cost-effectiveness was assessed by combining incremental costs and incremental QALYs using an incremental cost-effectiveness ratio (ICER). The mean costs among the CBT group were £621 more than for the CAU group. This difference was not statistically significant [95% confidence interval (CI) −£569 to £1462]. CBT resulted in 0.056 more QALYs over the follow-up period than CAU, and this was significant (95% CI 0.0029 to 0.083). The ICER was £9143 per QALY. At a threshold of £20,000 per QALY, there was more than a 90% likelihood that CBT would be more cost-effective than CAU. There was a 19% likelihood that CBT would produce more QALYs and result in lower health and social care costs than CAU.

A simulation model of the long-term cost-effectiveness of the intervention

A Markov model was used to extrapolate for 15 years, in 12-month cycles beyond the trial period. Health states were defined by CD4 T-cell counts and all-cause mortality. The expected costs for those receiving CBT and CAU in the 15 years after the trial follow-up were less for CBT than for CAU, but CBT also resulted in fewer QALYs. Combining the trial period with the 15-year extrapolation period resulted in CBT having costs that were lower by £470 and 0.47 fewer QALYs. Therefore, in the long term, CAU is cost-effective with an ICER of £1187 per QALY.

Workstream 5: preparing for implementation within the National Health Service

Workstream 5 was intended to address objective 7: prepare for implementation within the NHS. Owing to the extended time needed for recruitment to the RCT, we were unable to carry out a full implementation WS. We have planned implementation strategies informed by NICE guidance on how to change practice. These involve identifying barriers to implementation by conducting study discussion groups in HIV clinics, discussion of our findings with HIV commissioners and conducting focus groups with PLWH at AAF.

Workstream 6 (additional workstream): ancillary studies

During the programme, we conceived an additional seven ancillary studies (WS6):

1. patients' perceptions of standard care
2. ART perceptions and treatment outcomes in HIV-positive patients starting ART to protect their partners (treatment as prevention) compared with clinical need
3. the level ART adherence required to achieve virological suppression in treatment-naive patients
4. a systematic review and meta-analysis examining the content of effective adherence interventions
5. beliefs about ART as predictors of side effects (analysis of historical data)
6. associations between self-reported adherence and electronic monitoring of adherence
7. the effect of the SUPA intervention on rates of engagement with HIV services.

These ancillary studies were conceived on the assumption of complete and timely recruitment to the SUPA RCT; however, recruitment was lower and slower than expected for this hard-to-reach study population. Consequently, only six ancillary studies were feasible (1–6).

Conclusions

The SUPA programme fulfilled its objectives to develop and evaluate a pragmatic, theory-based intervention to support ART uptake and adherence among PLWH at risk of non-adherence by addressing perceptual and practical barriers. Recruitment to the SUPA RCT was slower than anticipated and our trial was underpowered with no effect on the primary outcome measure of adherence over 12 months. However, the SUPA intervention benefited recipients by reducing ART concerns, ART intrusiveness and depression and improving quality of life. It was also cost-effective during the follow-up period.

Study registration

The trial is registered as ISRCTN35514212 and the study is registered as CRD42019072431.

Funding

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Synopsis

Background

Antiretroviral therapy (ART) has transformed human immunodeficiency virus (HIV) from a terminal illness to a chronic condition.[1] People living with human immunodeficiency virus (PLWH) in the UK now have a near-normal life expectancy,[2] and sexual transmission of HIV is prevented by viral suppression in PLWH taking ART.[3]

A high level of adherence to ART is necessary to suppress HIV viral load to undetectable levels.[4] Modelling studies show that, if sufficient numbers of PLWH are diagnosed, initiate ART and have a suppressed viral load, new HIV infections could be eradicated. In 2014, the Joint United Nations Programme on HIV/acquired immunodeficiency syndrome (AIDS) (UNAIDS) set out three milestones to end the AIDS epidemic by 2030.[5] These were as follows: (1) 90% of PLWH knowing their HIV status, (2) 90% of diagnosed PLWH receiving treatment and (3) 90% of people on treatment having a suppressed viral load.[5] In the UK, these targets were met by December 2017.[6] In 2018, > 75% of newly diagnosed people with HIV who engaged with care began treatment within 90 days, with 97% of those in regular care achieving viral load suppression.[7] However, these figures may be misleading, as they do not include those who are newly diagnosed but not in care, or those who have not reattended within the year.[7]

Low levels of engagement with ART (delay in treatment uptake and low adherence) continue to pose important challenges. A substantial number of PLWH are not on ART or are on ART but have an unsuppressed viral load.[7] This is problematic because both a delay to start ART and non-adherence are associated with poorer patient outcomes, higher costs of care and increased risk of sexual transmission of HIV.[8,9] As rates of adherence tend to decline over time,[10] it is important that barriers to adherence are addressed at the start of treatment.

There is a need for pragmatic, evidence-based approaches to support ART uptake and adherence. To date, interventions to increase adherence to medicines for long-term conditions have had only limited success, and it is not yet clear which strategies are most effective.[11] The findings of systematic reviews of interventions to facilitate adherence to ART have been variable.[12–15] A recent meta-analysis showed that several types of intervention, including short message service (SMS)-delivered interventions, treatment supporters and counselling, could be effective.[12] However, effect sizes were generally small, and it is not yet clear how the content of interventions affects their effectiveness.[12]

To optimise engagement with ART, there is a need to understand why people with HIV may not want to or be unable to initiate and continue ART. In our preparatory research, a series of studies identified potentially modifiable causes of non-adherence, identifying targets for intervention. Our early studies found that, for a given individual, non-adherence often had multiple causes, both intentional and unintentional.[16] We subsequently identified the salient beliefs about medicines influencing adherence.[10,17–20] In studies spanning multiple chronic illnesses and cultural contexts, adherence was consistently related to how patients judged their personal necessity for treatment (necessity beliefs) relative to their concerns about potential adverse effects (concerns).[21,22]

Studies conducted with PLWH in the UK and the USA demonstrated that ART necessity beliefs and concerns were important determinants of ART uptake and adherence.[10,20] These applied the valid and reliable measure: the Beliefs about Medicines Questionnaire (BMQ) to quantify adherence-related beliefs (necessity and concerns).[23] The National Institute for Health and Care Excellence (NICE) recommends that support for adherence[24] is tailored to individual needs, and addresses both perceptions (e.g. adherence-related beliefs) and practicalities (e.g. capability and resources) that affect motivation and ability to adhere: the Perceptions and Practicalities Approach.[25–27] There is evidence that support based on this approach improves adherence in long-term conditions.[28–31] Our systematic review of ART adherence interventions [workstream 6 (WS6), study 1] showed that interventions were likely to be effective if they tailored content to address both perceptions and practicalities. To date, and to our knowledge, this approach has not been applied in UK studies of ART adherence.

Aims and objectives

The overarching aim of the Supporting UPtake and Adherence to antiretroviral therapy (SUPA) programme was to improve engagement with ART (uptake and adherence) by addressing perceptual and practical barriers, providing the evidence base for HIV care and informing the implementation of NHS policy imperatives. The programme focused on five areas: (1) understanding perceptual and practical barriers to ART uptake and adherence in PLWH at increased risk of non-engagement with ART; (2) developing an intervention to promote uptake and adherence to ART by addressing these barriers; (3) evaluating the benefit of the intervention on clinical and patient-reported outcomes; (4) establishing the mechanism of change and (5) establishing the cost-effectiveness and cost-utility of the intervention. In parallel, a series of ancillary studies were conducted to determine the impact of the intervention on engagement in care, and establish the optimal method for measuring adherence and determine the level of adherence required to achieve undetectable viral load in PLWH starting ART for the first time.

This programme comprises six WSs, using a variety of methodologies (interviews with PLWH, systematic reviews, longitudinal surveys, economic modelling and a clinical trial) to address the following objectives:

1. identify culturally specific beliefs and other factors influencing uptake and adherence to ART that have not emerged in previous research
2. refine our existing methods for eliciting and measuring the salient perceptual and practical factors influencing uptake and adherence to ART
3. develop an intervention (including intervention manuals, materials and therapeutic intervention) to increase uptake and adherence to ART
4. determine the feasibility and acceptability of the intervention
5. evaluate the efficacy of the intervention for increasing ART uptake and adherence
6. assess the costs and cost-effectiveness of providing the intervention in the short and long term.
7. prepare for implementation within the NHS.

Study preparation

Ethics approvals

Ethics approval for WS1 study 1 was received on 15 June 2011 from the City and East London Research Ethics Committee (11/LO/0970). Ethics approval for WS2/3 study 4 was received on 15 August 2013 by the NRES East of England–Essex Research Ethics Committee (13/EE/0235).

Research governance

The study was conducted in line with the Research Governance Framework.[32] Research and development (R&D) approvals were in place at each site prior to recruitment. The programme was overseen by the SUPA Programme Management Group (PMG), who managed the research, ensured that protocols were completed on time and to the required quality. A Programme Steering Committee (PSC) advised on all aspects of the programme to the PMG, sponsor and funder through its independent chairperson.

The randomised controlled trial (RCT) in WS3 was overseen by the Independent Data Monitoring Committee (IDMC) (see *Appendix 1*). The roles of these groups were clearly defined and circulated prior to the initial meetings of the committees. In the case of the IDMC, a charter was produced at the inception of the study, and this was signed and adhered to by all members. We recruited a Patient Advisory Group, which reviewed research protocols and materials.

Trial registration

The SUPA trial was retrospectively registered, as International Standard Randomised Controlled Trial Number (ISRCTN) registry as ISRCTN35514212, on 21 February 2014.

Patient and public involvement

The programme was designed and implemented in collaboration with representatives from HIV patient groups and organisations. Patient representatives contributed to programme management and the development of research materials and the SUPA intervention.

Representation on the Supporting UPtake and Adherence to antiretroviral therapy Programme Management Group and Trial Steering Committee

Simon Collins (co-applicant) is co-founder of HIV i-Base (London, UK), a community-led organisation providing timely and accurate HIV treatment information to PLWH and healthcare professionals. Winnie Ssanyu Sseruma (Christian Aid HIV mainstreaming co-ordinator) brought the perspective of a HIV-positive African woman to the research. Winnie Ssanyu Sseruma has worked extensively with HIV activist groups and has conducted social research on HIV. Both Simon Collins and Winnie Ssanyu Sseruma were members of the SUPA PMG. They contributed to the design of the programme, the development of the SUPA intervention and commented on publications and protocols. Two members of the PSC, Paul Clift and Memory Sachikonye, advised on the relevance and acceptability to patients of the intervention and research materials.

Development of research materials

A group of five patient representatives was recruited through the UK Community Advisory Board to review the study protocols and all study and intervention materials. To increase the representation of harder-to-reach patients, we recruited patient representatives through the Mildmay Mission Hospital (a registered charity that specialises in HIV and provides health care and treatment in the UK and East Africa) and Africa Advocacy Foundation (AAF) (a registered community-led charity that supports and empowers vulnerable and disadvantaged people to find health, safety, prosperity, happiness and fulfilment).

We also engaged patient support groups at Homerton Hospital and King's College Hospitals to assist in wording trial questionnaires and patient information leaflets. The support group at King's College Hospital also helped us to develop a leaflet, 'What is research?', which was given to patients at screening visits to help patients with little knowledge or experience of research to make an informed choice about participating (see *Appendix 3*). This leaflet utilised analogies that were recommended by group members (e.g. the use of dice to explain randomisation). This group also recommended to use graphics and colours in designing leaflets in preference to a text-only leaflet to increase its visual appeal and steer away from an overly medical appearance.

Development of the Supporting UPtake and Adherence to antiretroviral therapy intervention

Informal focus groups at the AAF and Mildmay Mission Hospital played a vital role in the development of the SUPA intervention. User testing was conducted in two voluntary, informal groups, each including attendees and facilitators of peer support services for people living with HIV at the AAF. We worked with patients and staff at the Mildmay Mission Hospital to develop our approach to addressing doubts about the necessity for ART among PLWH who had faith that God could cure their HIV.

We worked with In Tune for Life (London, UK), a UK-registered charity using music and film to engage and empower communities affected by poverty and poor health to develop animated videos to complement the SUPA manual. These were designed to engage people and to support those who have a poor understanding of English or low health literacy to understand concepts around adherence.

Alterations to the programme's original design

Substantive changes to the design of the programme

The relevant SUPA committee and the National Institute for Health and Care Research (NIHR) approved three substantial changes to the contract.

Substantial change 1: April 2013

In April 2013, a variation to contract was accepted by NIHR, outlining changes to the design of the programme, made in response to (1) analysis of the changing landscape of HIV treatment based on the latest data from Public Health England and from the UK CHIC (UK Collaborative HIV Cohort) study,[33] (2) the findings of our qualitative study with UK Black African and Black Caribbean patients (WS1), (3) our systematic review of the literature intervention targeting ART uptake and non-adherence and (4) discussions with our user advisory panel.

Our original application described five WSs: WS1 – development phase; WS2 – feasibility and piloting phase; WS3 – evaluation phase; WS4 – assessment of cost–utility and cost-effectiveness of the interventions and WS5 – implementation phase. In the original design, WS2 and WS3 were concerned with the development and proof of principle testing of an intervention designed to help realise the full potential benefits of ART by addressing treatment refusal and non-adherence. In this original design, we separated the development of the intervention into two components: (1) uptake intervention to address barriers to starting ART, among those who had refused treatment and (2) adherence intervention to address non-adherence among those who had accepted ART but subsequently reported non-adherence.

During WS1, it became clear that a more comprehensive single intervention targeted at the point of treatment offer would be of greater benefit than two separate interventions addressing uptake and adherence individually. As a result of changes in HIV treatment guidelines, our qualitative study ART adherence among UK Black African and Black Caribbean patients, our systematic literature review of adherence interventions and discussions with our PMG and user advisory panel, we made the following changes to the design of the SUPA intervention and RCT:

1. Uptake and adherence intervention components were combined in a single intervention designed to prevent treatment delay and non-adherence during the first 6 months of treatment when treatment patterns and habits are usually established. The primary outcome of the RCT was revised to incorporate both uptake and adherence.
2. A longer follow-up period was incorporated into the RCT to capture adherence patterns over 12 months. This was motivated by the literature review findings that trials evaluating adherence interventions frequently fail to assess adherence beyond 6 months. This allowed us to establish whether or not the intervention was effective in the long-term. WS2 (feasibility) was merged with WS3 (evaluation) to create an embedded feasibility study (n = 40) and extend follow-up from 6 to 12 months.
3. We had originally intended to recruit from large London teaching hospitals. WS1 findings and discussions with the PMG highlighted the need to target the intervention to people from Black African and Black Caribbean communities who are at increased risk of disengagement from care.[34] We, therefore, focused recruitment of trial participants to centres with greater representation of Black African and Black Caribbean patients, including the Homerton, King's College, Queen Elizabeth and North Middlesex hospitals.

Substantial change 2: May 2017

In May 2017, we submitted a variation to contract to the funder to extend the duration of the programme by 9 months (6 months' costs) to maximise recruitment to the RCT.

Substantial change 3: May 2018

Owing to difficulties in recruiting and retaining a statistician, NIHR agreed a 9-month (uncosted) extension to complete the statistical analysis of trial data. Owing to unforeseen circumstances, our programme manager left her post suddenly in August 2019, and NIHR kindly granted us a 3-month (uncosted) extension in October 2019.

Substantial change 4

In April 2016, in order to address some of the issues arising from WS1 and WS2, we developed seven ancillary studies which we grouped into an additional workstream (WS6).

Insubstantial changes to the programme design

As a result of delays to recruitment to the trial and subsequent difficulty recruiting to the statistician post, we were unable to complete WS5 in the way that it was initially planned. A series of interactive educational workshops at HIV clinics were originally planned; however, this was not possible because of a lack of time between the completion/statistical analysis of the trial and the end of the programme.

Workstream 1: development of the Supporting UPtake and Adherence to antiretroviral therapy intervention

Research aims

The aim of WS1 was to develop our intervention to increase uptake and adherence to ART by addressing perceptual and practical barriers. It consisted of three studies that addressed the following objectives:

1. identify culturally specific beliefs and other factors influencing uptake and adherence to ART that have not emerged in previous research
2. refine our existing methods for eliciting and measuring the salient perceptual and practical factors influencing uptake and adherence to ART
3. develop intervention manuals and materials to increase uptake of and adherence to ART.

From discussions with our patient and public involvement group, clinical advisors and our analysis of gaps in the published literature on adherence to antiretrovirals, it became apparent that people from the UK Black African and Caribbean communities often experience difficulties with HIV treatment, but few studies have focused on this group. We, therefore, paid particular attention to this group in our intervention development studies.

Study 1: identifying barriers to antiretroviral therapy uptake and adherence in United Kingdom Black African and Black Caribbean communities

Our preparatory research identified the causes of non-adherence and specified the types of beliefs about medicines that influenced adherence to ART. It confirmed the utility of the necessity concerns framework for predicting ART uptake and adherence. However, this research was conducted predominantly with white men who have sex with men (MSM). There was limited evidence about the types of barriers to uptake and adherence to ART experienced by women and men from Black African and Caribbean communities in the UK. Study 1 was conducted to identify culturally specific barriers to ART among people from these communities.

Study 2: refinement of the Beliefs about Medicines Questionnaire – antiretroviral therapy[23,35] for people from United Kingdom Black African and Black Caribbean communities

The BMQ-ART was developed in studies focusing on MSM.[10,36] The questionnaire items were refined wherever it was necessary, based on the findings of study 1 reported above.

Stakeholder consultation to confirm applicability of the Beliefs about Medicines Questionnaire – antiretroviral therapy to men who have sex with men

Our previous qualitative and quantitative research had characterised perceptual and practical barriers to ART uptake and adherence among MSM.[10,35,36] However, we wanted to ensure that our understanding of barriers to ART uptake and adherence was contemporaneous in the light of treatment advances.

Study 3: development of intervention manuals and materials to increase uptake and adherence to antiretroviral therapy

The aim was to use the findings of our preparatory research, theory development and study 1 to develop an intervention to increase uptake of and adherence to ART (the SUPA intervention).

Methods

Study 1: identifying barriers to antiretroviral therapy uptake and adherence in United Kingdom Black African and Black Caribbean communities

Men and women from Black African and Black Caribbean communities were invited to take part in an in-depth interview with an experienced qualitative researcher (see *Appendix 2*). Purposive sampling ensured the inclusion of people from a broad geographical provenance and those with asymptomatic and symptomatic HIV. Interviews were conducted in English or French, according to patient preference, and were audio-recorded and transcribed verbatim.

Two separate analyses were conducted. The first used interpretative phenomenological analysis (IPA)[37] to understand in-depth the lived experiences of taking ART among a group of women from West Africa living in London. The second used framework analysis[38] to identify perceptual and practical barriers to adherence among people of Black African or Caribbean ethnicity.[39]

Interpretative phenomenological analysis

We conducted a detailed examination of the experience of medication in a purposively selected group of 10 West African women of black heritage living in London. This group was of interest because people of African heritage are the second largest group affected by HIV in the UK,[7] and yet women and people of West African heritage had been under-represented in research into the causes of non-adherence. IPA is an idiographic, experiential, qualitative approach that can effectively unpack complex individual experiences and uncover nuances and details in a small group of people.[40]

Framework analysis[41]

Framework analysis identified perceptual and practical barriers to adherence among 52 men and women of Black African or Caribbean ethnicity. Framework analysis was chosen because it enables the exploration of predefined theory as well as the inductive exploration of patients' accounts.[41] In this analysis, the data were explored in relation to the necessity concerns framework.[21,42] An initial framework of key issues and themes was developed by two researchers, applied to code a subset of interviews and was refined through discussion. Segments of data from the transcripts were extracted and arranged in a matrix according to emerging themes. Data were managed using NVivo 10.0 (QSR International, Warrington, UK).

Study 2: refining our existing methods for eliciting and measuring barriers to antiretroviral therapy uptake and adherence

The results of study 1 were used to adapt the BMQ-ART-specific version.[35,43] The BMQ can be adapted by adding necessity and concerns items specific to the clinical context.[43] However, we were mindful that we did not want to overburden patients if items were unnecessary or adequately addressed by existing BMQ items. Therefore, our approach was to (1) develop a list of sample items based on the findings of study 1, (2) map each item on to a necessity or concerns construct, (3) consult with our patient advisory group to determine whether the construct was already adequately addressed by an existing item or whether an additional item should be added and (4) pilot additional items to ensure that the wording was comprehensive and comprehensible (*Table 1*).

Study 3: development of intervention manuals and materials

We followed the recommendations of the Medical Research Council (MRC) for the development of complex interventions.[44] The SUPA intervention was informed by our preparatory work developing appropriate theory,[42,43,45] our review of the existing literature and piloting with members of the target population. An Intervention Development Group (IDG), including experts in adherence, behaviour change theory and cognitive–behavioural therapy (CBT), HIV medicine, nursing, pharmacy and HIV patient advocacy, designed the intervention materials. In an iterative process, draft intervention materials were developed by the IDG and revised following feedback from members of the target population and the SUPA interventions in CBT developed to ensure that and PMG. A training manual was devised to guide those delivering the motivational interviewing (MI) techniques (see *Appendix 4*). Checklists were developed to ensure that relevant content was covered in intervention sessions.

TABLE 1 Adaptation of the BMQ (ART-specific version)

Themes identified in study 1	Was this item adequately addressed by existing questionnaires?	Addition made
Disconnect between treatment and health	Addressed by existing BMQ item: my health depends on antiretroviral medication	No
Fatalistic views – HIV is incurable	Addressed by existing BMQ item: without antiretroviral medication I would become very ill	No
Stigma and shame	Necessity: doubts about the validity of the HIV diagnosis was addressed by the IPQ item 'How well do you feel you understand your illness?'	*I'm worried that others will find out I am HIV positive if they see I am taking antiretroviral medication*
	Concern about medication leading to others finding out about the person's HIV diagnosis was not adequately addressed by existing questionnaires	
Conflict regarding roles of God and medicine	Not addressed in existing questionnaires	*God will cure my HIV*
Doubts about the effectiveness of ART	Addressed by existing BMQ item: antiretroviral medication would keep my HIV under control	No
Insufficient time to come to terms with HIV diagnosis	We will examine the association between time since diagnosis and engagement with ART in the analysis	No
Risk of disclosure of HIV through ART	Not addressed in existing questionnaires	*I'm worried that others will find out I am HIV positive if they see I am taking antiretroviral medication*
Decreased quality of life	No item added – this is covered by existing items: antiretroviral medication would give me unpleasant side effects and I would worry about long-term effects of these medicines	No
Physical repulsion stemming from the size and taste of tablets	Not addressed in existing questionnaires	*I worry that the taste of the medication will make me feel unwell* *I worry that the tablets will be hard to swallow*
Long-term effects	No items added – covered by existing item: I would worry about long-term effects of these medicines	No

User testing was conducted in two voluntary groups, each including attendees and facilitators of peer support services for people living with HIV at the AAF, a London-based community-led charity. Early drafts of the SUPA manual and animations were shown to attendees. These were discussed and feedback was used to adapt the materials.

The SUPA intervention was described using the Template for Intervention Description and Replication (TIDieR) checklist,[46] including the rationale for the intervention, description of intervention materials and procedures, intervention provider, mode of delivery, location, timing and number of intervention sessions, detail on tailoring, modifications and planned/actual assessments of intervention adherence or fidelity,[46] Perceptions and Practicalities Approach,[27] and Behaviour Change Techniques Taxonomy (version 1).[47]

Key findings

Study 1: identifying barriers to antiretroviral therapy uptake and adherence in United Kingdom Black African and Black Caribbean communities

Interpretative phenomenological analysis

Three themes were identified in the analysis, illuminating the difficulties that the women experienced with adherence to ART:

1. 'Negative experiences of medication': highlighted the importance of physical attributes of the medication, such as the number, size, colour, taste and shape of the pills, that impeded adherence and even triggered physical repulsion and a deep-felt shame associated with the diagnosis of HIV. Some women experienced a disconnect between treatment and feeling of health, such as when their health or blood test results failed to improve even when they were taking their treatment as prescribed. This led them to question the validity of the treatment. Some felt trapped in a monotonous 'prison sentence', created by the burden of taking daily treatment and the aversive experience of side effects. Non-adherence provided freedom from this unrelenting daily chore. The social context often exacerbated non-adherence. Weekends, living with many other people, taking pills at work, illness among other family members, depression and the break-up of a relationship all posed difficulties.
2. 'Temporal improvement in adherence': for some women, taking treatment had become easier over time, until it felt normal or natural. These women felt that, over time, ART became more tolerable, they became more accepting of the diagnosis and more positive about treatment. These positive attitudes were enhanced if treatment practicalities were addressed (by changing to smaller, more easily swallowed tablets). Undetectable viral load results in increased treatment satisfaction.
3. 'Spurs to adherence': comprising three subthemes – intrinsic motivators, relational motivators and collaborative agency. Intrinsic motivators included memories of ill health and aversive consequences of past non-adherence, gaining knowledge about how the medicines work and the perception that once treatment is established and effective, HIV becomes less salient. Relational motivators included the desire to stay alive and be there for their families, which was enhanced by encouragement and feedback from family members and others (e.g. positive feedback regarding the impact of adherence on the women's health or appearance). Collaborative agency illustrated how women sensed that they were collaborating with their healthcare teams, and that this partnership led to a heightened sense of agency over their health, leading to greater faith in their medication and more willingness to take it.

Framework analysis

This analysis identified perceptual barriers to adherence to ART that could be grouped into two themes: doubts about the necessity for ART and concerns about adverse effects.

Antiretroviral therapy necessity

No symptoms, no problem The participants' perceived need for ART was influenced by expectations of relief from symptoms, and that treatment was less necessary when symptoms were absent or resolved.

Fatalistic beliefs about the human immunodeficiency virus Many participants believed that they would die as a result of contracting HIV regardless of whether or not they were taking treatment.

Beliefs linked to stigma and shame The perceived shame of having a HIV diagnosis as well as denial of the HIV diagnosis, or the belief that the diagnosis must have been made in error.

Conflict regarding the roles of God and medicine Participants' belief that faith in God could cure HIV, as well as conflicting beliefs about the source of control of their HIV (e.g. God vs. ART).

Doubts about the effectiveness of antiretroviral therapy Including beliefs that natural remedies or healthy eating could replace ART and beliefs that regimens with more pills were more effective than those with fewer pills.

Concerns about antiretroviral therapy

Insufficient time to come to terms with a human immunodeficiency virus infection diagnosis before starting antiretroviral therapy Many participants were devastated and overwhelmed by their diagnosis and found it challenging to come to terms with being HIV positive and commit to lifelong treatment at the same time. There was insufficient time for them to articulate their concerns about ART to the doctor, meaning that they started treatment with strong concerns about taking it.

Risk of disclosure of human immunodeficiency virus infection through antiretroviral therapy Concerns that attending HIV clinics or taking ART (often large, colourful tablets) would reveal their HIV status to others, with potentially severe social and/or economic consequences, including homelessness and ostracism. Particularly when patients were dependent on people who were unaware of their HIV diagnosis.

Effect of antiretroviral therapy side effects on quality of life This concern was particularly salient among participants who had not experienced HIV symptoms before initiating treatment. For some, the promise of longer-term health was not enough to outweigh the negative experience of taking medication.

Physical repulsion The physical attributes of the ART, including the large size, taste and difficulty swallowing, were perceived as nausea inducing and repulsive.

Long-term effects of antiretroviral therapy Fears about potential damage to the body from taking ART in the long term.

Stakeholder consultation about antiretroviral therapy for men who have sex with men

Discussion with patient representatives from iBase, the UK-Community Advisory Board and with practising clinicians from HIV clinics with a large population of MSM confirmed that the issues identified in our preparative work were still relevant for MSM, and further adaptation of study measures was not necessary.

Study 2: refining our existing methods for eliciting and measuring barriers to antiretroviral therapy uptake and adherence

Table 1 itemises each of the necessity beliefs and concerns identified in study 1 and shows how decisions were made. The following questionnaire items were added:

- I'm worried that others will find out I am HIV positive if they see I am taking antiretroviral medication.
- God will cure my HIV.
- I worry that the taste of the medication will make me feel unwell.
- I worry that the tablets will be hard to swallow.

Study 3: development of intervention manuals and materials to increase uptake and adherence to antiretroviral therapy

A logic model characterised processes from the problem (delay to uptake and low adherence to ART) to the desired outcome (adherence and undetectable viral load) (*Figure 1*). Modifications to the original design of the intervention were made in response to changes to HIV treatment guidelines, the publication of new data, our research findings and user testing. The SUPA intervention was described in detail according to the TIDieR checklist;[46] Perceptions and Practicalities Approach[27] and Behaviour Change Technique taxonomy, Version 1.[48] The intervention comprised:

1. standardised information about HIV and its treatment, designed to address common, adherence-related misconceptions and concerns and signpost patients to further support to help overcome perceptual and practical barriers to ART uptake and adherence, delivered through an animated video and a booklet

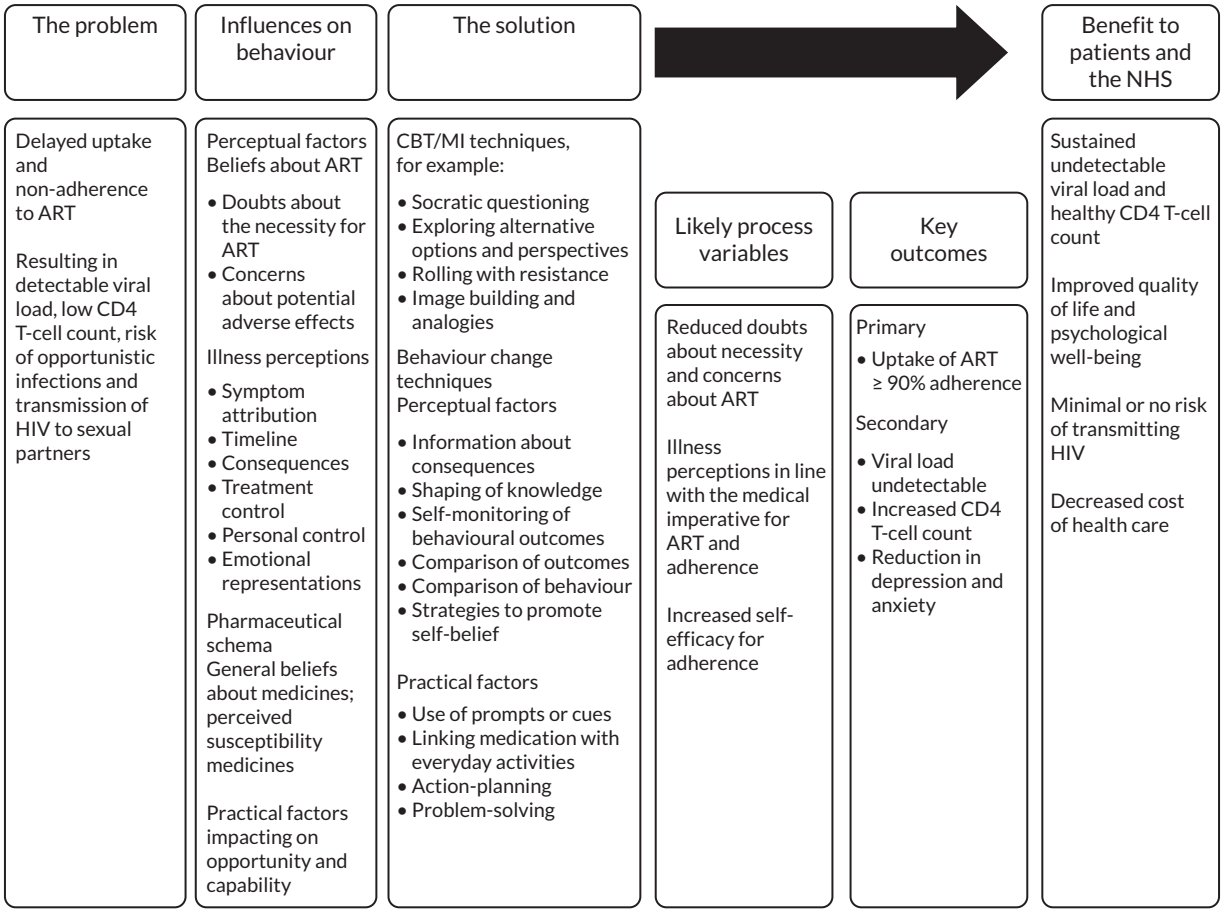

FIGURE 1 Logic model for the SUPA intervention. CD4, cluster of differentiation 4.

2. personalised discussion to introduce the SUPA video and booklet and address patient concerns about ART and barriers to adherence, applying CBT in up to four sessions. The first session was face to face with a HIV nurse and lasted up to 1 hour. A follow-up session was scheduled within 1 month with subsequent follow-up (booster sessions) at 3 and 6 months, which were held in clinic or by telephone according to patient preference.

Limitations

Study 1

Participants were selected on the basis of presumed non-adherence as determined through examination of patient notes and blood test results. This may have introduced bias, as many patients do not disclose non-adherence to health professionals, and missing doses does not always translate to detectable viral load. Patients who do not adhere to treatment are likely to miss the HIV clinic appointments or be lost to follow-up and, therefore, they were unavailable to recruit. Furthermore, we recruited only patients who we considered to be non-adherent. Additional recruitment of patients with high adherence may have been useful to identify facilitators of adherence. The IPA analysis was conducted among a homogeneous group of women from West Africa. This was valuable as it provided an in-depth examination of personal experiences of adherence in this group. However, further analyses of other homogeneous samples, such as men from West Africa or women from the Caribbean, are warranted. As we included the broader sample of men and women from Africa and the Caribbean in the parallel framework analysis, we did not consider including a diverse set of samples to be a priority for the IPA analysis. In accordance with this methodology, the priority was to focus in-depth on the perceptions and experiences of individuals rather than to obtain a sample that was representative of a wider population.

Study 2

We did not conduct a full pilot evaluation of the amended BMQ-ART (see *Appendix 5*), and were therefore unable to assess the validity of the updated scales. However, our methodology was in line with the recommendations for the adaptation of the BMQ for different contexts.[43]

Study 3

We kept detailed records of the rationale for decisions made during the development process and used the TIDieR checklist.[46] To overcome the difficulty of achieving a balance between the collaborative and personalised nature of intervention sessions and the generic content and educational language of the SUPA manual, we used collaborative language and illustrative quotations from our preparatory research and study 1.[36,39,49] The SUPA manual covers a range of perceptual and practical barriers, but only some sections of the manual are applicable to individual patients. This meant that the SUPA materials contained some information that was not relevant to individual patients. We did not create bespoke information tailored to each individual patient's needs and preferences. Intervention content was tailored to individual patient needs by the study nurse using CBT applied in up to four face-to-face or telephone consultations, according to patient preferences.

Interrelation with other workstreams

Workstream 1 informed the development of the SUPA intervention and the selection and refinement of outcome measures for our RCT (WS3; study 5). It led us to select participants who were at risk of non-adherence before they initiated treatment and to develop a comprehensive intervention to address both uptake and adherence, targeted at the point of treatment offer rather than two separate interventions for uptake and adherence as conceived. It also influenced our decision to recruit trial participants from centres with greater representation of Black African and Black Caribbean patients who are at greater risk of disengagement from treatment and care. The BMQ-ART refined in study 2 was used as a screening tool with patients for whom treatment initiation was recommended. Scores on the questionnaire determined risk of non-adherence behaviour (both treatment delay and suboptimal adherence following ART initiation) and, therefore, eligibly for the SUPA trial.

Workstream 2: feasibility and acceptability of cognitive–behavioural therapy-based adherence support for antiretroviral therapy

Aims

To determine the feasibility and acceptability of the SUPA intervention (study 4).

Methods of data collection and analysis

The feasibility of the SUPA intervention was established in two studies: (1) a quantitative study embedded in the SUPA trial (WS3) and (2) a qualitative study conducted in a subset of patients who received the SUPA intervention.

Quantitative feasibility study

A two-step process was used to recruit patients to the SUPA trial. In step 1, ART-naive patients who were offered ART were invited to participate in a study of patients' views about HIV and its treatment [i.e. the SUPA screen study (see *Appendix 6*)]. Those who accepted completed a questionnaire to assess their perceived necessity for treatment and concerns about treatment, indicating risk of non-adherence to ART (BMQ-ART) (see *Appendix 5*).

Those who received a score indicating low risk for non-adherence were asked to remain in an observational follow-up for 12 months. If patients received a score indicating a high risk for non-adherence, they were asked to take part in recruitment step 2 – the SUPA trial (see *Workstream 5: preparing for implementation within the National Health Service*) (*Figure 2*).

To assess feasibility, we examined recruitment and retention to both the SUPA screen and the SUPA trial over a 12-month period, assessing the number of patients who were eligible, screened, enrolled, randomised to receive CBT or care as usual (CAU), lost to follow-up, discontinued and analysed. This was reviewed by the IDMC and PMG. Data completeness at baseline was also reviewed. Recruitment to the SUPA trial was reviewed every 6 months in line with good practice.

Qualitative feasibility and acceptability study

Qualitative interview transcripts were thematically analysed to determine: acceptability of the intervention (see *Appendix 7*) and the process of change (see *Appendix 8*). A subset of 24 participants (*Table 2*) who received the SUPA intervention were interviewed by a research assistant (independent to the research nurse delivering the intervention to avoid bias) after receiving the last intervention session. Interviews were semistructured based on an interview guide with prompts to explore the participants' responses. Participants were asked about their perceptions of the intervention, including their overall impression, positive features, less good elements and ease of comprehension. Process of change was assessed in a second qualitative analysis of interview data to explore changes in beliefs and experiences of ART following the intervention. Interviews were audio-recorded and transcribed verbatim. Transcripts were subjected to thematic analysis.

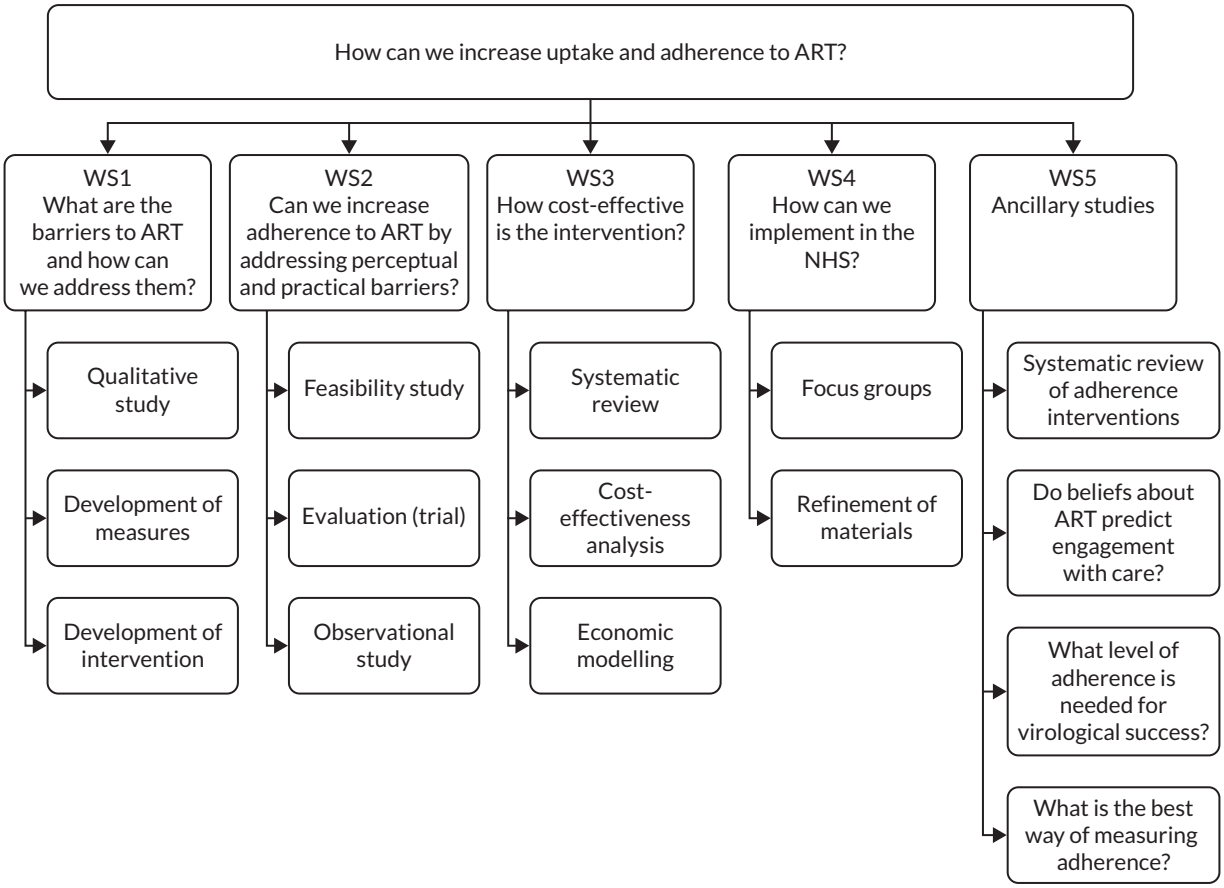

FIGURE 2 The SUPA programme research pathway.

TABLE 2 Characteristics of participants who took part in post-intervention interviews (*n* = 24)

Characteristic	Participants
Gender, *n* (%)	
Female	7 (30)
Male	17 (70)
Ethnicity, *n* (%)	
White	7 (29)
Black African	9 (38)
Black other	3 (12)
Other	4 (17)
Not stated	1 (4)
Sexual orientation, *n* (%)	
Heterosexual	14 (58)
MSM	10 (42)
Age (years), median (IQR)	6.5 (27.5–44.5)

IQR, interquartile range.

Key findings

Quantitative study

Recruitment and retention over the first year of the Supporting UPtake and Adherence to antiretroviral therapy studies

Enrolment to the SUPA screen and SUPA trial studies began in February 2014 at Birmingham and King's College Hospital, and, by May 2014, six sites were open. During the first year (WS3), 213 participants were recruited to SUPA screen, and baseline data were complete for 207 participants. Of the 207 participants with baseline data, 86 (42%) were eligible for the inclusion in SUPA trial, and 46 participants had been successfully randomised (CAU, *n* = 23; CBT, *n* = 23). Twenty-eight patients declined to take part, six were screen failures and seven were pending a decision. We could not assess the suitability of the primary end point because only five patients were due to complete and had completed the trial within the period of the feasibility study. Rates of attrition were low in both the SUPA screen and the SUPA trial studies: SUPA screen – 5 out of 213 patients had not been reached for follow-up appointments; SUPA trial – 2 out of 46 patients had withdrawn [1 because of difficulty using Medication Event Monitoring System (MEMS) caps and 1 because of competing time commitments].

Qualitative study

Acceptability of the Supporting UPtake and Adherence to antiretroviral therapy intervention

The thematic analysis identified two main themes: (1) reasons for participation trial and (2) experience of intervention content and delivery (*Table 3*).

Reasons for participation

Most participants had been recently diagnosed with HIV. They had a strong desire to learn more about HIV and its treatment to help them so that they can cope with their diagnosis and get on with their lives. Many were keen to play an active role in their treatment and thought that the SUPA intervention trial would help themselves, but also give something back to other PLWH. For some, especially those who had not disclosed their HIV diagnosis, the SUPA intervention sessions provided a place where they could talk about their experiences and concerns about HIV and ART and receive confidential advice and support.

Experiences of the intervention content and delivery

Participants generally found the SUPA manual and animations easy to understand, relevant and informative. Some participants would have liked more information about the emotional impact of living with HIV and ways of managing and coping with their own emotional response as well as other people's. Others felt that more information about managing relationships and meeting a new sexual partner when living with HIV would have been useful. Participants described the SUPA nurse as a source of emotional support. Because they found the nurse easy to speak to, they were able to open up about their concerns. For some, talking to the SUPA nurse was preferable and less anxiety-provoking than talking to their doctor. Participants valued being able to choose the timing of SUPA sessions and their scheduling

TABLE 3 Acceptability of the SUPA intervention: themes and subthemes

Themes	Reasons for participation	Experiences of intervention content and delivery
Subthemes	Increased knowledge	Intervention materials
	Taking an active role	Approachable staff
	Need for support	Convenience and timing
	Recommendation	

following routine appointments. Although many patients said that four sessions had been sufficient to gain the knowledge and support that they needed, others said that they would have benefited from extra sessions. Some would have liked to have been able to access additional support to address new issues if and when they arise. There were also differences of opinion regarding the length of sessions: many said that 1 hour was long enough, but others would prefer more time with the nurse. During the trial, adherence was monitored using MEMS caps. Although these were not part of the intervention (the control group also used MEMS caps), some participants felt that the MEMS caps had been a useful adherence aid.

Process of change

The impact of the intervention on participants' experiences of HIV and ART could be categorised into four themes, as follows.

Understanding human immunodeficiency virus

Participants reported that their knowledge about HIV had increased over time as a result of the SUPA intervention.

Perceptions of personal need for antiretroviral therapy (necessity beliefs)

The intervention addressed misconceptions about ART necessity and provided a rationale for taking ART to decrease the risk of illness and death and transform HIV into a manageable long-term illness. It gave participants a coherent rationale for continuing with their medication and not missing doses, for example, by providing an explanation about what happens to the virus when doses are taken or missed. This knowledge and the ability to see the impact of ART on their blood test results, encouraged participants to take and continue with their medications.

Concerns about human immunodeficiency virus/antiretroviral therapy

The intervention appeared to address participants' concerns about HIV. Some reported new awareness that having a diagnosis of HIV did not mean that they could not live a normal life or have children. However, this shift in perspective did not occur for all participants. Examples of ways in which the SUPA intervention addressed participants' concerns about ART included the provision of a coherent explanation of side effects, providing strategies for dealing with side effects and challenging the belief that taking medicines would alert other people to the fact that they were HIV positive.

Practical and emotional support

Some participants reported that they had learnt practical strategies to cope more effectively with their HIV diagnosis and adherence to ART. An example of this was supporting participants to discuss their concerns about HIV with other people. This had various benefits, such as enabling the participant to discuss their HIV status with sexual partners and enabling their partner to seek a HIV test. The SUPA nurse also helped patients to manage ART side effects by liaising with doctors, nurses and pharmacists on their behalf, and by addressing problems that they were having with side effects. Participants reported benefiting from simple strategies to help with the practicalities of taking ART (e.g. drinking more water to overcome difficulties in swallowing larger pills and using smart phone reminders to avoid forgetting doses). Many participants identified the emotional support that they received in their face-to-face sessions with the SUPA nurse as a major benefit. The sessions provided access to an approachable, friendly healthcare professional who they were able to talk to about their diagnosis and share their fears and concerns without fear of judgement. This was particularly beneficial to participants who had not talked to friends or family about their diagnosis.

Limitations

It was not possible to assess the feasibility of the primary outcome (electronic monitoring of adherence) data because only five patients were due to complete and had completed the trial. The qualitative interviews were conducted on a convenience sample of those willing to attend the clinic for an additional interview after the final trial follow-up. Those who agreed may have had a more positive experience of the intervention than those who declined, creating a risk of bias. Although participants were interviewed soon after completing the trial, they were required to remember their decisions and experiences for a period of 6 months, risking recall bias. Moreover, although the interviews were not conducted by SUPA nurses, the research assistant was a member of the SUPA research team and participants may have been predisposed to provide a positive account.

Conclusions

The findings of the embedded feasibility study to examine recruitment and retention over the first year raised some concerns about recruitment rates, but rates of attrition were very low. The qualitative analysis of interviews with PLWH who received the SUPA intervention suggested that it was acceptable to patients and that it addressed misconceptions about HIV and ART, enhanced patients' perceptions of their personal necessity for ART and reduced ART concerns and ART intrusiveness. In addition, the intervention provided a source of emotional support.

Workstream 3: randomised controlled trial to assess the efficacy of the Supporting UPtake and Adherence to antiretroviral therapy intervention

Aims

The primary aim was to assess the efficacy of the SUPA intervention in improving ART uptake and adherence among previously ART-naive PLWH who had received a recommendation to start treatment. The secondary aims were to assess the impact on clinical outcomes [viral load and cluster of differentiation 4 (CD4) T-cell count], patient-reported outcomes and engagement with care, and to determine whether or not patients' beliefs about ART change over time, in those participants who remained in the observational follow-up study (either because they were not eligible for the trial or because they declined to take part).

Methods of data collection and analysis

Recruitment to Supporting UPtake and Adherence to antiretroviral therapy trial and Supporting UPtake and Adherence to antiretroviral therapy screen (parallel cohort observational study)

The efficacy of the SUPA intervention was determined in a RCT.[50] ART-naive PLWH were recruited from eight HIV clinics in NHS hospitals across England. Informed by the findings of WS1, trial sites were selected on the basis of clinician-reported issues with disengagement with care and representation of people with a higher risk of non-engagement (women and people of Black African or non-white ethnicity).[34] Detailed inclusion and exclusion criteria are included in the protocol.

A two-step recruitment process was used.

Step 1

Patients offered ART were invited to take part in a study of 'patient views about HIV and its treatment': SUPA screen. This was an observational, longitudinal follow-up study examining changes in perceptions of ART over time. PLWH who met the inclusion criteria completed the BMQ-ART (see *Appendix 5*)[23] and were assigned to one of two groups based on their scores: (1) a group with a high risk of non-adherence or (2) a group with low risk of non-adherence. Those with low ART necessity scores or high ART concerns scores were deemed to be at high risk for non-adherence.[10]

Step 2

Patients at high risk of non-adherence and who met the trial eligibility criteria were invited to take part in the SUPA trial. Patients at low risk of non-adherence continued in the SUPA screen study.

Confidentiality, ethics and legal considerations are described in the protocol.[50]

Patients who met the inclusion criteria for SUPA trial were randomly assigned (1 : 1) to receive CBT-based adherence support or CAU. Participants were followed up at baseline and at 1, 3, 6 and 12 months, with an additional study visit at 1 month in the intervention arm to identify any immediate intervention effects. Self-report measures were completed at each study visit. CD4 T-cell count and viral loads were collected from the participant's medical file by a research assistant.

Participants randomised to the intervention group received the SUPA intervention (described in WS1, study 3) within 1 month of enrolment. The first two intervention sessions took place within 1 month of enrolment. Sessions 3 and 4 provided optional additional support, according to patient preference, approximately 3 and 6 months post randomisation (see *Scientific summary*, *Figure b*).

Participant follow-up and assessment

The baseline visit comprised enrolment, randomisation, trial study questionnaires and the first intervention session. Additional study visits were scheduled at 1, 3, 6 and 12 months post randomisation (see *Scientific summary*, *Figure b*). If a participant chose to initiate treatment during the study, the pharmacy at each site dispensed the prescription in a bottle with a MEMS® TrackCap (AARDEX Group, Seraing, Belgium). The research assistant explained to the participant how to use the MEMS bottle and cap and provided written instructions, if desired.

Assessment of intervention fidelity

All participants could decide whether or not to have their sessions recorded, which did not preclude inclusion in the trial. Seventy-five participants consented to recording. A rating scale previously used in similar studies comparing CBT and counselling in the treatment of chronic fatigue was modified for use in this trial.[51] Practice recordings were conducted with two trained clinical psychologists working independently to enable adequate inter-rater reliability (kappa coefficient = 0.7). The ratings were carried out on a computer-generated random selection of 20% of session 2 recordings. Two recordings were double-rated to check for inter-rater reliability, and the first five recordings were double-rated and cross-checked for consistency. Four areas were rated, with scores described as percentages: (1) overall therapeutic alliance (one item), (2) CBT skills (five items), (3) MI skills (two items) and (4) overall therapist adherence to the manual (one item). The mean scores across recordings were as follows, respectively: (1) 95%, (2) 67%, (3) 86% and (4) 83%.

Supporting UPtake and Adherence to antiretroviral therapy trial: primary outcome (Medication Event Monitoring System adherence)

Adherence to ART was assessed within each patient-month as follows: in the months prior to ART initiation, adherence was set to 0%; once ART had been started, the proportion of days within the month with full adherence was determined using daily MEMS data that recorded whether or not the recommended dose had been taken each day. Adherence within each patient-month was then classified as high (≥ 90%) or low (< 90%), and the prespecified primary outcome was met if individuals achieved good adherence in > 80% of the months during which they were followed up. The 80% threshold to define a good outcome was based on the fact that a 1- to 2-month delay to ART initiation following a recommendation to start ART could be reasonably expected but that after this, a consistent high level of adherence to ART (≥ 90%) would be necessary for the patient to achieve and maintain viral load suppression.

Supporting UPtake and Adherence to antiretroviral therapy trial: secondary outcomes

Prespecified secondary end points were as follows:

- treatment failure
- disengagement from care
- regimen switches (defined as the total number of regimen changes over the 12-month study period)
- regimen switches for any reason (one or more switches at the same time counts as one switch, excluding changes from lamivudine (3TC) to emtricitabine (FTC) and vice versa where these are simply due to changing a fixed dose combination tablet and excluding switches of a component from twice to once daily)
- referral out of the intervention
- changes in beliefs about ART (BMQ–ART)[23,35]
- perceived intrusiveness of ART [highly active antiretroviral therapy (HAART) Intrusiveness Scale (HIS)]
- depression and anxiety [Hospital Anxiety and Depression Scale (HADS)][52,53]
- health service use (Client Service Receipt Inventory)[54]
- health-related quality of life [EuroQol-5 Dimensions, five-level version (EQ-5D-5L)][55]
- symptoms associated with HIV and ART [Symptoms Associated with HIV and ART Questionnaire (SAQ)][17]
- perceptions of HIV [Brief Illness Perception Questionnaire (BIPQ)][56]
- self-reported adherence [measured using the Medication Adherence Report Scale-5 item version (MARS-5)][57]
- readiness to initiate ART (measured using the HIV Treatment Readiness Scale, a single item developed for this study)
- knowledge about HIV treatment (measured using 13 items from the HIV Treatment Knowledge Scale).[58]

Measures are described in the trial protocol.[50]

Supporting UPtake and Adherence to antiretroviral therapy screen: a parallel cohort, longitudinal, follow-up study of change in antiretroviral therapy beliefs over time

We examined changes in perceptions of ART over 12 months in people initiating their first ART regimen who were either not eligible for the SUPA trial, or who were eligible but declined to take part in the trial. Beliefs about ART (necessity beliefs, concerns, and necessity concern differential) were measured at the 3-, 6- and 12-month follow-ups, and changes in mean and median scores from baseline were calculated. A paired *t*-test for means and Wilcoxon matched-pairs signed-rank test were used to test for statistical significance. Viral loads and CD4 T-cell counts at baseline and at 3, 6 and 12 months were also described.

Statistical analysis

As the study selected for an at-risk group, and based on the expected costs of the intervention, we considered that a 15% difference in the primary outcome between the intervention and control groups would be clinically significant. We estimated that to detect a 15% difference in the primary end point of this size (80% power, two-sided alpha = 0.05), we needed to recruit 372 participants in total (186 per group).

Intention-to-treat analysis of the primary end point was carried out. The primary analysis excluded individuals randomised in error and those who had been withdrawn from the study at any time. In addition, on the basis that the estimate of the end point would not be reliable, we excluded participants with an average monthly adherence score of zero according to MEMS for > 60% of the available follow-up time where it was known that the participant had started ART at baseline. This was because it was unlikely that the individual was using the MEMS caps correctly.

Continuous variables were summarised by medians and interquartile ranges (IQRs) or means and standard deviations (SDs), as appropriate, depending on the distribution. These continuous variables were then compared between groups using rank-sum tests or *t*-tests, for medians and means respectively. Comparisons of change from baseline in continuous variables were adjusted for any baseline imbalances using either quantile or normal linear regression (depending on the shape of the distribution). Categorical variables were summarised by frequency tables, and compared between groups using chi-squared tests, unless any cell count was < 5 or cell percentage was < 5%, in which case exact tests were used. Binary variables were summarised by percentages, using standard exact 95% confidence interval (CI) for the risk differences. Time-to-event variables were summarised using Kaplan–Meier curves and average differences between randomised groups, estimated using Cox models. Patients without the event recorded were censored at their last clinic visit. Proportionality of hazards was tested; where significant departures existed, varying differences between randomised groups over time were estimated using flexible parametric models of Royston and Parmar. Rates of treatment switching were analysed using Poisson regression, including all changes to ART as events and the total time under follow-up through the earliest of 12 months or the last patient visit as the person-time at risk. The primary analysis was not stratified by clinical centre.

Subgroup analyses were performed to assess heterogeneity in primary end point according to differences between randomised groups. This included differences in gender, ethnicity, the number of intervention sessions attended, time of diagnosis (early, treatment indicated at point of diagnosis, vs. late, treatment not indicated at point of diagnosis), reasons for starting the treatment (for clinical need vs. starting for treatment as prevention), baseline CD4 T-cell count, and baseline BMQ scores (low necessity vs. high concern vs. both low necessity and high concern). Subgroup analyses used logistic regression to model interactions between randomised groups and the factors above. We used SAS (version 9.4; SAS Institute Inc., Cary, NC, USA. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc. in the USA and other countries. ® indicates USA registration) or Stata® (version 16; StataCorp LP, College Station, TX, USA) for all analyses (see *Appendix 9* for the full statistical analysis plan).

Key findings

Between March 2014 and July 2017, 1575 patients were assessed for eligibility. Of these patients, 349 were eligible to take part in the RCT and 213 were randomised: 107 to the CAU group and 106 to the CBT group (i.e. the SUPA intervention). The Consolidated Standards of Reporting Trials (CONSORT) study flowchart is reported in *Figure 3*. A total of 143 participants (CAU, *n* = 72; CBT, *n* = 71) met the inclusion criteria of having more than four concerns and fewer

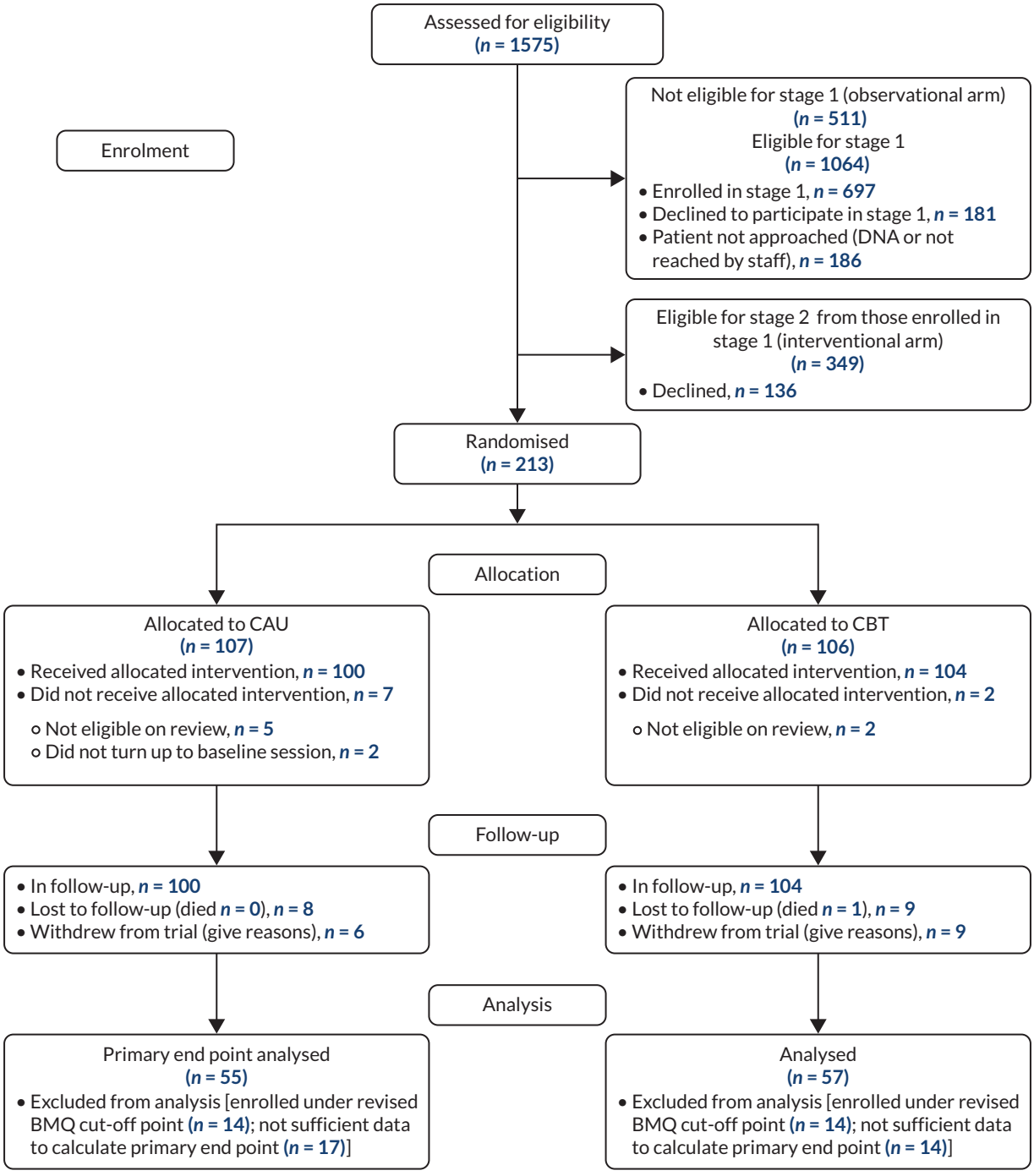

FIGURE 3 The CONSORT 2010 flow diagram. DNA, did not attend.

than two necessity beliefs. Our target of 372 was not reached. The baseline characteristics of participants are reported in *Table 4*.

A total of 141 (98.6%) participants initiated ART at/prior to the first visit: 71 (50.35%) in the CAU group and 70 (49.65%) in the CBT group (*Table 5*). The median number of days from randomisation to dispensing of ART was −25 days (IQR −39 to −8 days) for the total sample, −28 days (IQR −42 to −9 days) in the CAU arm and −19 days (IQR −39 to −7 days) in the CBT arm. *Table 6* shows the follow-up status at each visit. The retention rate, defined as proportion of sample remaining on the trial at 12 months, was 55.9% (58.3% in the CAU group; 53.5% in the CBT group).

TABLE 4 Baseline characteristics of SUPA trial participants

Characteristic	Total	Regimen	
		CAU	CBT
Number of participants	143	72	71
Site, *n* (%)			
10	33 (23.1)	16 (22.2)	17 (23.9)
20	25 (17.5)	14 (19.4)	11 (15.5)
30	35 (24.5)	18 (25.0)	17 (23.9)
40	21 (14.7)	9 (12.5)	12 (16.9)
50	12 (8.4)	6 (8.3)	6 (8.5)
60	6 (4.2)	3 (4.2)	3 (4.2)
70	11 (7.7)	6 (8.3)	5 (7.0)
Sex, *n* (%)			
Male	86 (60.1)	43 (59.7)	43 (60.6)
Female	57 (39.9)	29 (40.3)	28 (39.4)
Ethnicity, *n* (%)			
White	49 (34.3)	29 (40.3)	20 (28.2)
Black African	52 (36.4)	26 (36.1)	26 (36.6)
Black other	27 (18.9)	11 (15.3)	16 (22.5)
Other	13 (9.1)	5 (6.9)	8 (11.3)
Not stated	2 (1.4)	1 (1.4)	1 (1.4)
Years in the UK, *n* (%)			
< 5	18 (12.6)	5 (6.9)	13 (18.3)
≥ 5	78 (54.6)	38 (52.8)	40 (56.3)
N/A: born in the UK	45 (31.5)	29 (40.3)	16 (22.5)
Not stated	2 (1.4)	0 (–)	2 (2.8)
Sexuality, *n* (%)			
MSM	55 (38.5)	30 (41.7)	25 (35.2)
Other/not stated	88 (61.5)	42 (58.3)	46 (64.8)
Marital status, *n* (%)			
Married/in partnership	47 (32.9)	28 (38.9)	19 (26.8)
Single/separated	90 (62.9)	42 (58.3)	48 (67.6)
Widowed/other	6 (4.2)	2 (2.8)	4 (5.6)
Have children, *n* (%)			
No	85 (59.4)	44 (61.1)	41 (57.8)
Yes	58 (40.6)	28 (38.9)	30 (42.3)

continued

TABLE 4 Baseline characteristics of SUPA trial participants (*continued*)

Characteristic	Total	Regimen	
		CAU	CBT
Living with persons other than family, *n* (%)			
No	87 (60.8)	43 (59.7)	44 (62.0)
Yes	56 (39.2)	29 (40.3)	27 (38.0)
Education, *n* (%)			
Basic/school	34 (23.8)	17 (23.6)	17 (23.9)
Higher education	109 (76.2)	55 (76.4)	54 (76.1)
Employment, *n* (%)			
Working	75 (52.5)	41 (56.9)	34 (47.9)
Not working	63 (44.1)	26 (36.1)	37 (52.1)
Other/not stated	5 (3.5)	5 (6.9)	0 (–)
Age (years)			
Median	38	41	37
IQR	31–46	31–47	28–45
Range	18–71	21–69	18–71
18–29, *n* (%)	33 (23.1)	14 (19.4)	19 (26.8)
30–39, *n* (%)	40 (28.0)	20 (27.8)	20 (28.2)
40–49, *n* (%)	44 (30.8)	25 (34.7)	19 (26.8)
50–59, *n* (%)	16 (11.2)	11 (15.3)	5 (7.0)
≥ 60, *n* (%)	10 (7.0)	2 (2.8)	8 (11.3)
Mode of HIV transmission, *n* (%)			
Sexual	136 (95.1)	67 (93.1)	69 (97.2)
Blood contact	1 (0.7)	1 (1.4)	0 (–)
Needles	2 (1.4)	1 (1.4)	1 (1.4)
Other/not stated	4 (2.8)	3 (4.2)	1 (1.4)
Clinical diagnoses, *n* (%)			
AIDS	18 (12.6)	9 (12.5)	9 (12.7)
Other HIV morbidity	1 (0.7)	1 (1.4)	0 (–)
HBV, CD4 < 500 cells/mm^3	5 (3.5)	1 (1.4)	4 (5.6)
HBV, CD4 ≥ 500 cells/mm^3	2 (1.4)	0 (–)	2 (2.8)
HCV, CD4 < 500 cells/mm^3	5 (3.5)	2 (2.8)	3 (4.2)
Non-AIDS malignancy	0 (–)	0 (–)	0 (–)
Any of the above	27 (18.9)	12 (16.7)	15 (21.1)
Pregnant (women), *n* (%)	3 (5.3)	0 (–)	3 (10.7)

TABLE 4 Baseline characteristics of SUPA trial participants (*continued*)

Characteristic	Total	Regimen	
		CAU	CBT
CD4 T-cell count (cells/mm^3)[a]			
n	143	72	71
Median	351	364	333
IQR	160–529	132–530	170–529
Range	8–2224	10–1275	8–2224
HIV RNA (log_{10} copies/ml)[a]			
n	143	72	71
Median	3.7	3.9	3.4
IQR	2.3–4.9	2.5–4.9	2.1–4.9
Range	1.7–6.4	1.7–6.3	1.7–6.4
≤ 50 copies/ml, *n* (%)	27 (18.9)	11 (15.3)	16 (22.5)
Baseline ART necessity scores[a]			
Median	3.7	3.8	3.7
Range	2.2–4.8	2.3–4.8	2.2–4.8
Mean (SD)	3.71 (0.58)	3.73 (0.59)	3.69 (0.56)
n (%) with low necessity scores	22 (15.4)	9 (12.5)	13 (18.3)
Baseline ART concern scores[a]			
Median	3.4	3.3	3.5
Range	2.0–5.0	2.2–5.0	2.0–4.6
Mean (SD)	3.46 (0.47)	3.39 (0.48)	3.54 (0.46)
n (%) with high concern scores	137 (95.8)	68 (94.4)	69 (97.2)
Baseline knowledge scores (% correct scores out of total)[a]			
n	125	64	61
Median	76.9	76.9	76.9
IQR	53.8–84.6	53.8–84.6	46.2–84.6
Range	0–100	0–100	0–100
Mean (SD)	64.7 (27.0)	64.3 (28.3)	65.2 (25.7)
Baseline treatment readiness score[a]			
n	107	55	52
Median	5	4	5
IQR	3–5	3–5	3–5
Range	1–5	1–5	1–5
Mean (SD)	3.79 (1.50)	3.67 (1.58)	3.92 (1.43)

HBV, hepatitis B virus; HCV, hepatitis C virus; N/A, not applicable; RNA, ribonucleic acid.
a The last value on or preceding the baseline date.

TABLE 5 Initiation of ART at or prior to first visit

Characteristic	Total	Regimen	
		CAU	CBT
Number of participants	143	72	71
Total starting ART after first visit, *n* (%)	141 (98.6)	71 (98.6)	70 (98.6)
Days from randomisation to dispensing of ART[a]			
Median	−25	−28	−19
IQR	−39 to −8	−42 to −9	−39 to −7
Range	−70 to 513	−70 to 86	−56 to 513
Initial regimen (% of those starting ART)			
PI based	37 (26.2)	16 (22.5)	21 (30.0)
NNRTI based	42 (29.8)	23 (32.4)	19 (27.1)
INSTI based	55 (39.0)	29 (40.9)	26 (37.1)
Other	7 (5.0)	3 (4.2)	4 (5.7)
Was initial regimen a STR?, *n* (%)			
No	101 (71.6)	54 (76.1)	47 (67.1)
Yes	10 (28.4)	17 (23.9)	23 (32.9)

INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; STR, single-tablet regimen.
a A negative value indicates ART dispensing prior to randomisation (i.e. patient had already started ART).

TABLE 6 Follow-up status at each visit

Characteristic	Total	Regimen	
		CAU	CBT
Number of participants	143	72	71
Overall status, *n* (%)			
Died	1 (0.7)	0 (–)	1 (1.4)
LTFU	9 (6.3)	4 (5.6)	5 (7.0)
No MEMS	43 (30.1)	21 (29.2)	22 (31.0)
Withdrawn	10 (7.0)	5 (6.9)	5 (7.0)
Remaining on trial at 12 months	80 (55.9)	42 (58.3)	38 (53.5)
Randomisation date, range	March 2014–July 2017	April 2014–July 2017	March 2014–June 2017
Baseline date, range	March 2014–July 2017	April 2014–July 2017	March 2014–June 2017
Randomisation at baseline (entry into screening), *n* (%)	94 (65.7)	47 (65.3)	47 (66.2)
Maximum number of days after randomisation for baseline visit	69	38	69

TABLE 6 Follow-up status at each visit (*continued*)

Characteristic	Total	Regimen	
		CAU	CBT
Month 1 (CBT arm only)			
Number eligible	71	N/A	71
Withdrawn, *n* (%)	3 (4.2)		3 (4.2)
Incomplete, *n* (%)	2 (2.8)		2 (2.8)
Died, *n* (%)	0	0	0
Attended/complete, *n* (%)	66 (93.0)		66 (93.0)
Days from randomisation, median (range)	39 (12–103)		39 (12–103)
Month 3			
Number eligible[a]	140	72	68
Withdrawn, *n* (%)	5 (3.6)	4 (5.6)	1 (1.5)
Incomplete, *n* (%)	5 (3.6)	1 (1.4)	4 (5.9)
Died, *n* (%)	0	0	0
Attended/complete, *n* (%)	130 (92.9)	67 (93.1)	63 (92.6)
Number of days from randomisation, median (range)	92 (66–190)	88 (66–190)	97 (76–179)
Month 6			
Number eligible[a]	135	68	67
Withdrawn, *n* (%)	1 (0.7)	1 (1.5)	0 (–)
Incomplete, *n* (%)	8 (5.9)	4 (5.9)	4 (6.0)
Died, *n* (%)	1 (0.7)	0 (–)	1 (1.5)
Attended/complete, *n* (%)	125 (92.6)	63 (92.6)	62 (92.5)
Number of days from randomisation, median (range)	182 (142–476)	187 (149–340)	181 (142–476)
Month 12			
Number eligible[a]	133	67	66
Withdrawn, *n* (%)	1 (0.8)	0 (–)	1 (1.5)
Incomplete, *n* (%)	16 (12.0)	10 (14.9)	6 (9.1)
Died, *n* (%)	0 (–)	0 (–)	0 (–)
Attended/complete, *n* (%)	116 (87.2)	57 (85.1)	59 (89.4)
Number of days from randomisation, median (range)	355 (212–551)	364 (308–524)	344 (212–551)

LTFU, lost to follow-up; N/A, not applicable.
a Number eligible refers to the number of participants who had not been withdrawn or died at any of the previous visits.

Antiretroviral therapy trial primary end point

The number of participants with sufficient data for primary end-point analysis was 112 (CAU, *n* = 55; CBT, *n* = 57), of whom 17 (15.2%) met the primary end point (> 80% of months with an average monthly adherence of ≥ 90%): 9 (16.4%) in CAU group and 8 (14.0%) in CBT group (*p* = 0.94) (*Table 7*).

Median percentage adherence by Medication Event Monitoring System

The median percentage adherence according to MEMS was 64.3% (CAU, 61.9%; CBT, 66.5%; *p* = 0.40). At 12 months, the self-reported adherence (median MARS-5 score) at 12 months was 24.5 (IQR 19–25) in the CAU group and 24.5 (IQR 19–25) in the CBT group. At the 3-month follow-up, the number of those with high adherence (MARS-5 score ≥ 24) was significantly higher in the CBT group than in the CAU group (91% vs. 71%; *p* = 0.02) (*Table 8*).

Antiretroviral therapy trial secondary end points

Beliefs about antiretroviral therapy

The results concerning beliefs about ART are reported in *Tables 9* and *10*.

Antiretroviral therapy necessity

For the total sample, the median ART necessity scores at 12 months were 4.2 (IQR 3.8–4.6) in the CAU group and 4.2 (IQR 3.8–4.5) in the CBT group. The median change in necessity scores from baseline to the 12-month follow-up was not significantly different between the groups (*p* = 0.26).

Antiretroviral therapy concerns

For the total sample, the median ART concerns scores at 12 months were 2.7 (IQR 2.3–3.1) in the CAU group and 2.8 (IQR 2.2–3.1) in the CBT group. The median change in concerns scores from baseline to the 12-month follow-up was significantly greater in the CBT group than in the CAU group [median change −0.9 (IQR −1.4 to −0.5) and −0.6 (IQR −1.4 to 0.5), respectively; *p* = 0.03] (see *Table 10*).

The ART necessity concerns differential at each time point is reported in *Table 11*.

TABLE 7 Primary end point (based on MEMS data)

Characteristic	Total	Regimen	
		CAU	CBT
Number of participants	143	72	71
Number of participants with sufficient data for primary end-point analysis[a]	112	55	57
Median proportion of months with average adherence ≥ 90%	36.3	33.3	36.9
Range of months with average adherence ≥ 90%	0–100	0–100	0–100
Number of participants meeting primary end-point criteria[b]	17 (15.2)	9 (16.4)	8 (14.0)
Overall adherence (%)			
Median	64.3	61.9	66.5
Range	0–100	0–98.5	0–100

a Excluded individuals from the analysis if they were reported to have been withdrawn from the study at any time. In addition, and on the basis that the estimate of the end point would not be reliable, excluded any participant reporting an average monthly adherence of zero for > 60% of the available follow-up time where it was known that the participant had started ART at baseline (as it was unlikely that the individual was using the MEMs caps correctly).

b Defined as having > 80% of months with an average monthly adherence of ≥ 90%. The *p*-value for comparison between regimens at 12 months = 0.94. The *p*-value for comparison between median adherence over the 12 months between the CAU and the CBT groups. The *p*-value for comparison between proportion of months with average adherence ≥ 90% = 0.49.

TABLE 8 Self-reported adherence (Medication Adherence Report Scale) at each time point

Characteristic	Total	Regimen	
		CAU	CBT
Number of participants	143	72	71
Baseline			
n	104	52	52
Median	25	25	25
Range	17–25	19–25	17–25
High adherence,[a] *n* (%)	81 (77)	35 (67)	46 (87)[b]
Month 3[c]			
n	113	59	54
Median	25	24	25
Range	13–25	13–25	19–25
High adherence,[a] *n* (%)	95 (83)	44 (75)	51 (91)[b]
Month 6[c]			
n	102	51	51
Median	24	25	24
Range	19–25	19–25	20–25
High adherence,[a] *n* (%)	79 (76)	28 (76)	40 (75)[b]
Month 12[c]			
n	102	50	52
Median	24.5	24.5	24.5
Range	19–25	20–25	19–25
High adherence,[a] *n* (%)	75 (72)	36 (71)	39 (75)[b]

a A Medication Adherence Report Scale score of ≥ 24 is classified as high adherence.
b Comparison of Medication Adherence Report Scale at 3 months (p = 0.02), 6 months (p = 0.9) and 12 months (p = 0.91).
c Three- and 6-month values are taken as those that are closest to the dates of the 3- and 6-month visit, respectively, as long as measurements were taken within 6 weeks of the visit date. Twelve-month values are taken as those that are closest to the dates of the 12-month visit as long as measurements were taken within 6 months of the 12-month visit date.

Perceived intrusiveness of antiretroviral therapy (highly active antiretroviral treatment (antiretroviral therapy) Intrusiveness Scale)

The median ART-HIS score was significantly different between the CAU and CBT groups at the 12-month follow-up. Patients in the CBT group reported significantly lower ART intrusiveness (p = 0.03) than their counterparts in the CAU group (*Table 12*). The median HIS score at 12 months was 10.8 (IQR 3.4–32.2) in the CAU group and 7.2 (IQR 1.2–21.6) in the CBT group. The CBT group achieved a significantly greater reduction from baseline in ART-HIS scores than the CAU group: the median change was −5.6 (IQR −20.4 to 1.2) and −0.5 (IQR −5.6 to 18.0), respectively (p = 0.03) (see *Table 12*).

Perceptions of human immunodeficiency virus

The median BIPQ total scores did not differ between the CAU and CBT groups, and there was no significant difference in median change in BIPQ total scores from baseline to 12 months (p = 0.11) (*Tables 13* and *14*). The median number of symptoms experienced at 12 months was 4 (range 0–10) in the CAU group and 3 (range 0–9) in the CBT group (*Table 15*).

TABLE 9 Antiretroviral therapy necessity scores (and change from baseline) at each time point

Characteristic	Total	Regimen	
		CAU	CBT
Number of participants	143	72	71
Baseline			
n	143	72	71
Median	3.7	3.8	3.7
IQR	3.3–4.1	3.4–4.2	3.3–4.1
Range	2.2–4.8	2.3–4.8	2.2–4.8
Month 3[a]			
n	116	61	55
Median	4.1	4.1	4.0
IQR	3.6–4.6	3.6–4.6	3.6–4.6
Range	2.2–5.0	3.0–5.0	2.2–5.0
Change from baseline, median	0.3	0.3	0.3
Month 3 – baseline[a]			
IQR	0.0–0.6	0.0–0.6	0.0–0.6
Range	−0.8 to 2.0	−0.8 to 1.2	−0.6 to 2.0
Month 6[a]			
n	104	52	52
Median	4.2	4.2	4.2
IQR	3.8–4.6	3.8–4.6	3.8–4.7
Range	2.5–5.0	2.8–5.0	2.5–5.0
Change from baseline, median	0.3	0.3	0.4
Month 6 – baseline[a]			
IQR	0.1 to 0.8	−0.1 to 0.6	0.2 to 0.8
Range	−0.8 to 2.0	−0.8 to 1.7	−0.6 to 2.0
Month 12[a]			
n	103	51	52
Median	4.2	4.2	4.2
IQR	3.8–4.6	3.8–4.6	3.8–4.5
Range	2.7–5.0	2.7–5.0	2.7–5.0
Change from baseline,[b] median	0.4	0.4	0.5
Month 12 – baseline[a]			
IQR	0.1–0.8	0.1–0.7	0.1–0.9
Range	−0.6 to 1.6	−0.4 to 1.6	−0.6 to 1.6
Mean (SD)	0.43 (0.48)	0.39 (0.45)	0.48 (0.51)

a Three- and 6-month values are taken as those that are closest to the dates of the 3- and 6-month visit, respectively, as long as measurements were taken within 6 weeks of the visit date. Twelve-month values are taken as those that are closest to the dates of the 12-month visit as long as measurements were taken within 6 months of the 12-month visit date.
b The *p*-value for comparison between regimens at 12 months: median, 0.26; mean, 0.35.

TABLE 10 Antiretroviral therapy concerns scores (and change from baseline) at each time point

Characteristic	Total	Regimen	
		CAU	CBT
Number of participants	143	72	71
Baseline			
n	143	72	71
Median	3.4	3.3	3.5
IQR	3.1–3.7	3.1–3.6	3.2–3.8
Range	2.0–5.0	2.2–5.0	2.0–4.6
Month 3[a]			
n	116	61	55
Median	2.7	2.8	2.6
IQR	2.3–3.3	2.4–3.3	2.1–3.3
Range	1.3–4.7	1.3–4.7	1.3–4.3
Change from baseline, median	−0.7	−0.5	−0.9
Month 3 – baseline[a]			
IQR	−1.1 to −0.2	−0.9 to −0.2	−1.4 to −0.4
Range	−2.4 to 1.1	−2.3 to 1.1	−2.4 to 0.7
Month 6[a]			
n	104	52	52
Median	2.6	2.8	2.5
IQR	2.23.0	2.3–3.1	2.1–3.0
Range	1.2–4.4	1.2–4.4	1.3–4.2
Change from baseline, median	−0.9	−0.7	−1.0
Month 6 – baseline[a]			
IQR	−1.2 to −0.3	−1.0 to −0.2	−1.4 to −0.6
Range	−2.3 to 1.3	−2.2 to 1.3	−2.3 to 0.9
Month 12[a]			
n	103	51	52
Median	2.7	2.7	2.8
IQR	2.3–3.1	2.3–3.1	2.2–3.1
Range	1.3–4.7	1.7–4.6	1.3–4.7
Change from baseline,[b] median	−0.7	−0.6	−0.9
Month 12 – baseline[a]			
IQR	−1.1 to −0.4	−0.8 to −0.3	−1.4 to −0.5
Range	−2.4 to 1.4	−2.1 to 1.4	−2.4 to 0.8
Mean (SD)	−0.74 (0.68)	−0.60 (0.62)	−0.88 (0.72)

a Three- and 6-month values are taken as those that are closest to the dates of the 3- and 6-month visit, respectively, as long as measurements were taken within 6 weeks of the visit date. Twelve-month values are taken as those that are closest to the dates of the 12-month visit as long as measurements were taken within 6 months of the 12-month visit date.
b The *p*-value for comparison between regimens at 12 months: median, 0.03; mean, 0.04.

TABLE 11 Antiretroviral therapy necessity concerns differential at each time point

Characteristic	Total	Regimen	
		CAU	CBT
Number of participants	143	72	71
Baseline			
n	143	72	71
Median	0.3	0.4	0.1
IQR	−0.2 to 0.8	−0.2 to 0.8	−0.3 to 0.7
Range	−2.1 to 1.7	−1.3 to 1.7	−2.1 to 1.7
Month 3			
n	116	61	55
Median	1.2	1.2	1.2
IQR	0.5–2.0	0.5–1.9	0.6–2.2
Range	−2.1 to 3.4	−0.6 to 3.4	−2.1 to 3.3
Month 6			
n	104	52	52
Median	1.4	1.4	1.5
IQR	0.8 to 2.2	0.7 to 2.0	0.9 to 2.4
Range	−1.5 to 3.6	−1.5 to 3.5	−0.3 to 3.6
Month 12[a]			
n	103	51	52
Median	1.5	1.5	1.5
IQR	0.6 to 2.1	0.7 to 2.0	0.6 to 2.2
Range	−1.2 to 3.5	−1.2 to 3.0	−0.6 to 3.5

a The *p*-value for comparison between regimens at 12 months: median, 0.82; mean, 0.62.

TABLE 12 Antiretroviral therapy-HIS scores at baseline and month 12, and change from baseline at month 12 (where participant had a recorded baseline value)

Characteristic	Total	Regimen	
		CAU	CBT
Number of participants	143	72	71
HIS score			
Baseline			
n	112	55	57
Median	13.2	6.5	15.0
IQR	0–34.5	0–38.4	2.7–34.5
Range	0–117.8	0–106.6	0–117.8
Month 12[a]			
n	89	42	47

TABLE 12 Antiretroviral therapy-HIS scores at baseline and month 12, and change from baseline at month 12 (where participant had a recorded baseline value) (*continued*)

Characteristic	Total	Regimen	
		CAU	CBT
Median	10.4	10.8	7.2
IQR	2.2–24.0	3.4–32.2	1.2–21.6
Range	0–126.0	0–126.0	0–103.6
Change from baseline,[b] *n*	89	42	47
Month 12 – baseline[a]			
Median	−3.6	−0.5	−5.6
IQR	−14.0 to 6.1	−5.6 to 18.0	−20.4 to 1.2
Range	−93.6 to 98.6	−93.6 to 87.6	−72.0 to 98.6
Mean (SD)	−3.62 (30.44)	0.00 (31.40)	−6.86 (29.51)

a Twelve-month values are taken as those that are closest to the date of the 12-month visit as long as measurements were taken within 6 months of the 12-month visit date.
b The *p*-value for comparison of change from baseline to 12 months: median, 0.03; mean, 0.29.

TABLE 13 Total BIPQ scores at baseline and month 12, and change from baseline at month 12 (where participant had a recorded baseline value)

Characteristic	Total	Regimen	
		CAU	CBT
Number of participants	143	72	71
IPQ score			
Baseline			
n	129	66	63
Median	40	39	40
IQR	28–47	27–45	32–48
Range	0–67	0–67	0–59
Month 12[a,b]			
n	107	51	56
Median	35	35	34
IQR	28–43	28–45	28–42
Range	10–58	10–58	10–52
Change from baseline,[a] *n*	102	50	52
Month 12 – baseline			
Median	−4	−1.5	−6.5
IQR	−10 to 4	−8 to 6	−12 to 3
Range	−52 to 36	−52 to 23	−34 to 36
Mean (SD)	−3.07 (12.57)	−1.52 (12.3)	−4.56 (12.76)

a Twelve-month values are taken as those that are closest to the date of the 12-month visit as long as measurements were taken within 6 months of the 12-month visit date.
b The *p*-value for comparison between regimens at 12 months: median, 0.11; mean, 0.22.

TABLE 14 Components of the BIPQ scores at baseline and month 12, and change from baseline at month 12 (where participant had a recorded baseline value)

Characteristic	Total	Regimen	
		CAU[a]	CBT[a]
Number of participants	204	100	104
HIV consequences			
Baseline			
n	160	77	83
Median	5.5	5	6
IQR	2–8	2–7	3–8
Range	0–10	0–10	0–10
Month 12[a]			
n	142	67	75
Median	5	4	5
IQR	2–7	2–5	2–7
Range	0–10	0–10	0–10
Change from baseline, *n*	134	65	69
Month 12 – baseline			
Median	−1	0	−1
IQR	−3 to 0	−3 to 0	−3 to 0
Range	−10 to 10	−10 to 5	−10 to 10
HIV timeline			
Baseline			
n	151	73	78
Median	10	10	10
IQR	5–10	8–10	5–10
Range	0–10	0–10	0–10
Month 12[a]			
n	134	63	71
Median	10	10	10
IQR	8–10	8–10	8–10
Range	0–10	0–10	2–10
Change from baseline, *n*	124	60	64
Month 12 – baseline			
Median	0	0	0
IQR	0–1.5	0–0	0–2
Range	−6 to 10	−5 to 6	−6 to 10
HIV personal control			
Baseline			
n	157	77	80
Median	7	7	7

TABLE 14 Components of the BIPQ scores at baseline and month 12, and change from baseline at month 12 (where participant had a recorded baseline value) (*continued*)

Characteristic	Total	Regimen	
		CAU[a]	CBT[a]
IQR	4–9	4–10	4–9
Range	0–10	0–10	0–10
Month 12[a]			
n	142	67	75
Median	8	7	8
IQR	5–9	5–9	7–9
Range	0–10	0–10	0–10
Change from baseline, *n*	131	65	66
Month 12 – baseline			
Median	0	0	1
IQR	−1 to 2	−1 to 1	−1 to 3
Range	−10 to 9	−10 to 8	−3 to 9
HIV treatment control			
Baseline			
n	158	76	82
Median	10	10	10
IQR	8–10	8–10	7–10
Range	0–10	0–10	2–10
Month 12[a]			
n	140	67	73
Median	10	10	10
IQR	8–10	9–10	8–10
Range	2–10	3–10	2–10
Change from baseline, *n*	131	64	67
Month 12 – baseline			
Median	0	0	0
IQR	0–1	0–1	0–1
Range	−8 to 10	−5 to 10	−8 to 5
HIV identity			
Baseline			
n	155	74	81
Median	2	2.5	2
IQR	0–6	0–6	0–5
Range	0–10	0–10	0–10
Month 12[a]			
n	143	68	75

continued

TABLE 14 Components of the BIPQ scores at baseline and month 12, and change from baseline at month 12 (where participant had a recorded baseline value) (*continued*)

Characteristic	Total	Regimen	
		CAU[a]	CBT[a]
Median	2	1.5	2
IQR	0–5	0–5	1–5
Range	0–10	0–9	0–10
Change from baseline, *n*	130	63	67
Month 12 – baseline			
Median	0	0	0
IQR	−2 to 1	−2 to 0	−2 to 2
Range	−9 to 8	−8 to 8	−9 to 8
HIV concern			
Baseline			
n	159	76	83
Median	8	8	9
IQR	5–10	5.5–10	5–10
Range	0–10	0–10	0–10
12 months[a]			
n	142	68	74
Median	7	5.5	7.5
IQR	4–10	3–10	5–10
Range	0–10	0–10	0–10
Change from baseline, *n*	133	65	68
Month 12 – baseline			
Median	−1	−1	−1
IQR	−2 to 0	−4 to 0	−2 to 0
Range	−10 to 6	−10 to 6	−8 to 5
HIV coherence			
Baseline			
n	160	77	83
Median	8	8	7
IQR	5–9	6–10	5–8
Range	0–10	0–10	0–10
Month 12[a]			
n	143	68	75
Median	8	8	9
IQR	7–10	7–10	7–10
Range	0–10	0–10	0–10

TABLE 14 Components of the BIPQ scores at baseline and month 12, and change from baseline at month 12 (where participant had a recorded baseline value) (*continued*)

Characteristic	Total	Regimen	
		CAU[a]	CBT[a]
Change from baseline, *n*	135	66	69
Month 12 – baseline			
Median	1	0	1
IQR	0 to 2	−1 to 2	0 to 3
Range	−9 to 10	−9 to 10	−8 to 10
HIV emotional representations			
Baseline			
n	160	77	83
Median	7	7	7
IQR	4–9	3–9	4–9
Range	0–10	0–10	0–10
Month 12[a]			
n	141	67	74
Median	6	6	5
IQR	2–8	3–8	2–8
Range	0–10	0–10	0–10
Change from baseline, *n*	133	65	68
Month 12 – baseline			
Median	0	0	−0.5
IQR	−2 to 1	−2 to 0	−2.5 to 1
Range	−10 to 10	−10 to 8	−10 to 10

a Twelve-month values are taken as those that are closest to the date of the 12-month visit as long as measurements were taken within 6 months of the 12-month visit date.

TABLE 15 Symptoms Attribution Questionnaire results with values taken to be those from the nearest visit to each time point; values shown are median (range)

Characteristic	Total	Regimen	
		CAU	CBT
Number of participants	143	72	71
Baseline, n	***37***	***18***	***19***
Core symptoms, median (range)	*5 (0–14)*	*4.5 (0–14)*	*5 (0–11)*
Moderate/severe	2 (0–11)	2 (0–9)	2 (0–11)
Attributed to HIV	0 (0–5)	0 (0–5)	0 (0–4)
Attributed to ART	0 (0–8)	0.5 (0–4)	0 (0–8)
Attributed to HIV and ART	0 (0–7)	0 (0–2)	0 (0–7)
Attributed to neither	2 (0–12)	2 (0–6)	3 (0–12)

continued

TABLE 15 Symptoms Attribution Questionnaire results with values taken to be those from the nearest visit to each time point; values shown are median (range) (*continued*)

Characteristic	Total	Regimen	
		CAU	CBT
Additional symptoms, median (range)	*0 (0–4)*	*0 (0–4)*	*0 (0–4)*
Moderate/severe	0 (0–4)	0 (0–4)	0 (0–4)
Attributed to HIV	0 (0–1)	0 (0–1)	0 (0–1)
Attributed to ART	0 (0–3)	0 (0–3)	0 (0–3)
Attributed to HIV and ART	0 (0–1)	0 (0–1)	0 (0–1)
Attributed to neither	0 (0–4)	0 (0–2)	0 (0–4)
Month 3, n	***23***	***5***	***18***
Core symptoms, median (range)	*3 (0–9)*	*5 (0–7)*	*3 (0–9)*
Moderate/severe	1 (0–9)	2 (0–6)	1 (0–9)
Attributed to HIV	0 (0–3)	0 (0–0)	0 (0–3)
Attributed to ART	0 (0–5)	0 (0–5)	0 (0–3)
Attributed to HIV and ART	0 (0–8)	0 (0–2)	0 (0–8)
Attributed to neither	1 (0–5)	1 (0–5)	1 (0–5)
Additional symptoms, median (range)	*0 (0–1)*	*0 (0–1)*	*0 (0–1)*
Moderate/severe	0 (0–1)	0 (0–0)	0 (0–1)
Attributed to HIV	0 (0–0)	0 (0–0)	0 (0–0)
Attributed to ART	0 (0–1)	0 (0–1)	0 (0–1)
Attributed to HIV and ART	0 (0–0)	0 (0–0)	0 (0–0)
Attributed to neither	0 (0–0)	0 (0–0)	0 (0–0)
Month 6, n	***28***	***16***	***12***
Core symptoms, median (range)	*4 (0–11)*	*4 (0–10)*	*3 (0–11)*
Moderate/severe	2.5 (0–11)	2.5 (0–8)	2.5 (0–11)
Attributed to HIV	0 (0–4)	0 (0–2)	0 (0–4)
Attributed to ART	0 (0–5)	0 (0–5)	0 (0–3)
Attributed to HIV and ART	0 (0–10)	0 (0–3)	0 (0–10)
Attributed to neither	1 (0–8)	2 (0–8)	0.5 (0–8)
Additional symptoms, median (range)	*0 (0–2)*	*0 (0–2)*	*0 (0–1)*
Moderate/severe	0 (0–2)	0 (0–2)	0 (0–0)
Attributed to HIV	0 (0–1)	0 (0–1)	0 (0–0)
Attributed to ART	0 (0–1)	0 (0–1)	0 (0–1)
Attributed to HIV and ART	0 (0–0)	0 (0–0)	0 (0–0)
Attributed to neither	0 (0–2)	0 (0–2)	0 (0–0)
Month 12, n	***26***	***15***	***11***
Core symptoms, median (range)	*3.5 (0–10)*	*4 (0–10)*	*3 (0–9)*
Moderate/severe	2 (0–8)	2 (0–8)	2 (0–8)
Attributed to HIV	0 (0–4)	0 (0–2)	0 (0–4)
Attributed to ART	0 (0–3)	0 (0–3)	0 (0–3)

TABLE 15 Symptoms Attribution Questionnaire results with values taken to be those from the nearest visit to each time point; values shown are median (range) (*continued*)

Characteristic	Total	Regimen	
		CAU	CBT
Attributed to HIV and ART	0 (0–3)	0 (0–3)	0 (0–2)
Attributed to neither	1.5 (0–8)	0 (0–6)	1 (0–8)
Additional symptoms, median (range)	*0 (0–1)*	*0 (0–0)*	*0 (0–1)*
Moderate/severe	0 (0–1)	0 (0–0)	0 (0–1)
Attributed to HIV	0 (0–0)	0 (0–0)	0 (0–0)
Attributed to ART	0 (0–0)	0 (0–0)	0 (0–0)
Attributed to HIV and ART	0 (0–0)	0 (0–0)	0 (0–0)
Attributed to neither	0 (0–1)	0 (0–0)	0 (0–1)

Depression and anxiety

The median HADS-D depression score at 12 months was 4 (IQR 2–8) in the CAU group and 3 (IQR 1–7.5) in the CBT group. There was a significantly greater reduction in depression (HADS-D score) from baseline in the CBT group than in the CAU group: the median change was −1 (IQR −3 to 0) and 0 (IQR −1.5 to 2), respectively ($p = 0.02$) (*Table 16*). The median HADS-A anxiety score at 12 months was 8 (IQR 5–11) in the CAU group and 7 (IQR 3–10) in the CBT group. The reduction in HADS-A score from baseline was greater in the CBT group than in the CAU group: the median change was −3 (IQR −5 to 1) in the CBT group compared with −1 (IQR −4 to 2) in the CAU group. However, this difference did not reach statistical significance ($p = 0.07$). The results are reported in *Table 17*.

TABLE 16 Hospital Anxiety and Depression Scale depression scores (and change from baseline, if a baseline value had been recorded) at each time point

Characteristic	Total	Regimen	
		CAU	CBT
Number of participants	143	72	71
Baseline			
n	121	61	60
Median	5	6	4
IQR	2–9	2–9	2–9
Range	0–19	0–19	0–16
Month 3[a]			
n	116	60	56
Median	4	4	4
IQR	2–7	2–8	1–6
Range	0–16	0–16	0–13
Change from baseline, *n*	109	57	52
Month 3 – baseline[a]			
Median	−1	0	−1
IQR	−2 to 1	−2 to 1	−3 to 0

continued

TABLE 16 Hospital Anxiety and Depression Scale depression scores (and change from baseline, if a baseline value had been recorded) at each time point (*continued*)

Characteristic	Total	Regimen	
		CAU	CBT
Range	−10 to 5	−10 to 5	−9 to 0
Month 6[a]			
n	100	49	51
Median	3	5	3
IQR	1–6.5	2–8	1–6
Range	0–18	0–18	0–15
Change from baseline, *n*	92	46	46
Month 6 – baseline[a]			
Median	−1	0	−1
IQR	−3 to 1	−2 to 1	−3 to 1
Range	−11 to 8	−11 to 8	−9 to 7
Month 12[a]			
n	101	49	52
Median	4	4	3
IQR	1–8	2–8	1–7.5
Range	0–19	0–19	0–14
Change from baseline,[b] *n*	95	48	47
Month 12 – baseline[a]			
Median	−1	0	−1
IQR	−2 to 1	−1.5 to 2	−3 to 0
Range	−11 to 8	−11 to 8	−11 to 7
Mean (SD)	−0.87 (3.54)	−0.31 (3.92)	−1.45 (3.04)

a Three- and 6-month values are taken as those that are closest to the dates of the 3- and 6-month visit, respectively, as long as measurements were taken within 6 weeks of the visit date. Twelve-month values are taken as those that are closest to the dates of the 12-month visit as long as measurements were taken within 6 months of the 12-month visit date.
b The *p*-value for comparison between regimens at 12 months: median, 0.02; mean, 0.12.

TABLE 17 Hospital Anxiety and Depression Scale anxiety scores (and change from baseline, where participant had a recorded baseline value) at each time point

Characteristic	Total	Regimen	
		CAU	CBT
Number of participants	143	72	71
Baseline			
n	120	60	60
Median	9	9	9
IQR	6–13	5.5–13	6–13
Range	0–20	0–20	0–18

TABLE 17 Hospital Anxiety and Depression Scale anxiety scores (and change from baseline, where participant had a recorded baseline value) at each time point (*continued*)

Characteristic	Total	Regimen	
		CAU	CBT
Month 3[a]			
n	115	59	56
Median	7	8	7
IQR	4–10	5–11	4–9
Range	0–21	0–21	0–20
Change from baseline, *n*	107	55	52
Month 3 – baseline[a]			
Median	−1	0	−2
IQR	−4 to 1	−3 to 1	−4 to −0.5
Range	−11 to 5	−7 to 5	−11 to 4
Month 6[a]			
n	99	48	51
Median	7	8	5
IQR	4–9	5–9	3–10
Range	0–18	0–15	0–18
Change from baseline, *n*	91	45	46
Month 6 – baseline[a]			
Median	−2	−1	−3
IQR	−5 to 1	−4 to 1	−5 to 0
Range	−13 to 8	−13 to 8	−12 to 5
Month 12[a]			
n	102	50	52
Median	7	8	7
IQR	4–10	5–11	3–10
Range	0–20	0–20	0–18
Change from baseline,[b] *n*	94	47	47
Month 12 – baseline[a]			
Median	−2	−1	−3
IQR	−4 to 1	−4 to 2	−5 to 1
Range	−16 to 10	−16 to 10	−13 to 9
Mean (SD)	−1.63 (4.44)	−0.94 (4.47)	−2.32 (4.35)

a Three- and 6-month values are taken as those that are closest to the dates of the 3- and 6-month visit, respectively, as long as measurements were taken within 6 weeks of the visit date. Twelve-month values are taken as those that are closest to the dates of the 12-month visit as long as measurements were taken within 6 months of the 12-month visit date.
b The *p*-value for comparison between regimens at 12 months: median, 0.07; mean, 0.13.

Clinical and treatment-related outcomes

There was no significant difference between the randomised CAU and CBT groups in the median change from baseline in CD4 T-cell count or viral load (*Table 18*). At 12 months, the number of participants with viral load of < 50 copies/ml at 12 months was 79 out of 96 participants (82.3%): 42 out of 50 (84.0%) in the CAU group and 37 out of 46 (80.4%) in the CBT group ($p = 0.85$) (*Table 19*). At 12 months, the number of patients defined as having treatment failure at 12 months was 45 out of 143 participants (31.5%): 23 out of 72 (31.9%) in the CAU group and 22 out of 71 (31.0%) in

TABLE 18 Cluster of differentiation 4 T-cell counts (cells/mm^3) at each time point, and change from baseline at 12 months

		Regimen	
	Total	CAU	CBT
Number of participants	143	72	71
Baseline			
n	143	72	71
Median	351	364	333
IQR	160–529	132–530	170–529
Range	8–2224	10–1275	8–2224
Month 3[a]			
n	126	66	60
Median	390	405	377
IQR	240–590	225–580	263–623
Range	12–1275	36–1275	12–947
Month 6[a]			
n	122	61	61
Median	433	486	406
IQR	250–627	230–642	272–570
Range	50–1285	121–1285	50–1131
Month 12[a]			
n	109	53	56[b]
Median	489	495	483
IQR	302–690	288–711	318–674
Range	50–1851	144–1851	50–1131
Change from baseline,[a] *n*	90	53	37[b]
Month 12 – baseline[c]			
Median	132	125	135
IQR	0–240	0–240	72–236
Range	−341 to 837	−106 to 837	−341 to 375

a Three- and 6-month values are taken as those that are closest to the dates of the 3- and 6-month visit, respectively, as long as measurements were taken within 6 weeks of the visit date. Twelve-month values are taken as those that are closest to the dates of the 12-month visit as long as measurements were taken within 6 months of the 12-month visit date.
b Dates of CD4 measurements were missing for a large number of participants in the CBT group at month 12 despite values being present. But as it cannot be confirmed that these were taken within 6 months of the visit date, the values have not been used when calculating the difference at 12 months.
c The *p*-value for comparison between regimens at 12 months: 0.92.

TABLE 19 Viral load values (log_{10} copies/ml) at each time point

Characteristic	Total	Regimen	
		CAU	CBT
Number of participants	143	72	71
Baseline			
n	143	72	71
Median	3.7	3.9	3.4
IQR	2.3–4.9	2.5–4.9	2.1–4.9
Range	1.7–6.4	1.7–6.3	1.7–6.4
n (%) ≤ 50 copies/ml	27 (18.9)	11 (15.3)	16 (22.5)
Month 3[a]			
n	69	35	34
Median	1.7	1.7	1.7
IQR	1.7–2.0	1.7–2.0	1.7–2.1
Range	1.7–4.0	1.7–4.0	1.7–3.7
n (%) ≤ 50 copies/ml	48 (69.6)	24 (68.6)	24 (70.6)
Month 6[a]			
n	51	24	27
Median	1.7	1.7	1.7
IQR	1.7–1.7	1.7–1.7	1.7–1.9
Range	1.7–3.4	1.7–3.3	1.7–3.4
n (%) ≤ 50 copies/ml	39 (76.5)	19 (79.2)	20 (74.1)
Month 12[a,b]			
n	96	50	46
Median	1.7	1.7	1.7
IQR	1.7–1.7	1.7–1.7	1.7–1.7
Range	1.7–5.1	1.7–3.3	1.7–5.1
n (%) ≤ 50 copies/ml	79 (82.3)	42 (84.0)	37 (80.4)

a Three- and 6-month values are taken as those that are closest to the dates of the 3- and 6-month visit, respectively, as long as measurements were taken within 6 weeks of the visit date. Twelve-month values are taken as those that are closest to the dates of the 12-month visit as long as measurements were taken within 6 months of the 12-month visit date.
b The *p*-value for comparison between regimens at 12 months: 0.85.

the CBT group ($p = 1.00$) (*Table 20*). The number of participants who switched regimen over the follow-up period was 44 out of 143 (30.8%): 25 out of 72 (34.7%) in the CAU group and 19 out of 71 (26.8%) in the CBT group ($p = 0.40$) (*Table 21*).

Supporting UPtake and Adherence to antiretroviral therapy screen: change in antiretroviral therapy beliefs over time among those who were not eligible or declined the trial

In total, 484 people were enrolled in the observational study (i.e. SUPA screen). Of these, 92 (19%) were eligible for the trial but declined participation. At 3 months, 382 (79%) participants completed the BMQ-ART; at 6 months, 346 (71%) participants completed the BMQ-ART; and at 12 months, 331 (68%) participants completed the BMQ-ART. Baseline clinical and demographic characteristics of the observational sample ($n = 484$) are reported in *Table 22*. The majority

TABLE 20 Treatment failure at 12 months

Characteristic	Total	Regimen	
		CAU	CBT
Number of participants	143	72	71
Treatment failure: yes, *n* (%)[a]	45 (31.5)	23 (31.9)	22 (31.0)
Reason for failure, *n* (% of those with treatment failure)			
No ART within 6 months	3 (6.7)	1 (4.4)	2 (9.1)
No viral load < 50 copies/ml within 6 months of ART start	36 (80.0)	20 (87.0)	16 (72.7)
Viral load > 400 copies/ml or 2 viral load 50 copies/ml after viral load suppression and within 12 months after randomisation	6 (13.3)	2 (8.7)	4 (18.2)

a The *p*-value for comparison between two groups: 1.00.

TABLE 21 Treatment switches over follow-up

Characteristic	Total	Regimen	
		CAU	CBT
Number of participants	143	72	71
Any switch: yes, *n* (%)[a]	44 (30.8)	25 (34.7)	19 (26.8)
Number of switches (%)			
0	99 (69.2)	47 (65.3)	52 (73.2)
1	35 (24.5)	20 (27.8)	15 (21.1)
2	9 (6.3)	5 (6.9)	4 (5.6)
Reason for switch 1 (% of *n* with a switch)			
VF (including intensification)	1 (2.5)	1 (4.6)	0 (–)
Toxicity	17 (42.5)	9 (40.9)	8 (44.4)
Drug–drug interaction	2 (5.0)	0 (–)	2 (11.1)
Simplification	13 (32.5)	8 (36.4)	5 (27.8)
Pill burden	4 (10.0)	3 (13.6)	1 (5.6)
Cost-saving	1 (2.5)	0 (–)	1 (5.6)
Patient choice	1 (2.5)	0 (–)	1 (5.6)
Not known	1 (2.5)	1 (4.6)	0 (–)
Reason for switch 2 (% of *n* with a switch)			
VF (including intensification)	3 (33.3)	2 (40.0)	1 (25.0)
Simplification	1 (11.1)	1 (20.0)	0 (–)
Pill burden	3 (33.3)	0 (–)	3 (75.0)
Patient choice	1 (11.1)	1 (20.0)	0 (–)
Other clinician reason	1 (11.1)	1 (20.0)	0 (–)

VF, virological failure.
a The *p*-value for comparison between two groups: any switch, $p = 0.40$; number of switches, $p = 0.59$.

TABLE 22 Observational cohort: demographic and clinical characteristics

Characteristic	Number of participants	Demographic	Value, *n* (%)
Age (years), mean (SD)	465		38.9 (11.4)
Sex	468	Female	104 (22)
		Male	363 (77)
		Transgender	1 (1)
Ethnicity	468	White	239 (51)
		Black African	122 (26)
		Black other	43 (9)
		Other	64 (14)
		Not stated	0
Eligible for trial?		Yes	92 (19)
Years in the UK	480	< 5	56 (12)
		≥ 5	184 (38)
		N/A: born in the UK	196 (41)
		Not stated	44 (9)
Sexuality	462	MSM	247 (53)
		Other/not stated	215 (47)
Marital status	219	Married/in partnership	69 (32)
		Single/separated	134 (62)
		Widowed/other	16 (6)
Education	249	Basic/school	63 (25)
		Higher education	136 (55)
		Not stated	50 (20)
Employment	257	Working	153 (59)
		Not working	83 (32)
		Other/not stated	21 (9)
Mode of HIV transmission	469	Sexual	437 (93)
		Blood contact	4 (1)
		Needles	6 (1)
		Other/not stated	22 (5)
Clinical diagnoses	472	Other HIV morbidity	9 (2)
	470	Hepatitis B positive	12 (3)
	472	Hepatitis C positive	8 (2)
	472	Non-AIDS malignancy	1 (0.2)
Time since HIV diagnosis	470	< 1 year	336 (71)
		1–5 years	74 (16)
		> 5 years	60 (13)
Agreed to start ART	472	Yes	420 (89)
		No	32 (7)
		N/A	20 (4)
Been prescribed ART	470	Yes	405 (86)
		No	65 (14)

N/A, not applicable.

were male (77%) and white (51%). Over half (53%) were MSM. Most (89%) agreed to initiate ART and 86% had been prescribed ART at the time of the baseline visit.

Antiretroviral therapy necessity, concerns, and necessity concern differentials are indicators of the relative weighting of necessity versus concerns for each individual and is reported in *Table 23*. Necessity beliefs increased from a median score of 4.0 (IQR 3.6–4.4) at baseline to 4.2 (IQR 3.7–4.6) at 12 months. Concerns declined from a median score of 2.5 (IQR 2.0–2.9) at baseline to 2.2 (IQR 1.8–2.7) at 12 months. The necessity concern differential score increased from 1.5 (IQR 0.8–2.2) at baseline to 2.0 (IQR 1.0–2.7) at 12 months. The median difference in scores between baseline and each follow-up is shown in *Table 24*.

TABLE 23 Observational study: mean and median ART necessity, ART concerns and ART necessity concerns differential at baseline and at 3, 6 and 12 months

	Time point			
Measure	**Baseline**	**3 months**	**6 months**	**12 months**
ART necessity				
Number of participants	475	382	346	331
Mean (SD)	4.0 (0.6)	4.0 (0.6)	4.1 (0.6)	4.1 (0.6)
Median (IQR)	4.0 (3.6–4.4)	4.1 (3.7–4.5)	4.2 (3.7–4.6)	4.2 (3.7–4.6)
ART concerns				
Number of participants	475	381	346	331
Mean (SD)	2.5 (0.7)	2.3 (0.7)	2.3 (0.7)	2.3 (0.7)
Median (IQR)	2.5 (2.0–2.9)	2.3 (1.9–2.7)	2.2 (1.8–2.7)	2.2 (1.8–2.7)
ART necessity concern differential				
Number of participants	475	381	346	331
Mean (SD)	1.5 (1.0)	1.7 (1.0)	1.8 (1.0)	1.8 (1.1)
Median (IQR)	1.5 (0.8–2.2)	1.7 (1.1–2.5)	1.8 (1.175–2.6)	2.0 (1.0–2.7)

TABLE 24 Observational study: mean and median difference in ART necessity, ART concerns and ART necessity concerns differential between baseline and 3, 6 and 12 months

Measure	**Mean difference (SD)**	***p*-value**	**Median difference (IQR)**	***p*-value**
Between baseline and 3 months				
ART necessity	0.05 (0.5)	0.002	0 (−0.2 to 0.4)	0.008
ART concerns	−0.16 (0.6)	< 0.001	−0.1 (−0.5 to 0.2)	< 0.0001
ART necessity concern differential	0.23 (0.05)	< 0.001	0.2 (−0.2 to 0.7)	< 0.0001
Between baseline and 6 months				
ART necessity	0.08 (0.5)	0.002	0.1 (−0.2 to 0.4)	0.0002
ART concerns	−0.15 (0.6)	< 0.001	−0.1 (−0.5 to 0.2)	< 0.0001
ART necessity concern differential	0.2 (0.8)	< 0.001	0.3 (−0.3 to 0.7)	< 0.0001
Between baseline and 12 months				
ART necessity	0.09 (0.5)	0.0016	0.1 (−0.2 to 0.4)	0.0005
ART concerns	−0.20 (0.6)	< 0.001	−0.2 (−0.6 to 0.2)	< 0.0001
ART necessity concern differential	0.30 (0.9)	< 0.001	0.3 (−0.3 to 0.8)	< 0.0001

At 12 months, 79% of participants had a suppressed viral load (< 50 copies/ml). There was a significant increase in ART necessity beliefs ($p < 0.001$), a decrease in ART concerns ($p < 0.001$) and an increase in the necessity concern differential score ($p < 0.001$), between baseline and 12 months. These findings indicate that patients developed more positive perceptions of ART over time.

There was a significant difference between those who were eligible for the SUPA trial (i.e. at a high risk of non-adherence) but declined and those who were not eligible (i.e. at a low risk of non-adherence). Trial decliners had more negative views about ART throughout the 12-month follow-up period than those who were not eligible. Trial decliners had significantly greater doubt about ART necessity ($p = 0.001$) and greater ART concerns ($p = 0.001$) at 12 months. This difference was clinically meaningful, as indicated by trial decliners being less likely to have a suppressed (undetectable) viral load (i.e. < 50 copies/ml) at 12 months ($p = 0.004$).

Limitations

Supporting UPtake and Adherence to antiretroviral therapy trial

Primary outcome measure

The primary end point, defined as achieving 90% adherence in 80% of each month, lacked sensitivity. Extremely low levels of adherence were recorded, as only approximately 15% achieved the end point, with no difference between the CBT and CAU groups. However, these levels of non-adherence did not appear to have a deleterious effect on outcomes, as only 17% of patients had a detectable viral load at 12 months, with no significant difference between the CAU and CBT groups.

Recruitment and retention

Retention rates were relatively high for this 'hard-to-reach' population, but the recruitment rate was much lower than anticipated. Despite every effort to increase recruitment, our trial was underpowered.

Risk of cross-arm contamination

Randomisation was performed at a patient level and not at a cluster level (i.e. randomisation by site). This may have introduced a bias, whereby participants randomised to the control group received an active intervention (i.e. cross-arm contamination within the trial). We were careful to avoid this (e.g. staff delivering the intervention were deliberately excluded from any study-related procedures in either arm of the trial), but the fact that the intervention target variables (perceptual and practical barriers to adherence) reduced over time in both arms of the trial and in the non-trial cohort study (i.e. SUPA screen) may be suggestive of a significant degree of cross-arm contamination within the study centres.

Supporting UPtake and Adherence to antiretroviral therapy screen cohort study

There was a considerable dropout rate ($n = 144$; 30%), which may have inflated the increase in necessity beliefs and decrease in concerns scores, as it is likely that people with more negative beliefs about ART were at an increased risk of dropout. As the majority of participants did not have perceptual barriers to ART at baseline (and were therefore not eligible to receive the SUPA intervention), this was a biased sample of people with positive beliefs about ART. The number of people throughout the same period who were unavailable for enrolment or who were eligible and did not attend the clinic during this period created a selection bias towards favouring those with positive beliefs about ART.

Conclusions

Supporting UPtake and Adherence to antiretroviral therapy adherence support (CBT-based intervention) did not result in an improvement in the primary outcome of full ART adherence at 12 months. However, the study was underpowered to detect this. The median ART adherence rates (%) were higher in the CBT group than in the CAU group, representing a 7% improvement in adherence relative to controls, but the study was underpowered to assess the significance of this finding.

The intervention resulted in a non-significant effect on adherence as assessed using MEMS. However, because of the limitations of the data set, we cannot rule out the possibility that the intervention might have enhanced engagement as indicated by (1) a 7% increase adherence (MEMS) over the course of the study and (2) a significant difference in self-reported adherence between the two groups at 3 months.

The SUPA intervention resulted in a significant reduction in the following secondary outcomes: perceptual barriers to ART (ART concerns) and practical barriers to adherence (ART intrusiveness) and depression, compared with CAU. The perceptions of ART became more positive over the 12 months' follow-up (ART necessity and concerns) in both groups as well as in the parallel cohort study of patients who were not eligible or did not take part in the trial, suggesting that patients' experiences of ART were more positive than their expectations in all conditions. However, ART concerns and intrusiveness were significantly improved in the CBT group compared with to the CAU group.

Interrelation with other workstreams

These results complement WS1 and WS2 by revealing the effects of the SUPA intervention. They are augmented by the economic evaluation (i.e. WS4) and inform a series of ancillary studies to improve our understanding of the determinants of ART adherence and implications for HIV care and outcomes.

Workstream 4: cost-utility and cost-effectiveness effectiveness of the Supporting UPtake and Adherence to antiretroviral therapy intervention

Aims

The aims of WS4 were to (1) assess evidence on cost-effectiveness of interventions to improve adherence, (2) assess the cost-effectiveness of the SUPA intervention over the trial period and (3) assess the longer-term cost-effectiveness of the SUPA intervention using simulation modelling.

Systematic review (see *Appendix 13*)

Systematic reviews have shown that interventions to increase adherence to ART improve adherence and clinical outcomes, but their cost-effectiveness is unclear. The aim of this systematic review was to determine the costs and cost-effectiveness of interventions aimed at improving adherence to ART.

Methods

A search strategy was developed and used to search 12 online databases. Studies were included if they reported on the costs or cost-effectiveness of interventions designed to increase adherence to ART among PLWH. Data were extracted using a predesigned form. The Drummond Checklist was used to assess the quality of economic evaluations. Meta-analysis was considered inappropriate because of substantial heterogeneity in study methodology and an absence of agreed methods for pooling combined estimates of cost-effectiveness. A narrative synthesis was carried out and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[59] were followed (*Figure 4*).

Key findings

Twenty studies met the inclusion criteria (13 were full economic evaluations and were seven partial economic evaluations). Adherence interventions were categorised as adherence support provided by a health professional, directly observed therapy, electronic interventions, practical adherence support, financial incentives or multiple interventions. There was evidence of improved adherence and favourable cost-effectiveness ratios in people receiving interventions compared with the control, but these effects tended to be short term. Relative cost-effectiveness was greater for interventions with low adherence or risk factors for low adherence at baseline and in studies that included onward transmission of HIV to sexual partners as an outcome.

Limitations

Conclusions were limited by methodological heterogeneity, including differences in costing perspectives, types of analysis and model design (economic or mathematical), ways of dealing with uncertainty, the cost-effectiveness threshold applied, and the type of intervention and measure of adherence. Most studies included narrow cost perspectives (e.g. estimates of direct healthcare costs) and did not include societal costs (e.g. absenteeism from work).

Links with other parts of the programme

This review sets the subsequent economic evaluation in context.

Trial-based cost-effectiveness analysis

The aims of this component of the programme were to compare the costs and cost-effectiveness in terms of quality-adjusted life-years (QALYs) of the SUPA intervention with CAU.

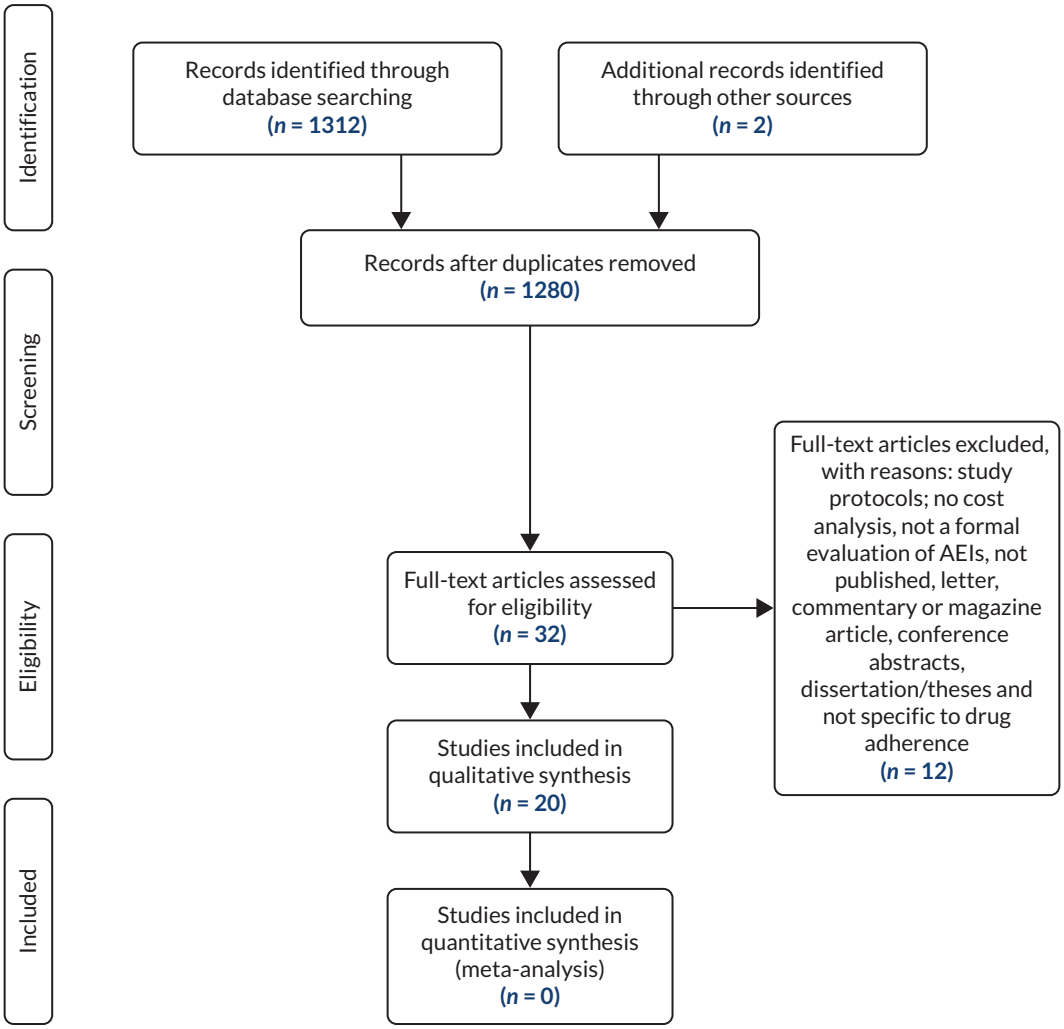

FIGURE 4 Cost-effectiveness of interventions to enhance adherence to ART: PRISMA flow diagram. AEI, adherence enhancing interventions.

Methods

We adopted a health care and social care perspective in these analyses. The receipt of the SUPA intervention was recorded and costed using the unit cost of training nurses by a clinical psychologist and the actual intervention. The use of other health and social care services was recorded with the Client Service Receipt Inventory at baseline, and at the 3-, 6- and 12-month follow-ups. Service use was valued using unit cost information from the University of Kent[60] and NHS reference costs.[61] Use of ART was also recorded and costed. QALYs were generated from the EQ-5D-5L and tariffs produced by the Office of Health Economics using area under the curve methods.[55,62,63]

Costs, including for the intervention, were compared over the entire follow-up, with baseline costs controlled for. QALYs were compared, controlling for baseline EQ-5D-5L tariffs. Cost-effectiveness was assessed by combining incremental costs and incremental QALYs using an incremental cost-effectiveness ratio (ICER). Uncertainty around the ratio was addressed using a cost-effectiveness plane, and interpretation was aided with a cost-effectiveness acceptability curve. Both of these were generated using 1000 bootstrapped incremental cost and QALY combinations.

Key findings

Detailed results are provided in *Appendix 1*. The mean cost of the SUPA intervention was £204. The mean cost over the 12 months' follow-up, including the intervention and antiretroviral treatment, was £9687 for CBT and £9068 for CAU. Costs were £621 higher in the CBT group than in the CAU group, but this difference was not statistically significant (95% CI −£506 to £1683).

The CBT group had slightly lower EQ-5D-5L tariff scores (0.7965) at baseline than the CAU group (0.817). By the 3-month follow-up, CBT resulted in higher scores (0.8947) than CAU (0.814), and this differential was maintained at the 6-month follow-up (CBT, 0.8994; CAU, 0.8285). At 12-month follow-up, the CBT group still had a higher mean tariff (0.8823) than the CAU group (0.8467), but the difference was reduced. CBT resulted in a greater number of QALYs (0.8857) over the entire follow-up period than CAU (0.8505). The difference in mean QALYs was 0.056, and this was statistically significant (95% CI 0.029 to 0.083).

The incremental cost of £621 and incremental QALYs of 0.056 combined to produce an ICER of £11,189 per QALY. At a willingness-to-pay threshold of £20,000 per QALY, there was a 90% likelihood that the intervention would be more cost-effective than CAU. There was also a 13% likelihood that the intervention would produce more QALYs and result in lower health and social care costs than CAU. Changing the cost of CBT downwards by 25% and 50% resulted in improved cost-effectiveness. Increasing the costs by these same amounts decreased cost-effectiveness of CBT but not sufficiently to take the ICER above the £20,000 threshold.

Limitations

The data required for these analyses were from self-reported service use; therefore, information and recall accuracy may have been problematic. The QALY gain was clear for the intervention, but it was also relatively small. It was also short-lived, as the improvement in quality of life occurred mainly in the first 6 months of follow-up.

Links with other parts of the programme

These analyses supplement those produced for the clinical outcomes. It is interesting that, while the intervention did not produce substantial differences in adherence, there was a benefit in terms of QALYs.

Long-term modelling of cost-effectiveness

We initially proposed to assess the long-term cost-effectiveness of the SUPA intervention to see if any improvement over the trial period could be maintained and at what cost. The clinical results have revealed that adherence is not significantly benefited by the intervention, and EQ-5D-5L tariffs are converging by the 12-month follow-up. However, we have still produced a model to demonstrate what happens over the longer term.

Methods

A Markov model was used to extrapolate for 15 years, in 12-month cycles, beyond the trial period. Health states were defined by CD4 T-cell counts and a state for those who died was also included. The CD4 states were (1) > 500 cells/mm^3, (2) 351–500 cells/mm^3, (3) 200–350 cells/mm^3 and (4) < 200 cells/mm^3. The model was run for a cohort of 100 CBT and CAU patients separately, and the starting health state distribution was based on the 12-month data in the trial. This was appropriate given that we wished to extrapolate specifically from this trial and other data were not available. The trial data revealed that one person died during the study. However, over a 15-year period, we would expect some people to die from causes related to other conditions and so all-cause mortality rates were used. Those surviving were assumed to transit between the other health states according to transitions observed between the baseline and 12-month follow-up points. Costs (excluding intervention costs) and QALYs were assigned to each health state at each cycle, and these were derived from the trial data. The expected costs and QALYs were computed and discounted at 3.5%. These were then combined with the costs and QALYs from the trial period. Probabilistic sensitivity analyses were conducted, and a cost-effectiveness acceptability curve produced.

Key findings

The findings are presented in more detail in *Appendix 10*. The expected incremental cost for those receiving CBT compared with CAU over 16 years (i.e. 1-year trial period and 15-year long-term follow-up) was −£4709. The incremental QALY for CBT compared with CAU was −0,73 QALYs. Therefore, in the long run, CBT was associated with slightly lower costs but also slightly fewer QALYs. In this situation, it is helpful to consider the cost-effectiveness of CAU relative to CBT. The incremental cost per QALY for CAU is £642, suggesting that it is the preferred option in the long run. Sensitivity analyses revealed that the results were robust to changes in key parameters.

Limitations

The model was relatively simple and took health states defined by CD4 T-cell count as the starting point. This is different from the primary outcome measure used in the trial, and CD4 T-cell counts were not substantially different for the two groups at 12 months. We derived QALYs according to CD4 groups during the trial period. It is likely that the QALYs were also influenced by other factors.

Links with other parts of the programme

These results complement those of the trial-based economic evaluation. They reveal that that there are no further gains in cost-effectiveness in the long term. However, short-term gains may still make the intervention warranted given its low cost.

Workstream 5: preparing for implementation within the National Health Service

Workstream 5 was intended to address objective 7: prepare for implementation within the NHS. Owing to the extended time needed for recruitment to the RCT, we were unable to carry out a full implementation WS. We have planned implementation strategies that are informed by NICE guidance on how to change practice.[64–66] These involve identifying barriers to implementation by conducting study discussion groups at HIV clinics, discussion of our findings with HIV commissioners and conducting focus groups with PLWH at AAF.

Workstream 6: ancillary studies

Workstream 6 comprises seven ancillary studies that were not included in the original Programme Grants for Applied Research funding application, but were designed to address issues that emerged during the implementation of the programme. They replaced the planned full implementation programme (WS5), which could not be conducted because of extended time scales for the trial (WS3). The specific studies were as follows:

- patients' perceptions of standard care in the SUPA trial (*Table 25*)
- assessing beliefs about medicines and treatment outcomes in HIV-positive patients starting ART to protect their partners (treatment as prevention) compared with clinical need
- assessing the level of adherence to ART required to achieve virological suppression over a 12-month follow-up period in patients initiating their first ART regimen (*Table 26*)
- systematic review and meta-analysis of adherence interventions
- beliefs about ART as predictors of side effects (analysis of historical data)
- linking self-reported adherence with MEMS data (*Tables 27* and *28*)
- exploring the effect of the SUPA intervention on rates of engagement with HIV services among ART-naive patients.

TABLE 25 Standard Care Perceptions Questionnaire items

Item	Agree, *n* (%)	Uncertain, *n* (%)	Disagree, *n* (%)
1. I feel I have been able to talk about my diagnosis	108 (94)	3 (3)	3 (3)
2. My clinical team has helped me understand enough about HIV	108 (94)	6 (6)	0 (0)
3. My clinical team has helped me understand enough about taking ART	109 (96)	5 (4)	0 (0)
4. I feel like I have been able to talk about how I will fit my medication into my daily life	105 (92)	6 (5)	3 (3)
5. The clinical team asked me if I have any worries about taking medications	106 (93)	7 (6)	1 (1)
6. If I do have challenges, my team would help me deal with/overcome these worries	94 (83)	17 (15)	2 (2)
7. My clinical care team give me the opportunity to ask questions	110 (96)	2 (2)	2 (2)
8. I feel like I am being heard/listened to	107 (94)	4 (4)	2 (2)
9. My clinical care team spends enough time with me	110 (96)	1 (1)	3 (3)

TABLE 26 Average adherence (MEMS) stratified by viral load at 6 months

Month 6 viral load (copies/ml)	*n* (%)	Average adherence (MEMS), median (IQR)			
		Month 1	Month 2	Month 3	Months 1–3
All participants					
> 50	29 (19.3)	63.2 (20.2–82.6)	90.0 (18.3–95.0)	86.7 (3.3–95.0)	73.1 (18.3–89.8)
≤ 50	121 (80.7)	80.0 (44.8–96.6)	90.0 (60.0–98.3)	90.0 (50.0–100.0)	82.1 (52.6–92.2)
p-value		0.09	0.19	0.17	0.08
With a value within 42-day window (*n* = 61)					
> 50	15 (24.6)	64.4 (19.0–96.6)	90.0 (3.3–98.3)	90.0 (0–95.0)	73.1 (16.2–95.6)
≤ 50	46 (75.4)	82.6 (48.3–96.6)	91.5 (66.7–100.0)	91.1 (56.7–100.0)	85.9 (67.0–96.2)
p-value		0.21	0.28	0.25	0.17

TABLE 27 Agreement between MEMS (average over months 1–3) and the 3-month Medication Adherence Report Scale (MARS): dichotomised

	High adherence: MEMS (> 80%) (*n*)		
High adherence: MARS (≥ 24)	**No**	**Yes**	**Total (*n*)**
No	17	2	19
Yes	39	66	105
Total	56	68	124

TABLE 28 Average adherence (MEMS) stratified by 3-month Medication Adherence Report Scale (MARS)

	Average adherence (MEMS), median (IQR)			
High adherence: MARS (≥ 24)	**Month 1**	**Month 2**	**Month 3**	**Months 1–3**
No (%)	50.0 (4.6–73.0)	13.3 (3.3–86.7)	40.0 (10.0–81.1)	30.8 (17.0–68.5)
Yes (%)	81.1 (50.0–96.6)	93.3 (83.3–100.0)	93.3 (73.0–100.0)	87.5 (70.0–96.6)
p-value	0.0008	0.0001	0.0001	0.0001

Ancillary study 7 was an amalgamation of two ancillary studies: 'Patterns of engagement in care in ART-naive patients: retrospective analysis of clinic attendance in patients' and 'Exploring the effect of the SUPA intervention on rates of engagement with HIV services among ART-naive patients'. The HIV parameters were collected at routine appointments. However, it was not possible to assess which appointments were planned as part of routine care and which were ad hoc. This meant that ancillary study 7 was not feasible.

The feasible ancillary studies (1–6) are described in *Appendices 11–16*.

Summary of the Supporting UPtake and Adherence to antiretroviral therapy programme findings and conclusions

Workstream 1: intervention development

Our preparative research found a high prevalence of delays in the initiation of a clinically appropriate treatment offer and subsequent non-adherence to treatment and identified potentially modifiable determinants of delay in ART uptake and non-adherence. For each individual, non-adherence often had multiple causes, both intentional and unintentional. Patients' beliefs about ART were particularly influential. We found that many patients were sceptical about ART, holding beliefs that were at odds with the medical view, but often hidden from prescribers. Many patients doubted their personal need for ART in the absence of symptoms and harboured strong concerns about ART. Concerns extended beyond ART side effects and were often related to commonly held beliefs that regularly taking ART would lead to harm in the long term. Patients were also concerned about ways in which ART affected how they perceived themselves and were seen by others.

Although ART beliefs were important determinants of uptake and adherence, few NHS clinics routinely elicited patients' beliefs about ART or addressed necessity beliefs and concerns. Our research suggested the need for a service targeted at individuals who were ambivalent about ART to help to ensure that decisions about treatment are informed by evidence of the likely benefits and risks of ART, rather than by misconceptions and misplaced concerns. The overarching aim of WS1 was to design this service.

Much of our preparative work had focused on MSM. Although there was some evidence that our findings also applied to other relevant communities, fewer studies had been conducted with women and within the UK Black African and UK Black Caribbean communities. Therefore, our first studies in the SUPA programme focused on the UK Black African and UK Black Caribbean communities, exploring culturally specific beliefs and other factors, influencing uptake and adherence to ART, that have not emerged in previous research. These findings were applied to refine our existing methods for assessing adherence-related perceptions of ART, adding four items to the study questionnaire ART (BMQ-ART).

We worked with PLWH, experts in adherence, behaviour change theory, CBT, HIV medicine, nursing, pharmacy and HIV patient advocacy, applying MRC guidance to develop a CBT-based intervention to increase uptake and adherence to ART. This comprised (1) standardised information about HIV and its treatment, delivered through an animated video and a booklet, and designed to address common, adherence-related, misconceptions and concerns and signpost patients to further support to help in overcoming perceptual and practical barriers to ART uptake and adherence; and (2) personalised discussion to introduce the SUPA video and booklet and address barriers to adherence, applying CBT in up to four sessions: the first a face-to-face session with a HIV nurse, with up to three further sessions in clinic or by telephone follow-up, determined by patient preference.

The findings from WS1 led us to reconsider our initial plans for the SUPA interventions, combining interventions to address ART uptake and adherence, delivered as soon as possible after the first offer of ART and testing its impact in a RCT with a 12-month follow-up (i.e. SUPA trial). In parallel to the trial, we conducted a prospective follow-up study to examine how perceptions of ART changed over time (12 months) among those who were not eligible for the trial (low risk of non-adherence) and those who were eligible (high risk of non-adherence) but declined (i.e. SUPA screen).

Workstream 2: assessing intervention acceptability and randomised controlled trial feasibility

We examined recruitment and retention over a 12-month period to both the SUPA screen and the SUPA trial in an embedded study assessing the number of eligible patients, screened and enrolled, who were randomised to receive CBT

or CAU, who were lost to follow-up, who discontinued treatment and who were analysed. Recruitment to the SUPA trial was reviewed every 6 months in line with good practice for clinical trials. Recruitment rates were slower than expected, but retention was high.

The qualitative analysis of interviews with PLWH who received the SUPA intervention suggested that the SUPA intervention was acceptable to patients. The intervention addressed misconceptions about HIV and ART, enhanced patients' perceptions of their personal necessity for ART, and reduced ART concerns and practical barriers to adherence. In addition, the intervention provided a source of emotional support.

Workstream 3: randomised controlled trial assessing the efficacy of the Supporting UPtake and Adherence to antiretroviral therapy intervention (Supporting UPtake and Adherence to antiretroviral therapy trial) and parallel cohort study (Supporting UPtake and Adherence to antiretroviral therapy screen)

Recruitment was challenging. Between March 2014 and July 2017, we screened 1575 patients for inclusion in the SUPA trial (and SUPA screen cohort study). Only 213 (13%) patients were eligible for the trial, based on the high risk of non-adherence [BMQ-ART score of ≥ 4 for concerns (range 1–5) and of < 2 for necessity beliefs (range 1–5)]. Of these patients, 143 consented to the trial and were randomised (CAU, *n* = 72; CBT, *n* = 71). This was far short of our target of 372 to power our primary outcome. We examined whether or not relaxing our inclusion criteria to include patients with a lower risk of non-adherence [defined as a BMQ-ART score of ≤ 3, a concerns score ranging between 1 and 5, and a score of < 3 necessity beliefs (range 1–5)] might enable us to reach target. However, this only increased the number of trial-eligible patients to 349 and potential inclusion in the trial to 107 in the CAU group and 106 in the CBT group. Our analysis of the trial was, therefore, conducted using more stringent inclusion criteria.

The number of participants with sufficient data for primary end-point analysis was 112 (CAU, *n* = 55; CBT, *n* = 57), of whom only 17 (15.2%) met the primary end point (> 80% of months with an average monthly adherence of ≥ 90%), with no difference between groups at 12 months. However, there was a 7% improvement in median percentage adherence by MEMS at 12 months in the CBT group compared with the CAU group (61.9% CAU and 66.5% CBT; $p = 0.40$).

The intervention resulted in some benefits for those who received it. Intervention recipients experienced a significantly greater reduction in ART concerns, practical barriers to adherence and depression scores between baseline and 12 months than those in the CAU group. At 3 months, there was a significant increase in the proportion of people with high adherence (as assessed using MARS-5 self-report): 75% in the CAU group and 81% in the CBT group ($p = 0.02$).

Perceptions of ART (ART necessity and concerns) become more positive over the 12 months' follow-up in both groups of the trial and in our parallel cohort study of patients who were not eligible or did not take part in the trial, suggesting that patients' experiences of ART were more positive than their expectations in all conditions. However, ART concerns and intrusiveness were significantly improved in the CBT group compared with the CAU group.

Workstream 4: economic studies

The economic analyses conducted on the SUPA trial compared costs and QALYs, and each follow-up time point controlling for baseline EQ-5D-5L tariffs. Cost-effectiveness was assessed by combining incremental costs and incremental QALYs using an ICER. The mean cost was £621 higher in the CBT group than in the CAU group. This difference was not statistically significant (95% CI −£506 to £1683). CBT resulted in significantly higher QALY gain over the follow-up period than CAU, and this finding was significant (difference 0.056; 95% CI 0.0029 to 0.083). The ICER was £9143 per QALY. At a threshold of £20,000 per QALY, there was more than a 90% likelihood that the intervention would be more cost-effective than CAU. There was a 19% likelihood that CBT would produce more QALYs and result in lower health and social care costs than CAU.

Markov modelling of the long-term cost effects extrapolated for 15 years in 12-month cycles beyond the trial period showed a different picture. Costs in the 15 years after the trial follow-up were lower in the CBT group than in the CAU group, but CBT also resulted in a lower QALY gain. Combining the results of the trial period with those of the 15-year extrapolation period showed that, over the total 16-year period, CBT would cost £887 less than CAU and result in a smaller QALY gain (by 0.75 QALYs). Therefore, in the long term, CAU is cost-effective, with an ICER of £1187 per QALY.

Taken together, these findings suggest that it could be cost-effective for the NHS to provide the intervention while it is being delivered, but that these effects diminish over time after the intervention is withdrawn and are lost in the long term.

Interpretation of the trial findings

Although underpowered for our primary outcome, the SUPA trial and related economic studies provided interesting insights into the effects and cost-effectiveness of the SUPA intervention. At first sight, our main findings seem anomalous. The SUPA intervention did not lead to a significant improvement in the proportion of patients achieving full adherence over a 12-month follow-up. Yet it improved quality of life and was likely to be cost-effective for the NHS. Moreover, the high levels of non-adherence (according to the primary outcome) found in both arms of the trial did not translate into deleterious clinical outcomes: most patients were classed as non-adherent (85% non-adherent at 12 months), yet only 17% had a detectable viral load at 12 months.

We explored several explanations for these findings (outlined below). Our parallel observational study (SUPA screen) was helpful in this respect because it allowed us to compare changes in perceptions of ART and clinical outcomes (viral load suppression at 12 months) between three cohorts: (1) those who were not eligible for the trial (low risk for non-adherence), (2) those who were trial eligible (high risk for non-adherence) and declined to take part in the trial, but remained in observational study and (3) trial participants (high risk for non-adherence).

Suitability of the primary outcome measure

Our primary outcome, developed in discussion with the PSC and NIHR, was informed by evidence for the levels of adherence to ART necessary to achieve viral suppression (90% adherence). It also took account of the principle that gross percentage adherence, over the course of the study, may not reflect differences in 'cover' over that time period. For example, an adherence rate of 75% might be achieved by a patient taking treatment on three out of every four consecutive days and also by a patient who took 100% of the drug for the first 9 months and then no drug at all for the last 3 months. These two hypothetical scenarios could have very different clinical outcomes – with the last scenario more likely to lead to viral breakthrough (months 9–12) and greater risk of viral resistance. Our expert panel considered that adherence would be clinically acceptable if adherence rates ≥ 90% were achieved in > 80% of months by the 12-month follow-up. This measure would also account for a treatment delay [delay would register as zero adherence for the month(s) between treatment offer and treatment initiation].

However, the apparently paradoxical finding that only 15% of participants attained the full adherence represented by our primary outcome and yet 83% had undetectable viral load at trial end point, calls into questions the validity of our primary end point as a clinically relevant measure of ART adherence.

This creates a challenge for how to assess the implications of our findings for the NHS with broader implications for our understanding of the relationship between ART adherence and HIV outcomes, as discussed in *Appendix 7*, *Implications for research*. It is possible that newer treatments available since the conception of the programme are more 'forgiving of non-adherence', explaining why low adherence did not translate into poor virological control. A lower threshold may have been a more realistic reflection of a problematic adherence based on a dichotomous model.

Effect of intervention on process variables and secondary outcomes

Relative to CAU, the SUPA intervention resulted in a significant reduction in concerns about ART (BMQ-ART concerns) and perceived intrusiveness of the regimen (ART-HIS), suggesting an effect on process variables consistent with our theoretical model. However, because of low recruitment, we lacked the power to fully access the effect of these

changes on adherence and viral load suppression. Moreover, challenges with the MEMS caps (see *Appendix 17*) may have reduced our ability to detect effects on adherence. It is interesting that there was a significant improvement in self-reported adherence [Medication Adherence Report Scale (MARS]) in the CBT group compared with the CAU group, but this effect was not retained after withdrawing the intervention. The SUPA intervention also benefited patients by significantly reducing depressive symptoms at 12 months.

Comparison between trial and observational study

A possible explanation for the observed intervention effects, with potential implications for the NHS, was revealed when we compared changes in perceptions of ART and clinical outcomes (viral load suppression) between the trial and observational studies (SUPA trial vs. SUPA screen).

First, we compared two cohorts: those who were eligible for the trial and accepted (i.e. trial acceptors) and those who were eligible and declined the trial (i.e. trial decliners). We found a significant difference between perceptions of ART over the 12 months follow-up. At baseline, both cohorts were sceptical about ART and were judged to be at a high risk of non-adherence (based on BMQ-ART scores). However, trial decliners had significantly more negative perceptions of ART than trial acceptors, with significant differences in ART necessity beliefs and ART concerns at baseline and at each follow-up.

It is interesting that perceptions of ART became more positive over time in both arms of the trial and also in the trial decliner cohort. However, the trial decliners remained significantly more negative than trial acceptors (both arms combined) at 12-months. Comparison of BMQ-ART scores between the trial acceptor cohort (negative BMQ-ART scores indicating high risk of non-adherence) and the cohort who were not eligible for the trial (positive BMQ-ART scores indicating low risk of non-adherence) produced an interesting result. Perceptions of ART among trial acceptors had become progressively more positive. By 12 months, they had equally positive beliefs about ART as those who were deemed not to require the intervention because they were accepting of ART and motivated to adhere (see *Appendix 18*).

This effect was clinically significant. At the 12-month follow-up, trial decliners were significantly less likely to have achieved viral load suppression than trial acceptors (76% vs. 82%). Clinical outcomes within the trial acceptors cohort (high risk of non-adherence) were similar to those in the low risk of non-adherence cohort.

Intervention fidelity and dose–response effects

Our assessment of intervention fidelity showed that it had been delivered properly. However, we found that not everyone received the intervention as described, which was reflected in the patient choice of the number of follow-up sessions received. Only 52% elected to receive the full four sessions. Those who received fewer than four sessions had significantly lower median adherence (MEMS) at 12 months ($p < 0.001$), implying a 'dose–response' effect of the intervention on adherence. A greater proportion of those receiving the full intervention also attained the primary end point than those who received fewer than four sessions (67% vs. 33%).

Challenges and limitations

Several challenges were encountered from designing the RCT to examining the effectiveness of the intervention. There were rapid and welcome changes in HIV treatment and care during the first years of the programme. For example, although our preparatory research indicated that more than one-quarter of PLWH who were recommended treatment declined it or delayed ART initiation, treatment delay was much less common once we had secured funding. Because of the sensitive nature of the research programme, and concerns from hospital staff as to whether MEMS caps would either (1) be burdensome for patients or (2) compromise the safety of the medicines by needing to be decanted from the original packaging, there were significant delays in acquiring NHS permissions in local sites. This led to issues in recruiting patients within both the required time frame and the budget.

The SUPA trial had a number of limitations. Our primary outcome measure lacked sensitivity, as described above. We encountered numerous challenges and difficulties with the use of MEMS caps that compromised our ability to

assess adherence and the effect of the trial fully. Although retention rates were relatively high for our hard-to-reach population, recruitment was much slower than anticipated and, despite every effort to increase recruitment, our trial was underpowered. In retrospect, we also believe that retention in the trial may have been higher if we had included fewer measures at each follow-up. Our population found the questionnaires burdensome, which may have contributed to missing data. There was also a risk of contamination between intervention and control groups – randomisation was at the patient level and not cluster randomised by site, creating the potential for 'bleed' between intervention and control groups. We were careful to avoid cross-contamination across trial arms. For example, staff who delivered the intervention were deliberately excluded from any study-related procedures in either arm of the trial. The intervention target variables (perceptual and practical barriers to adherence) reduced over time in both arms of the trial and in the non-trial cohort study (SUPA screen). This may suggest a significant degree of cross-contamination between trial arms occurring within the study centres.

Implications for the National Health Service

Rates of ART uptake and adherence have improved dramatically since the programme was conceived, perhaps attributable to improvements in the tolerability and ease of use of ART regimens. Our findings suggest that, during this time, patients have become much more accepting of ART with a lower prevalence of treatment delay and non-adherence.

However, the study showed that 17% of patients did not achieve full suppression at 12 months, with implications for HIV outcomes and transmission; the problem still exists. Screening patients at treatment initiation, using the BMQ-ART to identify patients at risk of non-adherence, identified a cohort of at-risk patients. Participating in the trial seemed to reduce this risk in both the intervention and the control arms, and we could not rule out 'bleed' between the arms. Our cohort study of trial decliners helped us understand the potential consequences of not intervening in this group. Trial decliners had more negative views about ART at 12 months and were significantly less likely to have achieved viral suppression.

This observation, coupled with the quantitative and qualitative evidence, demonstrates benefits of the SUPA intervention in reducing ART concerns, treatment intrusiveness and depression, and improving quality of life relative to CAU. The benefits were modest, but the intervention costs were low, suggesting that it might be worth implementing, despite the observed lack of effect on the primary outcome. Our economic analyses suggest that doing so is likely to be cost-effective for the NHS.

The benefits of the SUPA intervention to patients and the NHS diminished over time and, after 1 year, the benefits to the intervention and control groups were equivalent. This suggests that, to maintain benefits and cost-effectiveness, a 'top-up' of the intervention is necessary, and adherence support should be considered as a continuous process. Our economic studies suggest that provision of the SUPA intervention as an ongoing support for patients is likely to be cost-effective for the NHS.

Recommendations for research

There is a need for innovative methods for testing behavioural interventions.[67] The need to commit to a RCT design within our programme meant that we did not have capacity to conduct smaller, less rigorous studies to determine how best to influence the perceptions and practicalities influencing motivation and ability to engage with treatment. Our studies focused on individual factors, and future research could examine in more detail how these factors are shaped by environmental factors, such as resources and access to support. Use of electronic monitors (MEMS) as a measure of adherence created difficulties for sites, researchers and PLWH, suggesting the need for research to identify alternative, less intrusive, methods for assessing adherence behavioural studies. Although we explored the mechanism of effect of the intervention, we were limited by relatively low numbers, and further studies are necessary to fully understand. The finding that our primary outcome did not relate to viral suppression suggests the need for definite research to recalibrate our understanding of the relationship between ART adherence and outcomes as well as viral

load suppression, with the possibility that newer treatments are more 'forgiving' and that lower levels of adherence are necessary to achieve viral suppression than previously anticipated.

Conclusion

The SUPA programme fulfilled its primary aims, harnessing the expertise of a multidisciplinary team including academics, clinicians and patient advocates to develop and evaluate a pragmatic, theory-based intervention to support PLWH to overcome perceptual and practical barriers to ART. The SUPA intervention was effective at reducing ART concerns and intrusiveness and improving quality of life, and was cost-effective to the NHS within 12 months.

Additional information

Contributions of authors

Rob Horne (https://orcid.org/0000-0002-3068-8438) (Professor of Behavioural Medicine, UCL School of Pharmacy) was the principal investigator and led on the conception and development of the study design as well as the development of the intervention and associated materials. He also oversaw the whole programme and is the lead author of the report.

Caroline Sabin (https://orcid.org/0000-0001-5173-2760) (Professor of Medical Statistics and Epidemiology, UCL) was a co-applicant and she significantly contributed to the study design, conducted the statistical analysis, prepared the results for publication and co-authored the report.

Trudie Chalder (https://orcid.org/0000-0003-0775-1045) (Professor of Cognitive Behavioural Psychotherapy) was a co-applicant, was involved in all aspects of the programme and significantly contributed to the programme design and intervention development. She led on CBT aspects of the work, providing training and supervision for the delivery of the SUPA intervention, conducted the embedded fidelity study and co-authored the report.

Vanessa Cooper (https://orcid.org/0000-0002-4525-2792) (Senior Research Fellow, UCL School of Pharmacy) was part of the team that developed the proposal. She was involved in the conception and development of the programme, contributed significantly to the development of the protocol, intervention design and materials, and contributed to the study's processes and paperwork. She also led on the analyses, interpretation of results and drafted academic outputs. She also co-authored the report.

Lucy Campbell (https://orcid.org/0000-0002-0783-1195) (Research Manager/Fellow, King's College London) assisted in the day-to-day management of the study and was involved in all aspects of the programme, including development of the intervention design and materials, centre recruitment and set-up, support of site staff, data collection and management, analyses, interpretation of the results, and preparation of outputs. She co-authored the report and acted as programme manager (2019–20).

Elizabeth Glendinning (https://orcid.org/0000-0002-6766-0113) (Research Assistant, UCL School of Pharmacy) had day-to-day responsibility for project management and was involved in all aspects of the study. This included the development of the protocol, development of the intervention design and materials, recruitment of study centres, recruitment of patient and data, conducting patient interviews, study centre administration, and interpretation of results. She also co-authored the report.

Iris Mosweu (https://orcid.org/0000-0001-6797-2478) [Research Fellow, London School of Economics (at King's College London throughout the duration of the study)] helped to conduct the economic analysis, the analysis of health service use and prepared the results for publication. She also co-authored the report.

Paul McCrone (https://orcid.org/0000-0001-7001-4502) [Professor of Healthcare Economics, University of Greenwich (at King's College London throughout the duration of the study)] was a co-applicant, conducted the economic analysis, conducted the analysis of health service use and prepared the results for publication. He also co-authored the report.

Contributions of others

Sarah Walker [Professor of Medical Statistics and Epidemiology, University College London (UCL) MRC Clinical Trial Unit] was a co-applicant and contributed to study design and the statistical analysis plan.

Martin Fisher (Professor of HIV Medicine/Consultant Physician, Brighton and Sussex Medical School 2011–5) contributed to the development of the programme and research bid, and led on clinical aspects of the SUPA programme. Sadly, Martin passed away in 2015 and so could not contribute directly to the authorship of this report. However, his influence on the SUPA programme and the work contained in this report was pivotal.

Heather Leake-Date (Consultant Pharmacist HIV/Sexual Health, Brighton and Sussex University Hospitals NHS Trust) was a co-applicant, led on aspects of the study related to pharmacy and advised on the conduct of the study.

Susan Michie (Professor of Health Psychology, UCL) was a co-applicant, was involved in the conception and development of the study, contributed to the development of the protocol, and also contributed to the intervention design and materials.

Mark Nelson (HIV Consultant, Chelsea and Westminster Hospital NHS Foundation Trust) was a co-applicant and advised on the conduct of the study.

Nicky Perry (Consultant Pharmacist HIV/Sexual Health, Brighton and Sussex University Hospitals NHS Trust) was a co-applicant and advised on the conduct of the study.

Jonathan A Smith (Professor of Psychology, Birkbeck, University of London) contributed significantly to the qualitative analyses, was a co-applicant and advised on study design and on the conduct of the study.

Scott Harfield (R&D Lead Brighton and Sussex University Hospitals NHS Trust) hosted the SUPA grant on behalf of NIHR and led on governance and financial aspects of the grant

Katherine King (SUPA UCL Research Assistant/Research Nurse) delivered the SUPA intervention and co-ordinated data collection at several of the SUPA sites.

Jane Anderson (HIV Consultant, Homerton University Hospital NHS Trust) was a co-applicant, was involved in the conception and development of the study, contributed significantly to the development of the protocol and to the intervention design and materials, the study's processes and paperwork, advised on the conduct of the study and was clinical lead for a study centre.

Simon Collins (HIV i-Base) was a co-applicant and advised on intervention development and on the conduct of the study.

Winnie Sseruma (Christian Aid) was a co-applicant and advised on intervention development, and on the conduct of the study.

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Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it is important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

Data-sharing statement

The chief investigator will act as custodian for the research data and materials. All data requests should be submitted to the corresponding author for consideration. Once available, study data will be made available to the scientific community with as few restrictions as feasible, while retaining exclusive use until the publication of major outputs.

Ethics statement

The study has been given a favourable ethical opinion for conduct by the NRES East of England–Essex Research Ethics Committee (13/EE/0235). It was overseen by the SUPA Trial Management Group (TMG), Programme Management Group (PMG), Independent Data Monitoring Committee (IDMC) and Programme Steering Committee (PSC). The trial was retrospectively registered with the ISRCTN (35514212) on 21/02/2014.

Information governance statement

UCL is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, UCL is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer here: https://www.ucl.ac.uk/data-protection/reporting-breach-or-subject-access-request/contact-data-protection-team.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/KPPW8401.

Primary conflicts of interest: Rob Horne has undertaken speaker engagements with honoraria with the following companies: AbbVie (Lake Bluff, IL, USA), Amgen Inc. (Thousand Oaks, CA, USA), Biogen Idec Ltd (Maidenhead, UK), Gilead Sciences Inc. (Foster City, CA, USA), GlaxoSmithKline plc (Brentford, UK), Janssen: Pharmaceutical Companies of Johnson & Johnson (Beerse, Belgium), Pfizer Inc. (New York, NY, USA), Roche (Basel, Switzerland), Shire Pharmaceuticals (Lexington, MA, USA), MSD (Merck & Co., Inc., Kenilworth, NJ, USA), Astellas Pharma Inc. (Chuo City, Tokyo, Japan), AstraZeneca plc (Cambridge, UK), Erasmus and Novartis (Basel, Switzerland) and TEVA Pharmaceuticals (Petah Tikva, Israel). Rob Horne is founder and shareholder of a University College London (UCL) Business (UCL Business plc, London, UK) company (Spoonful of Sugar Ltd) providing consultancy on supporting patients with medicines and treatment-related behaviours to healthcare policy-makers, providers and industry. Caroline Sabin reports grants from National Institute for Health and Care Research, during the conduct of the study; and personal fees from Gilead Sciences Inc. and ViiV Healthcare Ltd (Research Triangle, NC, USA) outside the submitted work.

Publications

Moon Z, Kilic Z, Amirova A, Campbell LJ, Cooper V, Bondaronek P, *et al*. Interventions to increase adherence to antiretroviral therapy in people living with HIV – what works? Systematic review and meta-analysis. [Manuscript submitted for publication].

Glendinning E, Spiers J, Smith JA, Anderson J, Campbell LJ, Cooper V, *et al.* A qualitative study to identify perceptual barriers to antiretroviral therapy (ART) uptake and adherence in HIV positive people from UK Black African and Caribbean communities. AIDS *Behav* 2019;**23**:2514–21. https://doi.org/10.1007/s10461-019-02670-x

Horne R, Campbell L, Cooper V, Sabin C, McCrone P, Mosweu I, *et al. Efficacy of the Supporting UPtake and Adherence to Antiretrovirals (SUPA) Intervention: A Randomised Controlled Trial*. [Manuscript submitted for publication].

Horne R, Chapman S, Poliquin E, Leake Date H, Cooper V. Mind matters: treatment concerns predict the emergence of antiretroviral therapy side effects in people with HIV. AIDS *Behav* 2019;**23**:489–98. https://doi.org/10.1007/s10461-018-2239-6

Horne R, Glendinning E, King K, Chalder T, Sabin C, Walker AS, *et al.* Protocol of a two-arm randomised, multicentre, 12-month controlled trial: evaluating the impact of a cognitive behavioural therapy (CBT)-based intervention Supporting UPtake and Adherence to antiretrovirals (SUPA) in adults with HIV. *BMC Public Health* 2019;**19**:905. https://doi.org/10.1186/s12889-019-6893-z

King K, Horne R, Cooper V, Glendinning E, Michie S, Chalder T; SUPA Group. The development of an intervention to support uptake and adherence to antiretroviral therapy in people living with HIV: the SUPA intervention. A brief report. *Transl Behav Med* 2022 Jan 18;**12**(1):ibab104. https://doi.org/10.1093/tbm/ibab104

Mosweu I, Byford S, Cooper V, Glendinning E, Horne R, McCrone P, the SUPA Programme Management Group. *Cost and Cost-effectiveness of Interventions to Increase Adherence to Antiretroviral Therapy for People Living with* HIV*: A Systematic Review*. [Manuscript submitted for publication].

Spiers J, Smith JA, Poliquin E, Anderson J, Horne R. The experience of antiretroviral treatment for black west African women who are HIV positive and living in London: an interpretative phenomenological analysis. AIDS *Behav* 2016;**20**:2151. https://doi.org/10.1007/s10461-015-1274-9

Posters

What are the Barriers to Antiretroviral Adherence in People from UK Black African and Black Caribbean Communities? A Qualitative Study. BHIVA (British HIV Association) Spring Conference April 2013; Manchester, UK.

The Development of an Intervention to Support Uptake and Adherence to Antiretroviral Therapy in People Living with HIV*: The* SUPA *Intervention*. BHIVA (British HIV Association) Autumn Conference November 2013; London, UK.

Conference presentations

Costs and Cost-effectiveness of Interventions to Enhance Uptake and Adherence to Antiretroviral Therapy for HIV *Patients: A Systematic Review.* BHIVA (British HIV Association) Spring Conference April 2013; Manchester, UK.

Brian Gazzard Lectureship in HIV Medicine – *Understanding Patients Beliefs and Improving Adherence.* BHIVA (British HIV Association) Autumn Conference November 2013; London, UK.

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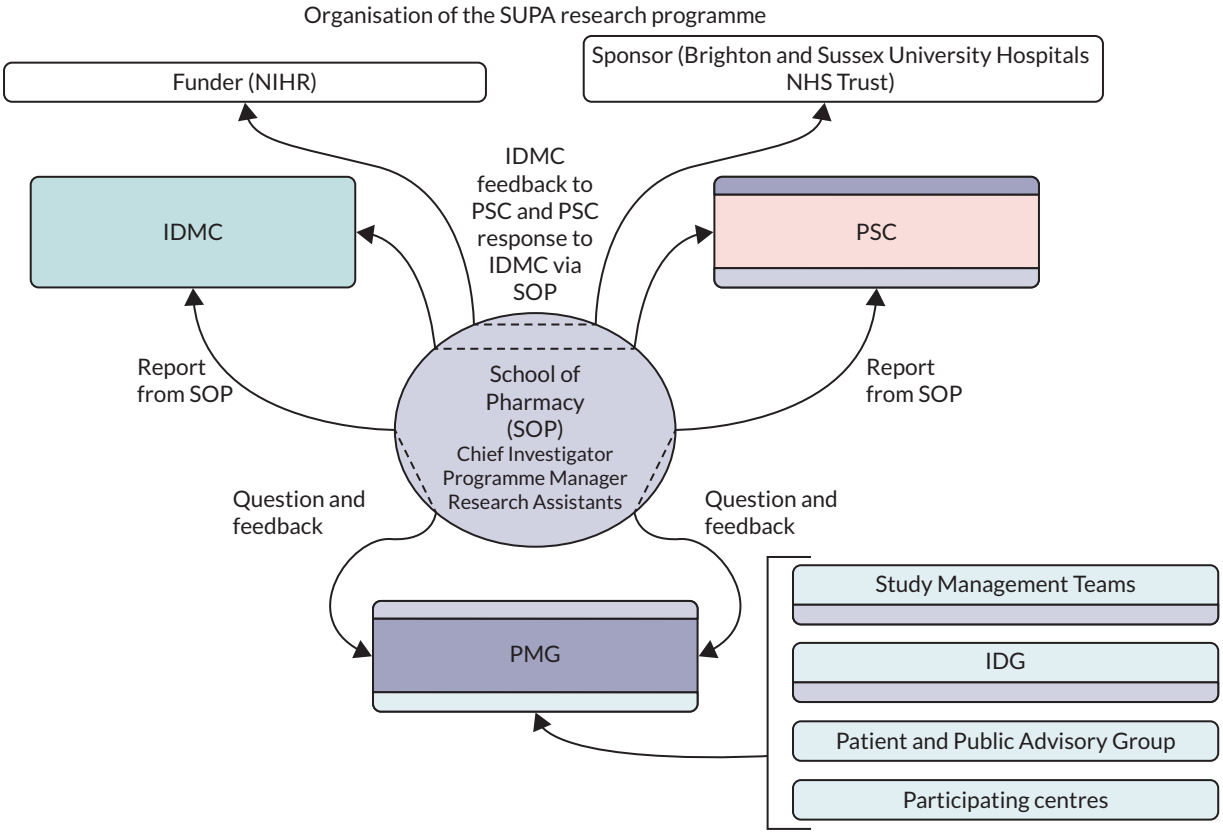
Appendix 1 Programme management structure



Role of the main committees

PMG

Manages the research, including clinical and practical aspects

Ensures protocols are completed in the set time frame with the required quality

IDMC

Safeguards interests of programme participants, by assessing safety and efficacy of interventions during the programme

PSC

Provides advice through its independent chairperson to the PMG, sponsor and funder on all aspects of the programme

Membership of Programme Management Group

Name	Post held
Rob Horne	Professor of Behavioural Medicine, UCL and chairperson
Trudie Chalder	Professor of Cognitive Behavioural Psychotherapy, Institute of Psychiatry, King's College London
Paul McCrone	Professor of Health Economics, King's College London
Simon Collins	Director, HIV I-Base
Winnie Sseruma	HIV Mainstreaming Co-ordinator, Christian Aid
Susan Michie	Professor of Health Psychology, UCL
Caroline Sabin	Professor of Medical Statistics and Epidemiology, UCL
Sarah Walker	Professor of Medical Statistics and Epidemiology, UCL MRC Clinical Trial Unit
Martin Fisher	Director of HIV Services, Professor of HIV Medicine, Brighton and Sussex University Hospitals NHS Trust
Jane Anderson	Director, Centre for Study of Sexual Health and HIV, Homerton NHS Trust
Mark Nelson	Director of HIV Services, Chelsea and Westminster Hospital
Heather Leake-Date	Consultant Pharmacist HIV/GUM, Brighton and Sussex University Hospitals NHS Trust
Nicky Perry	Research Manager HIV/GUM, Brighton and Sussex University Hospitals NHS Trust
Jonathan Smith	Professor of Psychology, Birkbeck University
Scott Harfield	R&D Manager, Brighton and Sussex University Hospitals NHS Trust

GUM, genitourinary medicine.

Programme Steering Committee

Member	Role
Alison Wearden	Chairperson
Nick Freemantle	Statistician
Steve Morris	Health economist
John Walsh	HIV consultant/adherence
Rosy Weston	HIV pharmacist
Zoe Sheppard	HIV specialist nurse
Paul Clift	HIV community representative
Ian Williams	British HIV Association representative
Brian Angus	Reader in infection disease, Oxford
Annemiek De Ruiter	HIV consultant, St Thomas'
Memory Sachikonye	UK Community Advisory Board

The purpose of this committee was to review the results of feasibility studies (recruitment, acceptability, health economics and effectiveness) and decide whether or not to proceed to evaluative trials after the pilot. The committee also provided advice through its independent chairperson to the PMG, sponsor and funder on all aspects of the programme. The committee met at the end of WS2 and as required.

Independent Data Monitoring Committee membership and function

Membership

- Independent chairperson and HIV expert: Julie Fox.
- Independent statistician: Toby Prevost.
- Independent adherence expert: Kav Vedhara.
- Independent HIV statistician: Peter White.

Role of the independent Data Monitoring Committee

The IDMC should:

- review accruing trial data
- assess if there are any safety issues that should be brought to participants' attention or any ethical reasons why the trial should not continue
- be independent of both the investigators and the funder/sponsor
- report to the PMG
- meet at least twice throughout the duration of the trial.

Appendix 2 Study 1: interview guide

Your views about your condition

1. Could you tell me how you came to know that you were HIV positive?
2. Please can you tell me something about the ways that living with HIV affects your life?

    i. Prompt: activities, work, relationships.

3. Do you feel differently about yourself since you found out that you have HIV?
4. What do you think caused you to get HIV?
5. How much have you felt able to talk to other people about your condition/HIV?
6. Has being HIV positive changed the way other people see you?
7. On a day-to-day basis, how do you deal with having HIV?

    i. Prompt: is there anything you do to help you with it?

Your views about treatment

1. What do you think will happen to your health in the future?
2. Is there anything that could be done to improve your health or stop it getting worse?
3. Can you tell me about your experiences of treatment for HIV up until now?

    i. Prompt: what has the treatment been like?

4. How easy or difficult is it for you to stick to the treatment plan?
5. How often would you say you were late with or missed doses of your antiretroviral medicine? Why is that?
6. Can you give me an example of a time when you were late with/missed your medicine?

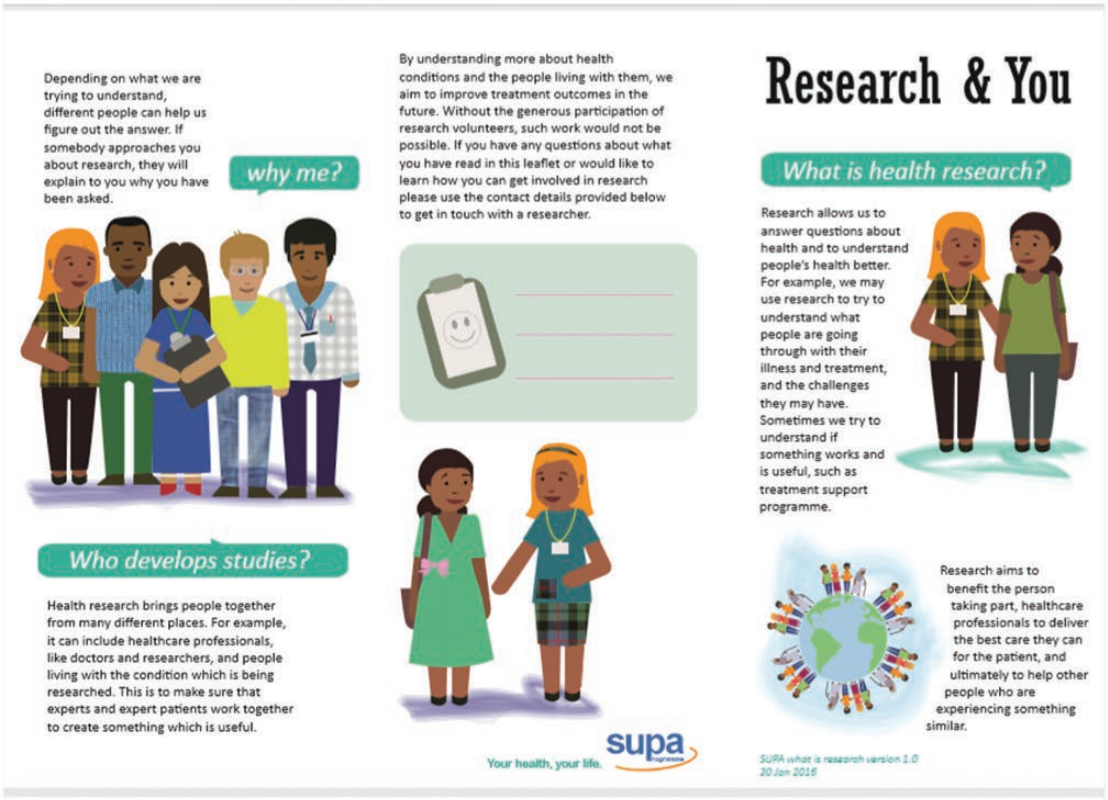
    i. Prompt: what caused it/what happened?

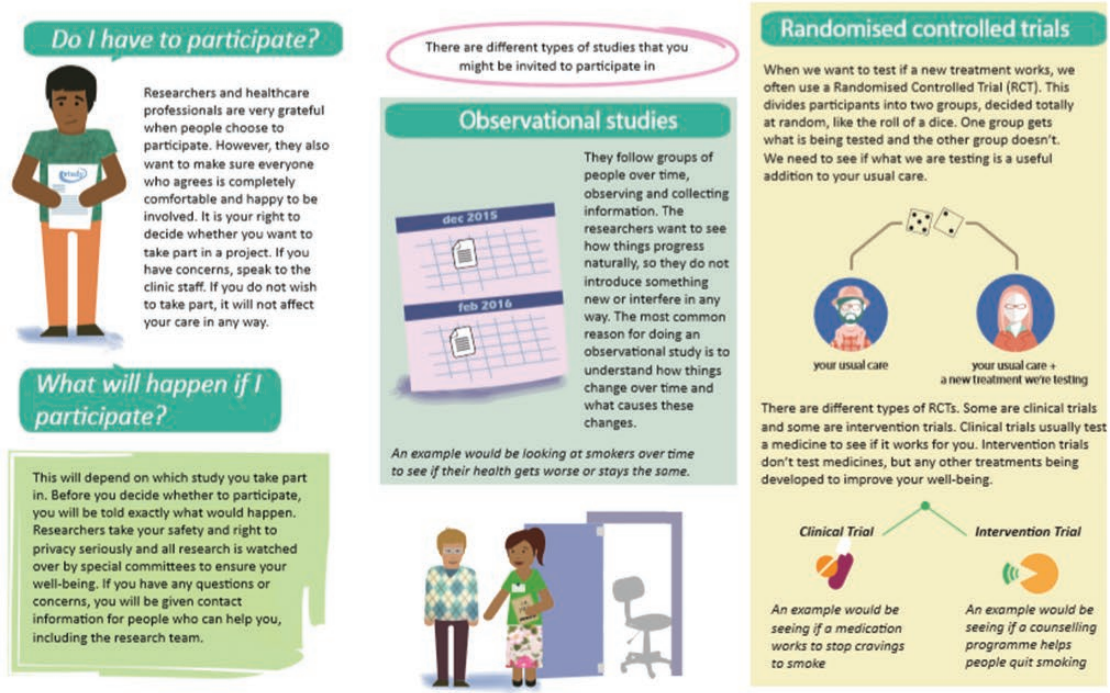
7. Is there anything you can think of that would make it easier to take your medicines?
8. What's been your experience of the health service in this country?

    i. Prompt: do you think you have been treated well/badly, fairly/unfairly?

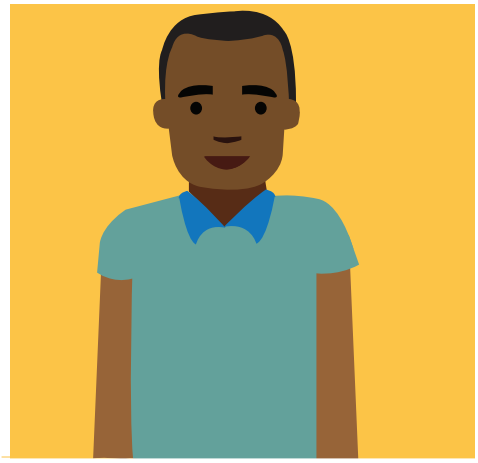
Thank you for your time and for talking to me today. Is there anything that you want to add, that I haven't picked up on and that you feel is important or that you want to say?

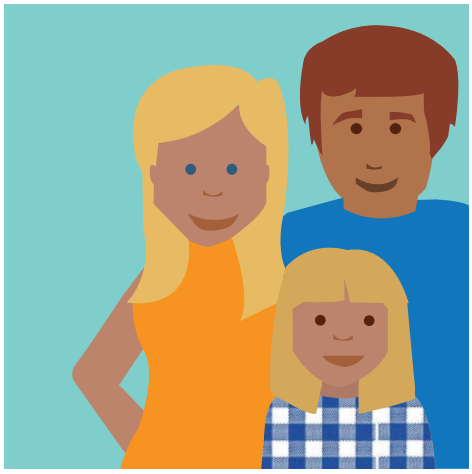
Appendix 3 Research patient leaflet: 'What is research?'





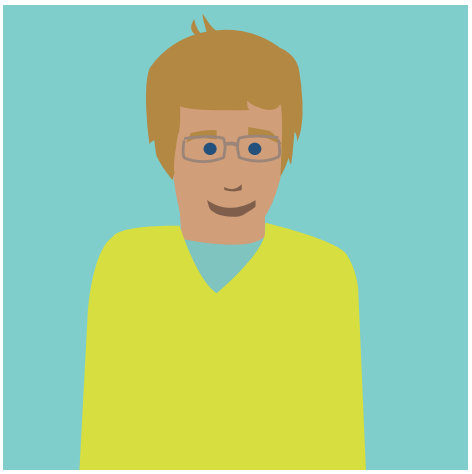
Appendix 4 Intervention manual (booklet)





supa programme

Your health, your life.



SUPA manual© version 1.0

going onto treatment: myths & reality

Being told you need HIV treatment can bring up many questions and concerns. There is a lot of information about it and everyone seems to have a view. There are still a lot of myths about HIV and its treatment. This can be confusing for people who are preparing to go onto treatment.

We hope that reading this booklet will help you to sort out the myths from the reality and help you to start and continue to get the full benefits of HIV treatment.

The booklet should be used alongside the session you get with your SUPA nurse. Your SUPA nurse will go through this booklet with you at your visits (face-to-face or on the phone). If you have any questions, write them down and ask them the next time you see your SUPA nurse.

table of contents

supa programme

how we hope to help you

This booklet aims to answer your questions about HIV and its treatment. It will help you to:

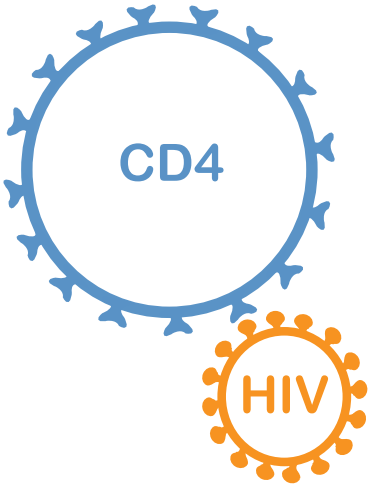
- Understand why your doctor has suggested treatment
- Find out how HIV treatment can help you
- Think through what being on HIV treatment will mean for you and your life
- Overcome your concerns about being on treatment
- Get the support you need
- Be in control of the HIV and stay in control so you can lead a normal and full life

This was funded by the NHS through the National Institute for Health Research.

This booklet has been made by many people, including doctors, nurses, researchers, pharmacists, psychologists and other people living with HIV.

why now?

HIV is a virus that cannot be cured. **BUT –**



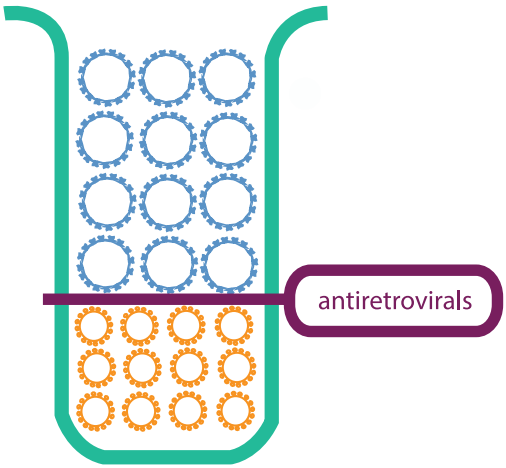
It can be controlled by ART.

Taking ART regularly controls HIV and protects from HIV-related illnesses so that people can live a full and normal life the way they want to live it.

But why has your doctor recommended treatment now?

This is a question that many people ask. Some may have known they are HIV positive for some time. For others, the offer of treatment can come as a surprise or shock, especially if you have only just been told that you are HIV positive.

To answer why you need to start treatment now, it's important to know about how HIV damages your body and how ART stops this from happening.



why now?

Your body's natural way of protecting itself against infection relies on CD4 cells. These travel in the bloodstream to all parts of the body, guarding against infections. The HIV attacks and destroys our CD4 cells. It does this gradually over time and often we don't even know it's happening. If HIV is left untreated, it can eventually destroy most or all of our CD4 cells. The more CD4 cells HIV destroys, the more likely we are to get ill.

BUT – there is good news **–**

ART can prevent this from happening. It stops HIV from attacking CD4 cells. When you take treatment, CD4 cells increase and the HIV virus decreases. Eventually, the amount of HIV is so low that the HIV is undetectable.

To put it very simply – treatment for HIV works!

If you want more information about the HIV virus and its effect on your immune system, see our FAQ section, p. 30.

why now?

myth

I don't look or feel ill so I don't need medication.

reality

It's understandable that someone may doubt taking treatment when they feel fine. This often happens and people may miss or skip doses when they feel better. This only helps the virus get stronger. Without treatment, HIV silently damages the immune system (the body's defence system), normally without you knowing about or feeling it.

If you miss a few doses you probably won't feel any worse, but don't be deceived. Without treatment, HIV in your body will increase. Eventually, symptoms are likely to appear, you may become ill, and it becomes even more complicated to treat the HIV.

why now?

myth

I think I might be too sick to start medication.

reality

You can't be too sick to start treatment. If you feel sick, that is because the HIV has had the time to damage the immune system. If you are sick when you start treatment, treatment will improve your health and you will feel less ill.

ART will help restore balance in your body, by lowering the amount of virus and improving the health of your immune system.

ART is very effective

even if your immune system has already been damaged. After starting treatment your CD4 cells should increase to healthier levels. It is normal to worry about starting treatment, but it is very important that you don't delay any longer with a low amount of CD4 cells. The longer you wait to start treatment, the more likely it is that you will get very ill.

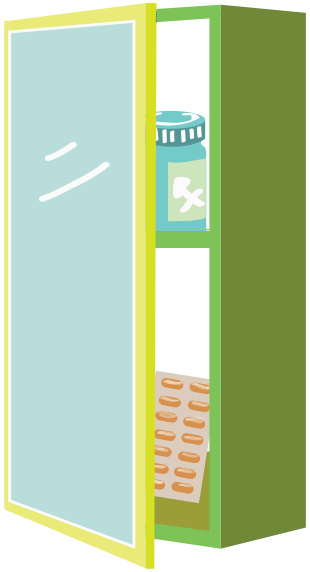
Some people think that if they're very ill that it might be dangerous to take treatment because treatment will add to the harm that HIV is causing. This is simply not true. Although some people get side effects from ART, having untreated severe HIV infection is far worse.

taking it: adherence

To get the most from treatment, you must take them at the recommended time, every day. Treatment only works if it is taken as prescribed.

This is called adherence.

Taking medication exactly as prescribed over a long period of time can be difficult, no matter what condition you are taking it for. Many people at one time or another have periods when either they take their treatment in a different way than it was prescribed, miss a dose or have a break from taking it altogether.



People stop taking their medicines or take less than prescribed for many reasons. For example, they might forget or find it difficult to fit it into their day-to-day lives. Or, they might decide not to take it because they are not sure they really need it. This might be because they feel fine or because they are concerned about harmful effects, or they don't like the idea of taking medication in the long term.

taking it:
making ART work for you and preventing resistance

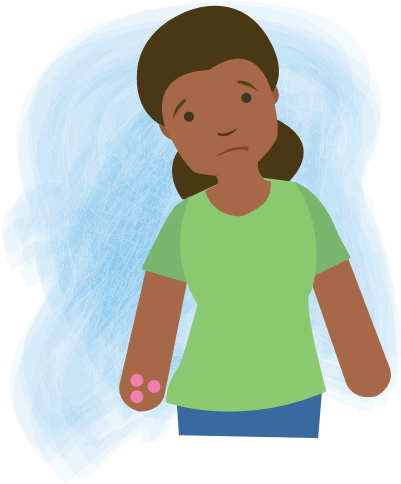
myth

Once my HIV is undetectable, I don't need to keep taking treatment.

reality

Unfortunately, the bad news is that right now we don't have a complete cure for HIV.

The problem with HIV is that it is silent; it hides away in your body and gets stronger and stronger. It tricks you into thinking you are well. It damages your ability to fight off infection (called your **immune system**), but without you being aware. In reality, the virus is hard at work, hiding away, damaging your immune system.



The good news is that taking ART regularly over time is similar to being cured in that the HIV cannot damage your CD4 cells. This means that people who are successfully treated can lead a normal, healthy life.

However, some people think that once their HIV virus is undetectable that treatment is less important. BUT – don't be fooled – even when it is undetectable you still need to take treatment every day. This is important to keep the virus down. If you don't take treatment, the virus will come out of hiding and attack your CD4 cells, eventually making you ill.

taking it:
making ART work for you and preventing resistance

myth

Skipping doses or taking a break from medication won't affect me.

reality

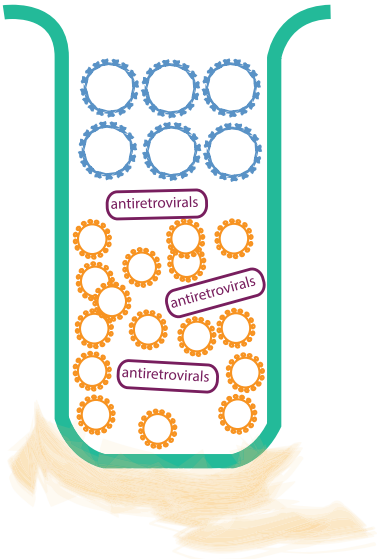
If you are taking HIV treatment, it is important to make sure that you take enough of the medicines every day. Missed or late doses can damage your health:

1) ART becomes less effective by allowing the virus to come out of hiding and damage your body

2) If there isn't enough medication in your body the HIV will become too strong and treatment may no longer work

This is called resistance.

If this happens, you will need to start a different HIV treatment which can be more complicated to take and have more side effects.



coping with HIV

Getting a diagnosis of HIV can make people feel different about themselves and about how other people see them. For some people, getting a diagnosis of HIV can be upsetting. Even if being reminded of being HIV positive feels difficult now, it may not feel that way forever.

The more we experience and repeat something, the more we tend to adjust to it. For example, think about how you felt on your first day at a new job or course; maybe excited, worried or nervous. Think about how you feel about it now.

With support and through facing difficult situations, one step at a time, you can learn to cope with even the most difficult feelings. These feelings are understandable and common. Accepting that you have HIV means that eventually you won't think about it very much.

The diagnosis and problems associated with HIV may be part of your life, but they do not need to be your whole life.

Remember, you are not alone. Talk to us!

Every clinic has patient representatives who are here to help.

Your patient rep is

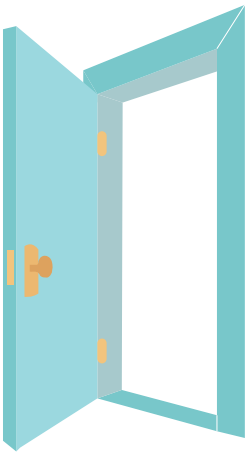
_____

and you can reach them on

_____.

There are also many community groups to meet people who have gone through, or are going through, similar experiences. One suggestion is:

_____.



coping with HIV

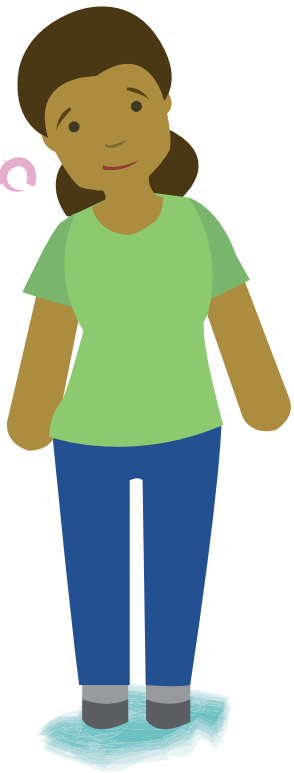
concern

I don't want the medication to remind me that I'm HIV positive.

suggest

There are different ways of thinking about taking medication, some of which might be helpful for you. Some people have told us that they see their medication as a tool to help regain control over their lives.

'I got really sick because I stopped taking the medication, I couldn't be bothered. I thought, 'What's the point? I'm going to die anyway'. But when I got really sick you know, in the hospital, I didn't think it would get that far. I took medication seriously and I got better. I'm in control now.'



When some people are diagnosed with HIV, they can only see themselves as someone who is ill. But with ART, you don't need to see yourself as a 'sick person'. When ART is working it makes HIV fade into the background. People successfully treated with ART can live a normal, healthy life.

what is it?

myth

"Many tablets are more effective than just one.

reality

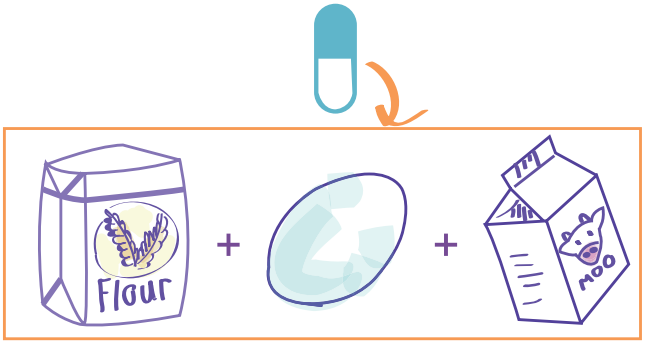
There are different combinations of HIV treatment. **Combination therapy** is the term for using 3 or more medications to treat HIV. To stop HIV making copies of itself, it is necessary to take a combination of medications that each target the virus in a slightly different way.

This combination is like a recipe for pancakes. Just like pancakes require eggs, milk and flour, combination therapy requires ingredients. There needs to be all the ingredients to work – they all have a job to do.

Some tablets are like a boxed pancake mix.

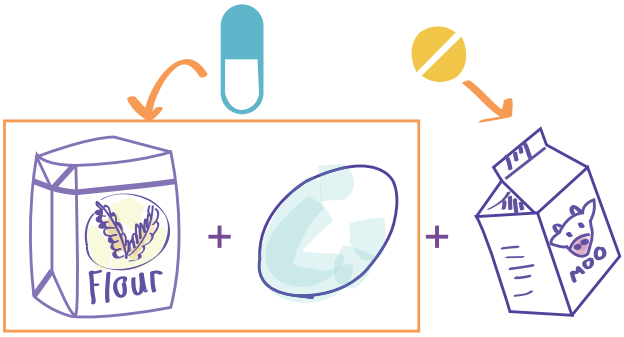
For example, many combinations have 3 ingredients.

In one-tablet combinations, each tablet already contains all the 3 ingredients.

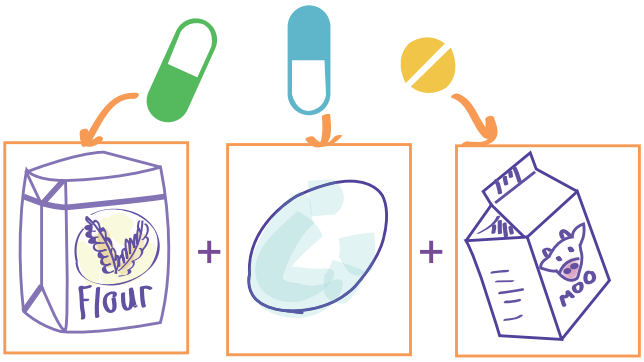


what is it?

In two-tablet combinations, one tablet contains 2 ingredients and one tablet contains the third ingredient.



In three-tablet combinations, each tablet contains a different ingredient.



All the medications need to be taken, or else the recipe won't work!

Some regimens have more than 3 ingredients – but the principle is the same. You must take all of the ingredients for the treatment to work.

If you want more information about combination therapy, please see iBase

http://i-base.info/guides/starting

side effects

concern

"HIV treatment has terrible side effects."

suggest

Medications for HIV are very effective in working against HIV, but they can also have unwanted side effects. Today's treatment for HIV has fewer and less severe side effects than the medication used previously. It's important to remember that

the benefits of HIV treatment by far outweigh the risk of side effects.

What is a side effect?

When medication goes in your blood, it travels everywhere in your body. So, although the medication's purpose is to protect your CD4 cells from HIV, it also can affect other areas of your body.

side effects

ART can cause side effects in anyone. But that doesn't mean that you will definitely experience side effects – in fact many people who take HIV treatment don't have any side effects at all.

Most side effects are caused by the body getting used to a new medication and they go away after a few weeks. Many people find that they initially experience side effects that then become less severe or go away completely. It's a bit like renovating a house – you have to make things worse before they get better. These are called **short-term side effects**.

Some people find that, although they have side effects, these are mild and they can live with them without distress or inconvenience.

Side effects are not always something you feel. Doctors will look for the signs of some side effects when they run blood and other tests at your HIV clinic appointments. This helps them check for any side effects you may not even notice. It is important you attend your regular clinic appointments so you are monitored for these side effects. If they find something, the Doctor can change your treatment.

side effects

It isn't just ART that can cause side effects – all medicines such as paracetamol and antibiotics and 'natural' medicines can have side effects.

But, a small number of people find that side effects don't go away even when their body gets used to treatment, and can affect their quality of life. These are called **long-term side effects**.

There are two important things to remember:

1) There are ways to manage side effects

whether you experience them when your body is getting used to treatment, or if you experience them for a long time. In this manual we have listed a range of options for each of the main side effects. See p. 38.

2) The choice of medication is much greater now than it used to be

and something can usually be done if your medication does cause side effects. Think of the many ART combinations we've been talking about! Changing treatment is an important option that you can discuss with your Doctor. Finding the right treatment for you is part of your Doctor's job – so don't be afraid to speak to them!

long-term effects

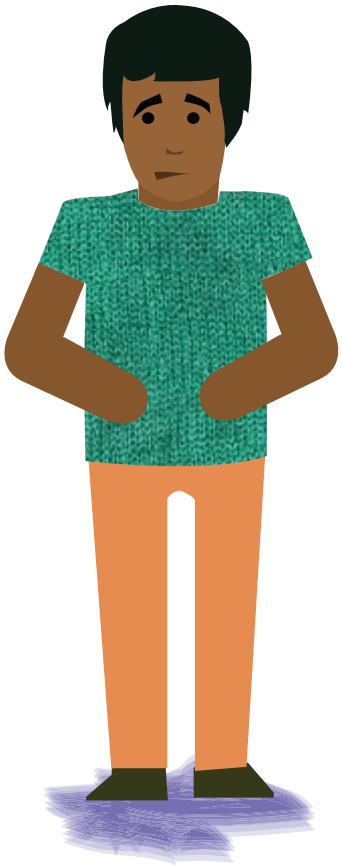
concern

"Taking this for so long, surely it will have an impact on my body?"

suggest

Having concerns about potential long-term effects of taking your medication is common and understandable.

We may not even know what we are concerned about, we just think that something bad might happen if we take the medicine for too long because it builds up in our body.



The possible risk of long-term effects of any medication needs to be balanced alongside the positive effects

of taking it and the risk of getting sick if you don't take it.

It doesn't mean they will definitely happen after taking medication in the long term, just that there is an increased risk of it happening. It is important to remember that the risks of developing long-term effects can be reduced by regular monitoring of your health to identify and prevent any problems.

long-term effects

concern

"HIV medication is not safe."

suggest

Every medication for treating HIV has been through years of research, including clinical trials with hundreds, if not thousands, of people with HIV.

Many people who became infected with HIV in the 1990s are still with us and are enjoying a full and healthy life thanks to ART (and some have helped write this booklet!)

There is increasingly more and more research about people ageing and living with HIV – because people with HIV are living long, normal lives.

In fact, people with HIV get constant 'A-Z checks'. Like car MOTs, people with HIV get regular checks such as tests for the blood, kidneys,liver, etc. People who don't have HIV don't have these tests regularly and may be unaware of illnesses and become ill unexpectedly.

long-term effects

myth

"I will become dependent on HIV medication."

reality

Many people who take medication worry that these may be addictive, like an addiction to cigarettes.

HIV medication will not make your body addicted to their chemical ingredients, which means your body will not crave their effects and you will not have withdrawal symptoms.

Although HIV medications are not addictive, they have to be taken daily in the long term to prevent damage to your immune system.

practical barriers

concern

"I don't think I can manage taking medication every day."

suggest

Many people would rather not have to take treatment long term, but across the world, millions of people are taking medication daily for some reason or another. About 10 million people take ART every day! So, taking treatment in the long term is actually very common and many people make ART a daily part of their life.

People can find it difficult to take their medication exactly as prescribed for a whole range of reasons. Busy lives, complicated prescriptions and how you are feeling can mean that it is sometimes hard to remember. However, with ART it's extremely important to take it on time, every day.

Although it may take time to get adjusted to taking treatment every day, over time it will get easier. Things that initially feel like a chore or feel stressful can become routines or habits that you rarely have to think about. For example, can you imagine not brushing your teeth every day?

Over time, brushing your teeth becomes a natural part of your daily routine and you don't even think about it. Taking medication for HIV will be the same.

It is sometimes possible to go onto a combination where you take fewer tablets. Ask your Doctor about this.

scheduling

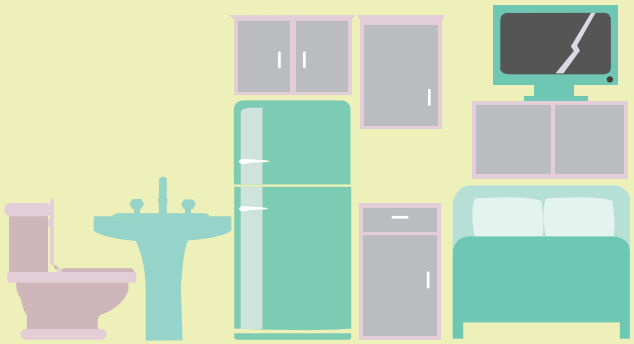
It is a good idea to make taking your medication part of your routine. This is a way that has been shown to be helpful for people in remembering to take their medication for a variety of conditions. Why not use the space to make a plan for how you can fit your medication into your routine...

If it is

e.g. 8 am

And I am in

e.g. in the bathroom



And I

e.g. have finished brushing my teeth

Then

e.g. I will take my first tablets of the day

scheduling

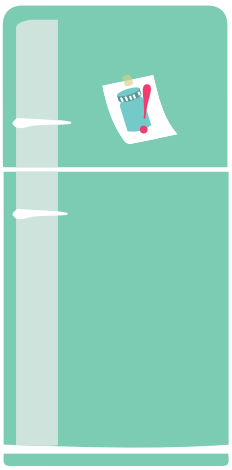
Tips for remembering to take ART

• Link taking medication to another activity such as brushing your teeth or before having a cup of tea/coffee or at dinner

• Keep your medications somewhere you will see them. This could be near your toothbrush, or in the kitchen

• Set an alarm on your phone or watch to remind you when it is time to take your medication – you can ask your Doctor or Nurse to help you with this

• If you use your computer regularly, you could set up a reminder to appear on your screen



• Find a place to put a reminder note (for example, on the bathroom mirror, fridge or television)

• Put a note on the back of your front door to remind you to take your medication with you when you are going out

• Ask for help from friends, family and flatmates – let them know when you need to take medication

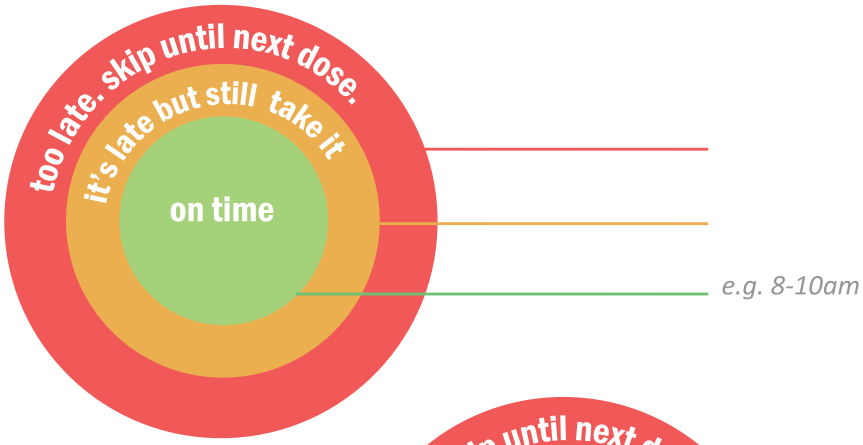
scheduling

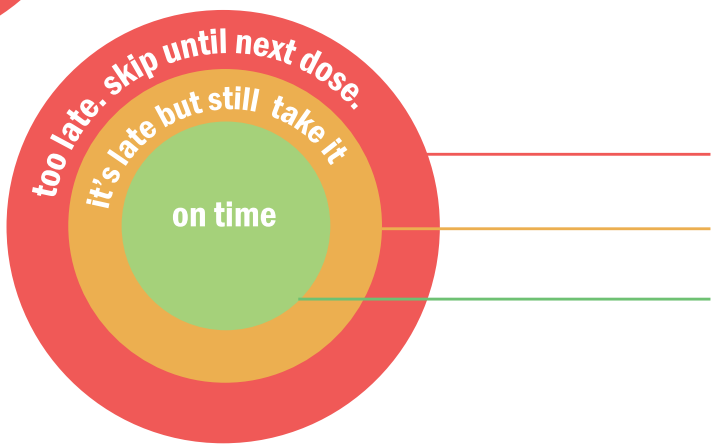
What if I'm late taking my dose?

For many treatments, the exact time you take your tablets is important. For others, you may have a 'window' in which you can take your tablets. Check with your Doctor to find out what applies to your treatment. Make sure you know what your window of opportunity is.

Plan ahead. For example if you are going out or away, making sure you have enough medication

Speak with your Doctor to find out when you should take each of your tablets and fill out the charts below.





practical barriers

concern

"I have difficulty swallowing large tablets. I'm scared of choking or sometimes tablets make me want to vomit."

suggest

- Ask your Doctor if you can break the tablet to swallow in smaller pieces
- Discuss with your Doctor whether there are any smaller tablets
- Drink a lot of fluids and always keep fluids on you

concern

"I just hate the taste of tablets."

suggest

- Take it with a little piece of bread so that it doesn't touch your tongue
- Take it with a flavoured juice or milk
- Hold your nose when you swallow
- Remember to ask your Doctor or Pharmacist if this is OK, because some medication cannot be taken with food or certain fluids
- Carry around water crackers and have immediately after swallowing your tablets

practical barriers

concern

"My living situation keeps changing and I will have nowhere to store my tablets."

suggest

- You could ask a friend or family member to store them for you
- You could store them at work
- You could store them with your toiletries

concern

"I won't be able to travel abroad with my medication.'

suggest

It is completely legal to travel with ART and you should not have to worry about explaining what the medication is for.

disclosure

concern

"Other people will see that I'm taking medication every day, they'll find out I have HIV."

suggest

It is your choice if or when you decide to tell others that you have HIV. Taking treatment does not make that decision for you.

Some people think that HIV medication stands out too much and that other will know straight away that their tablets are for HIV.

Can you say what the following tablets are for?

Pink, from the top: HIV, allergy, coughs and colds
Orange, from the top: HIV, pain, antibiotic

Remember, although you may think that other people notice you taking your medication, they are usually more focussed on what they are doing and unlikely to notice.

Many tablets look the same as the tablets for HIV (for example, migraine medication, antibiotics, etc). If someone sees your tablets, they won't automatically know that the tablets are for HIV. It's up to you if and when or to who you disclosure your HIV status to.

God and medication

Some people are concerned that taking medicines means that they lack faith in God to heal them. God gives us all things – there is no need to choose between taking medication and the belief that God will heal you.

The Lord created medicines out of the earth,
and the sensible will not despise them.
And he gave skill to human beings
that he might be glorified in his marvelous works.
By them the Physician heals and takes away pain;
the Pharmacist makes a mixture from them.
God's works will never be finished;
and from him health spreads over all the earth.

Concerning Physicians and Health,
Sirach 38 - New Revised Standard
Version Catholic Edition

God makes the ingredients for the medications that Doctors can provide.

God and medication

Consider this story –

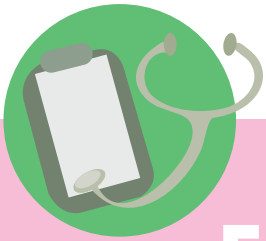
A man is drowning in the sea. A boat passes by and offers to bring him on board. The man replies '*No, God will save me*'. Another boat passes and the man once again replies '*I don't need your help, God will save me*'.

The man eventually drowns. When he meets God, he asks why God did not save him. God replies, '*I sent two boats for you, but you did not accept my help*.'

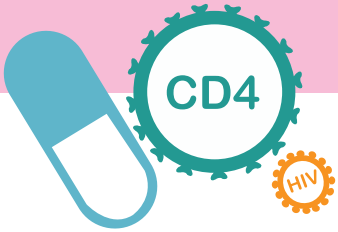
'For everything God created is good, and nothing is to be rejected if it is received with thanksgiving, because it is consecrated by the word of God and prayer.

Timothy, Chapter 4 verses 4 and 5.

Through prayer and medicine, God will work to bring you back to health.



FAQ section



this section goes through commonly asked questions

FAQ

What is resistance?

Research has shown that in general, people with HIV who don't take their medication all the time or who stop taking their medication altogether are more likely to get sick, be admitted to hospital, and even have an early death. So, although having doubts or concerns about medication is normal, it is important to discuss these with your health professional rather than stopping treatment or missing doses.

Skipping tablets and taking breaks from medication may lead to the development of **resistance**. This is a term doctors often use. It means that the type of HIV you have is, or has become, resistant to some HIV medication. In other words, the medication doesn't work well any more.

Every time HIV makes a new copy of itself, it is slightly different. Often these differences are not important but sometimes the new copy is different in a way that is 'resistant' to the medication you've been taking. This means that it will be able to reproduce again, even when you take ART.

Medication-resistant HIV could lead to the treatment not working, and you not being able to use the same medication (and, sometimes, other medications in the same class) again in the future. The next combination of medications you are given might be more complicated to take, or cause more side effects.

If you are able to take each dose of the medication at the right time each day, then the development of medication-resistant HIV is unlikely. That means the medications will work for many years.

If you do develop resistance to some medications, don't panic – there will still be other treatment options available to you. New medications have been developed that are effective against medication-resistant strains of HIV. However, it is very important that these medications are taken properly. If not, you may develop resistance to them, and this could mean that your HIV becomes very hard to treat. It is important to take resistance seriously.

FAQ

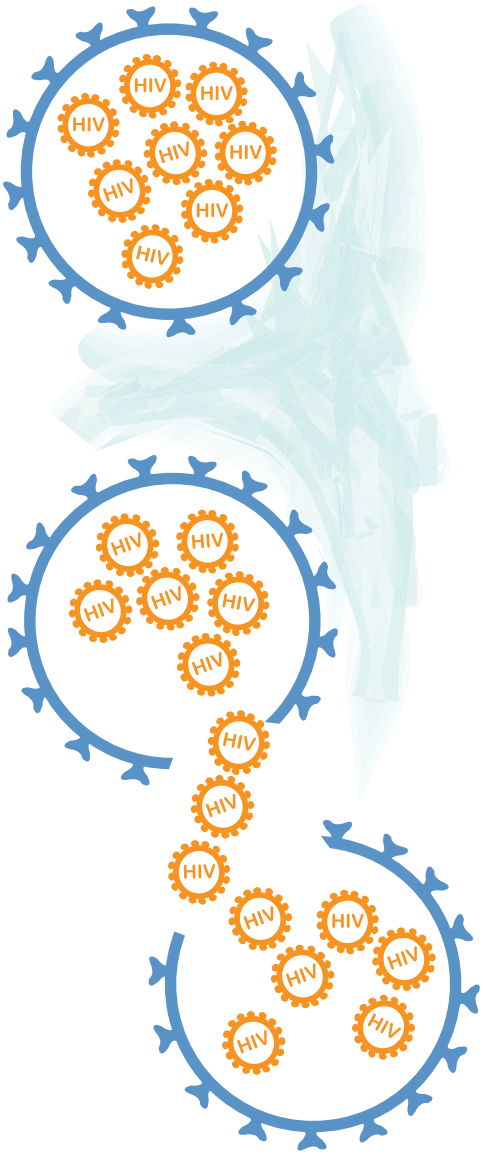
What is HIV?

HIV stands for **Human Immunodeficiency Virus**. It was identified in the early 1980s and belongs to a group of viruses called **retroviruses**.

HIV stops the body's immune system working properly. It does this by getting inside cells (called CD4 or T-cells) in our immune system. HIV destroys or damages these cells, makes copies of itself and then goes on to infect and destroy or damage more cells.

As more cells are destroyed, your immune system gets weaker and can't fight infections properly. This means you can get illnesses more easily. HIV treatment can stop this process so that the immune system can still do its job properly.

Although HIV cannot yet be cured, it can be treated. Modern HIV treatment means that many people with HIV are living long, healthy lives.



FAQ

What is AIDS?

AIDS stands for **Acquired Immunodeficiency Syndrome**.

If HIV isn't treated, the gradual weakening of the immune system it causes leaves the body vulnerable to serious illnesses it would normally be able to fight off.

In the UK, if you develop certain **AIDS-defining illnesses** (serious and life-threatening diseases that occur in HIV-positive people) or **opportunistic infections** (infections that take advantage of an immune system weakened by HIV), you are diagnosed as having AIDS – sometimes also called **late-stage HIV**.

You cannot catch AIDS and there is no AIDS test.

AIDS is not considered a disease, but a syndrome – a collection of different signs and symptoms, all caused by the same virus, HIV.

If you've developed an AIDS-defining illness, this doesn't mean that you can't recover. Thanks to HIV treatment, many people who were diagnosed as having AIDS in the past are now living long and healthy lives.

You need to have been infected with HIV to develop AIDS.

Without HIV treatment and care, people with HIV will experience damage to their immune system and will develop AIDS-defining illnesses at some point in the future.

A small number of people deny that HIV causes AIDS and some claim that AIDS has been created artificially as part of a conspiracy or to make profits for drug companies, for example, but this is not the case.

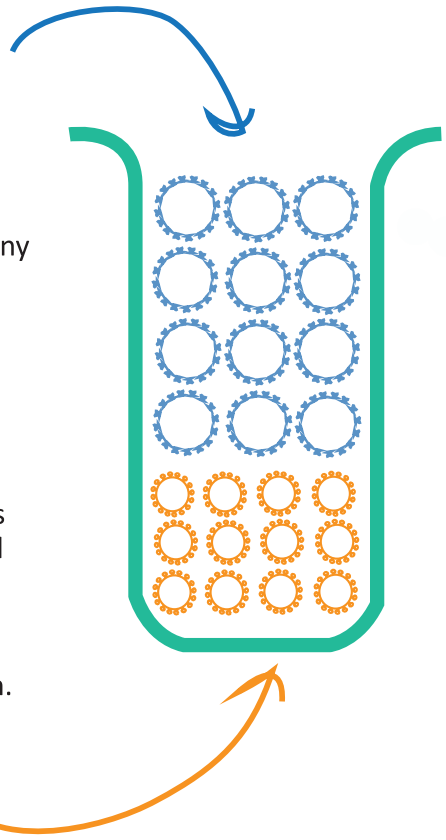
FAQ

Understanding blood results

HIV blood test results can be quite confusing with all the different numbers and names given. If you are uncertain about anything, ask your Doctor or Nurse to explain it.

What does my CD4 count mean?

Your **CD4 count** results are given as a number (anything between 1 and 1600 cells/mm^3). Many things affect this including: lab processes, time of the day, what you have eaten, if you have exercised, or if you have other infections.



Even if your CD4 count is very low, you can still feel fine. If your CD4 count is low, it is important that you start treatment right away. This is because your immune system is very weak and you are at risk of developing infections like TB or pneumonia. Some people think if they start taking tablets it may cause harm to your body, as they believe their body is not strong enough.

What do my viral load results mean?

Your **viral load** tells you how much virus is in a millilitre of blood (or another body fluid being measured). Whether this is considered high or low depends on whether or not you are on treatment. Unlike CD4 counts where you want a high number, viral loads want to be small.

FAQ

Purpose of treatment

The aim of treatment is not to cure HIV. HIV cannot currently be cured, but it can be controlled by medication. Treatment works to restore the balance in your body by lowering the amount of HIV in your blood and increasing the amount of CD4 cells. When the amount of virus decreases, your immune system can recover and become strong enough to fight off normal infections. This makes you less likely to get sick.

The aim of treatment is to reach **undetectable** levels of virus. 'Undetectable' refers to under 40 because this is the lowest that most viral load tests can measure.

This means that although the HIV hasn't gone away completely, there is so little in your body that tests cannot measure it easily.

HIV cannot currently be cured by treatment, because although treatment decreases the amount of virus in your blood, HIV never completely goes away. There is always a little bit of HIV left. However, earlier treatment limits the time that HIV may be making copies of itself and gives your body back control over the HIV and you can live a normal, healthy life.

If you're on treatment your viral load should go down and eventually become undetectable. If you're not, it will go up until you start.

FAQ

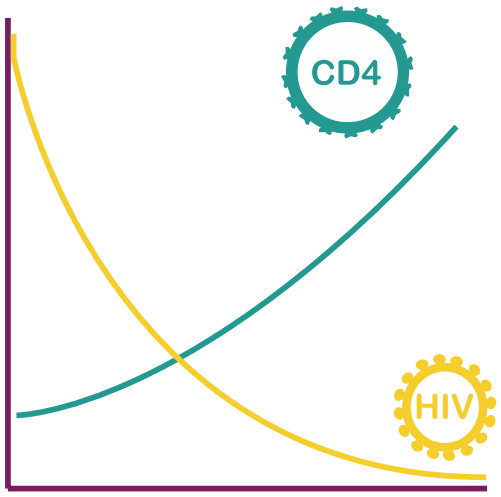
Understanding treatment: How quickly should CD4 and viral loads change after starting treatment?

Your viral load changes very fast after starting treatment. ART starts working in the body within the first few days of taking your first tablets, so viral loads drop by 90% and by 99% within the first 1–2 weeks. This is because CD4 cells infected with HIV only live for a few days and when you start treatment this virus and these cells are quickly reduced.

The speed of the response is related to your CD4 count when you start treatment. The lower your CD4 count is, the more slowly it is likely to take to respond. The lower your CD4 count is at the start, the less likely it is that you will reach high levels of CD4 cells. That doesn't mean that treatment does not work.

Individual factors will lead to different speeds of viral load reductions. These include:

- your CD4 and viral load results
- the medications in your treatment
- the amount of medicine in your blood (related to adherence and how they absorb and processes the medication).



FAQ

How doctors decide if you need to go onto treatment

Doctors make this decision based on:

- Your CD4 count and viral load test results
- Your current health, including whether you have other conditions such as TB or hepatitis
- Your age and how long you have been HIV positive
- Whether you are pregnant
- Current guidelines and available treatments.

side-effect management

this section goes through ways of manging any side effects you may experience

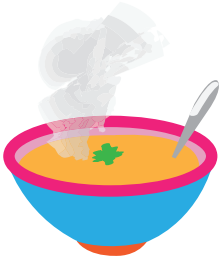
managing side effects

Headache

common culprits		Kivexa, Kaletra, Atripla, raltegravir, efavirenz, atazanavir, darunavir, ritonavir
common alternative causes		Stress Dehydration Too much coffee/tea (caffeine)
what you can do		Drink more water Take paracetamol or ibuprofen (check with your Doctor which one is best for you)
what your Doctor can do		Prescribe medication to reduce headaches Test for alternative causes – for example, if you have a low CD4 count, a headache can be a sign of opportunistic infection If headaches are too unbearable, switch regimen

managing side effects

Weight loss

common culprits		AZT
common alternative causes		Change in diet Ageing Stress Nausea/vomiting
what you can do		Eat small meals throughout the day If upsetting, ask a member of the clinic staff for Counselling If you have nausea/vomiting which is causing weight loss, see Section on Nausea and Vomiting
what your Doctor can do		If weight loss is too unbearable, switch regimen

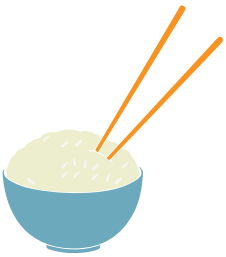
managing side effects

Weight gain

common culprits		ritonavir, efavirenz, Atripla
common alternative causes		Change in diet 'Return to health' weight gain Ageing and slowing metabolism
what you can do		Increase amount of fruit and vegetable you eat Reduce food with a high amount of fat or sugar Increase exercise – even small things like walking instead of taking the bus If upsetting, ask a member of the clinic staff for Counselling
what your Doctor can do		If weight gain is substantial, test for metabolic effects like increase in blood fats and sugars If weight gain is too unbearable, switch regimen

managing side effects

Diarrhoea

common culprits		Atripla, Kaletra, Stribild, Tenofovir, efavirenz, atazanavir, darunavir, abacavir
common alternative causes		Irritable bowel syndrome/disease Food poisoning Lactose intolerance
what you can do		*To prevent diarrhoea:* Keep hydrated and stay nourished Eat food like bananas, potatoes, chicken or fish which helps to replace potassium
		*When you have diarrhoea:* Use over-the-counter medication to reduce diarrhoea (Ask your Pharmacist or Doctor) Eat enough fibre – bran or fruit, white rice, white pasta, oats, beans Avoid coffee, raw vegetables, high-fat food, and spicy food
what your Doctor can do		Prescribe you medication for diarrhoea If diarrhoea is persistent (keeps being a problem), switch regimen
WARNING!		If you have diarrhoea longer than 2 days, call your clinic!

managing side effects

Tiredness and mood

common culprits		Efavirenz, Atripla
common alternative causes		Not sleeping enough Alcohol consumption Too much coffee/tea Stress
what you can do		Ensure you get enough rest and sleep Relax – take a few minutes for yourself Take it at night so you get these symptoms whilst asleep Exercise – even if just walking to the tube or walking around the park with a friend
what your Doctor can do		If the tiredness or change in mood is too unbearable, switch regimen

managing side effects

Nausea and Vomiting

common culprits		Kaletra, Maraviroc, Stribild, Abacavir, tenofovir, efavirenz, nevirapine, atazanavir, darunavir, ritonavir
common alternative causes		Pregnancy Flu Headache Alcohol consumption
what you can do		Take ginger biscuits or ginger tea Eat smaller, frequent meals Stay nourished and hydrated
what your Doctor can do		Prescribe anti-nausea/vomiting medication If nausea/vomiting is persistent, switch regimen
WARNING!		If you vomit after taking a dose, usually there is enough medication in your body, unless the tablet comes back up.

managing side effects

Skin problems

common culprits		Stribild, tenofovir, efavirenz, nevirapine, atazanavir, darunavir, raltegravir
common alternative causes		HIV Eczema Allergic reaction
what you can do		Wait – often it goes away within a few weeks Use calamine on the rash Use aloe vera on the rash
what your Doctor can do		Refer you to a skin specialist for assessment and treatment If the rash persists or is too unbearable, switch regimen

managing side effects

Flatulence

common culprits		Stribild, tenofovir
common alternative causes		Irritable bowel syndrome/disease Constipation Lactose intolerance Diet high in fruit and beans
what you can do		Eat more soluble fibre such as oats and linseed Eat probiotic yoghurt
what your Doctor can do		If the flatulence persists or is too unbearable, switch regimen

thank you!

We would like to thank everyone who helped create this booklet. This includes all the wonderful people at UK-CAB, Africa Advocacy Foundation, Christian Aid, and i-base.

We also want to thank those who participated in the SUPA interviews about their experience of taking treatment for HIV.

UK-CAB
HIV treatment advocates network

AFRICA ADVOCACY FOUNDATION

christian aid

i-base

Your health, your life.

supa programme

Appendix 5 Beliefs about Medicines Questionnaire – antiretroviral therapy for people who have initiated treatment

YOUR VIEWS ABOUT ANTIRETROVIRAL MEDICATION

- We would like to ask you about your personal views about antiretroviral medication.
- These are statements other people have made about their antiretroviral medication.
- Please show how much you agree or disagree with them by ticking the box.

There are no right or wrong answers.
We are interested in your personal views.

Views about ANTIRETROVIRAL THERAPY	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
My health depends on antiretroviral medication					
Having to take antiretroviral medication would worry me					
My life would be impossible without these medicines					
I would worry about long-term effects of these medicines					
Without antiretroviral medication I would become very ill					
Antiretroviral medication is a mystery to me					
My health in the future will depend antiretroviral medication					
Antiretroviral medication would disrupt my life					
I would worry about becoming too dependent on these medicines					
Antiretroviral medication would keep my HIV under control					
Antiretroviral medication would give me unpleasant side effects					
It would be difficult for me to take the tablets on time each day					
Antiretroviral medication is the best hope for the future					
I'm worried that others will find out I am HIV positive if they see I am taking antiretroviral medication.					
I worry that the tablets will be hard to swallow.					
I worry that the taste of the medication will make me feel unwell.					
Antiretroviral medication won't work as well for me as for other people.					
Missing doses won't be a problem if I get good blood test results.					
Breaks from antiretroviral medication will be good for my body.					
God will cure my HIV.					

Beliefs about Medicines - ART Specific (BMQ-ART) INITIATION ©

Appendix 6 Feasibility of the Supporting UPtake and Adherence to antiretroviral therapy study

Data cut-off point: 20 April 2015.

Findings from workstream 2: embedded randomised controlled trial

Lower recruitment than expected

Our first site was up and running in February 2014. Our embedded feasibility study identified significant recruitment challenges, with far lower throughput than anticipated from data supplied by centres. In 8 months we randomised 6 patients per site rather than the anticipated 32. Recruitment monitoring and analysis identified low rates of referral, rather than low participation, and high attrition as the cause. Referrals were 70% lower than estimated, but participation was high (80% of referrals to the observational study and 55% to the trial).

Recruitment of new sites

By July 2014 it was clear that the four-centre study would not be feasible. The PSC were strongly supportive of the trial and of our strategy of recruiting more centres. Since July, we have recruited a further nine centres to the RCT (i.e. Central Middlesex, Northwick Park, St Georges, Royal Victoria, Durham, Newcastle General, Lewisham, Birmingham and Brighton). To achieve this, we have diverted some resources from the initial four centres so that recruitment resources match patient referrals.

Update on trial centre initiation dates

The first site was up and running in February 2014. By August 2014, a further five sites were open for recruitment.

Recruitment (data correct up until 20 April 2015)

- Recruitment to study 1 (screen) = 86%.
- Patients screened and eligible for study 2 (trial) = 39%.
- Percentage eligible for and enrolled in study 2 (trial) = 53%.

Data quality and completeness

Data completeness was very good. Missing data are the result of electronic database errors that were rectified by the host company.

Descriptive data from screening

Data were extracted up to 20 April 2015 and were available for 213 participants who were enrolled in study 1 (screen), study 2 (trial) or both.

Data were examined for completeness, and baseline data were found to be complete for 207 of the 213 participants. Two of the six participants for whom no data were available withdrew before completion of the first case report form (CRF) (first visit of the trial). For the remaining four participants, source data were complete, but an error on the central database meant that the data were not downloaded.

Of the 207 patients, 121 were not eligible for study 2 (trial) and, therefore, remain in study 1 (screen).

All participants

After consenting to study 1 and administering the BMQ-ART, 86 out of 207 (42%) participants were eligible for study 2 (trial), of whom 46 were successfully randomised, 28 declined to take part, 6 were screen failures and 7 were pending a decision.

Participants failed screening primarily because of language difficulties that would make CBT impossible (*n* = 4), and two participants had severe psychosis, which the clinician responsible and researcher deemed too severe to consent.

Analysis of the primary outcome measure

The MEMS data were not analysed for the purposes of this report as only five patients were due to complete or had completed the trial.

Rates of attrition

- In the observational component (study 1: screen), 5 out of 213 patients could not be reached for their follow-up.
- In the trial, 2 out of 48 patients had withdrawn: 1 because of difficulty in using MEMS caps and 1 because of competing time commitments.

Protocol deviations

Patients followed up out of acceptable window (± 1 week)

A conservative follow-up window was set for ± 1 week around the follow-up due date, in line with clinical trials. Although our retention rate was high, it was evident that it was often difficult to complete measures within a narrow time frame with patients who frequently did not attend even clinic appointments. For our primary outcome measure, date of reading did not affect the quality of the outcome measure because the MEMS caps continues to record openings and data could be cleaned according to the necessary dates.

Attendance of intervention sessions in the intervention arm

- One patient in the intervention group received their initial two intervention sessions too late (i.e. past the 4-week window from baseline visit) and then was lost to follow-up (so did not receive their 3- and 6-month sessions).
- One patient in the intervention received their initial two intervention sessions 2 weeks later than the dates specified in the protocol to deliver the intervention.
- All other patients had attended all their intervention sessions within the acceptable window (two sessions within 1 month from randomisation, ± 1 week around due date for 3 and 6 months).

Patients misenrolled to study 2

Two patients were misenrolled into the trial. Their BMQ scores were ‘borderline’ (e.g. 3.1 when the cut-off score is 3.0), but were not correctly summed, so they appeared to be eligible for the trial when in fact, they were not.

Safety

There were no adverse events or serious adverse events to report.

Appendix 7 Acceptability of the Supporting UPtake and Adherence to antiretroviral therapy intervention

Aim

The aim of this study was to determine whether or not the SUPA intervention was acceptable to previously ART-naive PLWH in the SUPA RCT.

Methods

A convenience sample of participants who received the SUPA intervention were interviewed by a research assistant (independent to the research nurse delivering the intervention to avoid bias) after receiving the last intervention session. Interviews were conducted in a private room at the HIV clinic. They were semistructured, where research assistants followed an interview guide with prompts to explore the participants' responses. Participants were asked about their perceptions of the intervention, including their overall impression, positive features, less good elements and ease of comprehension. Interviews were audio-recorded and transcribed verbatim by an independent transcription company who had signed a non-disclosure agreement.

Analysis

Verbatim transcripts were subject to a thematic analysis.[68] Thematic analysis was chosen as the method of analysis because it allows for flexibility leading to unanticipated insights and can uncover similarities and differences across data.

The analysis followed the steps outlined by Braun and Clarke:[68]

1. Transcripts were read and reread to gain familiarity with the data.
2. Initial ideas were noted.
3. Transcripts were coded independently by two researchers to generate initial codes.
4. Coded text was compiled and organised using NVivo, a software package for qualitative research.
5. Codes were collated into potential themes that emerged from the data. This process was conducted by two researchers who discussed and agreed the themes.
6. The themes were reviewed, checking that they worked in relation to the coded extracts and the entire data set.
7. The themes were clearly defined and named in the ongoing analysis.
8. The themes were applied in informing the analysis of each of the interview transcripts.
9. Quotations were selected to illustrate each of the themes.

Results

Of the 71 trial participants randomised to receive the SUPA intervention, 24 (33.8%) completed an exit interview and were included in the analysis. Demographic characteristics of the sample are shown in *Table 29*.

Thematic analysis

Codes were collated into eight separate themes. These were organised into two master themes: reasons for participation (four themes) and experiences of the intervention (four themes). These themes are shown in *Table 30*.

TABLE 29 Sample characteristics (*N* = 24)

Characteristic	Unit	Value
Gender, *n* (%)	Female	7 (30)
	Male	17 (70)
Ethnicity, *n* (%)	White	7 (29)
	Black African	9 (38)
	Black other	3 (12)
	Other	4 (17)
	Not stated	1 (4)
Sexual orientation, *n* (%)	Heterosexual	14 (58)
	MSM	10 (42)
Age (years), median (IQR)		36.5 (27.5–44.5)

TABLE 30 Acceptability of the SUPA intervention: themes and subthemes

Themes	Reasons for participation	Experiences of intervention content and delivery
Subthemes	Increased knowledge	Intervention materials
	Taking an active role	Approachable staff
	Need for support	Convenience and timing
	Recommendation	

Reasons for participation

Four themes appeared to precipitate the participants' decision to take part in the intervention trial, as shown below.

Increased knowledge

Most of the participants were newly diagnosed with HIV and wanted to take part in the intervention trial to gain a better understanding of what their HIV status would mean for them, as well as to gain knowledge about HIV medicines. For some this was particularly important because they wished to reduce their fears so that they would be able to cope with it better and get on with their lives:

> *I wanted to get a good understanding of the virus, how it works, if I can handle it and to clear my mind of the impression I have about it.*
>
> *0303*

Taking an active role

Many participants expressed the desire to play an active role in dealing with their condition and felt that talking part in the research would mean that they were doing something positive for themselves and/or other people living with HIV:

> *I am happy to help if this research helps someone else . . . I just want to share my experience.*
>
> *0047*

Need for support

Most participants had not shared their HIV status with their friends and family and, therefore, confidentiality was of utmost importance to them. The SUPA intervention was seen as a safe and confidential means of gaining information and support. Participants discussed the need for someone to talk to because they felt frightened and isolated after receiving their diagnosis:

> *I'd just gotten the news about my condition and I was in a state where I actually had nobody to talk to, I was very low, and it's like the world had collapsed . . . so when SUPA came to me I said yes because I needed somebody to talk to.*
>
> *0144*

Recommendation

For some participants, the decision to take part was facilitated by a recommendation from a trusted healthcare professional, such as a doctor, nurse or psychologist:

> *It was referred to me by my psychologist, she suggested that I should go. When they explained everything, what is it that I needed to do then I felt that I needed to participate in the SUPA studies.*
>
> *0367*

Experiences of intervention content and delivery

Four themes represented participants' experiences of the intervention in terms of its content and delivery. These are shown below.

Quality of information

All participants reported that the SUPA manual and animations provided clear information that they found easy to understand. Most indicated that they found the information relevant, with many stating that they found that the materials increased their knowledge of HIV and ART:

> *SUPA's materials are simple and very easy to understand . . . It's all very relevant to anyone whose living with HIV or who has to live with it.*
>
> *0275*

Some limitations of the information provided within the SUPA programme were also reported by participants. These included the need for more information about the emotional impact of living with HIV and how to manage and cope with their own and other people's responses to their condition. One specific area of interest was more focus on managing relationships and meeting a new sexual partner when living with HIV:

> *Like the relationships and dating side, and the emotional aspects of living with it, things like that.*
>
> *0275*

Approachable staff

Participants found the SUPA staff to be friendly. They viewed the SUPA nurse to be a source of emotional support, who they felt was encouraging and easy to speak to. There was a sense that the support received from the SUPA nurse reduced their anxiety and this made it possible to open up and speak about their concerns and information needs, which was different from how they felt about expressing their concerns to the doctor:

> *The way they talk you don't feel nervous like with the doctor . . .You feel like the doctor is busy. When you know you're going to see the girls from SUPA, you get support and can say I would like to know this and ask that.*
>
> *0120*

Convenience and timing

Participants reported that they valued being able to choose the timing of sessions. Many found the sessions convenient because they were scheduled after their doctor's appointments and, therefore, did not require additional trips to the HIV clinic:

> *It's very convenient if they are related with appointments with the doctors because if you're dragging it out on different days then you're spending more time for the trouble, but it's no problem to chat for half an hour on the top of when you are at the clinic.*
>
> *0047*

Although many patients were happy with the number of face-to face sessions and felt that four sessions had been sufficient to gain the knowledge and support they needed, others said they would have benefited from extra sessions, and felt that it would be useful to be able to access additional support and information as new issues arise:

> *I needed more sessions to be honest . . . it helps because there may be a time where I would want to gain some information about certain things . . . if I'm not having enough sessions I won't be able to ask questions.*
>
> *0367*

There were mixed views on the length of time of the sessions. Most felt that the sessions should be no longer than 1 hour. However, some felt that 1 hour was not long enough because of the large gap in between sessions:

> *It's not enough time because you only have that particular session with your nurse for that particular month.*
>
> *0367*

Discussion

This study provided qualitative exploration of the acceptability of the SUPA intervention. It focused on reasons for participation in the SUPA trial as well as the perceived acceptability of the intervention materials and sessions. We found that the intervention was generally well accepted by participants, intervention materials were accessible and clear and that the intervention sessions were perceived as a helpful source of emotional support. A separate paper has explored patients' perceptions of the impact of the intervention on adherence behaviour and beliefs about HIV and ART.

Taking part in the SUPA trial was often a way of gaining support and information and to come to terms with the HIV diagnosis. This finding reinforces those from our qualitative work in WS1, which found that many people are overwhelmed by the need to start treatment very soon after receiving a diagnosis of HIV,[39] and suggests that offering a supportive intervention at the time of a treatment recommendation would be valued by patients as part of routine clinical care. The fact that many participants valued the SUPA nurse as a key source of emotional support because they had not discussed their HIV status with their family and friends emphasised that HIV stigma remains a very real concern for many people living with HIV. This highlights the possible need for specific support around disclosure fears among people initiating ART.

The fact that many participants had positive experiences of the intervention was encouraging. Information was experienced as being clear and informative. Participants' views on the number of intervention sessions varied – some believed four was enough, whereas others felt that they would benefit from additional sessions. This could be addressed by offering extra booster sessions to patients depending on need. Another suggested improvement was to have more information and support when discussing their HIV diagnosis with others or initiating new relationships.

Limitations

The are several limitations of this study. Participants were a convenience sample of those willing to attend the clinic for an additional interview after the final trial follow-up and, therefore, are a biased sample. It could be that those who took part in this study had more positive or more negative views about the intervention than those who did not agree to participate. Caution must therefore be exercised when seeking to generalise from these findings. It was possible to examine only reasons participants gave for choosing to take part in the SUPA trial, rather than reasons for not taking

part. Although participants were interviewed within 3 days of completing the trial, this was 6 months after the final intervention session and participants were required to remember their decisions and experiences. These memories may not have been accurate. Moreover, although we ensured that the interviews were not conducted by SUPA nurses, the research assistant delivering the SUPA intervention was a member of the SUPA team and, therefore, participants may have been predisposed to provide a positive account of their experience (social desirability bias).

Implications for research

The findings of this acceptability study suggest that the SUPA intervention sessions and materials were acceptable to the target group. It provided information that will be used to develop the intervention materials and content, such as piloting additional booster sessions and including more information and support for talking about HIV and ART with others.

Appendix 8 Process of change in people receiving the Supporting UPtake and Adherence to antiretroviral therapy intervention: a qualitative study

Aim

The aim of this study was to determine the process of change in previously ART-naive PLWH receiving the SUPA RCT.

Methods

Interviews were conducted in a private room at the HIV clinic. They were semistructured, in that research assistants followed an interview guide with prompts to explore the participants' responses. Participants were asked about the benefits of the intervention and what had changed for them as a result of receiving the intervention. Interviews were audio-recorded and transcribed verbatim by an independent transcription company who had signed a non-disclosure agreement.

Analysis

Verbatim transcripts were subject to a thematic analysis as defined by Braun and Clarke.[68] Thematic analysis was chosen as the method of analysis because it allows for flexibility leading to unanticipated insights and can uncover similarities and differences across data. It allows the exploration of predefined theory as well as inductive accounts. In this analysis, the data were explored in relation to the necessity concerns framework[23,27,42] and the extended common sense model of self-regulation.[42,69] The analysis of verbatim transcripts was conducted with the following research question in mind: what impact did the intervention have on participants' beliefs about HIV and ART?

The analysis followed the steps outlined by Braun and Clarke:[68]

- Transcripts were read and reread to gain familiarity with the data. Initial ideas were noted.
- Transcripts were coded independently by two researchers to generate initial codes. Coded text was compiled and organised using NVivo, a software package for qualitative research.
- Codes were collated into potential themes that emerged from the data. This process was conducted by two researchers who discussed and agreed the themes.
- The themes were reviewed, checking that they closely described the coded extracts and the entire data set.
    - The themes were clearly defined and named in the ongoing analysis.
    - The themes were applied to each of the interview transcripts. Quotations were selected to illustrate each of the themes.

Results

Of the 71 trial participants randomised to receive the SUPA intervention, 24 (33.8%) completed an exit interview and were included in the analysis. Demographic characteristics of the sample are shown in *Table 31*.

TABLE 31 Characteristics of participants who took part in post-intervention interviews (*N* = 24)

Characteristic	Value
Gender, *n* (%)	
Female	7 (30)
Male	17 (70)
Ethnicity, *n* (%)	
White	7 (29)
Black African	9 (38)
Black other	3 (12)
Other	4 (17)
Not stated	1 (4)
Sexual orientation, *n* (%)	
Heterosexual	14 (58)
MSM	10 (42)
Age (years), median (IQR)	36.5 (27.5–44.5)

Thematic analysis

The impact of the intervention on participants' experiences of HIV and ART could be categorised in terms of four separate themes: knowledge about HIV; beliefs about the necessity for ART; concerns about HIV and ART; practical and emotional support. These themes have been described in detail below.

Human immunodeficiency virus knowledge

Most participants reported that their understanding of HIV had increased as a result of the SUPA intervention. For some, the increase of knowledge was incremental and they learnt more at each of the sessions:

> *. . . session after session, my understanding of HIV got broader and broader because it's like it was step by step.*
>
> *0298*

A number of participants shared that they had a very limited knowledge about HIV prior to receiving the intervention, and many reported that intervention had addressed misconceptions about HIV. This included increased knowledge about how HIV can be transmitted:

> *When I was told I was HIV positive, I knew nothing apart from the weird stories that people share out there . . . If I had been told that somebody was HIV positive, I would have said oh, maybe even greeting them, maybe even sharing things in the house with them could make me catch it, but from the discussions we had, I am enlightened, and I know the ways which one can get HIV, and ways that one cannot.*
>
> *0144*

Beliefs about the necessity for antiretroviral therapy

For many participants, the intervention sessions with the SUPA nurse had addressed their misconceptions that a diagnosis of HIV meant imminent mortality. It had provided a rationale for taking ART to decrease the risk of illness and death and instead transform HIV into a long-term illness that is manageable:

> *I was thinking, 'oh. With HIV, very soon I will be a dead person', but with the session helped me to understand that HIV now is like any other sickness like high blood pressure or diabetes, as long as you are taking the medication you have no problem with it.*
>
> *0303*

In addition to addressing misconceptions about HIV, participants reported that the intervention had changed their views about antiretroviral medicine. The sessions provided participants with a coherent rationale for continuing with their medication and not missing doses, for example, by providing an explanation about what happens to the virus when doses are taken or missed. This knowledge, and the ability to see the impact of ART on their blood test results, encouraged participants to take and continue with their medications:

> *The session made me understand that you don't stop taking the medication otherwise the virus would get resistant, so that helped me to be taking the medication every day.*
>
> *0303*

> *I remember when I started I was anti-medication. But the sessions they helped me to see the reason why I needed to take the medication so then the knowledge that I was given and the purpose that the medication was designed for . . . came as a sense of comfort to see that oh well taking this medication it is making a difference.*
>
> *0367*

Most participants believed that receiving the intervention had helped them to improve their adherence. For many this was as a result of the realisation that it would be necessary to continue with their treatment and to take it as prescribed to achieve and maintain an undetectable viral load. The intervention helped participants to understand the link between decreased viral load and prevention of ill health:

> *So the viral load would go up because they'd missed their meds, but if they continued taking it, it would go down, so I knew I had to put that in my mind that I either take it or get into worse problems you know health wise.*
>
> *0144*

Concerns about human immunodeficiency virus/antiretroviral therapy

Many participants reported that the intervention sessions had helped to alleviate their concerns about HIV and ART. Several participants reported that the intervention had helped them to reassess their pre-existing view that having HIV would prevent them from having the life that they had planned for themselves; for example many reported that they had realised that having HIV did not mean that they would not be able to live a normal life, which for many included having children:

> *I have learnt, it's not over . . . I still have life to live, normal life and stuff . . . I can impregnate a woman, I can still have children.*
>
> *0350*

This shift in perspective did not occur for all participants. For example, one participant revealed that the intervention had not helped him to come to terms with his diagnosis of HIV:

> *I can't accept this and I still try to avoid like this cannot be, I'm just waiting for somebody to call and say it was a mistake, you know.*
>
> *0120*

One way in which the intervention addressed concerns about ART was by providing a coherent explanation of side effects that people were experiencing as well as ways of dealing with side effects:

> *It made me understand the problems I was going through and how to handle them, the effects of the drugs I was having, the side effects, so the books they gave me, I read them, so I was coping with the way I was facing it.*
>
> *0303*

Some people found that the intervention had helped them adhere to their treatment because it had reduced their fear that taking ART in public would alert other people to the fact that they were HIV positive:

> *. . . taking the medication in public and things like that and the worries that you have it just, sort of takes that weight off your shoulders.*
>
> *Like actually people haven't got a clue what I'm taking they don't know what it is and if they did I can just say it's a vitamin they're not gonna research what's on your bottle.*
>
> *0275*

Practical support

Participants reported that the intervention provided practical strategies to help them to cope more effectively with their HIV diagnosis and adherence to ART. An example of this was helping participants to discuss their HIV diagnosis and concerns about HIV with other people. This had various benefits, such as enabling the participant to discuss their HIV status with their partners and enabling them to seek a HIV test:

> *Well they encouraged me to speak to my wife which I had done and she has come for a test which was negative, they provided me with materials like condoms to enable me to live a normal life. So generally, they encouraged me a lot.*
>
> *0303*

The SUPA nurse was able to provide practical support for side effects by liaising with doctors, nurses and pharmacists on behalf of the patient to address problems that they were having with side effects of their medications:

> *I get many side effects, like dizziness, everything and at the same time I was doing the SUPA so that things and that's why I came to see her and then I told her, then she talked to doctor. I talked to doctor but every time she asked me about those things and then she passed to the pharmacy.*
>
> *0161*

Participants reported benefiting from practical advice offered by the SUPA nurse to help them to address practical barriers to taking their medication. These included the provision of strategies to address difficulties with swallowing pills, such as drinking more water, taking tablets with yoghurt to disguise the taste, changing the timing of dosing and strategies to address difficulties with remembering doses (e.g. the use of smart phone reminders):

> *It was actually off [SUPA nurse] I got advice about drinking more water with my medication and not taking it while I was laying down or had just woken up.*
>
> *0275*
>
> *She was super helpful in showing me ways of sorting out my problems. Like I found the tablets disgusting. I just wanted to vomit them up. Every time they touched my tongue I wanted to vomit. But she showed me how to have them my yoghurt so they would go down.*
>
> *She would ask me if I could put an alarm on my phone like to remember to take that specifically always at that time, yeah, I don't miss nothing.*
>
> *0056*

A few participants commented that the MEMS caps that were provided as a measurement tool to trial participants (both intervention and control groups) had helped them to adhere to their medication because they reminded the participant that their adherence was being monitored, and that someone would know whether or not they were taking their medication as prescribed. For some, this awareness helped to establish a routine which they had maintained after the MEMS caps had been removed:

> *I felt like there was big brother watching me, you know, with the MEMS I knew I had to do it at the right time, and it sort of put me into a routine which I still carry out today, I never forget any medication.*
>
> *0144*

Emotional support

Many participants reported that a major benefit of the SUPA intervention was the emotional support they received in their face-to-face sessions with the SUPA nurse. The sessions provided access to an approachable, friendly healthcare professional who they were able to talk to about their diagnosis and share their fears and concerns without fear of judgement. This was particularly beneficial to participants who had not talked to friends or family about their diagnosis. Receiving care from another human being helped some participants to take care of themselves:

> *I think psychologically it helped me a lot because here I had found somebody else to share with whatever I was going through, my worries, my fears.*
>
> *0144*

> *Sometimes I feel really down and I think I can't be bothered with the medication . . . what's the point of living this life? But I came in to talk about things. Sometimes I cried. She listened. I think in a way she made me care a bit more about myself because I think she cared about me.*
>
> *0021*

> *I know they said it was something like counselling but it wasn't really counselling. It was more like being able to talk to a friend which I really needed at the time. I mean friends give you counselling don't they? I mean I guess they have support groups and stuff and that is what they're for but at the beginning when you get diagnosed the last thing you want is to go in a room full of people.*
>
> *0236*

Conclusion

The findings from this qualitative analysis of interviews with PLWH who received the SUPA intervention as part of a RCT suggest that meeting with a healthcare professional who used a theory-based approach to tailor information and support to individual patients addressed misconceptions about HIV and ART, increased participants' perceptions of their necessity for treatment, reduced concerns about ART and addressed practical barriers to adherence. In addition, the intervention provided a means of emotional support, which was particularly important to participants who had not spoken to others about their HIV diagnosis.

Limitations

The are several limitations of this study. Participants were a convenience sample of those willing to attend the clinic for an additional interview after the final trial follow-up and, therefore, are a biased sample. It could be that those who took part in this study experienced more benefit and or greater change than who did not agree to participate. Caution must therefore be exercised when seeking to generalise from these findings. Although participants were interviewed within 3 days of completing the trial, this was 6 months after the final intervention session and participants were required to remember their decisions and experiences. These may not have been remembered accurately (i.e. recall bias). Moreover, although we ensured that the interviews were not conducted by SUPA nurses, the research assistant delivering the SUPA intervention was a member of the SUPA team. Therefore, participants may have been predisposed to provide a positive account of the benefits of the intervention and the changes they had experienced as a result of receiving the intervention (i.e. social desirability bias).

Implications for research

The findings of this study suggest that the SUPA intervention was able to address misconceptions about HIV and ART as well as addressing practical barriers to adherence. This will be tested quantitatively by exploring changes in perceptual and practical barriers to ART (measured using the Beliefs about Medicines Questionnaire and HAART Intrusiveness Scale) and perceptions of HIV (measured using the brief Illness Perceptions Questionnaire). Further quantitative analyses will be conducted to determine whether or not changes in beliefs about ART and illness perceptions increase adherence to ART, consistent with an extended common sense model of adherence.

Appendix 9 The Supporting UPtake and Adherence to antiretroviral therapy statistical analysis plan

Version number and date: draft 1.0 4 January 2016.

Supersedes version: N/A.

Authors	Position	Signature	Date
Professor Caroline Sabin	Statistician on the PMG		
Professor Sarah Walker	Statistician on the PMG		
Approved by			
Professor Rob Horne	Principal Investigator		

Revision history

Version	Author(s)	Date	Reason for revision
Draft 0.1	CS and ASW	28 July 2015	Initial draft based on protocol and CRF
Draft 0.2	CS and ASW	16 October 2015	Incorporates comments from CS and ASW and information from the data dictionary
Draft 0.3	EP	11 November 2015	Version circulated to PSC and DMC without approval from CS and ASW
Draft 0.4	CS and ASW	19 December 2015	Incorporates superseded version 0.3 comments from CS and ASW
1.0	CS and ASW	4 January 2016	Accepts changes in 0.4: approved by DMC and TSC

ASW, Ann Sarah Walker; CS, Caroline Sabine; DMC, Data Monitoring Committee; TSC, Trial Steering Committee.

Design

This statistical analysis plan relates to the interventional component of the SUPA programme, which is a two-arm, parallel-group, randomised multicentre controlled trial of patients for whom starting ART is recommended. The intervention is (2 or 3) + 1 + 1 sessions of CBT and education alongside usual care. The control group receives usual care only (*Figure 5*). Randomisation is open and 1 : 1.

The primary objective of the trial is to investigate the impact of the intervention on adherence to ART through 12 months from randomisation. Patients will be followed for 12 months.

The secondary objectives are to assess (1) how patients' beliefs about ART change over time and how this may predict adherence and engagement in care and (2) the costs and cost-effectiveness of providing the intervention in the short and long term in a separate health economics evaluation.

Randomisation will be stratified by clinical site. Randomisation lists will be computer-generated by the King's Clinical Trials Unit, based at King's College London.

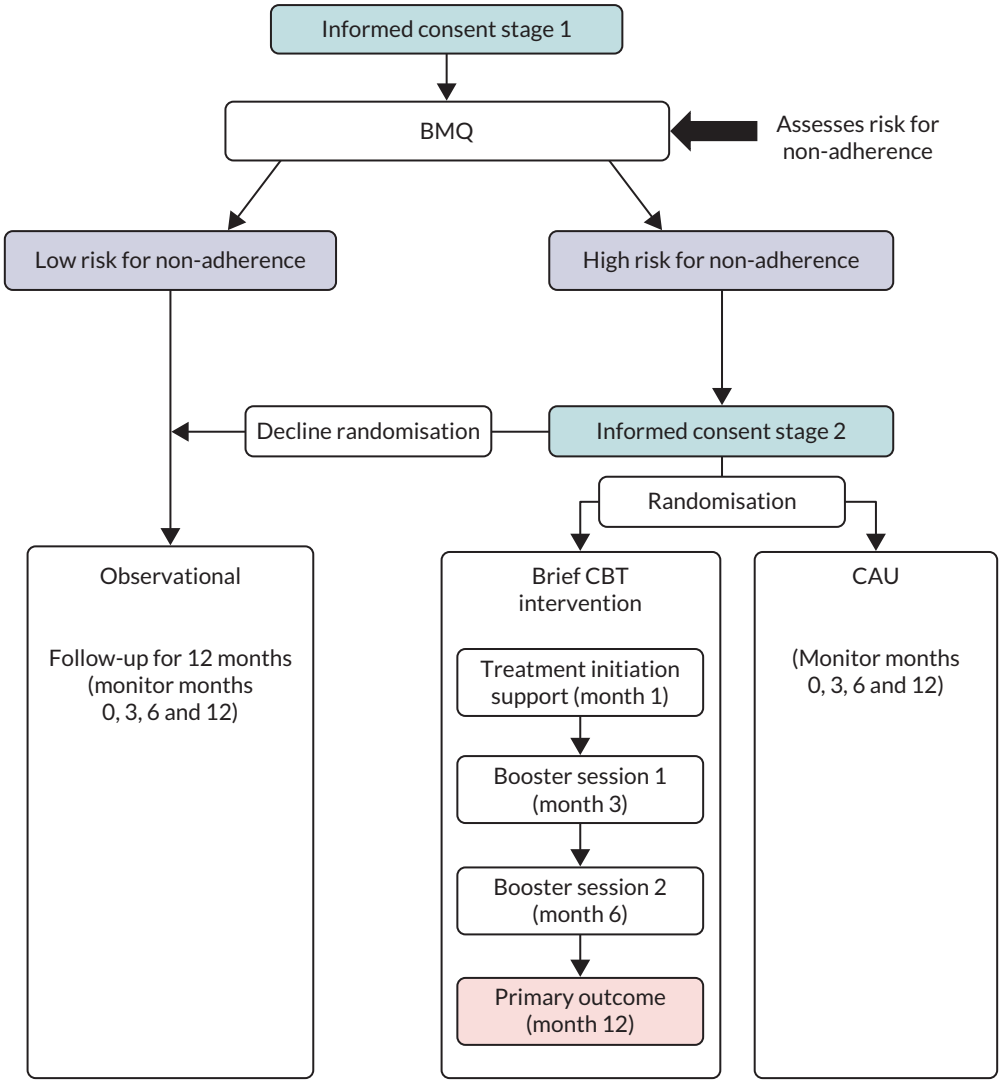


FIGURE 5 Trial schema.

Outcome measures

The trial's primary outcome is:

- the proportion of months under follow-up where adherence is ≥ 90%, counting adherence as 0% when patients are not taking ART (either not yet started or stopped or non-adherent).

The secondary outcomes are:

- treatment failure at 12 months
- change in perceptual and practical barriers at 12 months
- disengagement from care at 12 months
- rate of ART regimen switching
- ratings of depression and anxiety at 12 months
- referral out of the intervention at 12 months
- health and social service use at 12 months
- quality of life at 12 months
- HIV-related dementia
- reporting of symptoms attributed to having HIV and/or taking ART.

Sample size calculations

As this study uses a novel measure combining both uptake and adherence, there are no data to inform a sample size calculation. In particular, it is plausible that the distribution could be bimodal or highly skewed. As the proportion will also be bounded by (0,1), standard sample size calculations based on the normal distribution would likely be inappropriate, even if a SD could be hypothesised. This study, therefore, defines a good primary outcome as ≥ 80% of follow-up months with ≥ 90% adherence (binary outcome).

As this study selects for an at-risk group, we would expect a large difference between the control and intervention groups. A 15% difference between groups is considered clinically significant based on estimated intervention costs. *Table 32* shows the number of patients needed in each arm to detect a 15% difference in adherence from a range of possible control group percentages with ≥ 80% of follow-up months with ≥ 90% adherence (80% power, two-sided $\alpha = 0.05$).

We will, therefore, recruit 372 participants.

Selection of patients

The SUPA programme will utilise a two-stage consent/enrolment process. In the first stage, the patient will consent to take part in an observational cohort study (see *Figure 5*), which also establishes eligibility for the intervention trial. If deemed eligible, the patient will consent to the full trial in the second stage, including randomisation, treatment and follow-up assessments. This has the added advantage of allowing at least 24 hours of consideration by potential participants before consenting to the full trial.

Patient inclusion criteria for the observational study

- Aged ≥ 18 years.
- Known HIV infection.
- Have never been prescribed ART in outpatient clinic care.
- Being offered antiretroviral treatment according to the British HIV Association (BHIVA) guidelines[70,71] (may be subject to change throughout the study) or as deemed appropriate by the patient's clinician.
- If patients are pregnant, treatment should be recommended following pregnancy for at least 12 months following enrolment, according to BHIVA guidelines.
- Able to provide written informed consent and available for long-term follow-up.

TABLE 32 The number of patients needed in each arm to detect 15% difference in adherence

Standard of care group (%) with ≥ 0.8 of follow-up months with ≥ 90% adherence	Intervention group (%) with > 0.8 of follow-up months with ≥ 90% adherence	Number per arm	Total
35	50	183	366
45	60	186	372
50	65	183	366
60	75	165	330
70	85	134	268

Patient exclusion criteria for the observational study

- Patients who do not speak English.
- Patients who will be leaving the country for 12 months after their treatment offer and hence will not be available for the follow-up appointments or telephone follow-ups.
- Patients who lack the capacity to consent for themselves.
- Patients who have been hospitalised for a mental disorder in the past 2 years.
- Current suicidality or self-harm.
- Pervasive developmental disorders.
- Active substance misuse/dependence in the last 3 months that renders the patient unable to adhere to the study protocol in the opinion of the physician or investigator.
- Patients who have ever received ART in outpatient care.
- Psychiatric or addictive disorders that could preclude obtaining informed consent.

Once the participant has consented, they will complete the BMQ-HAART (pre-HAART version) and baseline questionnaire. Patients who have high concerns about treatment and/or low perceived necessity for treatment according to the BMQ-HAART (score ≥ 3) will be invited to participate in the interventional component of the study. If the patient consents, they will be randomly allocated to control or intervention arms.

Trial interventions

Control: care as usual

These patients will be recipients of current standard practice. Although usual care may vary slightly across clinics, the standard practice follows the same framework across all sites. Therefore, the variation in usual care across clinics is likely to be insignificant.

If the participant is starting ART, standard care includes the following:

- Discussion with a health professional (doctor) about starting ART, including the rationale for the treatment, what it may involve and the importance of adherence.
- Consultation with a pharmacist, at the point when the patient picks up their first prescription, which involves a discussion about the importance of adherence.
- Collection of 2–4 weeks' supply of medication.
- Appointment with clinic nurse for blood test at the 2- to 4-week follow-up (unless they are on Nevirapine, then the visit occurs at the 2-week follow-up and the 4-week follow-up with dose escalation at 4 weeks).
- Review with their HIV clinic (doctor) at 1 month.
- Routine clinic visits every 3 months (i.e. at 3-month intervals) with nurse and HIV doctor.

If the participant is not starting ART:

- Consultation (every 3 months) with HIV doctor, discussing readiness and beliefs about medication with a view to commencing ART.
- Blood tests every 3 months caried out by nurse.

Intervention: (cognitive–behavioural therapy + education) + care as usual

These patients will receive treatment initiation support within 1 month of enrolment into the intervention trial. This intervention will include two or three (depending on patient preference) tailored treatment support sessions utilising a CBT approach. The first session will be conducted face to face, and the following two to three sessions will be face to face or via telephone (according to the patient's preference).

The sessions will communicate a rationale for the personal necessity of medication, elicit and address concerns (practical, physical, emotional, cognitive) about medication, and include problem-solving of potential perceptual and

practical barriers to adherence. During the initial sessions, participants will be shown an animation that illustrates the rationale for the personal necessity of ART, concerns and appropriate solutions. This will closely adhere to the content communicated by the research nurse.

The specific timing of the sessions will differ according to different patients' needs and availability; however, all the sessions will take place within 1 month of enrolment.

'Booster' sessions providing additional support will be offered at 3 and 6 months' randomisation. Patients will choose to conduct the booster sessions in person or via telephone. These sessions will utilise the same approach as in the initial session, but will elicit and address existing barriers to adherence. Patients who have experienced no difficulties or concerns will discuss progress and receive positive reinforcement. Patients will be followed up at 3, 6 and 12 months.

If patients delay starting antiretroviral therapy (both arms)

If patients delay or decline ART when treatment is offered by their clinician, they will continue in the study. They will be asked to attend follow-up sessions at 3, 6 and 12 months. For patients randomised to the intervention, sessions at 3 and 6 months will continue to focus on barriers to starting treatment, rather than provide ongoing support with adherence. The participant will be followed up at 12 months for outcome measures, like other participants, and data will be collected on whether or not they have started treatment.

Data

Case report forms and variables

Full details of data collection and timing are described in the trial protocol (current version 3.0, 16 February 2015). CRFs form appendices 3–14 of the protocol. In brief, these are:

- appendix 3 – main trial CRF covering demographics, medications including antiretrovirals, attendance for study visits and to receive the intervention
- appendix 4 – observational study demographics (identical to visit 1 in appendix 3, not covered in this SAP)
- appendix 5 – Beliefs in Medicines Questionnaire before starting ART
- appendix 6 – Beliefs in Medicines Questionnaire on ART
- appendix 6 – Beliefs in Medicines Questionnaire on ART
- appendix 7 – ART intrusiveness scale
- appendix 8 – Brief Illness Perceptions Questionnaire
- appendix 9 – Hospital Anxiety and Depression scale
- appendix 10 – HIV Treatment Readiness scale
- appendix 11 – ED-5D-5L
- appendix 12 – service use measures (health economics study not covered in this SAP)
- appendix 13 – HIV treatment knowledge scale
- appendix 14 – MARS.

Management of data sets

The statistician will file out from SUPA data sets of all data stored in the database. This will act as the frozen data set. It is the responsibility of the statistician to accurately record the date of freezing and ensure that all data are retrieved.

New data can continue to be entered onto the SUPA database.

If any outstanding data queries are resolved during the analysis that relate to data in the frozen data set (e.g. problems that are found during analysis or amended CRFs that are data entered post freeze), the data should be changed at the start of the set of analysis programs using an auditable statistical program, separate from all other programs (by the trial/delegated statistician). The main SUPA database will be amended in parallel at sites.

The MEMS data will be downloaded by an external statistician not directly involved in the SUPA trial in a similar manner as above. As MEMS data are electronically downloaded from the monitoring caps, there are no data queries or amendments that can be made.

Data verification

Basic data verification, consistency and range checks will have been performed by the SUPA research manager (Elizabeth Poliquin) without reference to the randomised allocation, as well as checks for missing data. Additional range, consistency and missing data checks will be performed, as appropriate, when the analysis is performed (and when the data sets for analysis are constructed). All variables will be examined for unusual, outlying, unlabelled or inconsistent values.

Any problems with trial data will be queried with the local site. If possible, data queries will be resolved and amended, although it is accepted that because of administrative reasons and data availability, a small number of problems will continue to exist for interim analyses.

Derivation of data to be analysed

Time will be measured from randomisation (baseline).

Definition of nominal day

Data at any nominal day are defined as those taken nearest to the nominal day within equally spaced windows according to the protocol assessment schedule. The mid-point between two scheduled assessment days should be taken as belonging to the latter window. Where there are two values within one of these equally spaced windows, but both equidistant from the nominal assessment day, the later value will be used.

Missing data

Unless otherwise specified below, all analyses will be based on observed data only (i.e. will assume that data are missing completely at random). For rating scales, if any item is missing, the whole scale will be considered missing. If missing data are > 15% for specific outcomes, then predictors of missing data will be explored, and sensitivity analyses making further adjustments (i.e. valid under missing at random) or using imputation methods will be considered. The strategy would be to use sensitivity analyses to provide plausible bounds for effect estimates under different missingness mechanisms, rather than to provide a single estimate of effect.

Specific definitions for primary and secondary end points

Primary end point: proportion of months under follow-up where adherence is ≥ 90%

Adherence will be defined by MEMS cap data as follows.

Each day will be defined as adherent (1), half adherent (0.5) or non-adherent (0).

An adherent day is one on which the bottle was opened twice, with two openings at least 8 hours apart for a patient on twice daily ART, or opened once for a patient on once daily ART (ART frequency obtained from main trial CRF). Frequency of ART administration will be determined from the records in the MEMS database.

A half adherent day is one on which the bottle was opened once, or twice within 8 hours, for a patient on twice-daily ART.

A non-adherent day is a day with no opening, or before an individual has initiated ART.

When there are more MEMS openings than dose prescribed that day, these extra openings (which may be due to extra intakes or artificial openings for a refill/data download) are not taken into account in the calculation. This implies that the calculation is capped by 100% and overdose is not taken into account.

It is expected that most patients will take once-daily regimens. However, because only patients taking twice-daily regimens can be half adherent, the proportion of patients in the two groups will also be formally compared. However, one of the theoretical advantages of twice-daily regimens is that missing one dose may have less of an impact on viral load suppression because the other half of the total daily dose will still be taken.

Time from randomisation through to 1 year post randomisation will be divided into months of alternating 30 and 31 days (30, 31, 30, 31, etc., totalling 366 days in the year). In each month, for each individual, the proportion of adherent days will then be calculated as the sum of the adherent/half adherent/non-adherent indicators divided by the total number of days in the month.

Missing data due to MEMS cap failure or failure to use the MEMS cap will be treated as non-adherent. This means that the adherence measure will be conservative; however, there is no reason to think that failure to use a MEMS cap will be different in the two intervention arms, and it removes any subjectivity from decisions about whether or not reported MEMS cap failure could be non-disclosed non-adherence. A sensitivity analysis will be performed excluding patients who have more than 2 months of missing data due to MEMS cap failure or failure to use the MEMS cap (so the 0.8 threshold corresponds to at least 8 out of 10 months in included patients).

Missing data due to lost to follow-up will also be counted as non-adherence.

The proportion of the 12 months under follow-up where adherence is ≥ 90% will be calculated.

The binary outcome is an indicator of whether or not this proportion is ≥ 80%.

Essentially, this assesses whether the patient has been ≥ 90% adherent for at least 80% of their time spent in the trial. The 80% threshold to define a good outcome is based on the fact that 4–6 weeks' delay to ART initiation is reasonable, and that, if followed by consistent ≥ 90% adherence for the remainder of the trial (i.e. 10 of the 12 months), the patient is likely to achieve and maintain viral load suppression on ART.[72]

Secondary end point: treatment failure at 12 months

Treatment failure is defined as either failure to uptake treatment or experiencing virological failure once taking treatment, namely:

- Failure to start within 6 months (patients who start ART but > 6 months after randomisation will be considered as treatment failures because of their delay in accepting a treatment offer under the BHIVA guidelines).[71]
- Failure to achieve a viral load of < 50 copies/ml 6 months after commencing ART or following viral suppression to < 50 copies/ml a viral load rebound to > 400 copies/ml on one occasion (single values > 50 copies/ml will be used rather than requiring confirmation because the number of viral load measurements during the 1 year follow-up are too few for confirmation to be possible).
- Following viral suppression to < 50 copies/ml, two consecutive viral loads > 50 copies/ml.

Secondary end point: change in perceptual and practical barriers at 12 months

This will be measured by the BMQ-ART developed by Horne *et al.*[10] adapted during workstream 1 to include items on culturally specific and practical barriers to ART.[39] Change will be defined as the BMQ score on the post-HAART initiation version minus the BMQ score on the pre-ART initiation version.

The HIS score is also included as a measure of perceived practical barriers to adherence.

Secondary end point: disengagement from care at 12 months

This will be defined as missed one or more routinely scheduled clinic visits, including visits either:

- Not attended and not rescheduled.
- Rescheduled but *not* attended before the patient's next routine appointment is due.

This information is recorded on the CRF as appointments attended and/or rescheduled.

Secondary end point: rate of antiretroviral regimen switching through 12 months

This will be defined as changing from one drug to another drug for any reason (i.e. on a per-drug, not a per-regimen basis), regardless of duration over which changes take place (typically 0–7 days), excluding changes from 3TC to FTC and vice versa where these are simply due to changing a fixed dose combination tablet and including all drug changes (subsequent as well as first).

Secondary end point: ratings of depression and anxiety at 12 months

Depression and anxiety will be rated using the HADS.[73]

Secondary end point: referral out of the intervention at 12 months

This will be defined as being referred out of the intervention for more appropriate or intensive care (e.g. seeing a psychiatrist or clinical psychologist for adherence issues). This is being recorded in clinic notes and monitored by Elizabeth Poliquin.

Secondary end point: health and social service use at 12 months

Service use at all study periods as collected by the service use questionnaire will be analysed within the health economic substudy and is not covered in this SAP.

Secondary end point: quality of life at 12 months

This will be measured by the EQ-5D-5L.

Secondary end point: human immunodeficiency virus-related dementia

This will be measured by the International HIV Dementia Scale.

Secondary end point: symptoms attributed to having human immunodeficiency virus and/or taking antiretroviral therapy

These will be measured by the Symptoms Associated with HIV and HAART Questionnaire.[17] Individual item scores are recorded in the database.

Other outcomes

The other outcomes include brief illness perceptions, MARS (adherence measure), HIS, HIV Treatment Readiness Scale (for those not currently on ART) and the HIV Treatment Knowledge Scale.

Statistical analysis

The CBT-based intervention is hypothesised to be superior to CAU and, therefore, the planned analysis is intention to treat, including all randomised patients with all participants analysed according to the study group to which they were randomised regardless of subsequent treatment received. Primary analysis will include all randomised patients other than those randomised in error (defined as not intending to randomise the patient through, e.g. miscommunication, rather than a patient or clinician decision once the allocation has been given).

A per-protocol analysis will be carried out on the primary end point including all patients in the intervention group who attended 2 + 1 + 1 sessions. If the intention-to-treat and per-protocol analyses on the primary end point lead to inconsistent results, then per-protocol analysis will also be carried out on all the other end points.

Frequency of analysis

An IDMC will be the only group that sees the confidential, accumulating data for the trial separately by randomised group. The IDMC consists of Peter White (independent chairperson), Toby Prevost (independent statistician), Kav Vedhara (adherence expert) and Alan Winston (independent HIV expert).

Interim analyses will be carried out at the request of the IDMC at the routinely scheduled meetings. They will review accumulating baseline data and primary outcome data only. This will be sent in strict confidence by the trial statisticians to the IDMC for review, as per the request of the IDMC.

The IDMC will review information on the progress and accruing data and provide advice on the conduct of the trial to the PMG and PSC. The IDMC will inform the chairperson of the PSC if, in their view, the results are likely to convince a broad range of clinicians, including those supporting the programme and the general clinical community, that, on balance, one trial arm is clearly indicated or contraindicated for all participants or a particular category of participants, and there was a reasonable expectation that this new evidence would materially influence patient management.

Data on baseline characteristics and follow-up will be provided to the PMG/PSC not subdivided by randomised group.

Analysis methods

Continuous variables will be summarised by medians and IQRs or means and SD, as appropriate depending on the distribution, and compared between groups using rank-sum tests or *t*-tests respectively. Comparisons of change from baseline in continuous variables will adjust for any baseline imbalances using either quantile or normal linear regression (depending on the shape of the distribution).

Categorical variables will be summarised by frequency tables, and compared between groups using chi-squared tests, unless any cell count is < 5 or cell percentage is < 5%, in which case exact tests will be used.

Binary variables will be summarised by percentages, using standard exact 95% CI for the risk differences.

Time-to-event variables will be summarised using Kaplan–Meier curves and average differences between randomised groups estimated using Cox models. Patients without the event recorded will be censored at their last clinic visit. Proportionality of hazards will be tested; where significant departures exist, varying differences between randomised groups over time will be estimated using flexible parametric models of Royston and Parmar.

Rate of treatment switching will be analysed using Poisson regression, including all changes to ART as events and the total time under follow-up through the earliest of 12 months or the last patient visit as the person-time at risk.

Primary analysis will not stratify by clinical centre.

Recruitment

- Screening and randomisation by calendar month.
- Total screened and randomised by centre.
- Eligibility: number and reasons for any ineligibilities (recorded separately from the central database), classified as follows:

    - pregnant and stopping ART after pregnancy
    - prior exposure to ART in outpatient care
    - psychological issues or addiction limiting ability to obtain informed consent
    - enrolled in another trial
    - could not speak English fluently
    - transferred care to another trust.

Other (specify)

Meeting two or more of criteria above.

Baseline characteristics

- Gender.
- Age at last birthday.
- Ethnicity.
- Country of birth.
- Marital status.
- Highest level of education.
- Current employment status.
- Time since HIV diagnosis.
- Likely mode of transmission.
- Most recent viral load.
- Most recent CD4 T-cell count.
- Currently pregnant.
- ART regimen prescribed.
- Baseline values of secondary outcome measures: BMQ (overall and subdivided by necessity and concerns), HIS, Brief Illness Perceptions questionnaire, HADS (overall and subdivided by depression and anxiety), HIV Treatment Readiness scale, HIV treatment knowledge scale, EQ-5D.

Description of follow-up and receipt of intervention

- Scheduled assessments completed at months 3, 6 and 12.
- Time to initiation of ART.
- Intervention arm only: number of intervention visits completed.

Adherence

- (Primary end point.) Proportion of patients with ≥ 80% months with ≥ 90% adherence.
- Dichotomised MARS at months 3, 6, 12.
- Percentage adherence in each month from randomisation to month 12.

Other outcome scales

Change from baseline to 3, 6 and 12 months in:

- BMQ (overall and subdivided by necessity and concerns)
- HIS
- BIPQ
- HADS (overall and subdivided by depression and anxiety)
- HIV Treatment Readiness scale, HIV treatment knowledge scale
- EQ-5D.

Other outcomes

- Treatment failure at 12 months.
- Disengagement from care at 12 months.
- Rate of antiretroviral regimen switching (including all changes).
- Referral out of the intervention.

Subgroup analyses

Subgroup analyses will be performed to assess heterogeneity in differences between randomised groups for the primary end point according to:

- gender
- ethnicity
- number of intervention sessions attended
- early (treatment indicated at point of diagnosis) versus late diagnosis (treatment not indicated at point of diagnosis)
- starting for clinical need versus starting for treatment as prevention
- baseline CD4 T-cell count
- baseline BMQ scores – low necessity versus high concern versus both low necessity and high concern.

Subgroup analyses will use logistic regression to model interactions between randomised group and the above factors.

Safety analyses

All serious adverse events will be reported in a line listing.

Appendix 10 Cost-effectiveness analysis

Background and aims

The aims of the cost-effectiveness component were to (1) assess the cost-effectiveness of the SUPA intervention over the trial period and (2) assess the longer-term cost-effectiveness of the SUPA intervention using simulation modelling.

Methods

Trial-based analysis

The primary perspective of the economic evaluation was of the health and social care system. Impacts on informal carers and employment were also assessed. Service use was measured with an adapted version of the Client Service Receipt Interview (CSRI). This recorded use of services in the period prior to interview at baseline and each follow-up point. Service costs were calculated by combining the service use data with appropriate unit cost information (*Table 33*), for example from the Personal Social Services Research Unit at the University of Kent and NHS reference costs.[60,74] Cost of the intervention was calculated by combining the number of therapy sessions with the unit cost of a psychologist. Cost comparisons were made between the groups over the follow-up period controlling for baseline costs.

The QALYs were generated from the EQ-5D-5L and UK-specific tariffs using area under the curve methods. QALYs were compared with baseline scores controlled for. ICERs (extra cost for the intervention group divided by the extra number of QALYs) were computed, and uncertainty was addressed using a cost-effectiveness plane and cost-effectiveness acceptability curve.

These were produced from bootstrapped resamples.

Simulation model

The trial follow-up was 12 months and so a Markov model was used to extrapolate beyond this period. The time horizon was 15 years and cycle length was 12 months. The mutually exclusive health states in the model were defined by CD4 T-cell counts and a state for those who died was also included. The CD4 states were based on previous work by Grover *et al.*[75] and these were: (1) > 500 cells/mm^3, (2) 351–500 cells/mm^3, (3) 200–350 cells/mm^3 and (4) < 200 cells/mm^3. It was assumed that movement between any of the CD4 states was feasible. The model was run for a cohort of 1000 CBT and CAU patients separately and the starting health state distribution was based on the 12-month data from the trial. This was appropriate given that we wished to extrapolate specifically from this trial and other data were not available. The trial data revealed that one person died during the study. However, over a 15-year period we would expect some people to die from causes related to other conditions and so all-cause mortality rates were used. Those surviving were assumed to transit between the other health states according to transitions observed between the baseline and 12-month follow-up points. Costs (excluding intervention costs) and QALYs were assigned to each health state at each cycle and these were derived from the trial data. The expected costs and QALYs were computed and discounted at 3.5%. These were then combined with the costs and QALYs from the trial period.

Probabilistic sensitivity analyses were conducted and a cost-effectiveness acceptability curve. To conduct this sensitivity analysis, we assumed appropriate distributions around key parameters based on Briggs *et al.*[76] For transition probabilities we assumed a Dirichlet distribution; for costs we assumed a gamma distribution, and for utilities we assume a beta distribution.

TABLE 33 Unit costs used in economic evaluation

Item	Unit cost (£ 2017–18)	Source
Community services		
GP	33/9 minutes	GP: per patient minute – excluding direct care staff costs – with qualification costs[54]
Practice nurse	36/hour	Nurse (GP practice)[54]
District nurse	36/hour	Other specialist nursing, adult, face to face[54]
Clinical nurse specialist	77/hour	HIV/AIDS specialist nursing (adult), face to face
Psychologist	53/hour	Clinical psychologist band 7[54]
Psychiatrist	137/hour	Weighted average of all outpatient attendances, *NHS Reference Costs 2017-18*[74]
Counsellor	63/hour	Counsellor consultant band 8a
Physiotherapist	33/hour	Scientific and professional staff – band 5[54]
Social worker	43/hour	Social worker (adult services)[54]
Dietitian	86/hour	NHS reference costs for hospital services (dietitian)[74]
CBT	£100/contact	CBT[54]
Antiretroviral drugs	Varied	BNF 77 March – September 2019[77]
Hospital services		
Inpatient (length of stay)	648/night	Non-elective inpatient stays (short stay), *NHS Reference Costs 2017-18*[74]
Outpatient	137/contact	Weighted average of all outpatient attendances, *NHS Reference Costs 2017-18*[74]
Day hospital	345/episode	*NHS Reference Costs 2017-18*[74]
Ambulance use	119/contact	Ambulance services – average of all, *NHS Reference Costs 2017-18*[74]
Emergency visits	148/episode	Accident and emergency, *NHS Reference Costs 2017-18*[74]
Clinical decision unit	148/episode	Accident and emergency, *NHS Reference Costs 2017-18*[74]
Other hospital care	137/contact	Weighted average of all outpatient attendances, *NHS Reference Costs 2017-18*[74]
HIV clinic		
HIV consultant	140/hour	Consultant led (multiprofessional) – non-admitted, face to face
Specialist registrar	107/hour	Non-consultant led – non-admitted, face to face, first
Clinical nurse specialist	77/hour	HIV/AIDS specialist nursing (adult) face to face
Nurse	77/hour	HIV/AIDS specialist nursing (adult) face to face
Health advisor	23/hour	Support and outreach worker
Client support worker	23/hour	HIV/AIDS specialist nursing (adult) face to face[54]
Midwife	56/contact	Outpatient attendances – midwifery Service, *NHS Reference Costs 2017-18*[74]
Dietitian	86/contact	Dietitian, *NHS Reference Costs 2017-18*[74]
Laboratory tests		
Immunology	6/test	Directly accessed pathology services – immunology, *NHS Reference Costs 2017-18*[74]

TABLE 33 Unit costs used in economic evaluation (*continued*)

Item	Unit cost (£ 2017–18)	Source
Virology	8/test	Directly accessed pathology services – microbiology
Biochemistry (liver, renal, urine)	1/test	Directly accessed pathology services – clinical biochemistry
Haematology	3/test	Directly accessed pathology services – haematology
Cholesterol	3/test	Directly accessed pathology services – haematology
Glucose	3/test	Directly accessed pathology services – haematology
Syphilis	8/test	Directly accessed pathology services – microbiology
Hepatitis markers	8/test	Directly accessed pathology services – microbiology
Hepatitis B immunology	8/test	Directly accessed pathology services – microbiology
Viral genotype testing (resistance test)	8/test	Directly accessed pathology services – microbiology
Scan	77/test	Dual X-ray absorptiometry
MRI	132/test	MRI scan of one area, without contrast, 19 years and over, *NHS Reference Costs 2017-18*[74]
Diagnostic imaging	58/test	Outpatient attendances – diagnostic imaging, *NHS Reference Costs 2017-18*[74]
X-ray	77/test	Dual X-ray absorptiometry
Smear test	50/test	
STI check	8/test	Directly accessed pathology services – microbiology
Informal care		
All informal care	13.68/hour	Used the average weekly earnings of £513/37.5 hours
		Office for National Statistics – average weekly earnings and the *Annual Survey of Hours and Earnings*[78]
Productivity loss		
Days off work due to ill health	103/day	Office for National Statistics[78]
Hours off work due to ill health	14.71/hour	Office for National Statistics[78]

BNF, British National Formulary; GP, general practitioner; MRI, magnetic resonance imaging; STI, sexually transmitted infection.

Results

Healthcare utilisation patterns reported by participants over the entire study period are presented in *Tables 34–37*. Generally, there were no stark differences in service use between the two groups. Overall, participants accessed an array of health and social care services at all study points, especially laboratory tests and healthcare services offered through HIV clinics.

Community services

At baseline, contact with general practitioners (GPs) was the most commonly reported community service in both groups, and the proportion was 16 percentage points higher for the control group (see *Table 34*).

The mean number of contacts showed modest differences between groups (3.7 contacts for the intervention group compared with 3.4 contacts for the control group). A similar trend was observed for subsequent study points, although the mean number of contacts for GPs had reduced to 2.6 and 2.0, respectively, at 12 months (see *Table 37*). There was little reported service use for district nurses, physiotherapists, dietitians, clinical nurse specialists and social workers.

TABLE 34 Service use at baseline

Service category	Unit of measure	CBT (*N* = 71)			CAU (*N* = 72)		
		Number of users, *n* (%)	Number of contacts users only, mean (SD)	Range for users only	Number of users, *n* (%)	Number of contacts users only, mean (SD)	Range for users only
Community services							
GP	Contact	34 (48)	3.7 (2.5)	1–10	47 (64)	3.4 (3.5)	1–20
Practice nurse	Contact	7 (10)	1.4 (0.5)	1–2	11 (15)	2.0 (1.4)	1–5
Psychologist	Contact	3 (4)	4.3 (2.5)	2–7	3 (4)	4.3 (3.2)	2–8
Counsellor	Contact	2 (3)	3.3 (2.6)	1–6	2 (3)	2.5 (2.1)	1–4
District nurse	Contact	0 (0)	–	–	0 (–)	–	–
Psychiatrist	Contact	2 (3)	1.5 (0.7)	1–2	1 (1)	1.0 (–)	1
Physiotherapist	Contact	0 (0)	–	–	2 (3)	1.5 (0.7)	1–2
Self-help/support group	Contact	2 (3)	3.5 (0.7)	3–4	2 (3)	3.5 (3.5)	1–6
Dietitian	Contact	0 (0)	–	–	1 (1)	3.0 (–)	3
Clinical specialist nurse (HIV)	Contact	0 (0)	–	–	1 (1)	5.0 (–)	5
Social worker	Contact	1 (1)	10.0 (–)	10	0 (0)	–	–
HIV outpatient clinic							
HIV consultant	Contact	66 (93)	2.5 (1.3)	1–6	62 (85)	2.7 (1.7)	1–11
Specialist registrar	Contact	19 (26)	1.7 (0.9)	1–4	20 (27)	2.1 (1.3)	1–5
Clinical nurse specialist (HIV)	Contact	16 (23)	1.8 (0.9)	1–3	16 (22)	1.9 (1.5)	1–6
Other nurse	Contact	56 (79)	2.3 (1.3)	1–6	57 (78)	2.9 (1.7)	1–8
Health advisor	Contact	12 (17)	1.3 (0.5)	1–7	14 (19)	1.8 (1.1)	1–4
Client support worker	Contact	3 (4)	1.0 (0)	1	3 (4)	1.3 (0.6)	1–2
Dietitian	Contact	4 (6)	1.0 (0)	1	5 (7)	1.6 (0.9)	1–3
Midwife	Contact	2 (3)	2.5 (2.1)	1–4	1 (1)	1.0 (–)	1
Other	Contact	34 (48)	1.6 (1.0)	1–6	32 (47)	2.5 (3.0)	1–18
Hospital-based services							
Inpatient (length of stay)	Days	18 (25)	11.1 (10.4)	1–38	17 (23)	11.7 (14.0)	1–57
Outpatient	Contact	22 (31)	1.4 (0.7)	1–3	27 (37)	1.6 (1.0)	1–4
Day hospital	Contact	2 (3)	1.0 (0)	1	4 (5)	1.0 (0)	1
Emergency visits	Contact	21 (30)	1.1 (0.4)	1–3	27 (37)	1.4 (0.9)	1–4
Clinical decision unit	Contact	11 (15)	1.0 (0)	1	18 (25)	1.1 (0.3)	1–2
Ambulance	Contact	4 (6)	1.0 (0)	1	5 (7)	1.0 (0)	1

TABLE 34 Service use at baseline (*continued*)

Service category	Unit of measure	CBT (*N* = 71)			CAU (*N* = 72)		
		Number of users, *n* (%)	Number of contacts users only, mean (SD)	Range for users only	Number of users, *n* (%)	Number of contacts users only, mean (SD)	Range for users only
Medical laboratory tests							
Immunology		65 (92)	1.6 (0.9)	1–5	67 (92)	1.8 (1.5)	1–12
Virology		67 (94)	2.2 (1.4)	1–7	67 (92)	2.2 (1.1)	1–5
Biochemistry (liver, renal, urine)		57 (80)	3.7 (4.8)	1–24	47 (64)	3.6 (4.2)	1–21
Haematology		54 (76)	2.4 (2.7)	1–13	52 (71)	2.7 (3.1)	1–21
Cholesterol		21 (30)	1.3 (0.6)	1–3	23 (32)	1.4 (0.7)	1–3
Glucose		26 (37)	1.3 (0.6)	1–3	30 (41)	1.2 (0.4)	1–2
Syphilis		29 (41)	1.4 (1.0)	1–6	32 (44)	1.3 (1.0)	1–6
Hepatitis markers		42 (59)	1.2 (0.4)	1–2	47 (64)	1.2 (0.5)	1–3
Hepatitis B immunology		25 (35)	1.2 (0.4)	1–2	23 (32)	1.2 (0.4)	1–2
Viral genotype testing		33 (46)	1.2 (0.6)	1–3	43 (59)	1.3 (0.8)	1–5
Therapy drug monitoring		2 (3)	1.0 (0)	1	2 (3)	1.0 (0)	1
Scan		13 (18)	1.5 (0.9)	1–4	6 (8)	1.3 (0.5)	1–2
MRI		6 (8)	1.2 (0.4)	1–2	8 (11)	1.0 (0.3)	1
Diagnostic imaging		6 (8)	1.5 (0.8)	1–3	4 (5)	1.8 (1.5)	1–4
X-ray		22 (31)	1.4 (0.9)	1–4	10 (14)	2.3 (1.9)	1–6
Smear test		6 (8)	1.2 (0.4)	1–2	3 (4)	1.0 (0)	1
STI check		29 (41)	2.0 (3.4)	1–19	24 (33)	1.5 (0.7)	1–3
Other tests		30 (42)	4.5 (8.8)	1–48	34 (47)	4.1 (5.7)	1–33
Productivity loss							
Employed		46 (65)			53 (74)		
Days off work due to ill health	Days	27 (59)	20.9 (25.9)	1–98	34 (64)	26.0 (42.9)	1–182.5
Informal care		***17 (24)***			***22 (30)***		
Personal care	Weeks	3 (4)	112.0 (96.4)	1–168	3 (4)	140.0 (24.2)	126–168
Providing transport	Weeks	3 (4)	58.0 (95.2)	1–168	3 (4)	3.3 (1.2)	2–4
Meal preparation	Weeks	2 (3)	3.0 (2.8)	1–5	7 (10)	9.1 (12.3)	0.15–35
DIY	Weeks	1 (1)	2.0 (–)	2	2 (3)	2.0 (1.4)	1–3
Gardening	Weeks	2 (3)	31.0 (41.0)	2–60	1 (1)	10.0 (–)	10

continued

TABLE 34 Service use at baseline (*continued*)

Service category	Unit of measure	CBT (*N* = 71)			CAU (*N* = 72)		
		Number of users, *n* (%)	Number of contacts users only, mean (SD)	Range for users only	Number of users, *n* (%)	Number of contacts users only, mean (SD)	Range for users only
Shopping/collecting benefits	Weeks	3 (4)	41.0 (68.4)	1–120	4 (5)	9.8 (19.8)	1–35
Help outside home	Weeks	1 (1)	1.0 (–)	1	4 (5)	1.1 (0.6)	0.5–2
Socialising/companionship/emotional support	Weeks	15 (21)	65.4 (77.7)	1–168	15 (21)	30.5 (56.8)	0.5–168
Help managing bills	Weeks	2 (3)	85.0 (117.4)	2–168	1 (1)	0.5 (–)	1
Other informal care help	Weeks	0 (–)	–	–	6 (8)	21.7 (27.9)	1–70

DIY, do it yourself; MRI, magnetic resonance imaging; STI, sexually transmitted infection.

TABLE 35 Service use at the 3-month follow-up

Service category	Unit of measure	CBT (*N* = 64)			CAU (*N* = 68)		
		Number of users, *n* (%)	Number of contacts users only, mean (SD)	Range for users only	Number of users	Number of users, *n* (%)	Number of contacts users only, mean (SD)
Community services							
GP	Contact	23 (36)	1.7 (1.0)	1–4	21 (31)	2.3 (1.4)	1–5
Practice nurse	Contact	3 (5)	1.3 (0.6)	1–2	6 (9)	2.0 (1.3)	1–4
Psychologist	Contact	0 (0)	–	–	2 (3)	1.5 (0.7)	1–2
District nurse	Contact	2 (3)	2.0 (0)	2	3 (4)	1.3 (0.6)	1–2
Counsellor	Contact	0 (0)	–	–	1 (2)	12 (–)	12
Psychiatrist	Contact	0 (0)	–	–	0 (0)	–	–
Physiotherapist	Contact	1 (2)	4.0 (–)	4	0 (0)	–	–
Self-help/support group	Contact	2 (3)	1.0 (0)	1	4 (6)	6.5 (4.0)	1–12
Dietitian	Contact	0 (0)	–	–	2 (3)	2.0 (0)	2
Clinical specialist nurse (HIV)	Contact	0 (0)	–	–	0 (0)	–	–
Social worker	Contact	0 (0)	–	–	0 (0)	–	–

TABLE 35 Service use at the 3-month follow-up (*continued*)

		CBT (*N* = 64)			CAU (*N* = 68)		
Service category	**Unit of measure**	**Number of users, *n* (%)**	**Number of contacts users only, mean (SD)**	**Range for users only**	**Number of users**	**Number of users, *n* (%)**	**Number of contacts users only, mean (SD)**
HIV outpatient clinic							
HIV consultant	Contact	46 (72)	1.9 (1.1)	1–6	51 (75)	1.9 (1.1)	1–5
Specialist registrar	Contact	12 (19)	1.4 (0.7)	1–3	13 (19)	1.8 (1.3)	1–5
Clinical nurse specialist	Contact	10 (20)	1.2 (0.6)	1–3	10 (15)	1.3 (0.5)	1–6
Nurse	Contact	43 (67)	1.9 (1.3)	1–6	51 (75)	2.0 (1.1)	1–5
Health advisor	Contact	3 (4)	1.3 (0.6)	1–2	5 (7)	1.0 (0)	1
Client support worker	Contact	2 (3)	2.0 (1.4)	1–3	3 (4)	1.7 (0.6)	1–2
Dietitian	Contact	3 (4)	1.3 (0.6)	1–2	5 (7)	1.4 (0.9)	1–3
Midwife	Contact	1 (2)	2.5 (2.1)	1–4	0 (0)	–	–
Phlebotomist	Contact	3 (4)	2.0 (1.0)	1–3	3 (4)	1.0 (2.4)	1–6
Other	Contact	16 (25)	2.6 (2.1)	1–5	23 (34)	2.6 (2.2)	1–8
Hospital-based services							
Inpatient (length of stay)	Days	5 (8)	5.0 (4.7)	1–13	2 (3)	3.0 (0)	3
Outpatient	Contact	18 (25)	2.3 (5.4)	1–24	22 (32)	1.5 (0.7)	1–3
Day hospital	Contact	3 (4)	1.0 (0)	1	0 (0)	–	–
Emergency visits	Contact	5 (8)	1.0 (0)	1	6 (9)	1.3 (0.5)	1–2
Clinical decision unit	Contact	2 (3)	1.0 (0)	1	1 (2)	1.0 (.)	1
Ambulance	Contact	1 (2)	1.0 (0)	1	1 (2)	2.0 (.)	2
Medical laboratory tests							
Immunology		36 (53)	1.3 (0.6)	1–4	39 (57)	1.4 (0.6)	1–3
Virology		49 (77)	1.7 (1.0)	1–5	61 (90)	1.6 (0.7)	1–3
Biochemistry (liver, renal, urine)		32 (50)	2.3 (1.6)	1–7	46 (68)	2.4 (3.3)	1–16
Haematology		30 (47)	1.9 (1.2)	1–6	41 (60)	1.6 (1.1)	1–7
Cholesterol		11 (17)	1.1 (0.3)	1–2	12 (17)	1.5 (0.8)	1–3
Glucose		13 (20)	1.4 (0.8)	1–3	15 (23)	1.4 (0.7)	1–3
Syphilis		11 (17)	1.4 (1.0)	1–4	14 (21)	1.2 (0.4)	1–2
Hepatitis markers		6 (9)	1.0 (0)	1	11 (16)	1.2 (0.6)	1–3
Hepatitis B immunology		3 (5)	1.0 (0)	1	8 (12)	1.1 (0.4)	1–2

continued

TABLE 35 Service use at the 3-month follow-up (*continued*)

Service category	Unit of measure	CBT (*N* = 64)			CAU (*N* = 68)		
		Number of users, *n* (%)	Number of contacts users only, mean (SD)	Range for users only	Number of users	Number of users, *n* (%)	Number of contacts users only, mean (SD)
Viral genotype testing		5 (8)	1.0 (0)	1–3	2 (3)	1.0 (0)	1
Therapy drug monitoring							
Scan		3 (5)	1.3 (0.6)	1–2	0 (0)	–	–
MRI		1 (2)	1.0 (–)	1	3 (4)	1.3 (0.6)	1–2
Diagnostic imaging		1 (2)	1.0 (–)	1	3 (4)	1.0 (0)	1
X-ray		5 (8)	1.4 (0.5)	1–2	5 (7)	1.0 (0)	1
Smear test		5 (8)	1.2 (0.4)	1–2	3 (4)	1.0 (0)	1
STI check		12 (19)	2.0 (2.0)	1–7	5 (7)	1.0 (0)	1
Other tests		30 (42)	4.5 (8.8)	1–48	34 (47)	4.1 (5.7)	1–33
Productivity loss							
Employed		69 (65)			76 (75)		
Days off work due to ill health	Days	9 (14)	20.6 (28.8)	1–91	21 (31)	5.9 (12.6)	1–60
Informal care		***17 (24)***			***22 (31)***		
Personal care	Weeks	0 (0)	–	–	0 (0)	–	–
Providing transport	Weeks	2 (3)	1.0 (0)	1	2 (3)	2.5 (0.7)	2–3
Meal preparation	Weeks	1 (2)	10.0 (–)	10	1 (2)	7.0 (–)	7
DIY	Weeks	1 (2)	0.5 (–)	5	1 (2)	2.0 (–)	2
Gardening	Weeks	0 (0)	–	–	1 (2)	15.0 (–)	15
Shopping/ collecting benefits	Weeks	2 (3)	2.5 (2.1)	1–4	1 (2)	5.0 (–)	5
Help outside home	Weeks	1 (2)	1.5 (–)	1.5	0 (0)	–	–
Socialising/companionship/emotional support	Weeks	9 (16)	32.6 (59.2)	2–168	10 (15)	5.3 (7.5)	0.5–22
Help managing bills	Weeks	3 (5)	3.0 (3.5)	1–7	1 (2)	1.0 (–)	1
Other informal care help	Weeks	1 (2)	1.0 (–)	1	1 (2)	1.0 (–)	

DIY, do it yourself; MRI, magnetic resonance imaging; STI, sexually transmitted infection.

TABLE 36 Service use at the 6-month follow-up

Service category	Unit of measure	Intervention arm 3 (*N* = 64)			Control arm 2 (*N* = 68)		
		Number of users, *n* (%)	Number of contacts users only, mean (SD)	Range for users only	Number of users, *n* (%)	Number of contacts users only, mean (SD)	Range for users only
Community services							
GP	Contact	27 (42)	1.9 (1.2)	1–6	33 (49)	2.2 (1.3)	1–6
Practice nurse	Contact	5 (8)	1.4 (0.5)	1–2	5 (7)	1.2 (0.4)	1–4
Psychologist	Contact	2 (3)	3.5 (3.5)	1–6	3 (4)	5.3 (3.5)	2–9
District nurse	Contact	0 (0)	–	–	2 (3)	13 (15.6)	2–24
Counsellor	Contact	1 (2)	1.0	1	1 (1)	2.0 (–)	2
Psychiatrist	Contact	0 (0)	–	–	0 (0)	–	–
Physiotherapist	Contact	0 (0)	–	–	1 (1)	3.0 (–)	3
Self-help/support group	Contact	2 (3)	5.0 (1.4)	4–6	4 (6)	5.3 (1.5)	3–6
Dietitian	Contact	1 (2)	4.0 (–)	4	1 (1)	1.0 (–)	1
Clinical specialist nurse (HIV)	Contact	0 (0)	–	–	0 (0)	–	–
Social worker	Contact	0 (0)	–	–	0 (0)	–	–
HIV outpatient clinic							
HIV consultant	Contact	39 (61)	1.5 (0.9)	1–5	43 (63)	1.8 (1.1)	1–6
Specialist registrar	Contact	7 (11)	1.0 (0)	1	12 (18)	1.2 (0.4)	1–2
Clinical nurse specialist	Contact	3 (5)	1.3 (0.6)	1–2	7 (10)	1.1 (0.4)	1–2
Nurse	Contact	38 (59)	1.3 (0.7)	1–4	38 (56)	1.6 (0.9)	1–4
Health advisor	Contact	12 (19)	1.3 (0.5)	1–7	14 (21)	1.8 (1.1)	1–4
Client support worker	Contact	3 (5)	1.0 (0)	1	3 (4)	1.3 (0.6)	1–2
Dietitian	Contact	4 (6)	1.0 (0)	1	5 (7)	1.6 (0.9)	1–3
Midwife	Contact	2 (3)	2.0 (0)	1–4	1 (1)	1.0 (–)	1
Phlebotomist	Contact	10 (16)	2.4 (1.3)	1–4	4 (6)	2.5 (2.4)	1–6
Other	Contact	12 (19)	1.5 (1.2)	1–5	13 (19)	1.7 (1.2)	1–5
Hospital-based services							
Inpatient (length of stay)	Days	5 (8)	5.2 (5.7)	1–14	3 (4)	1.7 (0.6)	1–57
Outpatient	Contact	12 (19)	1.7 (1.0)	1–4	10 (15)	1.4 (0.7)	1–4
Day hospital	Contact	2 (3)	1.0 (0)	1	1 (1)	1.0 (0)	1
Emergency visits	Contact	6 (9)	1.2 (0.4)	1–2	8 (12)	1.1 (0.4)	1–4
Clinical decision unit	Contact	2 (3)	1.0 (0)	1	6 (9)	1.2 (0.4)	1–2
Ambulance	Contact	1 (2)	1.0 (–)	1	4 (6)	1.3 (0.5)	1
Medical laboratory tests							
Immunology	Test	29 (45)	1.3 (0.5)	1–7	29 (43)	1.3 (0.5)	1–3
Virology		40 (63)	1.6 (1.2)	1–7	51 (75)	1.5 (1.0)	1–6

continued

TABLE 36 Service use at the 6-month follow-up (*continued*)

Service category	Unit of measure	Intervention arm 3 (*N* = 64)			Control arm 2 (*N* = 68)		
		Number of users, *n* (%)	Number of contacts users only, mean (SD)	Range for users only	Number of users, *n* (%)	Number of contacts users only, mean (SD)	Range for users only
Biochemistry (liver, renal, urine)		32 (50)	1.5 (1.2)	1–7	40 (68)	1.8 (1.7)	1–9
Haematology		28 (44)	1.5 (1.2)	1–7	34 (50)	1.5 (0.7)	1–7
Cholesterol		6 (9)	1.0 (0)	1	8 (12)	1.3 (0.7)	1–3
Glucose		8 (13)	1.3 (0.7)	1–3	10 (15)	1.4 (0.8)	1–3
Syphilis		9 (14)	1.0 (0)	1	9 (13)	1.7 (0.9)	1–3
Hepatitis markers		5 (8)	1.2 (0.4)	1–2	10 (15)	1.2 (0.4)	1–2
Hepatitis B immunology		3 (5)	1.0 (0)	1	7 (10)	1.3 (0.5)	1–2
Viral genotype testing		0 (0)	–	–	3 (4)	1.7 (1.2)	1–3
Therapy drug monitoring		0 (0)	–	–	0 (0)	–	–
Scan		1 (2)	1.0 (–)	1–2	0 (0)	–	–
MRI		1 (2)	1.0 (–)	1	0 (0)	–	–
Diagnostic imaging		1 (2)	1.0 (–)	1	1 (1)	1.0 (0)	8
X-ray		5 (8)	1.4 (0.9)	1–3	5 (7)	3.2 (4.4)	1–11
Smear test		1 (2)	1.0 (–)	1	3 (4)	1.7 (1.2)	1–3
STI check		8 (13)	1.0 (0)	1	6 (9)	1.5 (1.2)	1–4
Other tests		14 (22)	2.8 (2.9)	1–11	18 (21)	3.5 (6.8)	1–30
Productivity loss							
Employed		33 (52)			42 (62)		
Days off work due to ill health	Days	10 (27)	9.7 (14.4)	1–42	16 (38)	5.4 (8.2)	1–30
Informal care							
Personal care	Weeks	2 (3)	4.5 (0.7)	4–5	1 (1)	6.0 (–)	6
Providing transport	Weeks	3 (5)	2.7 (1.5)	1–4	2 (3)	6.0 (2.8)	4–8
Meal preparation	Weeks	4 (5)	2.8 (1.0)	2–4	2 (3)	8.5 (7.8)	3–14
DIY	Weeks	2 (3)	1.3 (1.1)	0.5–2	1 (1)	3.0 (–)	3
Gardening	Weeks	0 (0)	–	–	0 (0)	–	–
Shopping/collecting benefits	Weeks	6	1.5 (0.5)	1–2	1 (1)	4.0 (–)	4
Help outside home	Weeks	4 (5)	2.1 (0.6)	1.5–3	1 (1)	2.0 (–)	2
Socialising/companionship/ emotional support	Weeks	11	19.0 (49.5)	0.5–168	11	17.7 (49.9)	0.5–168
Help managing bills	Weeks	6	4.3 (7.7)	1–20	1 (1)	1.0 (–)	1
Other informal care help	Weeks	1 (1)	1.0 (–)	1	0 (–)	–	–

DIY, do it yourself; MRI, magnetic resonance imaging; STI, sexually transmitted infection.

TABLE 37 Service use at the 12-month follow-up

Service category	Unit of measure	CBT (*N* = 56)		CAU (*N* = 55)			
		Number of users, *n* (%)	Number of contacts users only, mean (SD)	Number of users, *n* (%)	Number of contacts users only, mean (SD)	Number of users, *n* (%)	Number of contacts users only, mean (SD)
Community services							
GP	Contact	29 (52)	2.6 (2.6)	1–12	35 (64)	2.0 (1.2)	1–6
Practice nurse	Contact	7 (13)	1.4 (0.8)	1–3	11 (20)	2.5 (4.5)	1–16
Psychologist	Contact	2 (4)	1.5 (0.7)	1–2	1 (2)	10.0 (–)	10
District nurse	Contact	0 (0)	–	–	1 (2)	12.0 (–)	12
Counsellor	Contact	1 (2)	4.0 (–)	4	1 (2)	20.0 (–)	20
Psychiatrist	Contact	0 (0)	–	–	0 (0)	–	–
Physiotherapist	Contact	2 (4)	1.0 (0)	4	2 (4)	3.0 (2.8)	1–5
Self-help/support group	Contact	1 (2)	24.0 (–)	24	3 (5)	9.7 (12.4)	2–24
Dietitian	Contact	2 (4)	3.0 (1.4)	2–4	1 (2)	1.0 (–)	1
Clinical specialist nurse (HIV)	Contact	1 (2)	6.0 (–)	6	0 (0)	–	–
Social worker	Contact	0 (0)	–	–	1 (2)	10 (–)	10
HIV outpatient clinic							
HIV consultant	Contact	43 (77)	2.1 (1.5)	1–6	40 (73)	1.8 (1.1)	1–6
Specialist registrar	Contact	7 (13)	1.6 (0.8)	1–3	9 (16)	0.5 (0.8)	1–3
Clinical nurse specialist	Contact	3 (5)	1.3 (0.6)	1–2	7 (13)	1.4 (0.8)	1–3
Nurse	Contact	47 (84)	1.9 (1.2)	1–7	44 (80)	1.7 (1.0)	1–6
Health advisor	Contact	3 (5)	1.7 (0.6)	1–2	4 (7)	1.8 (1.5)	1–4
Client support worker	Contact	2 (4)	2.0 (1.4)	1–3	1 (2)	20.0 (–)	20
Dietitian	Contact	3 (5)	1.7 (0.6)	1–2	1 (2)	1.0 (–)	1
Midwife	Contact	1 (2)	2.0 (–)	2	0 (0)	–	–
Phlebotomist	Contact						
Other	Contact	13 (23)	3.0 (2.3)	1–8	12 (24)	2.0 (2.1)	1–8
Medication							
Concomitant medications							
Hospital-based services							
Inpatient (length of stay)	Days	3 (5)	6.3 (8.4)	1–16	2 (4)	2.5 (2.1)	1–4
Outpatient	Contact	16 (29)	1.3 (0.6)	1–3	10 (18)	2.0 (1.2)	1–4
Day hospital	Contact	1 (2)	1.0 (–)	1	5 (9)	1.0 (0)	1
Emergency visits	Contact	11 (20)	1.2 (0.4)	1–2	9 (16)	1.0 (0)	1

continued

TABLE 37 Service use at the 12-month follow-up (*continued*)

Service category	Unit of measure	CBT (*N* = 56)			CAU (*N* = 55)		
		Number of users, *n* (%)	Number of contacts users only, mean (SD)	Number of users, *n* (%)	Number of contacts users only, mean (SD)	Number of users, *n* (%)	Number of contacts users only, mean (SD)
Clinical decision unit	Contact	1 (2)	1.0 (0)	1	1 (2)	1.0 (–)	1
Ambulance	Contact	2 (4)	1.0	1	1 (2)	1.0 (–)	1
Medical laboratory tests							
Immunology							
Virology		40 (71)	1.9 (2.2)	1–13	36 (65)	1.3 (0.8)	1–4
Biochemistry (liver, renal, urine)		51 (91)	1.6 (0.8)	1–4	47 (85)	1.7 (0.9)	1–4
Haematology		39 (70)	3.9 (6.9)	1–37	34 (62)	2.8 (3.4)	1–15
Cholesterol		38 (68)	2.1 (55)	1–12	32 (58)	2.0 (1.6)	1–8
Glucose		6 (11)	1.3 (0.8)	1–3	8 (15)	1.1 (0.4)	1–2
Syphilis		10 (18)	1.3 (0.7)	1–3	11 (20)	1.0 (0)	1
Hepatitis markers		13 (23)	1.2 (0.4)	1–2	16 (29)	1.4 (0.9)	1–4
Hepatitis B immunology		13 (23)	1.4 (0.7)	1–3	9 (16)	1.0 (0)	1
Viral genotype testing		11 (20)	1.2 (0.6)	1–3	5 (9)	1.0 (0)	1
Therapy drug monitoring		4 (7)	1.3 (0.5)	1–2	4 (7)	1.0 (0)	1
Scan		2 (4)	1.5 (0.7)	1–2	1 (2)	1.0 (–)	1
MRI		1 (2)	1.0 (–)	1	3 (5)	2.0 (1.7)	1–4
Diagnostic imaging		0 (0)	–	–	2 (4)	2.5 (2.1)	1–4
X-ray		4 (7)	1.8 (1.5)	1–4	2 (4)	1.5 (0.7)	1–2
Smear test		4 (7)	1.0 (0)	1	3 (5)	1.0 (0)	1
STI check		4 (7)	1.0 (0)	1	3 (5)	1.0 (0)	1
Other tests		11 (20)	5.0 (9.1)	1–32	12 (24)	2.5 (2.3)	1–8
Productivity loss							
Total employed		32 (57)			39 (71)		
Days off work due to ill health	Days	13 (41)	30 (52)	1–164	25 (64)	16 (38)	2–180
Informal care		***16 (29)***			***8 (15)***		
Personal care	Weeks	1 (2)	3.5 (–)	3.5	0 (0)	–	–
Providing transport	Weeks	1 (2)	3.0 (–)	3	0 (0)	–	–
Meal preparation	Weeks	2 (4)	3.0 (0)	3	3 (5)	4.5 (3.0)	2.5–8
DIY	Weeks	0 (–)	–	–	0 (–)	–	–

TABLE 37 Service use at the 12-month follow-up (*continued*)

		CBT (*N* = 56)			CAU (*N* = 55)		
Service category	Unit of measure	Number of users, *n* (%)	Number of contacts users only, mean (SD)	Number of users, *n* (%)	Number of contacts users only, mean (SD)	Number of users, *n* (%)	Number of contacts users only, mean (SD)
Gardening	Weeks	1 (2)	5.0 (–)	5	0 (–)	–	–
Shopping/collecting benefits	Weeks	4 (7)	3.1 (1.3)	2–5	2 (4)	2.4 (0.4)	2–2.5
Help outside home	Weeks	3 (5)	4.0 (3.5)	2–8	1 (2)	2.0 (–)	2
Socialising/companionship/emotional support	Weeks	10 (18)	24.2 (52.2)	0.25–168	9 (16)	2.8 (4.6)	0.5–15
Help managing bills	Weeks	2 (4)	2.1 (2.7)	0.25–4	2 (4)	1.0 (–)	1
Other informal care help	Weeks	0 (0)	–	–	0 (0)	–	–

DIY, do it yourself; MRI, magnetic resonance imaging; STI, sexually transmitted infection.

Human immunodeficiency virus outpatient clinic

Looking at HIV outpatient clinics at baseline, contacts with HIV consultants were the most frequently reported, and this was the same for both groups (93% for CBT vs. 85% for CAU), and the average number of contacts were also quite close (see *Table 34*). Although the proportions reporting contact tended to be comparatively lower in the subsequent study points (see *Table 35*), this service was the most commonly reported except at the 12-month follow-up, where nurses appeared to have slightly higher utilisation (see *Table 36*). This is not surprising as at baseline nurses had the second most reported contact with participants in HIV clinics. Similarly, the mean contacts were almost identical for both groups at all time points. Contact with HIV clinical nurse specialists was reported by less than one-quarter of participants from both groups. It is unclear whether participants did not require their service as much as they did from general nurses or if they were not aware of their specialty.

At baseline, almost half of the participants from both groups reported contact with other professionals within HIV clinics. A decrease in the proportion of participants with contact for other professionals in outpatient clinics was observed at 12 months' follow-up, with less than one-quarter from both groups reporting contact. However, the average number of contacts reported had almost doubled for the intervention group, while the control group had slightly fewer contacts.

Hospital-based services

Inpatient care was reported by fewer than one-quarter of the participants at baseline. Those that did report this were hospitalised for an average of 2 weeks, in both groups. The proportion of participants reporting hospital admissions and the duration of inpatient stay reduced over the study period. The intervention group maintained the trend of higher inpatient stay and at the 12-month follow-up they reported 4 more days in hospital than those in the control group. Outpatient care and emergency visits had similar utilisation patterns at baseline, and both were reported by more participants in the CAU group (37%) than the intervention group.

The two least frequently reported services in this category were day hospital and ambulance care. The few participants who reported contact had at least one encounter with both of these, and there were limited differences between the groups at all four study points. In general, service use in this category had reduced by the 12-month follow-up. Less than one-third of the participants from both groups reported use of non-HIV-specific hospital-based care at baseline, and the most commonly reported service was outpatient care.

Medical laboratory tests

At baseline, almost all participants had some form of medical tests performed, and this is not surprising for the most commonly reported tests (immunology, virology, biochemistry and haematology), as these are primarily required to ascertain crucial clinical outcomes, such as the CD4 T-cell count and viral load. The results reveal a higher mean number of tests for biochemistry with each having at least two tests, and there were no stark differences between the two groups at all study points.

Informal care

Help from friends/family was reported by few participants at all time points. At baseline, less than one-quarter of the participants from both groups stated they had informal care, and the most common type of help was socialising, companionship and emotional support. The intervention group reported six times more hours per week of help for this category of support than the control group. All other categories had < 4% of the participants reporting them, with equally fewer hours per week. This trend was maintained during the study period and at 12 months.

Service costs

Table 38 shows the costs of the services described in the earlier tables along with the costs of informal care and lost work. Overall, there were few large differences between the two groups. The total mean cost of health and social care (excluding the intervention and ART) at baseline was £2539 for the CBT group and £2598 for the CAU group, and these costs were mainly driven by hospital-based services for both groups, inpatient care in particular. Costs associated with community care contributed the least to total health costs.

At the 3-month follow-up, the mean cost had reduced to £554 for CBT and £337 for CAU and, although this is mainly attributable to the decrease in hospitalisation for both groups, all other service items were also associated with lower costs. The trend was maintained at the 6-month follow-up with costs amounting to £462 for CBT and £369 for CAU. At 12 months, the costs were £534 for CBT and £414 for CAU.

The mean cost of the SUPA intervention itself was £204. The mean cost over the 12 months' follow-up, including the intervention and antiretroviral treatment, was £9687 for CBT and £9068 for CAU. The CBT group had costs that were £621 more than for CAU. This difference was not statistically significant (95% CI −£506 to £1683).

When considering a wider costing perspective, the CBT group still had higher societal costs than the CAU group (£14,482 vs. £11,096), and the difference (£3054) was statistically significant (95% CI £745 to £5381).

The CBT group had slightly lower EQ-5D-5L tariff scores (0.7965) at baseline than the CAU group (0.817). By the 3-month follow-up, CBT resulted in higher scores (0.8947) than CAU (0.814), which this was maintained by the 6-month follow-up (0.8994 CBT, 0.8285 CAU). At the 12-month follow-up, the CBT group still had a higher mean tariff (0.8823) than the CAU group (0.8467), but the difference was reduced. CBT resulted in a greater number of QALYs (0.8835) over the entire follow-up period than CAU (0.8382). The difference in mean QALYs was 0.056 and this was statistically significant (95% CI 0.029 to 0.083).

The cost-effectiveness results (i.e. QALYs, NHS costs and societal costs) are described in *Table 39*. The incremental cost of £621 and incremental QALYs of 0.056 combined to produce an ICER of £11,189 per QALY. *Figure 6* illustrates the uncertainty around the results. It can be seen that the majority of cost-QALY outcomes fall below the line indicating a £20,000 per QALY threshold. From *Figure 7*, it can be seen that there was a 90% likelihood that CBT would be more cost-effective than CAU at this threshold.

The Markov model showed that the CBT group had expected costs that were £470 lower than those in the CAU group over the 16-year long-term period and resulted in 0.73 fewer QALYs. The cost-effectiveness plane derived from the Markov model revealed that most incremental cost–outcome combinations fell in the lower left quadrant, indicating lower costs and fewer QALYs for CBT than for CAU (*Figure 8*). These results suggest that there was almost a zero probability that the intervention was cost-effective over the 16-year period.

TABLE 38 Service costs at each time point

	CBT, mean (SD)				CAU, mean (SD)			
Service category	**Baseline**	**3 months**	**6 months**	**12 months**	**Baseline**	**3 months**	**6 months**	**12 months**
Community services								
GP	85 (145)	25 (43)	41 (64)	54 (86)	127 (288)	34 (64)	42 (74)	50 (64)
Practice nurse	1 (3)	0.4 (2)	1 (4)	2 (7)	3 (7)	1 (6)	1 (3)	7 (39)
District nurse	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)	2 (8)	11 (80)	6 (44)
Psychologist	7 (34)	0 (0)	4 (30)	3 (16)	8 (51)	2 (14)	11 (63)	10 (71)
Counsellor	10 (50)	0 (0)	2 (16)	7 (51)	3 (15)	8 (69)	1 (8)	23 (170)
Psychiatrist	6 (35)	0 (0)	0 (0)	0 (0)	2 (16)	0 (0)	0 (0)	0 (0)
Physiotherapist	0 (0)	1 (11)	0 (0)	1 (6)	1 (6)	0 (0)	2 (16)	3 (18)
Dietitian	0 (0)	0 (0)	3 (22)	4 (20)	3 (20)	0.2 (1)	1 (5)	0.3 (2)
Clinical specialist nurse (HIV)	0 (0)	0 (0)	0 (0)	3 (21)	1 (11)	0 (0)	0 (0)	0 (0)
Social worker	2 (17)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	16 (118)
Total community costs	106 (174)	27 (47)	51 (85)	74 (110)	141 (290)	48 (112)	68 (134)	114 (241)
HIV outpatient clinic								
HIV consultant	145 (103)	86 (94)	56 (61)	93 (123)	208 (337)	90 (82)	61 (65)	69 (66)
Specialist registrar	27 (57)	11 (27)	5 (16)	9 (26)	28 (56)	18 (46)	8 (20)	11 (30)
Clinical nurse specialist	61 (404)	6 (14)	3 (20)	2 (9)	17 (60)	5 (12)	4 (15)	5 (19)
Nurse	37 (46)	26 (38)	15 (21)	29 (26)	67 (110)	33 (39)	17 (20)	26 (26)
Health advisor	3 (9)	1 (6)	0.2 (1)	1 (3)	3 (9)	1 (3)	1 (4)	1 (5)
Client support worker	1 (3)	1 (6)	0.1 (1)	1 (5)	1 (3)	1 (3)	0	8 (61)
Dietitian	5 (35)	4 (24)	1 (8)	4 (17)	5 (21)	4 (18)	1 (7)	1 (6)
Midwife	42 (249)	1 (7)	4 (20)	2 (15)	12 (98)	0 (0)	0 (0)	0 (0)
Other	103 (144)	86 (203)	39 (104)	93 (226)	147 (314)	118 (237)	45 (116)	58 (169)
Total HIV outpatient clinic	321 (498)	221 (261)	124 (141)	234 (296)	340 (191)	270 (283)	137 (160)	181 (204)

continued

TABLE 38 Service costs at each time point (*continued*)

	CBT, mean (SD)				CAU, mean (SD)			
Service category	**Baseline**	**3 months**	**6 months**	**12 months**	**Baseline**	**3 months**	**6 months**	**12 months**
Hospital-based services								
Inpatient (length of stay)	1755 (4416)	245 (1130)	258 (1270)	212 (1345)	1706 (5187)	55 (320)	47 (228)	57 (347)
Outpatient	58 (100)	90 (412)	43 (107)	49 (88)	81 (131)	64 (107)	29 (78)	50 (127)
Day hospital	10 (57)	16 (73)	11 (61)	6 (46)	19 (79)	0 (0)	5 (42)	31 (100)
Emergency visits	48 (82)	12 (40)	16 (54)	34 (75)	77 (128)	17 (60)	20 (57)	24 (55)
Clinical decision unit	23 (54)	5 (26)	5 (26)	11 (38)	41 (75)	2 (18)	19 (79)	3 (20)
Ambulance	14 (57)	4 (31)	5 (26)	9 (46)	17 (63)	7 (60)	16 (53)	4 (33)
Total hospital costs	1907 (4468)	371 (1226)	338 (1308)	321 (1353)	1940 (5250)	147 (338)	136 (360)	169 (417)
Medical tests								
Immunology	9 (6)	4 (8)	4 (7)	8 (12)	10 (9)	5 (5)	3 (4)	5 (5)
Virology	17 (12)	11 (9)	8 (10)	11 (7)	16 (10)	11 (7)	9 (9)	11 (8)
Biochemistry (liver, renal, urine)	9 (14)	3 (5)	2 (3)	8 (18)	7 (11)	5 (7)	3 (5)	5 (9)
Haematology	6 (8)	3 (4)	2 (3)	4 (6)	6 (9)	3 (3)	2 (3)	3 (5)
Cholesterol	3 (5)	2 (3)	1 (2)	1 (4)	4 (6)	2 (5)	1 (4)	1 (3)
Glucose	1 (2)	1 (2)	0.5 (1)	1 (2)	1 (2)	1 (2)	1 (2)	1 (1)
Syphilis	5 (8)	2 (5)	1 (3)	2 (4)	5 (7)	2 (4)	2 (5)	3 (6)
Hepatitis markers	6 (5)	1 (2)	1 (3)	3 (5)	5 (6)	2 (4)	1 (4)	1 (3)
Hepatitis B immunology	3 (5)	0.4 (2)	0.4 (2)	1 (3)	3 (5)	1 (3)	1 (3)	1 (2)
Viral genotype testing	5 (6)	1 (2)	0 (–)	1 (3)	6 (7)	0.2 (1)	1 (3)	1 (2)
Therapy drug monitoring	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Scan	22 (54)	5 (23)	1 (10)	4 (23)	8 (30)	0 (0)	0 (0)	1 (10)
MRI	14 (49)	2 (18)	2 (18)	3 (19)	15 (44)	8 (41)	0 (0)	15 (80)

TABLE 38 Service costs at each time point (*continued*)

	CBT, mean (SD)				CAU, mean (SD)			
Service category	**Baseline**	**3 months**	**6 months**	**12 months**	**Baseline**	**3 months**	**6 months**	**12 months**
Diagnostic Imaging	7 (28)	1 (7)	2 (10)	0	6 (29)	3 (12)	7 (57)	5 (32)
X-ray	34 (63)	8 (31)	9 (34)	9 (44)	24 (81)	6 (20)	19 (106)	4 (23)
Smear test	5 (17)	5 (17)	1 (6)	4 (13)	2 (10)	2 (10)	4 (20)	3 (11)
STI check	7 (19)	3 (9)	1 (3)	3 (6)	4 (6)	1 (4)	1 (4)	5 (14)
Other tests	55 (176)	49 (193)	18 (51)	28 (127)	55 (127)	20 (54)	28 (111)	16 (42)
Laboratory tests total costs	205 (293)	99 (210)	53 (104)	87 (148)	177 (233)	71 (110)	83 (198)	79 (148)
Total health and social care costs	2539 (4638)	718 (1341)	566 (1368)	716 (1519)	2598 (5427)	535 (507)	425 (540)	543 (565)
Informal care								
Personal care	1688 (9956)	0 (0)	25 (142)	22 (166)	2046 (10,057)	13 (109)	16 (131)	0 (0)
Help with transport	871 (7091)	6 (31)	23 (113)	57 (251)	49 (247)	13 (78)	32 (195)	19 (144)
Help with meals	30 (215)	28 (224)	31 (126)	38 (200)	310 (1589)	19 (152)	46 (312)	87 (422)
Help with DIY	10 (84)	1 (11)	7 (46)	0 (0)	19 (131)	5 (43)	8 (66)	0 (0)
Help with shopping	616 (5064)	28 (187)	26 (84)	40 (154)	190 (1458)	26 (216)	11 (88)	15 (76)
Help outside home	5 (42)	4 (33)	24 (96)	76 (400)	22 (102)	0 (0)	5 (44)	13 (96)
Socialising and emotional support	5040 (15,623)	814 (4266)	591 (3764)	1539 (8211)	2346 (9961)	137 (593)	524 (3676)	165 (736)
Time spent helping with bills	852 (7091)	25 (158)	73 (454)	27 (190)	2 (21)	3 (22)	3 (22)	13 (67)
Other informal care	0 (0)	3 (22)	6 (45)	0 (0)	633 (3371)	3 (22)	0 (0)	0 (0)
Informal care costs	9112 (37,963)	909 (4294)	806 (3952)	1799 (8399)	5619 (15,149)	218 (835)	645 (3736)	312 (1024)
Productivity loss								
Days off work due to ill health	818 (1937)	298 (1291)	152 (675)	710 (2812)	1247 (3280)	93 (203)	84 (290)	738 (2740)
Total societal costs	12,470 (39,677)	1925 (4818)	1524 (4293)	3224 (9061)	9464 (16,333)	846 (1100)	1154 (3769)	1594 (3093)

MRI, magnetic resonance imaging; STI, sexually transmitted infection.

TABLE 39 Cost-effectiveness results

Variables	CBT (*N* = 72), mean (SD)	CAU (*N* = 72), mean (SD)	Unadjusted mean difference (95% CI)	Adjusted mean difference (95% CI)
Outcome(s)				
QALYs complete cases	0.8861 (0.1376)	0.8245 (0.1605)	0.0594 (0.0008 to 0.1201)	0.0619 (0.2570 to 0.0984)
QALYs imputed	0.8835 (0.1264)	0.8382 (0.1405)	0.0453 (0.0002 to 0.0898)	0.0555 (0.0298 to 0.0825)
Perspective: NHS and social care				
NHS PSS costs (including intervention costs) complete cases (£)	10,580 (4458)	9031 (3033)	1549 (185 to 3169)	1409 (−284 to 2796)
Total NHS PSS costs (including intervention costs) imputed (£)	9687 (3404)	9068 (2980)	619 (−479 to 1658)	621 (−506 to 1683)
NHS/PSS perspective: costs per QALY gain (£) complete cases			£26,077/QALY	£22,763/QALY
NHS perspective: costs per QALY gain (£) imputed cases			£13,664/QALY	£11,189/QALY
Perspective: societal (including productivity loss and informal care)				
Societal costs (including intervention) complete cases (£)	14,818 (11,912)	10,416 (4249)	2920 (215 to 5931)	2596 (180 to 4949)
Societal costs (including intervention) imputed (£)	14,482 (10,341)	11,096 (4972)	3386 (1127 to 6287)	3054 (745 to 5381)

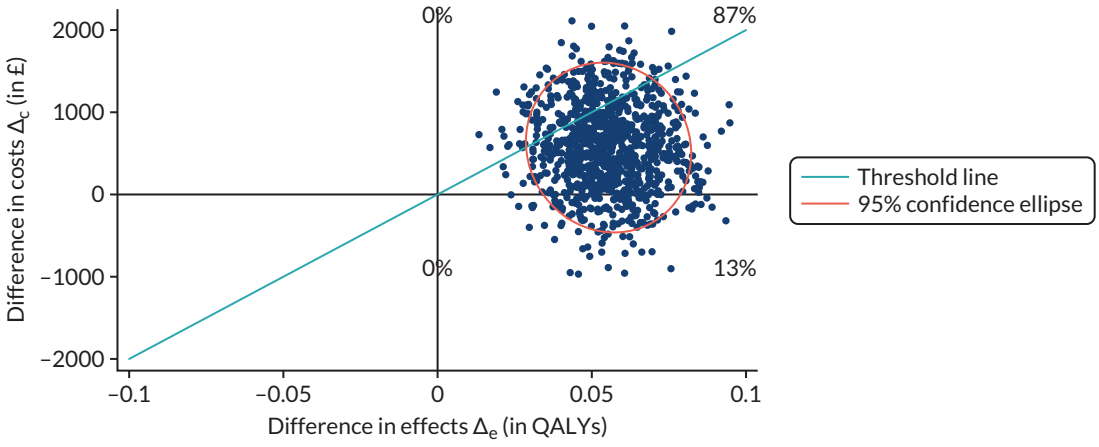


FIGURE 6 Cost-effectiveness plane (trial analysis).

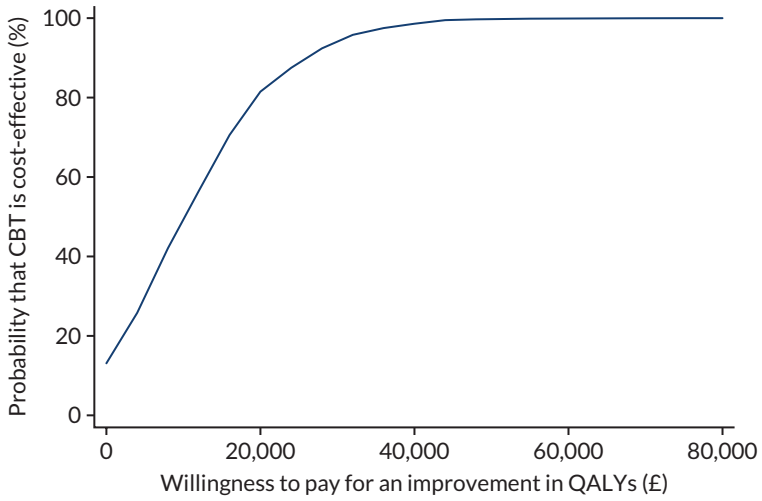


FIGURE 7 Cost-effectiveness acceptability curve (trial analysis).

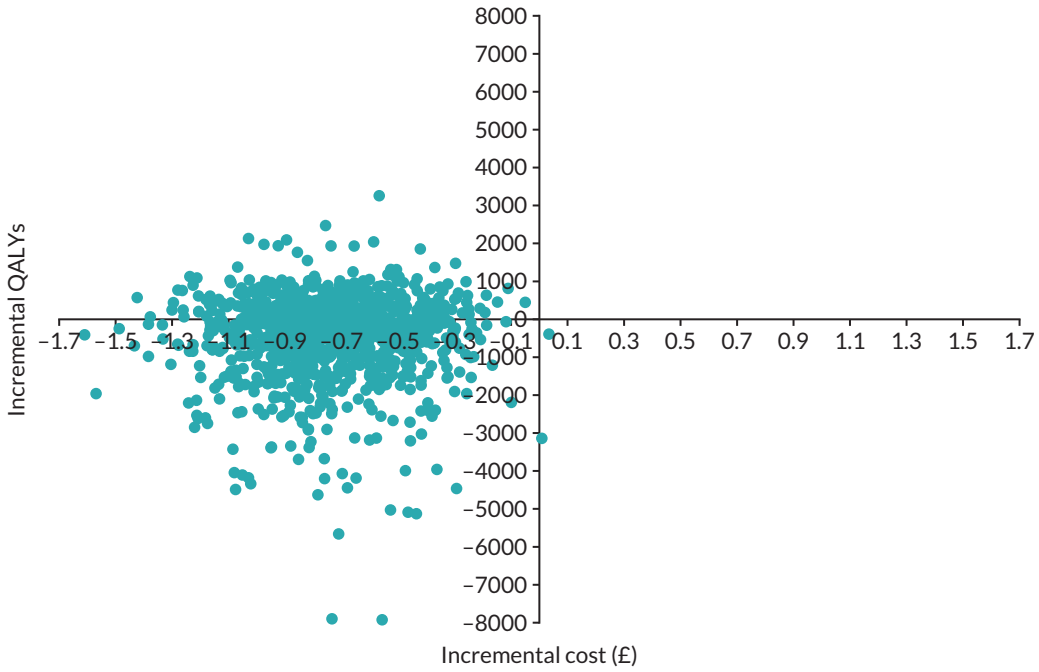


FIGURE 8 Cost-effectiveness plane from Markov model.

Discussion

These analyses have shown that the delivery of therapy to the CBT group resulted in higher costs for that group. That is not unusual in studies such as this where the provision of therapy is not offset by reduced costs elsewhere because such costs were limited to start with. Therefore, whether or not an intervention is considered to be cost-effective depends on the extent to which it results in improved outcomes. In this study, we found that CBT resulted in more QALYs than CAU and these were sufficient to result in an ICER that was below the threshold used by NICE. However, although the QALY gain was clear for the intervention it was also short lived, as the improvement in quality of life occurred mainly in the first 6 months of the follow-up.

The longer-term results revealed that CBT resulted in lower costs and fewer QALYs than CAU. However, the lower costs were not sufficient to offset the poorer outcomes and there was no evidence of long-term cost-effectiveness. The long-term results were based on extrapolating from the distribution of CD4 T-cell count groups at the 12-month follow-up. These were similar between the groups and so no long-term cost-effectiveness in favour of the intervention was not unexpected.

There were limitations to the analyses. First, the data were from self-reported service use information and recall accuracy may have been problematic. This was unavoidable as records would not have the breadth of service use information required, but under-reporting (or possibly over-reporting) may have occurred. There is though no reason to suppose that this differed between groups. Second, as well as recall issues there may have been some confusion over the definition of some services. Third, the sample size was relatively small and so we need to be cautious about the findings.

Appendix 11 Ancillary study 1: patients' perceptions of standard care

The aim of this study was to examine patients' perceptions of their HIV care in the SUPA trial. As there was no existing instrument to measure patients' perceptions of their care, a new measure of patients' perceptions of their HIV care was developed.

Methods of data collection and analysis

The quality of standard care has been found to impact on the interpretation and comparison of intervention effects in HIV adherence interventions.[79] The Standard Care Perceptions Questionnaire (SCPQ) was developed to measure patients' perceptions of their HIV care. Nine items were developed by the research team to measure aspects of the patient–provider relationship that have been found to facilitate adherence to ART based on the literature. This includes the extent to which patients perceived that (1) they were able to discuss their HIV diagnosis with their clinical team, (2) the clinical team addressed their needs for information about HIV and ART, (3) the clinical team elicited and addressed their practical and perceptual barriers to ART and (4) they had a relationship with their clinical team in which they felt that they were heard and listened to, had sufficient time and were given the opportunity to ask questions. The questions were introduced using a normalising statement: these are statements that other people have made about their care. Participants were asked to indicate if they agreed, were uncertain or disagreed with each statement.

Questionnaires contained nine questions and scored as follows: agree (3), uncertain (2) and disagree (1). A maximum score of 27 indicated that the participant agreed with each of the questions indicating a positive interaction with and perceived support from their clinical care team.

This questionnaire was included in the SUPA study in March 2017 and all participants (observational and interventional participants) were invited to participate at their next clinic/study visit. Participants who completed the study prior to March 2017 were invited if the last visit was completed within the previous 12 months.

Key findings

A total of 114 people completed the SCPQ questionnaire. The frequency distribution for the total SCPQ scores is reported in *Table 40*. These were 75, 21 and 17 participants in the observational, CAU and CBT arms of the study, respectively.

One questionnaire was incomplete and a total score was not available.

Overall, 71% of respondents were in agreement with all of the statements and scored the maximum score (i.e. 27). Distribution of responses to each SCPQ item is illustrated in *Figure 9*.

There were no statistically significant differences in the proportion who achieved this score across the three groups (72% observational, 62% CAU and 76% CBT; $p = 0.57$).

Each item was examined individually. Only one item showed < 90% agreement with the statement: 83% of participants agreed with the statement: 'If I do have challenges, my team would help me deal with/overcome these worries'. Responses to individual items did not differ between the study groups or clinical sites.

TABLE 40 Frequency distribution of SCPQ scores

Total score	Observational (*n*)	Regimen (*n*)		Total (*n*)
		CAU	CBT	
18	0	0	1	1
21	1	0	0	1
22	1	0	1	2
23	2	2	0	4
24	0	1	1	2
25	8	4	1	13
26	9	1	0	10
27	54 (72)	13 (62)	13 (76)	80 (71)
Total	76	21	17	113

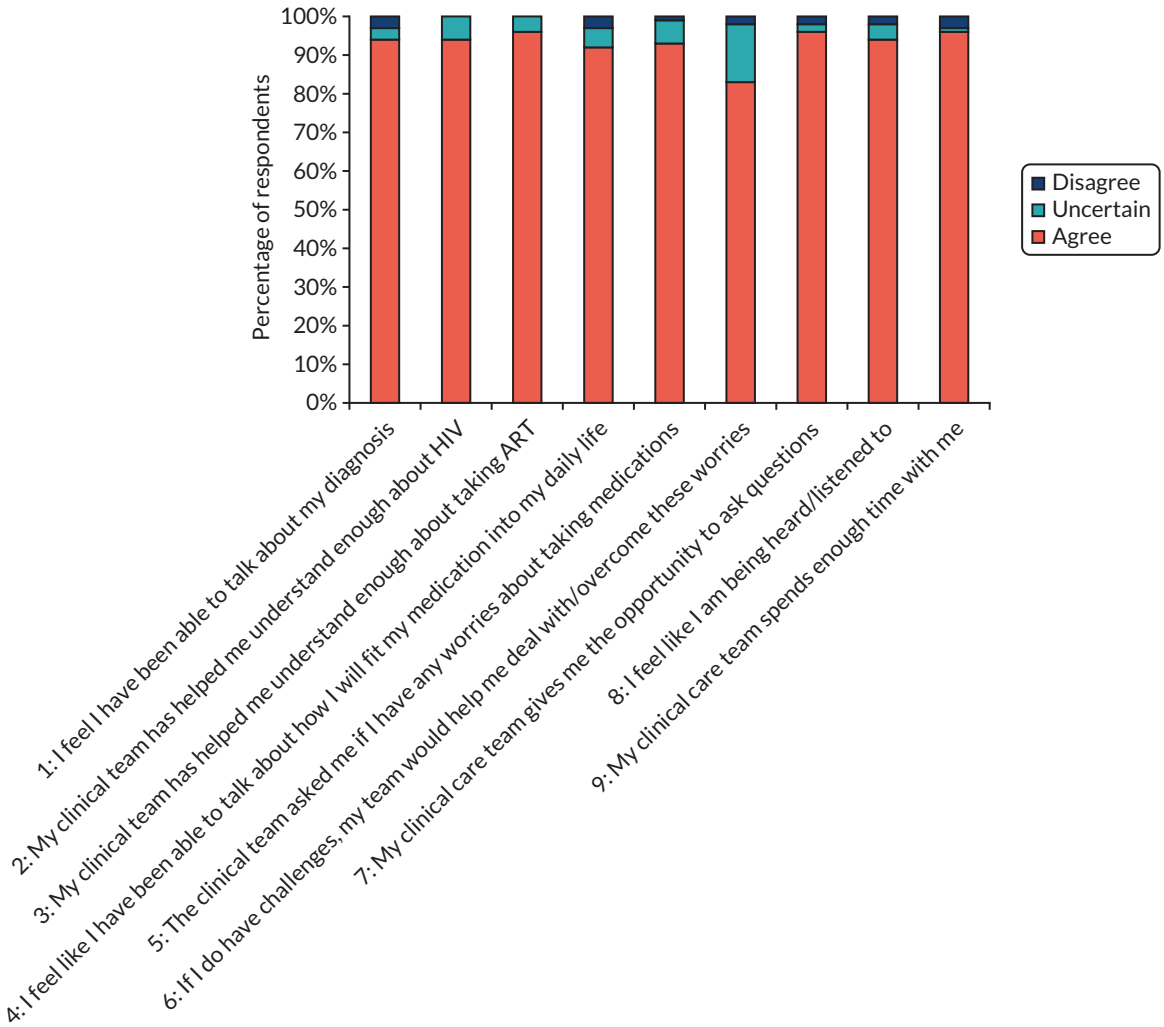


FIGURE 9 Distribution of responses to each SCPQ item (*n* = 113).

Limitations

The patients enrolled in the SUPA study reported very positive experiences of HIV care. There was very little variability in the responses and the results showed a high level of homogeneity in patients' views. It was difficult to draw any meaningful conclusions from the responses provided by a small number of participants. In addition, participants who agreed to complete the SCPQ several months after the end of their last study visit may have had a more positive experience of their clinic and clinical staff than the broader clinic populations.

There were no statistically significant differences in views stratified by study group or by site. This supports the idea that the perceived quality of care is similar despite randomisation within the trial or which clinic the patient attended for their HIV care. This is important because it indicates that there was consistency in the care received across HIV clinics and randomised groups.

The only item to show any heterogeneity was the statement 'If I do have challenges, my team would help me deal with/overcome these worries'. There was a larger number of participants answering 'uncertain' than 'agree' or 'disagree', which may imply that they have never been in that situation. Therefore, it is difficult to draw any conclusions from this result.

Appendix 12 Ancillary study 2: assessing beliefs about medicines and treatment outcomes in human immunodeficiency virus-positive patients starting antiretroviral therapy to protect their partners (treatment as prevention) versus clinical need within the observational cohort component of workstream 3

Aim

The aim of this analysis was to determine whether or not perceptions of ART (necessity and concerns beliefs) differed between people who started ART because of clinical need (e.g. low CD4 T-cell count) and those who started ART to protect their sexual partners from HIV infection (i.e. treatment as prevention).

Methods of data collection and analysis

Prior to 2016, the BHIVA treatment guidelines recommended initiation of ART in PLWH when their CD4 T-cell count was < 350 cells/mm^3. An exception to this recommendation was initiation of ART at CD4 T-cell counts > 350 cells/mm^3 to protect sexual partners from HIV. Results from the START (Strategic Timing of AntiRetroviral Treatment) trial[80,81] demonstrated better outcomes in those starting ART at higher CD4 T-cell counts compared with those waiting for a CD4 T-cell count drop to < 350 cells/mm^3. As a result, the UK treatment guidelines were amended in 2016 and a treatment offer was recommended for everyone regardless of CD4 T-cell count.[82] The sample for this analysis were individuals in the observational cohort study who enrolled in the SUPA observational study before 2016 (prior to the change in treatment guidelines). This sample was stratified by CD4 T-cell count (< 350; 350–500 and > 500 cells/mm^3). Demographics, laboratory test results and beliefs about ART, such as necessity, concerns, and necessity concerns differential, were compared between stratified groups.

Key findings

A total of 247 participants enrolled in the observational study between February 2014 and 31 December 2015 and formed the sample for this study. The majority (125; 50.6%) had a CD4 T-cell count of < 350 cells/mm^3; 58 participants (23.5%) had a CD4 T-cell count of 350–500 cells/mm^3 and 64 (25.9%) had a CD4 T-cell count of > 500 cells/mm^3. Those with a CD4 T-cell count of > 500 cells/mm^3 were younger, less likely to be female, more likely to be of white ethnicity and more likely to be MSM. As expected, those with a CD4 T-cell count of > 350 cells/mm^3 at time of enrolment were less likely than those with a CD4 T-cell count < 350 cells/mm^3 to have a HIV-related condition (0% vs. 5%, respectively). There were no significant differences between groups in the proportions of people with an undetectable viral load at 3, 6 or 12 months. Beliefs about ART (necessity, concerns and necessity concern differential) did not differ significantly between groups at baseline and at 3, 6 or 12 months.

Implications

The finding that people starting treatment for clinical need and those starting ART to protect their partners did not differ in terms of beliefs about ART or virological outcomes is relevant to clinical practice. These findings suggest that starting ART to protect others rather than for clinical need does not reduce personal necessity for treatment and does not raise concerns about adverse effects.

Furthermore, starting ART to protect others does not have a negative impact on virological outcomes.

Limitations

We made the assumption that people who were recommended ART at a CD4 T-cell count of > 500 cells/mm^3 had initiated treatment to protect sexual partners from HIV. There could be other reasons for initiating ART at a higher CD4 T-cell count, including patient choice. As the publication of the START study results in 2016,[80] the BHIVA guidelines now recommend a test and treat approach, where all patients are offered ART after receiving a HIV diagnosis. This means that the findings are now less directly relevant to clinical practice.

Appendix 13 Ancillary study 3: assessing the level of adherence to antiretroviral therapy required to achieve virological suppression over a 12-month follow-up period in patients initiating their first antiretroviral therapy regimen

Aim

The aim of this study was to examine associations between adherence and viral load suppression in the SUPA trial.

Methods of data collection and analysis

This analysis included all SUPA trial participants who had available MEMS data, reported viral load at 6 months and started ART on or before their baseline visit (to ensure that adherence data were complete for all three periods). Adherence was measured using MEMS caps and self-report questionnaire (i.e. MARS). Viral load test results were extracted from the patients' medical record.

Key findings

Of the 204 participants, 20 had no MEMS data. Of the remaining 184, 21 had no reported viral load at month 6. Finally, of the remaining 163 participants, 13 either had no ART start date (n = 1) or started after baseline (n = 12). The remaining 150 participants form the study set for these analyses. Of these, at month 6, only 61 had reported viral load that was within the 42-day window period (used for the main trial analyses). The analysis includes all participants but the repeated measures were available only for this smaller subgroup (*Table 41*).

Table 41 shows the monthly averages (from month 1 to 3) from the MEMS data set as well as the overall average calculated over months 1–3, stratified by the viral load at month 6 (suppressed or not suppressed). Although adherence rates in the first month were higher in those with a suppressed viral load at month 6 [median adherence was 80.0 (IQR 44.8–96.6) in those with a suppressed viral load and 63.2 (IQR 20.2–82.6) in those with an unsuppressed viral load], the difference was relatively small and not significant (p = 0.09).

In months 2 and 3, there were minimal differences between the two groups.

Overall, 124 participants had a reported MARS value at month 3 (median 25, IQR 24–25) – of these, 105 (84.7%) reported a MARS score of > 24 (labelled as high adherence – MARS). The median MARS scores at month 3 were 25 (IQR 24–25) in those without a suppressed viral load at their next month 6 follow-up, and also 25 (IQR 24–25) in those with a suppressed viral load at their next month 6 follow-up (p = 0.72). Among the subset with a very tightly defined viral load at 6 months, results were similar (median 25, IQR 24–25, and median 25, IQR 24–25, respectively; p = 0.99).

Limitations

Owing to a lack of statistical power and limitations in the study methodology, it was not possible to determine how much adherence was needed to achieve virological suppression.

TABLE 41 Observational study participants enrolled between February 2014 and December 2015 (*n* = 247)

Characteristic	Number of participants	CD4 T-cell count			*p*-value
		< 350 cells/mm³ (*N* = 125)	350–500 cells/mm³ (*N* = 58)	> 500 cells/mm³ (*N* = 64)	
Age (years), mean (SD)	465	40.4 (11.7)	38.2 (12.1)	34.1 (10.0)	0.0017
Sex, *n* (%)	468				
Female		35 (28)	6 (10)	5 (8)	0.002
Male		90 (72)	52 (90)	58 (91)	
Transgender		0 (0)	0 (0)	1 (1)	
Ethnicity, *n* (%)	468				
White		50 (40)	28 (48)	44 (69)	< 0.001
Black African		47 (38)	12 (21)	3 (5)	
Black other		13 (10)	7 (12)	5 (8)	
Other		14 (11)	11 (19)	12 (19)	
Not stated		0 (0)	0 (0)	0 (0)	
Eligible for trial: yes, *n* (%)		21 (17)	7 (12)	9 (14)	0.69
Years in the UK, *n* (%)	480				
< 5		17 (14)	9 (16)	7 (11)	0.19
≥ 5		56 (45)	24 (41)	19 (30)	
N/A – born in the UK		41 (33)	20 (34)	34 (54)	
Not stated		10 (8)	5 (9)	3 (5)	
Sexuality, *n* (%)	462				
MSM		48 (38)	40 (69)	49 (77)	< 0.0001
Other/not stated		77 (62)	18 (31)	15 (23)	
Marital status, *n* (%)	219				
Married/in partnership		18 (32)	8 (32)	9 (23)	0.85
Single/separated		34 (61)	16 (64)	27 (69)	
Widowed/other		4 (7)	1 (4)	3 (8)	
Education, *n* (%)	249				
Basic/school		24 (35)	6 (16)	6 (17)	0.09
Higher education		29 (43)	23 (62)	23 (66)	
Not stated		15 (22)	8 (22)	6 (17)	
Employment, *n* (%)	257				
Working		40 (57)	21 (50)	21 (58)	0.7
Not working		17 (24)	9 (21)	6 (17)	
Other/not stated		13 (19)	12 (28)	9 (25)	
Mode of HIV transmission, *n* (%)	469				
Sexual		115 (92)	52 (91)	61 (95)	0.79
Blood contact		2 (2)	0 (0)	0 (0)	
Needles		2 (2)	2 (4)	1 (2)	
Other/not stated		6 (5)	3 (5)	2 (3)	

continued

TABLE 41 Observational study participants enrolled between February 2014 and December 2015 (*n* = 247) (*continued*)

Characteristic	Number of participants	CD4 T-cell count			*p*-value
		< 350 cells/mm^3 (*N* = 125)	350–500 cells/mm^3 (*N* = 58)	> 500 cells/mm^3 (*N* = 64)	
Clinical diagnoses, *n* (%)					
Other HIV morbidity	472	6 (5)	0 (0)	0 (0)	0.0051
Hepatitis B positive	470	7 (6)	2 (3)	0 (0)	0.15
Hepatitis C positive	472	3 (2)	1 (2)	1 (2)	0.91
Non-AIDS malignancy	472	0 (0)	0 (0)	0 (0)	
Time since HIV diagnosis, *n* (%)	470				
< 1 year		97 (78)	42 (72)	50 (79)	0.58
1–5 years		16 (13)	12 (21)	7 (11)	
> 5 years		12 (10)	4 (7)	6 (10)	
Agreed to start ARVs, *n* (%)	472				
Yes		111 (89)	46 (79)	53 (84)	0.46
No		9 (7)	6 (10)	6 (10)	
N/A		5 (4)	6 (10)	4 (6)	
Been prescribed ARVs, *n* (%)	470				
Yes		104 (83)	46 (79)	51 (81)	0.81
No		21 (17)	12 (21)	12 (19)	
Undetectable viral load at 3 months, *n* (%)		52 (51)	23 (55)	25 (54)	0.89
Undetectable viral load at 6 months, *n* (%)		60 (68)	27 (71)	24 (77)	0.62
Undetectable viral load at 12 months, *n* (%)		87 (82)	39 (80)	38 (78)	0.79
Baseline					
BMQ score – necessity, mean (SD)	252	4.0 (0.6)	3.9 (0.5)	4.0 (0.5)	0.76
BMQ score – concerns, mean (SD)		2.5 (0.6)	2.4 (0.5)	2.5 (0.6)	0.85
BMQ score – NCD, mean (SD)		1.5 (1.0)	1.5 (0.8)	1.5 (0.8)	0.97
3 months					
BMQ score – necessity, mean (SD)	252	4.0 (0.6)	3.9 (0.5)	4.1 (0.5)	0.27
BMQ score – concerns, mean (SD)		2.3 (0.6)	2.3 (0.5)	2.2 (0.6)	0.64
BMQ score – NCD, mean (SD)		1.8 (0.9)	1.6 (0.8)	1.9 (0.9)	0.32
6 months					
BMQ score – necessity, mean (SD)	252	4.1 (0.6)	4.0 (0.6)	4.1 (0.4)	0.59
BMQ score – concerns, mean (SD)		2.2 (0.6)	2.3 (0.6)	2.3 (0.6)	0.63

TABLE 41 Observational study participants enrolled between February 2014 and December 2015 (*n* = 247) (*continued*)

Characteristic	Number of participants	CD4 T-cell count			*p*-value
		< 350 cells/mm^3 (*N* = 125)	350–500 cells/mm^3 (*N* = 58)	> 500 cells/mm^3 (*N* = 64)	
BMQ score – NCD, mean (SD)		1.8 (1.0)	1.8 (0.9)	1.8 (0.8)	0.89
12 months					
BMQ score – necessity, mean (SD)		4.1 (0.6)	4.1 (0.6)	4.0 (0.5)	0.79
BMQ score – concerns, mean (SD)		2.2 (0.6)	2.3 (0.7)	2.4 (0.7)	0.5
BMQ score – NCD, mean (SD)		1.9 (1.1)	1.8 (1.2)	1.7 (1.0)	0.56

ARV, antiretroviral; N/A, not applicable; NCD, necessity concern differential.
CD4 T-cell count at baseline enrolled before 2016.

We did not collect clinical data at study time points but relied on routinely collected data extracted from the patients' medical files. This meant that the proportion missing viral load data at key time points was higher than anticipated and left the study underpowered to address the study question. It is impossible to know whether the people with missing data were more likely to be detectable as they were not attending or whether they were more likely to be undetectable and subsequently offered less frequent appointments.

Missing MEMS data were also difficult to interpret. We cannot assume that if the MEMS cap was not used that this can be interpreted as non-adherent and the high level of virological suppression in patients with missing MEMS data would support this. Anecdotally patients often reported that as they became comfortable taking their medication their use of MEMS caps decreased and subsequently what looks like non-adherence actually may inversely represent good adherence.

Implications

Although we were not able to define the threshold of adherence necessary to achieve virological suppression, our findings suggest that the threshold of adherence required is lower than the 95% that is frequently cited.[1,2]

Appendix 14 Ancillary study 4: systematic review and meta-analysis of adherence interventions

Aim

The aim of this systemic review was to evaluate available adherence interventions and assess what type of behavioural determinants they addressed, to which extent the theory was applied, and what behaviour change techniques were used.

Methods

We conducted a systematic review and meta-analysis to determine the effectiveness of interventions to enhance adherence to ART (search December 2018). Moderation analyses were used to determine the impact of intervention channel (mode of delivery) and content (extent to which theory was used to inform the intervention, whether the intervention addressed perceptions, practicalities and whether it was tailored and behaviour change techniques) on efficacy. Validated checklists were used to annotate the interventions. The context was coded in relation to (1) if the study was conducted in a low–middle income or high-income country, (2) involvement of the target group in the development of the intervention and (3) selection of PLWH at risk of non-adherence and whether or not participants were previously ART naive. The Cochrane Risk of Bias tool[83] was used to assess risk of bias and the TIDieR checklist[46] was used to determine the quality of intervention description.

Key findings

Of the 2622 studies identified by the database search, 91 studies met the inclusion criteria, including 19,373 participants. Eighty studies (15,956 participants) provided adherence data that could be included in the meta-analysis. The weighted average effect size of these interventions on adherence was medium (d = 0.318, 95% CI 0.236 to 0.399; $p < 0.0001$; I^2 = 71.288). Fifty-three studies provided viral load data that could be used in the meta-analysis. The overall effect of the interventions on viral load was small (d = 0.151, 95% CI 0.085 to 0.216; $p < 0.0001$; I^2 = 35.896).

Content

The most effective interventions – defined as those producing medium effects ($d > 0.35$) – addressed perceptual barriers (κ = 46) (d = 0.352, 95% CI 0.229 to 0.474; $p < 0.0001$) and those that used macrotailoring (κ = 4) (d = 0.658, 95% CI 0.456 to 0.860; $p < 0.0001$); attention tailoring (κ = 8) (d = 0.569, 95% CI 0.361 to 0.777; $p < 0.0001$) or microtailoring (κ = 49) (d = 0.375, 95% CI 0.262 to 0.488; $p < 0.0001$). Thirty-four (37.4%) studies referenced the use of theories or models and 22 (24.2%) studies used theory and/or predictors to select intervention techniques. Use of theory was associated with higher larger effect sizes.

Context

Larger effect sizes were found for studies conducted exclusively in low- and middle-income countries (κ = 33) (d = 0.430, 95% CI 0.31 to 0.546; $p < 0.0001$); those that stated that members of the target group had been involved in development of the interventions (κ = 17) (d = 0.357, 95% CI 0.21 to 0.505), $p < 0.0001$), and those in which recipients of the intervention had been selected on the basis of non-adherence or risk of non-adherence (κ = 26) (d = 0.405, 95% CI 0.131 to 0.450; $p < 0.0001$).

Channel (mode of delivery)

The highest effect sizes were found in studies of interventions including incentives (κ = 1) (d = 0.533, 95% CI 0.088 to 0.979; $p < 0.019$); SMS (κ = 14) (d = 0.485, 95% CI 0.289 to 0.681; $p < 0.0001$); feedback from electronic monitors

(κ = 14) (*d* = 0.477, 95% CI 0.277 to 0.677; *p* < 0.0001); reminders to a device (κ = 21) (*d* = 0.383, 95% CI 0.247 to 0.519; *p* < 0.0001); and counselling (CBT/MI) (κ = 25) (*d* = 0.392, 95% CI 0.213 to 0.571; *p* < 0.0001).

Behaviour change techniques

Interventions that included the following BCTs had a significant impact on adherence with effect sizes larger than *d* = 0.35: 1.1 goal-setting (*d* = 0.719, 95% CI 0.342 to 1.096; *p* < 0.0001); 2.2 feedback on behaviour (*d* = 0.497, 95% CI 0.272 to 0.721; *p* < 0.0001); 3.1 social support unspecified (*d* = 0.351, 95% CI 0.255 to 0.447; *p* < 0.0001); 3.3 social support emotional (*d* = 0.442, 95% CI 0.107 to 0.777; *p* < 0.010); 4.1 instructions on how to perform the behaviour (*d* = 0.426, 95% CI 0.26 to 0.583; *p* < 0.0001); 4.2 information about antecedents (*d* = 0.566, 95% CI 0.092 to 1.040; *p* < 0.019); 5.1 health consequences (*d* = 0.411, 95% CI 0.240 to 0.532; *p* < 0.0001); and 7.1 prompts and cues (*d* = 0.386, 95% CI 0.241 to 0.532; *p* < 0.0001).

Limitations

Individual studies were judged to be at a high risk of bias because of the lack of blinding of participants and personnel and a fairly high risk of bias because of lack blinding of outcome assessment (adherence). The quality of description of interventions was also deficient for many studies, meaning that we could not be confident that our coding of intervention content was accurate.

Inter-relation with other workstreams

The findings of an original systematic review informed the development of the SUPA intervention in WS1 and the design of WS2/3, including the decision to provide support at the time at which participants initiated ART. Updating and extending the review with a meta-analysis helped to contextualise the findings of the SUPA trial.

Appendix 15 Beliefs about antiretroviral therapy as predictors of side effects (analysis of historical data)

Study publication

Horne R, Chapman S, Glendinning E, Date HL, Guitart J, Cooper V. Mind matters: treatment concerns predict the emergence of antiretroviral therapy side effects in people with HIV. *AIDS Behav* 2019;**23**:489–98. https://doi.org/10.1007/s10461-018-2239-6

Study abstract

The aim of this analysis of historical data was to determine whether or not patients' pre-treatment beliefs about ART predict the subsequent reporting of side effects. Data were collected as part of a prospective, 12-month follow-up study. Of 120 people starting ART, 76 completed follow-up assessments and were included in the analyses. Participants completed validated questionnaires assessing their beliefs about ART, beliefs about medicines in general, perceived sensitivity to adverse effects of medicines, depression and anxiety before initiating ART and after 1 and 6 months of treatment. Adherence was assessed at 1, 6 and 12 months. Pretreatment concerns about ART were associated with significantly more side effects at 1 month ($p < 0.05$) and 6 months ($p < 0.005$). Side effects at 6 months predicted low adherence at 12 months ($p < 0.005$). These findings have implications for the development of interventions to support patients initiating ART by providing a mechanism to pre-empt and reduce side effects.

Appendix 16 Ancillary study 6: linking self-reported adherence with Medication Event Monitoring System data

Aim

The aim of this study was to examine associations between electronic monitoring of adherence, self-reported adherence and viral load in the SUPA trial.

Methods of data collection and analysis

This analysis included all SUPA trial participants (n = 150) who had available MEMS data, reported viral load at 6 months and started ART on or before their baseline visit. This was carried out to ensure that adherence data were complete for all three periods. Adherence was measured using electronic monitors (MEMS) and self-reports (MARS-5).

Key findings

Overall, 124 participants had a reported a MARS value at month 3 (median 25, IQR 24–25). Of these, 105 (84.7%) reported a MARS score of > 24 (labelled as high adherence – MARS-5). In total, 68 (54.8%) of the group had an average MEMS adherence of > 80% (labelled as 'high adherence – MEMS'). Agreement between the groups was defined as having high adherence using MEMS and MARS (*Table 42*). A total of 66 out of 68 (97.1%) participants were classified as having high adherence on MEMS (average over months 1–3) and had adherence scores ≥ 24 according to MARS at 3 months, whereas 17 out of 56 (30.3%) participants were classified as having low adherence on MEMS and had adherence scores < 24 according to MARS. MEMS values were significantly higher in each month in those with a MARS score of ≥ 24 than in those with lower scores (see *Table 27*).

TABLE 42 Average adherence (MEMS) stratified by viral load at 6 months

Month 6 viral load (copies/ml)	*n* (%)	Average adherence (MEMS), median (IQR)			
		Month 1	Month 2	Month 3	Months 1–3
All participants					
> 50	29 (19.3)	63.2 (20.2–82.6)	90.0 (18.3–95.0)	86.7 (3.3–95.0)	73.1 (18.3–89.8)
≤ 50	121 (80.7)	80.0 (44.8–96.6)	90.0 (60.0–98.3)	90.0 (50.0–100.0)	82.1 (52.6–92.2)
p-value		0.09	0.19	0.17	0.08
With a value within 42-day window (n = 61)					
> 50	15 (24.6)	64.4 (19.0–96.6)	90.0 (3.3–98.3)	90.0 (0–95.0)	73.1 (16.2–95.6)
≤ 50	46 (75.4)	82.6 (48.3–96.6)	91.5 (66.7–100.0)	91.1 (56.7–100.0)	85.9 (67.0–96.2)
p-value		0.21	0.28	0.25	0.17

Limitations

The conclusions from this study are limited by the difficulties inherent in the measurement of adherence. Self-report measures, such as the MARS, may overestimate adherence because of social desirability bias, whereas MEMS may underestimate adherence because of patients taking their medication out of the pill container, for example, when travelling.

Appendix 17 Reflections on the use of Medication Event Monitoring System caps

Multiple methods to measure adherence have been used in the existing literature, including patient self-report, pill count by researchers or pharmacy staff, pharmacy records and electronic monitoring. Each method has limitations in ascertaining accurate measurement of adherence, although electronic monitoring has been described in the literature as 'a gold standard' of adherence assessment[85] because of its intended purpose to track adherence 'as it occurs' daily, rather than cumulative adherence or at random checks. It is also meant to measure adherence behaviour, rather than only the adherence outcome.

The MEMS TrackCap (AARDEX Ltd, Union City, CA, USA) is one of these electronic tracking methods. MEMS caps contain a computer chip that digitally records when medication bottles are opened to dispense tablets. The caps can then be read by a computer attachment, which downloads daily data on whether or not the cap has been opened and at what time. This is to allow the researcher to determine if the patient is taking the right number of dosages, properly spacing the dosages to maintain appropriate therapeutic 'coverage', and identify any drug 'holidays'.

Despite its intended purposes, it remains an indirect method of adherence as actual ingestion of the medication cannot be confirmed from the electronic data. For example, a patient may have intentionally opened the bottle and binned the medication or may have taken the medication out of the bottle for later use but not actually taken it as planned. Accurate adherence measurement relies on accurate usage from the patient. Unfortunately, clinicians and researchers have experienced challenges in the implementation of electronic monitoring, and its validity as a 'gold standard' has been questioned. For example, reports by Bova *et al.*[86] and Wendel *et al.*[87] on the adherence to ART found inconsistencies in the use of the MEMS caps, including multiple dosing during a single opening of the MEMS bottle, missed dosing, and/or MEMS opening without taking the medication.

The SUPA study encountered multiple limitations with the use of MEMS caps, which may have precluded significant conclusions about the effectiveness of the interventions. These challenges have been grouped below according to (a) the patient's perspective, (b) the researcher's perspective and (c) the clinical perspective.

Challenges from the patients' perspective

The reliability and validity of MEMS caps ironically rely on adherence to the adherence monitor. The SUPA study sought to recruit patients at risk of suboptimal adherence, with various practical and perceptual concerns about taking medicines, which also meant at risk of practical and perceptual barriers to using MEMS caps appropriately.

The use of Medication Event Monitoring System increased the perceived risk of involuntary status disclosure

As discussed in our findings from WS1, study 1, many patients are concerned that HIV medication bottles will disclose their status to others. MEMS caps are very large, sometimes even the size of the actual medication bottle, which further increases the perceived risk of involuntary disclosure. In addition, many patients decant their tablets from the actual ART bottle to a new bottle, such as for vitamins, to hide the fact that they are taking medicine for HIV. The caps often did not fit these less alarming bottles, which prevented patients from using a strategy which would decrease the perceived risk of unwanted HIV status disclosure. As such, it is very likely that patients abandoned MEMS caps use in favour of using strategies that would decrease risk of disclosure.

Let us consider a case of one of the trial patients: the patient lived in a communal home with many residents who had recently immigrated from West Africa, and one of the house 'rules' was that anyone with HIV would be evicted. For this patient, ART itself increased the risk of disclosure and threatened their access to shelter, and MEMS caps would further compound this issue. This was not an isolated case in the trial, with many patients reporting difficulties in using the caps or the researcher suspecting there were practical factors at home making the use of the caps difficult. These were the

patients in most need of intervention support, and measuring the effect of the intervention on adherence was simply not possible. Here, the use of MEMS caps is not a gold standard as it cannot accomplish its intended purpose. Patient issues around the use of MEMS caps will have given incorrect adherence data precluding a useful conclusion about the effectiveness of the intervention.

Use of Medication Event Monitoring System caps was a practical barrier to taking antiretroviral therapy

Normal life means that patients have to work, attend social outings, go on holidays, etc., meaning that often ART needs to be taken out of the comfort of their home. The medicine bottles are already too big to carry around, so, often, patients will keep their ART tablets in a keychain capsule, wallet, etc. MEMS caps make the bottle even bigger, and it cannot then fit in many bags. Many patients reported taking out tablets from their bottles for days at a time, or simply for taking later in the day, even though they were aware that this would compromise trial results. Unfortunately, there is no way of knowing if the tablets were actually ingested as planned, and this is likely to have had an impact on the adherence scores.

MEMS caps also made it impossible to utilise some adherence-promoting strategies. For example, MEMS caps precluded the use of Dosett boxes, where either the patient or the pharmacist puts tablets in a compartment for each day of the week. This meant that the patients who chose to use their MEMS caps could not use these boxes, or that patients simply discontinued the use of MEMS caps so that they could use the Dosett boxes as a memory aid.

Using Medication Event Monitoring System caps across multiple regimens was not practical for patients

Some patients who are on multitablet regimens decant all of their medicines into one bottle, as often the tablets look quite unique, and the patients can tell the difference between the different regimens and pick them out of the bottle (see *Appendix 17*). Although this goes against advice from pharmacists, as it may lead to error or may have a negative impact on the medicines' quality, we suspect that some patients decanted all their regimens in one bottle, which would explain why they would have a certain level of adherence to a regimen component (the one where all tablets were decanted) and zero adherence to others.

Medication Event Monitoring System caps were impossible to use because of lifestyle circumstances

Some patients in our trial were incarcerated or became homeless and, as such, had to stop using MEMS caps.

Challenges from the researchers' perspective

Medication Event Monitoring System caps do not fit well within regular clinical care and medication dispensing

Once a patient is stable with a suppressed viral load, ART will be given as longer than a month's supply in the bottles from the manufacturer. This means that once the bottle is empty, a new bottle needs to be opened, and the patient must place the MEMS caps on the new bottle and discard the standard cap. This is a big ask for patients, especially when dealing with patients at higher risk of lower adherence who are less interested in their treatment in general. In the SUPA programme, we scheduled calls when we knew the bottle would be coming to an end and remind them to switch the cap. This was time-consuming, often the patient could not be reached as they did not pick up the telephone, their telephone was disconnected, etc., and often the patient did not follow the instructions once they were reached by the researcher.

Medication Event Monitoring System caps have to be returned to download data

One of the biggest problems with MEMS caps is that patients have to bring them back for reading the data, and often patients failed to return them despite many reminders.

The caps were often lost by patients, which means that for long periods of time in between study visits, no data recordings took place. The caps had to be replaced, which was expensive as they cost €90. Patients who tended to lose their caps once would lose them again.

Medication Event Monitoring System caps have to be used for long periods of time in which malfunctioning cannot be checked

Sometimes the caps simply malfunctioned and did not record any data for long periods of time, which was only discovered when researchers attempted to download the trial data at study visits.

Challenges from the clinical perspective

The use of Medication Event Monitoring System caps is not appropriate for current models for trials

One of the major problems with MEMS caps is that their use is not suited to a typical clinical trial model, and pharmacies are often reluctant to take part in studies using the caps. Five potential SUPA sites pulled out of the study when the pharmacy department blocked the study because of the time-consuming nature of dispensing the medicines and concerns about drug stability (which are addressed by the manufacturer of MEMS, but not by specific drug companies).

The use of Medication Event Monitoring System caps has hidden costs

Once patients start ART and are stable with an undetectable viral load, they are most of the time transferred to ART home delivery, which reduces the cost of dispensing. This means that any study using MEMS cannot put their patients on home delivery, and, as such, is costly to the relevant trust.

Medication Event Monitoring System caps are not suitable for all medicines produced in the UK

Some of the ART regimens are bottled in bottles that do not fit the MEMS caps. This means that tablets will have to be decanted into standard high-density polyethylene bottles. This adds time and expense to the dispensing process. In addition, some of the ART bottles contain desiccants, which means that they cannot be transferred into a standard bottle.

Appendix 18 Additional analyses comparing trial participants with trial-eligible patients who declined (trial acceptors vs. trial decliners)

The SUPA study involved a two-stage process, where everyone starting ART was invited to take part in an observational study. They were enrolled in the observational study, and their risk of non-adherence was assessed at enrolment using the BMQ. If their score indicated a high risk of non-adherence (i.e. a BMQ necessity score ≤ 3 and/or concerns score ≥ 3) they were invited to participate in stage 2 – the SUPA trial.

As part of the informed consent process, participants may be eligible for the trial but decline to participate. At this point, they would be invited to remain in the observational arm and followed up for 12 months, as per the observational protocol.

We wanted to compare those who declined with those who participated as we wanted to examine if there are differences in:

- baseline characteristics between the interventional acceptors and the interventional decliners
- beliefs at 0, 3, 6 and 12 months between the interventional acceptors and the interventional decliners.

Methods

Decliners were included if they had a baseline necessity score BMQ necessity score ≤ 3 and/or concerns score ≥ 3.

Results

In total, 92 people were eligible for the trial and declined to participate. The demographic characteristics of trial acceptors and trial decliners are shown in *Table 28*.

We found a significant difference between perceptions of ART over the 12 months' follow-up. At baseline, both cohorts were sceptical about ART and were judged to be at a high risk of non-adherence (based on BMQ-ART scores). However, trial decliners had significantly more negative perceptions of ART than trial acceptors, with significant differences in ART necessity beliefs and ART concerns at baseline and at each follow-up (*Table 43*).

It is interesting that perceptions of ART became more positive over time in both arms of the trial and also in the trial decliner cohort. However, the trial decliners remained significantly more negative than the trial acceptors (both arms combined) at 12 months. Comparison of BMQ-ART scores between the trial acceptor cohort (negative BMQ-ART scores indicating a high risk of non-adherence) and the cohort who were not eligible for the trial (positive BMQ-ART scores indicating low risk of non-adherence) produced an interesting result. Perceptions of ART among trial acceptors had become progressively more positive. By 12 months, they had equally positive beliefs about ART as those who were deemed not to require the intervention because they were accepting of ART and were motivated to adhere.

This effect was clinically significant. Clinical outcomes within the trial acceptors cohort (high risk of non-adherence) were similar to those in the low risk of non-adherence cohort (*Table 44*). At the 12-month follow-up, trial decliners were significantly less likely to have achieved viral load suppression than trial acceptors (67% vs. 85%) (*Table 45*).

TABLE 43 Demographics of the trial acceptors and the trial decliners

Characteristic	Trial acceptors (*n* = 204)	Trial decliners (*n* = 92)	*p*-value
Age (years), mean (SD)	40.0 (11.9)	40.7 (11.7)	0.66
Sex, *n* (%)			
Female	70 (34)	40 (45)	**0.08**
Male	134 (66)	49 (55)	
Transgender	0 (0)	0 (0)	
Ethnicity, *n* (%)			
White	76 (37)	26 (28)	**0.025**
Black African	67 (33)	37 (40)	
Black other	38 (18)	14 (15)	
Other	21 (10)	11 (12)	
Not stated	2 (1)	4 (4)	
Years in the UK, *n* (%)			
< 5 years	24 (12)	12 (13)	**0.002**
≥ 5 years	110 (54)	44 (49)	
N/A – born in the UK	68 (33)	27 (30)	
Not stated	2 (1)	7 (8)	
Sexuality, *n* (%)			
MSM	48 (24)	25 (28)	0.38
Other/not stated	156 (76)	63 (72)	
Marital status, *n* (%)			
Married/in partnership	60 (29)	15 (34)	**0.023**
Single/separated	130 (64)	20 (47)	
Widowed/other	14 (7)	8 (19)	
Education, *n* (%)			
Basic/school	43 (21)	13 (30)	**< 0.001**
Higher education	160 (78)	24 (55)	
Not stated	1 (1)	7 (16)	
Employment, *n* (%)			
Working	113 (55)	33 (65)	**< 0.001**
Not working	80 (39)	12 (24)	
Other/not stated	11 (5)	6 (12)	
Clinical diagnoses, *n* (%)			
AIDS	26 (13)	3 (3)	**0.013**
Time since HIV diagnosis, *n* (%)			
< 1 year	145 (71)	59 (66)	0.49
1–5 years	33 (16)	14 (16)	
> 5 years	26 (13)	16 (18)	

Note
Bold indicates $p < 0.05$.

TABLE 44 Mean difference between 3, 6 and 12 months and baseline in those who accepted and declined to participate in the trial

Mean difference	Follow-up	Trial acceptors (*n* = 204), mean (SD)	Trial decliners (*n* = 92), mean (SD)	*p*-value
Between baseline necessity score (3, 6 and 12 months – baseline)	3 months	0.3 (0.5)	0.09 (0.4)	0.0015
	6 months	0.4 (0.5)	0.1 (0.4)	0.0002
	12 months	0.4 (0.5)	0.2 (0.5)	0.0005
Between baseline concerns score (3, 6 and 12 months – baseline)	3 months	−0.6 (0.7)	−0.5 (0.6)	0.3
	6 months	−0.7 (0.7)	−0.5 (0.7)	0.02
	12 months	−0.6 (0.7)	−0.4 (0.7)	0.04
Between baseline necessity concern differential score (3, 6 and 12 months – baseline)	3 months	0.9 (0.8)	0.6 (0.7)	0.008
	6 months	1.1 (0.9)	0.6 (0.8)	0.0001
	12 months	1.1 (0.9)	0.6 (0.9)	0.0003

TABLE 45 Cluster of differentiation 4 counts and virological suppression in those who participated in the trial and those who declined

Measurement	Follow-up	Number of participants	Trial acceptors (total *N* = 204)	Number of participants	Trial decliners (total *N* = 92)	*p*-value
Proportion with an undetectable viral load, *n* (%)	3 months	101	72 (69)	46	29 (63)	0.83
	6 months	76	59 (78)	33	22 (67)	0.23
	12 months	150	127 (85)	57	38 (67)	0.004
CD4 T-cell count, median (IQR)	Baseline	202	355.5 (160–538)	69	338 (152–521)	0.36
	3 months	175	401 (250–627)	38	377.5 (256–586)	0.32
	6 months	168	439.5 (269–630)	15	320 (243–474)	0.28
	12 months	153	479 (307–670)	43	418 (30–556)	0.38

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