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Extended Research Article

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

Rob Horne,[1*] Caroline Sabin,[2] Trudie Chalder,[3] Vanessa Cooper,[1] Lucy Campbell,[4] Elizabeth Glendinning,[1] Iris Mosweu[5] and Paul McCrone[6] on behalf of the SUPA Investigators

[1]Department of Practice and Policy, Centre for Behavioural Medicine, University College London School of Pharmacy, London, UK
[2]Centre for Clinical Research, Epidemiology, Modelling and Evaluation, Institute for Global Health, University College London, London, UK
[3]Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
[4]HIV Research Centre, King's College London, London, UK
[5]Department of Health Policy, London School of Economics, London, UK
[6]School of Health Sciences, Faculty of Education, Health and Human Sciences, University of Greenwich, London, UK

[*]**Corresponding author** r.horne@ucl.ac.uk

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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Scientific summary

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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

Workstream	Objectives	Studies	Outputs
WS1: intervention development	1. Identify culturally specific beliefs and other factors influencing uptake and adherence to ART that has not emerged in previous research	Study 1: qualitative interviews with 52 participants	IPA paper
			Perceptions paper
	2. Refine our existing methods for eliciting and measuring the salient perceptual and practical factors influencing uptake and adherence to ART	Study 2: refinement of the BMQ incorporating findings from study 1	Adapted BMQ
	3. Develop an intervention (including intervention manuals, materials and therapeutic intervention) to increase uptake and adherence to ART	Study 3: development of CBT-based intervention materials and animation	Intervention manual
			Intervention animation
WS2: feasibility, acceptability of the SUPA intervention	4. Determine the feasibility and acceptability of the intervention	Study 4: nested quantitative feasibility study and additional qualitative interviews with study participants	See *Appendix 6*
WS3: RCT efficacy of the SUPA CBT-based intervention	5. Evaluate the efficacy of the intervention for increasing ART uptake and adherence	Study 5: RCT looking the efficacy of the SUPA intervention	Primary outcome paper
WS4: economic analysis	6. Evaluate the efficacy of the intervention for increasing ART uptake and adherence	Study 6: substudy 1a – systematic review of economic evaluations of ART adherence interventions	Systematic review paper
		Study 6: substudy 1b – a trial-based cost-effectiveness analysis of the SUPA intervention compared with CAU	Primary outcome paper – economic section
		Study 6: substudy 1c – a simulation model of the long-term cost-effectiveness of the intervention	Modelling paper
WS5: prepare for implementation	7. Implementation within the NHS	No studies done	
WS6: ancillary studies	Additional WS including further ancillary studies	AC1: patients' perceptions of standard care	See *Appendix 11*
		AC2: ART perceptions and treatment outcomes in HIV-positive patients starting ART to protect their partners (TasP) vs. clinical need	See *Appendix 12*
		AC3: the level of ART adherence required to achieve virological suppression in treatment-naive patients	See *Appendix 13*
		AC4: a systematic review and meta-analysis examining the content of effective adherence interventions	Systematic review of interventions to support uptake and adherence to ART
		AC5: beliefs about ART as predictors of side effects (analysis of historical data)	Side effects paper
		AC6: associations between self-reported adherence and electronic monitoring of adherence	See *Appendix 16*

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).

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

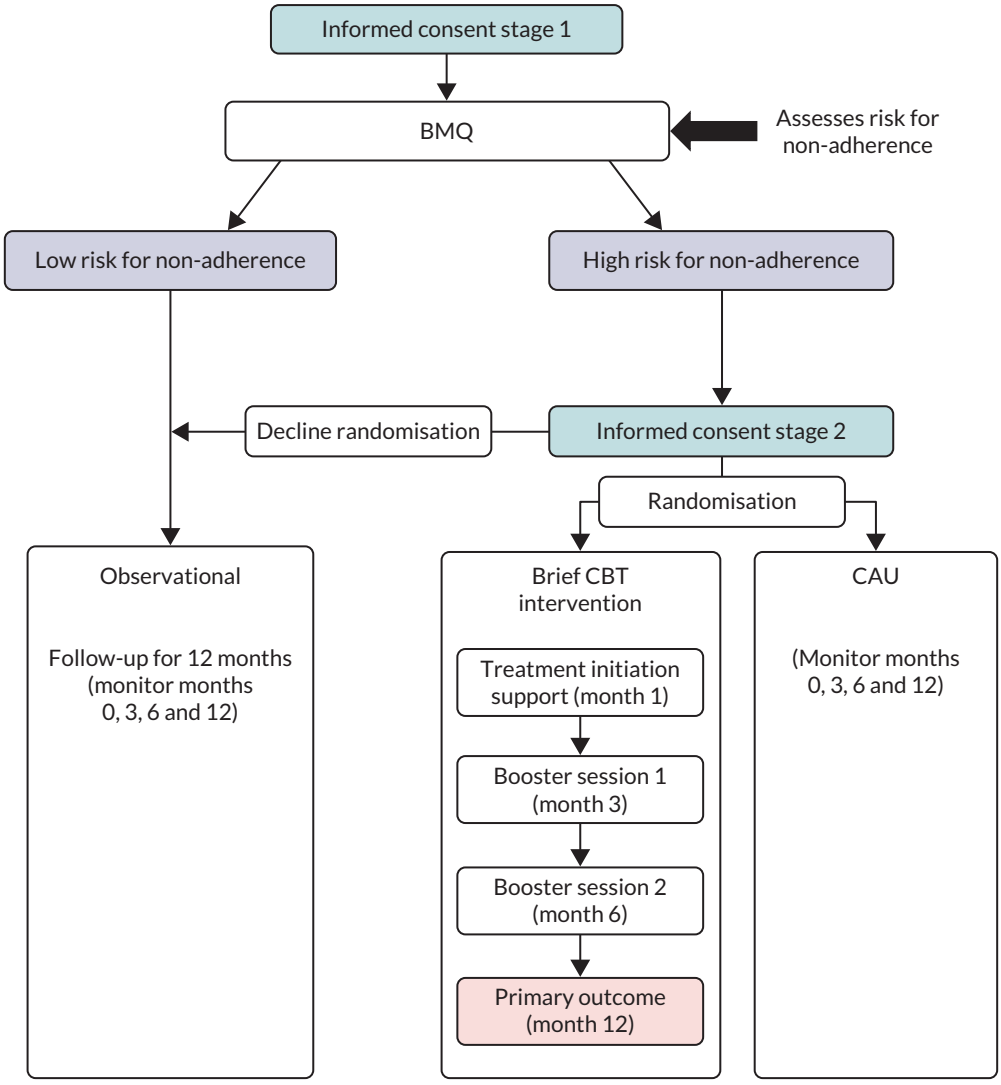

FIGURE b The SUPA study trial design.

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.

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