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## Individualised motivational counselling to enhance adherence to antiretroviral therapy is not superior to didactic counselling in South African patients: Findings of the CAPRISA 058 randomised controlled trial

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### Abstract

Concerns that standard didactic adherence counselling may be inadequate to maximise antiretroviral therapy (ART) adherence led us to evaluate more intensive individualised motivational adherence counselling. We randomised 297 HIV-positive ART-naïve patients in Durban, South Africa, to receive either didactic counselling, prior to ART initiation (n=150), or an intensive motivational adherence intervention after initiating ART (n=147). Study arms were similar for age (mean 35.8 years), sex (43.1% male), CD4+ cell count (median 121.5 cells/ $\mu$ l) and viral load (median 119 000 copies/ml). Virologic suppression at nine months was achieved in 89.8% of didactic and 87.9% of motivational counselling participants (risk ratio [RR] 0.98, 95% confidence interval [CI] 0.90-1.07, p=0.62). 82.9% of didactic and 79.5% of motivational counselling participants achieved >95% adherence by pill count at six months (RR 0.96, 95%CI 0.85-1.09, p=0.51). Participants receiving intensive motivational counselling did not achieve higher treatment adherence or virological suppression than those receiving routinely provided didactic adherence counselling. These data are reassuring that less resource intensive didactic counselling was adequate for excellent treatment outcomes in this setting.

## Keywords

antiretroviral therapy adherence; IMB; motivational interviewing; HIV

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## Introduction

In 2007, at the start of this study, it was estimated that South Africa had 5.7 million human immunodeficiency virus (HIV)-infected people (1) with approximately 1700 new infections daily (2) highlighting the growing importance of determining the best way to optimise HIV treatment. Since the introduction of combination antiretroviral therapy (ART), HIV disease has changed from being a predictor of a certain death, to a manageable chronic illness if the treatment is taken as prescribed (3, 4). This means ensuring the highest levels of treatment adherence, usually at least 95% of medication taken as prescribed (5-7).

Due to the high burden of both tuberculosis (TB) and HIV in South Africa, the development of active TB is often the first sign of underlying HIV infection and an important trigger for HIV testing and possible ART initiation (8). This was thought to be an efficient patient identification strategy at a time when the voluntary HIV testing rate among otherwise healthy people was very low (9). There were concerns that integrating HIV and TB treatment, with higher pill burden and potential for side effects, might require additional adherence support, and require tailored adherence motivation counselling as TB treatment is for a defined period of time whereas HIV requires life-long therapy. In the light of this, the Centre for the AIDS Programme of Research in South Africa (CAPRISA) established a programme of research into integrating TB and HIV treatment and care in 2002 in Durban, South Africa.

## Interventions to enhance adherence to ART

Early reviews were key in the conceptualisation of the current study. An initial overview of published adherence research indicated that adherence was inconsistently measured, and that most studies were conducted without control groups which resulted in inconclusive evidence (10). A further review of 21 intervention studies up to the end of January 2003, concluded that only four studies were randomised controlled trials (RCTs), and that most were underpowered but that some studies suggested positive outcomes, which justified additional research (11). A research synthesis of 24 intervention trials between 1996 and 2004 (12) confirmed that interventions that targeted participants with known adherence problems had a larger effect than those that did not.

A major review of RCTs published between 1996 and 2005 identified 19 studies that looked at behavioural interventions to enhancing adherence to ART (7). In terms of interventions, 55% used one-on-one counselling, and 16% used group counselling, mostly delivered by health practitioners such as doctors or nurses (47%) and mental health professionals (26%), and 53% of the studies used trial staff rather than routine clinical staff. Data from 14 RCTs included were analysed assessing the effect of adherence interventions on viral load between two weeks and six months post-intervention. It was found that 62% of the intervention arm participants controlled their virus, versus 55% of the participants in the control arm. This

gives a fairly weak aggregate effect size (OR=1.25, 95%CI 0.99-1.59, N=1247). Although the evidence against the null was not conclusive, the percentage of participants in the intervention arm that had undetectable viral load versus those in the control arm could translate into significant financial and health-systems benefits.

This review also reported 18 trials where the outcome was expressed as effect on adherence (the majority of studies measured adherence by self report, between two weeks and six months post-intervention), and in this case 62% of participants in the intervention arm and 50% of participants in the control arm achieved at least 95% adherence (7). This resulted in stronger evidence against the null and a stronger aggregated effect size (OR=1.5, 95%CI 1.16-1.94, N=1633). This larger effect for adherence is not likely to be due to unreliable measurement by self-report, as effect sizes were actually larger in studies that used more objective measures (e.g. electronic monitoring). Thus, participants in the intervention arm were 1.5 times more likely to be 95% or more adherent, and 1.25 times more likely to achieve suppressed viral load than participants in the control arm. This effect tended to be greater in studies that provided information on ART and interactive discussions regarding the cognitions, motivation, and participant expectations. Although it is inherently problematic to combine the diverse outcomes from studies with very different interventions and designs, this was the first attempt to synthesise the RCT outcome data and it was cautiously optimistic about the ability of behavioural interventions to enhance ART and strongly in favour of additional, rigorous assessment of adherence interventions by RCT, especially in Africa (13).

During the development of the intervention for the current study, we made a site visit to Harlem Hospital, and the 'medication manager' adherence intervention developed and being tested there was observed, and the approach modified and assimilated into the intervention being developed for our study (14). The medication manager provided personalised adherence support to participants, using a standard assessment protocol to identify and address any deficits in adherence information, motivation and behavioural skills. The primary endpoint was time to first virologic failure, defined as the first plasma viral load above 2000 copies/ml on or after the 4<sup>th</sup> monthly follow-up visit. In the main intention to treat analysis, the medication manager group had 13% lower rate of first virological failure, but this was not statistically significant. Participants in the medication manager arm also had significantly raised CD4 counts (mean difference of 22.5 cells/ $\mu$ L higher), and better long-term adherence by self-report. This study provided some evidence that the approach of using a theory-based model to identify and correct specific deficits in information, motivation and behavioural skills with counselling techniques based on motivational interviewing was feasible, and showed promise in enhancing adherence and treatment outcomes on ART.

In summary, the literature indicated that counselling interventions, based on models of behaviour change, that provided participant-specific problem-solving and interactive sessions, seemed to be most likely to have an effect on improving ART adherence (7, 10, 11, 15, 16). The motivation, information and behavioural skills model tied to motivational interviewing had been used and evaluated in the USA in ART adherence, with some preliminary indications that this may be a fruitful avenue for further research (14, 17-19).

ART adherence in the context of TB treatment was identified as a key data gap that needed to be addressed, as integrated treatment was not the recommended standard of care.

To address our concerns about the adequacy of standard didactic counselling in our setting, we conducted a RCT to assess whether intensive individualised motivational adherence counselling led to better adherence and treatment outcomes than standard didactic counselling in newly diagnosed HIV infected patients initiating antiretroviral therapy.

## Methods

### Study design and setting

The study was a parallel group (1:1 ratio), open-label randomised controlled trial, with concealment of allocation from the person conducting the enrolment. It was conducted at the CAPRISA eThekweni HIV-TB clinic, in Durban, South Africa. This research facility adjoins to the Prince Cyril Zulu Communicable Diseases Centre, one of the biggest TB outpatient treatment clinics in South Africa.

### Participants

Between August 2007 to February 2009, we recruited participants 18 years of age or older and eligible to initiate ART (at the time, a CD4 T-cell count of 350 or less). The majority of these participants were also included in a study of the optimal time to initiate ART in patients who were receiving TB treatment (20, 21). Just over 53% of participants were receiving TB treatment at the time of their participation in this study, and a further 25.6% had completed TB treatment within 4 weeks previous to initiation on ART (described further in Table 1 of the results).

### ART regimen

The ART regimen used was selected to be compatible with TB treatment (21). The first line regimen offered, free of charge, was a once-a-day regimen consisting of enteric-coated didanosine (250mg if <60kg, 400mg if >60kg), lamivudine 300mg, and efavirenz 600mg (or, nevirapine (200mg twice a day) in the case of pregnancy).

### Adherence counselling

TB treatment adherence support was provided separately from the HIV treatment programme. This TB treatment service was provided by the Department of Health, according to the provincial standard of care, and was not under the control or provision of study staff, although completion of the required number of TB drug doses and outcomes of TB treatment were assessed as part of the TB and HIV treatment integration studies underway at the clinic.

The standard HIV treatment adherence support counselling for this programme was delivered by a nongovernmental organisation, consistent with the requirements in the initial South African national guidelines for treatment provision for adolescents and adults (22), the World Health Organization (WHO) guidelines for scaling up ART in resource-constrained settings (23), and with the US Department of Health and Human Services guidelines (24).

The counselling focussed on treatment literacy, and was delivered in an educational, or didactic, style. The counselling was seen as essential for treatment readiness, and so focussed on preparation prior to ART initiation. No formal counselling post-initiation of ART was specified, although on-going monitoring of adherence was recommended. We were concerned that this approach to adherence support may become less effective over time, as counselling group size increased, and the didactic approach might be prone to rote repetition of information with inadequate engagement with the individual issues faced by patients<sup>1</sup>.

## Procedures

On determination of ART eligibility, all patients received two pre-initiation 20-45 minute didactic counselling sessions as standard at the clinic. At the time of the ART initiation visit, patients were consented, enrolled and randomised. The randomisation was set up by a statistician using a random number generator in SAS, and the randomisation codes contained in sequentially numbered, sealed opaque envelopes, stratified in blocks of four or six relative to time of TB treatment (described in the baseline characteristics table of the results). The didactic arm participants received the final 20-45 minute didactic counselling session only. The motivational counselling arm participants instead received the first 30-40 minute individualised motivational counselling session, and then the additional four individualised motivational counselling sessions at intervals up to six months after initiation of therapy (Figure 1). All participants were followed up to at least nine months on treatment. Participants still in care had viral load measures taken at 12 months. Adherence was assessed by clinic-based pill count at six months post-initiation of therapy.

**Content and delivery of the standard didactic counselling**—The standard didactic counselling consisted of three sessions. The first session covered stigma and discrimination, nutrition and taking control of the treatment regimen. The second session focused on HIV pathogenesis, routes of infection, HIV testing techniques, and a basic introduction to ART. The final session focused on information relating to ART, the drug regimen, the importance of adherence, side effects, and the importance of monitoring and the development of resistance. Due to the large numbers of participants expected to be enrolled into the treatment programme, with increasing pressure to meet the high treatment initiation targets, this counselling was designed to be delivered in groups if necessary. Two sessions could be provided on the same day, but not all three.

**Content and delivery of the individualised motivational counselling**—An individualised intensive motivational adherence counselling intervention was developed, using content based on the information, motivation and behavioural skills model (IMB) of adherence to ART (25-27), using counselling delivery techniques from motivational interviewing (MI) (28, 29). The counselling was designed to be provided exclusively on a one-to-one basis, using a client-centred rather than didactic approach. Counselling could be tailored to specific participant needs, promoting an experience that was supportive of individualised care.

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<sup>1</sup>We refer to patients in the treatment programme, and to participants when enrolled onto this study.

MI was developed initially to treat alcohol abuse, and it is amenable to brief counselling sessions (30). MI is directive in the sense that the counsellor pursues the goal of examining and resolving ambivalence about behaviour change, but also client-centred in that it was designed to elicit statements in favour of behaviour change from the clients themselves (29, 30). A review of trials of MI-based interventions in diverse settings, concluded that this approach was more effective than traditional advice giving (31). Although MI was not formally used in our study, the motivational counselling did use techniques based on this approach. For example, instead of informing participants about potential barriers to adherence, and associated solutions, the counsellors encouraged them to think about potential barriers to adherence in their own experience and encouraged participants to talk about, and opt for, solutions that they felt they could implement in their own lives. As the statements about barriers requiring potential behaviour change were made by the participants, and the solutions also suggested by them, these counselling sessions were expected to be self-motivating. Participants were more likely to take ownership of their adherence challenges and successfully enact solutions they had suggested.

According to the IMB model of HIV prevention, initiating and maintaining patterns of HIV preventative behaviour depends on individuals being well informed, highly motivated and in possession of effective behavioural skills, rather than solely on the possession of knowledge. Content for the individualised motivational counselling was identified from this model, specifically a version modified for ART adherence (27), a literature review of adherence barriers, reasons for non-adherence from our clinic patients, and interviews with adherence counsellors and pharmacy staff.

Information was provided on the regimen, correct dosing, identifying and coping with side effects, as well as key information on non-adherence and resistance. Personal motivation was enhanced through MI-based techniques. Social motivation was encouraged through managed disclosure, designed to bring about gradual and safe disclosure over the first six months of treatment. Specific behavioural skills were encouraged, including skills to ensure clinic visits were kept, integrating dosing into the routine of daily life, and for identifying and coping with side effects. Moderating factors like general psychological well being, unstable living conditions, and substance or alcohol abuse were address through referrals to appropriate services.

The content of the motivational counselling was displayed on table top flipchart folders in English and isiZulu, the main local language, with locally relevant imagery like a three legged cooking pot to aid understanding and retention, facing the participants. Counselling scripts, based on MI techniques, faced the counsellors. The slogans summarised key principles like “The Power of Three” (the regimen of three drugs) and “The System of Three” (three important strategies for taking the drugs correctly). Additional support materials included wall posters for summarising counselling content, symptom solution cards that included key slogans and side effect management strategies, ‘prescriptions’ for adherence that were participant-agreed commitments to behaviours necessary to adhere optimally, as well as a treatment plan card that included pictures of the drugs in the regimen and space for a concrete plan for integrating dosing into daily routine. The ‘prescriptions’

and treatment plan cards were prepared at the first counselling visit, and reviewed and amended over the course of the intervention.

Two health educators from the existing nursing staff were trained to administer motivational counselling. On the day of treatment initiation participants were counselled on preparing to take ART, especially identifying managing side effects, and this was followed up at week two with a session on adjusting to ART medications. At two and three months, sessions were conducted dealing with on-going treatment issues and managed disclosure. At month six, participants were counselled on lifelong therapy concerns.

In accordance with standard clinic practice, and essential to adequate standard of care, once initiated on treatment all participants could receive additional *ad hoc* counselling support, on the basis of increasing viral load, decreasing CD4 count, missing doses (either by self-report or pill count), or when the participants account of their treatment behaviour did not make sense. To provide this, the standard didactic counselling session three was repeated as required in both study arms.

### Study outcomes

The primary outcome was the proportion of participants with suppressed viral load (plasma viral load of <400 copies/ml, HIV-1 RNA-PCR – Roche Diagnostics) at nine months (range of eight to 10 months) post-initiation of ART. A secondary outcome looked at adherence by pill count over the previous inter-visit period at six months post-initiation of therapy. Pill count was expressed as a percentage of the pills taken as prescribed over the study visit interval (usually the previous 28 days), by assuming that all non-returned pills had been taken over the study visit interval. These data were verified from the clinic records based on previous study visit and drugs dispensed by the pharmacy. This measure was recorded at 6 months, as this was part of the counselling intervention study follow-up. Suppressed viral load at 12 months was assessed as an additional secondary outcome.

As early mortality is common in treatment programmes in this region (32, 33), deaths prior to three months were not considered as contributing to the primary outcome as they occurred too early for treatment adherence to have an impact, and these participants were excluded from all analyses. Participants who died after three months, but prior to nine months, were considered to have unsuppressed viral load in the analysis.

### Sample size and statistical analysis

The individualised motivational counselling was hypothesised to be superior as it was more intensive, and provided individually in a client-centred and participatory way. From data available during planning, we estimated that we would need at least 150 evaluable outcomes in each arm at 9 months, for the study to have 80% power to detect an absolute difference of at least 15% in suppressed viral load, estimating 65% suppressed in the didactic counselling arm, with a type 1 error of 5%.

As odds ratios exaggerate the magnitude of association for common events (34), and as viral load suppression was high in this study, the primary outcome was assessed using risk ratios with 95% confidence intervals (CIs). As no adjustment was necessary for the outcomes, no

regression model was needed to estimate the risk ratios. All analyses were performed using the STATA 11.0 statistical analysis program (College Station, Texas 77845, USA).

### Restricted and whole cohort analysis

In the first instance, each analysis was restricted to all participants with outcome data at six, nine and 12 months respectively, including those who died after three months who were considered to have unsuppressed viral load. To determine the impact of the lost, withdrawn from the treatment programme, or relocated participants, and those otherwise with missing data, whole cohort analysis was performed where those with no outcome data were assumed not to have confirmed suppressed viral load or adherence greater than 95%.

### Ethics

This study was approved by the Biomedical Research Ethics committees of the University of KwaZulu-Natal, Durban (E326/05), The London School of Hygiene and Tropical Medicine, London (5114), and, Columbia University, New York (IRBAAAC0202). The trial was registered Clinicaltrials.gov (NCT00408642) on the South African National Health Research Ethics Council (NHREC) trials register (DOH-27-0807-2004).

### Results

297 ART naïve patients were eligible and all consented to be enrolled, 150 randomised to the didactic and 147 in the individualised motivational counselling arm (Figure 2). All participants were followed up and analysed in the arms into which they were randomised. Baseline demographic and clinical characteristics were similar in both groups (Table 1).

#### Follow-up to nine months

Ten (3.4%) of the 297 participants died prior to three months and were excluded from all outcome analyses (Figure 2). Of the remaining 287, eight (2.7%) were lost to follow-up, three (1.0%) had withdrawn from the treatment programme, six (2.0%) had defaulted treatment, seven (2.4%) were known to have relocated and 11 (3.7%) were missing viral loads or had missed their visit. 250 (84.2%) had viral load measures, and two (0.7%) had died between three and nine months. 229 (77.1%) participants, 117 in the didactic and 112 in the motivational counselling arm, had recorded adherence measures at 6 months.

#### Intervention coverage

All participants in the didactic counselling arm had to have documented evidence of having completed the standard adherence support programme as this was a requirement prior to initiation on ART. Of the 131 participants from the individualised motivational counselling arm in follow-up for at least six months and, therefore, expected to have completed five sessions, 97.7% (128/131) completed at least three and 88.5% (116/131) completed all five sessions.

#### Ad hoc counselling support

During the course of the study there were 101 recorded instances of *ad hoc* adherence counselling for 49 study participants. 71 of these instances occurred in the 31 didactic

counselling participants, versus only 30 sessions in 18 of the motivational counselling participants (Mann-Whitney  $p=0.04$ ). One participant in the didactic counselling arm accounted for five of these sessions, and another for eight.

Reasons for repeat adherence counselling referral were captured in 99 of cases (Table 2). The most frequent reason given for referring a participant for *ad hoc* counselling was that the incorrect number of pills was returned at the study visit, slightly more frequent in the didactic counselling arm. Participants in the didactic counselling arm were also more than twice as likely to have been referred for poor knowledge of drug dosing instructions. However, there is no evidence that reasons for referral differed by counselling type (Fisher's exact  $p = 0.89$ ).

### Primary outcome: Suppressed viral load at nine months

A total of 252 participants were included in the restricted analysis; 250 with viral load measures at nine months, and two participants (one in each arm) who died between three and nine months. By nine months, suppressed viral load was achieved in 89.8% (115/128) of the participants in the didactic counselling arm and in 87.9% (109/124) of participants in the motivational counselling arm (RR=0.98; 95%CI 0.90-1.07,  $p=0.62$ )(Table 3). In the whole cohort analysis, suppressed viral load was achieved in 78.8% (115/146) of the participants in the didactic, and in 77.3% (109/141) of the motivational counselling arm (RR=0.98; 95%CI 0.87-1.11,  $p=0.76$ ).

In predetermined exploratory analysis (not shown here), adjustment for gender, age, employment status, education level, relationship status, point of HIV treatment initiation in relation to TB treatment, viral load and CD4 count by log binomial regression (35) had no major impact on the primary outcome of the trial.

### Secondary outcome 1: >95% adherence by pill count at six months

In the restricted analysis, 82.9% (97/117) of those in the didactic and 79.5% (89/112) of the individualised motivational counselling arm participants had a pill count greater than 95% (RR = 0.96; 95%CI 0.85-1.09,  $p=0.51$ ). In the whole cohort analysis, 66.4% (97/146) in the didactic arm versus 63.1% (89/141) of those in motivational arm had adherence >95% (RR = 0.95; 95%CI 0.80-1.13,  $p=0.56$ ).

### Secondary outcome 2: Suppressed viraemia at 12 months

As part of clinical follow-up of all retained participants, viral load data were available for 247 participants at 12 months post-initiation of therapy. Of those who provided data, 91.1% (112/123) in the didactic and 87.9% (109/124) in the motivational counselling arm had suppressed viral load (RR = 0.97; 95% CI 0.89-1.05,  $p=0.42$ ). In the whole cohort analysis, 76.7% (112/146) in the didactic versus 77.3% (109/141) in the motivational arm had suppressed viral load (RR = 1.0; 95% CI 0.89-1.14,  $p=0.91$ ).

## Discussion

In our trial, ART-naïve participants who received intensive individualised motivational counselling did not have improved viral suppression or adherence outcomes. Exposure to the motivational counselling was high, and poor coverage was not likely to be a factor. Viral suppression was high in both groups. While the 252 participants with treatment outcome at 9 months assessed in the restricted analysis was below the target of 300 evaluable participants, the whole cohort analysis of all 297 participants did not lead to materially different trial outcomes.

Treatment outcome data from the southern Africa region at the time of this study help to contextualise the results (Table 4). These data, mostly from other well-resourced treatment trials, seem to also show good outcomes. However, significant losses to follow up and early mortality are masked as most results are given for 'on treatment' participants. Where an intention to treat estimate is given, the result is much poorer (36), highlighting the good outcome in our current study. Including data from other southern African countries, which also includes real-world clinic data, indicate much lower estimates, especially in adolescent patients (37). One study from a rural setting in KwaZulu-Natal indicates that suppression rates have increased significantly from 2005, to 2007, most probably due to improved service provision and patient tracking procedures (38).

Factors other than the counselling are likely to have contributed to the good outcomes observed in the current study. It is possible that the repeated adherence assessments functioned as an adherence intervention in both arms by reminding participants of the importance of adherence. The tracking and tracing in place at the clinic required for trial follow-up reduced the likelihood of missed study visits and losses to follow-up. Tracking is key as it is a reminder for visits, ensures good refill rates, and also communicates to each participant that they are important. In this setting where access to treatment is difficult, the threat of losing access to treatment may have exerted a powerful motivational influence, as would direct experiences of morbidity and mortality in the community.

The clinic also provides a selection of other supportive activities, not formally considered to be part of the standard of care at the start of the study, but would have improved outcomes beyond what would be expected with didactic counselling alone. These include pillboxes to aid remembering to take pills, pill packet illustrations for illiterate participants and dosing instructions provided in the local language. *Ad hoc* counselling was provided to any participants who had clinical problems or adherence measures that concerned staff, as previously indicated. These sessions were significantly more likely to occur in the didactic counselling arm participants, which is not surprising as the motivational counselling participants were more likely to be scheduled for an individualised counselling session within which they would have dealt with any issues relating to poor adherence. Although it is possible that the *ad hoc* counselling meant that the control arm might be biased towards the null, this *ad hoc* counselling was part of the standard of care against which the intervention counselling would need to be an improvement, and so this was not unexpected, or avoidable. In addition to this, these sessions were only conducted in a relatively small

number of cases and participants, and the content remained didactic rather than motivational.

All of these factors are implementable in other settings, and would be amenable to study as adherence interventions in their own right. It is also possible that once the Hawthorne effect of being intensively followed up in this study wore off (39), that differences between the adherence strategies between the two arms might, over time, lead to greater sustained adherence and viral suppression in one of the arms, but this was not feasible to assess within the time frames of the current study.

Finally, the majority of participants were co-enrolled on a TB/HIV treatment study or were previous TB treatment patients. They remained a selected group of participants who had experience of, and likely success with, TB treatment adherence. It was considered probable during the conceptualisation of this trial that the burden of concurrent or sequential TB treatment and ART would negatively impact on treatment adherence. That the participants in this study have done so well is very promising in relation to the increased calls to integrate HIV and TB treatment, and the very large proportion of HIV patients this specific population represents in South Africa. These results support closer integration of HIV and TB treatment.

Major strengths of our study include the randomised controlled trial design, use of a theory-based intervention, the use of viral load as the primary outcome, and the trial setting of a TB clinic, which is a common entry point for HIV treatment in Africa. While adherence intervention studies report adherence and treatment outcomes for relatively short periods of time, often only for up to immediately after the completion of the intervention being tested (7, 40), this study assessed treatment outcomes up to 12 months post-initiation of treatment.

A limitation of this trial was that the high viral suppression rate following standard didactic counselling was not anticipated, the sample size calculation assumed only 65% suppression in the didactic arm, and the study was not powered for small incremental benefits of motivational counselling since substantial benefits would be needed from this intensive and more costly approach to warrant its implementation. A further limitation is that the setting of this trial in a TB clinic may reduce its generalizability.

Although this study showed that it is feasible to roll out this more intensive individualised motivational counselling in a resource-constrained setting, the counselling was designed to target issues with specific skills deficits at the individual level that may not have been appropriate for this setting. This intensive individualised motivational counselling approach is more likely to be necessary and effective where barriers to adherence are personal and motivational rather than structural, and in populations who experience many of these barriers. Identification of a population at high risk for non-adherence, or of participants who are experiencing difficulties, may be a more appropriate target for testing this intervention. This is likely to be even more important now that treatment provision has expanded so much outside of clinical research settings.

In summary, we conclude that the standard of care didactic counselling was adequate in the setting of our TB clinic, and that intensive personalised one-on-one motivational counselling

did not significantly improve adherence and treatment outcomes in this study. The finding that motivational counselling had no benefit over traditional didactic counselling in this setting is an important contribution to the literature on HIV treatment adherence counselling, as it does warn against implementing intensive individualised motivational counselling in settings where less resource intensive didactic counselling may be adequate. These study results empower health educators, nurses or community health workers to provide efficacious adherence support in a limited and structured counselling intervention.

## Acknowledgements

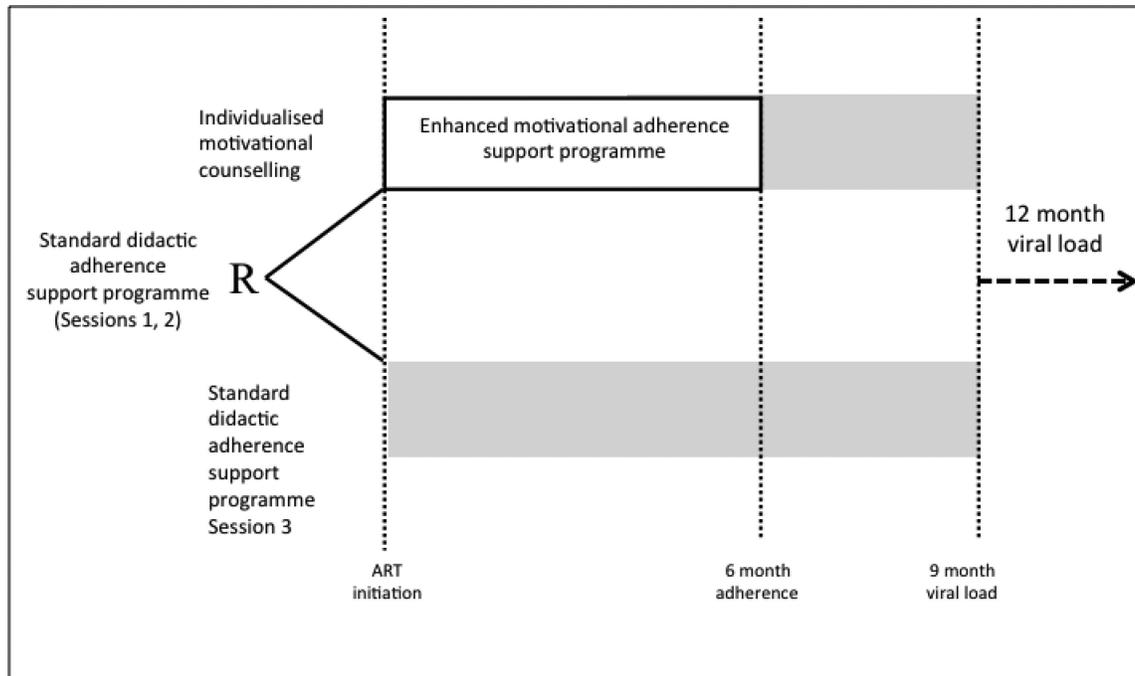
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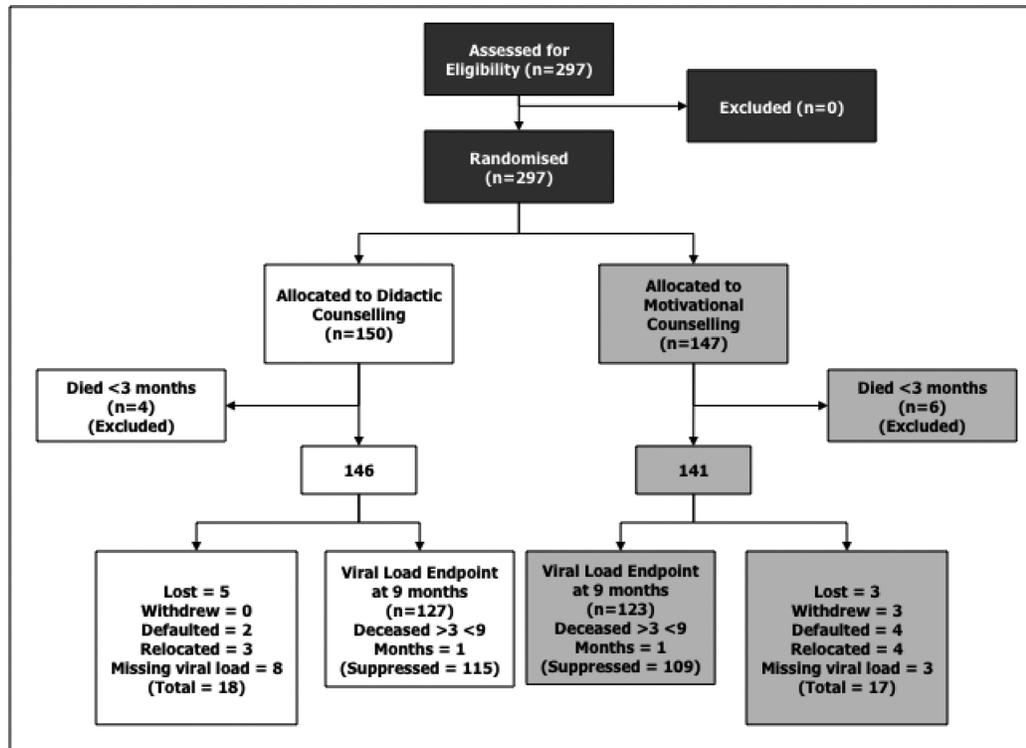
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**Figure 1.** Study schema; a parallel group RCT, ‘open label’/unblinded, with concealment of allocation from the person enrolling participants, and random assignment.



**Figure 2.**  
Participant enrolment and disposition at 9 months

**Table 1**

Characteristics and clinical features at time of enrolment, overall and by counselling arm

<b>Baseline factors</b>	<b>Overall (n=297)</b>	<b>Didactic counselling (n=150)</b>	<b>Motivational counselling (n=147)</b>
<b>Age, years (mean, SD<sup>~</sup>)</b>	35.8 (8.1)	36.5 (8.4)	35.2 (7.7)
Range	17.7 <sup>#</sup> - 59.8 n=296 <sup>*</sup>	17.7 <sup>#</sup> - 59.8 n=150	21.1 - 59.1 n=146
<b>Gender:</b>			
Male n (%)	128 (43.1%)	64 (42.7%)	64 (43.5%)
<b>Baseline CD4+ cell count, cells/<math>\mu</math>l (median, IQR<sup>~</sup>)</b>	121.5 (55-233) n=278	121.5 (55-231) n=142	117 (58-243) n=136
<b>Baseline viral load copies/mL (median, IQR)</b>	119 000 (27 650 – 433 500) n=280	135 853.5 (44 600 – 353 000) n=142	102 527 (16 600 – 521 000) n=138
<b>Marital status:</b>			
Single	266 (89.6%)	137 (91.3%)	129 (87.8%)
Married	22 (7.4%)	8 (5.3%)	14 (9.5%)
Widowed	9 (3.0%)	5 (3.3%)	4 (2.7%)
<b>Education:</b>			
Primary school and less	37 (12.7%)	20 (13.5%)	17 (11.8%)
Secondary school, not complete	135 (46.2%)	75 (50.7%)	60 (41.7%)
Secondary school complete and/or some tertiary	120 (41.1%) n=292	53 (35.8%) n=148	67 (46.5%) n=144
<b>Occupation:</b>			
Employed	171 (57.8%) n=296	82 (54.7%) n=150	89 (61.0%) n=146
<b>HIV treatment allocation<sup>%</sup>:</b>			
Early (within 4 weeks of starting TB treatment)	88 (29.6%)	44 (29.3%)	44 (30.0%)
Post-intensive TB (within 4 weeks of completing the intensive phase)	70 (23.6%)	33 (22.0%)	37 (25.1%)
Post-maintenance TB (within 4 weeks of completing TB treatment)	76 (25.6%)	39 (26.0%)	37 (25.1%)
Other (not specifically related to TB treatment)	63 (21.2%)	34 (22.7%)	29 (19.7%)

<sup>~</sup>SD = standard deviation, IQR = interquartile range<sup>#</sup> One participant was enrolled on the basis of self-reported age of 18, but was younger on confirmation. Ethics committee approved inclusion of data from this participant in the study.<sup>\*</sup> Numbers only shown when less than the column total. Data were extracted from participant clinic files and were not available for all participants<sup>%</sup> This refers to the timing of ART relative to TB treatment; 21.2% of participants did not currently have TB, or did not have a record of recently completed TB treatment

**Table 2**Reasons given for referral to *ad hoc* counselling, overall and by study arm

Arm:	Overall (n=99)	Didactic counselling (n=69)	Motivational counselling (n=30)
Incorrect number of doses returned	45 (45.5%)	33 (47.8%)	12 (40%)
Missed Clinic visits	21 (21.2%)	14 (20.3%)	7 (23.3%)
Self-reported missed doses	8 (8.1%)	5 (7.3%)	3 (10%)
Multiple reasons	8 (8.1%)	6 (8.7%)	2 (6.7%)
No doses returned	6 (6.1%)	3 (4.4%)	3 (10.0%)
Poor knowledge of drug dosing	6 (6.1%)	5 (7.3%)	1 (3.3%)
Treatment failure/drug resistance	2 (2.0%)	1 (1.5%)	1 (3.3%)
Other	3 (3.0%)	2 (2.9%)	1 (3.3%)

**Table 3**

Viral load and adherence outcomes for the study, restricted and whole cohort analyses

	Analysis	Didactic counselling	Motivational counselling	Risk Ratio (95% CI <sup>*</sup> )	p
Primary outcome					
% suppressed viral load at 9 months	Restricted	89.8% (115/128)	87.9% (109/124)	0.98 (0.90-1.07)	0.62
	Whole cohort	78.8% (115/146)	77.3% (109/141)	0.98 (0.87-1.11)	0.76
Secondary outcomes					
% suppressed viral load at 12 months	Restricted	91.1% (112/123)	87.9% (109/124)	0.97 (0.89-1.05)	0.42
	Whole cohort	76.7% (112/146)	77.3% (109/141)	1.0 (0.89-1.14)	0.91
% >95% adherence by pill count at 6 months	Restricted	82.9% (97/117)	79.5% (89/112)	0.96 (0.85-1.09)	0.51
	Whole cohort	66.4% (97/146)	63.1% (89/141)	0.95 (0.80-1.13)	0.56

\* Confidence Interval

**Table 4**

Treatment outcomes in southern Africa, including the current study, showing percentage with suppressed viral load

Study	Country	N	ARV Access, programme type	% VL <400 copies/ml
Orrell et al., 2003 <sup>30</sup>	South Africa	289	Free cART, clinical trials, no formal adherence intervention.	12 months: 70.9%
Coetzee et al., 2004 <sup>31</sup>	South Africa	254 244 165 72 34 (of 287 at baseline)	Free cART. Observational cohort, intensive adherence support with treatment supporters. Supported by Médecins Sans Frontières.	3 months: 88.1% 6 months: 89.2% 12 months: 84.2% 18 months: 75.0% 24 months: 69.7%
Michaels, 2005 <sup>32</sup>	South Africa	110	Free cART, observational cohort.	12 months: 89.0%
Barth et al., 2008 <sup>26</sup>	South Africa	609 ≥16 years 66 8m – 11yrs	Service fee, observational cohort.	12 months: 83.0% (on treatment) 12 months: 55.0% (whole cohort) 12 months: 71.0% (on treatment) 12 months: 53.0% (whole cohort)
Nachegea et al., 2009 <sup>27</sup>	Southern Africa (9 countries)	154 7622	Public sector HIV treatment programme.	<b>Adolescent (≤19 years)</b> 6 months: 63.0% 12 months: 45.7% <b>Adult (&gt;19 years)</b> 6 months: 69.3% 12 months: 62.1%
Boulle et al., 2010 <sup>33</sup>	South Africa	3932 2198	Free cART. Observational cohort. Update on Coetzee et al., 2004.	12 months: 87.6% 24 months: 86.7%
Mutevedzi et al., 2010 <sup>28</sup>	South Africa	3010	Rural KwaZulu-Natal, decentralised in public health clinics, free cART. 3 year observational cohort.	12 months: 76.7% (overall) 12 months: 78.5% (Sep. 07) 12 months: 58.6% (Mar. 05) ( <sup>#</sup> <25 copies/ml)
Current study	South Africa	297	Urban KwaZulu-Natal, free cART in RCT	9 months (whole cohort): Control: 78.8% Intervention: 77.3% 9 months (restricted cohort): Control: 89.8% Intervention: 87.9%

<sup>#</sup> Study has more stringent <25 copies/ml level for viral load suppression