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AIDS and Behavior

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 --Manuscript Draft--

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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/μl) 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.
Response to Reviewers:	Many thanks for the review of our article. We have revised the title to include reference to adherence to antiretroviral therapy, and have reviewed and cut down the introduction to make it flow better.

I hope and trust this will address all the final comments from the reviewers. Many thanks for the opportunity to submit and the review comments, which were very helpful in refining the paper for submission.

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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Running Head: RCT of motivational vs. didactic counselling in ART adherence

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6 **therapy is not superior to didactic counselling in South African patients: Findings**
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8 **of the CAPRISA 058 randomised controlled trial**
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12
13 **Abstract:**
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15 Concerns that standard didactic adherence counselling may be inadequate to maximise
16 antiretroviral therapy (ART) adherence led us to evaluate more intensive individualised
17 motivational adherence counselling. We randomised 297 HIV-positive ART-naïve
18 patients in Durban, South Africa, to receive either didactic counselling, prior to ART
19 initiation (n=150), or an intensive motivational adherence intervention after initiating ART
20 (n=147). Study arms were similar for age (mean 35.8 years), sex (43.1% male), CD4+
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26 p=0.51). Participants receiving intensive motivational counselling did not achieve higher
27 treatment adherence or virological suppression than those receiving routinely provided
28 didactic adherence counselling. These data are reassuring that less resource intensive
29 didactic counselling was adequate for excellent treatment outcomes in this setting.
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51 **Key Words:** antiretroviral therapy adherence, IMB, motivational interviewing, HIV
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Resumen

La inquietud de que la terapia didáctica de adherencia estándar pudiera ser inadecuada para maximizar la adherencia al tratamiento antiretroviral (ART), nos llevó a evaluar la terapia motivacional individualizada. Aleatorizamos 297 pacientes HIV-positivos sin ART previo en Durban, Sudáfrica, para recibir, ya sea terapia didáctica antes del inicio del ART (n=150), o terapia motivacional intensiva después de iniciado el ART (n=147). Los brazos del estudio fueron similares en edad (promedio 35.8 años), sexo (43.1% hombres), recuento de células CD4+ (mediana 121.5 células/ μ l) y carga viral (mediana 119 000 copias/ml). La supresión virológica a los nueve meses se logró en el 89.8% de los participantes que recibieron terapia didáctica y en 87.9% de aquellos en terapia motivacional (riesgo relativo [RR] 0.98, 95% intervalo de confianza [CI] 0.90-1.07, $p=0.62$). 82.9% de los participantes bajo terapia didáctica y 79.5% de los tratados con terapia motivacional alcanzaron >95% de adherencia por cuenta de píldoras a los seis meses (RR 0.96, 95%CI 0.85-1.09, $p=0.51$). Los participantes que recibieron terapia motivacional intensiva no mostraron una mayor adherencia al tratamiento o supresión virológica que aquellos bajo terapia didáctica rutinaria. Estos resultados son tranquilizadores ya que muestran que la menos costosa terapia didáctica es adecuada en este escenario.

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4 **Introduction**
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6 In 2007, at the start of this study, it was estimated that South Africa had 5.7 million
7 human immunodeficiency virus (HIV)-infected people (1) with approximately 1700 new
8 infections daily (2) highlighting the growing importance of determining the best way to
9 optimise HIV treatment. Since the introduction of combination antiretroviral therapy
10 (ART), HIV disease has changed from being a predictor of a certain death, to a
11 manageable chronic illness if the treatment is taken as prescribed (3, 4). This means
12 ensuring the highest levels of treatment adherence, usually at least 95% of medication
13 taken as prescribed (5-7).
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26 Due to the high burden of both tuberculosis (TB) and HIV in South Africa, the
27 development of active TB is often the first sign of underlying HIV infection and an
28 important trigger for HIV testing and possible ART initiation (8). This was thought to be
29 an efficient patient identification strategy at a time when the voluntary HIV testing rate
30 among otherwise healthy people was very low (9). There were concerns that integrating
31 HIV and TB treatment, with higher pill burden and potential for side effects, might require
32 additional adherence support, and require tailored adherence motivation counselling as
33 TB treatment is for a defined period of time whereas HIV requires life-long therapy. In
34 the light of this, the Centre for the AIDS Programme of Research in South Africa
35 (CAPRISA) established a programme of research into integrating TB and HIV treatment
36 and care in 2002 in Durban, South Africa.
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53 *Interventions to enhance adherence to ART*
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55 Early reviews were key in the conceptualisation of the current study. An initial overview
56 of published adherence research indicated that adherence was inconsistently measured,
57 and that most studies were conducted without control groups which resulted in
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4 inconclusive evidence (10). A further review of 21 intervention studies up to the end of
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6 January 2003, concluded that only four studies were randomised controlled trials
7
8 (RCTs), and that most were underpowered but that some studies suggested positive
9
10 outcomes, which justified additional research (11). A research synthesis of 24
11
12 intervention trials between 1996 and 2004 (12) confirmed that interventions that targeted
13
14 participants with known adherence problems had a larger effect than those that did not.
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20 A major review of RCTs published between 1996 and 2005 identified 19 studies that
21
22 looked at behavioural interventions to enhancing adherence to ART (7). In terms of
23
24 interventions, 55% used one-on-one counselling, and 16% used group counselling,
25
26 mostly delivered by health practitioners such as doctors or nurses (47%) and mental
27
28 health professionals (26%), and 53% of the studies used trial staff rather than routine
29
30 clinical staff. Data from 14 RCTs included were analysed assessing the effect of
31
32 adherence interventions on viral load between two weeks and six months post-
33
34 intervention. It was found that 62% of the intervention arm participants controlled their
35
36 virus, versus 55% of the participants in the control arm. This gives a fairly weak
37
38 aggregate effect size (OR=1.25, 95%CI 0.99-1.59, N=1247). Although the evidence
39
40 against the null was not conclusive, the percentage of participants in the intervention
41
42 arm that had undetectable viral load versus those in the control arm could translate into
43
44 significant financial and health-systems benefits.
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51 This review also reported 18 trials where the outcome was expressed as effect on
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53 adherence (the majority of studies measured adherence by self report, between two
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55 weeks and six months post-intervention), and in this case 62% of participants in the
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57 intervention arm and 50% of participants in the control arm achieved at least 95%
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59 adherence (7). This resulted in stronger evidence against the null and a stronger
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4 aggregated effect size (OR=1.5, 95%CI 1.16-1.94, N=1633). This larger effect for
5
6 adherence is not likely to be due to unreliable measurement by self-report, as effect
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8 sizes were actually larger in studies that used more objective measures (e.g. electronic
9
10 monitoring). Thus, participants in the intervention arm were 1.5 times more likely to be
11
12 95% or more adherent, and 1.25 times more likely to achieve suppressed viral load than
13
14 participants in the control arm. This effect tended to be greater in studies that provided
15
16 information on ART and interactive discussions regarding the cognitions, motivation, and
17
18 participant expectations. Although it is inherently problematic to combine the diverse
19
20 outcomes from studies with very different interventions and designs, this was the first
21
22 attempt to synthesise the RCT outcome data and it was cautiously optimistic about the
23
24 ability of behavioural interventions to enhance ART and strongly in favour of additional,
25
26 rigorous assessment of adherence interventions by RCT, especially in Africa (13).
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33 During the development of the intervention for the current study, we made a site visit to
34
35 Harlem Hospital, and the 'medication manager' adherence intervention developed and
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37 being tested there was observed, and the approach modified and assimilated into the
38
39 intervention being developed for our study (14). The medication manager provided
40
41 personalised adherence support to participants, using a standard assessment protocol
42
43 to identify and address any deficits in adherence information, motivation and behavioural
44
45 skills. The primary endpoint was time to first virologic failure, defined as the first plasma
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47 viral load above 2000 copies/ml on or after the 4th monthly follow-up visit. In the main
48
49 intention to treat analysis, the medication manager group had 13% lower rate of first
50
51 virological failure, but this was not statistically significant. Participants in the medication
52
53 manager arm also had significantly raised CD4 counts (mean difference of 22.5 cells/ μ L
54
55 higher), and better long-term adherence by self-report. This study provided some
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57 evidence that the approach of using a theory-based model to identify and correct specific
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4 deficits in information, motivation and behavioural skills with counselling techniques
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6 based on motivational interviewing was feasible, and showed promise in enhancing
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8 adherence and treatment outcomes on ART.
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13 In summary, the literature indicated that counselling interventions, based on models of
14
15 behaviour change, that provided participant-specific problem-solving and
16
17 interactive sessions, seemed to be most likely to have an effect on improving ART
18
19 adherence (7, 10, 11, 15, 16). The motivation, information and behavioural skills model
20
21 tied to motivational interviewing had been used and evaluated in the USA in
22
23 ART adherence, with some preliminary indications that this may be a fruitful avenue for
24
25 further research (14, 17-19). ART adherence in the context of TB treatment was
26
27 identified as a key data gap that needed to be addressed, as integrated treatment was
28
29 not the recommended standard of care.
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36 To address our concerns about the adequacy of standard didactic counselling in our
37
38 setting, we conducted a RCT to assess whether intensive individualised motivational
39
40 adherence counselling led to better adherence and treatment outcomes than standard
41
42 didactic counselling in newly diagnosed HIV infected patients initiating antiretroviral
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44 therapy.
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49 **Methods**

50 *Study design and setting*

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53 The study was a parallel group (1:1 ratio), open-label randomised controlled trial, with
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55 concealment of allocation from the person conducting the enrolment. It was conducted at
56
57 the CAPRISA eThekweni HIV-TB clinic, in Durban, South Africa. This research facility
58
59 adjoins to the Prince Cyril Zulu Communicable Diseases Centre, one of the biggest TB
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4 outpatient treatment clinics in South Africa.
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9 *Participants*

10 Between August 2007 to February 2009, we recruited participants 18 years of age or
11 older and eligible to initiate ART (at the time, a CD4 T-cell count of 350 or less). The
12 majority of these participants were also included in a study of the optimal time to initiate
13 ART in patients who were receiving TB treatment (20, 21). Just over 53% of participants
14 were receiving TB treatment at the time of their participation in this study, and a further
15 25.6% had completed TB treatment within 4 weeks previous to initiation on ART
16 (described further in Table 1 of the results).
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28
29 *ART regimen*

30 The ART regimen used was selected to be compatible with TB treatment (21). The first
31 line regimen offered, free of charge, was a once-a-day regimen consisting of enteric-
32 coated didanosine (250mg if <60kg, 400mg if >60kg), lamivudine 300mg, and efavirenz
33 600mg (or, nevirapine (200mg twice a day) in the case of pregnancy).
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43 *Adherence counselling*

44 TB treatment adherence support was provided separately from the HIV treatment
45 programme. This TB treatment service was provided by the Department of Health,
46 according to the provincial standard of care, and was not under the control or provision
47 of study staff, although completion of the required number of TB drug doses and
48 outcomes of TB treatment were assessed as part of the TB and HIV treatment
49 integration studies underway at the clinic.
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60 The standard HIV treatment adherence support counselling for this programme was
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4 delivered by a nongovernmental organisation, consistent with the requirements in the
5
6 initial South African national guidelines for treatment provision for adolescents and
7
8 adults (22), the World Health Organization (WHO) guidelines for scaling up ART in
9
10 resource-constrained settings (23), and with the US Department of Health and Human
11
12 Services guidelines (24). The counselling focussed on treatment literacy, and was
13
14 delivered in an educational, or didactic, style. The counselling was seen as essential for
15
16 treatment readiness, and so focussed on preparation prior to ART initiation. No formal
17
18 counselling post-initiation of ART was specified, although on-going monitoring of
19
20 adherence was recommended. We were concerned that this approach to adherence
21
22 support may become less effective over time, as counselling group size increased, and
23
24 the didactic approach might be prone to rote repetition of information with inadequate
25
26 engagement with the individual issues faced by patients¹.
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32 33 *Procedures*

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35 On determination of ART eligibility, all patients received two pre-initiation 20-45 minute
36
37 didactic counselling sessions as standard at the clinic. At the time of the ART initiation
38
39 visit, patients were consented, enrolled and randomised. The randomisation was set up
40
41 by a statistician using a random number generator in SAS, and the randomisation codes
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43 contained in sequentially numbered, sealed opaque envelopes, stratified in blocks of
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45 four or six relative to time of TB treatment (described in the baseline characteristics table
46
47 of the results). The didactic arm participants received the final 20-45 minute didactic
48
49 counselling session only. The motivational counselling arm participants instead received
50
51 the first 30-40 minute individualised motivational counselling session, and then the
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53 additional four individualised motivational counselling sessions at intervals up to six
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55 months after initiation of therapy (Figure 1). All participants were followed up to at least
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60 ¹ We refer to patients in the treatment programme, and to participants when enrolled onto this study.
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4 nine months on treatment. Participants still in care had viral load measures taken at 12
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6 months. Adherence was assessed by clinic-based pill count at six months post-initiation
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8 of therapy.
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10 11 12 13 Content and delivery of the standard didactic counselling 14

15 The standard didactic counselling consisted of three sessions. The first session covered
16
17 stigma and discrimination, nutrition and taking control of the treatment regimen. The
18
19 second session focused on HIV pathogenesis, routes of infection, HIV testing
20
21 techniques, and a basic introduction to ART. The final session focused on information
22
23 relating to ART, the drug regimen, the importance of adherence, side effects, and the
24
25 importance of monitoring and the development of resistance. Due to the large numbers
26
27 of participants expected to be enrolled into the treatment programme, with increasing
28
29 pressure to meet the high treatment initiation targets, this counselling was designed to
30
31 be delivered in groups if necessary. Two sessions could be provided on the same day,
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33 but not all three.
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40 Content and delivery of the individualised motivational counselling 41

42 An individualised intensive motivational adherence counselling intervention was
43
44 developed, using content based on the information, motivation and behavioural skills
45
46 model (IMB) of adherence to ART (25-27), using counselling delivery techniques from
47
48 motivational interviewing (MI) (28, 29). The counselling was designed to be provided
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50 exclusively on a one-to-one basis, using a client-centred rather than didactic approach.
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52 Counselling could be tailored to specific participant needs, promoting an experience that
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54 was supportive of individualised care.
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60 MI was developed initially to treat alcohol abuse, and it is amenable to brief counselling
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4 sessions (30). MI is directive in the sense that the counsellor pursues the goal of
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6 examining and resolving ambivalence about behaviour change, but also client-centred in
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8 that it was designed to elicit statements in favour of behaviour change from the clients
9
10 themselves (29, 30). A review of trials of MI-based interventions in diverse settings,
11
12 concluded that this approach was more effective than traditional advice giving (31).
13
14 Although MI was not formally used in our study, the motivational counselling did use
15
16 techniques based on this approach. For example, instead of informing participants about
17
18 potential barriers to adherence, and associated solutions, the counsellors encouraged
19
20 them to think about potential barriers to adherence in their own experience and
21
22 encouraged participants to talk about, and opt for, solutions that they felt they could
23
24 implement in their own lives. As the statements about barriers requiring potential
25
26 behaviour change were made by the participants, and the solutions also suggested by
27
28 them, these counselling sessions were expected to be self-motivating. Participants were
29
30 more likely to take ownership of their adherence challenges and successfully enact
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32 solutions they had suggested.
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40 According to the IMB model of HIV prevention, initiating and maintaining patterns of HIV
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42 preventative behaviour depends on individuals being well informed, highly motivated and
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44 in possession of effective behavioural skills, rather than solely on the possession of
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46 knowledge. Content for the individualised motivational counselling was identified from
47
48 this model, specifically a version modified for ART adherence (27), a literature review of
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50 adherence barriers, reasons for non-adherence from our clinic patients, and interviews
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52 with adherence counsellors and pharmacy staff.
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57 Information was provided on the regimen, correct dosing, identifying and coping with
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59 side effects, as well as key information on non-adherence and resistance. Personal
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4 motivation was enhanced through MI-based techniques. Social motivation was
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6 encouraged through managed disclosure, designed to bring about gradual and safe
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8 disclosure over the first six months of treatment. Specific behavioural skills were
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10 encouraged, including skills to ensure clinic visits were kept, integrating dosing into the
11
12 routine of daily life, and for identifying and coping with side effects. Moderating factors
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14 like general psychological well being, unstable living conditions, and substance or
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16 alcohol abuse were address through referrals to appropriate services.
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22 The content of the motivational counselling was displayed on table top flipchart folders in
23
24 English and isiZulu, the main local language, with locally relevant imagery like a three
25
26 legged cooking pot to aid understanding and retention, facing the participants.
27

28 Counselling scripts, based on MI techniques, faced the counsellors. The slogans
29
30 summarised key principles like “The Power of Three” (the regimen of three drugs) and
31
32 “The System of Three” (three important strategies for taking the drugs correctly).
33

34
35 Additional support materials included wall posters for summarising counselling content,
36
37 symptom solution cards that included key slogans and side effect management
38
39 strategies, ‘prescriptions’ for adherence that were participant-agreed commitments to
40
41 behaviours necessary to adhere optimally, as well as a treatment plan card that included
42
43 pictures of the drugs in the regimen and space for a concrete plan for integrating dosing
44
45 into daily routine. The ‘prescriptions’ and treatment plan cards were prepared at the first
46
47 counselling visit, and reviewed and amended over the course of the intervention.
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53 Two health educators from the existing nursing staff were trained to administer
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55 motivational counselling. On the day of treatment initiation participants were counselled
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57 on preparing to take ART, especially identifying managing side effects, and this was
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59 followed up at week two with a session on adjusting to ART medications. At two and
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4 three months, sessions were conducted dealing with on-going treatment issues and
5
6 managed disclosure. At month six, participants were counselled on lifelong therapy
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8 concerns.
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12 In accordance with standard clinic practice, and essential to adequate standard of care,
13
14 once initiated on treatment all participants could receive additional *ad hoc* counselling
15
16 support, on the basis of increasing viral load, decreasing CD4 count, missing doses
17
18 (either by self-report or pill count), or when the participants account of their treatment
19
20 behaviour did not make sense. To provide this, the standard didactic counselling session
21
22 three was repeated as required in both study arms.
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28 *Study outcomes*

29
30 The primary outcome was the proportion of participants with suppressed viral load
31
32 (plasma viral load of <400 copies/ml, HIV-1 RNA-PCR – Roche Diagnostics) at nine
33
34 months (range of eight to 10 months) post-initiation of ART. A secondary outcome
35
36 looked at adherence by pill count over the previous inter-visit period at six months post-
37
38 initiation of therapy. Pill count was expressed as a percentage of the pills taken as
39
40 prescribed over the study visit interval (usually the previous 28 days), by assuming that
41
42 all non-returned pills had been taken over the study visit interval. These data were
43
44 verified from the clinic records based on previous study visit and drugs dispensed by the
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46 pharmacy. This measure was recorded at 6 months, as this was part of the counselling
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48 intervention study follow-up. Suppressed viral load at 12 months was assessed as an
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50 additional secondary outcome.
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58 As early mortality is common in treatment programmes in this region (32, 33), deaths
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60 prior to three months were not considered as contributing to the primary outcome as
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4 they occurred too early for treatment adherence to have an impact, and these
5
6 participants were excluded from all analyses. Participants who died after three months,
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8 but prior to nine months, were considered to have unsuppressed viral load in the
9
10 analysis.
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12 13 14 15 *Sample size and statistical analysis*

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17 The individualised motivational counselling was hypothesised to be superior as it was
18
19 more intensive, and provided individually in a client-centred and participatory way. From
20
21 data available during planning, we estimated that we would need at least 150 evaluable
22
23 outcomes in each arm at 9 months, for the study to have 80% power to detect an
24
25 absolute difference of at least 15% in suppressed viral load, estimating 65% suppressed
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27 in the didactic counselling arm, with a type 1 error of 5%.
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33 As odds ratios exaggerate the magnitude of association for common events (34), and as
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35 viral load suppression was high in this study, the primary outcome was assessed using
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37 risk ratios with 95% confidence intervals (CIs). As no adjustment was necessary for the
38
39 outcomes, no regression model was needed to estimate the risk ratios. All analyses
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41 were performed using the STATA 11.0 statistical analysis program (College Station,
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43 Texas 77845, USA).
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48 49 *Restricted and whole cohort analysis*

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

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12 This study was approved by the Biomedical Research Ethics committees of the
13 University of KwaZulu-Natal, Durban (E326/05), The London School of Hygiene and
14 Tropical Medicine, London (5114), and, Columbia University, New York (IRB-
15 AAAC0202). The trial was registered Clinicaltrials.gov (NCT00408642) on the South
16 African National Health Research Ethics Council (NHREC) trials register (DOH-27-0807-
17 2004).
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28 **Results**

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30 297 ART naïve patients were eligible and all consented to be enrolled, 150 randomised
31 to the didactic and 147 in the individualised motivational counselling arm (Figure 2). All
32 participants were followed up and analysed in the arms into which they were
33 randomised. Baseline demographic and clinical characteristics were similar in both
34 groups (Table 1).
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44 *Follow-up to nine months*

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

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9 *Intervention coverage*

10 All participants in the didactic counselling arm had to have documented evidence of
11 having completed the standard adherence support programme as this was a
12 requirement prior to initiation on ART. Of the 131 participants from the individualised
13 motivational counselling arm in follow-up for at least six months and, therefore, expected
14 to have completed five sessions, 97.7% (128/131) completed at least three and 88.5%
15 (116/131) completed all five sessions.
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26 *Ad hoc counselling support*

27 During the course of the study there were 101 recorded instances of *ad hoc* adherence
28 counselling for 49 study participants. 71 of these instances occurred in the 31 didactic
29 counselling participants, versus only 30 sessions in 18 of the motivational counselling
30 participants (Mann-Whitney $p=0.04$). One participant in the didactic counselling arm
31 accounted for five of these sessions, and another for eight.
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42 Reasons for repeat adherence counselling referral were captured in 99 of cases (Table
43 2). The most frequent reason given for referring a participant for *ad hoc* counselling was
44 that the incorrect number of pills was returned at the study visit, slightly more frequent in
45 the didactic counselling arm. Participants in the didactic counselling arm were also more
46 than twice as likely to have been referred for poor knowledge of drug dosing instructions.
47 However, there is no evidence that reasons for referral differed by counselling type
48 (Fisher's exact $p = 0.89$).
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60 *Primary outcome: Suppressed viral load at nine months*
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4 A total of 252 participants were included in the restricted analysis; 250 with viral load
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6 measures at nine months, and two participants (one in each arm) who died between
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8 three and nine months. By nine months, suppressed viral load was achieved in 89.8%
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10 (115/128) of the participants in the didactic counselling arm and in 87.9% (109/124) of
11
12 participants in the motivational counselling arm (RR=0.98; 95%CI 0.90-1.07,
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14 p=0.62)(Table 3). In the whole cohort analysis, suppressed viral load was achieved in
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16 78.8% (115/146) of the participants in the didactic, and in 77.3% (109/141) of the
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18 motivational counselling arm (RR=0.98; 95%CI 0.87-1.11, p=0.76).
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24 In predetermined exploratory analysis (not shown here), adjustment for gender, age,
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26 employment status, education level, relationship status, point of HIV treatment initiation
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28 in relation to TB treatment, viral load and CD4 count by log binomial regression (35) had
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30 no major impact on the primary outcome of the trial.
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34 35 *Secondary outcome 1: $\geq 95\%$ adherence by pill count at six months*

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37 In the restricted analysis, 82.9% (97/117) of those in the didactic and 79.5% (89/112) of
38
39 the individualised motivational counselling arm participants had a pill count greater than
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41 95% (RR = 0.96; 95%CI 0.85-1.09, p=0.51). In the whole cohort analysis, 66.4%
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43 (97/146) in the didactic arm versus 63.1% (89/141) of those in motivational arm had
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45 adherence $\geq 95\%$ (RR = 0.95; 95%CI 0.80-1.13, p=0.56).
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51 *Secondary outcome 2: Suppressed viraemia at 12 months*

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53 As part of clinical follow-up of all retained participants, viral load data were available for
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55 247 participants at 12 months post-initiation of therapy. Of those who provided data,
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57 91.1% (112/123) in the didactic and 87.9% (109/124) in the motivational counselling arm
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59 had suppressed viral load (RR = 0.97; 95% CI 0.89-1.05, p=0.42). In the whole cohort
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4 analysis, 76.7% (112/146) in the didactic versus 77.3% (109/141) in the motivational arm
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6 had suppressed viral load (RR = 1.0; 95% CI 0.89-1.14, p=0.91).
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10 **Discussion**

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12 In our trial, ART-naïve participants who received intensive individualised motivational
13 counselling did not have improved viral suppression or adherence outcomes. Exposure
14 to the motivational counselling was high, and poor coverage was not likely to be a factor.
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16 Viral suppression was high in both groups. While the 252 participants with treatment
17 outcome at 9 months assessed in the restricted analysis was below the target of 300
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19 evaluable participants, the whole cohort analysis of all 297 participants did not lead to
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21 materially different trial outcomes.
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31 Treatment outcome data from the southern Africa region at the time of this study help to
32 contextualise the results (Table 4). These data, mostly from other well-resourced
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34 treatment trials, seem to also show good outcomes. However, significant losses to follow
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36 up and early mortality are masked as most results are given for 'on treatment'
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38 participants. Where an intention to treat estimate is given, the result is much poorer (36),
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40 highlighting the good outcome in our current study. Including data from other southern
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42 African countries, which also includes real-world clinic data, indicate much lower
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44 estimates, especially in adolescent patients (37). One study from a rural setting in
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46 KwaZulu-Natal indicates that suppression rates have increased significantly from 2005,
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48 to 2007, most probably due to improved service provision and patient tracking
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50 procedures (38).
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57 Factors other than the counselling are likely to have contributed to the good outcomes
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59 observed in the current study. It is possible that the repeated adherence assessments
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4 functioned as an adherence intervention in both arms by reminding participants of the
5
6 importance of adherence. The tracking and tracing in place at the clinic required for trial
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8 follow-up reduced the likelihood of missed study visits and losses to follow-up. Tracking
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10 is key as it is a reminder for visits, ensures good refill rates, and also communicates to
11
12 each participant that they are important. In this setting where access to treatment is
13
14 difficult, the threat of losing access to treatment may have exerted a powerful
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16 motivational influence, as would direct experiences of morbidity and mortality in the
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18 community.
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24 The clinic also provides a selection of other supportive activities, not formally considered
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26 to be part of the standard of care at the start of the study, but would have improved
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28 outcomes beyond what would be expected with didactic counselling alone. These
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30 include pillboxes to aid remembering to take pills, pill packet illustrations for illiterate
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32 participants and dosing instructions provided in the local language. *Ad hoc* counselling
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34 was provided to any participants who had clinical problems or adherence measures that
35
36 concerned staff, as previously indicated. These sessions were significantly more likely to
37
38 occur in the didactic counselling arm participants, which is not surprising as the
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40 motivational counselling participants were more likely to be scheduled for an
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42 individualised counselling session within which they would have dealt with any issues
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44 relating to poor adherence. Although it is possible that the *ad hoc* counselling meant that
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46 the control arm might be biased towards the null, this *ad hoc* counselling was part of the
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48 standard of care against which the intervention counselling would need to be an
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50 improvement, and so this was not unexpected, or avoidable. In addition to this, these
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52 sessions were only conducted in a relatively small number of cases and participants,
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54 and the content remained didactic rather than motivational.
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4 All of these factors are implementable in other settings, and would be amenable to study
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6 as adherence interventions in their own right. It is also possible that once the Hawthorne
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8 effect of being intensively followed up in this study wore off (39), that differences
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10 between the adherence strategies between the two arms might, over time, lead to
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12 greater sustained adherence and viral suppression in one of the arms, but this was not
13
14 feasible to assess within the time frames of the current study.
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20 Finally, the majority of participants were co-enrolled on a TB/HIV treatment study or
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22 were previous TB treatment patients. They remained a selected group of participants
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24 who had experience of, and likely success with, TB treatment adherence. It was
25
26 considered probable during the conceptualisation of this trial that the burden of
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28 concurrent or sequential TB treatment and ART would negatively impact on treatment
29
30 adherence. That the participants in this study have done so well is very promising in
31
32 relation to the increased calls to integrate HIV and TB treatment, and the very large
33
34 proportion of HIV patients this specific population represents in South Africa. These
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36 results support closer integration of HIV and TB treatment.
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42 Major strengths of our study include the randomised controlled trial design, use of a
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44 theory-based intervention, the use of viral load as the primary outcome, and the trial
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46 setting of a TB clinic, which is a common entry point for HIV treatment in Africa. While
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48 adherence intervention studies report adherence and treatment outcomes for relatively
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50 short periods of time, often only for up to immediately after the completion of the
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52 intervention being tested (7, 40), this study assessed treatment outcomes up to 12
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54 months post-initiation of treatment.
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60 A limitation of this trial was that the high viral suppression rate following standard
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4 didactic counselling was not anticipated, the sample size calculation assumed only 65%
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6 suppression in the didactic arm, and the study was not powered for small incremental
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8 benefits of motivational counselling since substantial benefits would be needed from this
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10 intensive and more costly approach to warrant its implementation. A further limitation is
11
12 that the setting of this trial in a TB clinic may reduce its generalizability.
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17 Although this study showed that it is feasible to roll out this more intensive individualised
18
19 motivational counselling in a resource-constrained setting, the counselling was designed
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21 to target issues with specific skills deficits at the individual level that may not have been
22
23 appropriate for this setting. This intensive individualised motivational counselling
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25 approach is more likely to be necessary and effective where barriers to adherence are
26
27 personal and motivational rather than structural, and in populations who experience
28
29 many of these barriers. Identification of a population at high risk for non-adherence, or of
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31 participants who are experiencing difficulties, may be a more appropriate target for
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33 testing this intervention. This is likely to be even more important now that treatment
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35 provision has expanded so much outside of clinical research settings.
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42 In summary, we conclude that the standard of care didactic counselling was adequate in
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44 the setting of our TB clinic, and that intensive personalised one-on-one motivational
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46 counselling did not significantly improve adherence and treatment outcomes in this
47
48 study. The finding that motivational counselling had no benefit over traditional didactic
49
50 counselling in this setting is an important contribution to the literature on HIV treatment
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52 adherence counselling, as it does warn against implementing intensive individualised
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54 motivational counselling in settings where less resource intensive didactic counselling
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56 may be adequate. These study results empower health educators, nurses or community
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health workers to provide efficacious adherence support in a limited and structured counselling intervention.

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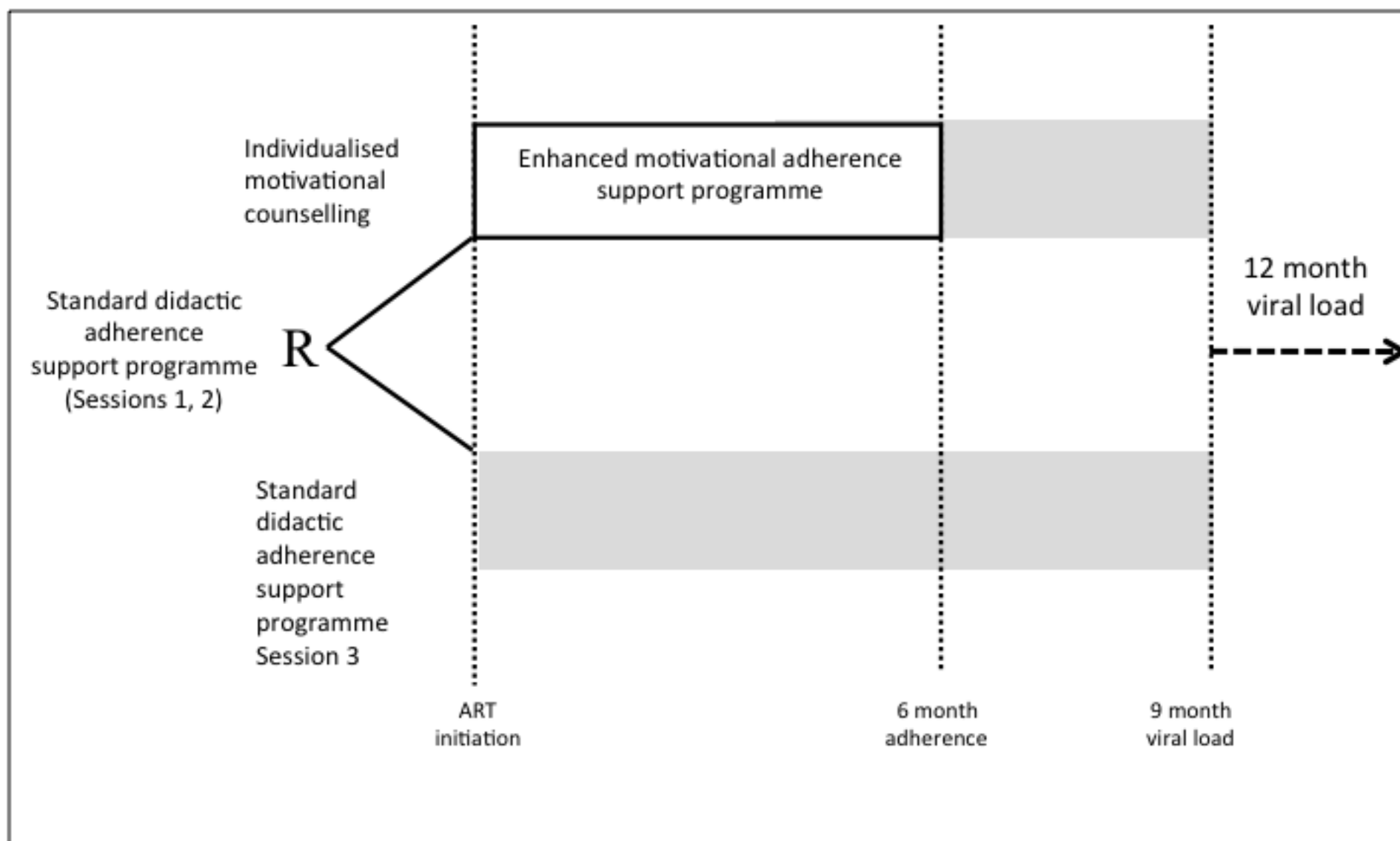


Figure 1: Study schema; a parallel group RCT, 'open label'/unblinded, with concealment of allocation from the person enrolling participants, and random assignment

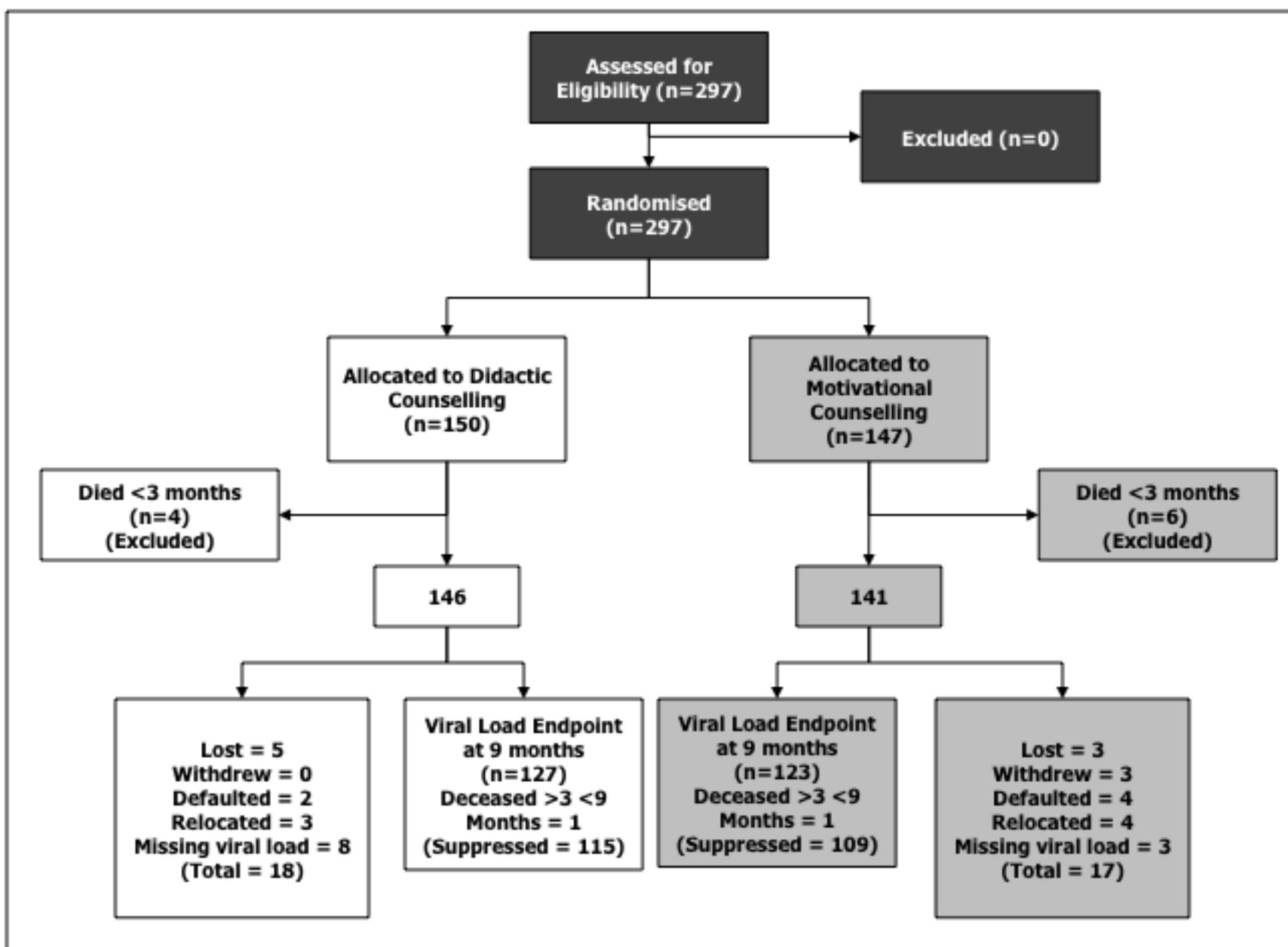


Figure 2: Participant enrolment and disposition at 9 months

Table 1: Characteristics and clinical features at time of enrolment, overall and by counselling arm

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

[~]SD = standard deviation, IQR = interquartile range

[#] 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.

* Numbers only shown when less than the column total. Data were extracted from participant clinic files and were not available for all participants

[%] 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*)	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 ³⁰	South Africa	289	Free cART, clinical trials, no formal adherence intervention.	12 months: 70.9%
Coetzee et al., 2004 ³¹	South Africa	254 244 165 72 34 (of 287 at base-line)	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 ³²	South Africa	110	Free cART, observational cohort.	12 months: 89.0%
Barth et al., 2008 ²⁶	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)
Nachega et al., 2009 ²⁷	Southern Africa (9 countries)	154 7622	Public sector HIV treatment programme.	Adolescent (≤19 years) 6 months: 63.0% 12 months: 45.7% Adult (>19 years) 6 months: 69.3% 12 months: 62.1%
Boulle et al., 2010 ³³	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 ²⁸	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) (#<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%

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