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ORIGINAL RESEARCH

Virological Outcomes After Switching to Abacavir/Lamivudine/Dolutegravir Combined with Adherence Support in People Living with HIV with Poor Adherence: A Phase IV, Multicentre Randomized Prospective Open Label Study (TriiADD-CTN 286)

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Background: Many people living with HIV struggle to consistently adhere to antiretroviral therapy, fail to achieve long-term virologic control and remain at risk for HIV-related disease progression, development of resistance and may transmit HIV infection to others.

Objective: To determine if switching from current multi-tablet (curART) to single-tablet antiretroviral therapy (abacavir/lamivudine/dolutegravir; ABC/3TC/DTG), both combined with individualized adherence support, would improve HIV suppression in non-adherent vulnerable populations.

Methods: TriiADD was an investigator-initiated randomized, multicentre, open label study. HIV+ adults with documented non-adherence on curART were randomized in a 1:1 ratio to immediately switch to ABC/3TC/DTG or to continue curART. Both arms received adherence support. The primary outcome was the proportion of participants in each arm with HIV RNA < 50 copies/mL 24 weeks after randomization.

Results: In total, 50 people were screened and 27 randomized from 11 sites across Canada before the trial was stopped early due to slow recruitment. Participants were predominantly from ethnocultural communities, Indigenous people and/or had a history of injection drug use. The proportion achieving HIV RNA < 50 copies/mL at week 24 was 4/12 (33%) in the curART arm vs 7/13 (54%) in the ABC/3TC/DTG arm; median Bayesian risk difference, 5% (95% CrI, −17 to 28%) higher for those randomized to ABC/3TC/DTG. We encountered difficulties with recruitment of participants without prior drug resistance, retention despite intensive support, reliably measuring adherence and in overcoming entrenched adherence barriers.

Conclusion: Results of our trial are consistent with a slight improvement in viral suppression in a vulnerable population when a single tablet regimen is combined with patient-level adherence support. Beyond treatment simplicity and tolerability, tailored interventions addressing stigma and social determinants of health are still needed. The numerous challenges we encountered illustrate how randomised trials may not be the best approach for assessing adherence interventions in vulnerable populations.

Keywords: adherence interventions, human immunodeficiency virus, HIV, antiretroviral therapy, single tablet regimen, vulnerable populations

Plain Language Summary

Many people living with HIV struggle to take their antiretroviral medication consistently. As a result, they may experience poor control of their infection and are at increased risk of developing resistance to treatment, getting sick and transmitting HIV infection to others. Vulnerable people face many barriers to taking medications regularly such as substance use, side effects, stigma, and financial and food insecurity. The aim of this study was to determine if simplifying treatment to a single tablet per day along with providing individualized adherence support could improve adherence and HIV control. Participants were randomly assigned to switch their current multiple tablet treatments to a single tablet of abacavir/lamivudine/dolutegravir or continue with their current multiple tablet treatment. Both groups received individualized adherence support to address their specific adherence challenges, reminders and financial support for co-payments. While switching to the single tablet appeared to improve control of HIV, the trial encountered many challenges and was stopped early due to slow recruitment. It was difficult to find participants without prior drug resistance. Many could not adhere or stay in the trial despite intensive support. Overcoming entrenched adherence barriers was difficult. Our trial illustrates that beyond improving treatment simplicity and tolerability, tailored interventions that address stigma and social determinants of health are still needed to ensure all people can benefit from HIV therapy. Alternatives to trials should be considered for assessing what interventions may work best to improve adherence in vulnerable populations.

Introduction

With the improved safety and efficacy of modern combination antiretroviral therapy (ART) and a growing recognition that prolonged viral suppression reduces both HIV and non-HIV morbidity and mortality and transmission, ART is now recommended for all HIV infected person regardless of CD4 cell count.[1] Despite the benefits of modern ART, an important sub-group (as many as 30%[2–4]) of HIV-infected persons is unable to maintain adherence to treatment.[5] Consequently, they fail to achieve long-term virologic control and remain at risk for HIV-related disease progression, development of resistance and may transmit HIV infection to others.[6] In Canada and elsewhere, vulnerable populations, such as people who inject drugs (PWID) and people from Indigenous and ethno-cultural communities are at higher risk of non-adherence.[7–10] A variety of factors contribute including stigma, financial and food insecurity, problematic substance use, mental illness, side effects and lack of perceived benefits of treatment.[10,11] Ongoing transmission in these at-risk populations, because of unsuppressed HIV, is an important driver of the epidemic[12,13] and has contributed to failing to meet UNAIDS 2020 targets for ending AIDS.[14]

For vulnerable populations, an ideal regimen should be simple, tolerable, combine well with treatment for hepatitis C virus (HCV) and other comorbidities, in addition to being easy to integrate into complex lives where barriers to treatment include financial and food insecurity. Because of poor adherence, clinicians are also concerned about past and future HIV resistance when recommending treatment. However, many regimens with high barriers to resistance (eg, boosted protease inhibitors) are inherently difficult to adhere to with multiple tablets or side effects.[15] Once daily ART and single tablet regimens (STR) have been associated with improved adherence and HIV suppression,[6,16,17] reduced hospitalizations and lower health-care costs compared multiple tablet regimens (MTR).[6,18,19] These previous studies however have been limited by their retrospective design and uncontrolled allocation of treatment – temporal changes and confounding may have biased results. The availability of the integrase strand inhibitor-based ART, abacavir/lamivudine/dolutegravir (ABC/3TC/DTG; Triumeq™), represented an opportunity to offer an STR with many features that could enhance adherence in vulnerable populations: a high barrier to resistance, no food restrictions, few drug–drug interactions and a good side effect profile.[20]

The aim of TriiADD was to determine if switching from current ART (curART) to ABC/3TC/DTG combined with adherence support would improve the rate of HIV suppression in vulnerable populations non-adherent to their

curART. This was to be the first randomized controlled trial to directly compare MTR and STR regimens in populations most in need of, and most likely to benefit from, enhanced adherence interventions. The trial was stopped early due to slow recruitment. This report describes the trial design and results and evaluates challenges and lessons learned from conducting research on adherence in vulnerable populations in order to inform future trials and interventions.

Materials and Methods

Trial Design

TriiADD was an investigator-initiated randomized, multicentre, open label study (Canadian Institutes of Health Research (CIHR)-Canadian HIV Trials Network (CTN) 286; Clinical trials.gov NCT02354053). Participants were randomized in a 1:1 ratio to immediately switch to ABC/3TC/DTG or to continue with their currently prescribed curART regimen. Both arms received adherence support (see below). Those randomized to maintain curART were permitted to switch to ABC/3TC/DTG after week 24 if they chose to (Figure 1). The funders had no role in the design, management, data collection, analysis, interpretation, reporting, or decision to publish results.

Participants

Patients recruited into the trial were adults aged over 18 years old with documented HIV infection, with negative HLA-B5701 testing and without chronic Hepatitis B infection (HBsAg surface antigen negative) and had to have been receiving ART for at least one year. Participants were required to have evidence of non-adherence to their curART regimen defined as: HIV RNA ≥400 copies/mL at least once in last 12 months (not explained by normal viral decay after initiating curART), or if HIV RNA <400 copies/mL, to have a clinical history of non-adherence by patient self-report or pharmacy refill data.

Given patients may have had virologic failure at the time of enrollment, they were excluded if they had evidence of resistance to any component of their current regimen or to ABC/3TC/DTG based on the presence of primary resistance-associated mutations with these drugs according to the Stanford HIV drug resistance database[21,22] on any available historical resistance test or on screening genotype for patients with HIV RNA ≥400 copies/mL. Additional exclusion criteria can be found in Figure 1 (footnotes) – however, no patient was excluded for these reasons.

The study was reviewed and approved by the ethics committee of each participating centre and by the Community Advisory Committee of the CTN. Written informed consent was obtained prior to screening.

Trial Management

An adjudication committee comprised of 3 persons (not including the principal investigator) reviewed all cases where non-adherence or the resistance test results were not clear and determined eligibility for the trial. The trial was reviewed every 6 months for safety and any ongoing procedural concerns by the CIHR CTN Data Safety Monitoring Committee (DSMC).

Randomization

A computer-generated randomization list was prepared prior to study onset by a statistician at the CIHR CTN unassociated with the study. Site coordinators accessed the allocation codes by interacting with a password-protected webpage. Randomization was stratified by study centre and whether HIV RNA was >400 copies/mL at screening using variable permuted blocks of size 2 and 4.

Interventions

Antiretroviral Therapy

Prescribed curART included any recommended or alternative regimen in the guideline current at the time[22] which the treating physician considered appropriate for their patient (except those containing dolutegravir) taken for at least 6 months. Eligible participants were randomized to continue curART or immediately switch to abacavir 600 mg/lamivudine
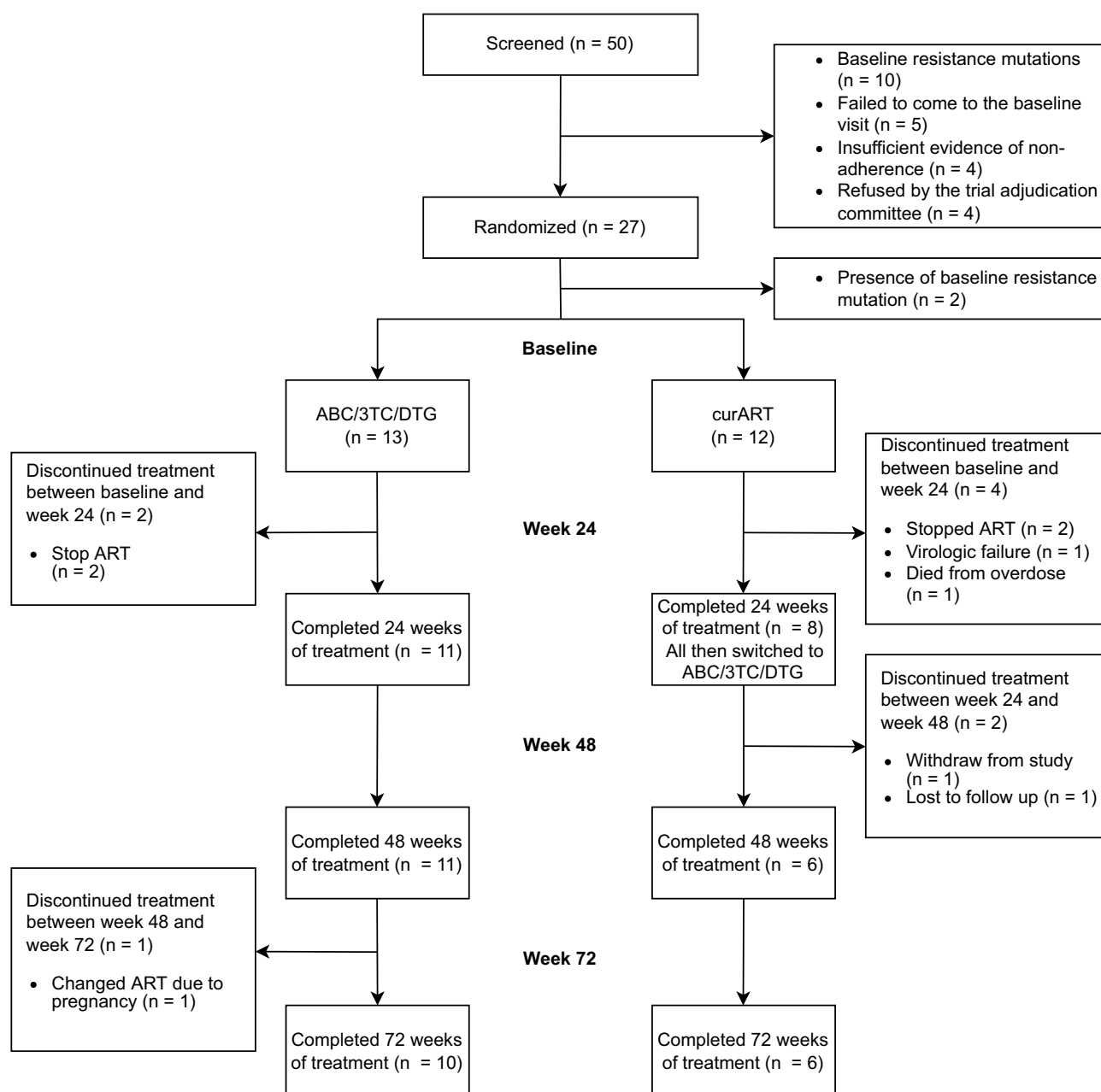
Figure 1 Study flow through 72 weeks. Additional study exclusion criteria were: women who were pregnant or breastfeeding, planning pregnancy or who did not use contraception if able to conceive; active Centers for Disease and Prevention Control (CDC) Category C disease[53] (except cutaneous Kaposi's sarcoma not requiring systemic therapy); moderate to severe hepatic impairment (Child-Pugh classification Class B or C); alanine aminotransferase (ALT) greater than 5 times the upper limit of normal, or ALT greater than or equal to 3 times the upper limit of normal and bilirubin greater than or equal to 1.5 times the upper limit of normal (with greater than 35% direct bilirubin); creatinine clearance of less than 50 mL/min via Cockroft-Gault method; and those taking dofetilide or immunosuppressants. None of the screened patients were excluded for these reasons.
Abbreviations: ABC/3TC/DTG, abacavir/lamivudine/dolutegravir; curART, current antiretroviral therapy.

300 mg/dolutegravir 50 mg once daily administered as fixed dose combination tablet (ABC/3TC/DTG; Truimeq™ supplied by ViiV Healthcare, Laval, Canada).

Adherence Support

As we recruited patients with documented non-adherence and poor virologic control, it was ethical to offer adherence counselling and support to all enrolled. However, based on prior literature, we anticipated that the effect of such counselling would be modest (at best a 20% increase in adherence and virologic control from baseline).[16] Patients in

both arms received an intervention made up of the same components: clinic-based assessment and follow-up specific to the individual's identified challenges with adherence to assess if they had been adequately addressed, telephone/electronic reminders and dosette boxes. The clinic-based adherence intervention was inspired by the "Treatment Manual for Managed Problem-Solving (MAPS)" which has been specifically designed for health-care professionals working with HIV-infected populations to improve ART adherence.[23] The intent was that everyone received an individualized adherence support program equal in approach and structure, but which could vary in intensity. In addition, co-pay coverage (where needed) was provided so there was no financial burden for participants randomized to the curART arm as ABC/3TC/DTG was supplied.

Outcomes

The primary outcome was the proportion of participants in each arm with HIV RNA < 50 copies/mL at week 24 after randomization. The secondary outcome was the median adherence score over time in the two arms at week 24 post randomization. The adherence score was determined from pill counts by calculating the proportion of ART medications used (dispensed minus returned) divided by the amount dispensed per month. Pill count was corroborated with self-reported adherence using the Visual Analogue Scale (VAS last week and/or last month) which measures item ratings by participants in percentile terms from 0 to 100%.[24] Adherence among all patients was also determined at weeks 48 and 72 post-randomization to assess durability of the intervention. Additional planned secondary outcomes were proportion of participants in each arm with HIV RNA < 50 copies/mL at weeks 48 and 72; changes in HIV viral load and CD4 cell counts through week 72; and the proportion of participants in each arm developing new drug resistance mutations.

Sample Size

We planned for a sample size of 100 patients (50 per arm) to provide 80% power to detect a difference between 85% and 60% in virologic suppression rates between the two arms at week 24. While this difference is large, for the population we were targeting, we considered that an improvement in virologic suppression rates of at least this amount would be required to be clinically meaningful.

Statistical Analyses

Planned Analyses

Planned analyses were based on intention-to-treat (ITT). Dropouts and crossovers were counted as treatment failures. For the primary outcome, the proportion of participants with HIV RNA < 50 copies/mL at week 24 was defined by the FDA snapshot analysis.[25] For the secondary outcome, mean adherence scores were compared between arms at week 24. Dropouts were considered to have 0% adherence. The effect of treatment on outcome was assessed using odds ratios estimated in logistic regression models with HIV RNA >400 copies/mL at screening as a covariate. This covariate was added to all regression models to reflect the stratified randomization. The logistic regression model for the secondary outcome was fitted using quasi-likelihood because the adherence score is a fractional response.[26]

Supplemental Analyses

Given the small sample size recruited prior to study termination, and the resultant lack of precision in estimates, we conducted Bayesian analyses to obtain more plausible estimates for the treatment effect from these data. We used a weakly informative prior for the effect of treatment, assuming that its effect should lie within the range from 0.25 to 4.0 with 95% confidence.[27] We fitted Bayesian logistic and beta regression models for the primary and secondary outcomes, respectively. In addition, adherence scores at week 24 were compared in the per-protocol population. This per-protocol analysis was added because it is not clear whether zero adherence ought to be attributed to those patients that withdraw, so results of this additional analysis represent the effect of treatment on adherence to study medication for those able to remain in the trial.

All estimates are reported with 95% confidence (CI) or credible (CrI) intervals. All models were fitted in SAS 9.4 (TS Level 1M5, procedures LOGISTIC, GLIMMIX and MCMC).

Qualitative Analysis

We used data collected in the standardized format of the MAPS adherence tool to conduct a post hoc qualitative content analysis of barriers and solutions used to overcome them for adherence support.[28,29] Barriers were inductively categorized in themes representing similar obstacles. Solutions were initially inductively organized in themes and then deductively categorized in the three domains of the Information-Motivation-Behavioural skill model (IMB), a framework to understand and promote HIV preventive behaviours.[30] DOP conducted the initial analysis using NVivo 12® for Mac and met with MBK in debriefing meetings to ensure reliability of the resulting themes.

Results

The trial opened for enrollment in December 2015 and closed in December 2018 before reaching the target sample size due to slow enrollment. In total, 50 patients were screened and 27 were randomized from 11 sites across Canada. Two participants, one in each arm, were determined after randomization to have had baseline resistance and then withdrawn leaving 25 enrolled; 13 were randomized to immediate switch to ABC/3TC/DTG and 12 to remain on curART.

Among patients who failed screening, the principal reasons were: the presence of baseline resistance mutations (n = 10), failure to come to baseline visit (n = 5) and insufficient evidence of non-adherence (n = 5). Eight patients were referred to the trial adjudication committee of whom 4 were determined not to be eligible (2 for resistance and 2 for insufficient evidence of non-adherence). The study flow through week 72 is shown in Figure 1.

Enrolled patients were diverse and had many sociodemographic characteristics that suggested vulnerabilities including history of mental illness and substance use (Table 1). HCV co-infection was common (n = 11; 44%). Participants in both arms were predominantly from ethnocultural communities (n = 11; 44%) or Indigenous people (n = 7; 28%). While injection drug use was the most common risk factor for HIV acquisition overall (n = 11; 44%), a large proportion of participants acquired HIV heterosexually in Canada (n = 10; 40%) or were immigrants from HIV endemic countries (n = 5; 20%). There were only 2 participants who identified as being men who have sex with men. Allowing for the small numbers of patients enrolled, there were no major differences between study arms (Table 1). Participants generally had lived for long time with HIV infection (median 12.5 years; interquartile range (IQR), 8.8, 15.3 years) and had many years of experience with ART (9.9 years; IQR, 6.4, 14.5 years). Baseline CD4 cell counts were relatively high and most had low level viremia (<500 copies/mL) or were undetectable at time of enrolment. curART regimens were similar in both arms with almost all participants receiving three or four tablets per day (two in each arm were receiving an STR). More participants had completely interrupted ART prior to enrollment in the ABC/3TC/DTG arm (n = 5 vs 0).

Virologic Suppression

The proportion of participants achieving HIV RNA < 50 copies/mL at week 24 was 4/12 (33%) in the curART arm vs 7/13 (54%) in the ABC/3TC/DTG arm. At week 24, the odds ratio (OR) for HIV RNA <50 copies/mL was 3.1 (95% CI, 0.57 to 21) for those randomized to ABC/3TC/DTG. With our weakly informative prior, the median Bayesian OR for HIV RNA <50 copies/mL was 1.2 (CrI, 0.46 to 3.3). Fitting a Bayesian logistic regression via Markov Chain Monte Carlo allowed us to calculate other statistics within the chain and sample these: the median Bayesian risk difference for the effect of treatment was 5% (95% CrI, −17 to 28%) higher for those randomized to ABC/3TC/DTG.

All seven participants achieving HIV RNA < 50 copies/mL at week 24 in the ABC/3TC/DTG continued in study and maintained viral suppression through week 72 (Figure 2). Of six remaining participants in curART arm who transitioned to ABC/3TC/DTG at week 24, 3 achieved HIV RNA < 50 copies/mL at weeks 48 and 72.

Adherence

All six participants who dropped out or stopped treatment (4 randomised to curART and 2 to ABC/3TC/DTG) were assigned an adherence of 0%. Reasons for dropouts are shown in Figure 1. The median reported adherence score was 90% (IQR 0% to 100%) for those randomised to curART (n = 12) and 90% (IQR 87% to 100%) for those to ABC/3TC/DTG (n = 13). The OR for mean adherence score at week 24 was 2.4 (95% CI, 0.42 to 14) for those randomised to ABC/3TC/DTG.

Table 1 Baseline Characteristics of Study Participants at Enrollment

Characteristic	ABC/3TC/DTG (n=13)	curART (n=12)
Age (median years, IQR)	48 (36, 49)	40 (33, 48)
Sex (female)	8 (62%)	6 (50%)
Ethnicity		
Black	6 (46%)	4 (33%)
Indigenous	4 (31%)	3 (25%)
White	3 (23%)	4 (33%)
Asian	0 (0%)	1 (8%)
HIV risk factor[a]		
IDU	4 (31%)	7 (58%)
Heterosexual	6 (46%)	4 (33%)
Endemic	3 (23%)	2 (17%)
MSM	2 (15%)	0 (0%)
HCV infection	4 (31%)	7 (58%)
History of depression/mental illness	7 (54%)	6 (50%)
Current Depression (PHQ-9 median score, IQR; n with score ≥ 10)	3 (2, 6); 1	6 (4, 8); 1
AUDIT-C (median score, IQR)	1 (0, 3)	1 (0, 5.2)
DUDIT (median score, IQR)	0 (0, 11)	11 (0, 18)
Time since HIV diagnosis (median years, IQR)	14 (12, 15)	10 (7, 15)
Time on ART (median years, IQR)	12 (9, 15)	7 (6, 13)
CD4 (median cells/ul, IQR)	347 (252, 550)	510 (286, 587)
HIV viral load (median copies/mL, IQR)	0 (0, 157)	150 (0, 443)
HIV viral load, <50 copies/mL	6 (55%)	3 (33%)
Prior resistance (184V/I mutation)	0 (0%)	0 (0%)
Baseline curART regimen backbone		
Protease inhibitor	5 (38%)[b]	6 (50%)
Integrase inhibitor	2 (15%)	4 (33%)
NNRTI	2 (15%)[b]	2 (17%)
No ART	5 (38%)	0 (0%)
Adherence VAS (last month) average, IQR	90 (80, 90)	95 (75, 100)
Adherence VAS (last week) average, IQR	100 (90, 100)	98 (58, 100)

Notes: [a]Patients may have > 1 risk factor so totals >100%. [b]One patient was receiving both rilpivirine and darunavir/ritonavir, so total >13. A score ≥10 signifies moderate depression necessitating a treatment plan, possible counseling, follow-up and/or pharmacotherapy.
Abbreviations: ABC/3TC/DTG, abacavir/lamivudine/dolutegravir; ART, antiretroviral; AUDIT, alcohol use disorders identification test; curART, current antiretroviral therapy; DUDIT, drug disorders identification test; PHQ-9, patient health questionnaire; HCV, hepatitis C virus; IQR, interquartile range; IDU, injection drug use; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitor; VAS, visual analog scale.

Reported adherence was high in both study arms for those remaining in the trial through to week 24 (n = 19). In this per-protocol population, the median reported adherence score was 100% (IQR 90% to 100%) and 90% (IQR 87% to 100%) in curART (n = 8) and ABC/3TC/DTG (n = 11) arms, respectively. The median Bayesian OR was 1.1 (CrI, 0.48 to 2.5) for those randomised to ABC/3TC/DTG. The median Bayesian risk difference for the effect of treatment was 1% (95% CrI, −9 to 10%) higher for those randomized to ABC/3TC/DTG.

Barriers to Adherence and Solutions Employed

Participants identified 119 barriers to adherence in total, which were grouped into six core themes (Table 2; Figure 3): forgetfulness, competing demands, substance use, negative treatment experiences, economic barriers/lack of insurance and insufficient support. Of these, forgetfulness was the most frequently reported (88% overall). This barrier was particularly important for PWID. Negative treatment experiences and competing demands, also commonly interfered with adherence.

In total, participants employed 113 different solutions which were grouped in the three categories (Table 2). Information-based solutions were used by 71% of participants. Behavioural skills were also commonly employed
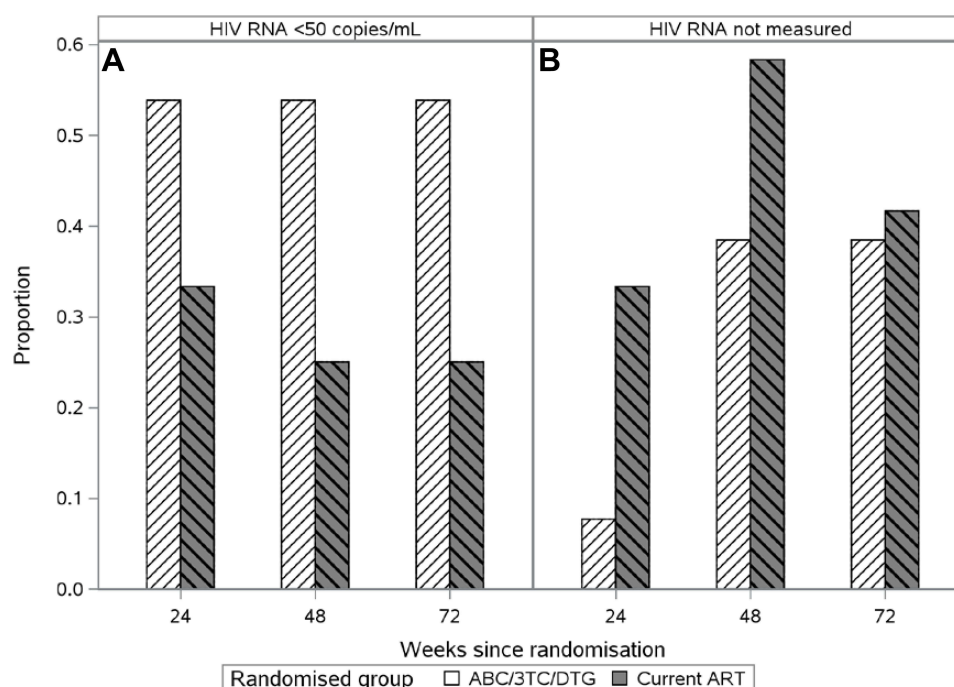
Figure 2 Virologic outcomes and retention by study arm over 72 weeks. Proportion of participants in each arm with (**A**) virologic suppression to <50 copies/mL by intention to treat analysis at week 24 (primary outcome), week 48 and week 72 and (**B**) without available HIV RNA measures at week 24, week 48 and week 72 (combines those withdrawn from study and those with missing visits and/or RNA values at the respective time points).
Abbreviations: White, ABC/3TC/DTG, abacavir/lamivudine/dolutegravir; dark grey, curART, current antiretroviral therapy.

(67%), particularly by PWID. Both information and behavioural solutions aimed to improve participants' "abilities and sense of self-efficacy concerning performance of a given health-related behaviour"[30] and thus principally targeted forgetfulness. Motivation-related solutions, especially those that sought to improve participants' social support, were used by 54%.

Discussion

Meeting the needs of vulnerable patients living with HIV remains a challenge and priority for reaching the enhanced UNAIDS 95-95-95 targets for ending AIDS worldwide by 2025.[31] In particular, ensuring 95% of those on ART maintain undetectable HIV RNA ("the last 95") is seen as critical to halting AIDS and onward HIV transmission.[31] Our trial was meant to address a specific knowledge gap at the time of its design: could an STR provide sufficient improvement in adherence to permit people with history of non-adherence to achieve viral suppression? The trial was stopped early due to slow enrollment. We can therefore only provide weak evidence that switching to ABC/3TC/DTG might improve rates of virologic suppression over 24 weeks compared to remaining on current ART when combined with enhanced adherence support. Viral suppression on ABC/3TC/DTG, once achieved, was durable through 72 weeks. However, despite providing personalised adherence support, almost 50% of those randomised to ABC/3TC/DTG did not achieve HIV RNA < 50 copies/mL, which was more than we expected and a reflection of the high risk, real-world population enrolled in this study. Many of these patients experienced low grade viremia, and while no resistance mutations were detected over the short term (data not shown), it is clear that solutions to improve adherence are still needed.

Since this study was designed, several large observational studies have shown that STRs are related to better adherence in real-world settings.[19] A recent meta-analysis of 8 studies and 30,470 patients led to an OR of 1.63 (95% CI, 1.52–1.74) when comparing STRs to MTRs with respect to optimal adherence (≥95%).[32] However, of five studies included that assessed the association between STR and virologic outcomes, the only one to include integrase inhibitor-based ART, from the Women's interagency HIV study, found that STRs were associated with greater virologic suppression (RR 1.06, 95% CI

Table 2 Barriers to Adherence Reported by Study Participants at Enrollment and Specific Solutions Employed to Improve Adherence

	ABC/3TC/ DTG n=13	curART n=11[a]
Core Barrier		
Forgetfulness Contributing factors: lack of motivation produced by exhaustion and mental health issues (eg, anxiety, loneliness); the fact that HIV can be largely asymptomatic; difficulties scheduling treatment with regular routines	11 (85%)	10 (91%)
Substance use of drugs or alcohol	4 (31%)	5 (46%)
Negative treatment experiences eg, difficulties swallowing pills and side effects	3 (23%)	4 (36%)
Competing demands eg, family responsibilities (eg, childcare), homelessness	4 (31%)	2 (18%)
Economic barriers and lack of insurance	1 (8%)	2 (18%)
Insufficient support from providers and others	3 (15%)	0
Solutions		
Information Education and counselling provided by the healthcare team and adherence-related heuristics (ie, automatic, cognitively effortless decision-making aids/strategies that helped patients prevent missing doses such as placing medications in a visible place, use of blister packs, delivery of medication, alarms, diaries and calendars, and check-in calls from providers).	8 (62%)	9 (82%)
Behavioural skills Linking HIV treatment with other daily routines (eg, a meal, teeth brushing, waking up) and keeping a consistent routine; making the intake of medications a neutral experience and knowing how to prevent side effects	9 (69%)	7 (64%)
Motivation Comprehensive addiction management and peer support programs (eg, Narcotics and Alcoholics Anonymous meetings), financial and employment assistance, having a trusting healthcare team, stable housing, establishing direct communication line with healthcare providers	8 (62%)	5 (45%)

Notes: [a]One participant randomised to curART failed to complete baseline questionnaires on barriers and solutions. Italics represent sub-categories of reported barriers and solutions.
Abbreviations: ABC/3TC/DTG, abacavir/lamivudine/dolutegravir; curART, current antiretroviral therapy.

1.01–1.11).[33] A 5% difference in the rate of virologic suppression associated with ABC/3TC/DTG is a plausible estimate of the treatment effect in our study where patients had prior non-adherence. By comparison, in an observational study of treatment-naive patients, the estimated risk difference for virologic failure was 3.4% when taking a single tablet rather than a three-pill efavirenz-based regimen for one year.[34] In randomised trials in naïve patients or those simplifying ART, it has been difficult to show any advantage of STR over MTR with respect to virologic suppression. Since virologic failure rates are so low with all modern ART regimens, any differences are generally driven by tolerability of trial regimens.[19] There have been no such randomized trials conducted specifically in non-adherent populations. Thus, while STR are associated with improved adherence, it remains unclear to what extent this benefit translates into improved virologic control, particularly in vulnerable, treatment experienced patients such as those included in our trial.

The very nature of non-adherence makes it difficult to study. Patients frequently under-report non-adherence and often re-start ART prior to clinic visits or blood testing due to social desirability bias.[35] This can result in difficulties with defining and capturing non-adherence in study inclusion criteria. Having a detectable viral load while receiving treatment, while easier to document, may not capture many people with suboptimal or intermittent adherence who could benefit from interventions. On the other hand, including many people with undetectable viral loads at baseline, despite clearly documented past non-adherence, can make it difficult to observe differences in virologic suppression
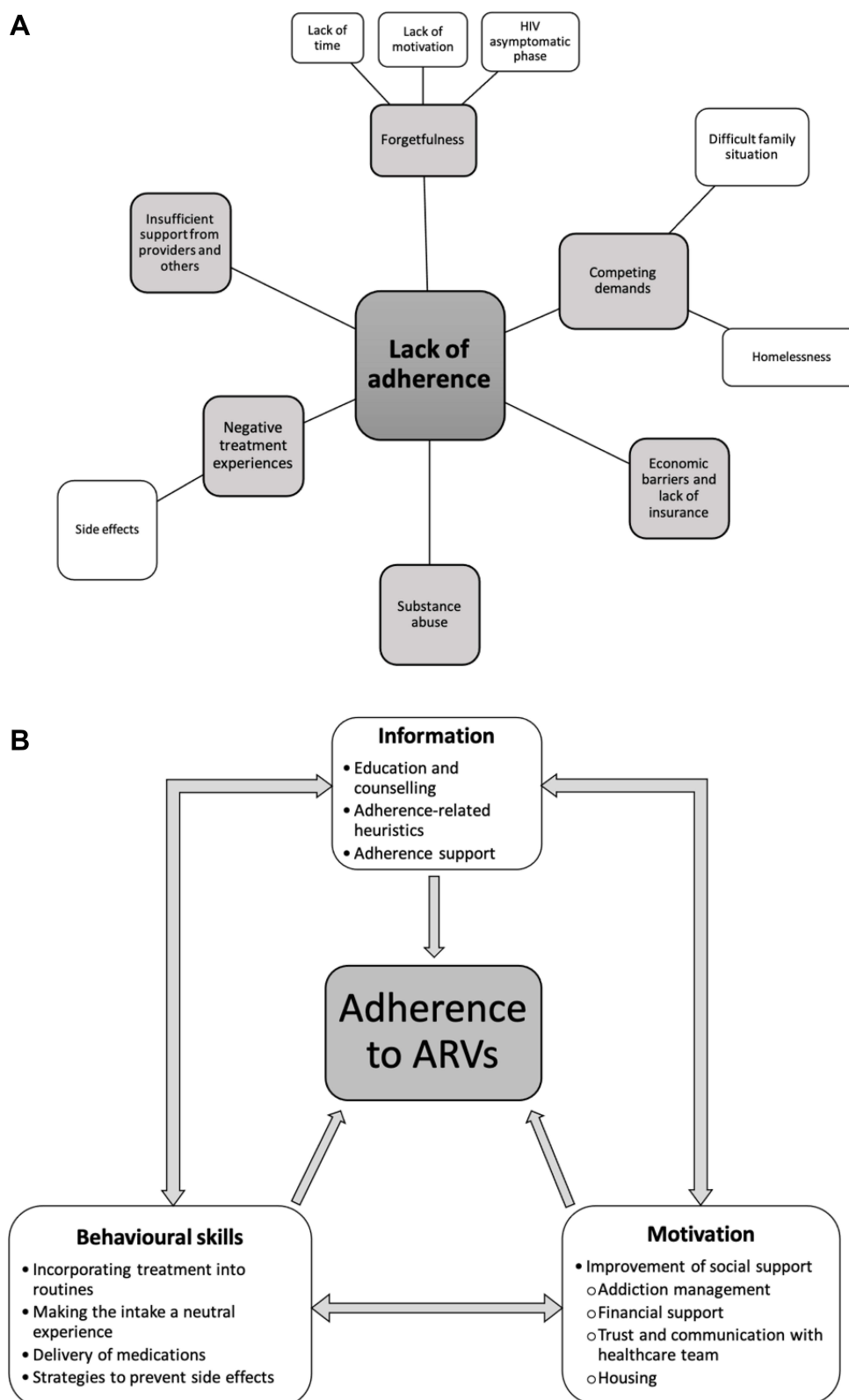
Figure 3 Adherence barriers experienced and solutions employed by participants. (**A**) The six core themes of barriers to antiretroviral adherence (in light grey) reported by participants and their contributing factors (in white). (**B**) Proposed solutions developed with participants grouped according to the Information-Motivation-Behavioral skill (IMB) model.[30]

between intervention and control arms over the short term. We chose to use broad inclusion criteria that would permit enrolment under a variety of scenarios – criteria which reflected the heterogeneity of the target population - and then stratified by HIV RNA at baseline. However, the resulting heterogeneity then made it impossible to draw conclusions about whether certain subpopulations might have benefited more from an STR than others.

There is also a need to ensure safety in trials. Finding non-adherent patients without major resistance was challenging. Indeed, the majority of screening failures (56%) were for this reason. The use of an adjudication committee was helpful in allowing us to assess patients for inclusion into the study given it was not always easy to apply simple inclusion and exclusion criteria. Given past histories of non-adherence, archived drug resistance was likely present in most enrolled participants. The impact of common nucleoside reverse transcriptase inhibitor mutations, such as the M184V/I, on the virologic success of triple regimens containing 3TC (ie, effectively resulting in dual therapy) was not clear early in the era of second-generation integrase inhibitors. While dual therapies using dolutegravir have now been shown to be effective,[36] at the time of our study's design, there was insufficient evidence to support enrolling patients with such mutations—the very patients for whom adherence interventions are most needed.

As we recruited non-adherent patients, it was appropriate to provide support to those randomised to the control arm and therefore all participants were offered adherence support. Combined approaches using patient education, behavioural change strategies and reminders are considered to be most effective for improving adherence.[37,38] However, their impact is at best modest (eg, 10–20% improvement)[16] in part because they fail to address structural and systemic barriers to treatment such as stigma,[39] racism and economic disparities.[40] We employed a number of measures in an attempt to address the numerous barriers faced by our study population. These measures included personalised adherence interventions, frequent study contact via telephone or text messaging and financial assistance with co-payments and with transportation to attend visits. Despite these labour intensive and costly measures, we were unable to recruit and retain sufficient participants to complete the trial. Indeed, a substantial proportion of eligible patients failed to return after screening for their randomization visit. The measures employed should have addressed forgetfulness, the barrier most commonly identified by participants. That the measures failed to substantially improve outcomes also suggests that participants themselves do not, or cannot, acknowledge the real reasons they struggle to adhere. Our study further underscores the importance of specifically addressing mental health and addictions which were among most common barriers we encountered.

Comparing the effect of a single versus multiple tablet regimens requires an open label trial design by necessity – increasing pill count to allow for blinding defeats the purpose of simplifying treatment. Indeed, it is not possible to blind adherence interventions in general. The lack of blinding is problematic in adherence trials as participants may intentionally or unintentionally change their actual and/or self-reported behavior to appear more adherent.[41] Regular study visits in a trial and added follow-up measures further create an artificial environment so that estimates may not reflect real-world effectiveness. Indeed, in our trial, more than 50% of participants had detectable viral loads during follow-up despite very high levels of reported adherence (>90%) in both study arms – this apparent disconnect suggests that participants over-reported adherence or failed to return pills. Virologic endpoints therefore provided an objective unbiased measure of actual adherence, at least over the short term. Alternate approaches for objectively measuring adherence over the long term could be introduced into adherence studies for example, electronic drug monitoring. Measurement of antiretroviral concentrations in short hair samples has also been shown to strongly predict HIV treatment outcomes.[42,43]

While randomised trials are considered the gold standard for assessing efficacy of interventions, as we experienced, they are not well suited to assessing the effectiveness of adherence interventions, especially in small populations of refractory non-adherent patients.[44] Alternative trial designs where the level of intervention is not the individual patient, such as cluster randomisation or step wedge designs with clinics, providers or health systems delivering the intervention could avoid issues related to individual patient recruitment and changing behaviours due to trial participation, but may be too complex and costly given the small number of patients who might benefit.[45] A trial nested within an existing cohort, with randomisation of non-adherent patients to an intervention desired by patients, might alleviate slow recruitment.[46] Alternatively, well-designed observational studies using statistical methods to mimic randomised trials[47,48] can provide estimates of effectiveness (rather than efficacy).[49]

At the time the trial was designed, there were few STR options available and gaining access to ABC/3TC/DTG through the trial was an incentive for patients and their providers to participate. During the study, however, multiple STR (including ABC/3TC/DTG) were approved and are now the mainstay of HIV care, both in high and low-and-middle-income countries which likely impacted trial recruitment. Participating in research, when other alternatives exist, can be difficult in populations that inherently mistrust research due to negative historical experiences (eg, Indigenous and ethnocultural communities).[50] The challenges we faced in recruiting and retaining participants and the small benefit of STR we observed demonstrates that despite the simplicity of STR, gains in adherence may only be possible using completely new approaches for some patients. Long-acting and injectable therapies provide promise to overcome issues of forgetfulness and to reduce stigma and negative feelings around HIV treatment that represent major barriers to adherence.[51] Unfortunately, long half-lives that permit long dosing intervals then mean that adherence is even more critical; otherwise patients are exposed to sub-therapeutic drug levels and the associated risk of developing resistance. In addition, prior drug resistance to integrase inhibitors or rilpivirine is a contraindication to the only approved long-acting treatment, further putting this option out of reach for many of the patients who need it most.[52]

Conclusions

Our trial, along with existing literature, is consistent with a slight improvement in viral suppression in a vulnerable population when an STR is combined with patient-level adherence support. However, even this comprehensive approach cannot be relied upon to reach the "last 95". Beyond treatment simplicity and tolerability, tailored interventions addressing stigma, substance use, financial and social determinants of health are still urgently needed for equitable treatment outcomes across all HIV infected populations. Our trial illustrates how randomised trials may not be the best approach for assessing adherence interventions given the heterogeneity of populations in adherence difficulties, treatment histories and the entrenched barriers they face.

Data Sharing Statement

De-identified participant data from the trial can be made available upon request by contacting MBK. Data will be available for 15 years following completion of the trial (July 2019). The study protocol is available through clinicaltrials. gov (NCT02354053).

Ethics Statement

The study has been approved by research ethics boards at each of the participating institutions as follows: community advisory committee of the Canadian Institutes of Health Research Canadian HIV Trials Network, the Research Ethics Board of the McGill University Health Centre (2016-1285), the Comité d'éthique de la recherche du CHUM (2016-5951), the Comité d'éthique de la recherche du CHU de Québec-Université Laval (2016-2730), the Veritas Independent Review Board (16030-11:28:5825-02-2016), the Ottawa Health Science Network Research Ethics Board (20160084-01H), the Research Ethics Board of Health Sciences North (15-039), the University Health Network Research Ethics Board (15-9172-B), the UBC-Providence Health Care Research Ethics Board, the Institutional Review Board Services of the Regina Qu'Appelle Health Region Research Ethics Board (REB-15-93), St Michael's Hospital Research Ethics Board (15-283). The study was conducted according to the Declaration of Helsinki. All participants provided written informed consent prior to being screened for the study.

Consent for Publication

All authors of this study have read the manuscript, accepted responsibility for the content of manuscript, consented for publication.

Acknowledgments

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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