

Randomized Controlled Pilot Study of Antiretrovirals and a Behavioral Intervention for Persons With Acute HIV Infection: Opportunity for Interrupting Transmission

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Background. Persons with acute HIV infection (AHI) have heightened transmission risk. We evaluated potential transmission reduction using behavioral and biomedical interventions in a randomized controlled pilot study in Malawi.

Methods. Persons were randomized 1:2:2 to standard counseling (SC), 5-session behavioral intervention (BI), or behavioral intervention plus 12 weeks of antiretrovirals (ARVs; BIA). All were followed for 26–52 weeks and, regardless of arm, referred for treatment according to Malawi-ARV guidelines. Participants were asked to refer partners for testing.

Results. Among 46 persons (9 SC, 18 BI, 19 BIA), the average age was 28; 61% were male. The median viral load (VL) was 5.9 log copies/mL at enrollment. 67% (10/15) of BIA participants were suppressed (<1000 copies/mL) at week 12 vs 25% BI and 50% SC ($P = .07$). Although the mean number of reported condomless sexual acts in the past week decreased from baseline across all arms (1.5 vs 0.3 acts), 36% experienced incident sexually transmitted infection by 52 weeks (12% SC, 28% BI, 18% BIA). Forty-one percent (19/46) of participants referred partners (44% SC, 44% BI, 37% BIA); 15 of the partners were HIV-infected.

Conclusions. Diagnosis of AHI facilitates behavioral and biomedical risk reduction strategies during a high-transmission period that begins years before people are typically identified and started on ARVs. Sexually transmitted infection incidence in this cohort suggests ongoing risk behaviors, reinforcing the importance of early intervention with ARVs to reduce transmission. Early diagnosis coupled with standard AHI counseling and early ARV referral quickly suppresses viremia, may effectively change behavior, and could have tremendous public health benefit in reducing onward transmission.

Keywords. acute HIV infection; HIV; Malawi; motivational interviewing; transmission.

Acute HIV infection (AHI) is the earliest possible period for HIV diagnosis, before emergence of HIV-specific antibodies [1]. The unchecked viral replication and high viral loads that occur in this phase, coupled with people being unaware of their infected status even if tested, results in AHI contributing a disproportionate share of all new infections, as compared with chronic infection [2–6]. Efforts to limit transmission during the high-risk AHI phase face several challenges: (1) persons with AHI must present for testing shortly after acquiring the virus; (2) during testing, they must be tested specifically for AHI, incorporating either a test for HIV p24 antigen with

a fourth-generation enzyme-linked immunosorbent assay (ELISA) or HIV RNA, because third-generation ELISA and most rapid antibody tests do not detect persons with very early infection; (3) after diagnosis, persons with AHI must either alter behavior rapidly or initiate antiretroviral therapy immediately in an attempt to lower infectiousness [7]. Taken together, these challenges represent a significant obstacle to the control of the HIV epidemic, especially in resource-limited settings.

In Malawi, we have successfully implemented routine testing for AHI within the context of clinical research for 15 years [8–11]. Recently, we expanded AHI screening to multiple sexually transmitted infection (STI) clinics and HIV testing and counseling (HTC) centers, demonstrating the feasibility of scaling up testing for AHI in an urban center [12]. Within this expanded testing, we embedded a randomized pilot study with the following primary objectives: (1) to evaluate the feasibility and acceptability of a behavioral intervention among persons with AHI and (2) to evaluate the feasibility and acceptability of short-term ARV use among persons with AHI. Secondary objectives were (1) to explore the effect of the interventions on HIV transmission risk behaviors; (2) to explore the effect of

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the interventions on uptake of partner HIV testing; and (3) to explore the effect of short-term preventative ARV use on markers of infectivity and resistance. This study was implemented within the context of the Malawian treatment guidelines in place at the time of this study, which included Option B+ for pregnant women and antiretroviral therapy (ART) initiation at a CD4 count of 350 cells/mL for men and nonpregnant women [13].

METHODS

Study Population and Setting

We screened for AHI at 2 STI and 2 HTC clinics in Lilongwe, Malawi. Enrollment and follow-up were completed between June 2012 and August 2014. AHI was defined as a detectable HIV RNA and a negative or discordant HIV antibody test. Per Malawi HIV testing algorithms, antibody testing included serial testing using Alere Determine HIV-1/2 (Alere) and Uni-Gold Recombigen HIV-1/2 (Trinity Biotech), with a tiebreaker for discordant results. Persons with 2 positive results were considered HIV-seropositive. Fingerstick specimens were tested for HIV RNA using a previously validated 9:1 pooling algorithm [14–16].

By protocol, persons with AHI were traced within 21 days of screening and asked to report to the clinic for test results. All successfully traced persons were given AHI-specific standardized post-test counseling, including information about AHI, and given the opportunity to enroll in the study.

Eligibility criteria for enrollment included documentation of a negative or discordant rapid HIV test and positive RNA within 21 days of enrollment, age ≥ 18 years, and intention to remain in the Lilongwe area for the duration of study follow-up (52 weeks). We excluded persons with a serious illness requiring systemic treatment or hospitalization, any drug or alcohol dependence that would interfere with adherence to study activities, or a history of imprisonment.

Primary participants were asked to refer sexual partners at any point during study follow-up for HIV testing using referral cards. To be eligible, partners had to bring the referral cards to 1 of the study clinics and be ≥ 18 years old. Partners with AHI were not co-enrolled as primary and partner participants.

The National Health Sciences Research Committee of Malawi, the Malawi Medicines and Poisons Board, the Biomedical Institutional Review Board at the University of North Carolina, Chapel Hill, and the National Institute of Allergy and Infectious Diseases' Prevention Science Review Committee approved all of the procedures for this study. All study participants provided written informed consent in the local language or English, if preferred. This study is registered at ClinicalTrials.gov (NCT01450189).

Study Arms and Randomization

Primary participants were randomized in a 1:2:2 ratio to 1 of 3 groups: (1) standard counseling (SC); (2) a multisession behavioral intervention (BI); and (3) the same multisession

behavioral intervention plus antiretrovirals (ARVs; BIA). We used blocked randomization with block sizes of 5, stratified by gender. Eligibility for ARV use, described below, was assessed after randomization to allow determination of the potential impact of the treatment regimen at a population level. All participants were referred for routine HIV care [17]. Participants not on study ARVs were asked to self-report ARV initiation that occurred outside of study drug distribution.

SC

Primary participants randomized to the SC group received a single standard post-test counseling session, encouraged to reduce transmission risk by reducing the number of sexual partners and using condoms consistently and correctly, and given supplemental information about AHI.

BI

The behavioral intervention was developed by adapting features of the Options Project [18] and Project SafeTalk [19–21]—interventions that have been shown to effectively reduce sexual risk behavior among people living with HIV [10]. Counseling sessions were delivered using a motivational interviewing-based approach [11, 22]. The intervention comprised 5 sessions within 8 weeks of enrollment: the first 4 early intervention behavioral sessions were at day 0, day 3, week 1, and week 2, with the fifth (booster) session at week 8.

These 5 sessions were designed to provide participants with the information, motivation, and skills needed to abstain from or practice protected sex during the brief 12-week acute HIV period, as well as plan for long-term behavioral risk reduction. Counselors worked with participants to develop patient-centered short-term risk reduction goals and strategies to achieve those goals. The booster session (week 8) emphasized articulating a long-term risk reduction plan.

BIA

In addition to the behavioral intervention, persons in the BIA group received a 12-week course of raltegravir (400 mg by mouth, twice daily) and emtricitabine/tenofovir (FTC/TDF; 200/300 mg by mouth, daily) beginning on day 3. The duration of therapy, 12 weeks, was based on a small trial that observed a reduction in HIV RNA levels in semen to undetectable using an unboosted protease inhibitor and results of a single-arm study in the North Carolina STAT Program for acute infection [23, 24]. Exclusion criteria for ARVs included hepatitis B surface antigen positivity, anemia, neutropenia, thrombocytopenia, renal or liver dysfunction, pregnancy, breastfeeding, known hypersensitivity to selected ARVs, or need for a contraindicated medication. Participants excluded from study ARVs within the BIA arm remained in the arm in an intention-to-treat design. Based on accepted practice at the time of this study, the ARV component of the intervention was not intended to provide

long-term HIV treatment, but rather to prevent transmission by reducing the viral load quickly.

Per the a priori protocol, ARVs were discontinued for any moderate (Grade 2) or worse toxicity, symptom, or laboratory abnormality, unless that abnormality was clearly unrelated to ARVs. ARVs could be discontinued at the discretion of the local investigator or clinician even if toxicity did not reach a specified grade. Integrase and reverse transcriptase (RT) genotypic resistance testing was performed on baseline, week 14, and week 26 samples. A safety and monitoring committee was charged with oversight of potential harms related to ARV resistance in the BIA group. ARV use in the BIA group would have been discontinued if the lower 95% confidence limit of the proportion of persons in the BIA arm with acquired resistance at 6 months exceeded 10%.

Study Visits: Laboratory and Clinical Evaluations

Primary participants in all groups had 10 scheduled visits over 52 weeks. Participants in the BIA group had 3 additional visits immediately after ARV discontinuation. A complete physical examination was conducted at enrollment. Genital ulcer exams were conducted quarterly, beginning at enrollment. All primary participants had repeat rapid HIV antibody tests at each visit until seroconversion was confirmed. Plasma HIV RNA was measured using Abbott RealTime HIV-1 Assay (Abbott Laboratories, Chicago, IL; m2000; reportable range of 40–10 000 000 copies/mL) or COBAS AMPLICOR HIV-1 MONITOR Test, version 1.5 (Roche Molecular Diagnostics, Pleasanton, California; reportable range of 50–750 000 copies/mL). Plasma viral loads were assessed at each study visit. Immunological (absolute CD4+/CD8+ counts and percentages), STI (*Chlamydia trachomatis* [Ct], *Neisseria gonorrhoea* [GC], using BD ProbeTec SDA assay, Franklin Lakes, New Jersey), *Trichomonas vaginalis* (Tv; BioMed InPouch TV, White City, Oregon), and herpes simplex virus type 2 (HSV-2; Focus Diagnostics HerpeSelect 2 ELISA IgG, Cypress, California) testing was conducted at entry and quarterly thereafter. STIs were treated upon diagnosis. Women received pregnancy testing every 4 weeks for the first quarter and quarterly thereafter.

Partner participants received HIV antibody testing at the time of presentation. HIV-seropositive partners had specimens collected for phylogenetic linkage and were not followed further. Partners with negative or discordant rapid antibody test results were screened for AHI. Partners who were confirmed uninfected or who were identified as having AHI were followed quarterly for the duration of the primary participant's enrollment, during which they received rapid HIV tests and AHI screening (if HIV-negative at the time of enrollment), as well as STI testing (if AHI- or HIV-negative at the time of enrollment). Partners who seroconverted after a previously negative test had plasma HIV RNA levels assessed. All partners with HIV infection were referred for routine HIV care.

Questionnaires

Participants completed questionnaires at each study visit using audio computer-assisted self-interview (ACASI) software. Content included demographics, sexual risk behaviors (including information on sexual partners), assessment of the confidence they felt for and the importance they placed on HIV disclosure and sexual risk reduction, and knowledge regarding acute and established HIV infection.

Analysis

All analyses were performed using Stata (version 13.0; StataCorp, College Station, TX) and SAS (version 9.4; SAS Institute Inc. Cary, NC). We conducted descriptive intention-to-treat analyses by intervention arm (SC, BI, BIA) for all outcomes. The Fisher exact test was used to compare the differences in proportions between arms for categorical variables, and *t* tests were used for continuous data. Differences were considered statistically significant when *P* values were <.05. We examined the cumulative incidence of a composite STI outcome of chlamydial infection, gonorrhea, or trichomoniasis at 12, 26, and 52 weeks.

RESULTS

Screening and Enrollment

A total of 9280 HIV-seronegative persons, including 55 (0.6%) with discordant rapid test results, were screened for AHI, and 59 persons were identified with AHI, a prevalence of 0.64% among those who were HIV-seronegative for HIV [12]. In the 4 weeks before screening, persons identified with AHI reported symptoms including genital ulcers or sores (42%), body aches (29%), fever (24%), and diarrhea (10%), which were all significantly more prevalent than in persons without AHI. Fifty-eight (98%) were successfully traced within the protocol-defined 21 days of AHI testing (median [range], 7 [4–17] days) (Figure 1). Forty-six of 58 (79%) were enrolled in this pilot study, with 9 participants randomized to the SC arm, 18 participants to the BI arm, and 19 participants to the BIA arm. Of the 21% who did not participate, all were eligible but refused further participation; no additional information is available regarding reason for refusal. Of the 46 participants, 14 (30%) were positive by both Determine and Uni-Gold 2 weeks after enrollment, 12 (26%) were positive by Determine only, and 15 (32%) were negative by Determine; 5 did not have rapid testing performed at 2 weeks.

Baseline Population Characteristics

The mean age of persons with AHI enrolled was 28 years. More men than women were enrolled (61% vs 39%, respectively) (Table 1), consistent with the proportion of men and women identified with AHI. Among those who reported at least 1 partner (*n* = 38), 32 (84%) reported no condom use. The overall median viral load (interquartile range [IQR]) was 5.9 (5.2–6.5) log₁₀ copies/mL. Sociodemographic characteristics were similar across study arms.

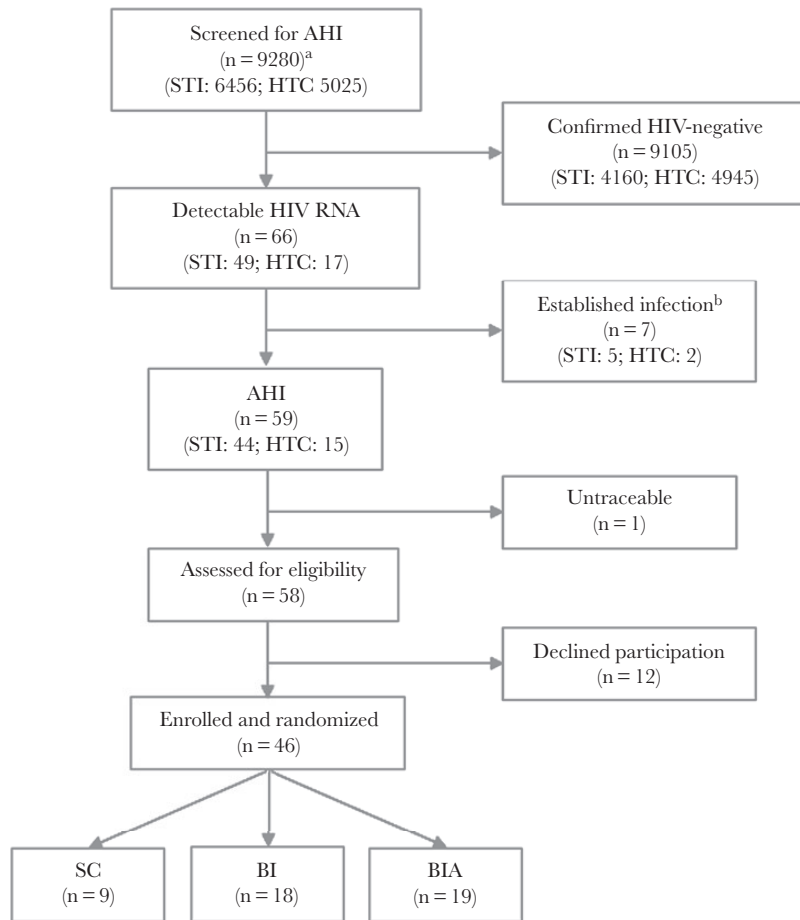


Figure 1. Participant screening, enrollment, and allocation to study arm. ^aBlood was not collected for 12 consenting participants; another 97 participants had insufficient volume for testing or the specimen clotted before testing. ^bFalse-negative antibody test from screening was confirmed on laboratory retest. Abbreviations: AHI, acute HIV infection; BI, behavioral intervention; BIA, behavioral intervention plus treatment; HTC, HIV testing and counseling; SC, standard counseling; STI, sexually transmitted infection.

Behavioral Intervention

The acceptability of the behavioral intervention was measured through the uptake of the intervention. Overall, 81% (30/37) of BI and BIA participants completed all 4 early intervention behavioral sessions, 28 (76%) of whom did so within 3 weeks of enrollment. The median time to session completion (IQR) was 16 (14–18) days.

We assessed the impact of the behavioral intervention on sexual HIV risk behavior by examining self-reported unprotected sex acts and STI incidence in each arm over the 52-week study period. Among all participants (SC, BI, or BIA) with data available, the mean number of unprotected sex acts in the past week was 1.5 (SD, 3.0; n = 44) at week 0, 0.7 (SD, 1.9; n = 36) at 12 weeks, and 0.3 (SD, 1.0; n = 25) at 52 weeks (Figure 2). A similar downward trend was observed when evaluating unprotected sex acts in the previous month. No meaningful difference was discernable across arms.

As an alternative measure of unprotected sex, we examined the cumulative incidence of a composite STI measure at 12, 26, and 52 weeks. Across all groups, the cumulative incidence was

15% (95% confidence interval [CI], 4%–25%) at 12 weeks, 22% (95% CI, 10%–35%) at 26 weeks, and 38% (95% CI, 21%–53%) at 52 weeks. The incidence was highest, although not statistically significantly so, in the BI arm (25% at 12 weeks, 31% at 26 weeks, 47% at 52 weeks) compared with SC (13% at 12 weeks, 13% at 26 weeks, 25% at 52 weeks) and BIA (6% at 12 weeks, 19% at 26 weeks, and 35% at 52 weeks). For HSV-2, 13 were negative at baseline; 4 of 10 with available results seroconverted by 26 weeks (SC 1, BI 2, BIA 1) and another 1 (BI) by 52 weeks.

Antiretroviral Intervention

Among the 19 persons assigned to the BIA arm, 12 initiated study ARV. Among those who did not initiate study ARV, 1 withdrew before initiation, 2 were breastfeeding and were referred to initiate Malawi firstline ARVs, and 4 were excluded due to hepatitis B surface antigen test positivity. Among the 12 who initiated study ARV, 10/10 with available week 12 results had a VL <1000 copies/mL, and 9/10 had a VL <50 copies/mL (Figure 3). Three of 6 participants in the BIA arm who were retained in the study but not initially eligible

Table 1. Basic Demographics and Baseline Behavioral Characteristics

	Overall(n = 46)		SC(n = 9)		BI(n = 18)		BIA(n = 19)	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Age, y^a								
18–24	19	(41)	2	(22)	8	(44)	9	(47)
25–34	20	(43)	4	(44)	8	(44)	8	(42)
35–44	6	(13)	3	(33)	2	(11)	1	(5)
≥45	1	(2)	0	(0)	0	(0)	1	(5)
Sex								
Male	28	(61)	5	(56)	11	(61)	12	(63)
Female	18	(39)	4	(44)	7	(39)	7	(37)
Education								
≤ primary completed	26	(57)	6	(67)	8	(44)	12	(63)
Some secondary	12	(26)	1	(11)	5	(28)	6	(32)
≥ secondary completed	8	(17)	2	(22)	5	(28)	1	(5)
Employment status								
Employed	30	(65)	7	(78)	11	(61)	12	(63)
Not employed	16	(35)	2	(22)	7	(39)	7	(37)
Marital status								
Never married	11	(24)	3	(33)	6	(33)	2	(11)
Married	23	(50)	4	(44)	8	(44)	11	(58)
Divorced/separated/widowed	12	(26)	2	(22)	4	(22)	6	(32)
Total partners (previous 4 wk)^b								
0	7	(16)	2	(22)	1	(6)	4	(21)
1	27	(60)	6	(67)	9	(53)	12	(63)
≥2	11	(24)	1	(11)	7	(41)	3	(16)
Condom use (previous 4 wk)^c								
None	19	(43)	5	(56)	7	(44)	7	(37)
Some	12	(27)	2	(22)	4	(25)	6	(32)
Every time	6	(14)	0	(0)	4	(25)	2	(11)
No sex reported	7	(16)	2	(22)	1	(6)	4	(21)
Total partners (previous 1 wk)^b								
0	22	(49)	4	(44)	12	(71)	6	(32)
1	19	(42)	4	(44)	4	(24)	11	(58)
≥2	4	(9)	1	(11)	1	(6)	2	(11)
Viral load^b								
≤6.0 log ₁₀ copies/mL	24	(53)	5	(56)	7	(41)	12	(63)
>6.0 log ₁₀ copies/mL	21	(47)	4	(44)	10	(59)	7	(37)

Abbreviations: BI, behavioral intervention; BIA, behavioral intervention plus treatment; SC, standard counseling.

^aMean age (SD), 28 (7) years.

^bn = 45.

^cn = 44.

for the study drug (2 breastfeeding and 1 HBV-positive) were started on firstline ARVs during the study follow-up period (weeks 4, 8, and 26, respectively); 1 of the 2 who were on standard firstline treatment by week 12 had a VL <1000 copies/mL at the week 12 visit. At week 26 (approximately 14 weeks off of the study drug), 10/12 who had been on the study drug had their VL rebound (VL >1000 copies/mL); the other 2 remained suppressed (255 copies/mL and <40 copies/mL) despite being off ARVs. Two BIA participants who received the 12-week study ARV were started on firstline ARVs later in their 52-week follow-up, 1 based on CD4 eligibility. We could not identify a reason for treatment initiation for the other with available data.

Among the 27 persons in the SC and BI arms, 4 initiated ARVs during the first 12 weeks (SC 2, BI 2; indications: 1 breastfeeding, 1 low CD4, 2 not specified); all 4 were virally suppressed at week 12. Five initiated ARVs later in follow-up (indication: 1 low CD4, 1 pregnancy, remainder not specified), and 3 were suppressed to <1000 copies/mL before study completion.

Among participants with available VL data, week 12 viral suppression was greatest in the BIA group (BIA 11/15, 73% [11 on therapy]; BI 4/16, 25% [2 on therapy]; SC 3/6, 50% [2 on therapy]; *P* = .07). Across all groups, 49% (18/37) of persons with available VLs were suppressed to <1000 copies/mL at week 12; 15/18 were on therapy. After accounting for missing data by

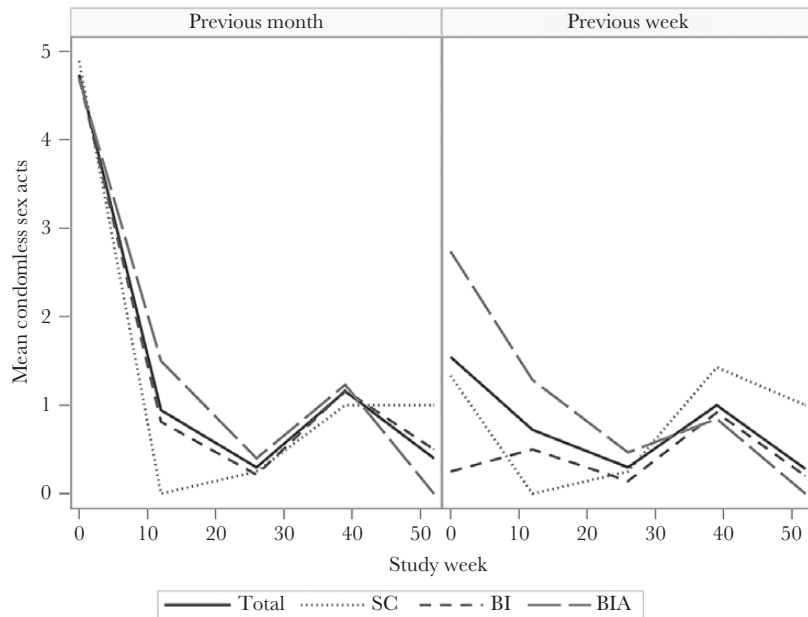


Figure 2. Mean number of condomless sex acts over the previous month (left) or previous week (right) over the course of the study, by study arm. Abbreviations: BI, behavioral intervention; BIA, behavioral intervention plus treatment; SC, standard counseling.

using the closest visit with an available RNA specimen, the proportion with a VL <1000 was more pronounced (20/42, 48%; BIA 13/18, 72%; SC 3/8, 38%; BI 4/16, 25%; $P = .02$).

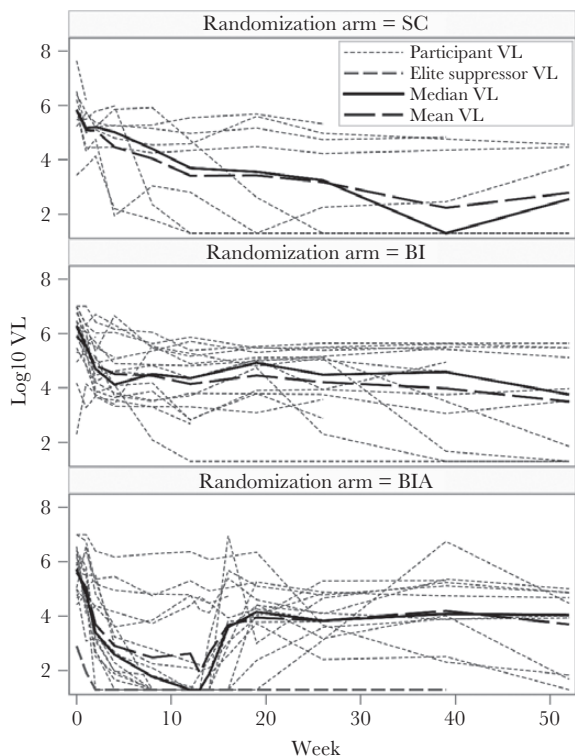


Figure 3. Log_{10} viral load by study arm. Median, mean, and individual viral loads are shown. Viral load for one elite suppressor in the BIA arm is also shown. Abbreviations: BI, behavioral intervention; BIA, behavioral intervention plus treatment; SC, standard counselling; VL, viral load.

After treatment interruption at 12 weeks, viral rebound was observed in all but 1 of the BIA arm participants, who received and then stopped study-provided ARV by week 16 (Figure 3). Rebound $>10^6$ copies/mL was seen in 2 participants; 1 of these was substantially delayed. Viral setpoints after discontinuation were comparable to the other arms.

One woman in the BIA arm was considered an elite suppressor. At screening, her VL was 13 780 copies/mL with a positive Determine and a negative Uni-Gold antibody test. Her VL declined before ART (Figure 3), and at the conclusion of the study, she was undetectable off of ART with negative Determine and Uni-Gold tests.

We examined antiretroviral resistance in the BIA arm at weeks 0, 14, and 26 (Table 2). None of the participants in this study had documented new mutations as a result of study treatment, although approximately half of the samples at week 14 did not amplify due to low HIV RNA levels. On or after week 14, 5 participants had a non-nucleoside reverse transcriptase inhibitor mutation, 2 had an nucleoside reverse transcriptase inhibitor mutation, and 1 had an integrase strand transfer inhibitor accessory mutation: all mutations detected were present at week 0.

Partner Referrals and Transmission

Among 46 participants, 19 (41%) referred partners for evaluation, representing 14% of all reported sexual partners ($n = 136$) in the 52-week follow-up period. No participants referred >1 partner. The percentage of participants referring a partner was similar across arms (SC 44%, BI 44%, BIA 37%). All 19 partners reporting for evaluation agreed to HIV testing; 15/19 (79%) had

Table 2. Antiretroviral Resistance in the BIA Arm

	NRTI		NNRTI		Integrase Inhibitors	
	No.	(%)	No.	(%)	No.	(%)
Week 0 ^a	2	(11)	5	(26)	0 ^b	(0)
Week 14 ^c	0 ^d	(0)	2	(33)	0 ^e	(0)
Week 26 ^f	2	(15)	3	(23)	0 ^b	(0)

Abbreviations: BIA, behavioral intervention plus treatment; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; VL, viral load.

^aNineteen participants were screened.

^bAccessory integrase resistance was identified in 2 at week 0 and 1 at week 26 (week 0: L74I, H51Q; week 26: H51Q).

^cTwelve participants were screened for NRTI and integrase inhibitor resistance; 6 were screened for NNRTI resistance.

^dSix of 12 did not amplify; all VL <100 copies/mL.

^eFive of 12 did not amplify; all VL <100 copies/mL.

^fThirteen participants were screened.

established HIV infection, 1 (5%) had acute HIV infection (BI index, partner diagnosed with AHI 26 weeks into index participant follow-up), 1 (5%) seroconverted during the study (SC index, partner diagnosed 13 weeks into index participant follow-up), and 2 (10%) remained seronegative. All but 1 partner (13/14, 93%) were phylogenetically linked to the referring participant [25].

DISCUSSION

In this study, we assessed the potential public health benefit of intervening during the brief window of AHI to prevent HIV transmission. We successfully identified persons with AHI and engaged them in behavioral and antiretroviral-based interventions. Reductions in viral load were achieved rapidly in the BIA arm, with more than a log₁₀ difference by week 4 and suppression to <1000 in all participants eligible to receive study ARV. Most persons reported reduced sexual behavior risk, regardless of the intervention arm [10, 11, 22, 26].

This study is one of the first to explore AHI treatment in the Sub-Saharan African context, despite the focus on the feasibility of early treatment as a means to prevent AHI-associated transmission [27]. In our study, we limited the treatment period to 12 weeks, given the absence of World Health Organization (WHO) guidelines for AHI treatment at the time and our emphasis on rapidly reducing viral load for the purposes of decreasing transmission. This approach is not consistent with current WHO recommendations to initiate and maintain therapy when people are diagnosed with HIV, including AHI, based on a universal treatment strategy [28]. This duration of treatment before interruption is also considerably shorter than most other studies of treatment interruption after acute/early infection, making it difficult to compare to those studies [29]. Nonetheless, the lessons learned remain pertinent, and rapid identification of persons with AHI followed by rapid ARV initiation remains relevant, especially as point-of-care tests

capable of accurately detecting viral RNA in resource-limited settings become available.

Two-thirds of participants in the BIA arm achieved viral suppression by 12 weeks after ARV initiation. Several participants in the BIA arm did not initiate ARV because of hepatitis B surface antigen positivity to avoid exposure to a single active agent, tenofovir; this group would not be excluded from most treatment guidelines. The proportion of VL suppression within 12 weeks among those who actually received ARV was 100%. This rate of rapid viral suppression during AHI is comparable to that observed in the United States and Thailand [30, 31]. This rapid viral suppression is also consistent with a South African cohort study in which women were tested twice weekly for HIV using polymerase chain reaction by finger prick [27]. Immediate treatment for these women with Feibig stage I AHI led to viral suppression in <3 weeks. The rapid decline in viral load in our cohort may be due, in part, to use of an integrase inhibitor in the regimen—an alternative WHO firstline therapy that may soon be standard firstline in many Sub-Saharan African settings [32–35]. The initiation and subsequent discontinuation of ARV was not associated with any detectable antiretroviral resistance beyond what was present at baseline.

ARV use among persons in the other arms was common, due to both pregnancy/breastfeeding and CD4 eligibility. Overall, one-third (9/27) of persons in the non-ARV arms initiated ARV during study follow-up (up to 52 weeks for most); 4 started within 12 weeks of enrollment, but only 1 within the first 4 weeks. Despite success in terms of viral suppression post-ARV initiation, the potential transmission interruption during AHI was only realized in a small fraction as most initiated therapy well outside of the acute window. We also noted that a few people appeared to have periods of viral suppression without reported ARV use. This finding is consistent with other longitudinal studies of AHI, in which about 8% of persons with AHI had spontaneous viral suppression in the first year after diagnosis [36]. Unfortunately, in our case, we were limited by the self-reported nature of nonstudy ARV initiation, which may have led to some misclassification.

After diagnosis, reporting of risky sexual behaviors was substantially reduced. Participants in all arms reported <1 unprotected sex act per week after AHI diagnosis, a decrease that persisted through 52 weeks. This finding is consistent with HPTN 062, which used a similar behavioral intervention in Lilongwe [11]. The behavioral intervention was moderately acceptable, with about three-quarters of participants receiving the intervention within 3 weeks of enrollment. Nonetheless, the behavioral intervention (BI and BIA) appeared to have little if any additional protective effect beyond standard counseling on either reported condom use or STI acquisition. The standard counseling included specific information related to acute HIV infection, including the increased risk of transmission, which may have influenced behavior. At a minimum, we believe that

counseling for persons with AHI should emphasize the potential for early transmission, the need for partner notification and referral, and the importance of immediate ARV to prevent onward transmission [26].

The self-reported values of sexual behavior, despite the use of ACASI, may underestimate true levels of risk behavior [10]. Biological markers in the form of STI incidence indicate non-trivial amounts of condomless sex—the cumulative incidence of chlamydial infection, gonorrhea, or trichomoniasis was nearly 15% at 12 weeks and exceeded 20% at 26 weeks—suggesting that some persons continued to engage in behavior that could potentially result in HIV transmission, even in the extremely high-risk 3-month period after acquisition. Of course, STI incidence is not a perfect proxy for HIV transmission risk, as unprotected intercourse between 2 HIV-infected persons does not carry any HIV transmission risk, a distinction we were unable to make here in the absence of information about every partner's HIV status. Among the partners referred by ~40% of all participants (using passive partner notification), nearly 80% were already HIV-infected. However, 10% of the initially uninfected partners seroconverted after enrollment, indicating appreciable ongoing transmission risk in this cohort. The low yield of partners presenting via passive partner notification highlights the importance of active forms of partner services, especially to reach casual partners, with provider-initiated partner notification as a more effective means of testing partners and identifying new infections [37–40].

CONCLUSIONS

Despite challenges in identifying persons with AHI, once identified, they are generally readily linked into care and can quickly achieve viral suppression. Using STI incidence as a proxy for ongoing risk behaviors suggests that behavior change, particularly longer-term change, may have been less successful than self-reported measures indicate, emphasizing the importance of ARV initiation to reduce HIV transmission. The public health benefits of AHI detection and ARV initiation are not limited to transmission risk reduction in the weeks or months after HIV acquisition; this early detection and viral suppression could represent years' worth of averted transmissions, as these persons would otherwise be misdiagnosed as HIV-negative and potentially transmitting, not only during their acute phase but during established infection until they again sought testing services. Ramping up “test and start” will likely have a substantial impact on transmission, but in the absence of testing algorithms that identify persons with AHI, “test and start” will successfully decrease the transmission rates only among persons with established infection, ultimately increasing the contribution of AHI to the percentage of overall transmissions. Persons with AHI remain a critical population to identify and immediately treat, and we have demonstrated that both tasks are feasible even in resource-limited settings.

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