PLUS: Full Trial Protocol

Improving HIV and Alcohol-Related Outcomes among HIV+ Persons in Clinic Settings

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212-523-6500

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Mount Sinai Comprehensive Health Program - Downtown
275 7th Avenue – 12th Floor
New York NY 10011

SITE 3:
Morningside Clinic
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No-Treatment Control Group obtained at:
Samuels Clinic
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1000 10th Avenue, Suite 2T
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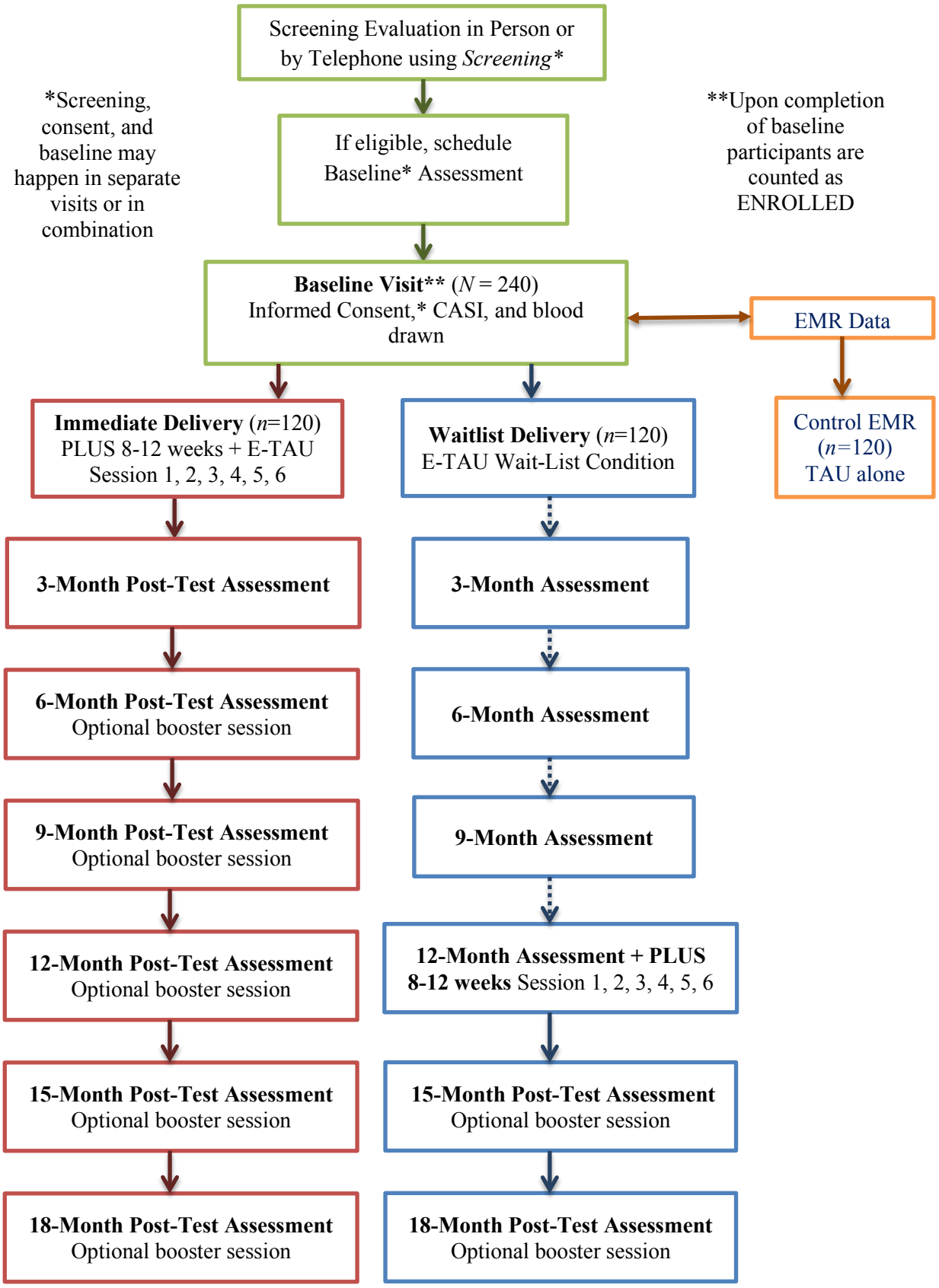
LIST OF ABBREVIATIONS

ART	Antiretroviral Therapy
AUDIT	Alcohol Use Disorders Identification Test
BL	Baseline
BSI	Brief Symptom Inventory
CASI	Computer Assisted Self Interview
CBT	Cognitive Behavioral Therapy
CBST	Cognitive Behavioral Coping-Skills Training
CET	Comparative Effectiveness Trial
DAST	Drug Abuse Screening Test
EMR	Electronic Medical Record
E-TAU	Enhanced Treatment as Usual
FU	Month Follow-Up
ICD	International Classification of Diseases
IP	Immediate Post-Test Assessment
IRB	Institutional Review Board
MI	Motivational Interviewing
MITI	Motivational Interviewing Treatment Integrity Coding System
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIH	National Institute of Health
PI	Principal Investigator
PID	Participant Identification Number
PLUS	Positive Living through Understanding and Support
QA	Quality Assurance
RA	Research Assistant
TAU	Treatment as Usual
VAS	Visual Analogue Scale
VL	Viral Load

PLANNED STUDY DESIGN



STUDY OBJECTIVES

Our goals were to better understand alcohol-related outcomes among HIV-positive persons over the lifespan and to implement a multisite comparative effectiveness trial (CET) in real-world clinical settings with three intensities of treatment to test their relative effectiveness in improving ART-adherence and alcohol-related outcomes among HIV-positive individuals who drink alcohol at harmful or hazardous levels. We aimed to achieve the following four Specific Aims:

Aim 1: Adapt the PLUS intervention for delivery in HIV clinic settings by mental health providers, and incorporate booster sessions designed to sustain longer-term effects. We aimed to conduct formative research, and utilize our findings as well as capitalize on existing systems and approaches utilized by SCCH (e.g., text messaging) to adapt PLUS for delivery in clinic settings as well as to develop booster sessions.

Aim 2: Test the effectiveness of the PLUS intervention delivered in a consortium of HIV clinics in New York City using a multisite CET with three intensities of treatment. Our primary goal was to test the PLUS intervention—an efficacious, theory-based intervention that integrates MI and CBST—versus an eTAU condition and TAU alone in reducing alcohol use and improving ART adherence, viral, and immunologic outcomes among HIV+ hazardous drinkers.

Aim 3: Assess the cost-effectiveness of PLUS. If effective, we aimed to conduct analyses to assess the cost-effectiveness of PLUS in treating HIV+ hazardous drinkers compared to eTAU and TAU alone as estimated over 5- and 10-year windows.

Aim 4: Collect and analyze retrospective cohort data and prospective natural history data, via Electronic Medical Records (EMR) at the SCCH clinics. We aimed to conduct retrospective cohort analyses to compare virologic, immunologic, medical outcomes, and adherence to medical appointments/engagement in care between those who do (n = 1505) and do not (n = 3692) meet diagnostic criteria for alcohol abuse/dependence. We aimed to use the third SCCH clinic (which will not receive any intervention) as a natural history comparison group, and conduct prospective analyses of data to better understand the natural history of the intersection between problematic alcohol use and HIV medication adherence and HIV health outcomes. Of particular focus were analyses of potential differences by age, race/ethnicity, gender, sexual identity, viral hepatitis co-infection, years living with HIV, and years on ART.

Trial Design

This study utilized a CET design to evaluate the effectiveness of the PLUS intervention components against a waitlist condition, and for VL and CD4, against a No-Treatment control group. Four sites were distributed across three study conditions in a quasi-experimental design. Two sites (Sites 1 and 2) implemented immediate treatment (Condition 1). Immediately after baseline, participants were offered the PLUS intervention. Participants then completed follow-up assessments at 3, 6, 9, 12, 15 and 18 months post-baseline. Site 3 implemented both the waitlist condition (Condition 2) from March 26, 2015 to October 31, 2016, and an immediate condition. Due to challenges in participant accrual, this site shifted to enrolling participants in the immediate intervention condition from November 1, 2016 through the end of the study. Participants in the waitlist condition received the intervention following completion of their 12-month follow-up. Site 4 is the no-Treatment Control EMR Group.

METHODS: Participants, Interventions and outcomes

Inclusion Criteria

- 18 years of age or older
- HIV-positive
- Currently receiving ART
- Current VL >200 copies/ml
- Report drinking at hazardous levels, operationalized as exceeding 14 standard drinks per week for men or exceeding 7 standard drinks per week for women, as per NIAAA guidelines. In a later amendment, criteria were expanded to also include reported use of illicit drugs exclusive of marijuana or illicit use of prescription opioids within the past 3 months.
- Must be a current patient at the clinic with current lab results

Exclusion Criteria

- Effectiveness trials should enroll participants that reflect the population for which the treatment is intended. Thus, we are keeping exclusion criteria to a minimum and imposing few eligibility criteria to identify our target clinical population.
- Given that the PLUS manual with guided step-by-step instructions, questions, and probes, as well as various modules and hand-outs for participants are all in English, study candidates will need to be able to communicate effectively in English.

- Any thought disorder (e.g., psychosis, schizophrenia, bipolar, having severe symptoms of psychological disorder) that would impair the individual's ability to provide informed consent or interfere with the study procedure.
  *** **NOTE:** Co-morbidities such as mental health problems, i.e., depression and anxiety disorder, and drug use are NOT considered exclusion criteria. Additionally, current or previous participation in behavioral or neurocognitive studies or interventions is NOT considered an exclusion criterion.
- Intoxication or under the influence of alcohol or other substances at the time of consent that would impair the individual's ability to provide informed consent or interfere with the study procedure.

INTERVENTION PROCEDURES

The six-session intervention is based on the PLUS (Positive Living through Understanding and Support) Clinical Protocol Manual. PLUS is an efficacious, theory-based intervention that utilizes motivational interviewing and cognitive behavioral skills training to reduce alcohol use and improve medication adherence. The participants were informed that the sessions would focus on alcohol use, other drug use and medication adherence. Sessions were delivered by a study therapist (psychologists, social workers and psychiatrists) employed at the clinics.

Six Sessions of PLUS

Session 1: Guidance on Participant Engagement in MI

In Session 1, the therapist spends some time talking about the participant's perception of their behaviors (drinking, substance use and medication adherence) and what types of changes they would like to make. During these first sessions, the therapist *focuses on a target behavior and offers them feedback* from the assessment instruments they completed at baseline. In an MI-consistent style, the therapist proceeds with strategies such as using *open questions and reflections to elicit and evoke participant's readiness for change,* and may move towards the planning phase collaborating on a change plan.

Session 2: Overview of Functional Analysis Session

The second session began with re-engagement briefly summarizing the last session's major themes on alcohol, substance use and adherence, highlighting any goals or plans that were discussed. The therapist *explores recent episodes of all relevant target behaviors* – drinking,

using drugs, and missing doses of HIV medication in order to gain a comprehensive understanding of the common *contexts of the participant's risk behaviors.* Although in this session the therapist begins using *CBST techniques*, the goal was to continue to communicate with the participant in an *MI* consistent fashion, using "OARS" (Open Questions, Affirmations, Reflections and Summaries) reflective listening skills. As these patterns become more clear, the therapist organizes them into a *functional analysis,* which summarizes the chain (or sequence) of events, behaviors, and consequences typically involved in the target behaviors. The therapist can then examine patterns across these chains to create a *case conceptualization.* Next step involves orienting the participant to the idea that chains can be disrupted. The creation of this functional analysis provides a starting point for discussing the rationale for CBT intervention and also for planning the specific CBST skills that a particular participant might focus on.

Sessions 3-5: Overview of Session Protocol for CBST Sessions

Each of the three CBST sessions follows a similar protocol, although a different module/s may be covered in each session. Although modules are general guidelines for delivering skills, content covered with the participant should be specific to the participant's needs. The therapist should *try to complete at least two modules for each target behavior* (substance use / medication adherence). More than one module may be presented to the participant during a single session, but it is important that the participant doesn't become overwhelmed by information. ***With permission, teach coping skills, conduct in-session exercise, and assign practice exercise.***

Session 6: Overview of Relapse Prevention Protocol

Initial step of this session is to ***briefly review the goals previously identified*** in the change plan. This summary should acknowledge ongoing discrepancy between current and desired status; however, it should also incorporate an ***emphasis on progress made*** during treatment. If the participant is in action or maintenance phase, the therapist needs to assess the participant's interest and willingness to discuss a ***relapse prevention plan.*** The therapist also needs to collaborate with the participant to develop an ***emergency plan*** on how they might cope with a high risk situation and what they would do should a slip or relapse occur.

Booster Session:

The purpose of the optional booster session was to 'check in' with the participant on how they are doing with their drinking, substance use and HIV medication adherence, and remind them of when their next booster is (except for when this is the final booster session). At the end of the

session, summarize the main points affirming any efforts the participant has made to proceed towards their goals. Briefly recap any plans made during the session, including any plans to access referrals.

Timeline

The PLUS intervention was adapted from an original eight session intervention to six sessions based on feedback from mental health staff at the sites. c. Research staff will keep track of participant's attendance during PLUS intervention period via the tracking log. Booster sessions will also be scheduled and conducted but will not be required for treatment exposure to the PLUS intervention.

Enrollment in Immediate and Waitlist control conditions

Potential participants in the immediate and waitlist control conditions were identified through a prescreening review of EMR, which provided study staff members with lists of patients with scheduled clinic visits who had one or more detectable viral load within the past year. Study staff approached these patients during clinic visits to introduce PLUS and invited them to participate in screening. Participants provided verbal consent for screening and provided written informed consent if they were eligible and interested in enrolling. They also granted permission for the study team to abstract their EMR data for study screening and enrollment purposes.

Once consent to use the EMR was granted, eligibility criteria were verified for ART regimen and viral load. Participant self-report was used to determine alcohol and substance use criteria on the screening questionnaire. Eligible participants who enrolled in the study were scheduled for a baseline visit, which could take place the same day post-screening or be scheduled within the ensuing month. The full protocol was approved by the institutional review boards at Hunter College and Mt Sinai.

Therapist Training

All therapists involved in the PLUS intervention were trained on Motivational Interviewing (MI), Cognitive Behavioral Skills Training (CBST), and the PLUS Clinical Manual. MI and CBST trainings were provided by the Center for HIV Educational Studies and Training (CHEST). After trainings, therapists held four mock-sessions with a mock participant. All MI mock sessions were coded via the Motivational Interviewing Treatment Integrity (MITI) system and were reviewed for fidelity with CBST. Therapists were given feedback from trainers

and were asked to repeat session based on feedback to reach competency in intervention as needed.

Intervention Monitoring and Quality Control

Standardized rating systems (MITI Coding with a CBST checklist) were used to evaluate the competency of study therapists prior to rollout of the full trial. Once the trial began, we monitored the implementation and select 25% of taped sessions to assess fidelity to protocol.

MEASURES

Primary Outcome Measures

- Biological Marker of HIV-Related Health Outcomes
    - Viral load and CD4 extracted from EMR
- Alcohol Use
    - Alcohol Use Disorders Identification Test (AUDIT)
    - Hazardous Drinking
- Medication Adherence
    - Visual Analog Scale (VAS) for Medication Adherence

Secondary Outcome Measures

- Substance Use
    - Drug Abuse Screening Test (DAST)

Other Self-Reported Measures

- Demographics
- Brief Symptom Inventory-18 (BSI-18)
- Self-Efficacy VAS for Alcohol, Drugs, Adherence, Sex Risk, and Doctor's Visits
- Patient Satisfaction
    - Participant Experience of Motivational Interviewing (CEMI) Scale
    - Patient's Experience with the Provider

Data Collection

All baseline and follow-up assessments are administered at the study sites. Baseline data collection was completed within the same day, and no later than 7 days after the screener is completed. All follow-up data collections (3M, 6M, 9M, 12M, 15M, and 18M) could be collected up to 14 days prior/post to their follow-up target date and up to 28 days post their follow-up target date.

Compensation

To compensate participants for their time and efforts in taking part in the PLUS trial, gift cards and metro cards were given out at each assessment and therapy visit, respectively, in two different denominations for participant compensation:

$25 Gift cards- which will be dispersed during study assessments (BL, 3M, 6M, 9M, 12M, 15M, and 18M)

$10 Metro cards- which will be dispersed during therapy visits (Sessions 1-6)

Throughout the course of the PLUS trial, a study participant may receive $235 for their participation.

Selection of No Treatment control patients

The EMRs of randomly selected patients who belonged to the TAU site and were not enrolled in the PLUS trial were matched on key patient characteristics for comparisons with EMRs of patients in the PLUS intervention and Waitlist control conditions. This matched cohort of patients received care at a fourth clinic that did not receive any intervention (i.e., PLUS or eTAU) and was considered as a natural history comparison group. We generated a pool of patient records from which to randomly select the TAU matched cohort of patients (n = 120). We included patient records of patients with an HIV diagnosis who had at least 1 primary care visit at the TAU clinic, received ART, and had a viral load (VL) >200 copies/mL during the PLUS enrollment period from March 26, 2015 to March 16, 2017. EMRs of 20 patients who were enrolled in PLUS and possibly transferred to receive HIV care at the TAU clinic during the study period were excluded. Additionally, records of 9 patients with only one primary care visit and no follow-up visits during the study period were excluded from the pool of patient records.

Case control matching using the pool of patients meeting the criteria described above allowed us to randomly select the TAU cohort of 120 patients while matching as closely as possible to patients enrolled in the trial on key variables: age group (with ranges 18-29, 30-39, 40-49, and 50 or older), racial and ethnic identity (Black, Hispanic/Latinx, White, Asian/Pacific Island, Other/Multiracial), and gender (recorded as male or female). Additionally, we matched on indicators of substance misuse based on EMRs of trial participants using documentation of substance use problems or ICD-10 diagnostic codes, such as documentation of alcohol abuse or dependence, having had a substance use diagnosis, or any indication of substance misuse during the study period. EMRs were then extracted for the TAU cohort of patients similar to the records

for the trial participants. A de-identified dataset was generated linking all patient EMRs to an unique study ID number with the following variables: demographic variables, HIV diagnosis, HIV clinical outcomes, ARV regimen, ICD-10 diagnoses of AIDS defining illness, substance use disorders, psychiatric disorders, non-AIDS defining infections (bacterial pneumonia, cellulitis, sepsis), cardiovascular, gastrointestinal, liver, kidney, pulmonary, endocrine, immune, and oncologic diseases, as well as sexually transmitted infections. In addition, records about services received and type of outpatient clinic visits were extracted, such as whether the visit was an HIV primary care visit, a specialty or non-HIV primary care visit type (dentist, OB/GYN, hematology), mental health visit, and substance use visit.

Data Analysis Plan

To assess the effectiveness of our randomization procedure, we used chi-square tests and ANOVAs to investigate the equivalence of possible cofounders across each of the PLUS-enrolled four site/conditions at baseline. Specifically, we examined proportional differences across demographic characteristics (race and ethnicity, sexual and gender identity, and education), and mean differences across age and baseline outcome values (alcohol severity, drug use severity, medication adherence, viral load, and CD4). Where cell sizes were too small ($n < 5$) to permit chi-square tests, we utilized a Fisher's exact test, at $p < .05$. The matching of the No Treatment control group ($N = 120$) was assessed by bivariate comparisons with the entire PLUS-enrolled sample ($N = 174$) on the available variables of age, race and ethnicity, and gender.

We also conducted analyses to test for the presence of differential attrition between conditions and sites where appropriate. First, we conducted chi-square analyses to test for differential attrition by site and study arm at each follow-up. We also tested for differential attrition at each follow-up across site, as well as several demographic characteristics (race and ethnicity, sexual and gender identity, and education). Finally, we conducted a series of point-biserial correlations to examine attrition at each wave by age and baseline outcome values (alcohol severity, drug use severity, medication adherence, viral load, and CD4).

Outcome analyses were conducted using piece-wise longitudinal growth curve models, adjusting for baseline scores on the corresponding outcome and, for the models predicting medication adherence, AUDIT, and DAST, we also adjusted for gender identity and sexual orientation, whereas for the models predicting viral load and CD4 we adjusted for gender (male, female) as sexual identity was not indicated in the EMR records for the matched cohort. For the

DAST model, DAST was treated as a count variable having a negative binomial distribution. The latent intercept represented the initial 3-month follow-up time point. Slope 1 quantified linear change across the 3-, 6-, 9- and 12-month follow-ups. Where possible for outcomes variables extracted from EMR (i.e., CD4 count and viral load), Slope 2 quantified changes in trajectory at the 15- and 18-month follow-up corresponding to the point at which the waitlist control condition received the intervention. The fixed effect of clinic and condition was entered as a 4-category predictor that was dummy-coded. For viral load and CD4 models – where data were taken from EMR records – the EMR cohort control participants were included as an additional subgroup and served as the referent category.

All models were estimated using full-information maximum likelihood estimation in MPlus Version 8.0. Good model fit was assumed when the χ^2/df ratio was 3 or less, root-mean square error of approximation (RMSEA) ≤ 0.05, Tucker-Lewis fit index (TLI) > 0.95, and comparative fit index (CFI) > 0.95.

Data Monitoring

The study protocols are approved by the research ethics board of the principal investigator's academic institution and Mt Sinai, and are registered with clinicaltrials.gov (NCT02390908).

DECLARATIONS:

Availability of data and material: Not applicable as this manuscript contains no data.

Competing interests: The authors declare that they have no competing interests.

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