

The results of a web-based randomized controlled intervention trial to improve antiretroviral therapy (ART) adherence among Youth with HIV (YouTHrive, ATN 135) during the COVID-19 pandemic

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Background: Two-thirds of youth with human immunodeficiency virus (HIV) (YWH) were virally suppressed at the end of 2022 in the United States. We developed and evaluated the YouTHrive intervention in a multi-site 2-arm randomized controlled trial (RCT) for effects on viral suppression. Additionally, we evaluated the impact of the coronavirus disease 2019 (COVID-19) pandemic on participants.

Methods: The 5-month mHealth intervention included participant interaction features, adherence information and monitoring, goal setting, and gamification, and was compared to an HIV information-only control condition. Viral suppression was defined as viral load <50 copies/mL, with secondary outcomes including examining viral load <200 copies/mL, viral load as a continuous outcome, and self-reported adherence using a visual analog scale (VAS). At baseline and 5-month follow-up, log-binomial regression models were used to estimate rate ratios (RRs) between study arms for viral suppression outcomes, and ordinary least squares linear regression models estimated mean differences (MDs) between study arms for antiretroviral therapy (ART) adherence and continuous viral load. The impacts of COVID-19 on different aspects of youth's lives were examined for the full sample and by intervention group. We also compared the responses of youth who were enrolled pre- vs. post-COVID-19 on self-reported adherence and treatment engagement outcomes.

Results: From August 2019 to December 2022, 208 youth across 8 recruiting sites were enrolled. The trial was stopped in March 2020 due to the COVID-19 pandemic, during which study procedures were modified before reopening in October 2020. Over half of participants (64%) were between 21 and 24 years of age, and 29% were between 18 and 20 years of age. Most were cisgender males (68%), Black/African American (66%), non-Hispanic (76%), and identified as gay (50%). Of the 120 participants with complete viral load data at both time points, most were virally suppressed at baseline and at the 5-month follow-up (67%). No significant group differences in primary or secondary outcomes were found in either the complete case models or models that used multiple imputation to account for missing variables. Youth reported that the COVID-19 pandemic overall reduced their quality of life, with the greatest impacts on anxiety levels,

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finances, and reducing opportunities for sex, although relatively few participants reported that it negatively impacted access to HIV treatment and care services.

Conclusions: The YouTHrive intervention did not improve ART adherence or HIV viral load in this sample of youth. However, substantial changes to study procedures made in response to the COVID-19 pandemic may have contributed to these findings. Teams conducting similar studies in the future should consider ways of mitigating the impacts of possible future pandemics or similar disruptions early in their timeline to consider the impacts of changes to the study.

Trial Registration: The study is registered as a clinical trial (clinicaltrials.gov, NCT03149757).

Keywords: Human immunodeficiency virus (HIV); young people; medication adherence; digital health interventions; coronavirus disease 2019 (COVID-19)

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Introduction

Background

Youth with human immunodeficiency virus (YWH) in the United States (US) experience poor human immunodeficiency virus (HIV) treatment and care outcomes. Adolescents and young adults ages 13–24 years

old accounted for 20% of new HIV diagnoses in 2022 (1). Although 80% of the 27,725 YWH at the end of 2022 had received any HIV-related medical care, only 66% of YWH were virally suppressed at their last viral load test (2). Viral suppression confers marked improvements in morbidity and mortality rates and prevents onward transmission of HIV (3), but requires consistent adherence to antiretroviral therapy (ART), which can be particularly difficult for YWH (4). Effective adherence support strategies and services tailored to YWH are needed for the US to reach the Ending the HIV Epidemic goals (5).

Advances in ART over the past decade have resulted in tolerable, single-dose co-formulated oral regimens; these single-dose formulations are most often taken by YWH in the US (6), although new injectable and long-acting formulations are also available (7). Several correlates of ART adherence have been identified, and models have been proposed to understand factors underlying ART adherence challenges, which can result in unsuppressed viral load or virological failure among youth. Empirical correlates of non-adherence and/or unsuppressed viral load in youth include male sex, having a minoritized racial and/or ethnic identity, lower educational attainment, psychological distress (e.g., depression), substance use, school- and work-related problems, stigma, social support, and transportation access (8,9). Beyond correlates, models of adherence position individual factors influencing adherence in the context of social and structural realities of navigating HIV-care, suggesting that adherence-related information, social support and personal attitudes and beliefs motivating or challenging adherence, and adherence-related behavioral

Highlight box

Key findings

- The YouTHrive intervention, although overall acceptable to youth with human immunodeficiency virus (HIV), did not impact HIV viral load during the intervention period.
- The coronavirus disease 2019 (COVID-19) pandemic impacted the well-being and financial status of youth with HIV, although little disruption in access to HIV care and medication was reported in this sample.

What is known and what is new?

- Youth with HIV are at high risk for non-adherence to antiretroviral medication because of individual, social, and structural factors.
- This article provides critical information about the impact of the COVID-19 pandemic on the lives of youth with HIV in the United States.

What is the implication, and what should change now?

- Studies should consider ways of mitigating the impacts of any future pandemics or similar disruptions early in their timeline to consider the impacts of changes to the study.
- For multisite and multilocation studies involving HIV care sites, careful detailing of changes in standard of care services, particularly those that are like the intervention content being evaluated, should be collected over time.

skills play critical roles in ART adherence (10-12). For YWH who are also navigating developmental and social demands of late adolescence and early adulthood, ART adherence services should address issues related to HIV stigma, promote autonomy and educate youth about HIV and understanding test results (13).

Knowledge gaps and rationale

Digital health interventions for YWH are accumulating a robust literature, with common features that include remote coaching, mobile apps with community forums and medication reminders, tailored text messages, social media, and peer navigation (14,15). However, the success of digital ART adherence interventions remains mixed. For example, a computerized counseling intervention to support ART adherence by Kurth and colleagues showed significant reductions in plasma HIV viral load among adults at a US-based HIV clinic who were randomized to the treatment arm compared to the control arm (16). However, other studies showed impacts on HIV viral load for only a subset (e.g., male) of participants (17) or effects only on self-reported ART adherence (18). Furthermore, relatively few digital ART adherence interventions for young people with HIV in the US. In a recent review of digital interventions for 10–24-year-old persons with HIV (19), two interventions were conducted in the US (20,21). While neither interventions showed primary effects on HIV viral load, there were secondary effects on HIV viral load among regular app users (20) and effects of the intervention when assessed by electronic dose monitoring openings (21). These findings suggest that digital approaches for YWH are promising, but would benefit from more consistent evidence for their effectiveness before being incorporated into HIV clinical care (14). We developed, implemented, and evaluated a digital health intervention for YWH, called YouTHrive, to determine impact on ART adherence and viral suppression.

Additionally, we report results from a brief measure of coronavirus disease 2019 (COVID-19) impact on HIV-care access and use, and on mental, sexual and physical health functioning during the COVID-19 pandemic, which occurred during the implementation of our study. The COVID-19 pandemic promoted a national emergency declaration in March 2020 that, in many US jurisdictions, resulted in mandates for social distancing and closure of, or substantial limitations on, in-person services. These restrictions had the potential to severely disrupt HIV

treatment and care options by reducing access to HIV care appointments, laboratory testing (e.g., viral load testing), and ART medications. In addition, the COVID-19 pandemic may have disrupted ART adherence by exacerbating risk factors for non-adherence, such as depression and substance use (22). Indeed, disruptions in ART adherence during the pandemic were reported among substance-using PWH enrolled in an mHealth intervention (23), older people living with HIV in California (24), and men who have sex with men residing in the southern US (25). On the other hand, a study of people with HIV in Miami, Florida who were part of a research cohort showed no impact of the pandemic on ART adherence (26). A review of HIV services utilization and outcomes in the US between 2019 and 2021 showed that the number of HIV diagnoses and the number of viral load tests performed decreased in the second quarter of 2020 (April 1 to June 30, 2020) compared to the first quarter (January 1 to March 30, 2020), but rebounded to more typical levels in last two quarters of that year (27). The proportion of persons linked to HIV care, prescribed ART, and achieving viral suppression remained stable across all quarters of 2020. Taken together, the COVID-19 pandemic appeared to have had impacts on some, but not all, HIV services; these impacts might have varied by region of the US. To contextualize experiences of YWH in our intervention study, we characterized the challenges related to the COVID-19 pandemic in our sample of YWH.

Objectives

We present outcomes of a 2-arm parallel randomized controlled trial (RCT) conducted within the Adolescent Medicine Trials Network for HIV Interventions (ATN 134) to assess the efficacy of the YouTHrive digital intervention to promote ART adherence and viral suppression among YWH, compared to an HIV information-only control condition. Study hypotheses were:

- ❖ H1: participants in the YouTHrive intervention arm will report higher ART adherence at the 5-month follow-up time point than those in the information-only control arm.
- ❖ H2: a higher proportion of participants in the YouTHrive intervention arm than in the information-only control arm will have undetectable viral load at the 5-month follow-up time point.

We additionally provide results from our COVID-19 impact assessment. Approximately one-quarter of YWH for the YouTHrive study were enrolled prior to the onset

of the COVID-19 pandemic, with most youth enrolled after its onset. Local, state, and national restrictions on in-person meetings might have impacted clinic and research appointments; therefore, examining youths' experiences of the COVID-19 pandemic and the impact of the pandemic on access to HIV treatment and care provides critical information to contextualize the YouTHrive RCT findings. We present this article in accordance with the CONSORT reporting checklist (available at <https://mhealth.amegroups.com/article/view/10.21037/mhealth-25-47/rc>).

Methods

YouTHrive and control conditions

The YouTHrive intervention is described in greater detail elsewhere (28). Briefly, YouTHrive is grounded in the Information-Motivation-Behavioral Skills (IMB) model (10,29) and was developed as a “webapp”, which is a website that was optimized for display on a smartphone and appeared much like a native mobile application. YouTHrive had the following components:

- ❖ An asynchronous message posting and commenting feature, like common social media platforms. Youth were encouraged to create a username that did not contain any identifying information to maximize confidentiality. The messages were monitored by study staff to ensure that they met community standards and to address any instances of potential self-harm ideation.
- ❖ Youth-tailored ART multi-media adherence and HIV content were developed; this included information on how to live with HIV and to better manage medication adherence and videos of youth discussing challenges to ART adherence and ways to overcome them. Based on priorities of YWH assessed through focus groups, study staff created approximately 300 pieces of content that participants could access during the RCT.
- ❖ Youth were given access to an adherence self-monitoring feature to report whether they took their dose(s) of ART each day, and to indicate their daily mood by selecting a representative emoji.
- ❖ A goal-setting feature prompted youth through the steps of setting and monitoring a goal. Suggested goals were provided related to living with HIV and ART adherence; however, youth could set their

own goal if they chose to.

- ❖ As youth engaged with the webapp, they accumulated points and achieved higher “levels”, which were displayed as points and badges on the site. As participants levelled up, new features were unlocked, such as having a wider variety of avatars to choose from and having more color theme options.

In addition to these features, we sent youth a weekly text message to encourage youth in the YouTHrive arm to visit the webapp and engage with the intervention.

The control condition consisted of 21 brief informational texts and graphic-based webpages that were released weekly (1 webpage per week for 5 months), similar to a newsletter. An email was sent to control participants once a week with a link to that week's newsletter, which could be opened on a web browser. The weekly newsletters contained information on topics related to living with HIV (e.g., disclosure of HIV at school and work) and improving general well-being (e.g., managing depression); however, no topics specifically related to ART adherence were provided.

Participants

At the onset of the study in July 2019, YWH were eligible to be enrolled if they met the following inclusion criteria: (I) were 15–24 years of age at the enrollment visit; (II) had HIV, verified by clinical records; (III) had one or more ART adherence challenges [defined as having one or more detectable viral load test result (i.e., above the lower limit of detection for the clinical assay if medical-chart verified) in the past 12 months while on ART for at least 3 months, missing 1 or more scheduled HIV care appointment in the past 12 months, having a more recent HIV care visit more than 6 months ago, or self-reporting less than 90% ART adherence in the past 4 weeks]; (IV) resided in a city where an ATN subject recruitment venue (SRV) was located (i.e., Chicago, Houston, New York City, Philadelphia, Atlanta, Tampa, Charlotte, or Chapel Hill) and were available to meet with SRV staff for study visits; (V) were English-speaking (because the intervention was available only in English); (VI) self-reported they would have continuous internet access and SMS messaging during the intervention period; (VII) were not participating in another ART adherence intervention research study at the time of screening; (VIII) had or was willing to create an e-mail address to use during the study period; and (IX) was not a member of the ATN youth advisory board that informed intervention development.

All YouTHrive study procedures were paused in March 2020 due to the COVID-19 pandemic, after which time study activities were modified to operate remotely and to conform to state and local social distancing mandates. With respect to eligibility, youth who were enrolled after the onset of COVID-19 were no longer required to have evidence of being ART non-adherent or at risk for non-adherence (criteria “c” above) to enroll in the study. The modifications to eligibility requirements were made to be more inclusive of YWH, considering the potential disruptions to HIV care posed by the COVID-19 pandemic. The study was reopened in October 2020 after the revised study procedures (see below) were approved and staff at the SRVs were trained in remote procedures.

Procedures

Participants were primarily recruited within established HIV clinics aligned with the SRVs; other SRVs that were not HIV clinics conducted community-based recruitment by partnering with local HIV clinics and agencies that served people with HIV and by social media advertising. Before the COVID-19 pandemic, study staff at HIV clinics reviewed charts of youth to identify those who appeared to have adherence or linkage to care difficulties; staff either approached those youth during clinic visits or contacted them by email or telephone to offer the online eligibility screener. SRVs recruiting in the community identified potentially eligible youth from eligibility screeners completed by those responding to social media ads. In addition, youth who were referred from partnering clinics or agencies or were identified during outreach activities were also asked to complete the online screener. Identifying potential eligible youth after the onset of the COVID-19 pandemic was similar, although SRVs used the new eligibility criteria and adhered to local and institutional distancing requirements (i.e., in-person outreach activities were largely restricted during the pandemic).

Regardless of how youth completed the online screener, if their responses to eligibility items met criteria for inclusion, they were contacted by SRV staff to schedule an in-person (pre-COVID-19) or remote (post-COVID-19) enrollment visit. During the enrollment visit, eligibility criteria were confirmed, the consent process completed, a HIPPA waiver and release of information form signed, and the self-administered baseline online survey was completed. Next, each participant was randomized 1:1 to either the intervention (YouTHrive) or control condition

using an automated procedure within the survey software once the participant completes the baseline survey, and onboarded (i.e., instructed on what to expect and assisted in accessing the interventions) to their respective condition. The randomization sequence was stratified by city and used random permuted blocks of sizes 2 and 4. As such, study staff were not blinded as to which arm the participant was assigned.

Participants enrolled before the onset of COVID-19 were asked to complete in-person follow-up study visits at months 5, 8, and 11; visits consisted of a self-administered online survey, a viral load assessment (either through chart review or a blood draw if a viral load had not been conducted in their medical chart in the past 30 days), and a urinalysis to detect recent drug use. The study was halted for 6 months because of the COVID-19 pandemic to adjust to the requirement that all procedures occur remotely. The following changes were made to the protocol and administered to all participants who enrolled after the onset of the COVID-19 pandemic: (I) urine samples to detect drug use were no longer collected; (II) given the potential for pandemic disruption in HIV care and the possibility of negative impacts on participants' lives, we reduced the follow-up assessment to only the 5-month follow-up timepoint. As such, the analyses described below focused on the differences between baseline and the 5-month assessment, rather than examining the effects of the intervention across 11 months. This study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. Study procedures were reviewed and approved by the University of North Carolina Institutional Review Board (UNC IRB 16-3136) as the single IRB of record, and IRB authorization agreements with all participating research entities were enacted. A Certificate of Confidentiality was obtained from the National Institute of Child Health and Human Development, and a waiver of parental consent was obtained for participants who were 15–17 years old. All participants participated in an informed consent/assent process. The study is registered as a clinical trial (clinicaltrials.gov, NCT03149757).

Measures

Demographic factors

Participants self-reported age (in years), gender (categorized as cisgender man, cisgender woman, transgender, or gender diverse), race, ethnicity (Hispanic/non-Hispanic), sexual

orientation (categorized as gay, bisexual, straight, or other), whether or not they were currently a student, employment status (categorized as employed or not employed), relationship status (categorized as single or partnered), and whether or not.

They currently have insurance.

Primary outcomes

Two primary outcome measures were used to assess the effect of the YouTHrive intervention on treatment adherence at the 5-month follow-up timepoint. First, we used a measure adapted from a widely used adherence measure (30) to ask youth to report the percentage of HIV medicines they took in the past 30 days on a visual analog scale (VAS) with 10% increments. Second, viral load data were collected through chart review or a blood specimen (if a viral load test result was not reported in the medical chart within a 30-day window prior to the study visit date). An undetectable viral load was defined as <50 copies/mL, representing a value that encompassed the lower limit of detection of the viral load tests in use at all SRV-related clinics in the study. Sensitivity analyses were conducted, defining undetectable viral loads as <200 copies/mL, a level associated with a very low risk for transmission to partners (31), and by examining viral load as a continuous measure.

Intervention ease of use, acceptability, and satisfaction

Based on a prior study that assessed participants' perceptions of a digital intervention (32), all participants answered questions to assess information quality (e.g., "The information on YouTHrive is accurate"), perceived usefulness of the information (e.g., "YouTHrive helps me quickly find information and support for healthy living"), and overall satisfaction with the intervention. Responses to these items were on a 7-point Likert scale with 1 representing "strongly disagree", 4 representing "neither disagree or agree", and 7 representing "strongly agree" (with the exception of "How likely would you be to continue using YouTHrive if it were available?", which was on a 7-point Likert scale from "very unlikely" to "neither unlikely or likely" to "very likely").

Impact of COVID-19

Youth who enrolled after the onset of the COVID-19 pandemic were asked on the baseline survey to report the degree to which the COVID-19 pandemic impacted several aspects of their lives (i.e., overall, anxiety, sleep, connection to family and friends), including their finances (e.g., access

to money, employment), sexual health [e.g., access to sex partners, access to sexually transmitted infection (STI) testing] and access to HIV medications and HIV care. Response options for most items included: not changed/no different, 0; highly decreased, 1; somewhat decreased, 2; somewhat increased, 3; or highly increased/more, 4. In addition, participants were given the option to indicate that the item was not applicable to them. Other items (e.g., lost job, lost insurance, had trouble getting HIV medications) were asked as "yes" or "no", with options to indicate that no change has occurred or that they have not tried (e.g., to make an HIV appointment).

The impact of COVID-19 on self-reported HIV treatment and care was also assessed by comparing responses on both the baseline and 5-month surveys of youth enrolled pre- and post-COVID-19 onset across categories of past 30-day ART adherence (100%, 90%, 80%, and 70% or less) and past 30-day missed ART doses (no missed doses, 1–3 missed doses, 4–6 missed doses, 7 or more missed doses). In addition, on the baseline survey only, we compared the responses of pre- vs. post-COVID-19 enrolled participants for months since their last viral load (past 3 months, 4–6 months ago, more than 6 months ago) and the result of their last viral load test (undetectable, detectable, not sure).

Power analysis

We conducted a power analysis following the changes to the protocol due to the COVID-19 pandemic, using self-reported adherence, given the potentially large amount of missing viral load data due to the COVID-19 pandemic. Assuming approximately 85% follow-up, we based our power calculations on 240 participants. A study by Belzer *et al.* (33) suggested a standard deviation of 43 on a VAS measure of ART adherence; assuming a type 1 error of 5% and equal allocation of participants between the 2 arms, we have 80% power to detect a difference of 15.6 points between the two groups.

Statistical analysis

Descriptive statistics (i.e., frequencies and percentages or means and standard deviations) were calculated for demographic characteristics and outcomes of interest in the total sample and in each study arm. Fisher's exact test was used to evaluate baseline equivalence in demographic characteristics and viral suppression between the intervention and control arms. Chi-square test was used to

examine differences in intervention acceptability variables.

As a first step in understanding YouTHrive intervention impacts, the study team created viral suppression groups using a viral load cutoff of <50 copies/mL. Chi-square tests were used to examine the proportion of participants in each of the following viral suppression groups: (I) suppressed at baseline and suppressed at month 5; (II) suppressed at baseline and unsuppressed at month 5; (III) unsuppressed at baseline and suppressed at month 5; and (IV) unsuppressed at baseline and unsuppressed at month 5.

Next, at baseline and 5-month follow-up, log-binomial regression models were used to estimate rate ratios (RRs) between study arms for viral suppression outcomes, whereas ordinary least squares linear regression models estimated mean differences (MDs) between study arms for ART adherence and continuous viral load. In addition, an adjusted RR (aRR) or adjusted MD (aMD) between study arms at 5-month follow-up was calculated for each outcome using autoregression on baseline viral suppression values with no other covariates. A type I error rate of 5% was used, with statistical significance for estimates determined based on their 95% confidence intervals (CIs).

Complete case analysis was used for our primary models, which included 120 participants with viral load data at both timepoints. In addition, we conducted sensitivity analyses for viral load outcomes using multiple imputation by chained equations to account for missing data (34). There were 66 individuals with baseline viral load and no 5-month follow-up viral load. For these participants, we imputed 5-month viral load using baseline viral load and the following baseline covariates: ART adherence, housing instability, student status, health insurance status, and Hispanic ethnicity. Twenty imputations were conducted and used to estimate descriptive and comparative statistics for viral load outcomes at 5-month follow-up.

HIV care experiences during COVID-19 and related impacts were characterized. Non-parametric tests (chi-square and Fisher's exact tests) were used to examine baseline differences in self-reported impact of COVID-19 across multiple domains (e.g., quality of life, finances, sexual health, and HIV treatment and care). Chi-square and Fisher's exact tests were also used to examine self-reported baseline differences in ART adherence variables (i.e., percentage ART adherence and missed ART doses) and viral load testing (i.e., months since last viral load test and last viral load test result) between youth enrolled pre-COVID-19 (n=50) to those enrolled post-COVID-19 (n=158). Similarly, we assessed differences in percentage

ART adherence and missed ART doses between youth enrolled pre- and post-COVID-19 at the 5-month timepoint. Finally, Fisher's exact tests were used to examine differences in the percentages of participants in each of the viral suppression groups described above, by whether they were enrolled pre- or post-COVID-19 changes in study procedures.

All statistical analyses were performed using STATA/SE version 16.1.

Results

Sociodemographic characteristics

Between August 2019 and December 2022, 208 YWH were enrolled in the YouThrive study (see *Figure 1*), and followed through May 2022 (to align with the end of grant funding). The YouTHrive sample included (see *Table 1*): 132 youths ages 21 to 24 years (64%; percentages in text rounded throughout), 60 youths ages 18 to 20 years (29%), and 16 youths ages 15 to 17 years (8%). Among those who provided baseline data, most self-identified as cisgender men (68%), Black/African American (66%), non-Hispanic (76%), and gay (50%). Most also reported being employed (58%) and/or a student (54%), being single (70%), and having health insurance (80%), as well as stable housing (77%) at baseline. No statistically significant difference in demographic characteristics was observed between the intervention and control arms at baseline.

Impact of YouTHrive on HIV viral load

HIV viral suppression (<50 copies/mL) groups overall and by study arm are presented in *Figure 2*. Of the 120 participants with complete viral load data at both time points, most were virally suppressed (<50 copies/mL) at baseline and remained virally suppressed at 5-month follow-up (80, 67%). Compared to the control arm, a higher proportion (75% versus 56%) of participants in the intervention arm maintained viral suppression at 5-month follow-up, although this difference was not statistically significant.

Descriptive and comparative statistics for outcomes of interest at baseline and 5-month follow-up using complete case data and imputed data are presented in *Table 2*. With respect to complete case data, baseline differences in HIV viral load were observed between the intervention and control arms: compared to youth in the control arm, youth in the intervention arm were more likely to have baseline

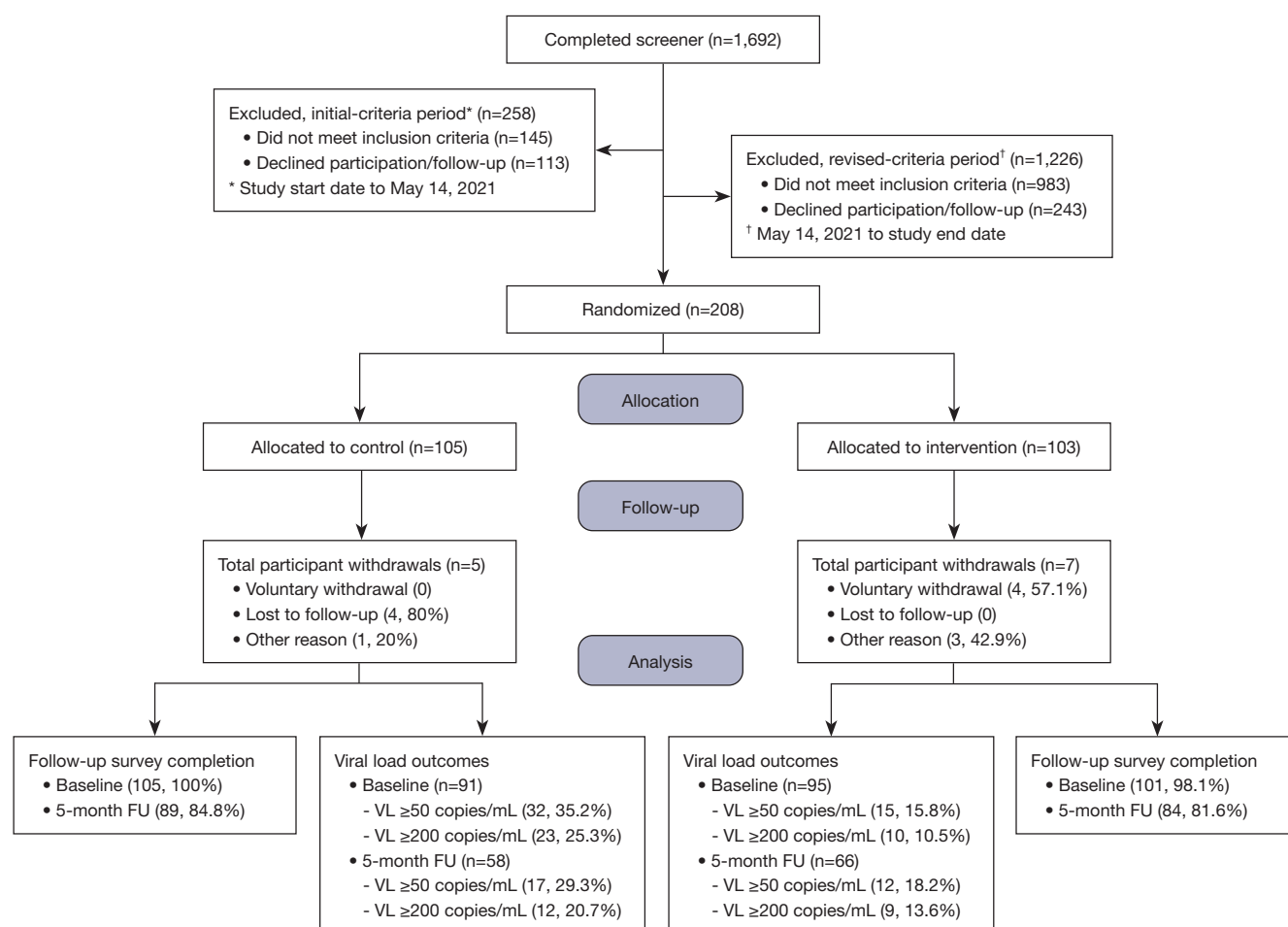


Figure 1 Consort flow diagram for the YouTHrive intervention to improve antiretroviral adherence in youth with HIV, 8 US cities, 2019–2022. FU, follow-up; HIV, human immunodeficiency virus; VL, viral load.

viral loads less than 50 copies/mL (RR =1.24, 95% CI: 1.02–1.50) and had baseline viral loads that were 0.45 (95% CI: –0.84 to –0.06) $\log_{10}$ copies/mL lesser on average than control arm participants. No other statistically significant differences were observed between study arms at baseline. The complete case analysis (Table 2) showed that a slight decline in viral suppression at <50 copies/mL was observed in both groups between baseline and 5 months (71% to 69% in the control arm and 88% to 82% in the intervention arm), with no significant difference by study arm. Changes in VAS scores were not significantly different between the study arms.

The results using the imputed data (bottom half of Table 2) were largely analogous to those found using complete case analysis. The analyses using imputed data showed that youth in the intervention arm were more likely

to have baseline viral loads less than 200 copies/mL (RR =1.20, 95% CI: 1.04–1.37) compared to youth in the control arm in addition to being more likely to having baseline viral loads less than 50 copies/mL (RR =1.30, 95% CI: 1.09–1.55) and having baseline viral loads that were 0.51 (95% CI: –0.81 to –0.20) $\log_{10}$ copies/mL lesser on average than control arm participants. Like the complete case analysis, no meaningful differences were found between study arms on the VAS or viral load outcomes at 5-month follow-up, and adjustment for baseline viral suppression reduced associations even further toward the null.

Intervention acceptability

Acceptability ratings for YouTHrive and control arms at 5-month follow-up are presented in Table 3. Most

Table 1 Demographic characteristics of the sample in total and by study arm in the YouTHrive intervention to improve antiretroviral adherence in youth with HIV, 8 US cities, 2019–2022

Characteristic	Total (N=208)		Control (N=105)		Intervention (N=103)	
	n	%	n	%	n	%
Age group, years						
15–17	16	7.7	6	5.7	10	9.7
18–20	60	28.9	30	28.6	30	29.1
21–24	132	63.5	69	65.7	63	61.2
Gender identity (3 missing)						
Cisgender man	139	67.8	76	72.4	63	63.0
Cisgender woman	49	23.9	21	20.0	28	28.0
Transgender/gender diverse [†]	17	8.3	8	7.6	9	9.0
Race (8 missing)						
Black/African American	132	66.0	68	66.7	64	65.3
White/European American	33	16.5	19	18.6	14	14.3
American Indian/Alaskan Native	8	4.0	3	2.9	5	5.1
Asian/Asian American	4	2.0	2	2.0	2	2.0
Native Hawaiian/Pacific Islander	1	0.5	0	–	1	1.0
Other race	6	3.0	2	2.0	4	4.1
Multiracial	16	8.0	8	7.8	8	8.2
Ethnicity (8 missing)						
Non-Hispanic	151	75.5	76	75.3	75	75.8
Hispanic	49	24.5	25	24.8	24	24.2
Sexual orientation (5 missing)						
Gay	102	50.3	48	46.2	54	54.6
Bisexual	33	16.3	18	17.3	15	15.2
Straight	54	26.6	29	27.9	25	25.3
Other/multiply-identified [‡]	14	6.9	9	8.7	5	5.1
Student status (4 missing)						
Current student	110	53.9	57	54.3	53	53.5
Not a current student	94	46.1	48	45.7	46	46.5
Employment status (7 missing)						
Currently employed	117	58.2	62	60.2	55	56.1
Not currently employed	84	41.8	41	39.8	43	43.9
Relationship status (6 missing)						
Single	141	69.8	73	70.9	68	68.7
Partnered	61	30.2	30	29.1	31	31.3
Insurance status (20 missing)						
Insured	151	80.3	76	76.8	75	84.3
Uninsured	37	19.7	23	23.2	14	15.7
Housing security (12 missing)						
Stable housing	151	77.0	75	74.3	76	80.0
Unstable/interrupted housing	45	23.0	26	25.7	19	20.0

P values derived from Fisher's exact tests comparing intervention and control arms. [†], total includes 11 genderqueer, 5 transfeminine, and 1 transmasculine; [‡], total includes 6 gay and bisexual, 3 bisexual and straight, 3 pansexual, 1 gynosexual, and 1 non-conforming. HIV, human immunodeficiency virus.

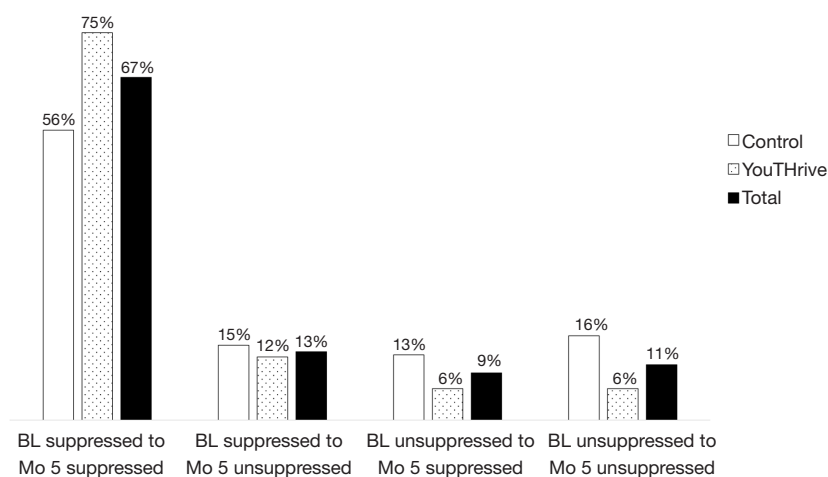


Figure 2 Viral suppression groups from baseline to month 5 in total and by study arm, using complete cases in the YouTHrive intervention to improve antiretroviral adherence in youth with HIV, 8 US cities, 2019–2022. BL, baseline assessment; HIV, human immunodeficiency virus; Mo 5, month 5 assessment.

participants reported trusting the information provided in YouTHrive (87%) and rated it as easy to understand (91%), and approximately three-quarters of participants in the YouTHrive intervention expressed overall satisfaction with it. Youth in the control condition also perceived benefit, with a greater percentage of youth (in comparison to youth in the YouTHrive arm) reporting that the intervention helped them deal with health challenges [80% *vs.* 69%, $\chi^2_{(1, N=168)}=2.87$, $P=0.09$] and that they would recommend it to their friends [80% *vs.* 64%, $\chi^2_{(1, N=166)}=5.62$, $P=0.02$].

Impact of the COVID-19 pandemic on youth with HIV

Among participants enrolled after the onset of the pandemic ($n=158$), over half (55%) reported that their quality of life decreased after the start of the pandemic (Table 4). One-third or more of youth reported that, as a result of the pandemic, they had decreased feelings of connection to friends (37%), access to money (43%), number of paid work hours (43%), number of sexual partners (38%), and opportunities to have sex (40%). Few youth reported an interruption in their HIV treatment and care during the pandemic; specifically, 10% reported having decreased access to their HIV medications, 8% having decreased ART adherence, 17% having less access to their HIV care, and 12% having more difficulty getting viral load and other laboratory tests. Similar percentages of youth reported that HIV-care had actually increased during COVID-19: 10% had more access to HIV medication; 14% were more

adherent to ART; 10% had more access to HIV care; 12% had more access to viral and other laboratory tests. Notably, a somewhat higher percentage of youth in the control group, compared to the YouTHrive group, reported decreases in feeling connected to family, having access to the internet, the number of work hours; a higher percentage of those in the control group also reported increased difficulty paying rent than those in YouTHrive (see notes in Table 4).

Differences in self-reported ART adherence and viral load measures between participants enrolled pre- ($n=50$) and post-COVID-19 ($n=158$) are shown in Table 5. Overall, participants who enrolled post-COVID-19 had somewhat higher self-reported ART adherence at baseline and month 5 than those who enrolled before the pandemic. There were no significant differences in self-reported measures related to the time since the last viral load test or the viral load test result at baseline.

Among participants who had viral load data at both baseline and month 5 ($n=120$), differences in the percentage of YWH in each of the viral load groups by whether they were enrolled pre- or post-COVID-19 changes in study procedures are shown in Figure 3. There was a significant difference in viral load group membership by COVID-19 enrollment group for only youth assigned to the control arm (Fisher's exact =0.016), but not for those assigned to the YouTHrive arm (Fisher's exact =0.878). Notably, 46% of youth in the control arm who were enrolled pre-COVID-19 had an unsuppressed viral load at baseline and

Table 2 Baseline and 5-month primary outcome summary statistics and comparisons of intervention versus control arm in the YouTHrive intervention to improve antiretroviral adherence in youth with HIV, 8 US cities, 2019–2022

Outcome	Baseline				5-month follow-up				aRR or aMD† (95% CI)
	Total	Control	Intervention	RR or MD (95% CI)	Total	Control	Intervention	RR or MD (95% CI)	
Complete cases									
Viral load <50 copies/mL	96/120 (80.0)	39/55 (70.9)	57/65 (87.7)	1.24 (1.02–1.50)*	91/120 (75.8)	38/55 (69.1)	53/65 (81.5)	1.18 (0.96–1.46)	1.08 (0.90–1.31)
Viral load <200 copies/mL	101/120 (84.2)	43/55 (78.2)	58/65 (89.2)	1.14 (0.97–1.34)	99/120 (82.5)	43/55 (78.2)	56/65 (86.2)	1.10 (0.93–1.31)	1.03 (0.91–1.18)
Viral load (log ₁₀ copies/mL)	1.55±1.09 (N=120)	1.80±1.37 (N=55)	1.34±0.73 (N=65)	−0.45 (−0.84 to −0.06)*	1.52±0.97 (N=120)	1.70±1.12 (N=55)	1.38±0.81 (N=65)	−0.32 (−0.67 to 0.03)	−0.12 (−0.43 to 0.19)
VAS adherence rating	87.79±17.68 (N=154)	89.61±15.51 (N=77)	85.97±19.55 (N=77)	−3.64 (−9.26 to 1.98)	86.62±17.87 (N=154)	87.53±16.40 (N=77)	85.71±19.29 (N=77)	−1.82 (−7.52 to 3.88)	−0.45 (−5.79 to 4.89)
Using multiple imputation for missing values at 5 months									
Viral load <50 copies/mL	139/186 (74.7)	59/91 (64.8)	80/95 (84.2)	1.30 (1.09–1.55)*	133/182 (73.1)	60/89 (67.4)	73/93 (78.5)	1.17 (0.93–1.46)	1.09 (0.89–1.33)
Viral load <200 copies/mL	153/186 (82.3)	68/91 (74.7)	85/95 (89.5)	1.20 (1.04–1.37)*	148/181 (81.8)	69/90 (76.7)	79/91 (86.8)	1.13 (0.96–1.33)	1.03 (0.90–1.18)
Viral load (log ₁₀ copies/mL)	1.61±1.09 (N=186)	1.87±1.32 (N=91)	1.36±0.74 (N=95)	−0.51 (−0.81 to −0.20)*	1.53±1.27 (N=179)	1.67±1.47 (N=90)	1.38 ±0.93 (N=89)	−0.29 (−0.65 to 0.07)	−0.06 (−0.41 to 0.28)

Data are presented as n/N (%) or mean ± standard deviation unless otherwise indicated. [†], adjusted using autoregression on baseline values, no other covariates included. *, statistical significance at a 5% type I error rate. aMD, adjusted mean difference; aRR, adjusted rate ratio; CI, confidence interval; HIV, human immunodeficiency virus; MD, mean difference; RR, rate ratio; VAS, visual analog scale.

Table 3 Intervention acceptability at 5-month follow-up in total and by study arm in the YouTHrive intervention to improve antiretroviral adherence in youth with HIV, 8 US cities, 2019–2022

Item	Control arm (N=89)		YouTHrive arm (N=84)	
	n	%	n	%
1. I trust the information in YouTHrive	74	87	70	88
2. The information in YouTHrive is easy to understand	78	91	75	91
3. The information in YouTHrive is accurate	71	83	67	84
4. YouTHrive helps me to quickly find information and support for healthy living	68	79	64	79
5. YouTHrive helps me make healthy choices for my life	68	78	61	75
6. YouTHrive helps me deal with health challenges that might come up	70	80 [†]	56	69 [†]
7. YouTHrive is useful to me	68	78	57	70
8. Overall, I am very satisfied with YouTHrive	75	86	63	78
9. Using YouTHrive is very frustrating	14	27	8	17
10. I would recommend YouTHrive to my friends	69	80 [*]	51	64 [*]
11. How likely would you be to continue using YouTHrive if it were available?	67	79	57	69

Frequencies and proportions represent participants who rated items 1–10 as strongly agree, agree, or somewhat agree and item 11 as very likely, likely, or somewhat likely. *, $P < 0.05$; [†], $P < 0.10$. HIV, human immunodeficiency virus.

month 5 assessment, compared to only 7% of those enrolled post-COVID-19. In comparison, among youth assigned to the YouTHrive arm, the proportion of participants in each of the viral load groups was roughly equivalent regardless of whether they were enrolled pre- or post-COVID-19.

Discussion

Key findings and implications

The YouTHrive intervention was developed to improve ART adherence and viral load outcomes for YWH given the need for accessible, sustainable, and novel strategies to address suboptimal HIV care outcomes among youth in the US. Contrary to our hypotheses, we did not find evidence that the YouTHrive webapp intervention improved self-reported ART adherence or viral load outcomes for this sample of youth in the US. However, these findings should be considered in the context of the substantial changes to the study procedures and inclusion criteria in response to the COVID-19 pandemic, which may hold important lessons for future digital health ART adherence intervention trials.

Although the superiority of the YouTHrive intervention over the control condition was not demonstrated, among youth who had a viral load measure at both baseline and

month 5 ($n=120$), two-thirds (and a majority in each of the intervention arms) were virally suppressed (<50 copies/mL) at both study visits. Although a lower percentage of youth who were enrolled pre-COVID-19 and assigned to the control arm were virally suppressed during the trial than control arm youth enrolled post-COVID-19 or youth in the YouTHrive arm enrolled pre- and post-COVID-19, any potential intervention effects were neutralized after controlling for baseline viral load. The null findings on viral load in this sample of YWH add to those of existing published studies showing overall mixed evidence of the effect of digital interventions to improve ART adherence and viral load (as a proxy for high ART adherence). A recent review of 262 ART adherence interventions from 2015 to 2024 showed that 34% of interventions were digital health interventions (representing the most common delivery method) and, among those, two-thirds showed evidence of effect (i.e., showing any signal or trend favoring the treatment arm) (35). However, in that same review, only one-quarter of digital health interventions that used viral load as an outcome ($n=13/53$ studies) showed significant effects on viral load. A higher percentage of other intervention strategies and methods, such as economic interventions (48%) and task shifting (60%), showed effects on viral load compared to digital health delivery models (35). Digital health interventions may be most impactful

Table 4 Baseline self-reported impact of COVID-19 on HIV care and other life domains among youth enrolled during the COVID-19 pandemic (n=158) in the YouTHrive intervention to improve antiretroviral adherence in youth with HIV, 8 US cities, 2019–2022

Life domains	n	Somewhat/highly decreased or yes, % [n]	No change or I haven't tried, % [n]	Somewhat/highly increased or no, % [n]
Overall [†]				
General quality of life	143	55 [78]	29 [42]	16 [23]
Levels of anxiety	147	17 [25]	40 [59]	43 [63]
Quality of sleep	144	22 [32]	55 [79]	23 [33]
Feeling connected—family [†]	148	27 [40]	41 [60]	32 [48]
Feeling connected—friends	144	37 [53]	37 [53]	26 [38]
Financial [†]				
Access to money	146	43 [63]	36 [53]	21 [30]
Access to internet [†]	146	17 [25]	62 [90]	21 [31]
Number paid work hours [†]	135	43 [58]	41 [55]	16 [22]
Financially support others	130	17 [22]	51 [66]	32 [42]
Difficulty buying food	137	20 [27]	54 [74]	26 [36]
Difficulty paying rent [†]	134	19 [26]	46 [62]	34 [46]
Sexual health [†]				
Number of sex partners	138	38 [53]	49 [67]	13 [18]
Opportunities to have sex	139	40 [55]	45 [62]	16 [22]
Access to STI testing/treatment	138	18 [25]	65 [89]	17 [24]
Use of drugs	132	20 [26]	55 [73]	25 [33]
Alcohol consumption	131	23 [30]	57 [75]	20 [26]
HIV treatment & care [†]				
Access to HIV meds	146	10 [14]	81 [118]	10 [14]
Adherence to HIV meds	144	8 [11]	78 [113]	14 [20]
Getting HIV care	144	17 [24]	74 [106]	10 [14]
Getting viral load or other labs	147	12 [18]	76 [112]	12 [17]
Have you lost your job? [§]	155	30 [46]	15 [23]	56 [86]
Have you lost your insurance? [§]	155	3 [4]	15 [23]	83 [128]
Have you become homeless? [§]	155	14 [21]	11 [17]	75 [117]
Trouble getting STI tests? [§]	154	17 [26]	6 [9]	77 [119]
Trouble getting HIV medications? [§]	155	14 [21]	0	86 [134]
Trouble getting or making HIV care appointments? [§]	155	14 [21]	0	86 [134]

[†], sample size varies as participants could respond “not applicable” to each item. [‡], intervention group differences were found for the following items: (I) feeling connected—family, $P<0.05$; control: 33% decreased, 30% no change, 37% increased; YouTHrive: 21% decreased, 51% no change, 28% increased. (II) Access to internet, $P<0.05$; control: 27% decreased, 54% no change, 20% increased; YouTHrive: 8% decreased, 69% no change, 23% increased. (III) Number paid work hours, $P<0.01$; control: 55% decreased, 37% no change, 7% increased; YouTHrive: 31% decreased, 44% no change, 25% increased. (IV) Difficulty paying rent, $P<0.01$; control: 28% decreased, 32% no change, 40% increased; YouTHrive: 11% decreased, 61% no change, 29% increased. [§], sample size varies as participants could respond “decline to answer” to each item. COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; STI, sexually transmitted infection.

Table 5 Self-reported HIV treatment and care adherence and engagement among youth enrolled pre-COVID-19 (n=50 at baseline) and post-COVID-19 (n=158 at baseline) in the YouTHrive intervention to improve antiretroviral adherence in youth with HIV, 8 US cities, 2019–2022

HIV treatment/care factor	Total, % [n]	Pre-COVID-19, % [n]	Post-COVID-19, % [n]	P value [†]
Baseline				
Percent ART adherence, past 30 days (n=201)				0.03
100%	43 [87]	33 [16]	47 [71]	
90%	30 [60]	25 [12]	32 [48]	
80%	8 [17]	16 [8]	6 [9]	
70% or less	18 [37]	27 [13]	16 [24]	
Missed ART doses, past 30 days (n=199)				0.07
No missed doses	34 [68]	21 [10]	38 [58]	
1–3 missed doses	41 [82]	45 [21]	40 [61]	
4–6 missed doses	15 [30]	17 [8]	15 [22]	
7+ missed doses	9 [18]	17 [8]	7 [11]	
Months since last viral load (n=198)				0.74
Within past 3 months	83 [165]	80 [37]	84 [128]	
4–6 months ago	14 [27]	15 [7]	13 [20]	
More than 6 months ago	3 [6]	4 [2]	3 [4]	
Last viral load test result (n=199)				0.81
Undetectable	70 [139]	67 [31]	71 [108]	
Detectable	19 [37]	22 [10]	18 [27]	
Not sure	12 [23]	11 [5]	12 [18]	
Month 5				
Percent ART adherence, past 30 days (n=159)				0.01
100%	41 [65]	21 [8]	48 [57]	
90%	29 [46]	41 [16]	25 [30]	
80%	11 [18]	10 [4]	12 [14]	
70% or less	19 [30]	28 [11]	16 [19]	
Missed ART doses, past 30 days (n=142)				0.28
No missed doses	34 [48]	25 [10]	37 [38]	
1–3 missed doses	43 [61]	43 [17]	43 [44]	
4–6 missed doses	8 [12]	10 [4]	8 [8]	
7+ missed doses	15 [21]	23 [9]	12 [12]	

[†], chi-square tests or Fisher's exact test when cell counts were 5 or less. ART, antiretroviral therapy; COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus.

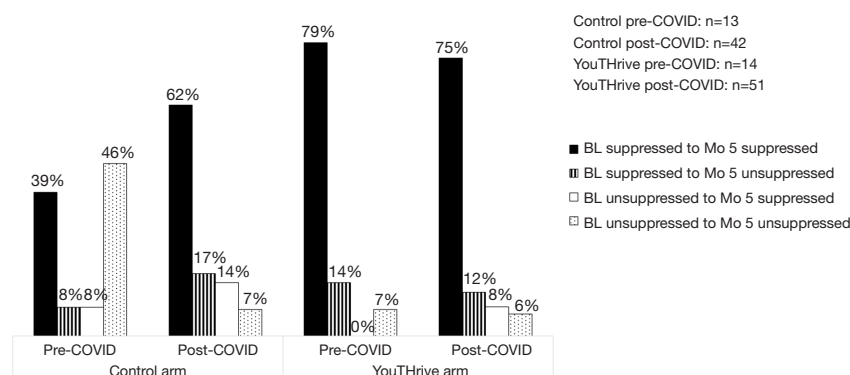


Figure 3 Percentage of youth in viral suppression groups by whether they were enrolled pre- or post-COVID-19 and by study arm, using complete cases in the YouTHrive intervention to improve antiretroviral adherence in youth with HIV, 8 US cities, 2019–2022. BL, baseline assessment; COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; Mo 5, month 5 assessment.

as adjuvants to support in-person or more intensive intervention approaches to have the greatest impact (36), which could be more thoroughly evaluated in future intervention trials.

It is noteworthy that the proportion of youth in the YouTHrive arm who were virally suppressed at the end of the study was higher than the national average (75% *vs.* 66%, respectively) (2), especially given that most participants were enrolled during the COVID-19 pandemic. The relatively high proportion with viral suppression at both timepoints may, in part, reflect that many of the clinics involved in this study were highly resourced and quickly implemented effective strategies to maintain HIV care in the face of COVID-19 pandemic restrictions (e.g., social distancing). Indeed, youth's own reports of the impacts of the COVID-19 pandemic did not show any consistent patterns of reducing their overall access and engagement in HIV care. These findings are consistent with a nationwide study of HIV care outcomes during 2020—the year COVID-19 mandates were implemented and most stringent—that suggested that HIV care services were relatively durable during the pandemic (27).

In contrast, the most negatively impacted areas of youths' lives appeared to have been financial and with on their sexual health. Youth in our sample reported few sexual partners and opportunities to have sex. This is consistent with the relatively high proportion of individuals in 26 countries (mean age =34.6 years) who reported decreased sex with a main or causal partners during the pandemic (37), and with other data showing a decrease in physical contact with partner(s) during this time (38). Although the financial and sexual health toll of the COVID-19 pandemic might

have increased risks for depression and substance use, both of which are risk factors for ART non-adherence (22), the continued access to HIV medications and services in this study may have offset these factors to sustain high levels of ART adherence.

Approximately two-thirds of youth in the control condition intervention (a weekly newsletter of topics important to YWH that did not contain ART adherence information) had an undetectable viral load at month 5, despite a number of youth in this arm reporting financial difficulties and accessing the internet because of the COVID-19 pandemic. Control participants had an overall positive evaluation of the weekly newsletters, with many reporting that they helped them with life challenges and that they would recommend them to their friends. Although both interventions were relatively “low touch” interventions (i.e., neither was not highly intensive intervention), the control condition required less effort to engage with, because the newsletter arrived each week in their email and the youth only had to click on the link to access it. In contrast, youth in the YouTHrive intervention were required to navigate to the website and log in before they could access the intervention features. This increased effort—or interaction costs (39)—might have reduced youth's willingness or ability to interact with YouTHrive intervention compared to the weekly newsletter. The negative effects of additional interaction costs on intervention engagement might have been particularly acute during the COVID-19 pandemic, during which youth experienced high levels of emotional distress (40) and some had increased requirements to manage school or work tasks online. In addition, the control newsletters focused

on topics, such as mental health, that may have resonated particularly during the COVID-19 pandemic (41).

Limitations

These findings should be considered in light of the limitations of the study. First, most participants in this study were 21 to 24 years old and identified as cisgender men and sexual minorities. As such, this sample is not representative of all YWH, and more extensive efforts should be made to provide adherence interventions for adolescent (<18 years old) racial and ethnic minority YWH. Second, the clinics involved in this RCT were highly resourced and made strategic investments in responding to COVID-19 restrictions that likely reduced the impact of the pandemic on youth's HIV care outcomes. Thus, it is unknown whether these results would be replicated in less well-resourced settings. Third, we were only able to collect objective HIV viral load data on 120 participants due to distancing mandates that arose from the COVID-19 pandemic. This reduction in sample size decreased the precision of effect estimates from the study. Although we used multiple imputation to account for missingness, these methods rely on the missing at random assumption and the inclusion of necessary predictors of missingness in the imputation model. Finally, study implementation was significantly impacted by the COVID-19 pandemic, which prompted a change in inclusion criteria, follow-up length, and study procedures. For example, the change in inclusion criteria to not require evidence of problematic adherence after the onset of the COVID-19 pandemic may explain why a higher percentage of youth enrolled after the onset of the COVID-19 pandemic reported perfect adherence in the past 30 days than those enrolled before the onset of the pandemic (47% *vs.* 33%, respectively). Importantly, changes to standard of HIV care during the implementation of COVID-19 mitigation strategies may have impacted findings in other unpredictable ways. There was a widescale pivot to remote strategies across medical care services (e.g., use of cell-phones and texts for as-needed outreach). It is possible that these necessary migrations to mHealth approaches may have made the intervention less unique in some ways. Because we could not capture the variety of clinic-level changes in procedures, we are unable to model or evaluate the impact of these changes. The results we obtained may have been different if the study was conducted as originally designed—in particular, enrolling YWH who evidenced

adherence challenges—and not during a pandemic.

Conclusions

Overall, although the results did support the YouTHrive intervention in this sample of YWH, the study provides important lessons for future programming. First, because the study team anticipated that the COVID-19 pandemic would severely impact the ability of clinics to provide HIV care services, a number of important aspects of the study were altered to be more inclusive of YWH (i.e., not requiring a detectable viral load or reporting adherence disruptions to enroll in the study), and to reduce the burden on participants and research staff. Although understandable at the time, in hindsight, the HIV care services were much more robust than expected and these changes may have resulted in enrolling youth who might not have needed additional adherence supports (and indeed the results may be different if the original inclusion criteria and procedures were implemented). Studies should consider ways of mitigating the impacts of any future pandemics or similar disruptions early in their timeline to consider the impacts of changes to the study. For multisite and multilocation studies involving HIV care sites, careful detailing of changes in standard of care services, particularly those that are like the intervention content being evaluated, should be collected over time. Second, although the complete YouTHrive intervention package was not shown to impact ART adherence in this study, some of its components may be useful in future digital interventions for YWH. For example, the results of an intervention study of older men who have sex with men living with HIV suggested that the use of message boards that allow participants to interact with each other for support was associated with improved viral suppression (36). Thus, future work to “unpack” the intervention components to better understand what features are most impactful is needed (42,43).

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Footnote

Reporting Checklist: The authors have completed the

CONSORT reporting checklist. Available at <https://mhealth.amegroups.com/article/view/10.21037/mhealth-25-47/rc>

Trial Protocol: Available at <https://mhealth.amegroups.com/article/view/10.21037/mhealth-25-47/tp>

Data Sharing Statement: Available at <https://mhealth.amegroups.com/article/view/10.21037/mhealth-25-47/dss>

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. Study procedures were reviewed and approved by the University of North Carolina Institutional Review Board (UNC IRB 16-3136) as the single IRB of record, and IRB authorization agreements with all participating research entities were enacted. A Certificate of Confidentiality was obtained from the National Institute of Child Health and Human Development, and a waiver of parental consent was obtained for participants who were 15–17 years old. All participants participated in an informed consent/assent process.

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