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## **iVY: Protocol for a comprehensive, tailored, technology-based intervention to improve virologic suppression among youth and young adults with HIV**

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3 **Title: iVY: Protocol for a comprehensive, tailored, technology-based intervention to**  
4 **improve virologic suppression among youth and young adults with HIV**  
5

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## Abstract

**Introduction:** Young adults with HIV (YWH) experience worse clinical outcomes than adults and have high rates of substance use and mental illness that impact their engagement in care and adherence to antiretroviral therapy (ART). The intervention for Virologic Suppression in Youth (iVY) aims to address treatment engagement/adherence, mental health and substance use in a tailored manner using a differentiated care approach that is youth friendly. Findings will provide information about the impact of iVY on HIV virologic suppression, mental health (MH), and substance use (SU) among YWH who are disproportionately impacted by HIV and at elevated risk for poor health outcomes.

**Methods and analysis:** The iVY study will test the effect of a technology-based intervention with differing levels of resource requirements (i.e., financial and personnel time) in a randomized clinical trial with an Adaptive Treatment Strategy (ATS) among 200 YWH (18–29 years old). This piloted and protocolized intervention combines: (1) brief weekly sessions with a counselor via a video-chat platform (video-counseling) to discuss MH, SU, HIV care engagement/adherence, and other barriers to care; and (2) a mobile health app to address barriers such as ART forgetfulness, and social isolation.

**Discussion:** The remarkable biomedical advances in HIV prevention and treatment have resulted in discussions toward ending the HIV epidemic. However, this will not happen without addressing MH and SU barriers experienced by YWH. iVY has the potential to address important, distinct, and changing barriers to HIV care engagement (e.g., MH, SU) to increase virologic suppression among YWH at elevated risk for poor health outcomes.

**Ethics and dissemination:** This study and its protocols have been approved by the University of California, San Francisco (UCSF) Institutional Review Board. Study staff will work with a Youth Advisory Panel to disseminate results to the YWH, participants, and the academic community.

**Trial registration:** NCT05877729

### Strengths and limitations of this study

- iVY has the potential to impact HIV health outcomes and mental health (MH) and substance use (SU) among youth with HIV (YWH) who are disproportionately impacted by HIV and who experience more MH challenges than the general population.
- iVY will enhance efficiency of care delivery because it provides a brief, out-of-facility, youth-friendly video-counseling and mobile health app to 18–29-year-olds that is customizable to the needs of YWH.
- The study uses an adaptive treatment strategy to individualize the intervention to YWH based on their viral response to the intervention providing a differentiated care model which tailors care to individuals with the greatest need.
- Given HIV related stigma, the influence of the COVID-19 pandemic on MH and SU challenges, and other barriers to care, the use of video-counseling and provision of remote research and services will likely remain high.
- The intervention will not be available to those who do not have a smartphone or who are Spanish speakers.

## Introduction:

Young adults with HIV (YWH) in the U.S. have the lowest level of virologic suppression<sup>1-3</sup> compared with older age groups. They experience significant health disparities in HIV clinical outcomes<sup>4-8</sup>, including lower rates of antiretroviral therapy (ART) initiation<sup>8</sup>, suboptimal ART adherence<sup>8-10</sup> and retention in care<sup>11</sup>, and higher virologic failure rates<sup>12</sup>. Lack of virologic suppression is a major contributor to mortality, morbidity, and secondary transmission events<sup>13,14</sup>. Additionally, mental health (MH) and substance use (SU) impact every step of the HIV care continuum from diagnosis to virologic suppression<sup>15-19</sup> and exacerbate socioeconomic challenges of linkage and sustained access to healthcare<sup>20-24</sup>. There is also an increased risk of substance use disorders, psychiatric disorders, and mortality with SU at a younger age<sup>25-27</sup>. Overcoming these barriers is key to improving life expectancy, HIV-related disabilities, and quality of life<sup>28,29</sup>. Given the strong evidence for the influence of MH and SU on worsening HIV health outcomes, there is a clear need for increased access to and provision of MH and SU services. Despite the need to address these critical barriers to care among YWH, there is a severe shortage of MH professionals<sup>30-32</sup> and evidence-based interventions for YWH.<sup>33,34</sup>

Addressing this gap calls for interventions with differentiated or individualized approaches to tailor care to individuals with the greatest need. Adaptive Treatment Strategies (ATs) involve adapting a treatment to an individual's changing needs using pre-defined decision rules,<sup>32-36</sup> making them patient centric by design and potentially reducing cost by only giving the appropriate therapy rather than a one size fits all approach.

### *Study Objective:*

We describe the protocol for a study to assess the efficacy of a technology-based intervention on HIV viral suppression (primary outcome). Intervention for Virologic Suppression in Youth (iVY) aims to address MH and SU in a tailored manner using a differentiated care

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3 approach that is youth-friendly.<sup>35</sup> iVY combines two components to address SU and MH among  
4 YWH: (1) brief weekly sessions with a counselor via a video-chat platform (video-counseling) to  
5 discuss MH, SU, HIV care engagement, and other barriers to care<sup>37,38</sup>; and (2) a mobile health  
6 app called WYZ designed and developed using a Human Centered Design approach with YWH  
7 to address barriers<sup>39,40</sup>. The primary goal is to address important, distinct, and changing barriers  
8 to HIV care engagement (e.g., MH, SU, forgetting, social isolation)<sup>41–44</sup> among YWH.  
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## 15 **Methods and Analysis:**

### 16 *Study Overview and Design:*

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21 iVY is testing the effect of a technology-based mobile health app and video-counseling  
22 intervention in a randomized clinical trial (RCT) with an ATS<sup>45–49</sup> among YWH (18–29 years old).  
23 Individuals who are not durably virologically suppressed are randomized (Figure 1) to video-  
24 counseling+app or standard of care (SOC). At 16 weeks, HIV virologic suppression between the  
25 intervention and control arms will be compared using data from home-collected HemaSpot test  
26 kits. Through this study, we are (1) testing the efficacy of video-counseling+app vs. SOC on  
27 virologic suppression and (2) assessing the impact of video-counseling+app vs. SOC on MH  
28 and SU. We are evaluating HIV virologic suppression, MH and SU differences between the  
29 intervention vs. control arms at 16 weeks. We are also (3) exploring an ATS to individualize the  
30 intervention by assigning the virologic “non-responders” in the intervention arm to intensified  
31 video-counseling+app for 16 more weeks, and the virologic “responders” (responder =  
32 virologically suppressed; non-responder = virologically unsuppressed) in the intervention arm to  
33 continue only app use for 16 more weeks. Participants complete an assessment survey and  
34 home-collected VL testing at baseline, 16, 32, and 48 weeks.  
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### 50 *Study Setting:*

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53 We are working with AIDS Healthcare Foundation (AHF) to implement the study and  
54 recruit YWH receiving HIV primary care. In 2019, AHF served 1,292 YWH in California, 927  
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3 (72%) of whom are in five AHF Healthcare Centers: Downtown Los Angeles, San Diego,  
4 Westside, Hollywood, and Oakland. Among these 927 patients, 44% had a viral load (VL) <200  
5 copies/mL. Additionally, we are opening recruitment for YWH at other non-AHF CA clinics. All  
6 study activities are conducted remotely with previous methods successfully used by our team.  
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### 12 13 *Participant Population:*

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15 The study includes 200 YWH who are between the ages of 18–29, live and receive care  
16 in CA, have a lack of durable viral suppression (any HIV VL ( $\geq 20$  copies/mL in the past 12  
17 months), have access to a smartphone, and speak English. We have chosen to include young  
18 adults aged 18-29 as they are in a distinct developmental phase with unique needs and  
19 challenges compared with individuals younger than 18 or older than 29 years or younger than  
20 18. Those with a history of hemophilia or who are unable to conduct finger pricks at home for  
21 the VL test are excluded because participants are required to do at-home VL testing. Individuals  
22 with MH or SU challenges are included, unless their symptoms are too severe for them to safely  
23 participate in the study.  
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### 34 General Study Procedures:

#### 35 *Recruitment:*

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39 AHF is contacting patients from their database of YWH ages 18–29 who have a lack of  
40 durable viral suppression (any HIV VL ( $\geq 20$  copies/mL in the past 12 months) to offer study  
41 information. Interested patients are handed off to the study team for further information,  
42 screening, and enrollment; or they may be asked for permission to share their contact  
43 information with the study team to be contacted later. Non-AHF participants are recruited via  
44 social media and flyers posted at healthcare clinics serving YWH.  
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#### 51 *Screening, Consent and Enrollment:*

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54 The study team screen interested individuals over the telephone to determine eligibility  
55 and enroll them in the study. Interested individuals are given adequate time to read the consent  
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3 form; the study team member is available to answer any questions via phone. The consent  
4 form, to be signed electronically, includes information about potential risks and benefits, that  
5 participation is completely voluntary and will not affect SOC that participants receive, and that  
6 participants may withdraw from the study at any time. Any individual displaying MH or SU  
7 challenges that may impede the understanding and completion of consent is excluded and  
8 referred to appropriate services.  
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16 *Randomization:*

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18 We are using a random number generator in REDCap (Research Electronic Data  
19 Capture) to randomize 1:1 allocation to intervention or SOC arms.<sup>52</sup> Participants are assigned to  
20 groups via block randomization with block size permuted to promote group balance on  
21 covariates. Given the lack of an appropriate time- and attention-matched control group and  
22 need to establish generalizable efficacy, we are comparing the video-counseling+app arm to a  
23 SOC arm. The SOC arm includes the current care delivery model: regularly scheduled visits  
24 with a healthcare provider and lab testing every 3–6 months or more/less frequently, depending  
25 on the individual's HIV health outcomes (e.g., viral suppression). The study team asks  
26 participants to complete the first study assessment. After completion of the survey, the  
27 participants will get randomized, and the study team will mail the participants' baseline VL  
28 home-collected test. The VL sample is collected via a Hemaspot HF device, which uses  
29 advanced dried blood spot (DBS) technology. Hemaspot-HF is an improved collection over the  
30 traditional DBS cards because it protects the sample from contamination, allows for safe  
31 transport and easy storage and shipment, and provides a rapid sampling mechanism that does  
32 not require drying.  
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49 *Patient Retention and Incentives:*

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51 Retention is supported through the collection of detailed contact information, short  
52 message service (SMS) messaging, and incentives. We have monthly check-ins with  
53 participants during which we ask about app use, provide support for logistical challenges with  
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3 the app, and update any contact information. We also work with a Youth Advisory Panel (YAP)  
4 on maintaining and enhancing participant retention throughout the study. Incentives include \$20  
5 for completing the baseline survey, \$30 for the 16, 32, and 48-week surveys, \$30 for the  
6 baseline and 16-week home-collected VL's, and \$40 for the 32 and 48-week home-collected  
7 VL's plus a \$10 for VL kits that are returned on time. Incentives are distributed through Venmo  
8 or CashApp via a study account that uses a study-specific mobile phone number and email and  
9 is accessible only by the study staff. Participants are asked to provide their Venmo username,  
10 which is verified. The default is set to "private" so that payment information cannot be viewed by  
11 others.  
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### 23 *Risks to Participants:*

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25 Risks to participants are monitored regularly by trained study staff and documented at  
26 each intervention session and study assessment. At each assessment, we review participant  
27 responses to examine acute need for referral to medical, mental health, or substance use  
28 services.  
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### 33 *Adverse Events and Auditing:*

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35 In this study, we do not anticipate moderate, severe, life-threatening, disabling, or fatal  
36 adverse events. Potential adverse events include loss of confidentiality or emotional distress.  
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### 40 *Youth Involvement:*

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42 To inform study implementation and dissemination, we have identified 10 YWH from  
43 AHF Healthcare Centers in CA to form the YAP. YAP meetings are held twice yearly virtually  
44 and last for 2 hours. YAP members will review study materials before study launch and will  
45 provide input/feedback about the intervention, recruitment and retention strategies, next steps,  
46 and dissemination of findings. In addition to keeping the YAP updated about study progress, we  
47 will discuss any implementation challenges, engagement, attrition, and other issues to obtain  
48 the YAP's feedback to improve study implementation.  
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### Intervention Procedures:

The intervention arm (video-counseling+app) receives 12 brief weekly counseling sessions (given over 16 weeks) with a masters level mental health professional (e.g., social worker), along with access to the WYZ app to use based on their needs. After 16 weeks, responders in the video-counseling+app arm continue to use the app only. Non-responders in the intervention arm continue with intensified video-counseling+app for 16 more weeks. The additional 16 weeks aims to reinforce counseling points by targeting participant-specific barriers to virologic suppression based on the needs of non-responders.

### Video-Counseling:

The goal of video counseling is to provide information, motivation, and behavioral skills for dealing with MH, SU, and HIV care engagement challenges to address mild–moderate MH symptoms or low–moderate levels of SU; and assist with linking/relinking to more extensive MH, SU, and/or HIV treatment, as needed. The intervention tailors the counseling based on baseline factors as follows: **(1)** HIV care acuity: due to unsuppressed VL of all participants, each individual receives two core HIV sessions and sessions will be tailored based on barriers to achieving virologic suppression; **(2)** MH acuity: based on elevated PHQ-9<sup>53,54</sup> (10+), GAD-7 (10+)<sup>55</sup>, or PCL-5; (33+)<sup>56</sup> score or **(3)** SU acuity: based on elevated AUDIT (8+)<sup>57</sup>, DAST (3+)<sup>58</sup>, or monthly or more use of drugs (besides marijuana) or daily use of tobacco or marijuana as measured by ASSIST<sup>59,60</sup>. Individuals with “high acuity” receive two core sessions related to HIV care (2 A/B), MH (2A/B), and/or SU (3A/B), each. “A” sessions assess barriers and build motivation, while “B” sessions provide information and deliver health education. A&B core sessions map onto the Information, Motivation, Behavior (IMB) model<sup>61</sup>, which was used to develop the intervention.

For the remaining sessions, we use an integrated behavioral health and HIV care-focused approach to further the conversations in the core sessions. Participants choose from a

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3 list of menu sessions identified in the first session which allows the counselor to spend more  
4 time on HIV care, MH, or SU based on the participants' needs. In this manner, the intervention  
5 is tailored to the unique and changing needs of participants and can address other specific  
6 topics related to their experiences of racism, transphobia, stigma, discrimination, gender  
7 identity, racial/ethnic identity, classism, and current events.  
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13 SMS messages are used to enhance the intervention and for participant retention by:  
14 (1) assessment of completion of health goals (i.e., behavioral skills) set during weekly sessions  
15 (e.g., schedule appointment with provider); (2) provision of MH/SU or community resources  
16 based on participant's needs (e.g., housing); (3) follow-up to ensure participant's linkage to MH,  
17 SU, or HIV care; (4) reminder of video-counseling session; and (5) monthly check-in to update  
18 contact information.  
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26 Fidelity to intervention. A session fidelity checklist is completed for each session to  
27 ascertain whether the focus area and barriers were identified, education/information was  
28 provided, motivation was enhanced, and problem-solving was initiated. The study team  
29 assesses intervention fidelity during weekly meetings with the counselors to review each  
30 session's length, technical issues, topics covered, goals established, and narrative progress  
31 notes.  
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39 Counselor training. Prior to conducting sessions, counselors participate in >25 hours of  
40 interactive training to learn the protocol and intervention manual intimately and role-play pre-  
41 prepared vignettes. Counselors must attend the entire training and demonstrate proficiency of  
42 knowledge of the intervention manual.  
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#### 47 *WYZ App:*

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49 WYZ was designed and developed using a human-centered design approach with a  
50 YAP, formative research with YWH, and is grounded in the IMB model.<sup>39,40</sup> WYZ contains 3  
51 main features: My Health, My Community, and My Team. Each of these features are described  
52 in more detail in Table 1 and Figure 2. Tailoring is achieved based on the individual's needs at a  
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3 given time (e.g., My Community may be used more if social isolation is a barrier). For the My  
4 Community feature, all original posts must be approved by research staff before posting. On a  
5 weekly basis, research staff review new responses to all posts to ensure that there aren't any  
6 critical issues to be addressed. Any issues are brought to the study team's attention and  
7 referred to a clinical psychologist on the team if needed. Monthly check-ins help improve  
8 engagement through checking contact information and answering any questions.

#### 15 Data Collection Procedures:

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18 Quantitative study assessments with home-collected HIV VL testing are done at  
19 baseline, 16, 32, and 48 weeks after enrollment and randomization. Quantitative assessments  
20 collect information about sociodemographic characteristics, substance use, technology use,  
21 mental health, HIV-related outcomes, and experiences with the intervention for those in the  
22 intervention arm. All measures are described in Table 2. REDCap is used for all data collection  
23 such as surveys, intervention implementation and clinical data.<sup>52</sup> REDCap is a secure web  
24 application for building and managing online surveys and databases, and data are stored and  
25 managed on a University of California San Francisco (UCSF) server.

#### 34 Qualitative Exit Interviews:

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37 At 16 and 32 weeks, we will conduct semi-structured individual exit qualitative interviews  
38 with a sample YWH from the intervention arm, stratified by response or non-response (i.e.,  
39 suppressed, or unsuppressed HIV VL) and levels of engagement (attended  $\geq 80\%$  of counseling  
40 session versus  $< 80\%$  attendance). The interviews explore (a) barriers/facilitators to intervention  
41 participation, (b) barriers/facilitators to intervention response/non-response, (c) need for future  
42 modifications, and (d) preferences for longer term support.

#### 49 Security and Confidentiality:

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51 All data are stored on a secure, HIPAA compliant, password-protected server.  
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53 Participants' contact information and other identifying data are stored separately from other  
54 study data, the key linking names to study ID is stored separately and destroyed at the end of  
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3 data collection, and all other study documents only have participant codes. Only the research  
4 team have access to participant identities. All data are de-identified prior to analysis and  
5 individuals will not be identified in any reports or publications of the research.  
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9 We use Zoom for video-counseling, which is the UCSF-preferred HIPAA-compliant video  
10 chat platform. We have developed study protocols related to video-counseling privacy and  
11 security. For SMS messages, study staff demonstrate how to set up privacy settings on  
12 smartphones, such as keeping SMS message previews from showing up on locked screens and  
13 adding a security code to lock the smartphone. For the WYZ app, we have partnered with the  
14 UCSF School of Medicine Technology (SOM Tech) team to maximize security. SOM Tech has  
15 built this app within best practices for developing HIPAA-compliant apps and has worked closely  
16 with the UCSF Enterprise Security team to review the app architecture in an iterative manner to  
17 ensure the highest level of security. All qualitative interviews are conducted remotely and audio-  
18 recorded via HIPAA-compliant web conference platform (e.g., Zoom) with audio-recordings  
19 stored on a HIPAA-compliant server with access available only to select study staff. All audio-  
20 recorded files are deleted upon completion of the study.  
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#### 34 Data Monitoring:

35 A data safety monitoring board consisting of three external reviewers meet annually to  
36 review the research protocol and materials, evaluate the progress, and report on safety and  
37 concerns.  
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#### 43 Study Outcomes:

44 The primary outcome is HIV VL using the Hemaspot-HF device.<sup>62</sup> We mail participants  
45 home test kits (including the Hemaspot-HF device, gauze, bandages, lancets, alcohol wipes,  
46 and pre-addressed stamped envelopes) at baseline, 16, 32, and 48 weeks. After a finger prick,  
47 they place two drops of blood on the Hemaspot-HF device. The device dries in one minute;  
48 participants then close the lid and mail the device to the laboratory. The laboratory uses the  
49 Abbott RealTime HIV-1 DBS assay with a lower limit of 400 copies/mL<sup>63</sup>. To minimize missing  
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3 data, we request missing VL data (+/- one month around the four VL time points) from  
4 participants' clinical electronic medical records. The secondary outcomes are MH (PHQ-9<sup>64</sup>,  
5 GAD-7<sup>55</sup>, and PCL-5<sup>65</sup>); and SU (AUDIT<sup>57</sup>, DAST<sup>58</sup>, and ASSIST<sup>59</sup>).  
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10 *Quantitative Data Analysis:*

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12 Frequency tables for all variables and measures of central tendency and variability for  
13 continuous variables will be used to characterize the sample. In addition to describing important  
14 sample characteristics, these descriptive analyses will summarize the app paradata listed in  
15 Table 2, which will provide important information on overall app engagement and specific  
16 features used most. If the study arms differ significantly at baseline on covariates, we will use  
17 methods based on the Rubin causal model (e.g., propensity scores, double-robust estimation)  
18 to obtain the effect estimates under the counterfactual assumption of balanced groups<sup>66-70</sup>. We  
19 will address missing data with multiple imputation.<sup>71</sup>  
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29 To assess efficacy of video-counseling+app vs. SOC on virologic suppression in YWH,  
30 we will compare HIV virologic suppression of those randomized to the intervention vs. control  
31 arms at 16 weeks. We hypothesize that at 16 weeks the odds of our primary outcome, virologic  
32 suppression, will be higher for video-counseling+app intervention participants than for SOC  
33 participants. To test this comparison, we will fit a logistic regression model. To assess the  
34 impact of video-counseling+app vs. SOC on the secondary outcomes, we will evaluate the MH  
35 and SU differences between the intervention vs. control arms at 16 weeks. We will employ  
36 general linear modeling (GLM) methods to test whether mean levels of MH and SU at 16 weeks  
37 are lower in the video-counseling+app group vs. the SOC group. Demographic and pre-  
38 specified covariates based on theory and literature will be included and moderated mediation  
39 will be explored using causal inference-based methods.  
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52 We will also explore differences between those who were (a) virologic “non-responders”  
53 in the intervention arm who received intensified video-counseling+app for 16 more weeks, and  
54 (b) virologic “responders” in the intervention arm who continued only app use for 16 more  
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3 weeks. Frequency tables for all variables and measures of central tendency and variability for  
4  
5 continuous variables stratified by virologic response status will characterize responders and  
6  
7 non-responders on measures at 16 weeks including MH and SU. An exploratory multivariable  
8  
9 logistic regression analysis will be performed on the subgroup of participants exposed to the  
10  
11 intervention to predict which participants will be responders vs. non-responders. Additionally, we  
12  
13 will use logistic regression to explore whether responders vs. non-responders at 16 weeks  
14  
15 exhibit higher odds of virologic suppression at 32 weeks.

#### 16 17 18 *Qualitative Analysis:*

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20 Data will be analyzed using thematic and content analysis frameworks<sup>72</sup>. Data analysis  
21  
22 will draw on an inductive approach<sup>73</sup> and by deductively applying codes developed from the  
23  
24 interview guide. This dual approach will allow for themes to emerge from the data using  
25  
26 inductive coding while also using an a priori template of code from which to frame the analysis<sup>74</sup>.

#### 27 28 29 *Power Analysis:*

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31 Power analyses were generated using NCSS PASS 2021<sup>75</sup> to compute the minimum  
32  
33 detectable effect sizes for the proposed primary analyses. The study is beginning with 200  
34  
35 participants assigned to the video-counseling+app (N= 100) intervention group and the SOC  
36  
37 control group (N= 100). Assuming 20% attrition based on our pilot studies<sup>40,76</sup> and prior research  
38  
39 among YWH<sup>77</sup>, data from 160 participants will be available to test hypotheses. Assuming total  
40  
41 N= 160,  $\alpha = 0.05$ , power= 0.80, and 44% in the control group virologically suppressed based on  
42  
43 data supplied by AHF, we computed the minimum detectable odds ratio (OR), proportion  
44  
45 difference (*pdiff*), and standardized proportion difference (*h*) for the proposed primary  
46  
47 comparison, which yielded  $OR = 2.46$ ,  $pdiff = 0.22$ , and  $h = 0.44$ . For continuous MH and SU  
48  
49 outcomes, we used the same inputs as above and computed the minimum detectable  
50  
51 standardized mean difference *d* across the video-counseling+app and SOC groups, yielding  $d =$   
52  
53 0.45. Our proposed primary analyses can detect effects that are between small and medium<sup>78</sup>.  
54  
55 In addition, a 22% increase in virologic suppression or an OR of 2.46 is an effect size equal to  
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3 or smaller than other studies among YWH or older adults living with HIV<sup>79</sup> and is clinically  
4 meaningful.  
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### 8 **Ethics and dissemination:**

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10 We received approval from the University of California, San Francisco Institutional Review  
11 Board (IRB) to conduct this study and written consent from all participants. Reliance  
12 agreements were signed by RTI international and AHF. The study team will work with the YAP  
13 to disseminate results to YWH, participants, and the academic community. A manuscript with  
14 the results of the primary study will be published in a peer-reviewed journal along with separate  
15 manuscripts for the secondary aims.  
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### 23 **Discussion:**

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25 Our intervention protocol uses a tailored approach to impact engagement in HIV care  
26 by focusing on mental health, and substance use among YWH using a tailored approach,  
27 focusing on various barriers to care to different degrees, based on their changing needs.<sup>41-44</sup>  
28  
29 Despite YWH experiencing more MH challenges than the general population substantially fewer  
30 interventions have been developed and evaluated in YWH compared to older adults.<sup>33</sup> Most  
31 intervention studies for YWH have been conducted with small sample sizes, limited follow-up  
32 times, and not examined impact of the intervention to sustain or improve MH.<sup>33,80</sup> While there  
33 are interventions for HIV prevention and SU among youth<sup>81-84</sup>, they are limited by requiring  
34 lengthy in-person sessions with a trained counselor, involving the youth's families, focusing  
35 specifically on SU (versus a holistic approach), and were developed for younger adolescents.  
36  
37 iVY is innovative because it provides a "self-service" model that is customizable to the needs of  
38 YWH. Additionally, a recent review suggests the need for multi-component interventions that go  
39 beyond health facilities to address social barriers to engagement in HIV care.<sup>34</sup> Thus, our study  
40 is significant and will enhance efficiency of care delivery because it provides a brief, out-of-  
41 facility, youth-friendly video-counseling and mobile health app to 18-29-year-olds with HIV,  
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3 which focuses on HIV care, MH, and SU, and connects participants to community resources to  
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5 continue receiving MH and SU services, as needed.  
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8 We acknowledge that there will be more marginalized groups who may not have  
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10 smartphone access (~4%) or may not have been diagnosed with HIV, and our study results may  
11  
12 not be generalizable to them. Given this high level of smartphone ownership<sup>85</sup>, we are confident  
13  
14 that the vast majority of our target population will have a smartphone. Additionally, a Spanish  
15  
16 version of the app is not currently available. Given the need to fully develop the intervention in a  
17  
18 culturally relevant manner for non-English speakers, we aim to translate our intervention in  
19  
20 future iterations of this project.  
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23 In summary, the remarkable biomedical advances in HIV prevention and treatment have  
24  
25 resulted in discussions toward ending the HIV epidemic. However, this will not happen without  
26  
27 addressing MH and SU barriers experienced by YWH.<sup>86</sup> iVY will examine an innovative  
28  
29 intervention to achieve the goal of ending the HIV epidemic. This study will provide valuable  
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31 data about the characteristics of virologic responders and non-responders to the intervention,  
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33 individualization of the intervention based on these variables, and linkage to MH and SU  
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35 treatment services among those in need. If efficacious, in future research we will investigate the  
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37 intervention's sustainability for implementation across the United States. Given the influence of  
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39 the COVID-19 pandemic on MH and SU challenges<sup>87</sup>, the use of video-counseling and provision  
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41 of remote research and services will remain high<sup>88,89</sup>. iVY has the potential to impact HIV health  
42  
43 outcomes and MH and SU among YWH who are disproportionately impacted by HIV and at  
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45 elevated risk for poor health outcomes.  
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50 **Authors' contributions:** MCDS was the lead author of the manuscript with support and input  
51  
52 from the study Principal Investigator, PS. All coauthors reviewed and approved the manuscript  
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54 and are involved in study implementation.  
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Figure 1: Overview of Study Design

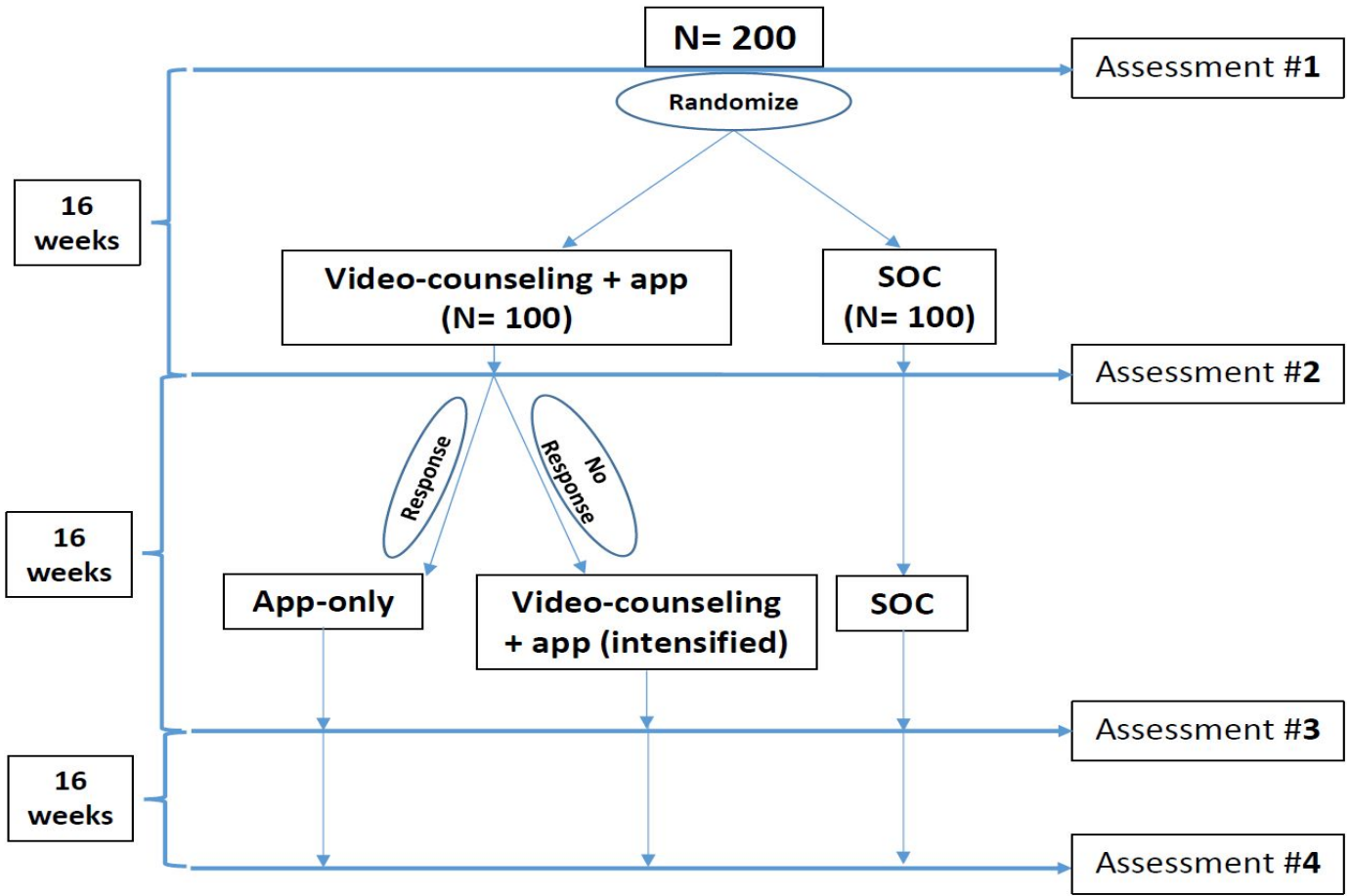
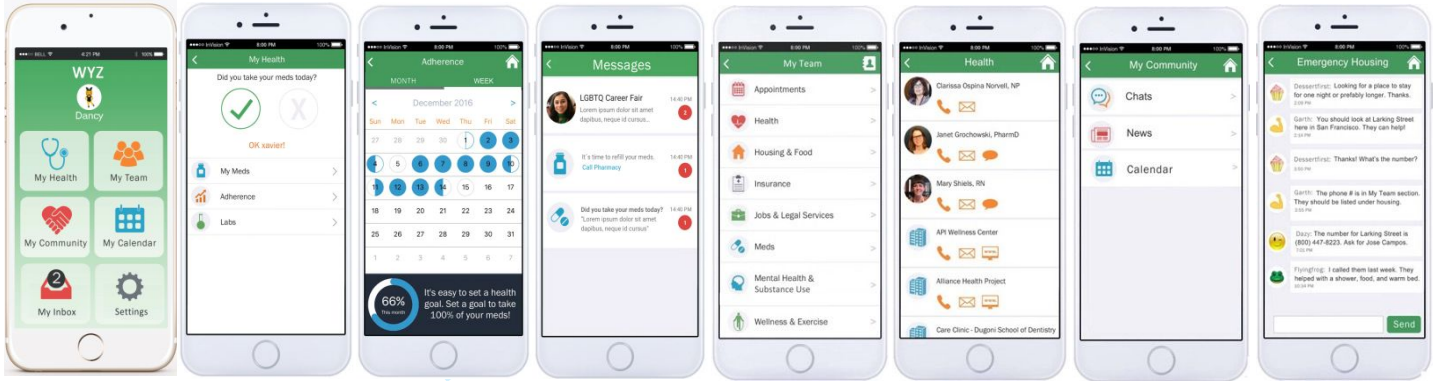


Figure 2. Mobile app screenshots



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<b>Feature</b>	<b>Function</b>	<b>Barriers Addressed</b>
My Health	Set customized ART adherence reminders (B), refill/injection reminders (B), graph adherence over time (M), keep track of VL & CD4+ test results (I/M)	Too busy, forgot, changed my routine, ran out of pills, unstructured lifestyle
My Team	Increase access to community organizations & resources using the participant's geo-location (I)	Lack of access to MH & SU services or other community services, limited mobility
My Community	Allow users to interact with other YWH through moderated forums (M), stay up-to-date on health news (I), provide a calendar of community events (I)	Low health literacy, social isolation, stigma, lack of community support

Table 2. Outcome and Descriptive variables.			
Variables		Items	Interpretation
<b>Outcome</b>			
1°	HIV viral load	Virologic suppression using Hemaspot device	Suppressed VL: <400 copies/mL* Unsuppressed VL: ≥400 copies/mL
2°	Mental Health	Depressive symptoms: PHQ-9 <sup>64</sup> (10 items; score= 0–27)	Higher score indicates more depressive symptoms
		Anxiety: GAD <sup>55</sup> (7 items; score= 0–21)	Higher score indicates more anxiety
		Trauma: PCL-5 <sup>65</sup> (score= 0–80)	Higher score indicates more trauma
	Substance use	DAST <sup>58</sup> (10 items; score= 0–10)	Higher score indicates more drug misuse
		AUDIT <sup>57</sup> (10 items; scores= 0–40)	Higher score indicates more alcohol misuse
		ASSIST <sup>59</sup>	Frequency of alcohol, smoking, and SU
<b>Other Descriptive Variables</b>			
	Demographics	Age, sex/gender, race/ethnicity, sexual identity, education, income, work, school, living situation, city of residence, ever homeless or incarcerated	
	MH & SU	Type & frequency of MH & SU services ever received or being received; timeline follow-back method for more recent SU <sup>190,91</sup> ; The Quick Inventory of Depressive Symptomatology (Self-Report) (QIDS-SR16) <sup>92</sup>	
	Healthcare accessibility	Distance to get to HIV clinic, ease of getting appointments at clinic, ease of getting in touch with provider <sup>93</sup>	
	Social isolation	PROMIS Item Bank <sup>94</sup> (14 items, score= 14–70)	Higher score indicates greater isolation
	Technology use	Use of technology to email providers, refill medications, or making medical appointments, frequency of break in service or lost/stolen phone, reliability of service, access to Wi-Fi <sup>95</sup> , mobile technology vulnerability scale (MTVS) <sup>96</sup> , System Usability Scale (SUS) <sup>97</sup> for WYZ	MTVS range= 0–17 with higher scores indicating more vulnerability <sup>96</sup> , SUS range= 0–100 & scores >68 considered above average <sup>98</sup>
	Perceived engagement in HIV care	Index of Engagement in Care <sup>99</sup> (10 items, score= 0–10)	Higher score indicates higher ART adherence, clinic attendance, VL suppression
	HIV knowledge	HIV treatment knowledge scale <sup>100</sup> (15 items, score= 0–15)	Higher score indicates more knowledge
	Engagement	Healthcare provider engagement <sup>101</sup> (13	Higher score indicates



	with provider	items, score= 0–52)	poorer engagement
	Subsistence needs	Unmet subsistence needs <sup>42,102</sup> (5 items, score= 0–5)	Higher score indicates more subsistence needs
	Resilience	Brief resilience scale <sup>103,104</sup> (6 items; score= 1–5)	High score indicates more resilience
	App paradata	Number of minutes in app; change in app use over time; number of push notifications opened from those sent through the application; use of My Health (adherence tracking), My Team (identification of community services), My Community (chat with peers, use calendar)	

# BMJ Open

## **iVY: Protocol for a randomized clinical trial to test the effect of a technology-based intervention to improve virologic suppression among young adults with HIV in the United States**

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3 **Title: iVY: Protocol for a randomized clinical trial to test the effect of a technology-based**  
4 **intervention to improve virologic suppression among young adults with HIV in the United**  
5 **States**  
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## Abstract

**Introduction:** Young adults with HIV (YWH) experience worse clinical outcomes than adults and have high rates of substance use and mental illness that impact their engagement in care and adherence to antiretroviral therapy (ART). The intervention for Virologic Suppression in Youth (iVY) aims to address treatment engagement/adherence, mental health and substance use in a tailored manner using a differentiated care approach that is youth friendly. Findings will provide information about the impact of iVY on HIV virologic suppression, mental health (MH), and substance use (SU) among YWH who are disproportionately impacted by HIV and at elevated risk for poor health outcomes.

**Methods and analysis:** The iVY study will test the effect of a technology-based intervention with differing levels of resource requirements (i.e., financial and personnel time) in a randomized clinical trial with an Adaptive Treatment Strategy (ATS) among 200 YWH (18–29 years old). The primary outcome is HIV virologic suppression measured via dried blood spot. This piloted and protocolized intervention combines: (1) brief weekly sessions with a counselor via a video-chat platform (video-counseling) to discuss MH, SU, HIV care engagement/adherence, and other barriers to care; and (2) a mobile health app to address barriers such as ART forgetfulness, and social isolation. iVY has the potential to address important, distinct, and changing barriers to HIV care engagement (e.g., MH, SU) to increase virologic suppression among YWH at elevated risk for poor health outcomes.

**Ethics and dissemination:** This study and its protocols have been approved by the University of California, San Francisco (UCSF) Institutional Review Board. Study staff will work with a Youth Advisory Panel to disseminate results to the YWH, participants, and the academic community.

**Trial registration:** NCT05877729

### Strengths and limitations of this study

- iVY has the potential to impact HIV health outcomes and mental health (MH) and substance use (SU) among youth with HIV (YWH) who are disproportionately impacted by HIV and who experience more MH challenges than the general population.
- iVY will enhance efficiency of care delivery because it provides a brief, out-of-facility, youth-friendly video-counseling and mobile health app to 18–29-year-olds that is customizable to the needs of YWH.
- The study uses an adaptive treatment strategy to individualize the intervention to YWH based on their viral response to the intervention providing a differentiated care model which tailors care to individuals with the greatest need.
- Given HIV related stigma, the influence of the COVID-19 pandemic on MH and SU challenges, and other barriers to care, the use of video-counseling and provision of remote research and services will likely remain high.
- The intervention will not be available to those who do not have a smartphone or who are Spanish speakers.

## Introduction:

Young adults with HIV (YWH) in the U.S. have the lowest level of virologic suppression[1–3] compared with older age groups. They experience significant health disparities in HIV clinical outcomes[4–8], including lower rates of antiretroviral therapy (ART) initiation[8], suboptimal ART adherence[8–10] and retention in care[11], and higher virologic failure rates[12]. Lack of virologic suppression is a major contributor to mortality, morbidity, and secondary transmission events[13,14]. Additionally, mental health (MH) and substance use (SU) impact every step of the HIV care continuum from diagnosis to virologic suppression[15–19] and exacerbate socioeconomic challenges of linkage and sustained access to healthcare[20–24]. There is also an increased risk of substance use disorders, psychiatric disorders, and mortality with SU at a younger age[25–27]. Overcoming these barriers is key to improving life expectancy, HIV-related disabilities, and quality of life[28,29]. Given the strong evidence for the influence of MH and SU on worsening HIV health outcomes, there is a clear need for increased access to and provision of MH and SU services. Despite the need to address these critical barriers to care among YWH, there is a severe shortage of MH professionals[30–32] and evidence-based interventions for YWH.[33,34]

Addressing this gap calls for interventions with differentiated or individualized approaches to tailor care to individuals with the greatest need. Adaptive Treatment Strategies (ATs) involve adapting a treatment to an individual's changing needs using pre-defined decision rules,[32–36] making them patient centric by design and potentially reducing cost by only giving the appropriate therapy rather than a one size fits all approach.

### *Study Objective:*

We describe the protocol for a study to assess the efficacy of a technology-based intervention on HIV viral suppression (primary outcome). Intervention for Virologic Suppression

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2  
3 in Youth (iVY) aims to address MH and SU in a tailored manner using a differentiated care  
4 approach that is youth-friendly.[35] iVY combines two components to address SU and MH  
5 among YWH: (1) brief weekly sessions with a counselor via a video-chat platform (video-  
6 counseling) to discuss MH, SU, HIV care engagement, and other barriers to care[37,38]; and (2)  
7 a mobile health app called WYZ designed and developed using a Human Centered Design  
8 approach with YWH to address barriers[39,40]. The primary goal is to address important,  
9 distinct, and changing barriers to HIV care engagement (e.g., MH, SU, forgetting, social  
10 isolation)[41–44] among YWH.  
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### 13 **Methods and Analysis:**

#### 14 *Study Overview and Design:*

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16 iVY is testing the effect of a technology-based mobile health app and video-counseling  
17 intervention in a randomized clinical trial (RCT) with an ATS[45–49] among YWH (18–29 years  
18 old). Individuals who are not durably virologically suppressed are randomized (Figure 1) to  
19 video-counseling+app or standard of care (SOC). At 16 weeks, HIV virologic suppression  
20 between the intervention and control arms will be compared using data from home-collected  
21 HemaSpot test kits. Through this study, we are (1) testing the efficacy of video-counseling+app  
22 vs. SOC on virologic suppression and (2) assessing the impact of video-counseling+app vs.  
23 SOC on MH and SU. We are evaluating HIV virologic suppression, MH and SU differences  
24 between the intervention vs. control arms at 16 weeks. We are also (3) exploring an ATS to  
25 individualize the intervention by assigning the virologic “non-responders” in the intervention arm  
26 to intensified video-counseling+app for 16 more weeks, and the virologic “responders”  
27 (responder = virologically suppressed; non-responder = virologically unsuppressed) in the  
28 intervention arm to continue only app use for 16 more weeks. Participants complete an  
29 assessment survey and home-collected VL testing at baseline, 16, 32, and 48 weeks.  
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#### 55 *Study Setting:*

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3 We are working with AIDS Healthcare Foundation (AHF) to implement the study and  
4 recruit YWH receiving HIV primary care. In 2019, AHF served 1,292 YWH in California, 927  
5 (72%) of whom are in five AHF Healthcare Centers: Downtown Los Angeles, San Diego,  
6 Westside, Hollywood, and Oakland. Among these 927 patients, 44% had a viral load (VL) <200  
7 copies/mL. Additionally, we are opening recruitment for YWH at other non-AHF CA clinics. All  
8 study activities are conducted remotely with previous methods successfully used by our team.  
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16 [50,51].

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18 *Participant Population:*

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20 The study includes 200 YWH who are between the ages of 18–29, live and receive care  
21 in CA, have a lack of durable viral suppression (any HIV VL ( $\geq 20$  copies/mL in the past 12  
22 months), have access to a smartphone, and speak English. We have chosen to include young  
23 adults aged 18-29 as they are in a distinct developmental phase with unique needs and  
24 challenges compared with individuals younger than 18 or older than 29 years or younger than  
25 18. Those with a history of hemophilia or who are unable to conduct finger pricks at home for  
26 the VL test are excluded because participants are required to do at-home VL testing. Individuals  
27 with MH or SU challenges are included, unless their symptoms are too severe for them to safely  
28 participate in the study.  
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39 *General Study Procedures:*

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41 *Recruitment:*

42  
43 AHF is contacting patients from their database of YWH ages 18–29 who have a lack of  
44 durable viral suppression (any HIV VL ( $\geq 20$  copies/mL in the past 12 months) to offer study  
45 information. Interested patients are handed off to the study team for further information,  
46 screening, and enrollment; or they may be asked for permission to share their contact  
47 information with the study team to be contacted later. Non-AHF participants are recruited via  
48 social media and flyers posted at healthcare clinics serving YWH.  
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56 *Screening, Consent and Enrollment:*



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3 The study team screen interested individuals over the telephone to determine eligibility  
4 and enroll them in the study. Interested individuals are given adequate time to read the consent  
5 form; the study team member is available to answer any questions via phone. The consent  
6 form, to be signed electronically, includes information about potential risks and benefits, that  
7 participation is completely voluntary and will not affect SOC that participants receive, and that  
8 participants may withdraw from the study at any time. Any individual displaying MH or SU  
9 challenges that may impede the understanding and completion of consent is excluded and  
10 referred to appropriate services.  
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20 *Randomization:*  
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22 We are using a random number generator in REDCap (Research Electronic Data  
23 Capture) to randomize 1:1 allocation to intervention or SOC arms.[52] Participants are assigned  
24 to groups via block randomization with block size permuted to promote group balance on  
25 covariates. Given the lack of an appropriate time- and attention-matched control group and  
26 need to establish generalizable efficacy, we are comparing the video-counseling+app arm to a  
27 SOC arm. The SOC arm includes the current care delivery model: regularly scheduled visits  
28 with a healthcare provider and lab testing every 3–6 months or more/less frequently, depending  
29 on the individual's HIV health outcomes (e.g., viral suppression). The study team asks  
30 participants to complete the first study assessment. After completion of the survey, the  
31 participants will get randomized, and the study team will mail the participants' baseline VL  
32 home-collected test. The VL sample is collected via a Hemaspot HF device, which uses  
33 advanced dried blood spot (DBS) technology. Hemaspot-HF is an improved collection over the  
34 traditional DBS cards because it protects the sample from contamination, allows for safe  
35 transport and easy storage and shipment, and provides a rapid sampling mechanism that does  
36 not require drying.  
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53 *Patient Retention and Incentives:*  
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3 Retention is supported through the collection of detailed contact information, short  
4 message service (SMS) messaging, and incentives. We have monthly check-ins with  
5 participants during which we ask about app use, provide support for logistical challenges with  
6 the app, and update any contact information. We also work with a Youth Advisory Panel (YAP)  
7 on maintaining and enhancing participant retention throughout the study. Incentives include \$20  
8 for completing the baseline survey, \$50 for the 16 week survey, \$40 for the 32 week survey, and  
9 \$30 for the 48-week survey; \$40 for the baseline, 16, 32, and 48week home-collected VL's, plus  
10 a \$10 for VL kits that are returned on time. Incentives are distributed through Venmo or  
11 CashApp via a study account that uses a study-specific mobile phone number and email and is  
12 accessible only by the study staff. Participants are asked to provide their CashApp or Venmo  
13 username, which is verified. The default is set to "private" so that payment information cannot  
14 be viewed by others.  
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#### 28 29 *Risks to Participants:*

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31 Risks to participants are monitored regularly by trained study staff and documented at  
32 each intervention session and study assessment. At each assessment, we review participant  
33 responses to examine acute need for referral to medical, mental health, or substance use  
34 services.  
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#### 39 40 *Adverse Events and Auditing:*

41 In this study, we do not anticipate moderate, severe, life-threatening, disabling, or fatal  
42 adverse events. Potential adverse events include loss of confidentiality or emotional distress.  
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#### 46 47 *Patient and Public Involvement:*

48 To inform study implementation and dissemination, we have identified 10 YWH from  
49 AHF Healthcare Centers in CA to form the YAP. YAP meetings are held twice yearly virtually  
50 and last for 2 hours. YAP members review study materials and provide input/feedback about the  
51 intervention, research questions, recruitment and retention strategies, next steps, and  
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3 dissemination of findings. In addition to keeping the YAP updated about study progress, we  
4 discuss any implementation challenges, engagement, attrition, and other issues to obtain the  
5 YAP's feedback to improve study implementation.  
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10 *Intervention Procedures:*

11 The intervention arm (video-counseling+app) receives 12 brief weekly counseling  
12 sessions (given over 16 weeks) with a masters level mental health professional (e.g., social  
13 worker), along with access to the WYZ app to use based on their needs. After 16 weeks,  
14 responders in the video-counseling+app arm continue to use the app only. Non-responders in  
15 the intervention arm continue with intensified video-counseling+app for 16 more weeks. The  
16 additional 16 weeks aims to reinforce counseling points by targeting participant-specific barriers  
17 to virologic suppression based on the needs of non-responders.  
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27 *Video-Counseling:*

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29 The goal of video counseling is to provide information, motivation, and behavioral skills  
30 for dealing with MH, SU, and HIV care engagement challenges to address mild–moderate MH  
31 symptoms or low–moderate levels of SU; and assist with linking/relinking to more extensive MH,  
32 SU, and/or HIV treatment, as needed. The intervention tailors the counseling based on baseline  
33 factors as follows: **(1)** HIV care acuity: due to unsuppressed VL of all participants, each  
34 individual receives two core HIV sessions and sessions will be tailored based on barriers to  
35 achieving virologic suppression; **(2)** MH acuity: based on elevated PHQ-9[53,54] (10+), GAD-7  
36 (10+)[55], or PCL-5; (33+)[56] score or **(3)** SU acuity: based on elevated AUDIT (8+)[57], DAST  
37 (3+)[58], or monthly or more use of drugs (besides marijuana) or daily use of tobacco or  
38 marijuana as measured by ASSIST[59,60]. Individuals with “high acuity” receive two core  
39 sessions related to HIV care (2 A/B), MH (2A/B), and/or SU (3A/B), each. “A” sessions assess  
40 barriers and build motivation, while “B” sessions provide information and deliver health  
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3 education. A&B core sessions map onto the Information, Motivation, Behavior (IMB) model[61],  
4  
5 which was used to develop the intervention.  
6

7 For the remaining sessions, we use an integrated behavioral health and HIV care-  
8  
9 focused approach to further the conversations in the core sessions. Participants choose from a  
10  
11 list of menu sessions identified in the first session which allows the counselor to spend more  
12  
13 time on HIV care, MH, or SU based on the participants' needs. In this manner, the intervention  
14  
15 is tailored to the unique and changing needs of participants and can address other specific  
16  
17 topics related to their experiences of racism, transphobia, stigma, discrimination, gender  
18  
19 identity, racial/ethnic identity, classism, and current events.  
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22 SMS messages are used to enhance the intervention and for participant retention by:  
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24 (1) assessment of completion of health goals (i.e., behavioral skills) set during weekly sessions  
25  
26 (e.g., schedule appointment with provider); (2) provision of MH/SU or community resources  
27  
28 based on participant's needs (e.g., housing); (3) follow-up to ensure participant's linkage to MH,  
29  
30 SU, or HIV care; (4) reminder of video-counseling session; and (5) monthly check-in to update  
31  
32 contact information.  
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35 Fidelity to intervention. A session fidelity checklist is completed for each session to  
36  
37 ascertain whether the focus area and barriers were identified, education/information was  
38  
39 provided, motivation was enhanced, and problem-solving was initiated. The study team  
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41 assesses intervention fidelity during weekly meetings with the counselors to review each  
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43 session's length, technical issues, topics covered, goals established, and narrative progress  
44  
45 notes.  
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47 Counselor training. Prior to conducting sessions, counselors participate in >25 hours of  
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49 interactive training to learn the protocol and intervention manual intimately and role-play pre-  
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51 prepared vignettes. Counselors must attend the entire training and demonstrate proficiency of  
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53 knowledge of the intervention manual.  
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56 *WYZ App:*  
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3 WYZ was designed and developed using a human-centered design approach with a  
4 YAP, formative research with YWH, and is grounded in the IMB model.[39,40] WYZ contains 3  
5 main features: My Health, My Community, and My Team. Each of these features are described  
6 in more detail in Table 1 and Figure 2. Tailoring is achieved based on the individual's needs at a  
7 given time (e.g., My Community may be used more if social isolation is a barrier). For the My  
8 Community feature, all original posts must be approved by research staff before posting. On a  
9 weekly basis, research staff review new responses to all posts to ensure that there aren't any  
10 critical issues to be addressed. Any issues are brought to the study team's attention and  
11 referred to a clinical psychologist on the team if needed. Monthly check-ins help improve  
12 engagement through checking contact information and answering any questions.

#### 23 Data Collection Procedures:

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26 Quantitative study assessments with home-collected HIV VL testing are done at  
27 baseline, 16, 32, and 48 weeks after enrollment and randomization. Quantitative assessments  
28 collect information about sociodemographic characteristics, substance use, technology use,  
29 mental health, HIV-related outcomes, and experiences with the intervention for those in the  
30 intervention arm. All measures are described in Table 2. REDCap is used for all data collection  
31 such as surveys, intervention implementation and clinical data.[52] REDCap is a secure web  
32 application for building and managing online surveys and databases, and data are stored and  
33 managed on a University of California San Francisco (UCSF) server.

#### 34 Qualitative Exit Interviews:

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37 At 16 and 32 weeks, we will conduct semi-structured individual exit qualitative interviews  
38 with a sample YWH from the intervention arm, stratified by response or non-response (i.e.,  
39 suppressed, or unsuppressed HIV VL) and levels of engagement (attended  $\geq 80\%$  of counseling  
40 session versus  $< 80\%$  attendance). The interviews explore (a) barriers/facilitators to intervention  
41 participation, (b) barriers/facilitators to intervention response/non-response, (c) need for future  
42 modifications, and (d) preferences for longer term support.

### *Security and Confidentiality:*

All data are stored on a secure, HIPAA compliant, password-protected server. Participants' contact information and other identifying data are stored separately from other study data, the key linking names to study ID is stored separately and destroyed at the end of data collection, and all other study documents only have participant codes. Only the research team have access to participant identities. All data are de-identified prior to analysis and individuals will not be identified in any reports or publications of the research.

We use Zoom for video-counseling, which is the UCSF-preferred HIPAA-compliant video chat platform. We have developed study protocols related to video-counseling privacy and security. For SMS messages, study staff demonstrate how to set up privacy settings on smartphones, such as keeping SMS message previews from showing up on locked screens and adding a security code to lock the smartphone. For the WYZ app, we have partnered with the UCSF School of Medicine Technology (SOM Tech) team to maximize security. SOM Tech has built this app within best practices for developing HIPAA-compliant apps and has worked closely with the UCSF Enterprise Security team to review the app architecture in an iterative manner to ensure the highest level of security. All qualitative interviews are conducted remotely and audio-recorded via HIPAA-compliant web conference platform (e.g., Zoom) with audio-recordings stored on a HIPAA-compliant server with access available only to select study staff. All audio-recorded files are deleted upon completion of the study.

### *Data Monitoring:*

A data safety monitoring board consisting of three external reviewers meet annually to review the research protocol and materials, evaluate the progress, and report on safety and concerns.

### *Study Outcomes:*

The primary outcome is HIV VL using the Hemaspot-HF device.[62] We mail participants home test kits (including the Hemaspot-HF device, gauze, bandages, lancets, alcohol wipes,

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3 and pre-addressed stamped envelopes) at baseline, 16, 32, and 48 weeks. After a finger prick,  
4 they place two drops of blood on the Hemaspot-HF device. The device dries in one minute;  
5 participants then close the lid and mail the device to the laboratory. The laboratory uses the  
6 Abbott RealTime HIV-1 DBS assay with a lower limit of 400 copies/mL[63]. To minimize missing  
7 data, we request missing VL data (+/- one month around the four VL time points) from  
8 participants' clinical electronic medical records. The secondary outcomes are MH (PHQ-9[64],  
9 GAD-7[55], and PCL-5[65]); and SU (AUDIT[57], DAST[58], and ASSIST[59]).

### 17 *Quantitative Data Analysis:*

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20 Frequency tables for all variables and measures of central tendency and variability for  
21 continuous variables will be used to characterize the sample. In addition to describing important  
22 sample characteristics, these descriptive analyses will summarize the app paradata listed in  
23 Table 2, which will provide important information on overall app engagement and specific  
24 features used most. If the study arms differ significantly at baseline on covariates, we will use  
25 methods based on the Rubin causal model (e.g., propensity scores, double-robust estimation)  
26 to obtain the effect estimates under the counterfactual assumption of balanced groups[66–70].  
27 We will address missing data with multiple imputation.[71]

28  
29  
30 To assess efficacy of video-counseling+app vs. SOC on virologic suppression in YWH,  
31 we will compare HIV virologic suppression of those randomized to the intervention vs. control  
32 arms at 16 weeks. We hypothesize that at 16 weeks the odds of our primary outcome, virologic  
33 suppression, will be higher for video-counseling+app intervention participants than for SOC  
34 participants. To test this comparison, we will fit a logistic regression model. To assess the  
35 impact of video-counseling+app vs. SOC on the secondary outcomes, we will evaluate the MH  
36 and SU differences between the intervention vs. control arms at 16 weeks. We will employ  
37 general linear modeling (GLM) methods to test whether mean levels of MH and SU at 16 weeks  
38 are lower in the video-counseling+app group vs. the SOC group. Demographic and pre-

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3 specified covariates based on theory and literature will be included and moderated mediation  
4 will be explored using causal inference-based methods.  
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7 We will also explore differences between those who were (a) virologic “non-responders”  
8 in the intervention arm who received intensified video-counseling+app for 16 more weeks, and  
9 (b) virologic “responders” in the intervention arm who continued only app use for 16 more  
10 weeks. Frequency tables for all variables and measures of central tendency and variability for  
11 continuous variables stratified by virologic response status will characterize responders and  
12 non-responders on measures at 16 weeks including MH and SU. An exploratory multivariable  
13 logistic regression analysis will be performed on the subgroup of participants exposed to the  
14 intervention to predict which participants will be responders vs. non-responders. Additionally, we  
15 will use logistic regression to explore whether responders vs. non-responders at 16 weeks  
16 exhibit higher odds of virologic suppression at 32 weeks.  
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#### 28 *Qualitative Analysis:*

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30 Data will be analyzed using thematic and content analysis frameworks[72]. Data analysis  
31 will draw on an inductive approach[73] and by deductively applying codes developed from the  
32 interview guide. This dual approach will allow for themes to emerge from the data using  
33 inductive coding while also using an a priori template of code from which to frame the  
34 analysis[74].  
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#### 41 *Power Analysis:*

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43 Power analyses were generated using NCSS PASS 2021[75] to compute the minimum  
44 detectable effect sizes for the proposed primary analyses. The study is beginning with 200  
45 participants assigned to the video-counseling+app (N= 100) intervention group and the SOC  
46 control group (N= 100). Assuming 20% attrition based on our pilot studies[40,76] and prior  
47 research among YWH[77], data from 160 participants will be available to test hypotheses.  
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49 Assuming total N= 160,  $\alpha = 0.05$ , power= 0.80, and 44% in the control group virologically  
50 suppressed based on data supplied by AHF, we computed the minimum detectable odds ratio  
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3 (OR), proportion difference (*pdiff*), and standardized proportion difference (*h*) for the proposed  
4 primary comparison, which yielded  $OR = 2.46$ ,  $pdiff = 0.22$ , and  $h = 0.44$ . For continuous MH  
5 and SU outcomes, we used the same inputs as above and computed the minimum detectable  
6 standardized mean difference *d* across the video-counseling+app and SOC groups, yielding  $d =$   
7 0.45. Our proposed primary analyses can detect effects that are between small and  
8 medium[78]. In addition, a 22% increase in virologic suppression or an OR of 2.46 is an effect  
9 size equal to or smaller than other studies among YWH or older adults living with HIV[79] and is  
10 clinically meaningful.  
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### 21 **Ethics and dissemination:**

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23 We received approval from the University of California, San Francisco Institutional Review  
24 Board (IRB) to conduct this study and written consent from all participants. Reliance  
25 agreements were signed by RTI international and AHF. The study team will work with the YAP  
26 to disseminate results to YWH, participants, and the academic community. A manuscript with  
27 the results of the primary study will be published in a peer-reviewed journal along with separate  
28 manuscripts for the secondary aims.  
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### 36 **Discussion:**

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38 Our intervention protocol uses a tailored approach to impact engagement in HIV care  
39 by focusing on mental health, and substance use among YWH using a tailored approach,  
40 focusing on various barriers to care to different degrees, based on their changing needs.[41–44]  
41  
42 Despite YWH experiencing more MH challenges than the general population substantially fewer  
43 interventions have been developed and evaluated in YWH compared to older adults.[33] Most  
44 intervention studies for YWH have been conducted with small sample sizes, limited follow-up  
45 times, and not examined impact of the intervention to sustain or improve MH.[33,80] While there  
46 are interventions for HIV prevention and SU among youth[81–84], they are limited by requiring  
47 lengthy in-person sessions with a trained counselor, involving the youth's families, focusing  
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3 specifically on SU (versus a holistic approach), and were developed for younger adolescents.  
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5 iVY is innovative because it provides a “self-service” model that is customizable to the needs of  
6  
7 YWH. Additionally, a recent review suggests the need for multi-component interventions that go  
8  
9 beyond health facilities to address social barriers to engagement in HIV care.[34] Thus, our  
10  
11 study is significant and will enhance efficiency of care delivery because it provides a brief, out-  
12  
13 of-facility, youth-friendly video-counseling and mobile health app to 18–29-year-olds with HIV,  
14  
15 which focuses on HIV care, MH, and SU, and connects participants to community resources to  
16  
17 continue receiving MH and SU services, as needed.  
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21 We acknowledge that there will be more marginalized groups who may not have  
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23 smartphone access (~4%) or may not have been diagnosed with HIV, and our study results may  
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25 not be generalizable to them. Given this high level of smartphone ownership[85], we are  
26  
27 confident that the vast majority of our target population will have a smartphone. Additionally, a  
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29 Spanish version of the app is not currently available. Given the need to fully develop the  
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31 intervention in a culturally relevant manner for non-English speakers, we aim to translate our  
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33 intervention in future iterations of this project.  
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36 In summary, the remarkable biomedical advances in HIV prevention and treatment have  
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38 resulted in discussions toward ending the HIV epidemic. However, this will not happen without  
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40 addressing MH and SU barriers experienced by YWH.[86] iVY will examine an innovative  
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42 intervention to achieve the goal of ending the HIV epidemic. This study will provide valuable  
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44 data about the characteristics of virologic responders and non-responders to the intervention,  
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46 individualization of the intervention based on these variables, and linkage to MH and SU  
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48 treatment services among those in need. If efficacious, in future research we will investigate the  
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50 intervention’s sustainability for implementation across the United States. Given the influence of  
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52 the COVID-19 pandemic on MH and SU challenges[87], the use of video-counseling and  
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54 provision of remote research and services will remain high[88,89]. iVY has the potential to  
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3 impact HIV health outcomes and MH and SU among YWH who are disproportionately impacted  
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5 by HIV and at elevated risk for poor health outcomes.  
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9 **Authors' contributions:** MCDS was the lead author of the manuscript with support and input  
10 from the study Principal Investigator, PS. CM, CB and VAG are developing and implementing  
11 the counseling intervention. KM, LS and DW are study coordinators. ASC is overseeing work at  
12 AIDS Healthcare Foundation. BC is providing expertise on adaptive treatment strategies. TBN is  
13 provided mentorship on statistical methods and MOJ is providing mentorship and technical  
14 expertise on intervention development and testing. All coauthors reviewed and approved the  
15 manuscript and are involved in study implementation.  
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26  
27

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29

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3 **Figure 1: Overview of Study Design**  
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**Figure 2.** Mobile app screenshots

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<b>Feature</b>	<b>Function</b>	<b>Barriers Addressed</b>
My Health	Set customized ART adherence reminders (B), refill/injection reminders (B), graph adherence over time (M), keep track of VL & CD4+ test results (I/M)	Too busy, forgot, changed my routine, ran out of pills, unstructured lifestyle
My Team	Increase access to community organizations & resources using the participant's geo-location (I)	Lack of access to MH & SU services or other community services, limited mobility
My Community	Allow users to interact with other YWH through moderated forums (M), stay up-to-date on health news (I), provide a calendar of community events (I)	Low health literacy, social isolation, stigma, lack of community support

<b>Table 2. Outcome and Descriptive variables.</b>			
<b>Variables</b>		<b>Items</b>	<b>Interpretation</b>
<b>Outcome</b>			
1°	HIV viral load	Virologic suppression using Hemaspot device	Suppressed VL: <400 copies/mL* Unsuppressed VL: ≥400 copies/mL
2°	Mental Health	Depressive symptoms: PHQ-9[64] (10 items; score= 0–27)	Higher score indicates more depressive symptoms
		Anxiety: GAD[55] (7 items; score= 0–21)	Higher score indicates more anxiety
		Trauma: PCL-5[65] (score= 0–80)	Higher score indicates more trauma
	Substance use	DAST[58] (10 items; score= 0–10)	Higher score indicates more drug misuse
		AUDIT[57] (10 items; scores= 0–40)	Higher score indicates more alcohol misuse
		ASSIST[59]	Frequency of alcohol, smoking, and SU
<b>Other Descriptive Variables</b>			
	Demographics	Age, sex/gender, race/ethnicity, sexual identity, education, income, work, school, living situation, city of residence, ever homeless or incarcerated	
	MH & SU	Type & frequency of MH & SU services ever received or being received; timeline follow-back method for more recent SU <sup>1</sup> [90,91]; The Quick Inventory of Depressive Symptomatology (Self-Report) (QIDS-SR16)[92]	
	Healthcare accessibility	Distance to get to HIV clinic, ease of getting appointments at clinic, ease of getting in touch with provider[93]	
	Social isolation	PROMIS Item Bank[94] (14 items, score= 14–70)	Higher score indicates greater isolation
	Technology use	Use of technology to email providers, refill medications, or making medical appointments, frequency of break in service or lost/stolen phone, reliability of service, access to Wi-Fi[95], mobile technology vulnerability scale (MTVS)[96], System Usability Scale (SUS)[97] for WYZ	MTVS range= 0–17 with higher scores indicating more vulnerability[96], SUS range= 0–100 & scores >68 considered above average[98]
	Perceived engagement in HIV care	Index of Engagement in Care[99] (10 items, score= 0–10)	Higher score indicates higher ART adherence, clinic attendance, VL suppression
	HIV knowledge	HIV treatment knowledge scale[100] (15 items, score= 0–15)	Higher score indicates more knowledge
	Engagement	Healthcare provider engagement[101] (13	Higher score indicates

	with provider	items, score= 0–52)	poorer engagement
	Subsistence needs	Unmet subsistence needs[42,102] (5 items, score= 0–5)	Higher score indicates more subsistence needs
	Resilience	Brief resilience scale[103,104] (6 items; score= 1–5)	High score indicates more resilience
	App paradata	Number of minutes in app; change in app use over time; number of push notifications opened from those sent through the application; use of My Health (adherence tracking), My Team (identification of community services), My Community (chat with peers, use calendar)	



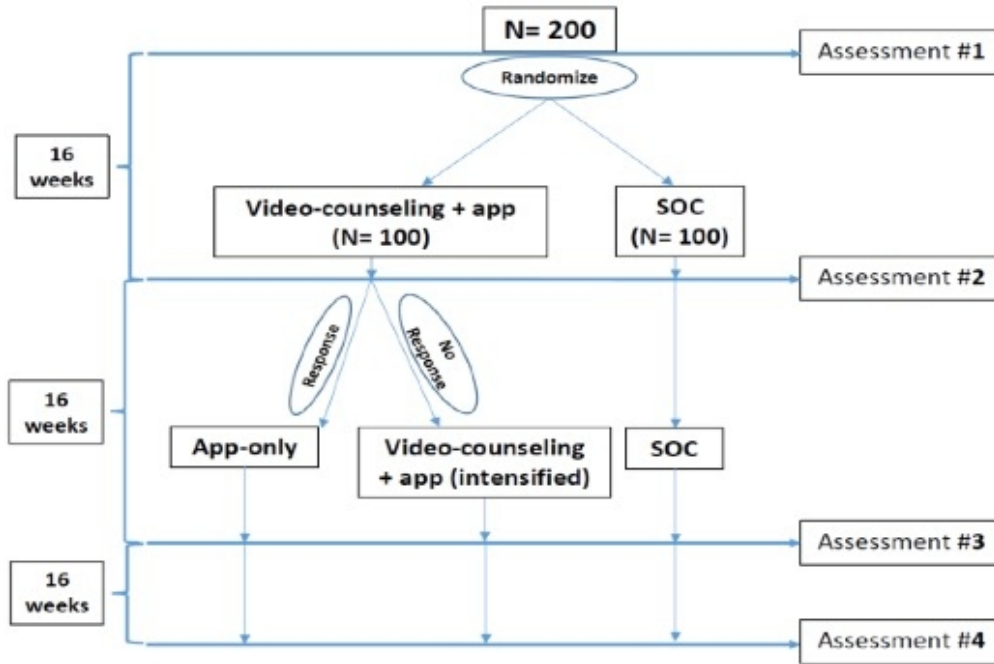


Figure 1: Overview of Study Design

182x121mm (72 x 72 DPI)

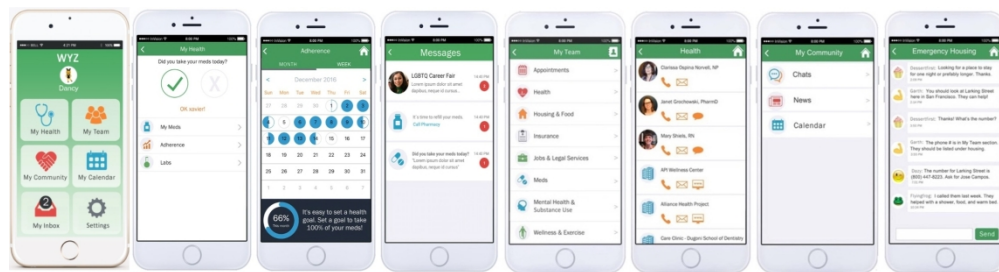


Figure 2. Mobile app screenshots

189x50mm (300 x 300 DPI)