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ORIGINAL PAPER

Competence to Consent to Oral and Injectable PrEP Trials Among Adolescent Males Who Have Sex with Males

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Abstract

Adherence to oral pre-exposure prophylaxis (PrEP) is challenging for adolescent males who have sex with males (AMSM). Once adult trials comparing oral to longer lasting injectable PrEP are completed, there will be a need for adolescent studies. However, lack of data on adolescent consent capacity may sustain guardian permission requirements identified as a barrier to AMSM participation in prior PrEP trials. This online study assessed AMSM's (14–17 years) consent capacity for these trials, comparing performance to MSM (18–19 years) for whom guardian permission is not required. Applying the MacCAT-CR, participants (N = 214) viewed a video and mock consent form followed by open-ended and yes/no items. Cognitive diagnostic models and means testing analyses supported AMSM capacity to consent to these trials: 16–17 and most 14–15 year-olds, demonstrated consent understanding, appreciation and reasoning at 18–19 year-old levels. Data also identified vulnerabilities requiring attention during informed consent.

Keywords Adolescent sexual minority males · Pre-exposure prophylaxis (PrEP) · Informed consent · MacCAT-CR · Randomized clinical trials · HIV prevention

Introduction

Adolescent males under the age of 18 who have sex with males (AMSM) account for disproportionally higher numbers of new HIV and sexually transmitted disease diagnoses than their heterosexual peers, are less likely than older MSM to have received an HIV test or to be linked to HIV care [1–5]. In response to this crisis, states have increasingly included HIV testing, access to pre-exposure prophylaxis (PrEP), and HIV treatment into mature minor laws providing youth under 18-years access to such services without guardian permission. However, mature minors' independent access to HIV services varies significantly by jurisdiction and some services remain unavailable to youth under 18 years [6].

In states in which minors have legal access to some HIV prevention services, there continues to be under-participation of AMSM in PrEP trials. This is due in part to institutional review board (IRB) reluctance to apply federal regulations permitting waiver of guardian permission for mature minors participation in PrEP studies based on concerns that the statutory language does not specifically refer to minors' access to HIV related research and a lack of empirical data on the extent to which AMSM are competent to independently consent to randomized clinical trials [7–10]. This is troublesome, since interventions for adolescents based on extrapolations of data from adult studies do not sufficiently address developmental challenges for medication uptake and adherence in this age group [11]. For AMSM, guardian permission is a particularly significant barrier to participation in HIV biomedical prevention studies because of fear

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of stigma, punishment, and in some cases victimization by family members if sexual orientation is disclosed [12–17]. For example, a multisite study on safety and adherence to an oral form of pre-exposure prophylaxis (PrEP; trade name Truvada) for AMSM was under-powered when guardian permission requirements led to youth refusals to participate [18, 19]. Despite these challenges, the urgent need for this prevention option for AMSM led the FDA in 2018 [20] to approve the medication for adolescents weighing at least 35 kg (77.16 lbs).

For critical research on PrEP safety and efficacy, recruitment limited to AMSM who agree to guardian permission, undermines the quality of science by skewing findings in ways that can lead to poorly conceived interventions and misapplication of HIV prevention resources [21]. For example, youth who fear repercussions from parents who are unaware of their sexual identity, compared to youth with supportive families, may not be able to benefit from strategies for increased access and adherence to PrEP assessed in an intervention study. Such variability and lack of explicit guidance places the burden on the science community to begin to establish empirical data that investigators and their IRBs can apply when determining whether AMSM have the competencies necessary to independently consent to these trials. Empirical data on AMSM's ability to consent to PrEP biomedical prevention studies is particularly urgent in light of oral PrEP adherence challenges observed in youth and adults [22]. To address this challenge, current clinical trials comparing the oral form of PrEP to new, long-acting injectable PrEP medications (e.g. cabotegravir) are currently being studied in adult MSM [23, 24]. Once these studies result in FDA approval of cabotegravir, or other medications, for adults, investigators and IRBs will have to determine whether AMSM have the consent competencies to warrant waiver of guardian permission for randomized oral and injectable comparative trials necessary for the successful implementation of developmentally appropriate PrEP services.

Prior research suggests that depending on the medical status of the population and the research design, beginning at age 14–15 years, adolescents can comprehend informed consent information on par with adults when information is presented at developmentally appropriate levels and conducted under minimal stress; although specific consent vulnerabilities have been reported, including misconceptions about random assignment for placebo controlled HIV vaccine studies and deference to authority jeopardizing voluntary participation in PrEP trials [14, 25–28]. Moreover, although research on adolescent brain development documents the interfering effects of emotions on adolescent decision-making, recent evidence suggests that by 15 years, many youth are competent to make medically relevant decisions when conditions of emotional arousal and peer pressure are minimized [29, 30]. However, there are limitations in applying such data to different research contexts and, to date, there is a paucity of research on AMSM's understanding of specific information necessary to make an informed decision to participate in the complex regimens required for oral and injectable PrEP trials, including pre-trial medication safety testing, multiple study visits, medication risks and benefits, and randomized assignment to medication conditions.

Purpose of this Study

The purpose of the present study is to provide empirical data on AMSM's competence to consent to a randomized clinical trial assessing safety and efficacy of oral and injectable PrEP to inform IRB decisions on waiver of guardian permission and future developmentally tailored consent procedures. To achieve this aim, we drew on the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) [31]. The MacCAT-CR is widely used for assessing consent competence for a range of health related clinical trials, although a variety of shorter tools are frequently used in actual practice when assessing capacity to consent to clinical research among adults [32, 33]. The MacCAT-CR uses open-ended questions to assess consent competence related to four standards: (1) understanding of disclosed information; (2) appreciation of effects of a participation decision on the participant's own situation; (3) the ability to communicate a participation decision; and (4) reasoning about their participation choices that includes a weighing of risks and benefits. The MacCAT-CR was originally designed to assess the research consent capacity of adults with dementia and severe mental illness, and thus places high weight on memory and cognitive errors that might not be reflective of youth with developing brains. However, in a recent study demonstrating strong psychometric properties of the MacCAT-CR for children aged 9.6–11.2, the authors concluded it could be used as an objective assessment of children's competence to consent [34].

In light of the variability of different RCT designs, the MacCAT-CR does not provide nor recommend cut-offs for consent competence. Rather it provides a conceptual framework for consent competence defined in terms of performance relative to a norm rather than an absolute threshold for autonomous decision-making. In this study we assessed the consent competence of 14–17 year-old AMSM through an empirical norm established by the level of understanding, appreciation and reasoning achieved by 18–19 year-old MSM whose competence to consent is unchallenged because of their adult legal status. This comparative framework is particularly appropriate for exploring AMSM's ability to consent to biomedical HIV prevention research since current

restrictions are based on a legal (below age 18) rather than a competency standard.

Methods

Participants

The sample included AMSM 14–15 (N = 62), 16–17 (N = 82), and MSM 18–19 (N = 70). Participants were assigned male at birth; reported attraction to or sexual experience with male partners; a U.S. resident; 8th grade English proficiency; and self-reported HIV-negative status or not previously tested. Participants were recruited beginning in April 2018 from online social media advertisements on Facebook and Instagram targeted to adolescents aged 14–19 years who listed interests relevant to sexual minority youth, and from research participant registries developed from prior studies. Interested respondents clicked on a URL to the eligibility screener. Upon screening, eligible participants were immediately sent an email with a URL to the consent form for the study. Upon confirming consent, they were automatically routed to the survey.

Based on Facebook and Instagram analytics, the number of unique people who were served the ad was 60, 279 (whether those people were all in our target population cannot be discerned by these analytics). A total of 786 individuals completed the online screener. Of the 607 who were eligible and were sent the survey URL, 372 did not complete the survey. Of these individuals, 288 did not click on the link to access the survey (possibly due to emails going to spam, our sender address not recognized as linked to the screener, and the time between screening and being invited to link to the survey); 1 declined to participate, and 83 started but did not complete the survey. Odds ratio test indicated study completers were more likely to have received an HIV test (42.1% vs. 31.5%, OR 1.59, $p < 0.01$), but there were no significant differences between completers and non-completers on any other variable. Of the 235 who completed the survey, 21 were eliminated for invalid responses [35], 50% or more unscorable answers, and device difficulties resulting in a final sample of 214. For exploratory factor analysis (EFA), 200 is considered an acceptable sample size [36].

Procedures

The study lasted 45–60 min. First, participants answered sociodemographic questions (e.g., race/ethnicity, education and typical grades in school), outness to parents, history of condomless anal sex, and anxiety about HIV risk [37]. Then, participants watched a 6-min mock consent video about an oral and injectable PrEP comparative study (described below) embedded in the survey platform. The video is available at https://doi.org/10.21985/N25R45.

When the video ended, consistent with the MacCAT-CR format [31], participants proceeded to read brief segments of a mock consent form for the hypothetical study. The consent information was tailored to an 8th grade reading level [34], used age-specific language and illustrations, and was modified following pilot testing (N = 65, mean age 17.54, SD = 1.42) and recommendations from the study's Youth Advisory Board. After each segment, participants viewed a new page on which they were asked to write in answers to questions assessing their understanding and appreciation about different aspects of the study. For these questions, they were not able to go back to view the information they had just read. Although in real-life scenarios, prospective participants would have the opportunity to re-read the consent information, we decided not to provide this opportunity in the present study since given the online format, once youth read the question, some youth could simply copy and paste the statements rather than providing their own response. The open-ended questions were followed by multiple choice items and a write-in question on reasoning described below. Since none of these latter items could be answered by copying elements of the informed consent, they were then given the opportunity to download and refer to the text of the informed consent video.

Participants who completed the survey and whose responses were validated received a $30 electronic gift card. Analysis of pilot data for this study indicated that some seemingly complete written responses to individual items, did not contain information relevant to the question posed. Such random responding to surveys has been associated with lack of motivation and identified as a threat to scientific validity [38]. To incentivize complete and accurate responses, those who scored in the top 10% of all participants received an additional $30. Procedures were approved by the universities' IRBs with a waiver of guardian permission. A Certificate of Confidentiality was issued to further protect the identities of participants in the event of subpoenas from law enforcement.

The Hypothetical Study

The hypothetical study was adapted from oral and injectable comparison protocols currently being conducted with adults [23] and guidance from our Scientific Advisory Board. Participants first viewed a mock consent video providing a broad overview of the information that was then detailed in the survey text. PrEP was described as a drug that protects against HIV, available for adults in a daily pill form (Truvada) and a longer lasting injection given every 2 months (cabotegravir: CAB). Both medications have common (e.g. headaches, diarrhea, fatigue)

and rare side effects (e.g. weakening in bones and kidney function which go away with treatment and when one stops the drug). The purpose of the hypothetical study was to determine if the medications are safe (side-effects are not greater than in adults) and effective (are taken as prescribed) for adolescents who are HIV negative and engage in unprotected anal sex with a male partner. Prior to the trial, participants would be screened for HIV and take CAB in pill form for 5 weeks to assess its safety and tolerability. Participants would then be randomized into one of two groups: Group A would take daily oral PrEP for the first 6 months and CAB injections every other month for another 6 months. Group B would take the medications in the reverse order. In the final 6-months, participants choose to take either the shot or the pill. Participation would also include blood, urine, and rectal samples and sexual health services. The mock consent also explained the difference between research and regular medical care, confidentiality protections, alternatives to and the voluntary nature of study participation. The role of the IRB office and liability if injured were also included.

Understanding and Appreciation

Following the video presentation, we used the semi-structured MacCAT-CR format [31] to sequentially present 14 brief statements describing key elements related to the purpose of the study, study procedures, research risks and benefits, voluntariness, confidentiality, and procedures in the event one tested HIV positive. Each description was immediately followed by youth providing a typed response to an open-ended question assessing their ability to recall and describe in their own words the consent information with the following two exceptions. First, during piloting for the open-ended question on whether participation was voluntary, respondents tended to write only "yes" or "no" answers. Second, for the open-ended question on random assignment, the majority wrote "like a coin toss" the exact term used in the preceding brief explanation of randomization. To better determine whether participants understood these concepts, *voluntariness* was assessed by 2 yes/no items asking: (1) whether they had to participate if they did not want to; and (2) whether if they withdrew from the study they would still receive regular clinic services. *Randomization* was assessed by a 2-choice item that asked participants to select the statement best describing how they would be assigned to groups A and B: "The researcher will place me in the group that is best for me" or "Which group I am in will be decided by chance." The full wording for each question is provided in Table 1.

Reasoning

After completing the above items, participants responded to a 4-point Likert-type question on their participation choice (1 = I would definitely not choose to participate; 4 = I would definitely choose to participate). Consistent with the MacCAT-CR assessments for *reasoning* about one's participation choice [31], the likelihood of participation question was followed first by one open-ended question tapping *comparative reasoning* defined as the ability to explain their decision to participate or not participate by comparing the perceived risks and benefits of participation. Skip logic programming was used to word the item to correspond to whether participants had indicated they were likely or unlikely to participate. This was followed by three Likert-type items (1 = strongly disagree, 5 = strongly agree) assessing *consequential reasoning* defined as the extent to which participation decisions were consistent with the respondents' anticipation of their psychological reactions to participation: anticipated regret, anxiety, or satisfaction with the research experience. The full wording for each question is provided in Table 5.

Analytic Plan

Coding Guide

Consistent with the MacCAT-CR scoring instructions [31], a coding guide was created for the open-ended items (0 = no credit, 1 = partial credit, 2 = full credit). The two yes/no items tapping voluntariness were each assigned a 0 for an incorrect answer and a 1 for a correct answer such that a combined score representing voluntariness could also be scored on the same no, partial and full credit indicators. For the item tapping random assignment to groups A or B, the correct response ("by chance") received a score of 2, and the incorrect response ("in the group that is best for me") received a score of 0.

The initial coding guide reflected the informational language provided in the video and text descriptions of the study. The first author analyzed all responses based on the initial coding guide, noting where participant word choices required additional exemplars. The first and second authors then applied the guide to the first 70 responses, discussed disagreements, and modified criteria where appropriate, creating a final coding guide applied to all 214 participant responses. A third rater was trained on the responses from the first 70 participants and then independently coded responses from an additional 131 participants. Inter-rater agreement for all open-ended items ranged from Kappa = 0.68 (the reason for terminating participation if HIV+) to 0.93 (pre-study safety testing; comparative reasoning) indicating adequate to excellent reliability [39]. A description of the scoring

Table 1 Factor loadings, means, standard deviations, number and percent of responses receiving no (N), partial (P) and full (F) credit for understanding and appreciation of elements of informed consent, across the three age groups

	Age groups			Factor[a]	
	14–15 Years N = 62	16–17 Years N = 82	18–19 years N = 70	1	2
Factor 1: Understanding[a]					
PrEP adherence requirements: How often do people need to *get the CAB shot* AND how often do they need to take the *Truvada pill* in order to protect themselves against HIV?	1.84 (0.52) *N. 4 (6.5%)* *P. 2 (3.2%)* *F. 56 (90.3%)*	1.76 (0.60) *N. 7 (8.5%)* *P. 6 (7.3%)* *F. 69 (84.1%)*	1.83 (0.51) *N. 4 (5.7%)* *P. 4 (5.7%)* *F. 62 (88.6%)*	**0.90**	−0.11
Side effects: Name one *common* side-effect AND one *rare* side effect you might experience in this study when you take CAB or Truvada drugs	1.69 (0.59) *N. 4 (6.5%)* *P. 11 (17.7%)* *F. 47 (75.8%)*	1.84 (0.40) *N. 1 (1.2%)* *P. 11 (13.4%)* *F. 70 (85.4%)*	1.86 (0.39) *N. 1 (1.4%)* *P. 8 (11.4%)* *F. 61 (87.1%)*	**0.72**	0.02
Study phases: You just read about 3 different phases of the study each lasting for 6 months. What are these 3 main phases?	1.79 (0.57) *N. 5 (8.1%)* *P. 3 (4.8%)* *F. 54 (87.1%)*	1.84 (0.43) *N. 2 (2.4%)* *P. 9 (11%)* *F. 71 (86.6%)*	1.84 (0.44) *N. 2 (2.9%)* *P. 7 (10.0%)* *F. 61 (87.1%)*	**0.46**	0.25
Pre-Randomization Safety Screening: What are the 2 types of tests we will do to make sure the study is safe for you?	1.42 (0.56) *N. 2 (3.2%)* *P. 32 (51.6%)* *F. 28 (45.2%)*	1.48 (0.63) *N. 6 (7.3%)* *P. 31 (37.8%)* *F. 45 (54.9%)*	1.46 (0.61) *N. 4 (5.7%)* *P. 30 (42.9%)* *F. 36(51.4%)*	**0.43**	0.16
Purpose: What is the purpose of this study? That is, what two main things are scientists trying to find out by conducting this research?	1.53 (0.67) *N. 6 (9.7%)* *P. 17 (27.4%)* *F. 39 (62.9%)*	1.55 (0.65) *N. 7 (8.5%)* *P. 22 (26.8%)* *F. 53 (64.6%)*	1.67 (0.58) *N. 4 (5.7%)* *P. 15 (21.4%)* *F. 51 (72.9%)*	**0.39**	−0.03
Additional medical procedures. List at least three medical procedures medical staff may conduct when you visit the clinic, not counting the pill or shot	1.69 (0.64) *N. 6 (9.7%)* *P. 7 (11.3%)* *F. 49 (79%)*	1.82 (0.48) *N. 3 (3.7%)* *P. 9 (11%)* *F. 70 (85.4%)*	1.84 (0.44) *N. 2 (2.9%)* *P. 7 (10%)* *F. 61 (87.1%)*	**0.37**	0.18
Factor 2: Appreciation[a]					
Random Assignment. Please select the statement that best describes how you will be assigned to group A or group B in this study	1.84 (0.55) *N = 5 (8.1%)* *F = 57 (91.9%)*	1.93 (0.38)[b] *N = 3 (3.7%)* *F = 78 (96.3%)*	2.00 (0.00)[c] *N = 0 (0.0%)* *F = 69 (100%)*	−0.01	**0.75**
Responsibilities: What are your 3 important responsibilities if you are in the study?	1.84 (0.45) *N. 2 (3.2%)* *P. 6 (9.7%)* *F. 54 (87.1%)*	1.84 (0.46) *N. 3 (3.7%)* *P. 7 (8.5%)* *F. 72 (87.8%)*	1.87 (0.41) *N. 2 (2.9%)* *P. 5 (7.1%)* *F. 63 (90%)*	0.02	**0.65**
Research-treatment distinction: What makes being in this study different from regular medical care	1.63 (0.71) *N. 8 (12.9%)* *P. 7 (11.3%)* *F. 47 (75.8%)*	1.80 (0.51) *N. 4 (4.9%)* *P. 8 (9.8%)* *F. 70 (85.4%)*	1.91 (0.37) *N. 2 (2.9%)* *P. 2 (2.9%)* *F. 66 (94.3%)*	0.24	**0.61**
Consequences of testing positive: Why will you be asked to stop taking the study drugs if HIV tests show that you have been infected with HIV after you are in the study?	1.69 (0.68) *N. 7 (11.3%)* *P. 5 (8.1%)* *F. 50 (80.6%)*	1.82 (0.50) *N. 4 (4.9%)* *P. 7 (8.5%)* *F. 71 (86.6%)*	1.83 (0.48) *N. 3 (4.3%)* *P. 6 (8.6%)* *F. 61 (87.1%)*	0.17	**0.60**
Confidentiality disclosures: Describe the two main times in which the researchers would have to break confidentiality and share your personal information	1.90 (0.30) *N. 0 (0%)* *P. 6 (9.7%)* *F. 56 (90.3%)*	1.89 (0.35) *N. 1 (1.2%)* *P. 7 (8.5%)* *F. 74 (90.2%)*	1.89 (0.36) *N. 1 (1.4%)* *P. 6 (8.6%)* *F. 63 (90%)*	0.01	**0.57**
Potential benefits: Name at least 3 potential benefits to people who participate in this study	1.56 (0.76) *N. 10 (16.1%)* *P. 7 (11.3%)* *F. 45 (72.3%)*	1.57 (0.69) *N. 9 (11%)* *P. 17 (20.7%)* *F. 56 (68.3%)*	1.80 (0.53)[c] *N. 4 (5.8%)* *P. 6 (8.7%)* *F. 59 (85.5%)*	−0.03	**0.47**
Voluntary nature of participation: Do you have to be in this study if you do not want to participate? If you withdraw from this study will you still be able to receive services from the clinic?	1.79 (0.41) [d] *N 0 (0%)* *P 13(21.3%)* *F 48 (78.7%)*	1.70 (0.46)[b] *N 0 (0%)* *P 24 (29.6%)* *F 57 (70.4%)*	1.80 (0.41)[c] *N 0 (0%)* *P 13 (20.3%)* *F 55 (79.7%)*	0.21	**0.46**

Table 1 (continued)

	Age groups			Factor[a]	
	14–15 Years N = 62	16–17 Years N = 82	18–19 years N = 70	1	2
Inclusion criteria: Name 1 personal characteristic and 1 behavior that are the reasons why you are being asked to participate in this study	1.39 (0.88) *N. 16 (25.8%)* *P. 6 (9.7%)* *F. 40 (64.5%)*	1.32 (0.78) *N. 16 (19.5%)* *P. 24 (29.3%)* *F. 42 (51.2%)*	1.48 (0.70) *N. 8 (11.4%)* *P. 20 (28.6%)* *F. 42 (60%)*	0.50	**0.34**

[a]An exploratory factor analysis (EFA) was conducted to ascertain the factor structure of the 14 items reflecting understanding and appreciation. Items are presented in decreasing order of factor loadings for understanding and appreciation, respectively. The item tapping inclusion criteria was classified as Appreciation since it most closely reflected participants' appreciation of why their own characteristics and sexual behaviors would determine their inclusion in the study consistent with the MacCAT-CR criteria

[b]N = 81: Sample size for missing data

[c]N = 69: Sample size for missing data

[d]N = 61: Sample size for missing data

criteria and exemplar full, partial, and no-credit participant responses for all open-ended questions are provided in the supplementary materials. Associated data for this study are available at https://www.fordham.edu/downloads/download/3971/ahrci_supporting_materials.

Statistical Analysis

Descriptive statistics were computed for demographic variables and MacCAT-CR items. To examine potential differences in consent competencies across the 3 age groups, we first conducted an exploratory factor analysis (EFA) to ascertain the factor structure of the 14 items reflecting understanding and appreciation. Following the EFA, to examine comparable ability to understand and appreciate informed consent across the 3 age groups, cognitive diagnostic models (CDMs) [40] were fit to these data. CDMs are structured latent class models that characterize item scores as a function of possessing or lacking certain attributes. In this case, the two attributes under consideration were understanding and appreciation. One outcome of the CDM is the ability to evaluate the proportion of examinees in each age group estimated to have neither competencies, either understanding or appreciation, or both [40]. We next turned to examine age differences in participation choice and reasoning. A cumulative mean score was computed for the 3 questions representing consequential reasoning; with the item tapping anticipated satisfaction with participation reversed score. Thus, lower cumulative mean scores indicated more positive consequences of participation. After assessing for homogeneity of variance and skewness we conducted analysis of variance tests on age differences related to the single item likelihood of participation and comparative reasoning scores, and on the consequential reasoning cumulative score. Correlations were conducted to further assess the extent to which participation choice was associated with comparative and consequential reasoning.

Results

Demographic Data

Demographic data are presented in Table 2. Across age most participants identified as non-Hispanic White or Hispanic/Latinx. According to Chi square tests of independence, the number of respondents who reported having had a sexual relationship with a male partner, engaged in condomless anal sex, and had been tested for HIV increased with age ($X_2^2 = 30.76$, 17.19, 25.71, respectively; $p < 0.001$). Chi square tests also indicated that older participants were more likely to be out about their sexual orientation to at least one parent ($X_2^2 = 9.82$, $p < 0.007$) and were more likely to have research experience (37.1%, 59.8% and 67.1%, respectively; $X_2^2 = 12.95$, $p < 0.002$), but did not differ in how much participants worried about becoming infected with HIV ($X^2_8 = 7.71$ $p = 0.46$). Chi square tests on race/ethnicity did not yield significance for any of the demographic variables described above.

Assessment of Consent Understanding and Appreciation

Means, standard deviations and percent of full, partial and no credit responses for the understanding and appreciation items are provided in Table 1. In this section we describe the exploratory factor analysis (EFA) specifying the items loading on the understanding and appreciation dimensions, and the cognitive diagnostic models (CDMs) analysis to assess the presence or absence of each attribute within each age group.

Table 2 Demographic information, prior research experience, and sexual experience across the 3 age groups

Demographic Information	Age groups		
	14–15 Years N = 62	16–17 Years N = 82	18–19 Years N = 70
Age	M = 15.3 SD = 0.52	M = 17.1 SD = .65	M = 18.7 SD = 0.5
Hispanic/Latinx	14 (22.6%)	16 (19.5%)	18 (25.7%)
Race/ethnicity			
White (European, Middle Eastern)	39 (62.9%)	49 (59.8%)	44 (62.9%)
Black or African American	6 (9.7%)	12 (14.6%)	8 (11.4%)
Asian	4 (6.5%)	9 (11.0%)	7 (10.0%)
American Indian Alaska Native	0 (0.0%)	1 (1.2%)	2 (2.9%)
Native Hawaiian or Pacific Islander	1 (1.6%)	1 (1.2%)	0 (0.0%)
More than one race/ethnicity	7 (11.3%)	5 (6.1%)	6 (8.6%)
Other	3 (4.8%)	2 (2.4%)	2 (2.9%)
Missing	2 (3.2%)	3 (3.7%)	1 (1.4%)
Highest grade completed			
Less than 8th grade	0 (0.0%)	0 (0.0%)	1 (1.4%)
8th grade	15 (24.2%)	0 (0.0%)	0 (0.0%)
9th grade	33 (53.2%)	10 (12.2%)	1 (1.4%)
10th grade	13 (21.0%)	30 (36.6%)	3 (4.3%)
11th grade	1 (1.6%)	31 (37.8%)	14 (20.0%)
12th grade	0 (0.0%)	0 (0.0%)	0 (0.0%)
High School Diploma or GED	0 (0.0%)	7 (8.5%)	28 (40.0%)
Some College	0 (0.0%)	4 (4.9%)	22 (31.4%)
College Degree	0 (0.0%)	0 (0.0%)	1 (1.4%)
Out to parent/guardian	41 (66.1%)	49 (59.8%)	58 (82.9%)
HIV risk			
Sex with a male partner	26 (42.0%)	60 (73.1%)	59 (84.3%)
Condomless anal sex	50 (80.6%)	40 (48.8%)	36 (51.4%)
Worry about HIV some to all of the time	33 (53.2%)	50 (60.9%)	48 (68.5%)
Not tested for HIV	50 (80.6%)	49 (59.8%)	26 (37.1%)

Factor Analysis

An exploratory factor analysis (EFA), specifying two factors, was conducted across all participant responses on the 14 items proposed to theoretically represent understanding and appreciation. Mplus 7.0 [41] was used to fit the EFA model using the weighted least squares estimator with mean and variance adjustments and the solution was rotated using the oblique GEOMIN rotation method [42, 43]. Table 3 displays the polychoric correlations variables used in the EFA. The EFA revealed that the two-factor model fit the data well in terms of interpretability and overall fit measures [44], $X_{64}^2 = 68.173$ ($p > 0.05$), CFI = 0.989, TLI = 0.984, SRMR = 0.094, RMSEA = 0.017 (lower 90 CI 0.000, upper 90 CI 0.045). Factor pattern coefficients 0.30 or higher, along with MacCAT-CR theoretical meanings of items, were examined to provide an interpretation, so that the first factor was labeled *Understanding* and the second was labeled *Appreciation* (see Table 1). The final factor structure yielded a factor correlation of 0.47 and was used to create the specification of the two-dimensional *Q*-matrix to specify the relationship between items and attribute for the CDMS.

Cognitive Diagnostic Models

The specific CDM model fit to these data was the multigroup sequential G-DINA model appropriate for polytomously scored items [40]. Two models were specified and fit to the full data. One model gives separate proportions of no, partial and full credit combinations for each of the three different age groups and the other model allows estimates of pooled parameters assuming that these credit proportions are the same in each age group [40]. As Table 1 indicates, for many items the majority of individuals received full-credit responses regardless of age. Model fit results for the single-group and the multiple-group CDMs suggest that the multiple-group model (all age groups) yields better fit to these data than the single-group model ($X_6^2 = 51.49$, $p < 0.001$). Table 4 presents the multiple-group model for each age group based on the estimated prevalence of the

Table 3 Means, standard deviations and polychoric correlations for all age groups for items representing Understanding and Appreciation

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Adherence														
Purpose	0.30***													
Safety Screening	0.46***	0.29***												
Phases	0.53***	0.10	0.32***											
Medical Procedures	0.43***	0.15*	0.08	0.43***										
Side effects	0.58***	0.26***	0.30***	0.41***	0.46***									
Benefits	0.24***	0.03	0.15*	0.29***	0.28***	0.04								
Inclusion criteria	0.51***	0.26***	0.40***	0.41***	0.18**	0.51***	0.17**							
Responsibilities	0.14*	0.18**	0.36***	0.22**	0.34***	0.24***	0.40***	0.31***						
Research-Treatment	0.36***	0.22**	0.30***	0.41***	0.37***	0.37***	0.22***	0.55***	0.25***					
HIV +	0.25***	0.27***	0.40***	0.19**	0.08	0.36***	0.23***	0.47***	0.46***	0.60***				
Confidentiality	0.19**	0.15*	0.28***	0.35***	0.31***	0.30***	0.13	0.31***	0.49***	0.40***	0.41***			
Randomization	0.32***	−0.06	−0.04	0.54***	0.39***	0.31***	0.46***	0.47***	0.26***	0.67***	0.36***	0.49***		
Voluntarism	0.39***	0.08	0.19**	0.37***	0.20**	0.30***	0.33***	0.42***	0.38***	0.44***	0.44***	0.24***	0.24***	
Mean	1.80	1.59	1.45	1.83	1.79	1.80	1.64	1.39	1.85	1.79	1.79	1.89	1.92	1.76
SD	0.55	0.63	0.60	0.48	0.52	0.46	0.67	0.78	0.44	0.55	0.55	0.34	0.38	0.43

*$p < 0.05$

**$p < 0.01$

***$p < 0.001$

Table 4 Estimated prevalence of understanding and appreciation capacity combinations under the multiple group Cognitive Diagnostic Model

Understanding-appreciation attribute combinations[a]	14–15 Years	16–17 Years	18–19 Years
(0,0)	1.61% [0.00%, 7.58%]	0.00% [0.00%, 0.00%]	0.00% [0.00%, 0.00%]
(1,0)	12.59% [0.00%, 23.13%]	0.00% [0.00%, 9.96%]	0.00% [0.00%, 0.00%]
(0,1)	3.25% [0.00%, 9.96%]	0.00% [0.00%, 0.00%]	1.43% [0.00%, 7.25%]
(1,1)	82.55% [72.53%, 98.11%]	100.00% [89.33%, 100.00%]	98.57% [92.67%, 100.00%]

This table presents the cognitive diagnostic multiple-group model for each age group based on the estimated prevalence of the 3 possible attribute combinations. Combinations in column 1 indicate competencies for neither understanding or appreciation (0,0), appreciation but not understanding (1,0); understanding but not appreciation (0,1) and both understanding and appreciation (1,1). Numbers in columns 2–4 reflect percentage of participants within each combination and brackets indicate a 95% confidence interval based on a nonparametric bootstrap with 1,000 samples

3 possible attribute combinations indicating competencies for neither understanding or appreciation (0,0), one of these competencies (1,0; 0,1), or both (1,1). As indicated in the last row in Table 4, 100% and 98% of participants in the 16–17 and 18–19 aged groups, respectively, were classified as possessing both understanding and appreciation. It is also notable that 83% of the 14–15 aged sample was classified as also possessing both competencies, and 16% were estimated to possess at least one of these competencies.

Participation Choice and Assessment of Comparative and Consequential Reasoning

Means, standard deviations, and percent responses for participation and reasoning items are provided in Table 5. Across age the majority of participants indicated they would probably or definitely choose to participate in the hypothetical study. For all age groups, approximately half the participants received full credit scores for comparative reasoning and less than a quarter received partial credit. Although the majority believed they would feel satisfied with the experience and few participants would regret their decision to participate, approximately 40% indicated they would feel anxious during the study. Across age groups, mean scores for likelihood of participation, and for comparative and consequential reasoning met criteria for an analysis of variance: Homogeneity of variance (Levene's test) was $p > 0.05$ and skewness yielded moderate–low levels (range 0.27–0.30; −0.47 to −0.68; and 0.28 to 0.44, respectively). Analysis of variance did not yield significance for age on participation choice ($F_{2,213} = 0.35$,

Table 5 Means and standard deviations for participation choice, comparative and consequential reasoning about that participation choice and number and percent of no credit (N), partial credit (P) and full credit (F) responses for comparative reasoning across the 3 age groups

	Age groups		
	14–15 Years N = 62	16–17 Years N = 82	18–19 Years N = 70
Participation choice			
Based on the information you have been given, do you think you would choose to participate or not participate in this study	M = 3.33 SD (0.54)[a]	M = 3.23 SD (0.58)[b]	M = 3.35 SD (0.64)[c]
I would definitely NOT want to participate	0 (0%)	0 (0%)	1 (1.40%)
I would probably NOT want to participate	2 (3.3%)	7 (7.6%)	3 (4.3%)
I would probably want to participate	36 (60.0%)	49 (62.0%)	36 (52.2%)
I would definitely want to participate	22 (36.7%)	24 (30.4%)	29 (42.0%)
Comparative reasoning[d]			
Explain why you think the potential benefits/risks of participating are more important than the potential risks/benefits. Be sure to specify both benefits and risks in your answer	M = 1.25 SD (0.86) *N. 16 (26.7%)* *P. 13 (21.7%)* *F. 31 (51.7%)*	M = 1.23 SD (0.88)[b] *N. 23 (29.1%)* *P. 15 (19.0%)* *F. 41 (51.9%)*	M = 1.32 SD (0.87)[c] *N. 18 (26.1%)* *P. 11 (15.9%)* *F. 40 (58.0%)*
Consequential reasoning			
If I agreed to participate in this study, I would probably… [e]	M = 2.16 SD (0.74)	M = 2.23 SD (0.61)	M = 2.08 SD (0.69)
Regret my decision (somewhat–strongly agree)	3 (4.8%)	2 (2.4%)	3 (4.3%)
Feel very anxious throughout the study (somewhat–strongly agree)	25 (40.4%)	35 (42.6%)	26 ((37.2%)
Feel very satisfied with the experience (somewhat–strongly agree)	52 (83.9%)	66 (80.5%)	59 (84.2%)

[a]N = 60: Sample size when there is missing data

[b]N = 79: Sample size when there is missing data

[c]N = 69: Sample size when there is missing data

[d]Skip logic programming was used to word the item to correspond to whether participants had indicated they were likely or unlikely to participate

[e]Mean and standard deviation reflect cumulative score for consequential reasoning with the "feel satisfied" item reverse scored

p = 0.71), comparative reasoning ($F_{2,207} = 0.21$, p = 0.81) or consequential reasoning ($F_{2,213} = 0.88$, p = 0.42). The comparative reasoning score was not correlated with participation likelihood. However, consequential reasoning was negatively correlated with participation likelihood ($r_{214} = -0.63$, $p < 0.001$) indicating that respondents who believed participation would result in regret, anxiety, or lower levels of satisfaction were less likely to participate.

Discussion

To date, PrEP biomedical prevention efforts for AMSM have too often been extrapolated from findings with adults and compromised by a lack of clinical trial evidence to support developmentally appropriate prevention approaches [11]. This is due in part to differences in statutory restrictions on and ambiguous language describing mature minor's access to a range of HIV services and to lack of empirical data to inform IRBs on policies regarding waiver of guardian permission. Guardian permission barriers have discouraged AMSM participation in PrEP trials for fear of being outed or punished by parents or guardians and in turn have dissuaded many investigators from including adolescents in these trials [9, 14, 45]. The goal of this study was to help reduce these barriers by providing a developmentally tailored presentation of consent information and application of the MacCAT-CR format to provide empirical data on the extent to which AMSM's ability to consent to comparative trials for forthcoming trials on oral and injectable PrEP is comparable to the ability of 18 and 19 year-olds who have reached the legal age at which their consent competencies are unquestioned.

AMSM's Competence for Consent Understanding and Appreciation

To determine whether there were meaningful differences between AMSM and MSM on understanding and appreciation of consent information we employed the cognitive diagnostic models (CDMs) analysis. The CDMS is a relatively new psychometric approach that permits identification and comparison across age groups of participants who

demonstrate passing performance on these two dimensions of consent. Applying this analysis, our results support the premise that 16–17 year-old AMSM are capable of understanding and appreciating consent information described in this hypothetical comparative oral and injectable PrEP trial at the same level as 18–19 year-olds; and that the majority (83%) of 14–15 year-olds demonstrate similar competencies. The data are consistent with the growing body of literature supporting adolescents' ability to self-consent across a range of research and medical contexts and recent data on consent comprehension of oral PrEP adherence demonstration studies and placebo controlled HIV vaccine trials [14, 26, 27]. Findings also complement data indicating parents' belief that research waivers of guardian permission would facilitate access to PrEP, particularly for teens who need it most [46].

The Research-Treatment Distinction

Ethical concerns have often been raised regarding both adolescents' and adults' consent understanding and appreciation of two inter-related concepts related to the nature of their participation in randomized clinical trials. The first, often referred to as therapeutic or preventive misconception, reflects participants' tendency to confuse the goal of clinical research to produce generalizable knowledge with the goal of clinical care to provide treatment tailored to a patient's individualized health needs [25, 47, 48]. The second, misunderstanding of random assignment, is closely tied to therapeutic misconception and occurs when participants believe they will be assigned to the experimental condition that is best for them. Our results indicate that across age the majority of respondents (75.8–94.3%) understood these concepts exemplified by this 14-year-old's response: "With regular medical care, a doctor would assist you in determining which option would be most beneficial for your specific needs. In this study, your needs aren't being considered and you will take both drugs in a random order." Similarly, over 90% of all age groups correctly chose the statement reflecting understanding that randomization meant group assignment would be decided by chance rather than "the group that is best for me." These findings support recent studies indicating both adolescents and adults understand that being in a study is different from seeing a regular doctor and the role of random assignment in ensuring the scientific validity and future value of the research [14, 47].

Consent Vulnerabilities

For most items, at least 75% of respondents received full-credit scores. However, across age groups there were items in which percentage of full-credit responses hovered around 50–60%. One such vulnerability was respondents' lack of understanding that engaging in unprotected anal sex, rather than simply being attracted to or having a male sexual partner, was the correct inclusion criteria for study participation. Misunderstanding of HIV risk is consistent with prior research with young MSM [14] and suggests that including additional information on sexual behavior inclusion criteria can enhance both informed consent and participants' understanding of behaviors that place them at HIV risk. Second, despite the use of the video and brief informational disclosures immediately followed by specific questions, participants had difficulty understanding the pre-randomization 5-week lead-in period of cabotegravir pills required to ensure the safety of the injectable form of PrEP during the experimental phase of the study. Many confused the cabotegravir pill with the oral Truvada pill. Third, respondents had poorer scores describing the purpose of the study. Some only focused on one medication, while others focused on either just safety (side effects) or efficacy (adherence). The fact that these consent vulnerabilities existed across age groups argues against using these vulnerabilities as a reason to deny minor adolescents with consent capacity the ability to engage in research without guardian permission. At the same time, these findings suggest that for both mature minors and young adults, for future PrEP RCTs the MacCAT-CR format should be utilized during pilot studies to identify the nature of prospective participant consent vulnerabilities and to inform strategies for remediating misconceptions and strengthening comprehension during informed consent procedures.

AMSM's Competence to Provide Justifiable Reasons for Their Participation Decision

The accepted standard for evaluating the ability to make a "reasoned" participation decision is defined broadly as the process of deciding about participation focused on participants' ability to compare alternatives in light of consequences [31]. No age differences were found for the comparative reasoning item. However, it is important to note that although most participants listed both risks and benefits in response to the comparative reasoning question, across age only half received full credit for this item. This was due to failure to justify how the balance of risks to benefits would influence their participation decision. Although the written question specifically asked them to explain why "the potential benefits/risks of participating were more important than the risks/potential benefits", it may not have been clear to all respondents that we were looking for a comparative answer. Comparative reasoning may actually be higher in these age groups when informed consent is conducted in-person with the opportunity to ask participants to elaborate on their answers. The study also found no age differences in respondents' evaluation of the consequences of participation. Moreover, across age those who believed participation would result in regret, anxiety, or lower levels of

satisfaction indicated they would be less likely to participate; further evidence that AMSM can make a reasoned participation decision.

Strengths and Limitations

One strength of our study is the adaptation of the MacCAT-CR presentation of consent information in an age appropriate and multimedia format enhanced by recommendations by our study's Youth Advisory Board. The second is the application of the cognitive diagnostic models (CDMs) analysis to evaluate the extent to which members of each age group demonstrate adequate understanding and appreciation. To our knowledge, this is the first study to assess AMSM comparative and consequential reasoning for participation in a comparative oral and injectable PrEP trial. Across age a majority of respondents received full-credit responses on understanding and appreciation items. However, the MacCAT-CR was not designed to provide an absolute criterion for consent competence and future research is needed to determine whether the survey format is aligned with actual clinical capacity to consent. In addition, consent comprehension and reasoning about a hypothetical trial may not fully reflect consent abilities for actual trials in which individuals have the opportunity to ask questions and research staff have the opportunity to provide feedback on misunderstandings.

A limitation of the study associated with online recruitment is that advertisements were targeted to youth who frequented social media identified as relevant to AMSM interests, and as such may not represent AMSM who do not visit these sites or who do not have these interests. Further, the open response format may have discouraged youth uncomfortable providing written narrative responses. This is underscored by the fact that nearly all study participants reported they were in grades appropriate for their age (e.g. all 14–15-year-olds were in eighth grade or higher and all but five 18–19 year-olds had completed 11th grade, graduated from high school or were in college). Thus, the sample reflects a highly educated group of sexual minority males and findings may not generalize to youth with lower literacy who may be at greater HIV risk. Population generalizability may also be limited by the relatively small sample sizes within each age group. In addition, although approximately 20% identified as Latinx, a group critically affected by HIV, the sample was predominantly non-Hispanic white, and other equally affected racial/ethnic minority groups were not as well represented [49, 50].

Conclusion

Ending the HIV Epidemic: A Plan for America [51] has called for new infections to be rare and access to preventive and medical care unfettered and free from stigma and discrimination within the next decade. Across the nation, AMSM account for disproportionally higher numbers of new HIV and sexually transmitted infections [2, 3]. Without developmentally appropriate evidence-based HIV biomedical preventive strategies for sexual minority youth, the vision for reduction in HIV infections within the next decade will not be fulfilled. This is particularly true for future trials testing different administration modalities for PrEP and other HIV preventive biomedical options. Current IRB apprehension for applying federal regulations to waive guardian permission due to lack of empirical evidence on adolescents' competence to consent to PrEP trials has led to a paucity of biomedical research to inform evidence-based interventions essential to AMSM health and wellbeing. This study provides empirical support for the ability of AMSM represented in this sample to independently consent to a comparative oral and injectable PrEP randomized clinical trial. This study also provides a methodological strategy for other investigators to demonstrate mature minors' consent abilities through comparison to older adolescents who have legal standing as adults. Instead of classifying AMSM as a consent vulnerable population based solely on age or sexual minority status, our findings support permitting AMSM to independently consent to PrEP trials based on their status as mature minors and their ability to understand, appreciate and reason about their participation choice at adult levels.

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