Ethical Aspects of Involving Adolescents in HIV Research: A Systematic Review of the Empiric Literature

Katherine R. MacDonald, MD, MPH[1], Leslie A. Enane, MD, MSc[2], Megan S. McHenry, MD[2], Neilkant L. Davis, MA[3], Elizabeth C. Whipple, MLS[4], and Mary A. Ott, MD, MA[3]

Objective To evaluate the ethics of involving adolescents in HIV research, we conducted a systematic review of the empiric literature.

Methods Electronic databases Ovid Medline, Embase, and CINAHL were systematically searched using controlled vocabulary terms related to ethics, HIV, specified age groups, and empiric research studies. We reviewed titles and abstracts, including studies that collected qualitative or quantitative data, evaluated ethical issues in HIV research, and included adolescents. Studies were appraised for quality, data were extracted, and studies were analyzed using narrative synthesis.

Results We included 41 studies: 24 qualitative, 11 quantitative, 6 mixed methods; 22 from high-income countries (HIC), 18 from low- or middle-income countries (LMIC), and 1 from both HIC and LMIC. Adolescent, parent, and community perspectives assert the benefits of involving minors in HIV research. Participants in LMIC expressed mixed views regarding parental consent requirements and confidentiality, given adolescents' both increasing autonomy and continued need for adult support. In studies in HIC, sexual or gender minority youth would not participate in research if parental consent were required or if there were confidentiality concerns. There was variation in the comprehension of research concepts, but adolescents generally demonstrated good comprehension of informed consent. Informed consent processes can be improved to increase comprehension and study accessibility. Vulnerable participants face complex social barriers that should be considered in study design.

Conclusions Data support the inclusion of adolescents in HIV research. Empiric research can inform consent processes and procedural safeguards to ensure appropriate access. *(J Pediatr 2023;262:113589).*

Approximately 1.8 million adolescents (ages 10-19) and 3.9 million youth (ages 15-24) are living with HIV globally, and approximately one-third of all new HIV infections are among youth.[1,2] Despite an increased risk of contracting HIV, adolescents are often excluded from HIV research. The ethical and regulatory safeguards designed to protect adolescents likely contribute to these limits on youth participation in clinical research.

International guidelines from the Council for International Organizations of Medical Sciences require parental consent for participation of children and adolescents in research and prefer that studies be conducted in adults first.[3] This is also in line with the US Food and Drug Administration (FDA) and Department of Health and Human Services regulatory guidance.[4,5] US regulations define a child as someone who cannot consent to clinical care under the relevant laws of their jurisdiction. If the research is on a procedure or treatment where the child or adolescent can consent to clinical care, parental permission may not be required. Under Department of Health and Human Services guidance, parental permission can be waived in lower risk research if the institutional review board (IRB) or research ethics committee finds that parental permission is not a reasonable requirement to protect the child, or if the research does not involve more than minimal risk, could not be practicably carried out without the waiver, and the waiver will not adversely affect the rights and welfare of the subjects.[4,6,7] When parental permission is waived, it can be substituted with adolescent self-consent or a surrogate decision-maker permission, depending on the population and contexts of the study.[4,6] The FDA does not allow waivers of parental permission, but Subpart D does not apply if the adolescent can consent to clinical care for the procedures under study.[5,8] The additional consent requirements for inclusion of adolescents as well as the ethical complexities of including adolescents with additional vulnerabilities related to HIV risk can

FDA	Food and Drug Administration
HIC	High-income country
IRB	Institutional review board
LMIC	Low- or middle-income country
PrEP	Pre-exposure prophylaxis
SGM	Sexual and gender minority

From the [1]Department of Pediatrics, Division of General Pediatrics and Adolescent Medicine, University of North Carolina School of Medicine, Chapel Hill, NC; [2]Department of Pediatrics, Ryan White Center for Pediatric Infectious Disease and Global Health, Indiana University School of Medicine, Indianapolis, IN; [3]Department of Pediatrics, Division of Adolescent Medicine, Indiana University School of Medicine, Indianapolis, IN; and [4]Ruth Lilly Medical Library, Indiana University School of Medicine, Indianapolis, IN

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dissuade investigators and institutions from involving adolescents in HIV research.

The reluctance to include adolescents in HIV clinical trials has caused delays in availability of effective HIV prevention, including HIV pre-exposure prophylaxis (PrEP). Adult clinical trials of combined emtricitabine/tenofovir disoproxil for oral PrEP started in 2007 and the FDA approved its adult use in 2012.[9] For adolescents, clinical trials evaluating PrEP only started in 2013, and FDA approval occurred in 2018—a 6-year delay.[9,10] For all sensitive issues, but for HIV specifically, parental permission can be an important barrier to appropriate access to research. Parental permission has been shown to discourage participation of minors aged <18 years in sexually transmitted infection research and participation of those with the highest risk behavior in substance use screening research.[11-13] This practice introduces bias and impacts the generalizability of findings.

The concept of appropriate access to research is described in the Declaration of Helsinki and states that vulnerable groups that have historically been excluded from medical research should be included with appropriate protections.[14] In their best practice guidance, the Society for Adolescent Health and Medicine lays out ethical safeguards regarding waiver of parental consent for sensitive issues research with

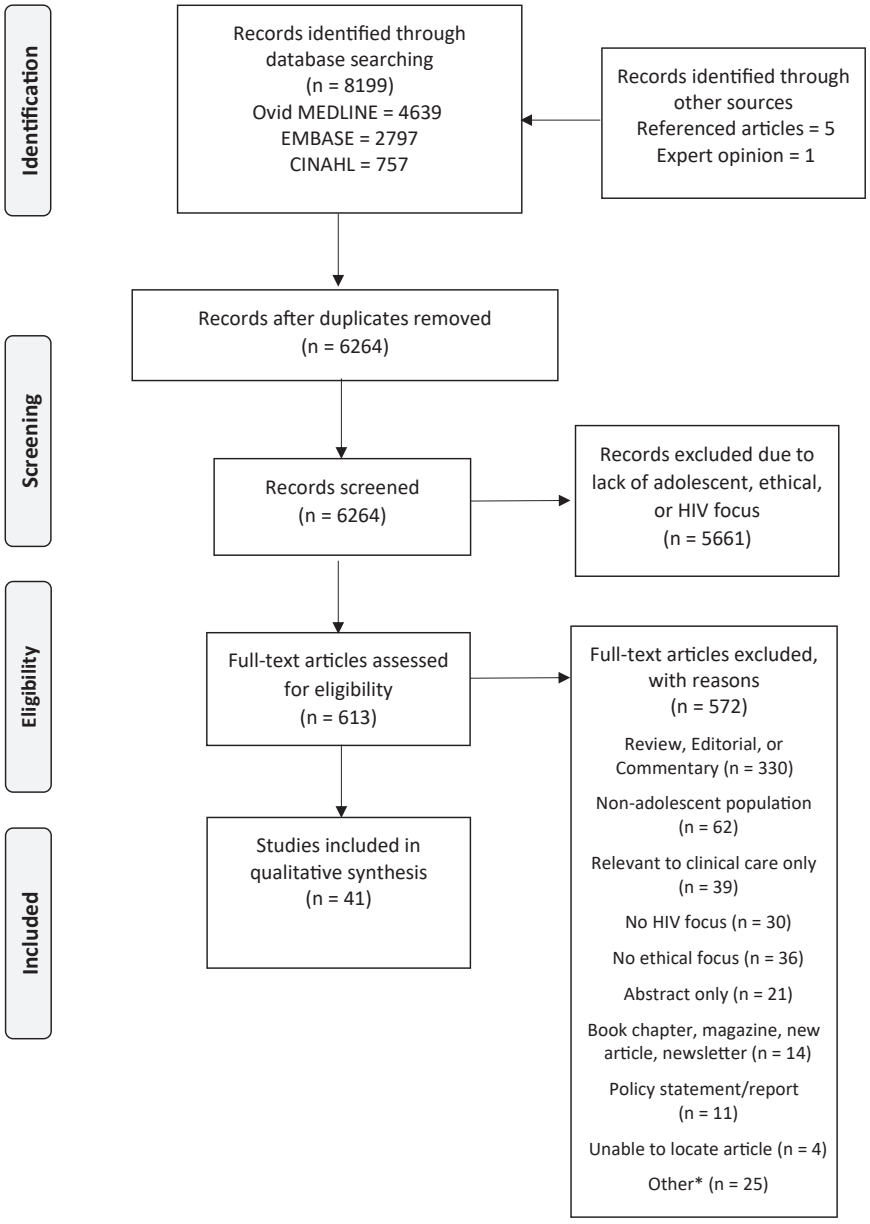

Figure. PRISMA flow diagram for study selection. *Other includes case studies (n = 17), educational material (n = 2), workshop report (n = 2), studies with low-quality methods (n = 1), and duplicates (n = 3).

adolescents, including ensuring adolescent understanding and capacity, maintaining adequate protections, and appreciating the roles of parents and community.[15] Many of the arguments for and against exclusion of adolescents from HIV research are based primarily on expert opinion. Missing are the experiences and perspectives of children, adolescents, parents, and community stakeholders in child and adolescent HIV research participation, empiric data on adolescents' capacities for consent, and strategies to adapt consent or assent procedures for adolescents. Our purpose is to systematically review empirical research on the ethics of involving adolescents in HIV research.

Methods

Search Strategy

This systematic literature review was conducted according to PRISMA guidelines (**Figure**).[16] An experienced medical librarian systematically searched Ovid MEDLINE, Embase, and the CINAHL databases for articles published between January 1, 1985, and April 30, 2022. Controlled vocabulary terms and keywords were used for ethics topics such as "disclosure," "confidentiality," "informed consent," and "beneficence," "HIV," and specific populations (eg, "adolescents," "child," "infant," "orphaned children," "pregnant women," "pregnancy"). We further limited our search to empiric research studies. We excluded maternal, infant, and child studies because they have distinct regulations and ethical considerations.[17]

Initial title and abstract screening were performed by 4 independent reviewers. Full texts of the remaining articles were independently reviewed to determine whether articles met the predetermined eligibility criteria, with disagreements between reviewers resolved through discussion and consensus. An additional researcher reviewed the article if consensus was not yet met.

Study Selection

From this search, we screened titles and abstracts (n = 6264) and selected studies for full-text review studies that collected qualitative or quantitative data on ethical issues related to participation of adolescents in HIV research (n = 613). To examine the unique concerns of adolescent involvement in research, we included studies focused on adolescents aged 10-19 years, as defined by the World Health Organization.[18] We also included studies that reported parental and community member perceptions and experiences of adolescent involvement in HIV research. We excluded reviews, commentaries, organizational policy statements, clinical care or public health ethical questions (not focused on research ethics), conference abstracts, and studies not related to HIV research. We additionally excluded case studies from HIV research projects raising ethical issues, as well as empiric ethical studies that focused generally on sexual and reproductive health, rather than HIV specifically.

Quality Appraisal

Article quality was assessed independently by multiple researchers. Quantitative studies were assessed using the STROBE guidelines.[19] Qualitative studies were appraised using a quality checklist that emphasizes validity and relevance.[20] All included studies met minimum quality criteria, and most were of moderate quality. One study was excluded owing to limited reported methodology.[21]

Data Extraction and Analysis

Studies that met the inclusion criteria and quality assessment were reviewed. Data for key study characteristics were extracted: research design, country, World Bank country classification, participants' age and gender, participant characteristics (ie community members, parents, healthcare providers, researchers, sexual or gender minorities), analytical methods, research topic, and central findings.[22]

Owing to the heterogeneity of study designs, participant characteristics, and specific research questions in the included studies, narrative synthesis was used to analyze the data. Narrative synthesis uses textual data to describe and synthesize the research evidence.[23] Our analytical approach included preliminary synthesis, exploring relationships, and assessing robustness.[24] Emerging themes relevant to our research topic were extracted from qualitative studies. Findings from quantitative studies were summarized and themes were extracted. Preliminary synthesis was conducted by grouping, tabulation, and thematic analysis. Studies were tabulated by emerging themes among included studies and were grouped based on geographical and sample characteristics. Assessing findings from high-income countries (HIC) and low- or middle-income country (LMIC) in turn facilitated broad consideration of settings with differing HIV epidemic contexts (ie, generalized or concentrated epidemics), HIV prevalence, care and research resources, and economic realities. Relationships within and between studies were explored by comparing and contrasting findings in different groups and themes to elucidate similarities and difference, as well as research gaps.

Robustness was ensured by excluding poor quality studies, and bias was minimized by not applying ethical theories in our analytic approach, so that our findings would not be biased toward a specific ethical framework. We also minimized bias by applying equal weight to studies and by reviewing studies to ensure internal consistency in themes and interpretation.

Results

The final review includes 41 studies (**Table I**). Of the 24 qualitative articles, 11 studies included adolescents, 4 included parents, 4 included community stakeholders, and 5 included multiple groups of participants. Of the 11 quantitative articles, 8 studies included adolescents, 1 included parents, and 2 included multiple groups of participants. The 6 mixed-methods studies included

Table I. Study characteristics

Studies	Country	Age of participants (years)	No.	Sample descriptiond	Study design and analysis	Area of investigation
Alexander et al (2015)*,[25]	US	16-19	33	Female or MSM adolescents.	Qualitative: Simulated consent process and semistructured interviews; ethnographic content analysis.	Decision-making capacity for participation in an HIV vaccine clinical trial.
Bonner et al (2021)[26]	South Africa	18-20	31	Adolescent females previously enrolled in HIV prevention trial.	Qualitative: FGDs, thematic content analysis.	Perspectives of using a trusted adult, as opposed to a parent, for consent in HIV prevention study.
Blake et al (2015)[27]	US	15-17	120	Adolescents.	Quantitative: Randomized controlled trial of web-based assent vs paper consent, descriptive and linear regression analysis.	Efficacy of web-based assent for an HIV vaccine clinical trial.
Chappuy et al (2006)[28]	France	Adults	68	Parents of children living with HIV or cancer enrolled in a clinical trial.	Quantitative: Semistructured interviews, scored understanding of consent to research study, descriptive and logistic regression analysis.	Parental understanding of consent in a clinical trial.
Chappuy et al (2008)[29]	France	8-18	29	Children and adolescents living with HIV or cancer enrolled in a clinical trial.	Quantitative: semistructured interviews, scored understanding of consent to research study, descriptive and logistic regression analysis.	Pediatric/adolescent understanding of consent in a clinical trial.
Cherenack et al (2020)[30]	Tanzania	15-21	135	AGYW enrolled in mock microbicide study.	Quantitative: cross-sectional questionnaire, descriptive and logistic regression analysis.	Research participants history of sexual trauma and mood disorder.
Essack et al (2010)[31]	South Africa	Adults	31	Stakeholders in HIV vaccine trials: community advisory board members, research and ethics committee staff, media, civil society and government representatives, and sponsors.	Qualitative: semistructured interviews, inductive analysis.	Stakeholder concerns on ethical challenges in HIV vaccine trials, including adolescent participation.
Fisher et al (2021)[21]	US	14-19	214	Adolescent men who have sex with men.	Quantitative; online questionnaire; cognitive diagnostic modeling and ANOVA analysis.	Adolescent competency to self-consent to a mock HIV biomedical trial assessed by MacCAT-CR.
Fisher et al (2016)†,[32]	US	14-17	60	SGM adolescents who have sex with or interest in men.	Qualitative: online asynchronous FGD; thematic content analysis.	Self-consent for HIV prevention research.
Francis et al (2009)[33]	South Africa	15-17	8	Out-of-school adolescents working as peer researchers.	Qualitative: observations of training process and research procedures, focus group discussions with adolescent peer researchers.	Ethical and other challenges of using adolescent peer researchers in HIV research.
Gilbert et al (2015)[34]	US	Adults	17	Adolescent Medicine Trials Network investigators and study personnel considering implementation of a phase II clinical trial of PrEP among 15-to 17-year-olds (ATN113).	Qualitative: moderately structured interviews, documented correspondence with IRBs, and formal IRB memoranda.	Process of decision-making among research personnel and IRB staff to allow adolescent self-consent for PrEP phase II study.

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Table I. Continued

Studies	Country	Age of participants (years)	No.	Sample descriptiond	Study design and analysis	Area of investigation
Groves et al (2018)[35]	Kenya	15-19	40	HIV-positive and HIV-negative members of a youth advisory board.	Qualitative: FGDs; thematic content analysis.	Self-consent, confidentiality of HIV testing results.
Guadamuz et al (2015)[36]	Thailand	Adults	33	MSM youth (aged 18 years) in high school and parents of 15- to 17-year-old males.	Qualitative: semistructured interviews and FGDs; thematic content analysis.	Parental and youth MSM perspectives on participation in and consent to HIV prevention research.
Gumede et al (2019)[37]	South Africa	13-19 and >50 years	12	Adolescents and their caregivers involved in HIV programs.	Qualitative: ethnographic report individual interviews with members of dyads.	Ethical challenges of conducting separate interviews with dyads.
Jaspan et al (2008)[38]	South Africa	Adolescents,‡, youth and adults	200	Community stakeholders: Adolescents and youth, parents, teachers, community-based organizations, community advisory boards.	Qualitative: FGDs; thematic content analysis.	Stakeholder attitudes toward adolescent involvement in HIV vaccine trials.
Knopf et al (2017)[13]	US	17-25	58	MSM and transgender women.	Mixed-methods: Web-based survey and in-depth interview; descriptive statistics and thematic content analysis.	Autonomous consent and study experiences in a phase II study of PrEP.
Knopf et al (2017)[39]	US	Adults	17	Researchers enrolling adolescents in an HIV prevention study.	Qualitative: semistructured interviews; thematic content analysis.	Ethical concerns of investigators of a phase II study of PrEP allowing self-consent for minors.
Lally et al (2014)[40]	US	16-19	120	Female or MSM.	Quantitative: Randomized controlled trial of persuasive messaging in educational brochures for a mock HIV vaccine trial; ANOVA and Correlations.	Understanding of randomization and placebo (to reduce preventive misconception).
Lee et al (2013)[41]	US	12-17	123	General adolescents.	Qualitative: Cross sectional, Questionnaire evaluating comprehension, descriptive statistics.	Comprehension of study concepts; capacity for informed assent.
Macapagal et al (2019)†,[42]	US	14-17	616	Sexual or gender minority adolescents.	Quantitative: online questionnaire, descriptive statistics and ANOVA.	Discomfort with HIV related research procedures in comparison with everyday events and routine medical care.
Macapagal et al (2017)†,[43]	US	14-17	74	Sexual or gender minority adolescents.	Mixed-methods: Survey and web-based focus group, descriptive statistics and thematic content analysis.	Adolescent perspectives on risk and benefits of completing a sexual health research survey.
Mathews et al (2005)[44]	South Africa	‡	516	Eighth- and ninth-grade students and their caregivers.	Quantitative, cross-sectional, structured interviews, descriptive statistics.	Informed consent for school-based HIV prevention.
Matson et al (2019)[45]	US	14-17	197	SGM adolescents, HIV negative.	Mixed-methods: online survey with open-ended questions, descriptive statistics, correlations, and thematic content analysis.	Adolescent perspectives on sharing deidentified data about sexual health.
Mustanski et al (2017)†,[46]	US	14-17	74	Sexual or gender minority adolescents	Mixed-methods: survey and web-based focus group, descriptive statistics and thematic content analysis	Perspectives of participating in research, parental consent, and informed consent process

(*Continued*)

Table I. Continued

Studies	Country	Age of participants (years)	No.	Sample descriptiond	Study design and analysis	Area of investigation
Mustanski et al (2018)[47]	US	Adults	30	Parents of adolescent males	Qualitative: semistructured interviews; thematic content analysis	Parental perspectives of adolescent participation in biomedical HIV prevention trials and self-consent.
Nakalega et al (2021)[48]	Uganda	16-21 Adults	265 plus 50 dyads	AGYW, community stakeholders, parents of adolescents.	Qualitative; descriptive content analysis of meeting summary notes.	Stakeholders' perspective toward adolescent self-consent and adolescent participation HIV prevention drug trial.
Newcomb et al (2016)[49]	US	Adults	31	Parents of SGM youth.	Qualitative: semistructured interviews, thematic content analysis.	Parental perspectives on waiver of parental consent for minimal risk studies of LGBTQ health inequities.
Nkosi et al (2020)[50]	South Africa	10-14 Adults	77	AGYW, caregivers, community members and researchers.	Qualitative: Semistructured interview and FGDs, thematic content analysis.	Ethical obligations of researchers in low-resource settings.
Ott et al (2013)*,[51]	US	16-19	33	MSM and females.	Qualitative: simulated consent, semistructured interviews; grounded theory analysis.	Components of preventive misconception in HIV vaccine trials.
Pagano-Therrien et al (2017)[52]	US	14-21 Adults	18	Adolescent with chronic health conditions, including HIV (8/18).	Qualitative: semistructured interviews; content analysis.	Decisional conflict with research participation, Lines between research and clinical care.
Ralefala et al (2021)*,§,[53]	Botswana	15-18 Adults	93	Adolescents and their parents/ caregiver who participated in HIV/ TB genomics study.	Qualitative: Semistructured interviews and FGD, thematic analysis.	Informed consent process for return of genomic results.
Ralefala et al (2020)*,[54]	Botswana	15-18 Adults	93	Adolescents and their parents/ caregiver who participated in HIV/ TB genomics study.	Qualitative: semistructured interviews and FGD, thematic analysis.	Adolescent and parental perspectives of reciprocity in genomics research.
Rennie et al (2017)[55]	Kenya	15-19, adults	68	HIV-positive and HIV-negative members of youth and community advisory boards.	Qualitative: FGDs; thematic content analysis.	Participation in HIV research.
Schenk et al (2014)[56]	South Africa	16-19	1078	Adolescent females enrolled in a phase III microbicide trial.	Quantitative: cohort study, secondary analysis of outcomes among 16- to 17-year-old vs 18- to 19-year-old participants.	Outcomes and risk behaviors among adolescent females in microbicide trials.
Shah et al (2020)[57]	South Africa and US	14-17	75	Adolescent females in South Africa, Adolescent males and females in the US.	Mixed methods, questionnaire with open ended questions, descriptive statistics, and content analysis.	Barriers to adolescent participation in HIV prevention research.
Sikand et al (1997)[58]	US	Adolescents† and adults	100 pairs	Adolescent-parent pairs.	Cross-sectional: questionnaire; quantitative analysis.	Perceptions of need for parental consent for adolescent minors.
Simons-Rudolph et al (2020)[59]	Kenya	15-19	82	HIV-positive and -negative adolescents who were tested in an HIV research study.	Qualitative, semistructured interviews.	Research benefits, understanding risks, and perception of HIV testing.
Stanford et al (2003)[60]	US	12-18	438	HIV-positive and HIV-negative participants in a longitudinal study.	Cohort: questionnaire.	Factors influencing recruitment and retention in research.
Traube et al (2013)[61]	US	9-11	170	African American.	Mixed-methods: individual interviews.	Research participation, trust in researchers, informed assent

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Table I. Continued

Studies	Country	Age of participants (years)	No.	Sample description‡	Study design and analysis	Area of investigation
Vig et al (2016)[62]	Botswana	Adults	32	Parents of adolescents ages 13-17.	Qualitative: FGDs; thematic content analysis.	Acceptability of adolescent participation in an HIV prevention trial, sharing of STI test results with parents.
Zhang et al (2019)[63]	China	15-19	517	Adolescent females engaged in high-risk sexual behavior.	Qualitative: thematic summarization of SRH studies with adolescent females.	Evaluating concepts of justice, beneficence, and respect for persons.

AGYW, adolescent girls and young women; *ART*, antiretroviral therapy; *FGDs*, focus group discussions; *GBV*, gender-based violence; *HIV*, human immunodeficiency virus; *MSM*, men who have sex with men; *SRH*, sexual and reproductive health.
*Publications by Alexander et al (2015) and Ott et al (2013) report on the same cohort of study participants.
†Publications by Fischer et al (2016), Macapagal et al (2019), Macapagal et al (2017), and Mustanski et al (2017) report on the same cohort of study participants.
‡Adolescent age group not described specifically.
§Publications by Ralefala et al (2020) and Ralefala et al (2021) report on the same cohort of study participants.

adolescent participants. The review included 22 articles from HIC, 18 from LMIC, and 1 with participants in both HIC and LMIC. Nine areas of study emerged (**Table II**) and included adolescents, parents, and community members perspectives on adolescent research involvement (**Table III**).

Adolescent Comprehension of Informed Consent

Eleven studies assessed adolescent comprehension of informed consent.[13,25,27,29,32,41,46,51,52,59,64] Of the 11 studies, most were conducted in HIC; one was conducted in Kenya.[59] Most HIC studies demonstrated that adolescents have good comprehension of informed consent, including understanding autonomy and protocol procedures, risks, and benefits (**Table II**).[25,27,32,51] Exceptions were found in 4 studies.[29,41,51,52] In a study of 8.5- to 18.0-year-olds with HIV and cancer diagnoses, Chappuy et al found that participants had more difficulty understanding procedures, duration of participation, option of alternative treatments, and voluntary nature of participation.[29] Lee et al administered a questionnaire to evaluate comprehension of an assent process, and approximately 75% of adolescent participants correctly answered ≥80%.[41] The most common incorrect responses were regarding treatment group masking and expectations of participating in a future vaccine study.[41] Ott et al further demonstrated nuances to adolescent understanding; overall comprehension of study procedures and purpose was good, but many of the youth had difficulty with the concepts of efficacy, placebo control, and randomization.[51]

Notably, the studies by Chappuy and Lee included young adolescents (<14 years).[29,41] When evaluating age and comprehension, Lee et al did not find a correlation with age and comprehension; however, Blake et al and Chappuy et al found that comprehension improved with older age.[27,29,41] Pagano-Therrien et al demonstrated that adolescents with chronic conditions decided to participate in studies based on established trust with their providers serving as physician-researchers and may not have paid close attention to components of the informed consent.[52] The study based in a LMIC found most participants (60%) did not accurately recall the anticipated risks of an HIV testing study 2 months after the study.[59] These studies highlight the need to tailor the consent process for adolescents, and specifically Pagano-Therrien et al demonstrated that consent procedures for research and for clinical care must be clearly distinguished.

Improving Adolescent Consent Processes

Eleven studies evaluated methods to improve adolescent consent.[26,27,37,38,40,44,46,51,53,61,63] Of these, 5 were based in HICs.[27,40,46,51,61] Blake et al and Lally et al presented randomized controlled trials of consent processes.[27,40] Lally et al found that supplemental brochures with 2-sided messaging—acknowledging common misperceptions followed by clarification—improves understanding of randomization and placebo control.[40] Blake et al found that comprehension of a self-administered web-based assent is similar to that of an investigator-administered paper-based

Table II. Areas of study and findings

Subtopic studies	Findings
Adolescent comprehension of informed consent	
Alexander et al (2015)[25]	Adolescents, female or MSM, demonstrate decision making capacity; specifically, by understanding trial procedures, personal implications, and autonomy.
Blake et al (2015)[27]	Adolescents understand assent process.
Chappuy et al (2008)[29]	Incomplete understanding of elements of informed consent/assent. Understanding of informed consent increases with age and timing of informed consent (at the time of diagnosis or >7 days afterwards).
Fisher et al (2021)[21]	Adolescents 16-17 years have same level competence of consent for biomedical research as 18-19 year olds. Most ages 14-15 have the same level of competence. Across age groups, most can distinguish between care and research. Improved communication about purpose and procedures are needed.
Fisher et al (2016)[32]	Most sexual or gender minority youth have capacity for informed consent. Participants demonstrated comprehension of risks/benefits, procedures, randomization, and choice.
Knopf et al (2017)[13]	Most participants possessed good understanding of informed consent elements in a phase II clinical trial for PrEP.
Lee et al (2013)[41]	Variable comprehension of study elements after assent procedures for a vaccine trial.
Mustanski et al (2017)[46]	Sexual and/or gender minority adolescents demonstrate ability to identify risks and benefits of HIV surveillance research. They felt autonomous in declining participation.
Ott et al (2013)[51]	Majority of adolescents understood concepts of the consent that would help mitigate preventive misconception. Some had difficulty with the nuances. Most endorsed safe sexual practices given nature of the research.
Pagano-Therrien et al (2016)[52]	Consent for clinical care and research was often blurred. Adolescents often recalled signing documents for informed consent/assent in clinic-based research studies, many youths did not understand research procedures and minimized risks; instead, placed more decisional weight on their clinical relationship and convenience factors.
Simons-Rudolph et al (2020)[59]	Many participants could not recall research risks 2 months after the study. Some recalled benefits (ie, financial help) and risks (ie suicide) that were not part of the study. Informed consent processes need to ensure appropriate risk benefit perceptions.
Improving the adolescent consent process	
Blake et al (2015)[27]	Comprehension of assent for a theoretical HIV vaccine trial was best when using a paper assent form with interspersed questions compared to Web-based and paper assent without questions.
Bonner et al (2021)[26]	Using trusted adults and selected adult representatives to consent for adolescent participation in research is an alternative to parental consent that maintains adolescent representation, privacy, and safety. Although some would participate if parental consent were required, many would not.
Gumede et al (2019)[37]	Consent process for dyads should be tailored and individualized for each member of the dyad.
Jaspan et al (2008)[38]	Community members recommend age-appropriate consent process with videos and multiple checks for comprehension for adolescents participating in an HIV vaccine trial.
Lally et al (2014)[40]	Brochures with 2-sided messages (which includes frequent misconceptions followed by fact) improve adolescent understanding of concepts related to preventive misconception: placebo and randomization.
Mustanski et al (2017)[46]	Sexual and/or gender minority participants wanted multiple methods of delivering information and ensuring understanding to facilitate informed consent in HIV surveillance research. Rapport- and trust-building were important.
Matthews et al (2005)[44]	Strategies for ensuring informed consent in school-based HIV prevention research should be developed in collaboration with the community.
Ott et al (2013)[51]	Engaging adolescents in active processing reveals areas of misunderstanding and clarifies nuances important for minimizing preventive misconception in HIV vaccine trials.
Ralefala et al (2021)[53]	Informed consent should be obtained regarding genomic test results at enrollment and when the results return. Researchers should support participant understanding of genomic research, maintain transparency of possible findings, and the results. Most participants expressed its their right to know results.
Traube et al (2013)[61]	Majority of participants believe African American researchers from their own neighborhood will inform participants with the most amount of information in the assent process, as compared to African American researchers from a different neighborhood or a White researcher.
Zhang et al (2019)[63]	Balance of including minors and legal requirements for parental consent is needed. Mechanisms should be considered to promote the balance, including using trusted adult for consent and assessing adolescent competency.
Parent comprehension of informed consent	
Chappuy et al (2006)[28]	Incomplete parental understanding of the consent process based on requirements in European legislation.
Matthews et al (2005)[44]	Parents had moderate recollection of consent form from school-based HIV prevention research. Parents had poor to moderate understanding of the study.
Pagano-Therrien et al (2016)[52]	Consent for clinical care and research was often blurred. Signing paperwork is routine in clinic and leads to reduced likelihood parents fully process the informed consent for research.
Confidentiality	
Gumede et al (2019)[37]	Some participants had limited trust in research confidentiality when interviewing individuals within dyads, researchers were concerned with accidental disclosure, and caregivers needed reminders of the adolescents' rights to confidentiality.
Groves et al (2018)[35]	Most adolescents wanted parental support while receiving HIV test results; some conflicted owing to discomfort related to sharing sexual behavior with parents or disappointing parents.
Jaspan et al (2008)[38]	Community members supported confidentiality of medical tests of adolescents participating in HIV trials, but had varying opinions about HIV and pregnancy test results.
Matson et al (2019)[45]	SGM adolescents overall willing to share deidentified survey data, but not blood samples. Concerns regarding sharing de-identified data included maintaining confidentiality and misuse of data. Recommended processes for sharing data focused on confidentiality, monitoring its use, and seeking permission in consent forms.
Mustanski et al (2017)[46]	Sexual and/or gender minority participants did not want HIV test results to be disclosed to parents in HIV surveillance research.
Traube et al (2013)[61]	African Americans trusted White researchers and African American researchers from outside their community to maintain privacy in an HIV-focused community-based participatory research.
Simons-Rudolph et al (2020)[59]	Confidentiality of HIV test results more important than location of testing. Participants trusted research staff to maintain privacy more than clinical staff.

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Table II. Continued

Subtopic studies	Findings
Vig et al (2016)[62]	Parents had mixed reactions of only adolescents receiving STI test results in an HIV prevention trial.
Zhang et al (2019)[63]	Privacy and confidentiality were utmost importance among participants who engage in high-risk sexual behavior.
Adolescent self-consent	
Essack et al (2010)[31]	Community stakeholders regarded parental consent as essential in an HIV vaccine trial, and some understood the challenges of recruitment if consent is required.
Fisher et al (2016)[32]	Many SGM youth find parental permission to be a barrier to participating in HIV-related research owing to fear of being "outed" or privacy concerns about their sexual behavior.
Gilbert et al (2015)[34]	IRB approval was mixed for a phase II PrEP trial allowing adolescent self-consent; leveraging collaboration with IRB aids in the process.
Groves et al (2018)[35]	Adolescent perspectives mixed regarding self vs parental consent. More than one-half favored parental consent for their supportive role.
Guadamuz et al (2015)[36]	Parents disagree with a waiver of consent in HIV prevention research.
Jaspan et al (2008)[38]	Most parents and adolescents agree parents should consent for their supportive role in HIV vaccine trials.
Knopf et al (2017)[13]	Researchers had moral conflict regarding adolescent self-consent in a phase II PrEP trial: concern for adolescent capacity to consent, ability to be in an intensive study, and ramifications from side effects verses commitment to scientific advancement and enabling youth to access PrEP.
Knopf et al (2017)[39]	Adolescent MSM and transgender females did not want parental involvement at enrollment for a phase II clinical trial for PrEP. Many prefer to have support from other adults.
Macapagal et al (2017)[43]	Approximately one-half of SGM adolescents would not participate in sexual health research if parental consent is required, most of whom are not out to parents, mostly owing to fear of disclosure, lack of support, and discomfort.
Mustanski et al (2017)[46]	Almost one-half of sexual and/or gender minority adolescents would not participate in an HIV surveillance study if parental permission is required. One-third of adolescents were unsure.
Nakalega et al (2021)[48]	Community stakeholders regarded parental consent essential in investigation HIV prevention drug trial. Adolescents felt they can self-consent. Parents and adolescents agreed parental and guardian consent is a main barrier to participation. Orphans concerned parental/guardian consent prevents participation.
Schenk et al (2014)[56]	16- to 17-year-olds did not experience detrimental health or behavioral outcomes as a result of participating in a microbicide clinical trial that did not require parental consent.
Shah et al (2020)[57]	Parental consent is a significant barrier to adolescent participation in HIV prevention research and removing parental consent would increase participation. Alternatively, most adolescents would seek support from trusted adult.
Sikand et al (1997)[58]	Parents perceive a greater need for parental consent in research than do adolescents. Older adolescents do not consider parental consent necessary for studies on more sensitive topics, such as STIs and HIV.
Additional vulnerabilities	
Cherenack et al (2020)[30]	Many AGYW had depression and almost half experienced GBV indicating a need for trauma informed practices in research.
Francis et al (2009)[33]	Adolescent peer researchers faced challenges with power, trust, and conflict between social and research ethics.
Zhang et al (2019)[63]	Adolescents engaged in sex work and/or illicit drug use who are excluded from research will not benefit from HIV/STI testing and education; community based participatory research can help identify and solve ethical issues, trusted referral mechanisms need to be in place, destigmatizing language needs to be used in research procedures. Parental consent is not practical as they often are not in contact with parents.
Enrolment and retention	
Gumede et al (2020)[37]	Enrolment of dyads requires a balance of respect for elders and respect for adolescent autonomy to minimize coercion of adolescent enrolment.
Pagano-Therrien et al (2016)[52]	Helping to "pay" the clinician-researcher back for their care, altruism, hope for a cure motivated participation.
Simons-Rudolph et al (2020)[59]	HIV testing and education about HIV motivated study participation. Hope for financial assistance motivated some.
Stanford et al (2003)[60]	Altruism, improved healthcare, privacy, and confidentiality are most influential factors in research retention in a longitudinal study. Compensation is least important.
Traube et al (2013)[61]	Most will participate without compensation in HIV-focused community based participatory research.
Moral obligations of researchers	
Gumede et al (2020)[37]	Participants may expect more benefits than research entails, including financial assistance and counseling for dyads in strained relationships. Researchers in low-income settings should be prepared to manage the participant expectations while maintaining their moral obligation to be supportive.
Nkosi et al (2020)[50]	Participants in LMIC have high unmet basic and socially complex needs, especially surrounding GBV. Participants expect research participation to facilitate needs, whilst researchers feel emotional distress when unable to meet them. Current frameworks do not adequately address researchers' moral obligations in resource constrained settings.
Ralefala et al (2020)[54]	Researcher and participant are in a mutual relationship. Meaningful reciprocation demonstrates respect, Return of genomic results more valued than monetary compensation. Lack of reciprocity will limit future study enrollment.

AGYW, adolescent girls and young women; *ART*, antiretroviral therapy; *GBV*, gender-based violence; *MSM*, men who have sex with men; *OVC*, orphans and vulnerable children; *STIs*, sexually transmitted infections.

assent.[27] Among participants with paper-based assent, those with interspersed questions in their consent process had better comprehension compared with those without interspersed questions.[27] Ott et al observed decreased preventive misconception when adolescents actively processed the study through discussion in qualitative interviews.[51] Participants in studies by Mustanski et al and Traube et al shared that informed consent can be improved by ensuring transparency regarding the study procedures, risks, benefits, and confidentiality.[46,61] The youth also recommended using multimedia to enhance comprehension.[46]

Six of the studies were based in LMIC.[26,38,63] Bonner et al and Zhang et al both demonstrated approaches for trusted adults, as opposed to parents, to provide informed consent.[26,63] Using this in loco parentis (in place of parent)—or proxy parental consent—procedure prevents disclosure of high-risk sexual behavior to parents or guardians, which may lead to physical or emotional harm. Proxy parental

Table III. Adolescent, parent, and community perspectives on adolescent involvement in HIV research

Perspectives	Findings
Adolescent perspectives	
Guadamuz et al (2015)[36]	YMSM would like to participate in research to contribute to society and to gain knowledge.
Macapagal et al (2017)[43]	SGM adolescents find sexual health research to be minimal risk. Most trust research teams, but those who are not "out" and racial/ethnic minorities had less trust. Contribution to science, HIV prevention education, and personal reflection were benefits to participation.
Macapagal et al (2019)[42]	SGM adolescents had high level of comfort in HIV/sexual health research—more comfort than everyday events. Comfort increased with outness, parental support, and being cis gender.
Mustanski et al (2017)[46]	SGM adolescents find participating in research beneficial to facilitate medical care, increase knowledge, and to contribute to society. Participants also identified emotional and physical risks to participation.
Nakalega et al (2021)[48]	Adolescent women felt HIV prevention research would be beneficial.
Pagano-Therrien et al (2016)[52]	Adolescents had high degree of certainty in their decision to participate in research. They also felt supported.
Traube et al (2013)[61]	Children are willing to participate in a study focused on HIV prevention and are motivated by education about the research.
Parent perspectives	
Guadamuz et al (2015)[36]	Most parents would like children to participate as an opportunity to learn and be engaged. Some, more educated parents, are cautious in their child's involvement.
Mustanski et al (2018)[47]	Most parents believe their child would benefit from HIV prevention research. Parents had appropriate concerns including side effects, increased risk behavior, and nonadherence. One-half of parents uncomfortable with waiver of consent and would be more comfortable if additional health protections in place. However, almost all identified benefit for waiver of consent.
Nakalega et al (2021)[48]	Parents concerned about their children participation in an HIV-related study would stigmatize their children and have a negative impact on family reputation.
Newcomb et al (2016)[49]	Most parents with SGM adolescents support participation in an HIV surveillance study without parental permission.
Vig et al (2016)[62]	Parents enthused about child's involvement in a trial evaluating an adolescent program promoting sexual health and testing for HSV. They believed the trial to benefit the child education, sexual health, and future. Some parents wanted results of HSV test.
Community perspectives	
Essack et al (2010)[31]	Community stakeholders expressed a need and urgency to involve adolescents in HIV vaccine trials. However, many expressed that safety should first be shown in adults, and that there is a need for increased monitoring. Many noted that ethical-legal frameworks hinder minor participation in research.
Nakalega et al (2021)[48]	Community stakeholders and regulators supported investigational drug HIV prevention study in adolescents. Recognized parental consent as a barrier to participation but agreed parental or guardian consent is needed.
Rennie et al (2017)[55]	Community members and adolescents found multifaceted individual and community benefits of adolescent participation in research. A few participants considered both the psychological impact of a positive HIV test and inappropriate compensation as potentially harmful. Participants expressed that research benefits outweighed the risks.

HSV, herpes simplex virus; *YMSM*, young men who have sex with men.

consent processes provided support to adolescents during the consent process, enabled adolescents to control the conversation with their family about their participation, and addressed confidentiality concerns about participation.[26,63] Jaspan et al and Gumede et al concluded tools and processes should be tailored based on the guardian and participants needs, such as incorporating age appropriate multimedia, accommodating the guardian's literacy level and vision, and considering the adolescent's limited time.[37,38] Ralefala et al demonstrated the importance of transparency in genomics research; participants wanted the informed consent to include possible genetic results and incidental findings.[53] Finally, Mathews et al concluded school-based consent can be improved by incorporating the community in the process.[44] Overall, studies in both LMIC and HIC identified multiple approaches to improve informed consent. These included assessing understanding throughout the consent procedures with interspersed questions, encouraging discussion during the consent process, improving message communication (eg, 2-sided messages, use of multi-media), engaging the community, being transparent, building trust, and emphasizing confidentiality.

Parental Consent

Three studies investigated parental informed consent, 2 of which were based in HIC.[52,44,28] Chappuy et al found that parents showed more difficulty understanding the procedures, duration of the study, and alternatives.[28] Pagano-Therrien et al found that parents of adolescents with chronic conditions felt overwhelmed by paperwork and, therefore, parental awareness of informed consent for clinic-based research was limited.[52] Matthews et al evaluated a school-based study in South Africa, and found that only 65% of parents recalled a letter requesting consent and that parents had a limited understanding of the study.[44]

Confidentiality

Studies evaluating adolescent confidentiality in research protocols included three from HIC and 6 from LMIC.[35,37,38,45,46,59,61,62,63] Confidentiality in the three HIC studies was highly important especially among sexual and gender minority (SGM) youth.[45,46,61] Mustanski et al showed that SGM youth wanted their participation and HIV test results in a hypothetical HIV surveillance study to be confidential; otherwise, they would likely not participate.[46] Matson et al showed that SGM youth were willing to have deidentified survey data shared, but not blood samples.[45] Participants reported that the consent process must be transparent and fully describe safeguards for data sharing, as they were fearful that data-sharing could result in accidental disclosure of their sexual identity to parents.[45] Traube et al found that African

American youth trusted researchers from outside their community to maintain privacy in an HIV-focused community-based participatory study.[61]

Studies based in LMIC demonstrated varied perspectives on confidentiality. Simons-Rudolph et al and Zhang et al show that confidentiality and privacy are important for adolescent participants with high-risk sexual behavior.[59,63] Gumede et al found that participants of adolescent and caregiver dyads had little trust that responses within the dyad would remain confidential.[37] Jaspan et al and Vig et al found that adolescents, parents, and community members respected adolescent autonomy, the privacy of HIV test results, and supported adolescents' decisions whether or not to disclose test results to parents.[38,62] In the Jaspan et al study, some participants noted that disclosure could potentially lead to verbal or physical abuse, including HIV status disclosure to others without consent.[38] Participants in the Vig et al study noted that disclosing results to parents could lead to adolescent distrust in research and suggested instead that the study team could help to facilitate disclosure on the adolescent's terms.[62] In both the Jaspan et al and Vig et al studies, some adolescents and adults supported disclosure of test results to parents owing to their supportive role.[38,62] This perspective was predominant in a study based in Kenya by Groves et al, where most adolescents wanted parents present for HIV test results.[35] Some participants in the study by Simons-Rudolph et al also preferred to have family present for HIV test results.[59]

Adolescent Self-consent

Fourteen studies evaluated adolescent self-consent, in which research ethics committees allow adolescents to consent to research without parent/guardian permission. Seven studies were based in HIC.[13,32,34,39,43,46,58] Of the 7 studies, 4 focused on SGM participants, one had general adolescent participants, and 2 evaluated researchers' experiences with waiver of parental consent in a phase II clinical trial for PrEP. In studies with SGM youth, the majority would not participate in HIV related research if parental or guardian permission were required, with youth citing the additional risks of disclosing their sexual orientation and gender identity.[13,32,43,46] In a general adolescent population, Sikand et al showed that adolescents perceived less need for parental consent for research procedures involving HIV testing, compared with their parents.[58] Gilbert et al interviewed investigators regarding their IRB or research ethics committee review process for a multisite phase II PrEP clinical trial allowing adolescents to self-consent.[34] All IRBs expressed concern for self-consent, and ultimately, only 7 of 13 IRBs approved the study. Notably, IRBs interpretation of the state laws resulted in different approval outcomes.[34] Investigators reported that engaging with legal, regulatory, and ethical experts and proactively sharing their guidance with IRBs was useful in the process.[34] In the same trial, Knopf et al described investigators' moral conflict related to adolescent self-consent.[39]

There were 6 studies based in LMIC settings with generalized HIV epidemics and high numbers of youth living with HIV.[31,35,36,38,48,56,57] Participants included adolescents, community members, and parents. One study included youth men who have sex with men.[36] Guadamuz et al found that parents disagreed with self-consent, while youth men who have sex with men described parental consent as a barrier, especially for those who have not disclosed their sexuality.[36] Across studies evaluating perspectives on adolescent self-consent in LMIC, the majority of adolescents and adults favored parental support during the consent process.[31,35,38] Jaspan et al found that parents and adolescents expressed that parents should provide consent owing to the supportive roles that parents have for adolescents engaged in a research study.[38] Among adolescents and adults who supported self-consent, adolescent participants were viewed within the context of a developmental framework, where maturity level and lived experience were seen as more important than numeric age.[38] Grove et al showed that approximately one-half of adolescents favored parental involvement for ensuring adequate protections as well as avoiding parent-child conflict if their participation was discovered, with the remainder ambivalent about or agreeing with self-consent.[35] Adolescents who agreed with self-consent expressed that it is the right of adolescents to gain knowledge about HIV through participation regardless of parental agreement.[35] Community stakeholders interviewed by Essack et al found parental consent imperative, but recognized that it could make recruiting adolescents challenging.[31] Community stakeholders interviewed in Nakalega et al also regarded parental consent as essential.[48] By contrast, Nakalega et al found most interviewed adolescents disagreed with requirement of parental consent, given that many were receiving sexual and reproductive health services without parental consent or did not live with their parent or guardian.[48] Parents also expressed concerns that required parental consent would lead to inappropriate disclosures regarding sexual relationships.[48] In one of the few studies including outcome data, Schenk et al compared 16- and 17-year-old self-consenting participants in a phase III microbicide trial for HIV prevention compared with their 18- and 19-year-old counterparts.[56] Schenk et al found that self-consent by participants ages 16-17 years did not lead to additional detrimental health, behavioral, or operational outcomes compared with their peers.[56]

The study by Shah et al was conducted in a HIC and a LMIC, and demonstrated that parental consent is a barrier to research participation among adolescents in both the US and in South Africa owing to fear that parents will think they are engaging in risky behaviors or infected with HIV.[57] Parental consent was a greater barrier for participants in South Africa than in the US.[57]

Overall, 8 studies in HIC and LMIC described parental consent as a barrier to adolescent HIV research participation, with reasons cited including the risk of harms related to disclosing sexual behaviors, exclusion of adolescents living separately from parents, and challenges navigating consent requirements when adolescents are orphaned.[13,32,36,38,43,46,48,57] Critically, requirement of

parental consent was a barrier to participation for most SGM youth.[13,32,36,43,46]

Additional Vulnerabilities

Three studies evaluated ethical concerns related to additional vulnerabilities of adolescents and all were conducted in LMIC.[30,33,63] Francis et al found that adolescent peer researchers—youths who perform research focused on youths, as part of a study team—face challenges from lack of authority, social and research relationships with peers, and conflicts between cultural expectations and maintaining research compliance.[33] Cherenack et al found that close to one-half of AGYW enrolled in a mock microbicide trial had experienced gender-based violence and emphasized a need for trauma-informed research procedures.[30] Zhang et al focused on adolescent females engaged in sex work and/or illegal drug use and found that a community-based participatory approach helped researchers understand and navigate the ethical issues of enrolling this vulnerable group and created more safeguards for participants.[63]

Enrollment and Retention

Five studies evaluated ethical issues in study enrollment and retention.[37,52,59,60,61] In both HIC and LMIC, primary motivators for adolescent participants enrolling in HIV research studies included altruism, access to health care and health education, and trust in the researchers.[52,59,60,61] Some participants described motivation from financial compensation.[59,60,61]

Three studies were from HIC.[52,60,61] Pagano-Therrien et al and Standford et al described adolescent participants' altruism and hope that research would help other children in the future, including in contributing to a cure.[52,60] Pagano-Therrien et al also demonstrated that in clinic-based research, participants were motivated by established trusted clinical relationships with the researcher.[52] One participant in this study expressed motivation to repay their clinician-researcher for the life-saving care they had received and did so by participating in research.[52] Standford et al showed that access to quality care, caring staff, and health education were the greatest motivators.[60] Assurance of privacy, confidentiality, and trust in researchers were also motivators.[52,60] Stanford et al and Traube et al found that compensation for participation is the least important factor motivating enrollment.[60,61] At the same time, Traube et al found that compensation for time was expected by some as an issue of justice.[61]

Two studies were conducted in LMIC.[37,59] Similar to studies by Standford et al and Traube et al, Simons-Rudolph et al found most adolescents were motivated to participate in research to receive HIV testing and education, and some were motivated by financial compensation.[59] Gumede et al found that the power differential between adolescents and their caregivers, enrolled as dyads, could result in coercion for the adolescent to enroll.[37] To navigate the ethical and logistical considerations of enrollment, caregivers were approached first, and then adolescents were then offered enrollment, with emphasis on their autonomy in the decision to enroll together.[37]

Moral Obligations of Researchers

Three studies evaluated the moral obligations of researchers and all were conducted in LMIC.[37,50,54] Gumede et al and Nkosi et al demonstrated that researchers are often faced with participants who have many unmet basic and systemic needs and hope the researchers can help to meet those needs, leading to researcher fatigue.[37,50] Ralefala et al demonstrated a researcher obligation of reciprocity in genomics studies; participants expressed that researchers should share the genomic results to participants and that the information gained from those results is more valued than monetary compensation.[54]

Adolescent, Parent, and Community Perspectives on Adolescent Involvement in HIV Research

Twelve studies evaluated perspectives on adolescent involvement in HIV research from adolescents (n = 7), parents (n = 5), and the community (n = 3) (**Table III**).[31,36,42,43,46-49,52,55,61,62] Studies evaluating community perspectives were all conducted in LMIC. Most community members supported adolescent involvement in HIV research. For example, focus group participants in Rennie et al discussed that research is a way to learn reliable information that can be shared throughout the community, gain life skills, and improve mental and physical health.[55] Although participants in Rennie et al recognized risks, the perceived benefits of participation in research outweighed the harm.[55] Essack et al and Nakalega et al found that community members recognize that parent or guardian consent is a barrier to much-needed adolescent participation.[31,48] In Essack et al, participants reported that safety of the adolescents is most important.[31]

Five studies evaluated parent perspectives of adolescent involvement.[36,47-49,62] One study was conducted in a HIC and three studies were conducted in LMIC. Three studies involved SGM.[36,47,49] Overall, parents supported adolescent involvement in research as a mechanism to gain sexual health education and social engagement.[36,47,49,62] Mustanski et al found parents believed their children would benefit from research, but expressed concerns for risks, the need for additional protections, and hesitancy with a waiver of parental consent.[47] In 1 study, by Nakalega et al, parents were not supportive of adolescent HIV research involvement, expressing concerned that participation would stigmatize their adolescent and family.[48]

Seven studies evaluated adolescent perspectives in HIV research. Of those, 2 were from LMIC.[36,48] Four of the studies were perspectives from SGM youth.[36,42,43,46] The studies demonstrated that adolescents would like to participate in research to gain education and contribute to society. The Macapagal et al studies found that most SGM adolescents are comfortable discussing sexual health and found sexual health research to be minimal risk.[43,42] Overall, adolescents, parents, and community stakeholders believed it is beneficial to involve minors in HIV research to gain health education,

contribute to society, and access quality medical care through participation.[31,36,42,43,46,47,49,55,61,62]

Discussion

This systematic review examined key ethical issues of involving adolescents in HIV research. Studies demonstrated that adolescents generally have adult-level comprehension of informed consent. Similar to studies including healthy adults and parents, adolescent samples included in this review showed adequate adolescent comprehension of research procedures, but difficulty with abstract research concepts.[65-69] Studies using enhanced consent processes, such as teach-back methods and supplemental educational materials, showed improve understanding of complex topics (eg, placebo control, randomization).

Empiric data on adolescent self-consent and confidentiality capture the conflict between respecting the young person's autonomy and providing protection. This review demonstrates nuances to perspectives on self-consent and confidentiality according to study topic, route of HIV infection, risk factors and vulnerabilities, geographic setting, and sociocultural context. In particular, studies with SGM participants consistently demonstrate that parental consent will limit their participation, potentially biasing study results, and limiting generalizability.

In studies where HIV risk is generalized (eg, Kenya, South Africa) but is high for females, adolescents held nuanced views of parental consent. Although many supported parental involvement, others described varying contexts and considerations that made self-consent necessary for adolescent participation. In these settings, logistical barriers to parental consent included orphanhood, living with extended family, or street-connected, where guardianship may not be formalized, relationships to caregivers may be more tenuous, and HIV-related risks and treatment barriers are acute.[70-72]

Studies also demonstrated the effective implementation of innovative approaches to consent. Schenk et al described optional parental consent in which a waiver of parental consent is granted, but procedures allowed the adolescent to choose whether or not to invite their parent to the consent process.[56] Another approach is to require adult permission, but to allow a nonparental supportive adult (eg, an ombudsman) as an alternative to a parent or guardian; this strategy may be beneficial to both adolescent decision-making and participation in research.[32,39] Community permission with adolescent consent is another approach to consider.[38,73,74] For example, the *baraza*, a traditional community meeting in East Africa, has been used to gather community perspectives on health research, including HIV research involving vulnerable populations.[74-76] Such an approach allows adaptations for cultural resonance in settings where communal approaches are favored, while still respecting adolescent autonomy. However, community consent models may not be appropriate for populations of youth, such as SGM or street-involved youth, experiencing stigma, marginalization, and/or criminalization.

Highly vulnerable adolescent populations, such as orphaned or street-connected youth, youth engaged in sex work or transactional sex, and SGM youth, each have unique needs and may require additional protections. Too often, the need for additional protection is interpreted as justification for exclusion. However, many of these vulnerable populations experience the greatest health disparities and barriers to care, and excluding these groups from HIV research exacerbates those disparities. Current ethical thinking about adolescent self-consent recognizes the concept of appropriate access, which underscores the importance of adolescent inclusion in research while minimizing harm with additional protections.[14,77]

The included studies come from countries with varying ethical and legal structures. For example, in Botswana, there are no current guidelines for parental waivers, whereas in South Africa, there are strict conditions in which waivers may be considered for 16- or 17-year-olds.[78,79] Some countries' ethical guidelines consider the nature of the study, mature minors, and key populations when considering a waiver of parental consent.[7,78,79] International guidance on adolescent consent will need to be flexible enough to account for this variation.

Across studies, factors that motivate adolescents to participate in HIV research frequently met the developmental needs of adolescents. In addition to access to HIV education, novel interventions, and HIV care and support, motivating factors also included altruism and the opportunity to give back to others. Motivations map to adolescents' developmental needs of belonging to something that contributes to the greater good of the community, feeling empowered by accessing education and care, and potentially having health benefits from accessing treatment, prevention and/or care support that might otherwise be inaccessible. Adolescents, community members, and parents appreciate an urgency for adolescent participation in HIV research so that adolescents can critically benefit from research participation, particularly given the HIV risks that impact this age group.

Our review identified significant gaps in empiric data. More engagement of youth and stakeholders is needed for research with highly vulnerable or marginalized groups across global settings, including pregnant adolescents, SGM youth in LMICs, historically oppressed racial and ethnic groups, street-connected and trafficked youth, and substance-involved youth. Currently, only one empiric study focused on the ethics of HIV research with SGM youth in LMIC.[36] The need is particularly urgent because there are often many unique cultural, structural, and legal barriers for SGM populations in LMIC. More geographical variation is needed. The HIV epidemic varies country to country, as do legal and regulatory contexts; however, most studies were conducted in the US and Sub-Saharan Africa. More intervention studies are needed to identify and test innovative approaches to minor consent. Only 1 study reviewed used a novel approach—optional parental consent. Although qualitative studies with youth, parents, and stakeholders mentioned the potential to use other novel

approaches to supporting adolescents during the consent process while simultaneously respecting their emerging autonomy (eg, use of a trusted adult or ombudsperson in lieu of a parent), there were no empiric studies describing these alternate methods. Missing also are studies examining the ethics of research with adolescents living with HIV. Most empiric studies focused on HIV testing or prevention with uninfected populations, rather than studies with adolescents living with HIV. This result is due, most likely, to the increased complexity of consent with healthy populations and the fact that adolescents living with HIV can frequently consent to their own clinical care, and, by extension, research.

Because of the broad nature of our research aim, studies were heterogeneous. Although this heterogeneity likely contributed to conflicting results, it also reflects the variable contexts and populations of young people affected by HIV. To maintain methodologic rigor despite such heterogeneity, we used strict inclusion and exclusion criteria and limited our scope to empiric research studies. This approach excluded commentaries and case studies which discussed ethical experiences confronted during HIV research implementation. ■

Declaration of Competing Interest

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Reprint requests: Katherine R. MacDonald, MD, MPH, 231 MacNider Building, CB#7225 333 S. Columbia St, Chapel Hill, NC 27599-7225. E-mail: katherine.macdonald@med.unc.edu

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