

Ethics and pre-exposure prophylaxis (PrEP) in adolescents: an integrative review

Ética e profilaxia pré-exposição (PrEP) em adolescentes: revisão integrativa

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ABSTRACT

Introduction: Worldwide estimates suggest an increase in the number of deaths by AIDS among adolescents. The Pre-Exposure Prophylaxis (PrEP) has been considered a potential intervention of major impact on new HIV infections. However, the discussion on PrEP in the adolescent population needs to expand mainly regarding ethical issues that emerge with its implementation. **Objective:** The objective of this research was to identify ethical issues related to PrEP in adolescents in the current scientific literature and discuss their impact in the implementation of this preventive strategy. **Methods:** An integrative review of the literature was performed on Medline, Scopus, and Web of Science databases using descriptors *Ethic* and *PrEP*. **Results:** The search retrieved 284 articles, of which 16 was related to adolescents and were kept in the sample after analysis. The issues detected were classified into two categories: 1) Ethics in research and 2) Ethical problems regarding access to PrEP. **Conclusion:** It seems that the issues discussed could diminish the potential impact of PrEP on new HIV infections among adolescents. Discussions on the theme must be deepened, as gaps regarding Ethics and HIV prevention in adolescents are evident, especially when it comes to sexual minorities, both in research and assistance.

Keywords: adolescent health; bioethics; HIV; primary prevention; sexually transmitted diseases; research ethics.

RESUMO

Introdução: Estimativas mundiais sugerem um aumento no número de mortes por AIDS entre adolescentes. A profilaxia pré-exposição (PrEP) tem sido considerada uma intervenção com potencialidade de causar um grande impacto nas novas infecções pelo HIV. Apesar disso, a PrEP na população adolescente necessita de mais discussões quanto às questões éticas que emergem com sua implementação. **Objetivo:** Os objetivos desta pesquisa foram identificar as questões éticas relacionadas à PrEP em adolescentes na literatura científica atual e discutir seu impacto na implementação dessa estratégia de prevenção. **Métodos:** Foi realizada uma revisão integrativa da literatura nas bases de dados MEDLINE, Scopus e Web of Science, com os descritores *Ethic* e *PrEP*. **Resultados:** Foi possível encontrar 284 artigos, dos quais 16 eram relacionados a adolescentes e permaneceram após a análise. Os problemas detectados foram classificados em duas categorias: 1) Ética em pesquisa e 2) Problemas éticos referentes ao acesso à PrEP. **Conclusão:** As questões identificadas podem diminuir o potencial impacto da PrEP nas novas infecções pelo HIV na população adolescente. É necessário aprofundar as discussões sobre o tema, pois existem evidentes lacunas em relação à ética e à prevenção do HIV em adolescentes, principalmente nas minorias sexuais, tanto na pesquisa quanto na assistência, e que podem se traduzir em barreiras à sua efetiva implementação.

Palavras-chave: saúde do adolescente; bioética; HIV; prevenção primária; doenças sexualmente transmissíveis; ética em pesquisa.

INTRODUCTION

Since the beginning of the 1990s, the use of antiretroviral drugs to prevent HIV progression has been one of the most significant interventions and the biggest impact on global response to the AIDS epidemic, being considered one of the great stories of success of public health policies in recent decades⁽¹⁾.

It is estimated that, by the end of 2018, there were 37.9 million people worldwide living with HIV – more than half living in the eastern and southern regions of the African continent⁽²⁾. Although the incidence rates of HIV infections and AIDS mortality are declining globally, this downward trend is not consistent and homogeneous worldwide⁽³⁾. Despite effective prevention programs available in several countries, the reduction in HIV incidence has been lower than expected in many regions⁽⁴⁾. Thus, in contrast to other population

groups' reduction, worldwide estimates suggest an increase in the number of deaths by AIDS among adolescents.

Young adults and adolescents are at increased risk of contracting HIV partially due to factors intrinsic to this period of life that implies biological and psychological transitions regarding identity definition. Moreover, there are key populations among young people at increased risk because of their most vulnerable conditions. For example, men who have sex with men (MSM), people deprived of their liberty, people who use injectable drugs, and transgender persons. Reaching and sensitizing adolescents and young people from key populations is especially critical, since in most locations they experience additional barriers to access health services. These conditions end up limiting autonomous and well-informed decisions on behalf of the adolescents, making this population especially vulnerable to HIV infection^(5,6).

Antiretroviral therapy (ART) has led to increased survival and improvement in the quality of life of people living with HIV through the development of more potent, less toxic, and simplified dosages over time⁽⁷⁾. Although HIV has progressively become a chronic management condition, at least in countries where people have access to ART, the infection implies lifetime use of medicines and high costs for health systems⁽⁸⁾.

Thus, while the possibility of a cure to HIV remains unlikely in the short and medium-term, all efforts have been focused on prevention

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strategies development. The Joint United Nations Program on HIV/AIDS (UNAIDS) recommends the so-called combined prevention strategy based on behavioral, biomedical, and structural approaches for HIV prevention⁽²⁾.

Pre-exposure prophylaxis (PrEP) is a measure whose effectiveness has been demonstrated in several studies in the last decade, being among the biomedical interventions for a combined prevention strategy. It consists of use of antiretroviral drugs by people not-infected with HIV but considered at high risk for acquiring the infection⁽⁹⁻¹¹⁾. In Brazil, the PrEP clinical protocol was published by the Ministry of Health in May 2017, and was incorporated in the antiretroviral medications offered by the Unified Health System (SUS) in the end of the same year⁽¹²⁾.

In 2018, the PrEP protocol was approved for use in adolescents by U.S. government agency Food and Drug Administration (FDA). Also, the Society for Adolescent Health and Medicine, an international multidisciplinary organization based in the United States of America that addresses adolescent health, released a publication recommending the promotion and use of PrEP among adolescents and young adults^(13,14).

PrEP is considered very promising but still requires broader discussions about the possible developments triggered by its implementation. Besides pharmacological intervention, a dynamic phenomenon that interacts with physiological, psychological, and social dimensions of the involved individuals must be considered⁽¹⁵⁾. Thus, Bioethics can highlight issues regarding PrEP to qualify the discussion, review and renew practices, so public policies that encompass this topic's ethical dimension can be considered.

Thus, this article analyzes the scientific production about ethical issues that emerge with PrEP as a strategy to prevent new HIV infections in the adolescent population.

METHODS

Integrative literature review aimed to map the scientific production on ethical issues about PrEP in adolescents. The integrative review is considered the broadest methodological approach as far as reviews are concerned, allowing the inclusion of experimental and non-experimental studies^(16,17). Therefore, the following guiding question was proposed: What ethical issues emerge from the Pre-Exposure Prophylaxis as an HIV prevention strategy for adolescents? An online bibliographic search was carried out in September 2019 without initial or final time delimitation to answer it, available on the Capes journal portal: Medline, Scopus, and Web of Science. The chosen search key were the terms *Ethic AND PrEP*, and variants. The exclusion criteria were articles addressing clinical studies with PrEP evaluating only its effectiveness, papers not addressing the use of PrEP in adolescents, and publications in other languages such as English, Spanish, and French.

In order to eliminate the bias and increase research rigor, the steps of this review were based on two methods of planning and systematizing the scientific search in a database, synthesizing the results in bibliographic portfolio with the aid of a bibliographic management software^(18,19). The flow of collection and selection of articles is represented in Figure 1 and was adapted by the authors

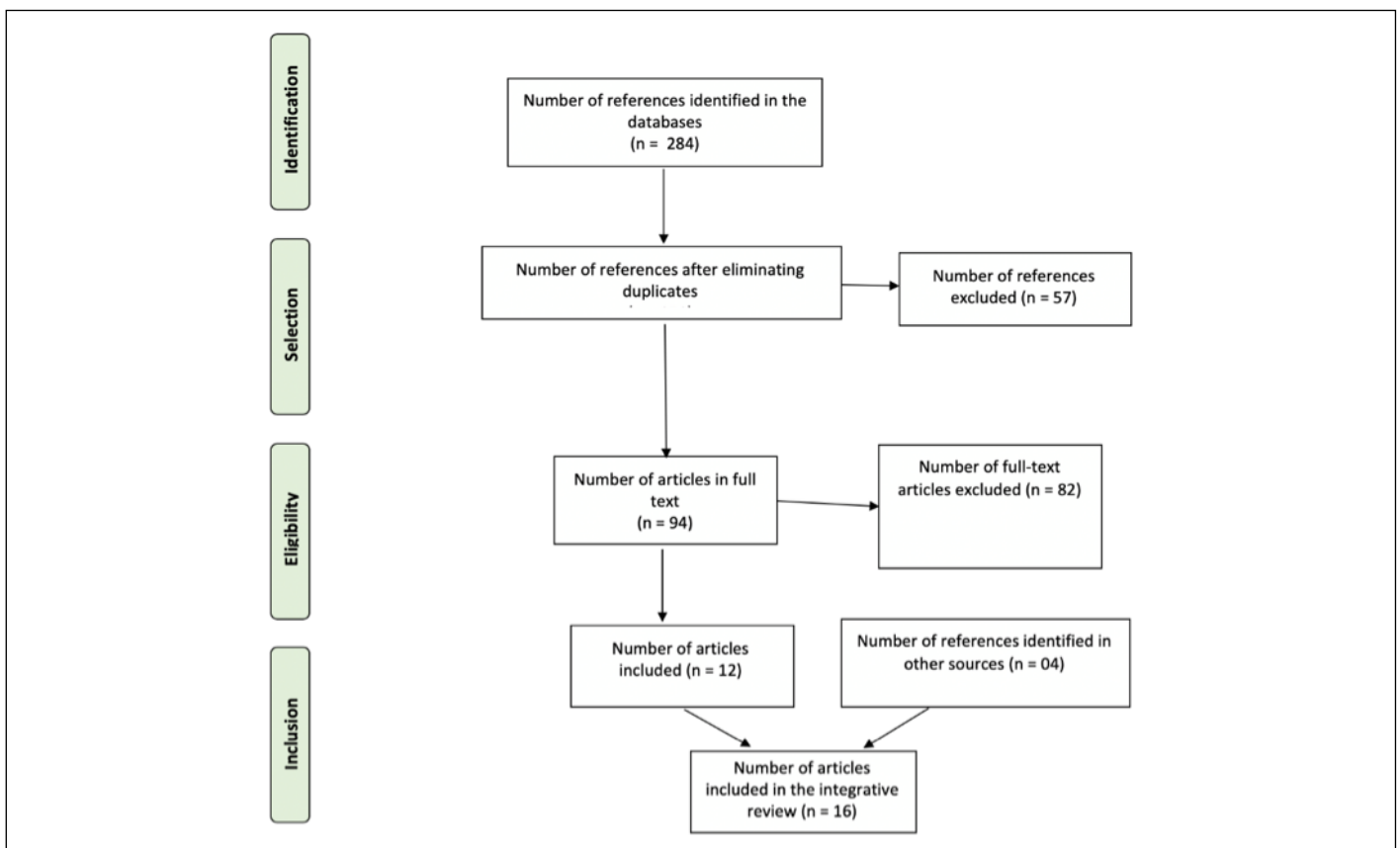


Figure 1 – Flowchart of the selection process, adapted from the PRISMA Group.

from the flowchart recommended by the PRISMA Group⁽²⁰⁾. It was possible to add some papers identified from reverse search in the references of articles found initially. Data were organized into categories, subcategories, and the respective identified ethical problems. Finally, there was a discussion of data and synthesis of the most important elements in an integrated manner. The present study is a research result performed by the authors under the Postgraduate Program in Public Health at the Federal University of Santa Catarina, Florianópolis, Brazil.

RESULTS

Eighty-five references were found in Medline, 116 in Scopus, and 83 in Web of Science, totaling 284 articles. After excluding duplicates, 151 papers were kept. Then, after reading the titles and keywords, 57 were discarded for not fitting the theme, and 94 were kept. After accessing the full text of 94 articles, 82 were discarded for not meeting the pre-established criteria, and 12 were selected for review. Four articles found in a reverse exploratory search in the references of selected papers, totaling 16 references^(13,21-34,35).

The oldest article dated from 2007 and the most recent from 2019. Most publications were from 2017 (four articles). Fifteen articles had the participation of authors from institutions in the United States or co-participation of authors from institutions in Africa. The South African authors participated in two papers and Tanzania's authors in one, along with authors from the United States. Also, one of the selected articles was from Brazil. All of them were published in English.

After the analysis, two categories of ethical issues came out.

Category 1 refers to ethical issues identified in the context of PrEP research, being subcategorized as problems regarding researchers, research institutions and their protocols, research ethics committees (REC), and research participants, as shown in **Chart 1**.

Category 2 refers to issues about adolescents' access to PrEP, being stratified into three subcategories with respective ethical problems identified, as shown in **Chart 2**.

DISCUSSION

The category Ethics in Research shows issues regarding researchers, research institutions and their protocols, research ethics committees, and research participants.

Institutions aimed for ethical review of research around the world first appeared in the 1960s. In Brazil, it dates from 1988, along with the creation of the Brazilian system of ethical review of research, that is, the National System of Research Ethics/National Commission for Research Ethics (CEP/CONEP). The purpose of Research Ethics Committees (REC) is to analyze biomedical investigation protocols related to research participants, while their effectiveness can be evaluated by their protective role, considering the different actors involved⁽³⁶⁾. Although the objective is to qualify research protocols, the system is often seen as time-consuming due to the various bureaucratic procedures required.

Divergences and difficulties related to the REC's position regarding consent for the participation of adolescents in research was an ethical problem identified in 10 out of 16 selected articles^(21-26,28-31).

In most biomedical studies, younger adolescents fall into the category of human beings whose reduced autonomy requires additional protections, which is represented by parental consent in most cases⁽²⁵⁾. As Fisher et al.⁽²³⁾ point out, reluctance derives from many RECs applying regulations that only allow the consent of adolescents, thus dispensing with parental authorization to participate in preventive interventions against HIV in the context of United States research, leading to the exclusion of the underage. For McQueen and Karim⁽²¹⁾, this exclusion implies an important loss of opportunity to assess the efficacy, acceptability and safety of innovative interventions, which could help to identify and solve possible problems specific to this group.

Denying the right to self-consent to adolescents on certain occasions appears to oppose to the ethical discourse on young people's right to participate in trials that will protect them from receiving untested or inappropriate treatments. Thus, this ends up hampering access to evidence-based interventions that are essential to their health and well-being⁽²³⁾.

Chart 1 – Category 1 - Ethics in Research.

Subcategory	Ethical problem
Researchers, research institutions and their protocols	Expectations of ethical and legal difficulties discourage researchers from conducting research with adolescents ⁽²¹⁻²⁶⁾ Lack of research protocols that address the dynamic and intersectional nature of gender identity and sexual orientation of sexual minorities ⁽²⁹⁾
Research ethics committees	Lack of informed consent forms adapted for adolescents, including discussions and opportunities for questions ⁽¹³⁾ Problems in REC positioning regarding consent for adolescents to participate in research ^(21-26,28-31)
Research participants	Difficulties related to adherence of sexual minorities to the research ^(29,34,37)

Chart 2 – Category 2 - Ethical problems regarding access to PrEP.

Subcategory	Ethical problem
Confidentiality	Insecurity about sexual orientation disclosure or HIV serological status ^(13,22,24,33)
Stigmas regarding minorities and HIV	HIV-related stigmas and discrimination, making it difficult to accept and adhere to PrEP ^(28,34) Criminalized homosexual orientation ⁽³³⁾
Qualification/disqualification of prescribers regarding PrEP	Unfamiliarity with Guidelines for the use of PrEP by non-specialist physicians ^(24,26,34)

Furthermore, the researchers' expectation of facing ethical and legal difficulties in research with adolescents was identified in 6 out of the 16 articles evaluated and, to a certain extent, it overlaps with the previous finding⁽²¹⁻²⁶⁾.

Recognizing the need to produce scientific evidence that enables safe use of PrEP in adolescents, in a way that meets the specificities of this group, is a highlight in the analyzed studies. However, the need for research contrasts with the fact that researchers express, formally or informally, a reluctance to carry out studies with the underage population, especially when it comes to sexual minorities, due to real experiences or to anticipated fears regarding approval from the RECs^(20,22,24,25).

Thus, adolescents and the underage are often excluded from biomedical HIV prevention research due to the legal and regulatory complexity of including them in protocols, given the ethical concerns about their vulnerability and ability to make decisions related to the research. Such findings are corroborated by concrete reports, such as the one mentioned by Hosek et al., who point out that starting a PrEP cohort with male adolescents who have sex with men (MSM) required more time and alternative strategies than the same cohort aged over 18 years, which highlights the challenges that this population represents for researchers regarding the feasibility of studies⁽²⁴⁾.

The analysis of selected articles showed a need for ways to carry out research with populations of adolescents in an ethical manner, so that the fear of having studies' protocols approved by REC is not a reason for researchers to give up on working with this population. It can still be questioned whether the ethical difficulties encountered by researchers are to be considered barriers to overcome or inherent prerogatives of scientific research with vulnerable populations.

Likewise, the lack of research protocols suitable for different gender identities and sexual orientations, and the need for an informed consent adapted to adolescents were also identified as ethical problems^(21,23,27).

One of the selected articles pointed to the lack of research protocols that address the dynamic and intersectional nature of gender identity and sexual orientation of sexual minorities⁽²⁷⁾. The authors examined the facilitators and barriers to the participation of transgender adolescents in a study on adherence to PrEP and pointed out that multiple sexual orientation identities endorsed by the participants highlight the need for research projects that incorporate an understanding of how stigma, added to the marginalization of gender identity and sexual orientation, increase the syndemic risk of HIV infection among transgender adolescents.

Syndemic means the adverse interactions between diseases and/or illness with social/environmental condition. Syndemic theory seeks to draw attention to and provide a framework for analyzing these biosocial connections, including their causes and consequences for people's lives and well-being. Thus, it considers that social conditions contribute to the formation, grouping and dissemination of diseases and, by increasing susceptibility and reducing immunological conditions, contributes to their progression⁽³⁷⁾.

Transgender adolescents are identified as key populations as they are particularly vulnerable to HIV infection. Fisher et al.⁽²⁷⁾ point to studies that suggest a prevalence of between 5 and 22% of HIV infection in these groups. In a survey to assess barriers and enablers to transgender teen participation in a PrEP study, the authors report

that less than 5% of subjects interviewed had discussed PrEP with their physicians. Likewise, those who reported open discussions with their physicians about their sexual orientation and HIV prevention were more likely to consider participating in the study. These findings suggest that building trust among transgender adolescents to participate in HIV prevention studies may require efforts to address past histories of gender discrimination and sexual orientation, as well as lack of attention from health professionals. Still, it can be questioned to which extent the lack of trust in researchers and the low adherence to studies can relate to the negligence and mistreatment to which these populations have historically been submitted in most health services.

Similarly, Fletcher et al.⁽³²⁾ point out, in the context of the United States, that African-American girls are disproportionately affected by HIV when compared to other groups of women. The authors note that PrEP education efforts and strategies tailored to the needs of key populations are needed, with a strong emphasis on reducing HIV stigma, which continues to undermine HIV prevention, diagnosis and treatment in these populations. Lack of trust in new prevention technologies and skepticism about participation in research are attributed by the authors to the history of exploitation in medical research in the United States, which occurred with African-American men and women. In this sense, they state that more studies are needed to examine the role of institutional racism and exploitation in attitudes towards the use of PrEP, and how these experiences are perpetuated between generations.

The issue related to the need for informed consent forms adapted for adolescents, including discussions and opportunities for questions, was identified by Fisher et al.⁽¹³⁾ The authors highlighted the importance of adequate sexual health education procedures during recruitment and the process of obtaining consent, as well as clarification on the randomization procedure and on the distinction between research and health care services, to ensure that the agreement is voluntary, without misunderstandings or undue influence.

The same theme was analyzed by Moore et al.⁽³⁰⁾, who described, in the American context, how the lack of laws' clarity regarding the underage's consent to access preventive services or participate in research translates into significant legal barriers to studying PrEP and other prevention strategies in the adolescent population. Hosek et al.⁽²⁴⁾ also observed, in the context of the United States, that only half of the sites eligible to participate in a multicenter study had the PrEP protocol with self-consent approved by their respective RECs. Also, Gilbert et al.⁽²²⁾ examined the process by which researchers applied for REC approval for a PrEP protocol with adolescents' self-consent within the scope of a multi-centered study. The authors emphasize the importance of developing collaborative relationships with REC members, establishing transparent exchanges, providing as much information as possible in advance, and communicating in person.

The complexity of legal, regulatory, and practical barriers to conduct PrEP studies with adolescents is as evident as it is the need for coherent and comprehensive standards for their participation in studies⁽²⁶⁾. Many countries with a high incidence of HIV among young people do not have well-defined laws and policies for HIV prevention services, including PrEP, aimed at this population⁽³⁴⁾. In a survey conducted in Tanzania, Tolley et al.⁽³⁵⁾ listed multiple barriers to the recruitment of adolescent girls, including concerns about

their cognitive ability to give informed consent to participate in the study, and legal and social challenges of recruiting young under-age who are sexually active. Adolescent's access to PrEP without parental consent remains limited or uncertain in many countries.

Mustanski et al.⁽³¹⁾ showed that RECs and researchers faced challenges in defining the extent to which parents should be involved to decide adolescents' participation in biomedical HIV prevention research. On the one hand, parental consent presumes to be in the best interest of their children and, as such, aims to protect them from emotional, psychological, or physical harm resulting from research. On the other hand, requiring some young people to obtain permission from their parents may not be feasible or increase the risk of harm, as in the case of adolescents whose parents disapprove or are unaware of their sexual orientation or behavior. In such cases, RECs could waive parental permission as long as adequate substitute protections are in place and still adhere to ethical principles in research.

According to Nelson et al.⁽²⁸⁾, some advocates of parental consent abdication in HIV surveys with adolescents highlight the ability of older adolescents to make decisions about their own interests similarly to adult decision-making, while others argue that abdication of parental permission shall be limited to circumstances where there is a reasonable argument; for example, that informing parents may result in harm to the adolescent or the parents may not act in the child's best interests.

Pace et al.⁽²⁹⁾ state that, to ensure timely and safe access to PrEP by the under-age, it is essential that policy makers, health professionals, the community and other opinion leaders address this huge gap in HIV prevention efforts. Ethical issues about informed consent for under-age adolescents and their ability to make informed decisions should be further explored, a dialogue should be established with regulatory institutions, and REC should be encouraged to discuss necessary changes in policies in order to ensure that more vulnerable young people have access to research and new HIV prevention actions as they emerge.

In category 2, Ethical problems regarding access to PrEP, the concern with the confidentiality of information after its use was an ethical problem mentioned in four references surveyed^(13,22,24,33). It is noteworthy that such confidentiality issues refer to the use of PrEP as both a prevention strategy and its use in research.

As for confidentiality in the context of care, Arora and Streed Jr⁽³³⁾ report that, once breaches of confidentiality occur more often in relation to HIV-positive people and/or MSM, it is not surprising that concerns regarding this issue continue to be an obstacle to the search service. In this sense, they point out that physicians involved with PrEP should be aware of privacy and confidentiality concerns around the disclosure of MSM behavior and HIV serology. According to Hosek et al.⁽²⁴⁾, in the United States, there is wide regional variation in laws on adolescent access to preventive services, and the eventual need for parental consent can inhibit both access to and adoption of PrEP among adolescents, as consent may force unwanted disclosure of sexual activity and/or orientation.

Fisher et al.⁽¹³⁾ assessed the motivations of 14- to 17-year-old MSM adolescents to participate in a hypothetical study about PrEP and noted concerns about confidentiality, including the adolescents' fear that "others" would know about their participation in the study and their concern that taking a daily pill made parents inquire about

their sexual behavior. Similarly, Gilbert et al.⁽²²⁾ point out that young MSM are afraid to participate in studies that might reveal their sexual orientation and/or sexual activity to their family due to potential reactions of rejection or violence. Therefore, confidentiality is suggested to be reinforced and considered a factor to increase the adherence of adolescents to PrEP.

HIV-related stigma and discrimination hindering acceptance and adherence to PrEP and criminalized homosexual orientation were identified in three of the selected articles^(26,32,33).

In a study that assessed perceptions of PrEP use among African-American adolescent girls, Fletcher et al.⁽³²⁾ point to the potential of PrEP giving them a "bad reputation" and stigma imposed by members from the community, particularly the boys, as one of the concerns reported. The authors also identified barriers to accessing health services in the African-American community studied, which include HIV/AIDS stigma and discrimination, social marginalization, and inadequate access to health information and preventive services. By the same token, Machado et al.⁽²⁶⁾ identified stigma as a potential barrier in the reporting of some adolescents regarding concerns about what people would think when they found out they were using PrEP, as well as the association of its use with sexual behaviors and risk groups. According to Machado et al., young people anticipated the perception of stigma, as living with HIV would mean living with fear and the effects of stigma such as social rejection, discrimination, and violence.

Arora and Streed Jr⁽³³⁾ point out the criminalization of homosexuality in several countries, some with a high prevalence of HIV, as one of the factors that limit an open discussion around PrEP and the risks of HIV. It can be inferred that, even in countries where there is no criminalization of homosexuality, such as in Brazil, the fact that it could be considered a pathology or a deviation from normality by some end up inhibiting discussions over the topic and access to information about HIV prevention in these population groups.

Lack of knowledge about PrEP guidelines by non-specialist physicians was identified as an ethical problem in the context of access to PrEP^(24,26,34).

Machado et al.⁽²⁶⁾ point out that knowledge and confidence in prescribing PrEP remain limited among physicians, which compromises its acceptability among health professionals. Hosek et al.⁽²⁴⁾ report low levels of knowledge about PrEP protocols and guidelines among general practitioners. Taggart et al.⁽³⁴⁾ point out that adolescents' access to PrEP depends on several external factors, including the availability of health professionals who are skilled and trained to prescribe it.

Considering that PrEP should be prescribed for healthy people, the general practitioner has a fundamental role in identifying potential users. For PrEP to reach the most vulnerable adolescents, prescribing professionals must be able to identify potential users, offer medication, and monitor its use.

The aim of this study was to contribute to the discussion of ethical issues that arise with the possibility of using PrEP in adolescents. Although this research has addressed data from up to 2019, which is a limitation for findings, the identified barriers remain potential challenges to the implementation of PrEP as an effective HIV prevention strategy in the adolescent population.

CONCLUSION

HIV infection had its trajectory changed with the institution of ART. It changed from a potentially lethal disease to a chronic management condition when medication is instituted early and used regularly. The use of PrEP as an HIV prevention strategy is an expansion of the use of ART, and it has potential to largely impact the AIDS epidemic.

Research related to adolescents' sexual health must be approached in a way that protocols contemplate the population's specificities, especially sexual minorities. The ethical problems about PrEP in research or interventions' access need to be recognized so that their management makes it possible to expand investigation and assistance policies to meet social needs based on ethical standards.

The issues regarding research ethics and access to PrEP identified in this study represent barriers for adolescents, especially those belonging to groups most exposed to HIV who may benefit from this technology to prevent infection. Therefore, access to PrEP should be enabled to benefit the most vulnerable populations such as adolescents, and further studies on HIV prevention technologies should be ethically stimulated.

ART theoretically makes it possible to end the AIDS epidemic. However, the access to medication, stigmas attached to the disease, and difficulties in implementing effective, long-lasting public policies established in ethical prerogatives remain significant issues to consider when coping with the epidemic, especially among adolescents.

Approval by the Human Research Ethics Committee

Not necessary for this type of scientific study.

Participation of each author

All authors contributed equally to this work.

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Conflict of interests

The authors declare no conflicts of interest.

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