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Unraveling the complex interplay: HIV and male infertility

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Abstract

This review elucidates the complex interplay between HIV infection and male infertility, underscoring the multifaceted mechanisms through which HIV undermines male reproductive health. These mechanisms encompass diminished semen quality, orchitis, hypogonadism, and leukocytospermia. Concurrently, while antiretroviral therapy (ART) is salvific, it may pose additional fertility challenges. The introduction of highly suppressive ART has revolutionized the reproductive landscape for HIV-serodiscordant couples, enabling them to plan for children with minimal risk of HIV transmission, thereby justifying the Undetectable = Untransmissible (U = U) paradigm. Despite these impediments, sperm washing in conjunction with sophisticated assisted reproductive technologies (ARTs), such as in vitro fertilization and intracytoplasmic sperm injection, offers efficacious fertility solutions for HIV-positive males, substantially mitigating the risk of HIV transmission. Psychological and ethical considerations further shape fertility treatment decisions and outcomes within this demographic. Future research should focus on elucidating the long-term effects of ART on male fertility and devising targeted interventions to enhance reproductive health in HIV-positive men.

Keywords: *Male infertility. Antiretroviral therapy. Sperm washing technology.*

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Introduction

AIDS, precipitated by the HIV, constitutes a chronic, pernicious condition that profoundly debilitates the immune system, thereby heightening vulnerability to opportunistic infections and specific malignancies. The advent of antiretroviral therapy (ART) has significantly mitigated AIDS-related mortality and substantially prolonged the life expectancy of those afflicted, effectively transmuting AIDS from a fatal affliction into a manageable chronic ailment[1]. The World Health Organization has articulated ambitious benchmarks to ensure that 90% of individuals achieving viral suppression can sustain a healthy existence. Despite these therapeutic strides, HIV infection persists in exerting deleterious effects on reproductive health, with empirical evidence delineating a robust correlation between HIV and male infertility[2]. HIV can precipitate diminished sperm quality, azoospermia (the absence of sperm), or oligospermia (a reduced sperm count)[3], underscoring the imperative for further investigative endeavors into the potential ramifications of HIV on the male reproductive apparatus.

Infertility constitutes a pervasive global public health predicament, impacting approximately 15% of couples within the reproductive age bracket worldwide[4]. Within this demographic, male infertility is responsible for nearly half of the etiologies, with idiopathic asthenozoospermia – manifesting as diminished sperm motility – emerging as a predominant contributory factor[5]. In recent decades, the incidence of male infertility has exhibited a marked upward trajectory. By 2019, the global prevalence of male infertility had escalated to an estimated 56.53 million individuals, representing a staggering 76.9% increase from 1990. Furthermore, the global average sperm count has plummeted by 62% over the past 45 years, a trend that has elicited extensive concern and scholarly scrutiny[6].

HIV infection exerts a profound impact on reproductive health, with a robust correlation between HIV positivity and male infertility. The prevalence of male infertility among HIV-infected cohorts varies significantly across disparate geographical regions and demographic subsets. Comprehensive global studies have delineated that the incidence of infertility among HIV-positive males ranges from 20% to 50%, a figure substantially higher than the approximately 10% prevalence observed in the general male population[7]. In regions such as Sub-Saharan Africa, where the HIV pandemic is most acutely entrenched, the prevalence of male infertility among HIV-positive individuals can soar to as high as 40%[8].

The elevated prevalence of male infertility among HIV-positive individuals is attributable to multiple interrelated factors, including high rates of sexually transmitted infections (STIs) and concurrent comorbidities that synergistically impair reproductive function. Epidemiological data reveal significant geographical variations in this association, with approximately 30% of HIV-infected males in Western nations (the United States and Europe) experiencing fertility impairments. Asian populations demonstrate a slightly lower but still substantial prevalence of 25%, though regional disparities exist across different countries and healthcare contexts. This reproductive health burden extends beyond biological implications, manifesting in considerable psychosocial consequences through diminished mental health outcomes and strained interpersonal relationships[9]. The evolving landscape of antiretroviral therapy (ART) and improved life expectancy among people living with HIV (PLWH) has intensified the complexity of addressing their reproductive health needs and fertility aspirations. These developments necessitate a paradigm shift in public health approaches to simultaneously manage HIV treatment and fertility preservation. Elucidating the pathophysiological mechanisms linking HIV infection to male infertility is therefore critical for three primary objectives: (1) enhancing clinical management of reproductive health in PLWH, (2) refining evidence-based public health interventions, and (3) mitigating the growing global burden of infertility through targeted prevention strategies.

The impact of HIV on male fertility

HIV has emerged as a significant factor contributing to male infertility, with its influence extending beyond the well-documented immunological and clinical manifestations. The virus's impact on male reproductive health is multifaceted, involving direct and indirect mechanisms that disrupt normal spermatogenesis and sperm function[10]. Among the various pathways through which HIV affects male fertility, three key aspects stand out: impaired semen parameters, orchitis and hypogonadism, and leukocytospermia[3,11-13]. These factors collectively contribute to the complex interplay between HIV infection and male infertility, highlighting the need for a comprehensive understanding of the underlying mechanisms. Specifically, impaired semen parameters are a hallmark of HIV-associated male infertility, characterized by reduced semen volume, decreased sperm

motility, lower sperm concentration, and abnormal sperm morphology. In addition, orchitis and hypogonadism further exacerbate infertility by causing testicular tissue damage and disrupting the hormonal balance necessary for optimal sperm development. Finally, leukocytospermia, marked by an increased number of white blood cells in semen, leads to oxidative stress and DNA damage in sperm, further compromising fertility. Together, these mechanisms underscore the multifaceted nature of HIV's impact on male reproductive health and emphasize the need for targeted interventions to address this growing concern.

Impaired semen parameters

HIV infection has been shown to significantly impact semen quality, leading to alterations in various parameters essential for fertility. Studies have consistently demonstrated that HIV-infected men often exhibit reduced semen volume, decreased sperm motility, lower sperm concentration, and abnormal sperm morphology compared to uninfected individuals[14]. These impairments are attributed to the direct effects of the virus on the male reproductive tract, as well as the systemic immune dysregulation associated with HIV infection. For instance, HIV can infiltrate the testes and epididymis, causing localized inflammation and oxidative stress, which in turn disrupt the normal spermatogenesis process[15].

Orchitis and hypogonadism

HIV infection is frequently associated with orchitis (inflammation of the testes) and hypogonadism (low testosterone levels), both of which have detrimental effects on sperm production and morphology. Orchitis can lead to testicular tissue damage, impairing spermatogenesis and resulting in reduced sperm counts[16]. In addition, hypogonadism, a common complication in HIV-infected individuals, can further exacerbate infertility by disrupting the hormonal balance necessary for optimal sperm development. Low testosterone levels can lead to decreased libido and erectile dysfunction, further complicating the reproductive potential of these individuals[17].

Leukocytospermia

Leukocytospermia, characterized by an increased number of white blood cells in semen, is another common finding in HIV-infected men[18]. The presence of excess leukocytes in semen is associated with elevated levels of reactive oxygen species, which can impair sperm motility and viability[19]. This condition is thought to result from chronic inflammation and immune activation in the male genital tract, driven by persistent HIV infection. The oxidative stress caused by leukocytospermia can lead to DNA damage in sperm, further compromising fertility.

In summary, HIV infection exerts multifaceted adverse effects on male fertility through mechanisms that include impaired semen parameters, orchitis, hypogonadism, and leukocytospermia. Understanding these complex interactions is crucial for developing targeted interventions to mitigate the reproductive health challenges faced by HIV-infected men.

The impact of antiretroviral therapy (ART) on male infertility

Antiretroviral therapy (ART), particularly highly active antiretroviral therapy, has revolutionized the management of HIV/AIDS, significantly improving the life expectancy and quality of life of individuals living with HIV. However, the impact of ART on male fertility remains a subject of considerable interest and concern. While ART effectively suppresses viral replication and restores immune function, it may also exert unintended effects on the male reproductive system[20].

Side effects of ART

One of the primary concerns regarding ART is its potential to negatively impact sperm quality[21]. While certain antiretroviral drugs, particularly nucleoside reverse transcriptase inhibitors (NRTIs) such as stavudine and didanosine, have historically been associated with mitochondrial toxicity, modern ART regimens have evolved to include safer alternatives[22]. Contemporary NRTIs, such as lamivudine and tenofovir, are now widely used due to their reduced mitochondrial toxicity[23]. However, the impact of these newer drugs on male fertility remains a subject of ongoing research.

Lamivudine, for instance, has been shown to have a more favorable safety profile regarding mitochondrial function compared to its predecessors. Similarly, tenofovir, especially in its newer formulations like tenofovir alafenamide, has demonstrated lower toxicity and improved renal and bone safety[24]. Despite these advancements, some studies suggest that tenofovir may still have subtle effects on sperm parameters, although

these are generally less pronounced than those observed with older NRTIs.

ART and semen parameters

The influence of ART on semen parameters is another critical area of investigation. Clinical studies have demonstrated that ART can have variable effects on sperm count, motility, and morphology[21]. Some reports suggest that ART initiation may initially lead to a transient improvement in semen quality, likely due to the overall health benefits and immune restoration. However, over time, many men on long-term ART experience a decline in sperm parameters[25]. This decline is attributed to several factors, including the direct cytotoxic effects of antiretroviral drugs on spermatogenesis, as well as the chronic inflammation and oxidative stress associated with HIV infection, which may persist despite viral suppression[26].

In summary, while ART has undoubtedly transformed the landscape of HIV treatment, its impact on male fertility cannot be overlooked. The potential side effects of ART, particularly mitochondrial toxicity, and its influence on semen parameters highlight the need for careful monitoring and management of reproductive health in men living with HIV. Future research should focus on identifying specific antiretroviral agents that minimize adverse effects on fertility and developing strategies to mitigate these impacts, thereby improving the reproductive outcomes for HIV-infected men.

HIV comorbidities and male infertility

HIV infection is often accompanied by various comorbid conditions that can further exacerbate the risk of male infertility. These comorbidities, including STIs and other infections, play a significant role in the overall reproductive health of HIV-infected men[27]. Understanding the interplay between these comorbid conditions and male infertility is crucial for developing comprehensive strategies to address reproductive health challenges in this population.

Sexually transmitted diseases

HIV-infected individuals are at an increased risk of acquiring other sexually transmitted diseases (STIs), which can have profound effects on male fertility. Common STIs such as gonorrhea, chlamydia, and syphilis can cause inflammation and scarring in the male reproductive tract, leading to obstructive azoospermia or impaired sperm function[28]. For instance, untreated chlamydia infections can result in epididymitis, which may cause irreversible damage to the epididymal tissue and disrupt sperm transport[29]. Similarly, gonorrhea can lead to urethral strictures and impaired sperm motility[30]. The presence of these infections can also contribute to systemic inflammation, further compromising sperm quality and fertility potential.

Other infections

In addition to STIs, other infections commonly found in HIV-infected individuals can also negatively impact male fertility. Human papillomavirus (HPV) infection, for example, has been associated with reduced sperm quality and increased DNA fragmentation[31]. HPV can infect the male genital tract, leading to cellular changes that impair sperm function and viability. Moreover, infections such as chlamydia trachomatis can cause chronic inflammation in the reproductive tract, resulting in decreased sperm motility and concentration. These infections can also lead to oxidative stress, which further damages sperm DNA and reduces fertility[32,33].

In summary, the presence of comorbid conditions, particularly STIs and other infections, significantly contributes to the risk of male infertility in HIV-infected individuals. The interplay between HIV infection and these comorbidities creates a complex environment that challenges reproductive health. Addressing these comorbid conditions through effective screening, treatment, and prevention strategies is essential for improving fertility outcomes in men living with HIV.

Psychosocial factors and HIV-related male infertility

The impact of HIV infection on male fertility extends beyond the physiological and extends into the psychological and social realms. Psychosocial factors, such as anxiety, depression, and reduced self-esteem, play a significant role in shaping the fertility desires and treatment outcomes of HIV-positive men[34]. These factors can influence not only the decision to pursue fertility treatment but also the success and satisfaction associated with such interventions.

Psychological factors

HIV infection is often accompanied by significant psychological distress, including anxiety, depression, and a decline in self-esteem. These psychological

conditions can profoundly affect the fertility desires and treatment outcomes of HIV-positive men. Anxiety and depression, common among individuals living with HIV, can lead to a reduced interest in pursuing parenthood and may negatively impact adherence to fertility treatments[35]. In addition, the stigma associated with HIV infection can further exacerbate feelings of low self-worth and contribute to a reluctance to seek fertility assistance. Studies have shown that psychological interventions, such as counseling and support groups, can help mitigate these effects and improve overall mental health, thereby potentially enhancing fertility treatment outcomes[36].

In summary, psychosocial factors, particularly anxiety, depression, and reduced self-esteem, significantly influence the fertility desires and treatment outcomes of HIV-positive men. Addressing these psychological challenges through comprehensive support and intervention strategies is essential for improving reproductive health outcomes and enhancing the quality of life for individuals living with HIV.

U=U: redefining reproductive possibilities

The paradigm of treatment as prevention (TasP) has revolutionized the field of parenthood for HIV-positive individuals. The concept of "U = U" (Undetectable equals Untransmittable) has emerged as a cornerstone of modern HIV care, fundamentally altering the reproductive landscape for serodiscordant couples. Extensive clinical evidence, including landmark studies such as the PARTNER and HPTN 052 trials, has demonstrated that individuals with an undetectable viral load (< 50 copies/mL) cannot sexually transmit HIV[37]. This principle has profound implications for fertility options and counseling for HIV-positive individuals and their partners.

Evidence from Barreiro et al.

Barreiro et al. (2007) have provided seminal work on the validity of natural conception for HIV-serodiscordant couples. Their study, "Is natural conception a valid option for HIV-serodiscordant couples?" published in Human Reproduction, demonstrated that with effective antiretroviral therapy (ART) achieving sustained viral suppression, the risk of sexual transmission of HIV is negligible[38]. This work supports the U = U principle and its application in clinical practice.

In addition, Barreiro et al. (2006) reviewed reproductive options for HIV-serodiscordant couples, highlighting the role of ART in reducing transmission risks[39]. Their findings underscore the importance of multidisciplinary care, including virologic monitoring and pre-exposure prophylaxis (PrEP) for the HIV-negative partner, in minimizing residual risks.

Furthermore, Barreiro et al. (2006) reported on natural pregnancies in HIV-serodiscordant couples receiving successful antiretroviral therapy. Their study, published in the *Journal of Acquired Immune Deficiency Syndromes*, documented successful pregnancies with no transmission of HIV when the HIV-positive partner maintained an undetectable viral load[40].

Clinical implications

For serodiscordant couples, where one partner is HIV-positive and the other is HIV-negative, the U = U principle significantly reduces the reliance on complex interventions such as sperm washing or assisted reproductive technologies (ARTs). With effective antiretroviral therapy (ART) achieving sustained viral suppression, the risk of sexual transmission of HIV becomes negligible. This allows for the possibility of natural conception with minimal risk, provided that the HIV-positive partner maintains an undetectable viral load and both partners adhere to recommended guidelines[41]. However, it is essential to recognize that while the U = U principle has transformed the approach to fertility, it also introduces new ethical considerations. Healthcare providers must ensure that couples are fully informed about the U = U principle and understand the importance of regular viral load monitoring and adherence to ART. In addition, counseling should address the psychological and social aspects of natural conception in the context of HIV, including stigma reduction and informed decision-making[42].

In summary, the U = U principle has redefined the reproductive possibilities for HIV-positive individuals, offering hope for parenthood with minimal risk of HIV transmission. This advancement underscores the importance of continued research, education, and support to ensure that all individuals living with HIV can achieve their fertility goals safely and ethically.

Fertility treatment options for HIV-positive men

Despite the challenges posed by HIV infection and associated comorbidities, advancements in medical technology have provided HIV-positive men with various fertility treatment options. These options aim to address

the unique reproductive needs of this population while minimizing the risk of HIV transmission to sexual partners and offspring. Two primary approaches have gained significant attention: sperm washing techniques and assisted reproductive technologies (ARTs) such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI)[43,44].

Sperm washing techniques

Sperm washing has emerged as a crucial intervention for HIV-positive men wishing to father children. This technique involves the separation of sperm from seminal plasma, effectively reducing the viral load in the processed sperm. Extensive research has demonstrated that sperm washing can significantly decrease the risk of HIV transmission during assisted reproduction procedures. By meticulously removing HIV particles from the sperm, this method allows for safer fertilization attempts[45]. Studies have shown that when combined with antiretroviral therapy (ART) to suppress viral replication, sperm washing can achieve undetectable viral levels in the washed sperm, thereby minimizing the risk of vertical transmission to the offspring[46].

Assisted reproductive technologies

In addition to sperm washing, assisted reproductive technologies (ARTs) such as IVF and ICSI have been successfully employed in HIV-positive men. IVF involves the fertilization of an egg by sperm outside the body, while ICSI is a more specialized technique where a single sperm is directly injected into an egg. Both methods have shown promising success rates in achieving pregnancies for couples where the male partner is HIV-positive. The combination of sperm washing and ARTs not only enhances the likelihood of successful fertilization but also provides a controlled environment to further reduce the risk of HIV transmission[47,48]. Clinical data indicate that these technologies can achieve pregnancy rates comparable to those in HIV-negative couples, offering hope for HIV-positive men who desire biological parenthood[49].

In summary, HIV-positive men now have viable fertility treatment options that balance the need for reproduction with the imperative to prevent HIV transmission. Sperm washing techniques, coupled with advanced assisted reproductive technologies such as IVF and ICSI, provide a comprehensive approach to achieving successful pregnancies while minimizing the risk of HIV transmission. Continued advancements in these fields hold promise for further improving reproductive outcomes and expanding the options available to HIV-positive individuals. As illustrated in figure 1, HIV-positive men and their partners have several evidence-based pathways to consider when planning for parenthood. These options are carefully designed to balance the need for reproduction with the imperative to minimize the risk of HIV transmission. Figure 1 provides a visual overview of the fertility options available to HIV-serodiscordant couples, highlighting the integration of antiretroviral therapy (ART) and assisted reproductive technologies (ARTs) to achieve successful pregnancies while reducing transmission risks.

Ethical considerations in HIV and male infertility

The intersection of HIV infection and male infertility raises several ethical concerns that must be carefully navigated to ensure the well-being of all parties involved. These concerns primarily revolve around the minimization of HIV transmission risks and the importance of informed consent in fertility treatments.

Risk mitigation

One of the central ethical issues in the context of HIV and fertility treatment is the minimization of HIV transmission risks. Advances in medical technology, such as antiretroviral therapy (ART) and sperm washing techniques, have significantly reduced the likelihood of HIV transmission during fertility treatments. However, these interventions also introduce complex ethical considerations. For instance, while ART can effectively suppress viral replication, ensuring that viral loads remain undetectable throughout the treatment process is crucial[50]. Similarly, sperm washing techniques, although effective in reducing viral loads in sperm, cannot entirely eliminate the risk of transmission[51]. Therefore, healthcare providers must carefully balance the potential benefits of these treatments with the residual risks, ensuring that all measures are taken to protect the health of both the HIV-positive individual and their partners.

Informed consent

Another critical ethical consideration is the importance of informed consent. Ensuring that all parties involved – HIV-positive individuals, their partners, and

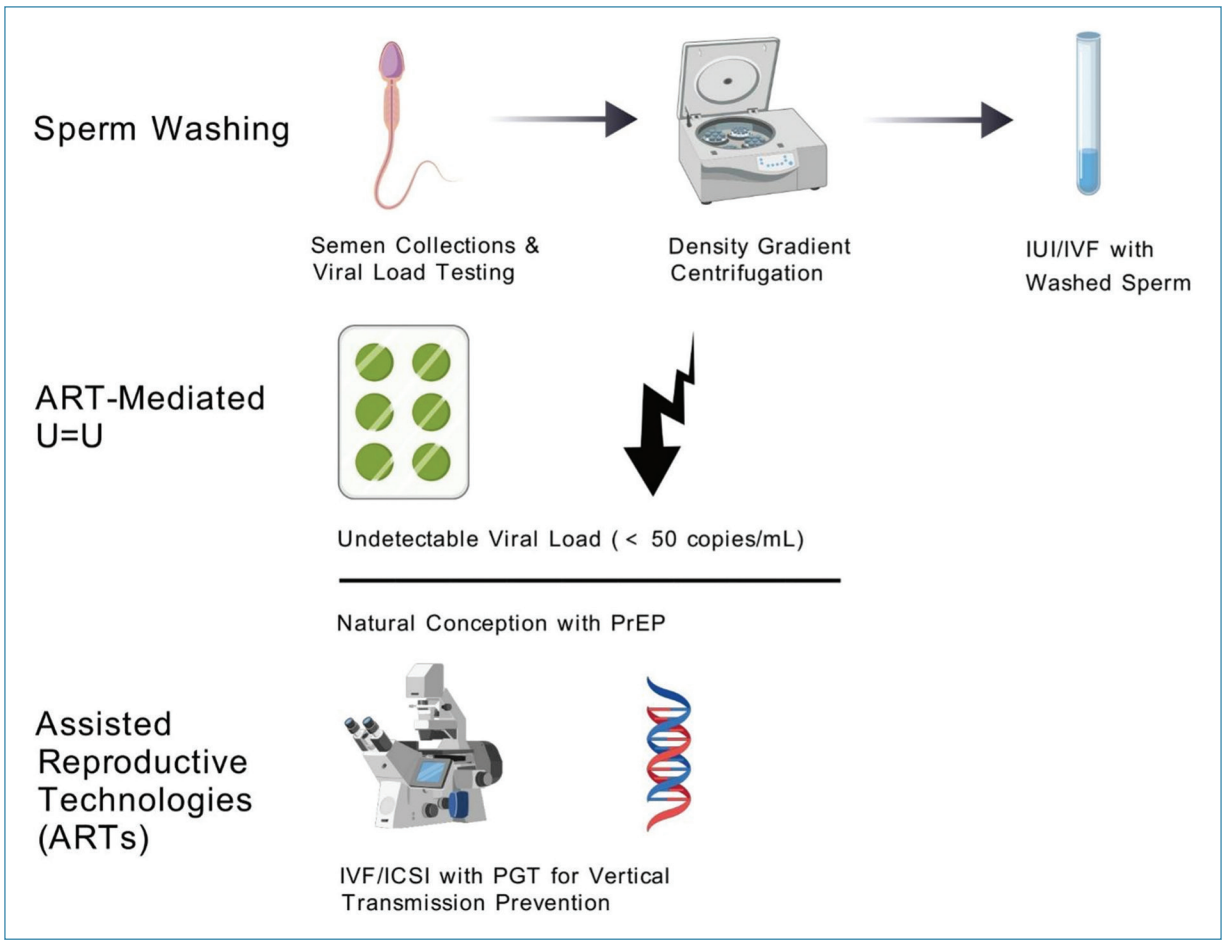

Figure 1. Flowchart of fertility options for HIV-positive men. This flowchart outlines evidence-based pathways for HIV-serodiscordant couples to achieve parenthood. This figure was created using templates and elements from Figdraw (www.figdraw.com).

healthcare providers – are fully aware of the potential risks and benefits of fertility treatments is essential. Informed consent involves providing comprehensive information about the procedures, potential outcomes, and residual risks associated with HIV transmission[42]. This process should be transparent and should allow for open discussion and decision-making. Informed consent is particularly important in the context of HIV, where the stigma and fear surrounding the virus can influence decisions and outcomes[52]. By ensuring that all parties have a clear understanding of the risks and benefits, healthcare providers can support informed decision-making and enhance the ethical integrity of fertility treatments.

In summary, addressing the ethical considerations in HIV and male infertility requires a careful balance between risk mitigation and informed consent. While technological advancements have significantly reduced the risk of HIV transmission during fertility treatments, ensuring that all parties are fully informed and consenting remains a cornerstone of ethical practice. By navigating these ethical challenges thoughtfully, healthcare providers can support the reproductive desires of HIV-positive men while upholding the highest standards of ethical care. In managing the reproductive health of HIV-serodiscordant couples, various strategies are employed to mitigate the risk of HIV transmission. Table 1 provides a comprehensive comparison of these strategies, including TasP, PrEP, timed intercourse, and sperm washing combined with assisted reproductive technologies (ARTs). The table outlines the efficacy, limitations, and clinical evidence supporting each approach, helping healthcare providers and patients make informed decisions (Table 1).

This table concisely synthesizes evidence-based strategies, their outcomes, and practical constraints for managing HIV transmission risks in serodiscordant couples.

Table 1. Comparison of risk mitigation strategies for HIV transmission in serodiscordant couples

Strategy	Efficacy	Limitations	Clinical evidence
Treatment as prevention (TasP)	Sexual transmission risk = 0 when sustained ART achieves viral load < 50 copies/mL (U = U principle).	Requires strict ART adherence and regular viral load monitoring; potential failure due to drug resistance.	37, 53
Pre-exposure prophylaxis (PrEP)	Reduces infection risk > 90% for HIV-negative partners using PrEP (e.g., TDF/FTC).	Requires daily dosing; potential renal toxicity or bone density loss; no protection against other STIs.	54, 55
Timed intercourse (ovulation window)	Reduces cumulative exposure risk by limiting sexual activity to fertile periods.	Requires precise ovulation tracking; limited effectiveness for natural conception.	56, 57
Sperm washing + assisted reproductive technologies (ARTs)	Vertical transmission risk < 1% when combined with ART and sperm processing.	High cost; requires specialized fertility centers; residual viral risk not fully eliminated.	58-60
Combined strategy (TasP + PrEP)	Near-zero transmission risk under dual protection.	Requires long-term adherence by both partners; potential additive drug side effects.	41, 61

U=U: undetectable=untransmittable; ART: antiretroviral therapy; PrEP: pre-exposure prophylaxis; TDF/FTC: tenofovir disoproxil fumarate/emtricitabine.

Conclusion and perspectives

HIV infection significantly impacts male fertility through various mechanisms, including impaired semen parameters, orchitis, hypogonadism, leukocytospermia, and ART side effects. These challenges are compounded by psychosocial factors and ethical considerations, highlighting the complexity of reproductive health in HIV-positive men. While advancements in sperm washing and assisted reproductive technologies offer hope, ongoing research is essential.

Future studies should focus on the long-term effects of ART on male fertility, identifying less toxic antiretroviral agents, and exploring the molecular mechanisms underlying HIV's impact on sperm function. Addressing psychosocial challenges through targeted interventions and ensuring rigorous informed consent processes are also critical. Continued innovation and ethical deliberation will be vital in improving fertility outcomes and quality of life for HIV-positive men.

In summary, a comprehensive approach that integrates medical, psychological, and ethical considerations is necessary to advance our understanding and management of HIV-related male infertility.

Author contributions

X. He provides details of how this author contributed to the article and the reported findings. J. Yin provided critical revisions that contributed to the final version of the manuscript, particularly in the analysis and interpretation of data. K. He contributed to the acquisition of data and performed statistical analysis. H. Yang and Y. Wu assisted in the collection of data and provided input on the manuscript preparation. M. Liu contributed to the design and coordination of the study as well as to the critical revision of the manuscript.

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Conflicts of interest

The authors declare that no conflicts of interest exist.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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