Shaping the Conversation: A Secondary Analysis of Reproductive Decision-Making Among Black Mothers with HIV

Supplementary Issue: Health Disparities in Women

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ABSTRACT: The purpose of this qualitative secondary data analysis is to examine the major influencers on mothers with HIV in their childbearing decisions, as well as how those influencers shape conversations with clinicians and health-care providers regarding HIV treatment and prevention. The original study gained insight into the reproductive decision-making of mothers with HIV. By analyzing a subsample of 15 interviews from an original cohort of 25 participants in the earlier study, three major themes were identified as follows: (1) family members, not health-care providers, influence reproductive decisions; (2) negative attitudes toward subsequent pregnancies are mainly due to HIV transmission; and (3) birth control decisions were predominately supported by family members, while health-care providers were not consulted.

KEYWORDS: HIV, reproductive decision-making, pregnancy, family, health-care providers, birth control

Introduction

According to the Centers for Disease Control (CDC), in the United States alone, more than 1.2 million people are living with HIV infection, of which almost one in seven people are unaware of their infection.1 In 2010, 20% of the estimated 47,500 new HIV infections in the United States were among women, with 84% of these new infections arising from heterosexual contact.2 In addition, Black and Hispanic/Latina women are disproportionately affected by HIV, with Blacks accounting for more new HIV infections, people estimated to be living with HIV disease and HIV-related deaths than any other racial or ethnic group in the United States.3

The number of women with HIV giving birth increased by 30% from 2000 to 2006, and the estimated number of perinatal HIV infections per year continues to decline.4 In addition, Black children were affected at higher rates, with 100,000 infants being born infected with HIV during 2007–2009.4 In light of these statistics, this secondary data analysis was conducted to examine the concerns and trends in reproductive decision-making among women as they pertain to knowledge of their HIV-positive status. Understanding childbearing influencers among HIV-positive Black women is part of a larger, multifaceted approach that is needed to help end the HIV disparities that continue to disproportionately affect Black women.

Thus, the purpose of this secondary data analysis is to examine the major influencers on mothers with HIV in their childbearing decisions, as well as how those influencers shape conversations with clinicians and health-care practitioners regarding HIV treatment and prevention. This differs from the original study that sought to gain insight on the reproductive decision-making of mothers with HIV. By analyzing a subsample of 15 interviews from an original cohort of 25 participants in the earlier study, three major themes were identified as follows: (1) family members, not health-care providers, influence reproductive decisions; (2) negative attitudes toward subsequent pregnancies are mainly due to HIV transmission; and (3) birth control decisions were predominately supported by family members, while health-care providers were not consulted.
women living with HIV globally received effective ART to avoid transmission to their children. In addition, the United States National Institutes of Health’s HIV guidelines recommend that HIV-positive women be offered a planned cesarean delivery when their HIV RNA is \( \geq 1,000 \) copies/mL or above at 34 weeks of gestation. A study by Ohwodo et al conducted at the Lagos HIV Treatment Centre, Nigerian Institute of Medical Research, found that of the 2,381 pregnancies included in the cohort, 1,170 HIV-positive women delivered through a cesarean section, compared with only 651 of their HIV-negative counterparts. For this particular study, the recommended option for delivery for HIV-positive women with a viral load of 10,000 copies/mm\(^3\) was cesarean and, when offered, over 95% of women accepted the cesarean option.

Recent empirical evidence similar to the original study data suggests that health-care providers are not the primary source of information that female patients use to discuss reproductive decision-making. By examining these data, we found that there are still implications for patient-provider interactions and the overall quality of the health care that women receive.

**Theoretical framework.** The purpose of the original study was to gain insight into the reproductive decision-making of mothers with HIV. Fishbein’s theory of reasoned action was the framework that guided the original study, which predicts that behavioral intent is triggered by personal attitudes and subjective norms. Since the publication of that study, the theory has been revised, extended, and is now known more commonly as the theory of planned behavior and the theory of reasoned action.

As Miller states in the article *Childbearing motivations, desires, and intentions: A theoretical framework*, there are many types of childbearing norms with important effects on fertility behavior, including social norms, family size norms, and timing of childbearing. His Traits-Desires-Intentions-Behavior (TDIB) framework, though based off of Fishbein’s theory of reasoned action, was developed to outline the sequence of how childbearing motivations lead to fertility desires, fertility intentions, and, ultimately, childbearing (Fig. 1). This has been utilized in this study as the primary conceptual model.

**HIV-positive women and their childbearing decision influencers.** Previous studies have been conducted to assess what influences women and their decisions to have subsequent children, given their HIV-positive status. It has been found that a person’s HIV status does not diminish their desire to bear children, but rather a person’s HIV status is one of the several factors that are considered when making the decision to have children. Societal ideals and beliefs surrounding motherhood make pregnancy decisions even more complex for HIV-positive women, as having children is still widely viewed as socially and psychologically fulfilling and desirable. This notion is corroborated by Nattabi et al, who discuss how childbearing (fertility, motherhood, and family overall) is important to poorer Black and Latino communities.

According to a study by Bell et al, pressure from family, health workers, and communities to give up on the idea of having children often influence HIV-positive women’s childbearing decisions. In fact, a literature review of the studies in 1991 found that HIV status does not appear to affect women’s decisions to have children. Similar to our review, there was a positive association identified between cultural values and having children that was found among Latinos and African-Americans in the study.

In an analysis on the influencers of reproductive decision-making of HIV-positive individuals, the United States offered two main points of view. In one case, husbands of HIV-positive women were found to provide a strong influence in childbearing decisions, as women viewed having a child as a potential way to strengthen spousal relationships. In contrast, another study found that single African-American mothers had weaker partner influence marked by their independent reproductive decision-making. Nattabi et al attributed these marked differences as the result of changing dynamics of family and society as well as differing sociocultural influences on fertility desires of people of different races in the United States. The contrast between these two studies warrants further research in developing societal norms, racial differences, and the adapting stigmas of childbearing among HIV-positive women in the United States.

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**Figure 1.** Miller’s Traits-Desires-Intentions-Behavior (TDIB) framework depicted as a conceptual model.
Kirshenbaum et al found that HIV-positive women’s attitudes toward pregnancy were influenced by their personal ideas regarding the likelihood of mother-to-child infection. If they desired another pregnancy, then they would potentially consider their child’s risk of infection to be lower and vice versa. Even so, some women have admitted to becoming pregnant not by their desire per se, but by not speaking about their HIV status to their partner and not using condoms. In most of these instances, women feared being abandoned or physically abused by their partner for speaking about using protection or their HIV infection. Previous research by Bell et al found that pressuring a woman to get tested for HIV with her partner, or disclose to her partner her HIV status, might exacerbate domestic violence. A woman’s choice to not disclose her HIV status to her sexual partners oftentimes derives from fear of abandonment, rejection, and violence. With all the aforementioned familial and societal factors influencing HIV-positive women’s thoughts on childbearing, a deeper assessment of how the participants viewed health-care provider’s input is framed below.

How HIV-positive mothers perceive health-care practitioners’ attitudes toward their reproductive behaviors. In a review of the literature regarding HIV infection and childbearing influencers, Steiner et al 2013 found that the public health response to HIV prevention has focused primarily on vertical transmission from mother to infant. Thus, the reproductive desires of HIV-positive women themselves have oftentimes been ignored, discouraged, and stigmatized. Despite medical advances that have made childbearing more feasible, the stigma has persisted and is an underlying driver in reproductive decision-making. HIV-positive women have shown the same desire as HIV-negative women to have children and thus require the appropriate medical services and family planning guidance to ensure positive health outcomes for both mother and child.

A 2007 study by Burr et al showed that a critical factor in a woman’s decision to be tested for HIV is her health-care provider’s recommendation and encouragement. Similarly, health-care provider’s opinions may inadvertently affect a woman’s ability to make her own independent and informed decisions by interjecting their own personal opinions in counseling sessions. Some HIV-positive women have reported a mistrust with health-care providers and their preference in obtaining relevant information from other HIV-positive women. The women in the study felt that health-care workers provided biased information to discourage future pregnancies and were reticent to provide adequate information for them to make informed reproductive decisions on their own.

In a study by Craft et al, medical personnel were rated as most influential among HIV-positive women in pregnancy decisions, with women reporting about discussing matters of pregnancy more often with their physicians (39.2%) than their own family (25.7%). They also found that medical personnel were more influential in decisions to terminate a pregnancy than to become pregnant, though it is unclear whether this is related to the specific medical information shared with patients, or if the personal opinions, beliefs, and values of their medical personnel were what influenced reproductive decisions. These are important factors to consider when counseling, given that some women who are diagnosed with HIV during pregnancy have been reported to have inconsistent or delayed contact with medical providers.

In 2012, a study that examined the reproductive desires in a cohort of 127 HIV-positive women found that 50.6% of those sexually active had spoken with a provider in the past year regarding their contraceptive plans, with approximately 32.1% reporting that they never spoke to a provider. They also found that 44.4% had used sterilization as a means of birth control, with more than half stating that HIV/AIDS was one of the reasons they chose to be sterilized. Of those sterilized, 36.4% reported regret and 18.2% of these women admitted they desired a future pregnancy. This discrepancy shows a major need to counsel HIV-positive women on reversible contraceptive methods. Badell et al called for partnerships between HIV/AIDS services and family planning services, so that they can be responsive to the unique needs of reproductive-age HIV-positive women while providing complete, high-quality care.

HIV-positive women are oftentimes discouraged from having children altogether by their health-care providers. Given the daunting evidence of childbearing influencers and the lack of proper reproductive planning support and education for HIV-positive women, our current analysis of secondary data proceeded to examine our original data set to determine if any similar patterns and beliefs existed in the original study.

Methods
Secondary data analysis can provide new insights into previously conducted research and datasets through the review of unbiased evaluators and new theoretical frameworks. This particular method of analysis was used to review the qualitative dataset from the Reproductive Decision-Making in Mothers with HIV-1 study.

This secondary data analysis focused on a subsample of 15 interviews from an original cohort of 25 participants from a study approved by the Institutional Review Board of the University of Medicine and Dentistry of New Jersey. In addition, original data collection and secondary analysis both complied with the principles of the Declaration of Helsinki. HIV-positive mothers who met the study’s inclusion criteria (HIV positive at least four months postpartum and participant in the larger perinatal HIV natural history study) were approached during pediatric follow-up clinical visits. Of the 32 women originally approached, 25 women with at least one child agreed to participate.

Participation in the study was kept confidential, and participants were asked 29 qualitative questions pertaining to thoughts and attitudes on reproductive behavior given their HIV-positive status. The interviews included questions such as “Of the key people in your life, whose opinion do you value most? Whose opinion do you value second?” and “Have you
thought about or are you concerned about how a pregnancy might affect your health?/Your disease?"

The most complete transcriptions from the original data set were used, and one of the coauthors coded each question. An excel matrix was created to capture the major themes that arose from each question, and all questions were combined with the corresponding responses in its own separate tab. After all questions were coded, the remaining two coauthors analyzed the questions and searched for overarching themes. These themes were then analyzed collectively by the three coauthors and consensus was reached. Several considerations were kept in mind during this secondary data analysis, including the relationship between the researcher and the researched and the marked difference of the primary and secondary analyses.

As per recommendations found in Heaton’s Secondary analysis of qualitative data, steps were taken to ensure the integrity of the research. One coauthor participated in the original data collection and research, while the other two coauthors entered this secondary analysis without any previous background in the study. After interview coding, the purposes of the secondary analysis were identified and refined to ensure a clear and marked difference from the primary analysis. Utilizing Heaton’s recommendations for data analysis and management, new insights were gained and supported validity for the major themes that were identified.

**Results**

The mean educational level of the 25 participants in the original study was 11.3 years (SD = 2.05), with reported monthly income ranging from $0 to $2,100 (M = $454, SD = 459). Twelve individuals (48%) of the sample identified their religion as Baptist, six as Catholic, three as Pentecostal, one as Protestant, one as none, and two as others. Participants had high AIDS knowledge scores on DiClemente’s scale (M = 40.7, SD = 2.3) with scores ranging from 35 to 43. Twenty of the participants were Black, three were White, and two were Hispanic (Table 1).

The mean age of the 15 participants in the current study was 28 years (SD = 4.34). Seven (46%) of the mothers were taking azidothymidine (AZT), an antiretroviral medication used to prevent and treat HIV/AIDS, at the time of their pregnancies and all gave birth to live babies with an average birth weight of 2,852 g (SD = 606.15, range 1,605–3,755 g). Three of the mothers reported injection drug use and all were classified as HIV asymptomatic according to CDC’s 1993 standards at the time of their pregnancies. Thirteen of the participants were Black, one was White, and one was Hispanic (Table 2).

The following major themes emerged from the secondary analysis: (1) family members, not health-care providers, influence reproductive decisions; (2) negative attitudes toward subsequent pregnancies were mainly due to HIV transmission; and (3) birth control decisions were supported by family members, while health-care providers were not consulted.

**Family members as influencers.** Reproductive decisions among Black mothers with HIV in this study were found to be influenced mainly by family members, specifically mothers and grandmothers, but not health-care providers. As listed in Table 3, the opinions of family members such as sisters, fathers, husbands, and partners were also mentioned as persons valued most and second most. The opinions of these family members were elaborated upon in further questioning in the interviews, with the women more often than not agreeing with the perceived opinions of those valued most and second most. For example, when asked how person valued most would feel about them having more children given their HIV status;

"I think my mother would agree with me because we’re a very religious family and as far as we think, you know, God can handle anything. I mean He has taken care of

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Reproductive decision-making among black mothers with HIV

We haven’t talked about it, but I don’t think that she would approve of me having any more kids especially, you know … what’s going to happen to me when I finally do start to get sick and I would be left with the thought of knowing my son will be well taken care of by my mother but it will be a lot of things that I would be missing out on as far as him growing up and a lot of decisions that I probably would have been a part of that I don’t want to miss out on.”

Negative attitudes toward future pregnancies. The women in this study generally had negative attitudes toward subsequent pregnancies and shared that they would have liked more children if they were not HIV positive (Table 4). These negative attitudes were reflected in the possibility of mother-to-child infection and wanting to avoid any possible transmission of the HIV/AIDS virus.

Well I did want to have at least two children … But now that I know I’m HIV-positive I know that I shouldn’t, it’s not wise for me to have another child because that child could come out infected. I was blessed with my son but I don’t know the chances of my next child being infected and I wouldn’t want to subject them to that.”

Concerned that a subsequent child might be HIV infected, the women also shared the benefits and burdens of having more children. When discussing the benefits, most mothers shared sentiments of unconditional love and being able to raise a child while watching them grow in their own ways.

You know that they really love you, you feel good because you know that that’s an honest love. It’s not like having somebody else saying oh yeah I love you, you know pulling your mouth down, but when they do say it you know that they be meaning it because they’re your kids.”

As previously mentioned, most women had desires to have children, independent of their HIV infection.

Oh I love being a mother, I’m happy I’m a mother. I’ve always wanted to be a mother ever since I was 18 but I just didn’t. I was in school and had to wait. I’m glad I’m a mother now. You have someone who’s there for you, who loves you no matter what.”

When it came to the burden of having children, the general consensus was that the only real disadvantages were having the new responsibilities of a child and the occasional discipline.

Birth control decisions. While condoms, birth control pills, abstinence, tubal ligation, diaphragm, and spermicides were all mentioned as forms of birth control (Table 5), none of the women mentioned speaking to their health-care provider about the best option. Most of their opinions on the best form of birth control came from their own thoughts or the ideas of the people they valued.

Well for me, tubal ligation plus using a condom and you can try using some of those gels and stuff to go with the condom to be doubly sure. But if you, in my opinion, if I didn’t have my tubes tied or anything [or anyone else] and they was HIV infected, I wouldn’t advise them to get no abortion just because they baby would come out infected too. No, cause that’s not always the case. You just be taking a life that you don’t necessarily have to take. That’s how I felt, I wasn’t gonna get rid of my baby just cause of that.”

Some women even acknowledged changing their birth control method once learning of their HIV status.

The latex condoms are the only thing that I’ve used during my HIV. Before I found out I was [HIV-positive] I was on the birth control pill and that seemed to be a good form of protection but it had a lot of symptoms, a lot of bodily symptoms like bloating and you know other things that were a disadvantage.”

When prompted if the women would like to elaborate on any topics or provide additional input, some chose to give advice to health-care professionals. They called health-care providers to be supportive and empathetic to the wants of

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<th>Table 4. Interview question regarding subsequent children (N = 15).</th>
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<td>HOW DO YOU FEEL ABOUT HAVING MORE CHILDREN NOW THAT YOU KNOW YOU ARE HIV POSITIVE OR HAVE THE AIDS VIRUS?</td>
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<th>Table 5. Interview question regarding perceived best method of birth control (N = 15).</th>
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<td>WHAT DO YOU THINK IS THE BEST METHOD OF BIRTH CONTROL?</td>
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<td>Abstinence</td>
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<td>Tubal ligation</td>
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<td>Diaphragm</td>
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<td>Spermicide</td>
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HIV-positive women, while providing them with information on both birth control and childbearing options.

“You [the health care provider] should prepare her though. You should tell her you know, I mean if you’re gonna have more children you should have a choice of what you’re gonna do because you could have a healthy baby but then you could have a very sick baby. Tell them that they’re taking a gamble you know, that they’re playing Russian Roulette, they could have a healthy baby and they couldn’t have a healthy baby.”

Concerns about the stigmas that still exist with HIV were brought up as well. Health-care providers were urged to keep that in mind when consulting a patient on the disclosure of their HIV status.

“I got upset because of the fact that they also have to understand it’s still a lot of ignorance out here about the disease. People still have a fear that if they touch the person, get too close to them or this and that, they can catch it. I hear it all the time about oh don’t let them get near you or something like this and I have this greatest fear. That’s why I haven’t told my husband. I have this greatest fear that he’s just gonna disown me and the children. He loves me but this is a thing where it would really put this love to the test. Does he love me enough to understand?”

The results may have differed among the seven women who were elected to not participate in the study; however, qualitative methodology values the lived experience of an individual person.

While the findings of this secondary analysis have limited generalizability due to the nature of a qualitative design, rigor provided by following Heaton’s method of conducting secondary analysis of qualitative data has supported the trustworthiness of these findings.18

Discussion
This secondary data analysis was conducted to examine the concerns and trends in reproductive decision-making among women as they pertain to knowledge of their HIV-positive status. Studies show that Black women are disproportionately affected by HIV, accounting for more new HIV infections, people estimated to be living with HIV disease and HIV-related deaths than any other racial or ethnic group in the United States. It is important to identify childbearing influencers among HIV-positive Black women, and the potential role their health-care practitioners have in influencing such decisions, in order to eliminate the disparities that disproportionately affect Black women.

Additional research is needed to understand to what extent practitioner’s attitudes toward their HIV-positive patient’s reproductive behaviors affect their childbearing decisions. As the results indicated, most HIV-positive mothers valued the opinions of immediate family and friends and did not mention their health-care practitioners. Similar to the findings of Finocchario-Kessler et al,20 this secondary analysis of data demonstrates the lack of influence of health-care practitioners on reproductive decision-making among Black women with HIV. A 2007 cross-sectional survey of 700 HIV-positive women found that 30% of the women had been pregnant before the survey or would consider a pregnancy in the future. Of those women, 48% were never asked by their HIV provider about their reproductive intentions and desires.21

In another study in 2013 of two Los Angeles clinics, two-thirds of the 35 clients who expressed a desire to have a child reported that they had not discussed fertility desires with their providers. Meanwhile, 21 of 35 (60%) clients said that they would like to talk to their provider about their desire to have a child, and 23 of 35 (65%) felt that their provider would most likely support their desire to have a child. In the same study, providers who were surveyed noted the need for specific training in reproductive health services for people living with HIV.2 Comprehensive reproductive health-care trainings for health-care practitioners are important for providing and meeting the fertility needs of individuals with HIV. As the women in the study indicated, there lies a need for providers to exhibit a deeper sense of cultural competency in tandem with understanding the existing stigmas that shape sexual and reproductive decisions.

As mirrored in the results, providers who discourage HIV-positive women from having children may engage in stigmatization. According to Steiner et al, the stigma against individuals with HIV and their desire to have biological children can be compounded by stigmas associated with racism and poverty.16 This stigma continues to discourage pregnancy among HIV-positive individuals, even as medical developments have allowed for minimal transmission of HIV between a parent and a child. In 2014, a systematic review of factors affecting ART initiation, adherence, and retention found that, despite the progress in reducing maternal mortality, HIV-related maternal deaths remain high. This can be attributed to failure in adhering to ART treatments and loss in treatment retention rate. One of the reasons identified was the women’s concern with maintaining discretion regarding their HIV status within their families. This led women to oftentimes keep their HIV infection a secret, thus creating a barrier to ART therapy. Another widely reported influencer of ART therapy was stigma, with a woman’s direct exposure to stigma, or even anticipated stigma being considered as a barrier to successful ART outcomes.23

Furthermore, similar to opinions revealed in this secondary analysis, qualitative data from 20 semistructured in-depth interviews with HIV-positive adolescent and adult women receiving HIV clinical care by Finocchario-Kessler et al24 did not reveal significant differences in childbearing motives when

Amutah et al
Comparing a clinic-based sample of HIV-positive women to at-risk non-HIV-positive women aged 15–24 years from Baltimore. Another study in the Southwestern United States found that out of 212 HIV-positive pregnant women, about 40% had a serodiscordant partner (HIV negative), and 34% had a partner with an unknown HIV status.25 As these studies indicate, the desire to bear children does not diminish with HIV-positive status.

As for birth control decisions, the women in the study did not mention seeking advice from their health-care providers. Despite this, when health-care providers are sought out by their patients for council, they do have the power to positively influence their patients. Cuca’s qualitative study of childbearing decision-making in HIV-positive women living in the San Francisco Bay Area showed that health-care providers have an important influence on decision-making. Similar to data from the participants in our current study, Cuca’s participants had been pregnant at least once since their HIV diagnosis, were Black females, and spoke English.26

The Center for Disease Control/Agency for Toxic Substances and Disease Registry (CDC/ATSDR) Preconception Care Work Group developed and updated their recommendations to improve preconception health in the United States to even include HIV intervention efforts for health-care practitioners.27 In these recommendations, an emphasis is drawn on education and prevention efforts that avert HIV transmission to partners, prevent vertical transmission from mother to child, and improve pregnancy outcomes overall. It is strongly suggested that if HIV infection is identified before conception, timely ART should be administered, and “women (or couples) should be given additional information that can help prevent mother-to-child transmission”.27

Conclusion
This secondary analysis conducted demonstrates that one’s HIV status does not diminish a woman’s childbearing desire. However, our findings suggest a lack of influence of health-care practitioners on reproductive decision-making among Black women with HIV. Through this secondary data analysis and other studies, it is evident that health-care providers need to foster stronger relationships with their clients, especially around reproductive decisions. This work and that of others offer evidence that Black women with HIV can look to their health-care providers for fertility decisions. As previously discussed, several women called upon clinicians and health-care providers to be supportive and empathetic to the wants of HIV-positive women while providing them with accurate information on birth control and childbearing options.

Concurrently, in order for health-care providers to be positive resources for fertility-related desires for Black female patients, health-care providers should be provided with continuing education on the most effective and culturally competent methods to ensure medically accurate conversations with HIV-positive individuals. Although the data analyzed were from the viewpoint of the patient, other studies have suggested a need for health-care practitioners to broaden their education to understand the unique needs of HIV-positive women. It is imperative for clinicians and health-care practitioners to be well equipped in providing accurate and up-to-date information on birth control and childbearing options for HIV-positive women, and specifically for Black women. Provider-initiated communication could be the key to improving birth outcomes and destigmatizing the fertility desires among HIV-positive individuals. Not only should practitioners seek continuing education on improved HIV preconception counseling, but a conscious shift in the medical community to the promotion and accessibility to these trainings should be examined as well.

HIV disproportionately affects Blacks, more so than any other racial/ethnic group in the United States. Additionally, Blacks account for more new HIV infections and are estimated to be living with HIV disease and HIV-related deaths than any other group in the United States. The CDC has identified poverty, lack of access to health care, higher rates of some sexually transmitted infections, lack of awareness of HIV status, and stigma as some of the challenges contributing to the HIV epidemic among Black women. Understanding childbearing influencers among HIV-positive Black women can contribute to a multifaceted approach that can be utilized to help end the HIV disparity affecting Black women.

Further research is warranted to understand the opinions and influencers of HIV-positive individuals today to fill in the gaps of health care. Since the original study, medical advances have greatly reduced HIV transmission from mother to child and calls for updated research on the stigmas that may still exist today. If additional research were to be conducted in this field, a deeper look at the differences, if any, among socio-economic groups and their childbearing influences would provide a deeper look at the trends in patient–client conversations. Similarly, a comparative look at HIV-positive individuals living with and without long-term chronic illnesses and their childbearing desires would also be warranted.

Author Contributions
Conceived and designed the experiments: YW. Analyzed the data: JG, NNA, and YW. Wrote the first draft of the manuscript: JG. Contributed to the writing of the manuscript: NNA, JG, and YW. Agreed with manuscript results and conclusions: NNA, JG, and YW. Jointly developed the structure and arguments for the paper: NNA, JG, and YW. Made critical revisions and approved the final version: NNA, JG, and YW. All the authors reviewed and approved the final manuscript.

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