RESEARCH ARTICLE

Women and HIV: Addressing Contemporary Issues

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Abstract

In 2018, 18.8 million women were living with human immunodeficiency virus (HIV) and accounted for 52% of persons living with HIV worldwide. Despite exceptional gains made in reducing the HIV burden, women remain underrepresented and underserved. As we move toward ending the global HIV epidemic, key issues which impact women's risk for acquiring HIV and the barriers which may prevent effective epidemic control in women will have to be addressed. The risks of women as receptive sex partners, the scarcity of HIV prevention options for women and pregnancy concerns require specific attention. Additionally, as the projected lifespans of women living with HIV increases, our focus must also expand to those issues specific to the aging woman. We must aim to reduce comorbidities and address unintended medication induced effects. To reach and sustain global control of HIV, psychological well-being and the quality of life of women living with HIV should be prioritized. This report investigates a few of the biological, psychological and scientific issues surrounding women that challenge the feasibility and sustainability of an end to the HIV epidemic.

Introduction

In January 1981, acquired immunodeficiency syndrome (AIDS) was first reported among female partners of men with human immunodeficiency virus (HIV) and necessitated a widened surveillance of heterosexual sex partners in the United States. Globally, steady increases in new HIV infections in women, adolescent women, and newborn children called for concern and conventional intervention. As a result, HIV prophylaxis for unborn children was upscaled and has been widely successful. In many areas of the world, the incidence of perinatal transmission of HIV are at historic lows. Pre-exposure prophylaxis (PrEP) for men who have sex with men and transgender women has also had some success. Alongside treatment as prevention, PrEP is setting the pace for ending the global HIV epidemic. Despite these advances, 18.8 million women are currently living with HIV worldwide with 2,000 new infections occurring in women every day.[1] Thirty-eight years after the first US reports, HIV research, interventions, prevention, and education strategies are still falling short of meeting the needs of women.

Given that women are primarily receptors during heterosexual sex and potential vectors during pregnancy and postnatal periods, HIV in women deserves more attention. The inherent and acquired vulnerabilities of women that contribute to increased risk of HIV acquisition are well known. Heterosexual sex remains the most prevalent risk for women, and the route for which HIV prevention for women is most stagnant. Women negotiating condom use with men proved more feasible in the classroom than the bedroom where intimate partner violence against women can be prevalent. The uptake of the female condom is dismal due to design and is out of reach in cost and availability for those interested. Education surrounding non-occupational post exposure prophylaxis does not reach the women it could most benefit. Women lag behind in research advances in prevention measures; society appears to be apathetic to pursuing the unique differences from their male counterparts in regards to research.

Of the health providers women most frequent, many are not trained to detect signs of intimate partner violence or symptoms of acute HIV. Transient providers of women living with HIV fail to critically assess the social and medical drivers of comorbid disease processes and tend to focus instead on symptoms specific to the HIV diagnosis. Stable providers often fail to fully engage women in shared informed decision making at critical stages in their life cycle. Pregnancy is one of those critical times when informed choice is crucial for the woman, her unborn child and perhaps her partner.

The health of women is primarily viewed in the context of sexual and reproductive function. The well-being of the aging woman often receives less attention. More information is needed on the impact of slowed metabolism and altered body fat distribution common in women after age 40. Similar to HIV-negative peers, on average, women living with HIV out survive men. For successful aging and quality of life, meaningful goals for end of life plans should be prioritized for these aging women.

Given the potential burden of psychological and medical disease, the complexities of pregnancy, the evolution of HIV treatments and the paucity of prevention options, we bring these key concepts to attention with the hopes of refocusing and reevaluating our efforts on women living with HIV infection.

1. Barriers to Ending the HIV Epidemic in Women

Although issues such as transportation, access to medications, and housing are cited as traditional barriers to

decreasing HIV incidence, women often face esoteric challenges. Women are biologically and socially vulnerable; these nuances require identification and concentrated efforts to ensure that the gaps in the treatment and prevention of HIV in women are closed. Compared to male counterparts, genotypic women have increased heterosexual risk of HIV acquisition, challenges in prevention mechanisms, and pregnancy treatment complexities.

1.1 Heterosexual risk

In the United States, 86% of all new HIV infections in women are from heterosexual transmissions. Similarly, in sub- Saharan Africa, the main mode of HIV transmission in women of all ages is from unprotected heterosexual sex.[1] Women are biologically at increased risk of contracting HIV from their male partners due to their inherent anatomy. Unlike men in sexual exchange, the woman's role is traditionally as the receptive partner in oral, vaginal and anal sex acts. Receptive sex in comparison to insertive sex is associated with the highest risk of acquiring HIV. It is estimated that the risk of contracting HIV through unprotected vaginal-penile receptive sex is approximately 8/10,000 exposures. The risk of HIV transmission with unprotected receptive penile-anal intercourse is substantially higher and carries an estimated risk of HIV transmission of 138/10,000 exposures.[2] In contrast, oral sex is associated with low to rare risk for HIV transmission (Table 1).[2,3]

Table 1. Estimated per-act risk for acquiring HIV from an infected source, by exposure act

Exposure type	Rate for HIV acquisition per 10,000 exposures
Parenteral	
Blood transfusion	9,250
Needle sharing during injection drug use	63
Percutaneous (needlestick)	23
Sexual	
Receptive anal intercourse	138
Receptive penile-vaginal intercourse	8
Insertive anal intercourse	11
Insertive penile-vaginal intercourse	4
Receptive oral intercourse	Low
Insertive oral intercourse	Low
Other*	
Biting	Negligible
Spitting	Negligible
Throwing body fluids (including semen or saliva)	Negligible
Sharing sex toys	Negligible

*HIV transmission through these exposure routes is technically possible but unlikely and not well documented.

Notes: Factors that may increase the risk of HIV transmission include sexually transmitted diseases, acute and late-stage HIV infection, and high viral load. Factors that may decrease the risk include condom use, male circumcision, antiretroviral treatment, and pre-exposure prophylaxis. None of these factors are accounted for in the estimates presented in the table.

Source: Centers for Disease Control and Prevention[1]

Several sex positions allow the man a dominant stance over the woman. In these postures men can restrict movement, control the rhythm, depth of penetration and duration of activity with or without the woman's cooperation. Resistance to any maneuver can result in injury to the vagina and increase risk of HIV acquisition. Additionally, hormonal surges, menstrual cycles, vaginal pH changes, atrophy and friability can increase the risk of HIV transmission to women during heterosexual sex. In comparison, the risk for men is considerably less. During insertive male to female sex, the outer epithelium of the male genitalia serves as an effective protective barrier. As such, the exposure risk for a male in a single heterosexual act is 4/10,000, which is relatively low.[2]

Men's dominant gender roles and the social and economic inequality of women shape dynamics of relationships. These unbalanced differences may ultimately lead to aggressive or abusive behaviors resulting in intimate partner violence.[4] Oftentimes, these episodes of violence present in various forms including sexual, physical, and psychological harm. According to the World Health Organization (WHO), it is estimated that one in four women will experience violence from an intimate partner in her lifetime. Intimate partner violence is the most common form of violence against women and is reported by 55% of women living with HIV.[5] Many women perceive their HIV positive serostatus to be a direct result of a violent act from an intimate partner. The Nigerian Institute of Medical Research examined the frequency, pattern, and correlates of intimate partner violence among pregnant Nigerian women. The research concluded a high rate of intimate partner violence especially after an HIV diagnosis and during pregnancy.[6]

For two decades, gender-based violence and gender inequity in relationships have been associated with an increased risk of HIV acquisition in women.[7] The intersection of intimate partner violence and HIV include the direct transmission through forced sexual intercourse, transactional sex and failure to negotiate condom use. Intimate partner violence can have physical and emotional repercussions. Many victims of intimate partner violence experience humiliation and guilt but shame is most prevalent and can cause barriers to help seeking. Research indicates that shame contributes to isolation and increases the likelihood that the sexual violence will go unreported which perpetuates the difficulty of preventing and diagnosing HIV in women.[8]

Even when sexual contact is consensual, gender disparities persist in the negotiation of condom use, which is often left up to the woman. The female condom requires less male cooperation compared to the male condom; however, the uptake is lower due to diminished awareness, accessibility, cost and comfort.[9] Compared to the male condom, the female condom is less likely to leak or break during vaginal sex but it has not been investigated in receptive anal sex in women.[10, 11] Literature suggests that the practice of anal sex in women is growing. Recent data show that as many as 40% of HIV infections in U.S. women were attributable to anal sex.[11] As this trend continues, it is imperative that providers include safe anal sex as part of sexual health discussions.

The intimidation of male condom negotiation coupled with the diminished use of female condoms can lead women to look for another mode of contraception. Unfortunately, a woman's intention to avoid unwanted pregnancies may, in fact, put her at a higher risk of HIV acquisition. While hormone-based contraception is a widely used method to prevent pregnancy, its effect on HIV and other sexually transmitted

infections (STIs) has only been recently studied with some controversial outcomes. Some researchers postulate that hormonal contraception may increase susceptibility to HIV infection by progesterone mediated increases in inflammation; however, the data is limited.[12] A recent meta-analysis suggests a 20-50% increased risk of HIV acquisition with depot medroxyprogesterone acetate while other studies show no statistical association.[14,15]

The gaps in medical knowledge highlight the need to explore the mechanisms associated with increased heterosexual HIV transmission risk in women. It is imperative that further interventions are implemented to help women feel safe in reporting traumatic assaults and receive timely care.

1.2 Prevention

Women's knowledge of options for prevention after potential exposure to HIV is critically limited. Post-exposure prophylaxis when used in non-occupational exposures can be an effective measure in preventing HIV transmission. Non-occupational post-exposure prophylaxis (nPEP) is the use of select antiretrovirals to prevent HIV acquisition and can be administered regardless of route of exposure: needle stick, consensual or forced sex. Prophylaxis must be initiated within 72 hours of the sex act and continued for 28 days.[16] nPEP is an option available to all persons with unintentional exposures to HIV; however, the recommended treatment regimen for some women differ from the universally recommended regimen for heterosexual men, men who have sex with men (MSM), or men who have sex with transgender women. For genotypic men, the recommended guidance for nPEP is a two or three tablet regimen.[17] However, for genotypic women of childbearing age, the current recommendations are more complex and may present undue burdens on decision making at a time of extraordinary stress. As multi-tablet regimens and complex dosing schedules are difficult to manage, treatment adherence in women on nPEP may wane over the 28 days necessary for optimal treatment efficacy. This waning increases the risk of HIV transmission and drug resistant mutations. Additionally, the initiation of nPEP in heterosexual women on a large scale has not been intensively studied. Women of all ages rely on data extrapolated from occupational exposures, MSMs, and female sex workers. While nPEP has been a preventive measure since the 1990s, many women remain unaware of the option and the narrow window for effective treatment. Increased awareness of the urgency to initiate nPEP, may encourage those at risk to seek prophylactic treatment after potential exposures.

Whereas nPEP awareness is low, PrEP has become a widely publicized and major public health tool in combating the HIV epidemic. PrEP is intended for use in those at risk of HIV. Most studies show a significantly decreased risk of HIV acquisition when PrEP is used consistently.[18] Recently, the efficacy of PrEP to decrease new HIV diagnoses was compared to another concept, treatment as prevention. Treatment as prevention is the concept of a person living with HIV being on antiretroviral therapy (ART) not only for their personal benefit, but also to prevent further transmissions. A person on ART who achieves an undetectable HIV-1 RNA level has virtually no risk of transmitting the virus; this is also known as "U=U" or "undetectable equals untransmittable".[19] Based on a population model, the impact of PrEP on decreasing HIV incidence in U.S. metropolitan areas was double that of treatment as prevention (5.9% vs 2.9% decrease, respectively).[20]

PrEP uptake has been quite successful in the MSM and transgender

women population. Sixty percent of MSMs are aware of PrEP, but the uptake and awareness in women is low.[21] As a result of the diminished focus on women for PrEP, the primary population included in the clinical trials is men. However, relying on men to represent the entire population that can benefit from PrEP is not plausible. There are distinct sex based differences that affect how a drug is absorbed, distributed, metabolized and excreted. A prime example of this disparity can be seen in the efficacy of PrEP. It takes twenty days to reach maximal concentration in the cervicovaginal tissues, while it only takes 7 days to reach steady-state levels in rectal tissues.[22, 23] Many studies have further highlighted the fact that drug concentrations differ between rectal and vaginal tissues.[24] As a result, women who are at risk for acquiring HIV via vaginal sex require higher adherence in order to reach and maintain the same level of protection as men with the same drug, Truvada®.[25]

Truvada® (emtricitabine/tenofovir disoproxil fumarate) was the first product to receive the indication for PrEP in 2012. Truvada's updated formulation, Descovy® (emtricitabine/tenofovir alafenamide), has been available as an improved option for HIV treatment since 2016. Descovy® is associated with less bone mineral density loss and less kidney injury than Truvada®.[26] Many eagerly anticipated the U.S. Food and Drug Administration (FDA) approving Descovy® for PrEP and the matter came before the FDA in 2019. The major trial that provided the basis for seeking the PrEP indication was the DISCOVER trial. This trial included 5,387 participants from 94 sites: 99% were MSMs and 1% were transgender women.[27] Due to the omission of women in the DISCOVER trial, the panel voted 10-8 against extending the PrEP indication of Descovy® to women. Instead, Descovy was approved for PrEP in the United States for "at-risk adults and adolescents (≥35 kg) to reduce the risk of sexually acquired HIV-1 infection, excluding individuals at risk from receptive vaginal sex".[26] A drug approval that excludes men or women is rare, especially when it does not treat a sex specific condition. The FDA highlighted the disservice of the exclusion of women from this major trial and the attempt to extrapolate the data from men and transgender women.

Multiple attempts to deliver antiretrovirals as PrEP in vaginal rings and other formulations are ongoing but to date have been unsuccessful due to differences in efficacy, drug concentrations and absorption into vaginal epithelial cells.[28] It is important to develop prevention tools which factor in specific sex based differences and give women the power to make decisions regarding their sexual health and family planning.

1.3 Pregnancy

Women's innate barriers to ending the HIV epidemic are more pronounced during pregnancy. Pregnant women have physiological and sociological vulnerabilities which may lead to the transmission and acquisition of HIV. Elevated hormones, untreated sexually transmitted infections and changes in the vaginal microbiome cause cervical inflammation which leads to higher rates of acquisition. The aforementioned barriers combined with nutritional deficiency, lowered immunity, intimate partner violence, decreased condom use, and socio-economic adversity, add to the complexity of ending the HIV epidemic in this population. Existing safety data suggest that PrEP should be offered to at risk women during pregnancy and breastfeeding.[29] The option should be a discussion between the prospective mother and her healthcare provider as it could be an integral part in combating the epidemic.

Once pregnant, women living with HIV endure additional challenges including antiretroviral treatment choice and fear of pre- and postpartum transmission. During this time, women often require adjustment of their ART due to the changes in the volume of distribution and pharmacokinetics, usually resulting in multiple tablets. Despite the plethora of antiretrovirals, the U.S. Department of Health and Human Services (DHHS) guidelines do not include any preferred single tablet regimens that can be administered throughout all trimesters. The single tablet regimen containing dolutegravir (DTG), lamivudine and abacavir is only recommended after the first trimester. There are other single tablet regimens available to pregnant women living with HIV, however they are considered alternative treatments according to the DHHS guidelines.[30]

Dolutegravir was previously a preferred medication for pregnant women living with HIV. However, some countries no longer recommend the use of DTG in women of child bearing age or during the first trimester due to a possible increased risk of neural tube defects.[31] This recommendation stems from a study conducted in Botswana in 2018 showing 0.94% incidence of neural tube defects in women taking DTG at the time of conception compared to 0.10% in standard of care regimens.[32] Expanded studies have demonstrated that the risk of neural tube defects is less than previously published, although still increased.[32,33] As a result of the updated data, high barrier to resistance, potency, small tablet size and tolerability of dolutegravir, the WHO has taken a slightly different stance and suggests that the benefits may outweigh the risks.[34] Although recommendations vary for DTG use during pregnancy, raltegravir has extensive data during pregnancy. Raltegravir can quickly reduce HIV-1 RNA levels but requires twice daily dosing. Due to changes in volume of distribution and insufficient pharmacokinetic data, high dose (HD) raltegravir, which is dosed once daily, is not recommended during pregnancy.[35,36] This yields a potentially more complicated ART regimen with multiple tablets; unfortunately, this is not the only example.

Darunavir (DRV) also requires complex dosing during pregnancy. The dosing change is required due to decreased levels of the pharmacokinetic boosters (cobicistat or ritonavir) in later trimesters. DRV is dosed twice daily during pregnancy and the coformulation with cobicistat is not recommended.[35] Therefore, what could normally be taken as one tablet per day (DRV/cobicistat) is now required to be four tablets per day (DRV and ritonavir twice daily) during pregnancy. These four tablets are only one component of a fully active ART regimen. The pharmacokinetic changes and increased pill burden lend to risk of non-adherence, viral rebound and further propagation of HIV transmission.

Medication changes can be complicated during pregnancy. For example, Complera® (rilpivirine, emtricitabine, tenofovir disoproxil fumarate) is one of the few single tablet regimens approved as an alternative regimen during pregnancy. It does not contain an integrase strand transfer inhibitor, so it can be used in all trimesters. Common acid reflux medicines can decrease the levels of rilpivirine when administered together. Therefore, Complera® is not generally recommended for pregnant women who experience acid reflux, which is very common during pregnancy. It also is only approved in patients with an HIV-1 RNA level less than 100,000 copies/mL.[31] This limitation presents a barrier for newly diagnosed patients or those returning to care with high HIV-1 RNA levels requesting a single tablet regimen. Complera®, along with many other antiretrovirals, requires co-administration with food, which can be

difficult if the woman is experiencing gastrointestinal symptoms. Pregnant women must not only overcome the symptomatology of pregnancy in general, but must also tolerate complex antiretroviral regimens.

Without ART, mother-to-child-transmission rates are between 15-35%; however, with appropriate treatment and care, vertical transmission can be prevented altogether.[37] It is now standard of care to screen a pregnant woman for HIV upon entering into prenatal care as well as during the third trimester.[38] It is universally recommended that all pregnant women living with HIV receive ART. Just as recommendations for ART regimens during pregnancy differ, a woman's geographic location may determine the recommendations they receive regarding breastfeeding. There are many benefits to breastfeeding for both the mother and the child. However, in postpartum women living with HIV, breastfeeding yields yet another concern for transmission of HIV to their newborn child. Pregnant women are a vulnerable population and there is a gap in the data regarding ART use and safety during pregnancy and lactation. There are no antiretrovirals that are FDA-approved in breastfeeding; however there have been some studies to show that certain drugs appear to be safe.[39] The WHO suggests that breastfeeding recommendations be left to the country's respective national or subnational health organization. It may be more beneficial for women living with HIV in resource limited countries to breastfeed when diarrhea and malnutrition present a higher risk of mortality to the newborn infant than risk of HIV acquisition.[40] To date, the DHHS guidelines state that breastfeeding is not recommended in the United States.[39] Restricting breastfeeding may cause psychological distress on a mother as breastfeeding is a cherished bonding activity and a perceived maternal responsibility.[41]

Women are already predisposed to additional emotional stress during pregnancy, especially when their pregnancy coincides with a new diagnosis of HIV.[42] It is not unusual for a woman to experience guilt, shame and fear, which may lead to difficulties in disclosure of HIV status, isolation, medication nonadherence and poor attendance to provider appointments. This situation can cause undue anxiety and depression when a woman feels unable to safely address her concerns. There are many forms of coping with HIV, however, there is very little research on how women diagnosed during pregnancy internalize their diagnoses. Depression and inadequate coping skills among pregnant HIV positive women have the potential to affect psychological well-being, quality of life and clinical outcomes. It is essential for healthcare professionals to be aware of, and address, these psychological barriers.[43]

2. Improving the Quality of Life

In geographical locations where women have low socioeconomic status, education and participation in society, there tends to be a poor quality of life and a higher rate of HIV incidence.[44] Reductions in HIV incidence have been associated with educating and empowering women. Women living with HIV possess a unique challenge in addressing quality of life issues, given their psychosocial susceptibilities and hormonal changes which are compounded by the aging process and other medical comorbidities. Women of all ages and backgrounds should be incorporated into the decision making process for their care, HIV elimination initiatives, and women-specific clinical trials to better address a woman's needs from cradle to grave.

2.1 Aging

With the advent of efficacious ART, the life expectancy of people living with HIV

has increased. In 2017, 17% of new HIV infections were in people over the age of 50 and 70% of people living with HIV will be over the age of 50 by 2020.[45,46] Most of the current medical and prevention literature on HIV in older adults focuses on the aging population who are diagnosed with HIV at a younger age. Information for older partners or for those who receive their initial diagnosis at an older age is less available. Older women living with HIV are often an overlooked group. As such, health information pertinent to women at this life stage does not often include the impact of HIV as a comorbid or primary disease process. Previously, health and wellness were defined by sexual and reproductive function. However, after the age of 50, women are assumed to be less sexually active and therefore may not engage in conversations about healthy sex with their providers. Providers often do not have a high level of suspicion of STIs or unsafe sex activity among older women. Consequently, older women are often under-screened for STIs and diagnosed later in the progression of HIV infection. Late HIV diagnosis reduces the likelihood of 12 month survival to 86% in individuals 50-59 years of age. This outcome worsens with increased age; late diagnoses are more likely to be associated with increased comorbidities and complications.[13] Engaging older women in conversations about sexual health will help promote prevention and early detection which is necessary to curtail the HIV epidemic.

Menopause is an inevitable stage of aging for women. Women living with HIV may experience earlier onset of menopause; the mechanism of this prematurity remains unclear.[47] Primary care providers may be reluctant to treat HIV positive women with hormone therapy due to the lack of understanding about ART and hormone drug-drug interactions, the impact of hormones on HIV, and the changes in immune function during menopause. For some women who no longer desire or fear pregnancy, condom use may become less of a priority. For others, secondary to the decrease in natural lubrication, common in menopause, condom use may be an uncomfortable option. Other vaginally-inserted devices may have similar effects. Future health promotion strategies should include alternative modes of HIV and STI protection for this unique population of women.

Studies have shown that even when controlled, HIV infection increases non-AIDS related co-morbidities and induces chronic inflammation, both of which are factors that accelerate aging.[48] With the exception of the African region, where the number one cause of death in women is related to HIV, cardiovascular disease (CVD) is the primary cause of death in women across the globe.[49,50] The burden of heart and HIV diseases among women is significant, their impact on morbidity and mortality of women should no longer be discussed in isolation. Similar to HIV clinical trials, research driving the developments of treatment and prevention strategies in CVD in women are mostly derived from predictors and outcomes in men. As a result, there is a paucity of evidence of the mechanisms by which cardiovascular health uniquely affects women. Even less understood are the additional CVD risks for women living with HIV. Adding to this widening void of knowledge is new evidence suggesting an association of weight gain and second generation integrase strand transfer inhibitors (INSTIs) that is more pronounced than the previous generation. While weight gain associated with this class of medicines was not elucidated in early investigational drug studies, post marketing reports of substantial weight gain are increasing. The average

amount of INSTI-associated weight gain is relatively small. However, as demonstrated in a poster presentation at the 2019 American Conference for the Treatment of HIV in Miami, FL, excesses of 13 kilograms of weight gain can occur.[51] Investigations of the additional impact of INSTI-associated weight gain on CVD risks in women living with HIV are ongoing and essential. Voiced concerns of weight gain from women taking certain antiretroviral agents should not be ignored. Provider assisted realistic weight management, including offering a regimen change, are needed and should be encouraged.

Aging women living with HIV are also at increased risk of cognitive degeneration. HIV-associated dementia (HAD) and HIV-associated neuro-cognitive disease (HAND) can result in poor compliance with ART. Studies of cognitive health have shown that early initiation of behavioral interventions are successful at delaying cognitive regression; however, more specific studies in HAD and HAND are needed.[52] With increased life spans, providers must anticipate the subtle and overt sequelae of aging. High quality care for older women living with HIV should include a multi-disciplinary approach for providing medical, behavior and social support.

2.2 Informed Decisions

In a policy briefing from the Global Access Project, representatives pleaded that women should be provided "treatment literacy" and should be able to make informed decisions about their treatment options.[53] Prior to the era of highly active antiretrovirals, treatment options were limited and selection of ART promoted little conversation between patient and provider. Today, preferred and alternate regimens are extremely efficacious and only small nuances separate contemporary antiretrovirals from one another. This situation creates an opportunity for providers to involve patients in the decision-making process. Studies have shown the positive effect of shared decision making in HIV care. Patients engaged in regimen selection exhibit higher medication adherence rates than individuals who prefer their provider to direct treatment or those who prefer to dictate their own medical decisions.[54]

Providers must remember to take into consideration the person in front of them - their lifestyle, their apprehensions, and their health goals. While guidelines unanimously recommend the use of INSTIs, this class may not be the best option for those who are particularly concerned about weight gain. Ignoring such factors places the patient at risk of self-discontinuing their ART. It is no longer appropriate to expect patients to accept avoidable side effects that can affect their daily lives. Shared decision making to find the best regimen for the individual is paramount.

Another example that requires increased patient-provider discussion is pre, peri and postnatal HIV care. Pregnancy can be a wonderful and hopeful time for a woman, yet it can also elicit fear and increased vulnerability. This paradigm requires intensive discussions to achieve the best care for both mother and child. As discussed previously, oftentimes pregnant women require a temporary increase in pill burden due to changes in volume of distribution. Recent data have reclassified dolutegravir as no longer preferred in women of child-bearing age. This controversial decision limited choices of ART globally and lacked involvement of women directly affected. Some women felt that they deserved the option to use dolutegravir particularly due to the benefits (tolerability, small tablet size, potency, and increased barrier to resistance) outweighing the risk of neural tube defects.[53] Providers are urged to discuss contraceptive methods with women

of child bearing age, but simply being of child bearing age should not preclude a woman from taking dolutegravir.

The Global Access Project raises the point that there was previously a similar concern with an older antiretroviral causing potential neural tube defects. This concern led to a switch in recommendations to a less tolerable, and more toxic, antiretroviral.[53] This risk was later found to be minimal.[55] Perhaps something similar will occur with dolutegravir dosing recommendations during pregnancy. While it is important to acknowledge and respond to new information, we must also consider how it may ultimately affect a woman and afford her an audible voice in matters that concern her health.

Estimating the risks and benefits of medications requires research. Pregnant women are a vulnerable population and therefore difficult to enroll in clinical trials. Thus, it can be difficult to formulate guidelines and standard of care for this specific population, especially regarding breastfeeding. As previously discussed, breastfeeding is not recommended in the United States as it presents the potential for transmissibility of HIV. Data from Botswana indicated that the incidence of mother-to-child-transmission during breastfeeding is 1.1%, even in the setting of maternal viral suppression.[56] Unfortunately, this finding will likely prevent "U=U" from being expanded to breastfeeding. Decisions and recommendations on breastfeeding are determined at the local and sub-local levels but, theoretically, should also be an informed discussion between the mother and healthcare provider in all situations. Incorporating women into the conversation empowers them to take an active role in managing their health and improving their quality of life.

Discussion

As HIV is now a chronic condition, focus must shift. In the early epidemic, the primary goal in HIV care was to limit mortality, toxicities and side effects. Fortunately, advancements have diminished the previous impediments of ART. Specific barriers and vulnerabilities still impede ending the HIV epidemic in women. Some of these barriers can be addressed and overcome, while many vulnerabilities are non-modifiable.

Although we address HIV infection among women as a singular group, we are keenly aware of the heterogeneity of the epidemic within this subpopulation. For example, there may be extensive variability in access to contemporary medications among those living in a resource abundant versus resource limited country. However, care must be taken to not equate the economic health of a nation to a woman's ability to achieve viral suppression. For example, Botswana, a resource limited country, has achieved greater than 90% viral suppression among those on ART.[57]

When considering the development and implementation of programs and policies to combat the HIV epidemic, region specific realities in culture, religion, governmental infrastructure and resources must be considered. Understanding the influence of these realities on women's health is vital to help achieve maximum impact in overcoming barriers and improving quality of life. As women make up nearly half of the global population of those living with HIV, equal research, representation, and respect is justified.

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