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A Systematic Review on the Association Between Hormonal Contraception and Antiretroviral Therapy in HIV-Positive Women

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Abstract

Providing women with safe and effective means of contraception is important when assessing women's health needs. Women with HIV can spread the disease to their baby through vertical transmission but this may be curtailed by the use of antiretroviral therapy. Additionally, providing women who have HIV with safe contraception options improves women's overall health. However, there is concern that some hormonal contraceptives may affect the metabolism with certain antiretrovirals. A literature search was conducted using the databases Medline, PubMed, and Global Health. Articles meeting the inclusion criteria were then assessed. Thirteen peer-reviewed articles were identified. Several studies indicated that there were no relevant interactions for measures of disease progression, disease transmission and tolerability. However, some articles suggested that there were safer means of contraception that should be made available to women on antiretroviral therapy. Efavirenz was shown to induce adverse contraception efficacy when co-administered. Collectively, hormonal contraception is widely safe for women using antiretroviral therapy. HIV positive women should be educated on the risks associated with hormonal contraception as well as be provided with options that fit their reproductive health needs.

A SYSTEMATIC REVIEW ON THE ASSOCIATION BETWEEN HORMONAL CONTRACEPTION AND ANTIRETROVIRAL THERAPY IN HIV-POSITIVE WOMEN

by

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Author's Statement Page

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Introduction/ Purpose of the Study

Human Immunodeficiency Virus, commonly known as HIV, is a global epidemic, effecting over 36.7 million worldwide (WHO 2017). HIV can affect both women and men alike, additionally there is also risk for vertical transmission from mother to baby, especially in developing countries (Malunguza, Hove-Musekwa, & Mukandavire, 2017). Developing countries have limited access to perinatal and antiretroviral care, which may explain higher rates of vertical transmission (Malunguza et al., 2017). Although there has been a decline in death and birth rates due to HIV, many countries, such as those in sub-Saharan African are expecting exponential population growth within the next 30 years. With this increase in population, more people may be affected by HIV/AIDS than ever before. AIDS education exists in many of these countries, however, there is a lack of attention in maternal health services (Malunguza et al., 2017). With the global burden of HIV in these countries being the highest around the world, there is a desperate need for increased women's health services (WHO, 2017). Unintended pregnancies among HIV-positive women may have consequences for maternal morbidity and vertical transmission (Patel et al., 2015). Researchers explain that the most important component of good contraception in public health is the availability of choices (Stringer et al., 2007). Additionally, the use of contraceptives can decrease the prevalence of maternal morbidity and mortality (Tittle, Bull, Boffito, & Nwokolo, 2015). Women with HIV often use separate medications to prevent disease progression (antiretroviral therapy) and disease transmission (birth control). Almost 50% of those diagnosed with HIV use some form of antiretroviral therapy (WHO 2017). Additionally, the WHO states that up to 77% of women who are HIV-positive engage in ART (WHO 2017). Since the use of antiretroviral therapy is

increasing worldwide, assessing the impact of its use with hormonal contraceptives will be beneficial when addressing disease transmissibility of HIV-positive women on therapy (Kourtis et al., 2017).

It is important to examine the concurrent use of hormonal contraceptives for birth control, and antiretroviral therapy in women with HIV (Malunguza et al., 2017). There has been some concern with the efficacy of hormonal contraceptives and antiretroviral therapy when co-administered. Some pharmacokinetic data suggests potential interactions between the two medications (Kourtis et al., 2017). These interactions are a key concern for public health officials in regards to HIV, as disease transmission and progression are key concerns. Because antiretroviral therapy and hormonal contraceptives have common metabolic pathways, the blood levels of both hormonal contraceptives and antiretrovirals may be affected by their concurrent use (Landolt et al., 2013). Interactions between these drugs could potentially lead to decreased contraceptive effectiveness, therefore increasing the change of vertical transmission. Additionally, a decrease in ART effectiveness could lead to increased disease progression and horizontal transmission (Nanda et al., 2017). Enhanced toxicity is also a concern when assessing the relationships between these drugs (Landolt et al., 2013). It is important to provide women living with HIV with safe and effective contraception to prevent unintended pregnancy and decrease the incidence of maternal-to-child HIV-1 transmission (Day et al., 2014). Few studies examining the relationship between hormonal contraceptives and antiretrovirals have been conducted and studies have shown conflicting results (Landolt et al., 2013). Studies of interactions have been limited by short follow up times, inconclusive end points, small sample sizes and uninfected populations (Pyra et al., 2015). Since data in the field is limited, contraception

options for HIV-positive women receiving antiretroviral therapy is also limited (Watts et al., 2008). The primary purpose of this study is to provide a systematic review of research articles to determine the potential effects on hormonal efficacy and disease progression from concurrent use of hormonal contraceptives and antiretroviral therapy in HIV-positive women.

Literature Review

In 2015, there were over 36.7 million people living with HIV (WHO, 2016). Additionally, sub-Saharan Africa bears the greatest global burden of HIV/AIDS, which account for 70% of all HIV infections. Nearly 13 million women in Sub-Saharan Africa live with AIDS (Patel et al., 2015). HIV is spread through certain bodily fluids, such as breast milk, blood, semen, and vaginal secretions (CDC 2016). HIV targets the body's immune system, more specifically CD4+ cells (CDC 2016). Although there is no cure for HIV, it can be managed with the use of Antiretroviral therapy (ART). ART was introduced in the mid-1990s, and those who are infected have greater chances to live longer lives, and decrease the odds of transmission to others. Because no cure currently exists for HIV, prevention and decreasing the transmission of the disease is a concern among health professionals.

The proportion of HIV and AIDS cases among women continues to grow world-wide, with women accounting for over half of HIV-infected adults (Luque et al., 2015). Over ninety percent of the HIV positive women in sub-Saharan Africa are between 15 and 49 years of age (Day et al., 2014). Because these woman can be considered as being in child bearing age, it is important to address the reproductive needs of women living with the disease. Condom use is highly recommended for HIV-infected women, but this form of contraception is not always reliable or accessible, so therefore healthcare professionals encourage women to use additional forms of contraception (Leticee, Viard, Yamgnane, Karmochkine, & Benachi, 2012). Additionally, the availability of contraception among HIV-Infected women who desire to have it has been a key strategy in preventing pediatric AIDS, (Stringer et al., 2007).

Hormonal contraceptives are steroid hormones that serves as birth control (Nanda et al., 2017). Hormonal contraceptives, most of which contain some form of progestin, a synthetic progestogen that mimics progesterone alone or combined with estrogen, are widely used by women all over the globe, to prevent pregnancy and/or to alleviate hormonal imbalances (CDC 2016, Luque et al., 2015). Globally, hormonal contraceptives are the most widely used contraception method among women (Kourtis et al., 2017). Women in developing countries experience a high prevalence HIV (more than 95% of HIV infections are in developing countries), and these women tend to use contraceptive methods such as depot medroxyprogesterone (DMPA), a hormonal contraceptive (WHO 2016, Luque et al., 2015). Hormonal contraceptives are metabolized via cytochrome P450 enzyme system in the liver, especially via CYP3A4 (Kancheva Landolt et al., 2016). The metabolism of hormonal contraceptives allows the drug to be broken down by the body and to carry out its hormonal purpose (Landolt et al., 2013). Globally, 14% of women use hormonal contraception (Mitchell, 2004). A study conducted by Nieves and associates concluded that 54% of women used a form of hormonal contraception as a means of birth control for heterosexual couples (Nieves et al., 2015).

Treatment of HIV through antiretroviral therapy usually contains a combination of drugs, which target different stages of the HIV lifecycle (Tittle et al., 2015). Antiretroviral therapy has been shown to both increase and decrease the efficacy of hormonal contraception, depending on the drug it is administered with, however findings continue to be mixed in nature (Luque et al., 2015). There are six main classes of antiretroviral drugs (Sharma & Walmsley, 2015). The classes of antiretroviral therapy include: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors

(NNRTIs), Protease Inhibitors (PI), Integrase Inhibitors (INI), Entry Inhibitors (Sharma & Walmsley, 2015). All of these drugs target the HIV lifecycle in different ways. Usually, two or three of these drug classes are combined to decrease the progression of HIV (Sharma & Walmsley, 2015). Generally, most people start HIV treatment with two NRTI drugs, along with either one NNRTI or one PI and one INI (Nanda et al., 2017). Although NRTIs and INI are not generally inducers of the cytochrome P450 system, PIs and NNRTIs are metabolized by enzymes found in the cytochrome P450 system (Nanda et al., 2017) and may specifically inhibit cytochrome 3A4, however findings continue to be mixed in nature (Atrio et al., 2015).

Some antiretrovirals (ARVs), particularly Nevirapine and Efavirenz, are metabolically synthesized via the cytochrome P450 enzyme system (Kancheva Landolt et al., 2016). Since some protease inhibitors can inhibit enzyme systems like CYP3A4, the bioavailability of drugs that use the same enzyme systems, like hormonal contraceptives, may decrease (Atrio et al., 2015). Additionally, some studies suggest that CYP3A4 activity differs by gender, and suggest that women have 40% higher CYP3A4 activity than men (Luque et al., 2015). With increased activity of this enzyme, which aids in breaking down hormonal contraception in women, examining the relationship between these drugs is key, so that women with HIV have options that meet reproductive health needs.

Efavirenz is usually a first-line treatment for HIV, followed by nevirapine, which are both NNRTIs (Scarsi et al., 2016). Landlot and associates found that efavirenz, in contrast to nevirapine, when co-administered with combined oral contraceptives, is associated with unfavorable progesterone and antiretroviral levels (Landolt et al., 2013). Patel and associates documented a similar finding; efavirenz, compared to nevirapine experienced

higher rates of pregnancy among those using DMPA and hormonal contraceptives (Patel et al., 2015). Both studies note that the failure of contraceptives was minimal and was no statistically significant different than the general population.

Effects on Contraception

Hormonal contraceptives are known to thicken the mucus of the cervix, so that sperm cannot reach the egg (Atrio et al., 2015). Suppressed ovulation is a key determinate in judging the efficacy of hormonal contraceptives (Luque et al., 2015). Researchers did not observe any pregnancies concluding that DMPA is a safe and tolerable amongst women using antiretroviral therapy (Luque et al., 2015).

Pyra and associates suggest that both oral contraceptives and implants are effective in reducing pregnancy when co-administered with antiretroviral therapy (Pyra et al., 2015). Although researchers found that antiretroviral therapy did not significantly diminish the effectiveness of contraception, there was a non-statistically significant reduced effectiveness when co-administered with the antiretroviral, efavirenz (Pyra et al., 2015). Implants (IUDs) were the most protective contraceptive method for women engaging in ART (Pyra et al., 2015).

Atrio and associates found that women taking protease inhibitors demonstrated thickened cervical mucus similar to those not on antiretroviral therapy (Atrio et al., 2015). Thickened cervical mucus serves as a barrier to sperm penetration (Atrio et al., 2015). The findings of the research suggested contraceptive (pill) efficacy in HIV positive women taking antiretroviral therapy that includes protease inhibitors, is an appropriate method of birth control for HIV positive women (Atrio et al., 2015).

Effects on Disease Transmission and Progression

Stringer and associates concluded that women who used hormonal methods were more likely to become pregnant, as compared to the IUD (Stringer et al., 2007). Also, women who use hormonal contraception may experience disease progression more commonly than those using the IUD (Stringer et al., 2007). Research suggests the IUD may be a safer and more effective option than hormonal contraception in HIV+ women, in regards to disease progression (Stringer et al., 2007). However, these results are not consistent.

Using blood measures to assess CD4+ cell counts, Whitman and associates found that there was no statistically significant increase in disease progression among those that used hormonal contraception, including DMPA and the pill, as compared to those that used non-hormonal methods such as the IUD or condoms, (Whiteman et al., 2016). Additionally, those engaging in antiretroviral therapy saw no statistically significant difference in mean changes of CD4+ cell counts when comparing those that used hormonal methods to those that did not (Whiteman et al., 2016). The researchers concluded that hormonal contraception was not significantly associated with HIV disease progression or antiretroviral effectiveness among women with HIV (Whiteman et al., 2016).

Another study assessing DMPA's effect on HIV antiretroviral drugs evaluated the safety and tolerability of co-administration (Watts et al., 2008). Tolerability was measured by the instances of adverse side effects (Watts et al., 2008). Researchers assed DMPA use with various antiretroviral drugs including nelfinavir, efavirenz, and nevirapine (Watts et al., 2008). Although some participants experienced adverse side effects including vaginal bleeding, headache, abdominal pain, mood changes, and other symptoms, researchers attributed these findings to the general side effects of DMPA that could occur in all women

regardless of HIV status (Watts et al., 2008). The study found that there were no significant changes in CD4+ cell count or HIV RNA levels with the use of DMPA (Watts et al., 2008). This suggested that co-administration of hormonal contraceptives and antiretrovirals is safe among HIV-positive women.

Use of DMPA In a similar study, researchers investigated DMPA and antiretroviral use and compared plasma and genital HIV-1 RNA shedding (Day et al., 2014). Researchers found that DMPA expose did not increase detection of plasma nor cervical HIV-1 RNA (Day et al., 2014). Day and associates concluded that administration of DMPA among HIV-infected women is a safe option for those currently engaging in ART therapy.

Effects on Pharmacokinetics

Kancheva and associates suggest that there are no relevant interactions between hormonal contraceptives and antiretrovirals. However, The researchers observed that there was a high variability in estrogen levels of the participants (Landolt et al., 2013). This may warrant concern, as there could potentially be an issue in estrogen breakdown among participants. The study found no clinically relevant interactions between DMPA and the antiretroviral drugs lopinavir and a low dose ritonavir among HIV-positive women, compared to those that are HIV-positive, but are not receiving antiretroviral therapy. Both lopinavir and ritonavir are both protease inhibitors (Luque et al., 2015). There was no significant difference in hormonal levels of either contraceptive in blood samples between the two groups.

Some research has shown that certain classes of antiretroviral therapy, such as PIs and NNRTIs can inhibit hepatic enzymes such as cytochrome 3A4, however findings continue to be mixed in nature (Atrio et al., 2015).

Methods

The process of the systematic review started with the research question, "Does the use of antiretroviral therapy or hormonal contraceptives alter the efficacy of either drug when used concurrently in HIV-positive women?" Hormonal contraceptives in this study include birth control pills and the DMPA shot. The systematic review search was conducted through Georgia State University's library website using the following databases: Global Health, Medline, and PubMed. Based on the purpose of this study keywords such as: hormonal contraceptives, contraception, antiretroviral therapy, disease transmission/progression and ART were used to conduct the search. The search criteria included: ((hormonal contraception) OR (contraceptive)) AND ((antiretroviral) OR (art)). After this search was conducted the search criteria was again searched using disease transmission/progression. The search criteria included: ((hormonal contraception) OR (contraceptive)) AND ((antiretroviral) OR (art)) AND ((disease progression) or (disease transmission)). The results from both searches were combined as the results of the second search were yielded in the initial search. All articles from the systematic review were chosen from these databases. The flowchart (Figure 1) details the process of the systematic review and how the final articles were chosen. The primary goal for the systematic review was whether co-administration of hormonal contraceptives and antiretroviral therapy had an effect on efficacy of either drug. The secondary goals were to assess whether co-administration played a role in disease progression and pregnancy acquisition. The inclusion criteria for the systematic review consisted of randomized and nonrandomized studies, including randomized control trials and cohort studies. Also, all studies included the systematic review co-administered both antiretroviral therapy and hormonal

contraception. The inclusion criteria are detailed in Table 1. Only articles that assessed HIV-positive women were included. English language articles included the systematic review were published between the following dates: January 2007-March 2017. There were no restrictions based on age, country, or type of antiretroviral therapy used. After eliminating articles that did not fit the inclusion criteria, remaining articles were reviewed based on the research questions and the availability of full text articles. After assessing the articles that met all of the inclusion criteria, the final literature for the systematic review was chosen. Finally, a quality assessment was conducted on eligible articles based on the following criteria: study design, purpose clearly stated, use of antiretroviral therapy, use of hormonal birth control (pill/ DMPA) stated, conclusions appropriate per results. The quality assessment is detailed in Table 2.

Figure 1. Flowchart of Selection of Studies

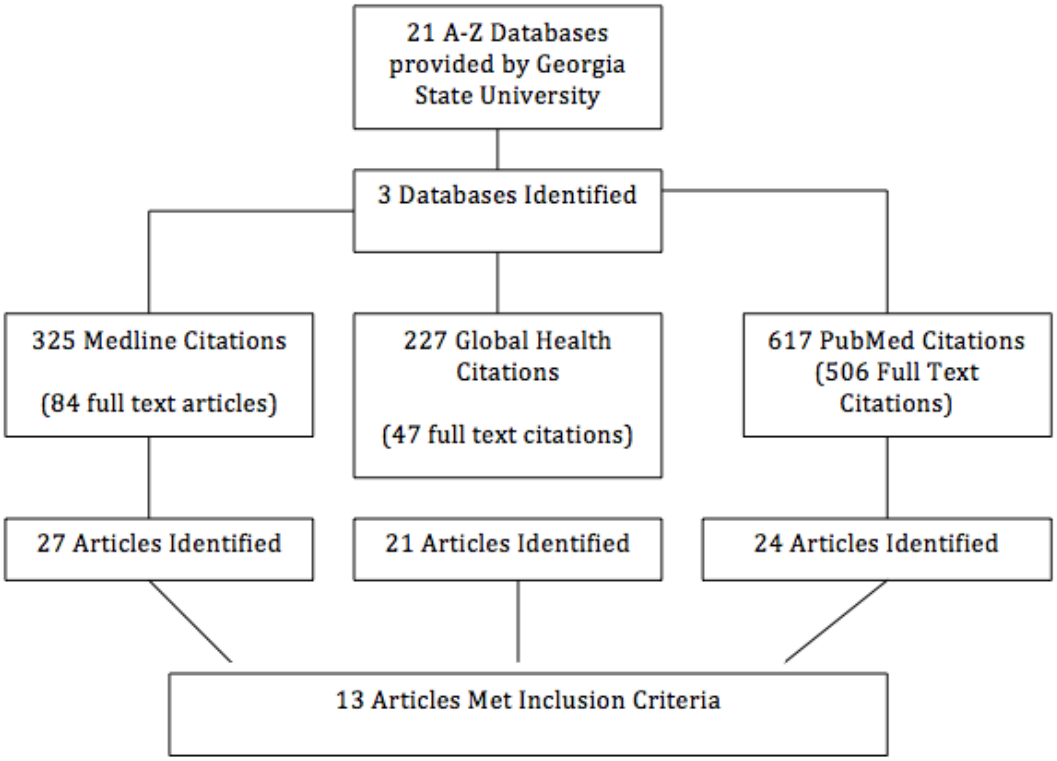

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Articles using both hormonal contraceptives and antiretroviral therapy within the study • Cohort Studies • Randomized/Non-randomized Control Trials • Female Subjects • Full text English Articles • Articles published between January 2007- March 2017 • Articles with primary outcomes of efficacy, disease progression, or pregnancy incidence (ovulation)	• Systematic Reviews • Articles not in English • Studies without full text available after search • Case Control Studies • Studies including nonhuman subjects • Secondary Analysis • Articles with behavioral outcomes (for the interest of this study, behavioral outcomes were excluded due to the initial purpose being drug efficacy)

Table 2. Quality Assessment of Reviewed Articles

Author	Purpose Clearly Stated	Use of Antiretroviral	Use of hormonal Contraception (Pill/DMPA)	Conclusions Appropriate per Results	Study Design
Atrio (2015)	Yes	Yes	Yes	Yes	Non-Randomized Clinical Trial
Day (2015)	Yes	Yes	Yes	Yes	Prospective Cohort Study
Kancheva Landlot (2016)	Yes	Yes	Yes	Yes	Non-randomized Clinical Trial
Landlot (2013)	Yes	Yes	Yes	Yes	Non-randomized Clinical Trial
Luque (2015)	Yes	Yes	Yes	Yes	Non-Randomized Clinical Trial
Nanda (2008)	Yes	Yes	Yes	Yes	Non-Randomized Clinical Trial
Nanda (2013)	Yes	Yes	Yes	Yes	Non-Randomized Clinical Trial
Patel (2015)	Yes	Yes	Yes	Yes	Retrospective Cohort Study
Polis (2012)	Yes	Yes	Yes	Yes	Prospective Cohort Study
Pyra (2015)	Yes	Yes	Yes	Yes	Retrospective Cohort Study
Stuart (2011)	Yes	Yes	Yes	Yes	Prospective Cohort Study
Watts (2008)	Yes	Yes	Yes	Yes	Non-Randomized Clinical Trial
Whiteman (2016)	Yes	Yes	Yes	Yes	Prospective Cohort Study

Results

Georgia State University's Library website provides 21 A-Z databases for student use. The databases most appropriate for this systematic review were PubMed, Medline, and Global Health. PubMed is maintained by the National Center for Biotechnology Information (NCBI) at the US National Library of Medicine (NLM) and provides biomedical literature from MEDLINE, life science journals, and online books in the fields of life sciences, behavioral sciences, chemical sciences and bioengineering. Using the keywords ((hormonal contraception) OR (contraceptive)) AND ((antiretroviral) OR (art)), and ((hormonal contraception) OR (contraceptive)) AND ((antiretroviral) OR (art)) AND ((disease progression) or (disease transmission)), PubMed yielded 617 citations. The articles were filtered to show only full text articles, which yielded 506 citations. The titles of the articles and the abstracts were reviewed for relevance, 24 articles were identified and 9 articles met the inclusion criteria.

Global Health is a public health database that provides information in international health, biomedical life sciences, public health nutrition, non-communicable diseases and more. The same keyword search was used for Global Health as PubMed. Global Health yielded 227 citations. The titles of the citations were evaluated as well as the abstracts for relevancy. There were 21 articles reviewed and 3 met the inclusion criteria for the systematic review.

The Medline database combines the National Library of Medicine's database with links to full text articles. The Medline database provides information from leading medical journals on information relating to medicine, dentistry, the healthcare system, preclinical sciences, and veterinary medicine. The keyword search yielded 325 citations.

The titles of the articles were evaluated as well as abstracts for relevancy. There were 27 articles reviewed and only one met the inclusion criteria for the systematic review. Most of the articles that met the inclusion criteria were provided on at least two of the databases. It is also important to note that all of the articles identified for the secondary outcomes, such as disease transmission were included in the above keyword search. All of the articles identified in the systematic review met all inclusion criteria and the outcomes were relevant to the study. Also, there were additional articles that could have been considered for the systematic review, but these databases were not available through the Georgia State University Library system.

Table 3 details the characteristics of the studies included in the systematic review. The studies in the systematic review varied in setting, however, all of the studies were published from 2007-2017. 6 (46%) of the studies were conducted in African countries. Of the 13 articles that met the inclusion criteria, one study (7.7%) had outcomes that found increased disease progression. 6 studies (46%) of the studies had outcomes that monitored ovulation, cervical mucus, or pregnancy rates. Four studies (31%) assessed the pharmacokinetics of co-administration of antiretroviral therapy and hormonal contraception. One study detailed virological failure rates, (defined as failure to achieve virologic suppression, switch to second line therapy, or death within 12 months of ART initiation), of antiretroviral therapy (7.7%) when co-administered with hormonal contraception. Also, there was one study that detailed HIV-1 cervical shedding.

All of the studies had a clearly stated purpose and co-administration of antiretroviral therapy and hormonal contraception (combined oral contraceptives, progesterone only, and/or injectable), and the conclusions were appropriate per the

results. Additionally, 11 of the studies reported a statistical significance of the results (Table 4), while two study reported pharmacokinetic results in graphic form. Of the 13 studies reviewed, 10 studies found no relevant interactions between co-administration of the drugs. Whitman and Associates conducted a study detailing disease transmission found no relevant interactions between co-administration (Whiteman et al., 2016). However, Day and associates found an increased risk of diseases transmission among women receiving DMPA and antiretroviral therapy (Day et al., 2014).

Table 3. Characteristics of Studies Included in the Systematic Review

Author	Title	Study Design	Sample Population & Setting	Intervention	Outcome
(Atrio et al., 2015)	The effect of protease inhibitors on the cervical mucus of HIV-positive women taking norethindrone contraception	Non-Randomized Clinical Trial	43 HIV+ women 18-44/ California	16 women were given protease inhibitors (ART) and Norethindrone(progesterone only pills), 17 women were controls, given only Norethindrone pills	No difference in cervical mucus score between HIV+ women taking PI and those not taking PI
(Day et al., 2014)	A Prospective Cohort Study of the Effect of Depot Medroxyprogesterone Acetate on Detection of Plasma and Cervical HIV-1 in Women Initiating and Continuing Antiretroviral Therapy:	Prospective Cohort Study	102 HIV positive women in Kenya under ART	Women on ART therapy were administered DMPA or received no DMPA	Results suggest that DMPA is unlikely to increase infectivity in HIV-positive women who are adherent to effective ART

(Kancheva Landolt et al., 2016)	High variability of hormonal levels and no clinically relevant interaction between ethinyl estradiol, desogestrel and lopinavir/ritonavir in a small sample of HIV-positive adolescents:	Non-randomized Clinical Trial	18 HIV+ women in Bangkok and Thailand	All women were administered ethinyl estradiol/desogestrel (combined oral contraceptives) and Lopinavir/ritonavir (ART)	No clinically relevant interaction between combined oral contraceptives and antiretroviral therapy
(Landolt et al., 2013)	Efavirenz, in Contrast to Nevirapine, is Associated With Unfavorable Progesterone and Antiretroviral Levels When Coadministered With Combined Oral Contracep	Non-randomized Clinical Trial	34 Thai HIV+ women	16 women were administered Efavirenz and desogestrel/ethinyl estradiol (Combined Oral Contraceptives), 18 women were administered Nevirapine and desogestrel/ethinyl estradiol	Coadministration of Efavirenz and COCs is associated with unfavorable progesterone and antiretroviral levels compared to Nevirapine.

	tives:				
(Luque et al., 2015)	Depot Medroxyprogesterone Acetate in Combination with a Twice-Daily Lopinavir-Ritonavir-Based Regimen in HIV-Infected Women Showed Effective Contraception and a Lack of Clinically Significant Interactions, with Good Safety and Tolerability: Results of the ACTG 5283 Study	Non-Randomized Clinical Trial	48 HIV+ women from 5 AIDS Clinical Trial Group clinical research sites (CRSs) and 8 National Institute of Child Health and Human Development (NICHD)-funded IMPAACT CRSs	The intervention group received DMPA and lopinavir/ritonavir, the control group received DMPA while no antiretroviral therapy.	No changes in lopinavir and ritonavir levels after DMPA initiation. DMPA was well tolerated and there was a suppression of ovulation.
(Nanda et al., 2008)	Pharmacokinetic interactions between depot medroxyprogestero	Non-Randomized Clinical Trial	30 HIV+ women	15 using ART (Efavirenz, zidovudine, lamivudine) receiving DMPA shots, and 15 non ART therapy users receiving DMPA	Pharmacokinetic interactions were similar in those engaging in ART and those who did not receive ART therapy. Suggesting no interference with

	ne acetate and combination antiretroviral therapy			shots	contraceptive effectiveness.
(Nanda et al., 2013)	Nevirapine-based antiretroviral therapy does not reduce oral contraceptive effectiveness:	Non-Randomized Clinical Trial	302 women in South Africa and Uganda	196 women received Nevirapine (ART) and Combined Oral Contraceptives, 206 women received Combined Oral Contraceptives and no ART	Use of ART did not affect the risk of pregnancy or ovulation, suggesting Nevirapine-based ART does not effect combined oral contraceptive effectiveness.
(Patel et al., 2015)	Pregnancy rates in HIV-positive women using contraceptives and efavirenz-based or nevirapine-based antiretroviral therapy in Kenya: a retrospective cohort study	Retrospective Cohort Study	24,560 HIV positive women enrolled in HIV health facilities in western Kenya	For birth control, women used either: DMPA, Combined Oral Contraceptives or Implants For ART regimens, women used either: Nevirapine-based ART, Efavirenz-based ART lopinavir/ritonavir based ART or no ART	Implant use was the most protective against pregnancy, regardless of ART use. Those using hormonal contraceptives (DMPA and COCs) saw higher incidences of pregnancy than those using implants. Those taking Efavirenz-based ART therapy saw the highest incidence of pregnancy.
(Polis et al., 2012)	Effect of injectable contraceptive use	Prospective Cohort Study	418 HIV-positive Ugandan Women	ART and hormonal contraceptive use (DMPA) levels were use measured	Virologic failure rates while administered with DMPA at 12 months

	on response to antiretroviral therapy among women in Rakai, Uganda			at baseline and 12 months after the start of the study among women who used both drugs	were similar to those virologic failure rates at baseline. No deleterious effect of DMPA use on response to ART Injectable contraception was not associated with an increased risk of ART failure
(Pyra et al., 2015)	Effectiveness of hormonal contraception in HIV-infected women using antiretroviral therapy:	Retrospective Cohort Study	5153 HIV-positive women followed in HIV prevention studies in Africa	Women using ART used a variety of ART regimens(Nevirapine and Efavirenz were the most common) and used the following types of birth control: COCs, Injectables, Implants, None	Hormonal contraceptives are highly effective in reducing pregnancy risk in HIV-positive women currently using ART
(Stuart et al., 2011)	Combined Oral Contraceptives and Antiretroviral PK/PD in Malawian Women: Pharmacokinetics and Pharmacodynamics of a Combined Oral	Prospective Cohort Study	9 Malawi Women who were HIV+ and taking ART, HIV+ women not taking ART and HIV negative women	All women, among the three groups were given hormonal contraceptives	Combined oral contraceptives maintained effectiveness regardless of ART use. Hormonal levels were higher in HIV-positive women than in HIV-negative women, which debunk the notion that COCs are less effective when co-administered with ART like

	Contraceptive and a Generic Combined Formulation Antiretroviral in Malawi:				(Nevirapine).
(Watts et al., 2008)	Safety and tolerability of depot medroxyprogesterone acetate among HIV-infected women on antiretroviral therapy: ACTG A5093	Non-Randomized Clinical Trial	56 HIV-positive women 16 HIV-negative women	HIV-infected women on selected ARV regimens or no ARV were administered DMPA 150 mg intramuscularly and evaluated for 12 weeks for adverse events, changes in CD4+ count and HIV RNA levels, and ovulation.	DMPA administration in HIV-infected women on ART regimens is similar to observations in HIV-negative women. DMPA prevented ovulation and did not affect CD4+ counts or HIV RNA levels
(Whiteman et al., 2016)	Associations of hormonal contraceptive use with measures of HIV disease progression and antiretroviral therapy effectiveness	Prospective Cohort Study	709 HIV-positive women in Russia	Women either used ART or No ART Therapy while assigned to the following contraception methods: COCs, DMPA, Non-hormonal methods	No significant association between use of hormonal contraception and disease transmission or ART effectiveness among HIV-positive women

Table 4. Detailed Results of Reviewed Articles

Author	Title	Intervention	Statistical Results
(Atrio et al., 2015)	The effect of protease inhibitors on the cervical mucus of HIV-positive women taking norethindrone contraception	Women in the intervention group were given protease inhibitor regimens, while the control group received no ART treatment. Women were administered norethindrone 0.35 mg contraception for 21 days.	Baseline Cervical Mucus Score (CMS) was similar to baseline (p>.01) CMS score after 21 days among those taking PI= 3.5 CMS score after 21 days among the control=4 (P-value> 0.28)
(Day et al., 2014)	A Prospective Cohort Study of the Effect of Depot Medroxyprogesterone Acetate on Detection of Plasma and Cervical HIV-1 in Women Initiating and Continuing Antiretroviral Therapy:	The standard ART regimen was: zidovudine or stavudine, lamivudine, and nevirapine Exposure to hormonal contraception was defined as reported use within the past 70 days. The comparison group was women not using hormonal contraception, which included no contraception, condoms only, hysterectomy or tubal ligation.	Compared to visits with no hormonal contraception exposure, DMPA exposure did not increase detection of plasma (adjusted odds ratio (AOR) 0.81, 95% CI 0.47–1.39) or cervical HIV-1 RNA (AOR 1.41, 95% CI 0.54–3.67)
(Kancheva	High variability	HIV-positive females on Lopinavir/ritonavir-	Geometric mean ratios (GMR) of C_{trough} (LPV/r concentration) in HIV-positive women on LPV/r

Landolt et al., 2016)	of hormonal levels and no clinically relevant interaction between ethinyl estradiol, desogestrel and lopinavir/ritonavir in a small sample of HIV-positive adolescents:	based regimen (LPV/r) were administered COC tablets, containing 0.030 mg ethinyl estradiol/0.150 mg desogestrel for 2 consecutive cycles, starting between the first and the third day of the cycle. (56 study days: 21 days hormonal tablets—7 days, repeated) HIV negative controls were administered the COC tablets, containing 0.030 mg ethinyl estradiol/0.150 mg desogestrel for 2 consecutive cycles, starting between the first and the third day of the cycle. (56 study days: 21 days hormonal tablets—7 days, repeated)	with COC versus HIV-negative controls with COC only were 0.68 (95% CI: 0.42 to 1.08) or 32% decreased (P = 0.10) for EE2; and 1.08 (95% CI: 0.73 to 1.60) or 8% increased (P = 0.68) for ENG (active metabolite in desogestrel). C_{trough} of LPV decreased statistically insignificantly with COC and remained above the desired therapeutic minimum of 1.0 mg/L in all.
(Landolt et al., 2013)	Efavirenz, in Contrast to Nevirapine, is Associated With Unfavorable Progesterone and Antiretroviral Levels When Coadmini	Oral contraceptive (COC) containing 0.150 mg desogestrel /0.030 mg ethinyl estradiol with either nevirapine (NVP) or efavirenz (EFV) were administered to 34 HIV-positive women. The targeted level for contraceptive effectiveness was endogenous progesterone level < 3.0 ng/mL. The targeted levels for	All subjects (18) in the NVP group had serum progesterone <1.0 ng/mL. Four of 16 subjects in the EFV group had serum progesterone >1.0 ng/mL, including 3 subjects with >3.0 ng/mL (may indicate ovulation). The difference in progesterone levels between the 2 groups was statistically significant (P = 0.04). The median C12 (concentration 12 hours after administration) of NVP increased insignificantly with COC. The median C12 of EFV decreased significantly (P = 0.02) by 22%. 3 of 16 subjects (19%) in the EFV group, C12 of EFV was below 1.0 mg/L.

	stered With Combined Oral Contraceptives:	antiretroviral therapy were >3.1 mg/L for NVP and 1.0-4.0 mg/L for EFV.	
(Luque et al., 2015)	Depot Medroxyprogesterone Acetate in Combination with a Twice-Daily Lopinavir-Ritonavir-Based Regimen in HIV-Infected Women Showed Effective Contraception and a Lack of Clinically Significant Interactions, with Good Safety and Tolerability: Results of the ACTG 5283 Study	24 HIV positive women receiving (10 Receiving Lopinavir (LPV)/Ritonavir (RTV) based therapy, 14 receiving no therapy) All women received DMPA	There were no changes in LPV or RTV exposure after DMPA. DMPA was well tolerated, and suppression of ovulation was maintained.
(Nanda et al., 2008)	Pharmacokinetic interactio	15 HIV-positive women in the control group (not on ART) received a	N/A The mean blood levels (area under curve) for

	ns between depot medroxyprogesterone acetate and combination antiretroviral therapy	single muscular injection of DMPA 150 mg. 15 HIV-positive women receiving ART received a single muscular injection of DMPA 150 mg.	the first 12 weeks after DMPA administration was 101.9 (30.2) in the ART group and 99.1 (21.6) in the non-ART group, with a ratio of 1.01 (95% CI 0.85–1.20). Mean C_{max} (maximum concentration) was 2.6 for the intervention group and 2.5 for the control group (ratio 1.01, 95% CI 0.84–1.22).
(Nanda et al., 2013)	Nevirapine-based antiretroviral therapy does not reduce oral contraceptive effectiveness:	196 women taking nevirapine-containing ART treated with combined oral contraceptives 206 HIV- positive women not yet eligible for ART as a control group treated with combined oral contraceptives.	In the ART group, 43 of 168 (26%) ovulated in cycle 1, 30 of 163 (18%) in cycle 2, and 18 of 163 (11%) in both cycles. In the control group, 26 of 168 (16%) ovulated in cycle 1, 31 of 165 (19%) in cycle 2, and 20 of 165 (12%) in both cycles. Unadjusted odds ratio 1.36 (95% confidence interval 0.85-2.18). Pregnancy rates 10.0 per 100-women-years in the ART group and 10.1 per 100-women-years in the non-ART group (no statistical significance).
(Patel et al., 2015)	Pregnancy rates in HIV-positive women using contraceptives and efavirenz-based or nevirapine-based antiretroviral therapy in Kenya: a retrospective cohort study	Women were administered Nevirapine or Efavirenz based ART, with co-administration of implants, DMPA or combined oral contraceptives.	For women using implants, adjusted pregnancy incidence was 1.1 per 100 person-years (95% CI 0.72-1.5) for nevirapine-based ART users and 3.3 per 100 person-years (1.8-4.8) for efavirenz-based ART users (adjusted incidence rate ratio [IRR] 3.0, 95% CI 1.3-4.6). Women using depot medroxyprogesterone acetate (DMPA) experienced adjusted pregnancy incidence was 4.5 per 100 person-years (95% CI 3.7-5.2) for nevirapine-based ART users and 5.4 per 100 person-years (4.0-6.8) for efavirenz-based ART users (adjusted IRR 1.2, 95% CI 0.91-1.5). Women using combined oral contraceptive methods had 3.1-4.1 higher rates of pregnancy than did those using implants, with 1.6-2.8 higher rates in women using efavirenz-based ART
(Polis et	Effect of	418 female Ugandan	Composite virologic failure rates 12 months

al., 2012)	injectable contraceptive use on response to antiretroviral therapy among women in Rakai, Uganda	ART initiators to examine the effect of injectable contraceptive	after initiation were similar to women not using injectable contraceptives at ART initiation (11% vs. 12%, p=0.99).
(Pyra et al., 2015)	Effectiveness of hormonal contraception in HIV-infected women using antiretroviral therapy:	5153 HIV-infected women followed prospectively to compare incident pregnancy rates by contraceptive method (implant, injectable, oral or none) and ART use. aHR= adjusted hazard ratio	Women not using any contraception: pregnancy incidence rates were 13.2 and 22.5 per 100 women-years for those on and not on ART, respectively. Women using implants: [aHR 0.06, 95% confidence interval (95% CI) 0.01-0.45] and not on ART (aHR 0.05, 95% CI 0.02-0.11). Pregnancy incidence rate was Less than 1.5 per 100 person-years among those both on and not on ART versus 1.4 for those not using ART. Women using Injectable (aHR 0.18 on ART and aHR 0.20 not on ART). Pregnancy incidence rate was 3.3 per 100 person-years among those both on and not on ART versus 5.3 for those not using ART. Women using oral contraceptives (aHR 0.37 on ART and aHR 0.36 not on ART) also reduced pregnancy risk, though by lesser degrees. Pregnancy incidence rates were 6.2 per 100 person-years among those both on and not on ART versus 11.1 for those not using ART.
(Stuart et al., 2011)	Combined Oral Contraceptives and Antiretro	Nine women enrolled, 3 in each group. The women in group 1 (HIV positive on ARVs)	N/A

	viral PK/PD in Malawian Women: Pharmacokinetics and Pharmacodynamics of a Combined Oral Contraceptive and a Generic Combined Formulation Antiretroviral in Malawi:	had been on ARVs for 121 days before starting COCs. The women in group 2 had HIV, but did not use ARVs. The women in Group 3 were HIV negative women. Measures were reported in Graphic form.	
(Watts et al., 2008)	Safety and tolerability of depot medroxyprogesterone acetate among HIV-infected women on antiretroviral therapy: ACTG A5093	HIV-positive women on ART or no ART were administered DMPA 150 mg intramuscularly and evaluated for 12 weeks for adverse events, changes in CD4+ count and HIV RNA levels, and ovulation	
(Whiteman et al., 2016)	Associations of hormonal contraceptive use with measures	HIV-positive female participants were administered: combined oral contraceptives (COCs), depot-medroxyprogesterone acetate (DMPA), a	Current use of COCs [adjusted hazard ratio (aHR) 0.91, 95% confidence interval (CI) 0.56–1.48] nor DMPA (aHR 1.28, 95% CI 0.71–2.31) was associated with a statistically significant increase risk for disease progression. Among participants using ART at enrollment

	of HIV disease progression and antiretroviral therapy effectiveness	copper intrauterine device (IUD) or condoms. Among participants not using ART at enrollment, multivariate Cox regression was used to assess the association between current contraceptive use and disease progression (CD4 decline to <350 cells/mm3, ART initiation or death).	(*n*=77), we found no statistically significant differences in the predicted mean changes in CD4 cell count comparing current use of COCs (p=.1) or DMPA (p=.3) with nonhormonal methods.

Discussion

Ten of the articles in the systematic review showed no relevant associations between the use of both hormonal contraception and antiretroviral therapy among HIV-positive women. However, two of the articles showed differences in hormonal blood levels or pregnancy risk. The purpose of this study was to address the research question ""Does the use of antiretroviral therapy or hormonal contraceptives alter the efficacy of either drug when used concurrently in HIV-positive women?" The secondary research question addressed disease progression with co-administration. While some studies assessed the effectiveness of specific antiretrovirals, such as Efavirenz or Nevirapine, which are both NNRTIs, most of the studies used a combination method of antiretrovirals, which is most commonly practiced among HIV-positive women.

Efavirenz, a NNRTI, was associated with higher progesterone levels in a study conducted by Landolt and associates (Landolt et al., 2013). Efavirenz based ART is the first-line therapy recommended by the WHO in resource limiting countries (Patel et al., 2015). Those using Efavirenz and combined oral contraceptives experienced higher progesterone levels compared using other forms of birth control. These higher progesterone levels may indicate ovulation and further confirm the notion that co-administration alters the efficacy of either drug. This finding may also indicate less uptake of hormonal contraception. Additionally, some women experienced higher pregnancy rates while receiving co-administration of antiretrovirals and DMPA, compared to other forms of contraception such as the IUD (Patel et al., 2015). It is important to note that the results of this study may not be due to the use of Efavirenz. The results may be a reflection of the real world efficacy of hormonal contraceptives versus other birth control methods such as implants, as

implants are among the most effective contraception methods available today (Patel et al., 2015). Among the general population, DMPA and combined oral contraceptives are more user dependent than implants, which may explain the effectiveness of the drugs (Patel et al., 2015). The results of these studies show that the IUD may be a safer option for women looking to avoid ovulation and minimize disease progression.

The studies addressing disease transmission showed that co-administration of the do not increase the risk of disease transmission. No significant changes in HIV RNA or CD4+ cell counts were observed in women receiving hormonal contraception versus women not receiving hormonal contraception (Watts et al., 2008). This was observed with both DMPA and pill users. Additionally, Day and associates detailed HIV-1 RNA shedding in HIV positive women engaging in ART and hormonal contraceptive practices versus those not receiving hormonal contraception (Day et al., 2014). Researchers found that those using hormonal contraception (DMPA) did not experience increased cervical and plasma HIV-1 RNA shedding. These findings indicate DMPA is unlikely to increase infectivity in HIV-positive women who use antiretroviral therapy (Day et al., 2014). In regards to a woman's own health, hormonal contraception seems to be well tolerated among antiretroviral users. Additionally, concurrent use does not seem to increase the risk of infectivity.

This systematic review had limitations in that there is limited data on the potential interactions of antiretroviral and hormonal contraception. The study only used databases made available by Georgia State University, which limited the search of articles that met the inclusion criteria. Additional databases were not used in this systematic review because these databases required payment to garner access. Also, in some of the studies, the sample sizes were relatively small. Therefore, without additional studies in the subject area, it may

be problematic to generalize the results of the studies to similar populations. Also, there were additional studies that assessed birth control in HIV-positive women, but these studies did not co-administer antiretrovirals and hormonal contraception.

Conclusion

It is important to for HIV-positive women to have safe and effective means of contraception. Because the proportion of AIDS cases continues to rise globally among women, vertical transmission is a topic of concern, especially among women in childbearing age (Watts et al., 2008). Women should also be provided options for birth control as some women may not want children, have health problems that will make pregnancy risky, or want to be engaged in their own family planning.

Although there are concerns about the metabolism of hormonal contraception and antiretroviral therapy along the cytochrome P450 pathway, published data has shown minimal interactions when the drugs are co-administered. Further research needs to be conducted in order to evaluate the efficacy of co-administration of hormonal contraception and HIV. Because data is currently limited on the potential interactions among hormonal contraception and antiretroviral therapy, options for safe and effective contraceptive options are also limited among HIV-positive women. The understanding and use of antiretroviral therapy has grown significantly over the past 30 years and co-administration with hormonal contraception should be further examined because it is important for HIV-positive women to have control over their health and fertility. Certain antiretroviral drugs such as Efavirenz has shown to have negative effects on the body when co-administered with hormonal contraception. This may indicate that more research should be done on specific NNRTIs and PIs as it relates to concurrent use. The results of this systematic

review indicate that women can use hormonal contraception and antiretroviral therapy concurrently without concerns about disease transmission and disease progression. However, there may be a warrant for concern in regards to pregnancy risk and women should use more effective forms of contraception such as the IUD. Additionally, women using NNRTIs or PIs should be advised of the risks associated with concurrent use, and are provided with other options as needed.

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