REVIEW PAPER

Patient safety and efficacy in using antiretroviral drugs in pregnant women: a systematic review

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Abstract

Human immunodeficiency virus (HIV) attacks human immune system by destroying CD4+ T cells, which are the main component of immune system, lowering body's resistance, so that HIV-infected patients are susceptible to other infections. HIV mainly attacks the productive age group, where half of new infection cases occur in people aged under 25.5 years. HIV affects not only an individual's health, but also households, communities, and development and economic growth of any country.

The aim of the study was to investigate the safety of antiretroviral (ARV) regimen use in pregnant women. For that, a systematic review was conducted in literature related to a pre-determined theme. The literature was searched systematically using PRISMA guidelines, and the published articles were search in PubMed, ScienceDirect, and Google Scholar electronic databases. After reading, 13 articles on interventions among pregnant women, neonates, and ARV drug usage were selected. Dolutegravir-based ARV therapy is safe and recommended for pregnant and lactating women. Most of the treatments consists of three ARV drugs, as recommended.

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Introduction

The number of people with human immunodeficiency virus (HIV) is increasing [1]. Based on 2019 data, approximately 38 million people are living with HIV/acquired immunodeficiency syndrome (AIDS), and 1.7 million people are newly infected worldwide [2]. Viruses and bacteria are the major causes of co-infections. HIV attacks the human immune system by destroying CD4+ T cells, which are the main component of the immune system, lowering the body's resistance, so that HIV-infected people are susceptible to other infections [3]. HIV mainly attacks the productive age group, where half of the new cases occur in people aged under 25.5 years. HIV affects not only an individual's health, but also households and communities as well as the development and economic growth of any country [4]. HIV is a blood-borne disease that can cause AIDS syndrome, the final stage of HIV disease. If left untreated and uncontrolled, HIV is a severe public health problem. The World Health Organization (WHO) and the United Nations Program on HIV/AIDS (UNAIDS) have submitted predictions of HIV global incidence since the late 1980s [5].

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AIDS was first reported in 1981. Since then, HIV/AIDS has been recognized as a persistent and deadly epidemic affecting humans [6]. The target of ending the AIDS threat by 2030 and achieving UNAIDS goals will depend on successful adherence to antiretroviral (ARV) therapy, leading to viral suppression, minimizing viral transmission, and preventing AIDS-related deaths [7].

ARV therapy (ART) in pregnant women, who started the treatment before pregnancy, can reduce the risk of HIV maternal vertical transmission [8]. In order to reduce it, a combination of ART (cART) is currently recommended for all pregnant women living with HIV [9], as ART effectively reduces the risk of mother-to-child transmission of HIV [10]. With maternal consent, HIV-positive infants are being started on ARV screening as an initial regimen, with doses of nevirapine (NVP): 6 mg/kg twice daily (BID), zidovudine (ZDV): 4 mg/kg BID, and lamivudine (3TC): 2 mg/kg BID [11]. ART refers to the use of a combination of three or more ARV drugs to treat HIV infection [12]. For the moment, a combination of ARV treatment is the best therapy for patients infected with HIV whose primary goal is suppressing the amount of virus (viral load), thereby increasing the immune status of HIV patients and reducing deaths from opportunistic infections [13]. The number of new HIV infections in children has decreased by more than half (54%) from 2010 to 2020, mainly due to augmented provision of ARV therapy in HIV-infected pregnant women on ARVs (11-18% in 2010 and 54-84% in 2020) and breastfeeding mothers [14]. This review aimed to expand and update the systematic review, and answer PICO (population, intervention, comparator, and outcome) questions on the appropriate regimen choices for pregnant women [15]. In previous reviews, dolutegravir (DTG) has been introduced to pregnant women, but not widely recommended for use [16].

This research used the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines for study design, search protocol, screening, and reporting. Publish articles were search through various electronic databases, including PubMed, ScienceDirect, and Google Scholar. Key words entered were as follow: PubMed – "(((((patient safety) AND (efficacy)) OR (lopinavir)) OR (ritonavir)) OR (dolutegravir)) AND (during pregnancy)"; ScienceDirect – "patient safety and efficacy of dolutegravir during pregnancy"; and Google Scholar – "patient safety and efficacy of dolutegravir or ritonavir or lopinavir during pregnancy". The first search using the above key words generated 117 PubMed articles, 84 ScienceDirect papers, and 1,960 Google Scholar publications. There were a total of 2,160 articles published between 2013 and 2023 investigating the development of ARV drugs over the past ten years. Inclusion criteria for the articles included abstracts, article research, open access, observational studies, randomized control trials, and clinical trials. According to inclusion criteria, 32 articles were obtained. After reading the articles and selecting them based on duplication and data completeness (references, purpose, design, samples, research sites, ARV drugs, and results), 13 articles were selected. Screening process was a collaborative effort of two authors (IRH and MS), who reviewed titles,

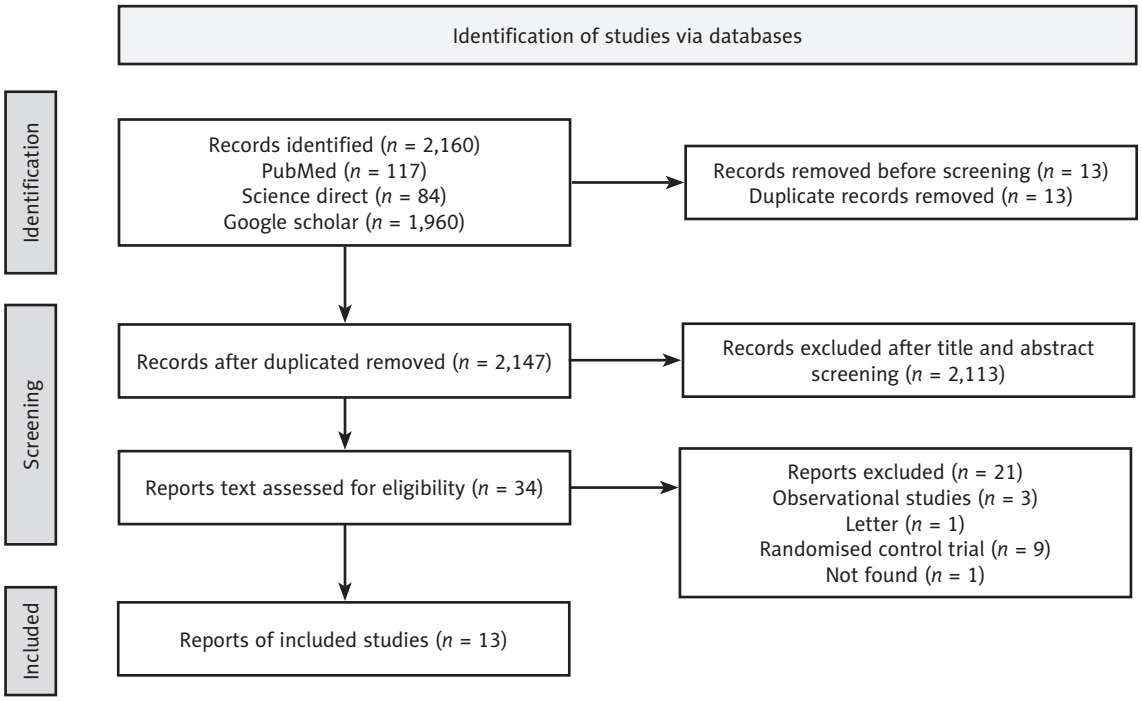

Figure 1. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of the study selection process

Table 1. Patient safety and efficacy in pregnant women with HIV/AIDS

Ref.	Purpose	Design	Samples and research sites	ARV drugs	Year of publication
[19]	Comparing the pharmacokinetics of standard and increased dosage of lopinavir/ritonavir co-formulation tablets in HIV-positive pregnant women	RCT, open-label prospective study	60 HIV-infected pregnant women	Lopinavir/ritonavir (LPV/r)	2014
[20]	Evaluating whether lopinavir/ritonavir-based antiretroviral therapy (ART) reduces the risk of placental malaria	RCT, open-label, single-site	389 HIV-infected pregnant women	Lopinavir/ritonavir (LPV/r) and efavirenz	2014
[21]	Comparing health-related quality of life among pregnant women with dolutegravir- or efavirenz-based ARV treatment	RCT, open-label study	203 pregnant women with an average age of 28 years, randomized to dolutegravir- or efavirenz-based ART	Dolutegravir and efavirenz	2022
[22]	Understanding the differences in safety and efficacy of three antiretroviral regimens started in pregnancy	RCT, open-label study	643 pregnant women (aged ≥ 18 years) with confirmed HIV-1 infection, who were eligible at 14-28 weeks gestation	DTG, emtricitabine, and tenofovir alafenamide fumarate (n = 217) Dolutegravir, emtricitabine, and tenofovir disoproxil fumarate (n = 215) Efavirenz, emtricitabine, and tenofovir disoproxil fumarate (n = 211)	2017
[23]	Determining the efficacy and safety of dolutegravir-based regimens compared with efavirenz-based treatments in mothers and infants	Randomized, open-label trial	Sample: 280 pregnant women, aged at least 18 years, with untreated but confirmed HIV infection and an estimated gestation of at least 28 weeks, starting ARV therapy in the third trimester of pregnancy	Dolutegravir and efavirenz	2022
[24]	Providing dosage recommendations for dolutegravir use in pregnancy based on dolutegravir total and unbound plasma concentrations. Also, it aimed at determining the impact of pregnancy-related physiological changes on dolutegravir metabolism	Open-label, non-randomized, multicenter study	Sample: 17 HIV-infected pregnant women with dolutegravir ART, registered in the PANNA study	Dolutegravir	2021
[25]	Assessing the effectiveness of first-line antiretroviral therapy (ART) regimens in achieving viral suppression at 12 months, from 2014 to 2017, in Brazil	Using data from three BMoH information systems (SICLOM, SISCEL, and SINAN)	Sample: 107,647 ART-active patients, aged 15-80 years, who started ART from January 2014 to July 2017, and had a viral load in 365 (approximately 90) days after starting treatment	Tenofovir/lamivudine/efavirenz (TLE), tenofovir/lamivudine/dolutegravir (TLD) and protease inhibitor	2019

Table 1. Cont.

Ref.	Purpose	Design	Samples and research sites	ARV drugs	Year of publication
[11]	Demonstrating that ART with NVP, ZDV, and 3TC can be started safely in early life, with an early transition to LPV/r-based ART, resulting in a rapid viral breakdown in most infants	Using the Early Infant Treatment Study (EIT), an open-label clinical trial of ART in HIV-infected infants conducted by the Botswana-Harvard AIDS Institute Partnership (BHP)	Sample: 40 EIT-registered infants with gestational age ≥ 35 weeks and weight ≥ 2,000 g, who tested positive for HIV < 96 hours after birth and were eligible to start ART < 7 days after birth	Nevirapine (NVP), zidovudine (ZDV), and lamivudine (3TC)	2021
[26]	For a better understanding of the DTG/DRV/r/DDI and its clinical relevance in patients with AHI; evaluating the need for dose adjustment of DTG when used in combination with DRV/r, plasma concentrations of total and unbound DTG, and concentrations of primary DTG metabolites	The NOVA study and a multicenter prospective cohort study	Sample: 46 respondents started ART within < 24 hours of registration: DTG 50 mg BID, DRV/r 800/ 100 mg QD, and two nucleoside reverse transcriptase inhibitors (NRTIs) for four weeks (phase I), followed by DTG 50 mg QD with two NRTIs	Dolutegravir, darunavir/ritonavir	2023
[27]	Evaluating the safety profile and pharmacokinetics of dose-adjusted darunavir/ ritonavir with rifampicin	Open-label, single-center, pharmacokinetic study	28 medically stable PLHIV on second-line ART regimen with ritonavir-boosted protease inhibitor (PI), along with dual NRTIs	Darunavir/ritonavir	2020
[28]	Evaluating dolutegravir pharmacokinetics during pregnancy compared to postpartum and in infant washout samples after delivery	Ongoing, non-randomized, open-label, parallel-group, multicenter phase IV prospective study	29 HIV-infected pregnant women receiving dolutegravir 50 mg once daily	Dolutegravir	2018
[8]	Comparing the risks of choosing an ART regimen for pregnant women against birth outcomes	Observational birth outcomes surveillance study	47,124 pregnant women, who gave birth (11,932 HIV-positive pregnant women)	Tenofovir disoproxil fumarate, emtricitabine, efavirenz, nevirapine, lopinavir/ritonavir, lamivudine, zidovudine	2017
[9]	Increasing the clinical relevance of antiretroviral toxicity in rat pregnancy models by determining the dose of the currently prescribed ARV regimen that will result in human therapeutic plasma concentrations Informing and encouraging the utilization of rat pregnancy models in studies on antiretroviral safety and toxicity	Clinical trials	Tests were conducted on rats approved by the Animal Use Committee of the University Health Network	PI: lopinavir (LPV), atazanavir (ATV), darunavir (DRV), and ritonavir (RTV) INSTI: raltegravir (RAL) and dolutegravir (DTG) NNRTI: efavirenz (EFV) NRTI: zidovudine (AZT), lamivudine (3TC), tenofovir disoproxil fumarate (TDF), and emtricitabine (FTC)	2018

abstracts, and full papers. Any disagreement was clarified by a joint discussion [17, 18].

A brief description of the status of knowledge

In the 13 selected articles, all studies were conducted in other than Indonesia countries. By using a quantitative method in the search, we did not find reports on studies carried out in Indonesia (Table 1).

From the results of the papers extracted and screened, 13 met the inclusion criteria, with most types of research being randomized control (RCT), open-label, and multicenter trials [20, 23, 28]. Lopinavir/ritonavir (LPV/r)-based regimens were recommended during pregnancy to reduce the risk of mother-to-child transmission of HIV, but the appropriate dosage was controversial [19]. There were no significant differences between DTG and efavirenz for use in pregnant women [21]. The combination of darunavir/ritonavir/rifampicin may be more toxic than double-doses of LPV/r as a second-line regimen for treating HIV with tuberculosis [27]. cART, including integrase inhibitor DTG, is the first-line treatment option for HIV/AIDS worldwide [26]. Another study stated that DTG is safe, well-tolerated, and recommended by the WHO for the treatment of HIV in pregnant and lactating women, and that lactating mothers need further testing even if the viral load is undetected [23]. DTG exposure decreases in pregnancy compared with postpartum at a therapeutic concentration during pregnancy with standard once-daily dosing [28]. DTG is already being used by many women with HIV who are pregnant or of reproductive potential [22].

In a clinical trial, the Botswana-Harvard AIDS Institute Partnership (BHP) conducted a pilot study in infants in Botswana to demonstrate that ART with NVP, ZDV, and 3TC can be started safely and primarily, with an early transition to LPV/r-based ART, resulting in a rapid viral breakdown in most infants. A transient viral boost occurs after the transition to LPV/r. However, between 12 and 24 weeks, most children achieve and retain viral suppression [11]. Furthermore, other studies demonstrated the predominance of DTG-based regimens over efavirenz and protease inhibitors in suppressing HIV viral replication in adults [25]. Treatment guidelines from the WHO recommend three ARV drugs for the treatment of HIV patients, including more than 1.5 million pregnant women infected with HIV each year [8].

One study showed that DTG-based ART started during pregnancy has a high virological efficacy compared with EFV/FTC/TDF regimen. This study compared DTG + FTC/TAF (dolutegravir, emtricitabine, and tenofovir alafenamide fumarate), DTG + FTC/TDF (dolutegravir, emtricitabine, and tenofovir disoproxil fumarate), and EFV/FTC/TDF (efavirenz, emtricitabine, and tenofovir disoproxil fumarate). This research confirmed the WHO recommendation to utilize DTG in all populations, including women starting treatment during pregnancy [22]. A study conducted in South Africa and Uganda also suggested that DTG is safe and well-tolerated treatment, supporting the latest WHO treatment recommendations in pregnant and lactating women [23].

The limitation of the current review is using 3 databases only. For future studies, it is advised to include other databases to represent good and viable results.

Conclusions

Out of the 13 articles obtained, majority of the studies support the WHO references of using DTG-based ART as safe and recommendable for pregnant and lactating women. Most of the treatments consists of three ARV drugs, as recommended.

Disclosures

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4. Conflicts of interest: None.

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