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ORIGINAL RESEARCH

A Single-Center Retrospective Cohort Analysis of Maternal and Infant Outcomes in HIV-Infected Mothers Treated with Integrase Inhibitors During Pregnancy

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ABSTRACT

Introduction: Integrase strand transfer inhibitors (INSTI) are currently being investigated for the treatment of HIV in pregnancy. The purpose of this study is to evaluate the differences in maternal and infant outcomes in HIV-positive mothers treated with INSTI-containing antiretroviral therapy (ART) during pregnancy compared to protease inhibitor (PI)-containing ART.

Methods: A retrospective, cohort study of INSTI- and PI-based ART used in pregnancy between 2007 and 2015 was performed. The primary objective was to evaluate the differences in viral load (VL) suppression prior to delivery. Secondary endpoints included time to and duration of VL suppression and safety parameters in both mothers and infants. For the primary analysis, the two arms were matched 1:2 INSTI to PI based on the presence or absence of viremia at the time of pregnancy determination. Additional analysis was performed on the entire matched and unmatched dataset.

Results: Twenty-one patients were matched (7 INSTI and 14 PI). There were no significant differences between groups with respect to the proportion of patients with VL suppression prior to delivery (71.4% INSTI vs. 92.9% PI, $p = 0.247$), and there were no significant differences in any of the secondary endpoints. Patients with documented adherence issues were statistically more likely to not be virologically suppressed prior to delivery ($p = 0.002$).

Conclusion: No differences in efficacy or safety were found between patients treated with INSTIs compared to PIs. This study supports the further investigation of the use of INSTIs during pregnancy to reduce HIV transmission.

Keywords: Dolutegravir; Elvitegravir; Integrase inhibitor; INSTI; Pregnancy; Protease inhibitor; PI; Raltegravir

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INTRODUCTION

The mother-to-child transmission of human immunodeficiency virus (HIV) can occur by in utero transmission, intrapartum transmission, or breastfeeding, yet the incidence is decreased by 95% with the use of antiretroviral therapy (ART) [1–4]. The antepartum and intrapartum viral loads (VL) of the mother correlate with the risk of perinatal transmission of HIV to the infant; therefore, rapid virologic suppression is the goal of ART in pregnancy [5]. It is recommended that all HIV-infected women contemplating or found to be pregnant be initiated on a maximally suppressive ART regimen in order to achieve an undetectable VL [2]. The availability of ART and achievement of virologic suppression, defined as an HIV-1 RNA VL <20–75 copies/mL, depending on assay used, decreases the risk of vertical transmission from mother to child to less than 1% [2, 5–7]. The recently updated United States Department of Health and Human Service (DHHS) Perinatal guidelines recommend an initial combination of preferred triple antiretroviral therapies, which includes either of the protease inhibitors (PIs), atazanavir/ritonavir or darunavir/ritonavir, or the integrase strand transfer inhibitor (INSTI), raltegravir, with two preferred nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) [2]. Raltegravir was added as a preferred option in the DHHS 2015 Perinatal guideline update. There is currently insufficient data to recommend the other INSTIs, elvitegravir and dolutegravir, during pregnancy based on the limited data for their use in this population.

Although raltegravir, the first FDA-approved INSTI, in 2007, is the only recommended INSTI to be initiated in pregnancy, INSTI-based regimens make up the majority of the ART regimens recommended in adult patients by the DHHS guidelines [1]. Since the INSTI class has become a mainstay of HIV therapy, women of child-bearing potential are likely to become pregnant on INSTI-based regimens. The use of INSTIs has previously been considered for initiation in pregnancy in cases of intolerance to other preferred agents and evidence of drug resistance, a potential for drug interactions, if the patient is stable on an INSTI-based regimen at the time of pregnancy, or with the presence of viremia late in pregnancy because INSTIs are able to decrease the VL as much as 2 log copies/mL within 2 weeks of initiation [2, 8, 9].

A retrospective study in Canada reported no safety concerns in mothers ($n = 18$) or infants treated with raltegravir in addition to atazanavir or lopinavir plus ritonavir [10]. In this study, there were no HIV transmissions and the only adverse effect noted was elevated bilirubin among the atazanavir-treated newborns. Preliminary data were presented in 2017 at the International AIDS Society Conference on HIV Science from an open-label pilot study comparing the use of raltegravir-based ART to lopinavir/ritonavir-based ART in treatment naïve pregnant women presenting after 28 weeks gestation in Brazil [11]. At the time of presentation, the study had enrolled 28 women and found that those initiated on raltegravir had a significantly higher rate of achieving an undetectable VL at delivery and had a lower incidence of adverse effects. The Antiretroviral Pregnancy Registry of prospective cases from January 1989 through January 2017 reported a total of 2 birth defects in 50 (4.0%) live births with an INSTI/NRTI combination, and 66 birth defects in 2542 (2.6%) live births with a PI/NRTI combination [12]. There were no reported birth defects with the combination of PI/INSTI/NRTI ($n = 26$).

To our knowledge there are no published studies comparing INSTIs as a class to PIs in pregnancy. Despite the limited published data on the use of INSTIs in pregnancy, they are now being used clinically in the treatment of HIV during pregnancy either as an add-on to a complete three-drug regimen or as part of a standard three-drug ART regimen. The purpose of this study is to retrospectively evaluate the differences in maternal and infant outcomes in HIV infected mothers treated with INSTI-containing ART regimens during pregnancy compared to those treated with PI-containing ART regimens during pregnancy.

METHODS

Study Design and Population

A retrospective, matched cohort study was performed at a single HIV clinic in Camden, New Jersey, USA. Patients were identified using HIV clinic records as having a confirmed pregnancy and delivering between January 2007 and May 2015. Pregnant women with HIV-1-confirmed infection that were exposed to an INSTI or PI during pregnancy were included in the study. Women were excluded if they received a NNRTI, fusion inhibitor, or CCR5 receptor antagonist during pregnancy. Other reasons for exclusion included HIV diagnosed during delivery of the infant, patient refusal to take ART or to receive any perinatal medical care, those that received HIV care outside of the study clinic, spontaneous abortion during the first trimester, or missing patient records pertaining to VL at delivery, VL at time of pregnancy determination, or HIV treatment regimen. This study was approved by the Institutional Review Board at Cooper University Hospital and all procedures followed were in accordance with the ethical standards of research. This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

Procedure

All pregnancies from January 2007 until May 2015 were evaluated and each pregnancy was counted individually. The primary endpoint was VL suppression prior to delivery. For the purpose of this study, an undetectable VL, or virologic suppression, was defined as <75 copies/mL due to the various assays used over the time span of the study.

The secondary endpoints included time to VL suppression after starting ART, the duration of viral suppression once achieved until delivery, delivery mode, the HIV status of the infant from birth until 6 months of age, and safety parameters of the infant and mother. Safety analysis included infant's birth weight, incidence of pre-term deliveries, gestational age, total bilirubin levels, and presence of complications at birth. Maternal safety parameters included the change from baseline to delivery of laboratory parameters and symptoms such as transaminases, total bilirubin, hemoglobin, nausea, and weight gain. These safety endpoints were chosen based on a prior PI study in pregnancy [13].

For the primary analysis, the INSTI-exposed cohort was matched 1:2 to the cohort treated with lopinavir/ritonavir or atazanavir/ritonavir, based on the presence or absence of a detectable VL at the time the patient was found to be pregnant. During the data collection period, lopinavir and atazanavir were the DHHS guideline-recommended PIs for initiation during pregnancy [2]. The purpose of matching was to minimize the large imbalance in the number of patients per treatment arm. The achievement of VL suppression prior to pregnancy was chosen as the matching variable because of its possible confounding effect on the outcome, since most patients would maintain VL suppression throughout the entire pregnancy if it had been achieved prior. Additional analyses were also performed on the full cohort including all of the unmatched and matched patients on PIs compared to the INSTI-exposed patients. Patients receiving an INSTI may have also received a PI as the INSTI was occasionally added to a complete ART regimen for intensification. In these cases, the patient was considered part of the INSTI-exposed treatment arm.

Statistical Analysis

Study data were collected and managed using REDCap electronic data capture tools hosted by the University of the Sciences [14]. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies. Atazanavir and lopinavir were matched by a random number generator available in Microsoft Excel (Microsoft, 2008). Data analyses were performed using SAS® software, v.9.4 (SAS Institute, Cary, NC, USA). Baseline demographics were analyzed using descriptive statistics, Wilcoxon rank sum test, and Fisher's exact test for non-parametric quantitative

data and categorical data, respectively. Fisher's exact test was used to determine differences in the achievement of VL suppression prior to delivery. A multivariate logistic regression model was then employed to control for potential confounding variables that could affect the primary outcome. For secondary outcomes, the Wilcoxon rank sum test was used for non-parametric quantitative data and Fisher's exact for nominal data. The p values were two-sided with a threshold of 0.05 for statistical significance.

RESULTS

A total of 60 pregnancies from 51 patients were screened (Fig. 1). Forty-one pregnancies met the inclusion criteria, and 14 patients had achieved VL suppression prior to pregnancy determination, whereas 27 patients had a detectable VL at the time of pregnancy determination (Fig. 1). Fourteen of 34 PI patients were matched 2:1 to the 7 INSTI patients based on the presence or absence of VL at the time of pregnancy determination. Within the INSTI-exposed patients, there was representation from all 3 currently available agents [raltegravir ($n = 4$), dolutegravir ($n = 2$), and elvitegravir ($n = 1$)]. There were a total of 21 infants from 21 mothers included in the secondary endpoints and safety analyses for the matched cohorts. In addition to the matched cohort, the full cohort of 41 mothers was also evaluated for differences in secondary endpoints. Within the sample size of 41, the majority of the mothers received atazanavir ($n = 20$), followed by lopinavir ($n = 9$), an INSTI ($n = 7$), or darunavir ($n = 5$) in addition to a standard dual NRTI backbone.

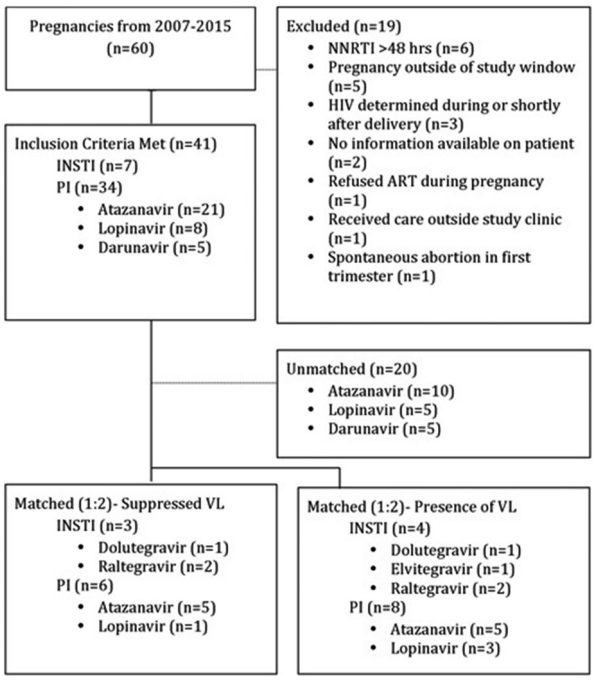

Fig. 1 Study design of pregnant women evaluating INSTI versus matched PI

Baseline demographics and clinical characteristics between the matched PI and INSTI groups were well balanced (Table 1). The median age of the mothers at the time of delivery was 31 years [interquartile range (IQR) 26–35 years]. The majority of patients were diagnosed with HIV before pregnancy (85.7% and 64.3% for INSTI and PI, respectively), yet patients that were exposed to an INSTI had been diagnosed with HIV longer compared to those on a PI [96 days (IQR 3–216) vs. 20 days (IQR 2–56), $p = 0.401$] and were less likely to be ART naïve (14.3% vs. 42.9%, $p = 0.337$), although these differences were not statistically significant. In fact, 2 of the 21 matched patients were perinatally infected themselves and both received an INSTI during pregnancy. Although the majority of patients in each arm were on treatment before pregnancy was determined, the patients with viremia that received INSTIs had it added to their ART regimen later in pregnancy in an attempt to achieve virologic suppression prior to delivery (average 7.5th month, range 5–9th month of pregnancy). In these cases, the INSTI was added to the standard ART regimen, which included a recommended PI; therefore, the ART for 4 of the 7 INSTI-exposed women was two NRTIs, a boosted PI, and an INSTI.

In the matched cohorts, we observed more patients in the INSTI-exposed arm having adherence issues documented prior to initiation of the INSTI and while on the agents (57.1% vs. 30.8%, $p = 0.356$). On account of the poor adherence, 3 of 4 INSTI-exposed patients with viremia when found to be

Table 1 Baseline characteristics of women on INSTIs and matched PIs

	INSTI ($n = 7$)	Matched PI ($n = 14$)	p value
Maternal age, years			
Median (IQR)	30 (25–33)	33 (26–37)	0.245
Race/ethnicity, n (%) ($n = 20$)			
African American	4 (57.1)	5 (35.7)	
Caucasian or White	1 (14.3)	2 (14.3)	
Hispanic	2 (28.6)	6 (42.9)	0.818
Timing of HIV diagnosis, n (%)			
Before pregnancy	6 (85.7)	9 (64.3)	
During pregnancy	1 (14.3)	5 (35.7)	0.613
Time between diagnosis and pregnancy, days			
Median (IQR)	96 (3–216)	20 (2–56)	0.401
ART naïve at time of pregnancy, n (%)	1 (14.3)	6 (42.9)	0.337
Term any ART was added, n (%)			
Before pregnancy	6 (85.7)	7 (50.0)	
1st Trimester	0 (0.0)	4 (28.6)	
2nd Trimester	1 (14.3)	3 (21.4)	0.247
Term INSTI was added, n (%)			
Before pregnancy	3 (43)	N/A	
1st Trimester	0 (0)	N/A	
2nd Trimester	1 (14)	N/A	
3rd Trimester	3 (43)	N/A	
Documentation of adherence issues, n (%) ($n = 20$)[a]	4 (57.1)	4 (30.8)	0.356
Maternal ALT, units/L			
Median (IQR)	11 (8–38)	16.5 (12–29)	0.206
Maternal AST, units/L			
Median (IQR)	19 (13–25)	21 (18–24)	0.421
Maternal total bilirubin, mg/dL			
Median (IQR)	0.2 (0.2–0.7)	0.7 (0.3–0.9)	0.126
Maternal weight, kg ($n = 20$)		$n = 13$	
Median (IQR)	86.5 (68.0–89.5)	86.5 (64.0–129.0)	0.655

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *ART* antiretroviral therapy, *INSTI* integrase strand inhibitor, *IQR* interquartile range, *PI* protease inhibitor

[a] Adherence was recorded if mentioned by the provider in the clinic notes

pregnant, were admitted to a local hospital for direct observation therapy in the 1–4 weeks prior to delivery.

Primary and Secondary Clinical Endpoints of the Matched Cohort

Overall, 95.7% of the matched patients achieved VL suppression prior to delivery. There were no significant differences between treatment groups with respect to the proportion of patients achieving VL suppression prior to delivery (71.4% vs. 92.9% for INSTI and PI, respectively, $p = 0.247$) (Table 2). Overall, three patients did not achieve VL suppression prior to delivery, two in the INSTI group and one in the PI group. These two INSTI patients were admitted to a hospital for direct observation therapy, during which the VL decreased from 4699 to 751 copies/mL for one patient and 1092 to 224 copies/mL for the other in the last 2 weeks of pregnancy. For these two patients, the INSTI was added in the 7th and 9th month of pregnancy, respectively.

Patients that had not achieved VL suppression prior to delivery were more likely to have

Table 2 Maternal clinical endpoints on INSTIs and matched PIs

	INSTI ($n = 7$)	Matched PI ($n = 14$)	p value
VL suppression prior to delivery, n (%)			
Yes	5 (71.4)	13 (92.9)	
No	2 (28.6)	1 (7.1)	0.247
Time to VL suppression after starting ART, weeks ($n = 12$)	$n = 4$	$n = 8$	
Median (IQR)	9.5 (2.0–26.0)	15.5 (8.0–16.0)	0.502
Time VL suppression maintained, weeks ($n = 13$)	$n = 4$	$n = 7$	
Median (IQR)	19.5 (1.0–40.5)	16.0 (8.0–20.0)	0.820
Delivery mode, n (%) ($n = 18$)		$n = 11$	
Vaginal	4 (57.1)	6 (54.6)	
Cesarean	3 (42.9)	5 (45.5)	1.000

ART antiretroviral therapy, *INSTI* integrase strand inhibitor, *IQR* interquartile range, *PI* protease inhibitor, *VL* viral load

adherence issues documented (100% vs. 29.4% for not-suppressed and suppressed at delivery, respectively, $p = 0.049$). A logistic regression model demonstrated no significant difference in the achievement of VL suppression at the time of delivery between treatment groups, while controlling for documented poor adherence, as well as time from HIV diagnosis to pregnancy.

There were no significant differences between treatment groups with respect to the following secondary endpoints: time to VL suppression after starting any ART, duration of viral suppression once maintained on any ART, and delivery mode (Table 2). There were no delivery complications, including eclampsia, documented in either group. The mode of delivery was evenly distributed between vaginal or cesarean procedure between the two groups. Although the time to VL suppression was not statistically different between the two groups, there was a tendency towards INSTI-exposed patients achieving VL suppression faster than PI patients [9.5 weeks (IQR 2.0–26.0) INSTI vs. 15.5 weeks (IQR 8.0–16.0) PI, $p = 0.502$].

Safety Endpoints of Mothers and Infants of Matched Cohort

All infants, for whom data were available, tested negative for HIV at birth ($n = 19$). At the time of data collection, not all children had reached 6 months of follow-up, yet those with follow-up tested negative at 6 months ($n = 16$). Due to deliveries outside of the health system, not all endpoints were reportable for all infants. There were no significant differences between the treatment groups with respect to the safety endpoints for the infants (Table 3). Overall, the median gestational age of the infants was approximately 38.0 weeks (IQR 37.5–39.0), and the majority of infants were born having a normal birth weight (>2500 g). There was a tendency for infants exposed to a PI to have an elevated total bilirubin level at birth (42.9% vs. 0.0% for PI and INSTI, respectively, $p = 0.475$), but this is likely secondary to the known side effect of atazanavir [2, 15]. All infants received zidovudine for at least 4 weeks post-delivery for post-exposure prophylaxis. Pertaining to the mother's safety endpoints, there were no significant differences between the treatment groups with respect to ALT, AST, total bilirubin, weight change, or reported symptoms from baseline to delivery (Table 4).

Clinical and Safety Endpoints of Full Study Cohort

There were no statistically significant differences between the clinical or demographic

Table 3 Clinical and safety endpoints of infants exposed to INSTIs and matched PIs

	INSTI ($n = 7$)	Matched PI ($n = 14$)	p value
HIV status of infant at birth, n (%) ($n = 19$)		$n = 12$	
Negative	7 (100)	12 (100)	
HIV status of infant at 6 months of age, n (%) ($n = 16$)	$n = 4$	$n = 12$	
Negative	4 (100)	12 (100)	
Low birth weight (<2500 g), n (%) ($n = 16$)	$n = 6$	$n = 10$	1.000
	2 (33.3)	4 (40.0)	
Gestational age at birth, weeks			
Median (IQR)	38.0 (38.0–39.0)	38.5 (37.0–39.0)	0.706
Total bilirubin at birth >5 mg/dL, n (%) ($n = 10$)	$n = 3$	$n = 7$	
	0 (0.0)	3 (42.9)	0.475
APGAR score ($n = 14$)	$n = 6$	$n = 8$	
Median (IQR)	9 (7.0–9.0)	9 (7.5–9.0)	1.000
Pre-term delivery, n (%)	1 (14.3)	2 (14.3)	1.000

ART antiretroviral therapy, *INSTI* integrase strand inhibitor, *IQR* interquartile range, *PI* protease inhibitor

characteristics of the two groups for the full cohort. Regarding the endpoints for all three individual PIs compared to INSTIs, there was a significant difference between treatment groups with respect to the proportion of patients virologically suppressed prior to delivery. Overall, INSTI-exposed patients were less likely to have VL suppression compared to those exposed to each of the three PIs (71.4% INSTI vs. 85.0% atazanavir, 80.0% darunavir, and 100.0% lopinavir, $p = 0.001$) (Table 5). In addition to the sample size bias, there were two identifiable potential confounders on the primary endpoint. Documentation of adherence issues and the time from diagnosis of HIV to pregnancy were significantly associated with not achieving VL suppression prior to delivery and only 14.7% of the patients with adherence issues documented achieved viral load suppression (14.7% vs. 83.3%, $p = 0.002$). After controlling for these two confounders, there was no significant effect of treatment group on the chance of VL suppression prior to delivery {time from diagnosis to pregnancy [odds ratio (OR) 0.98; 95% confidence interval (CI) 0.96–1.00; $p = 0.052$]; adherence issues (OR 4.08; 95% CI 0.19–86.05; $p = 0.366$)}.

There were no significant differences between the four treatment groups with respect to any of the secondary efficacy outcomes in the mothers or infants. However, there was a significantly higher rate of diarrhea reported with the use of lopinavir compared to other treatment groups (44% lopinavir, 0% darunavir, 5% atazanavir vs. 0% INSTI, $p = 0.026$). There were no documented delivery complications in any of the groups. Overall, approximately half of the infants were delivered vaginally (54.6%). The majority of infants exposed to any ART were born at term (80.5%) in which there were no differences observed between any of the PIs or INSTIs in the rate of pre-term versus term delivery ($p = 0.302$).

Table 4 Maternal safety endpoints of those on INSTIs and matched PIs

	INSTI ($n = 7$)	Matched PI ($n = 14$)	p value
Symptoms reported, n (%)			
Nausea	3 (42.9)	4 (28.6)	0.638
Vomiting	3 (42.9)	3 (21.4)	0.354
Diarrhea	0 (0.0)	3 (21.4)	0.521
Headache	2 (28.6)	1 (7.1)	0.247
Dizziness	2 (28.6)	2 (14.3)	0.574
Change in ALT, units/L[a]			
Median (IQR)	−2.5 (−3.0, 6.0)	0.0 (−18.0, 4.0)	0.829
Change in AST, units/L[a] ($n = 19$)	$n = 6$	$n = 13$	
Median (IQR)	−3.0 (−8.0, 4.0)	−2.0 (−9.0, 4.0)	0.829
Change in total bilirubin, mg/dL[a] ($n = 18$)	$n = 6$	$n = 12$	
Median (IQR)	0.1 (0.1, 0.4)	0.1 (0.0, 0.7)	0.770
Change in weight, kg[a] ($n = 18$)	$n = 5$	$n = 13$	
Median (IQR)	3.0 (3.0, 4.5)	10.0 (5.5, 15.0)	0.157

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *INSTI* integrase strand inhibitor, *IQR* interquartile range, *PI* protease inhibitor

[a] Change was calculated from baseline to delivery

DISCUSSION

In this study, there was no difference found in the efficacy or safety of INSTIs when used in pregnancy compared to the use of previous guideline recommended PI regimens. Due to the small number of women exposed to INSTIs, the difference in the percentage of patients achieving VL suppression between groups was reflective of only one patient with 71.4% of mothers exposed to an INSTI with VL suppression prior to delivery and 92.9% of mothers exposed to PI-based regimens with VL suppression prior to delivery. Although the time to VL suppression was not statistically different between the two groups, there was a trend towards INSTI-exposed patients achieving virologic suppression faster than PI patients. The patients that received INSTIs in this study had medication adherence issues or late pregnancy viremia, which supports the potential niche uses of INSTI in pregnancy suggested by previous studies and guidelines [2, 16–19].

There were no significant differences in the change in maternal aminotransferases (ALT and AST) in those exposed to either class of antiretrovirals in this study. One previous case report of raltegravir use in 35 weeks of pregnancy observed a 23-fold increase in serum aminotransferase and a tenfold increase in serum aspartate aminotransferase levels after 11 days of raltegravir when added to zidovudine, lamivudine, lopinavir, and ritonavir [20]. The elevated serum transaminase levels normalized after discontinuation of raltegravir and no safety concerns were identified in the infant.

Despite three mothers not achieving VL suppression prior to delivery, there were no documented perinatal transmissions up to 6 months of age. There was a low incidence of pre-term delivery with the use of intrapartum ART overall in this study. In addition, there

Table 5 Selected demographic characteristics, efficacy, and safety endpoints of full study cohort

	INSTI ($n = 7$)	Unmatched PI ($n = 34$)			p value
		Atazanavir ($n = 20$)	Darunavir ($n = 5$)	Lopinavir ($n = 9$)	
Maternal age, years					
Median (IQR)	30 (25–33)	31 (26–36)	25 (23–26)	27 (25–34)	0.206
Timing of HIV diagnosis, *n* (%)					
Before pregnancy	6 (85.7)	14 (70.0)	5 (100.0)	5 (55.6)	
During pregnancy	1 (14.3)	6 (30.0)	0 (0.0)	4 (44.4)	0.361
Time between diagnosis and pregnancy, days					
Median (IQR)	96 (3–216)	12 (3–47)	20 (5–39)	1 (−2, 12)	0.300
ART naïve at time of pregnancy, *n* (%)	1 (14.3)	9 (45.0)	0 (0.0)	6 (66.7)	0.392
Documentation of adherence issues, *n* (%) ($n = 40$)[a]	4 (57.1)	$n = 19$ 5 (26.3)	1 (20.0)	0 (0.0)	0.066
Primary endpoint:					
VL suppression prior to delivery, *n* (%)					
Yes	5 (71.4)	17 (85.0)	4 (80.0)	9 (100.0)	0.001
Secondary endpoints:	$n = 4$	$n = 13$	$n = 3$	$n = 7$	
Time to VL suppression after starting ART, weeks ($n = 27$)					
Median (IQR)	9.5 (2.0–26.0)	12.0 (8.0–16.0)	18.0 (16.0–18.0)	15.0 (6.0–16.0)	0.207
Delivery mode, *n* (%) ($n = 33$)		$n = 14$		$n = 7$	
Vaginal	4 (57.1)	7 (50.0)	3 (60.0)	4 (57.1)	1.000
Cesarean	3 (42.9)	7 (50.0)	2 (40.0)	3 (42.9)	
Symptoms reported, *n* (%)					
Nausea	3 (42.9)	5 (25.0)	0 (0.0)	3 (33.3)	0.440
Vomiting	3 (42.9)	4 (20.0)	0 (0.0)	2 (22.2)	0.400
Diarrhea	0 (0.0)	1 (5.0)	0 (0.0)	4 (44.4)	0.026
Change in T. bilirubin, mg/dL[b] ($n = 29$)	$n = 5$	$n = 13$	$n = 4$	$n = 7$	
Median (IQR)	0.1 (0.1–0.4)	0.7 (0.0–1.2)	0.1 (0.1–0.2)	0 (0–0.2)	0.504

ART antiretroviral therapy, *INSTI* integrase strand inhibitor, *PI* protease inhibitor, *IQR* interquartile range, *VL* viral load

[a] Adherence was recorded if mentioned by the provider in the clinic notes

[b] Change was calculated from baseline to delivery

were very few adverse effects documented in the infants through 6 months of age in either ART class. Elevated bilirubin was common in those exposed to atazanavir, which has been observed in previous studies examining infants exposed to atazanavir in utero [2, 10, 13].

The results from this study concur with current knowledge regarding the association between poor medication adherence and achieving VL suppression. Older studies with unboosted PIs suggested greater than 95% adherence was required for sustained virologic suppression, yet data with boosted PIs or NNRTIs suggest that greater than 80% is sufficient [21]. This study shows an association between clinician-reported poor adherence and a failure to achieve virologic suppression prior to delivery. There was no reasonable method of measuring adherence in this study due to the retrospective data collection and the lack of standard adherence assessment documentation throughout the time range of data collection. Thus, the qualitative determination of poor adherence was established solely on available provider documentation.

There was a greater incidence of diarrhea with the use of lopinavir. Lopinavir was downgraded to an alternative PI for use in pregnancy because of its twice-daily dosing and side effect profile, which includes nausea [2]. Other than diarrhea associated with lopinavir use in our study, there were no differences in the secondary efficacy or safety endpoints for the mother or the infant between all four treatment arms. Atazanavir is also known to potentially cause maternal hyperbilirubinemia [2]. Our study did result in a larger change in maternal total bilirubin from baseline to delivery with the use of atazanavir compared to other treatment groups, but this did not reach statistical significance.

Limitations of this study include the small sample size analyzed as well as the retrospective chart review study design. Based on the rates of VL suppression prior to delivery observed in this study, to find a statistically significant difference between groups at alpha 0.05, with a power of 0.8 and an allocation ratio of 1:2, the necessary sample size would be 36 subjects in the INSTI group and 72 in the matched PI group. In addition, the INSTI and PI groups were not completely independent as some patients were on both an INSTI and a PI during pregnancy; therefore, a pure comparison between classes was not possible. With the retrospective nature, there is a risk of incomplete data. In this study, there were some incomplete data affecting secondary endpoints primarily due to infant deliveries outside of the health system. The low utilization of INSTIs during this study period show-cased the reluctance to use a newer class of ART in pregnancy in clinical practice at the time. The 2:1 matching of PI to INSTI, although it reduced the sample size for the primary endpoint, was chosen in order to minimize biases and provide the greatest potential for internal validity. Since published literature on ART in pregnancy is limited, we also analyzed the entire dataset although unmatched with the hope of providing more information for clinical decisions. The lack of statistical significance of the endpoints could be due to the small sample size resulting in underpowering of the study.

Primarily case reports and pharmacokinetic studies of the use of INSTIs in pregnancy have been published. INSTIs uniquely possess the ability to rapidly decrease the VL by as much as 2-log copies/mL within 2 weeks of initiation [8, 9]. Several case reports and case series suggest the efficacy of raltegravir in pregnant women with high VLs when added to standard therapy late in pregnancy [16–20, 22]. A pharmacokinetic study of raltegravir in pregnancy reported a 50% reduction in area under the curve (AUC) in the second and third trimesters compared to postpartum [23]. No dose-adjustment recommendations have been made because of the high rate of virologic response despite this reduction and the large inter- and intra- subject variability of plasma concentrations in both pregnant and non-pregnant adults [2, 24]. A more recent pharmacokinetic study by Blonk et al. reported an AUC only 29% lower during the third trimester compared to post-partum [25]. This study also showed that raltegravir was well tolerated, and no birth defects were reported in the 9 HIV-negative infants that were exposed to raltegravir from the first trimester to birth. Of the four women who received

raltegravir in pregnancy in our study, two were on raltegravir-containing ART regimens prior to becoming pregnant and maintained virologic suppression throughout their pregnancies, and two had raltegravir added to their ART regimens in the eighth and ninth months of pregnancy, respectively, due to persistent viral loads and documented adherence issues. One of those two women achieved virologic suppression prior to delivery.

A published pharmacokinetic case report of dolutegravir in pregnancy described its use in a 33-week pregnant mother with late pregnancy virologic failure requiring intensification of ART [26]. The C_{24}, or C_{min}, for dolutegravir in the mother was greater than the geometric mean steady state C_{min} value found in non-pregnant patients in phase 2 and 3 trials [27]. Dolutegravir accumulated in the neonate, born at 35 weeks. The calculated terminal half-life of dolutegravir using a one-compartment model was fourfold longer in the infant compared to adults (46 h) [27]. The premature infant was born underweight (1600 g), but was overall healthy and tolerated the accumulation of dolutegravir without any untoward side effects noted. A poster presentation by Mulligan et al. at the Conference on Retroviruses and Opportunistic Infections (CROI) in February 2016 described pharmacokinetic data of dolutegravir 50 mg daily given to 21 pregnant women from the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) [15]. In this study, dolutegravir concentrations were 25–30% lower during the second and third trimesters compared to the paired post-partum concentrations, although paired samples were only available for 4 women in the second trimester and 7 in the third [overall median (IQR) C_{min} 0.86 μg/mL (0.64–1.37) and 0.86 μg/mL (0.55–1.13) for second and third trimesters, respectively vs. 1.70 μg/mL (0.70–2.00) post-partum]. In addition, the dolutegravir elimination half-life in the infants was prolonged at 32 h (32–55 h), which is a comparable effect seen in the previously described pharmacokinetic case. Four infants were born with congenital abnormalities deemed unlikely to be due to dolutegravir exposure. Despite lower dolutegravir exposure observed during pregnancy, the authors do not recommend alternate dosing of dolutegravir in pregnancy, but instead recommend further studies. Of the two women who received dolutegravir during pregnancy in our study, one was suppressed on a dolutegravir-containing ART regimen prior to becoming pregnant and remained suppressed through delivery, and the other had dolutegravir added to her regimen in the seventh month due to a viral load and documented adherence issues. Her viral load decreased to 224 copies/mL by the time of delivery.

Finally, a poster presentation by Best et al. at CROI in February 2017, described the pharmacokinetics of elvitegravir in pregnancy in 29 women from the IMPAACT P1026s study, an ongoing pharmacokinetic study of antiretrovirals in pregnancy [28]. Elvitegravir concentrations were similarly lower during the second and third trimesters compared to post-partum. The median (IQR) elvitegravir C_{24} and AUC_{0-24} in the second trimester was compared to post-partum for 5 women with a resultant geometric mean ratio (GMR) of only 0.14 (0.06–0.34) for C_{24} and 0.51 (0.33–0.78) for AUC_{0-24}. The median (IQR) elvitegravir C_{24} and AUC_{0-24} in the third trimester was compared to post-partum for 15 women with a resultant GMR of only 0.13 (0.09–0.17) for C_{24} and 0.58 (0.48–0.69) for AUC_{0-24}. There was one case of pre-term labor and delivery that was deemed possibly related to treatment, and there were two congenital abnormalities reported. The authors concluded that elvitegravir concentrations are substantially lower during pregnancy compared to post-partum and standard doses may not be adequate. The one subject who received elvitegravir-based ART during pregnancy in our cohort began taking it in the second trimester as part of a standard ART regimen and did, in fact, achieve virologic suppression prior to delivery.

CONCLUSIONS

With the scarcity of data on the use of INSTIs in pregnancy, our retrospective, matched cohort study provides more information regarding the safety and efficacy of all three

INSTI agents in pregnancy when compared to other standard treatment options. In addition, the observed lack of safety concerns or differences in efficacy compared to the preferred options further supports the new addition of raltegravir to the list of preferred ART options for initiation in pregnancy. Now that the DHHS adult guidelines and clinical practice within the United States favor INSTIs as the mainstay in the treatment of adults with HIV, it is likely that they will increasingly be used during pregnancy. More studies investigating the INSTI class in pregnancy would provide useful information for clinicians. A larger study comparing the various INSTI agents for differences within the class, and further studies with elvitegravir and dolutegravir, would provide the information needed to inform on the efficacy and safety of these agents, and to assist with dosing recommendations for use in pregnancy.

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Compliance with Ethics Guidelines. This study was approved by the Institutional Review Board at Cooper University Hospital and all procedures followed were in accordance with the ethical standards of research. This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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