21 Integrase strand transfer inhibitors given to HIV-infected women late in pregnancy decrease HIV viral load more quickly than other antiretroviral therapy (ART)

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OBJECTIVE: Minimizing time to HIV viral suppression is critical in pregnancy. Integrase strand transfer inhibitors (INSTIs), like raltegravir, are known to rapidly suppress plasma HIV RNA in nonpregnant adults. We describe time to clinically relevant reduction in HIV RNA in pregnant women using INSTI-containing and non-INSTI-containing ART options.

STUDY DESIGN: We conducted a retrospective cohort study of pregnant HIV-infected women in the U.S. from 2009 to 2015. We included women who initiated ART, intensified their regimen or switched to a new regimen due to detectable viremia (HIV RNA > 40c/mL) at > 20 weeks gestation. Among women with a baseline HIV RNA permitting 1-log reduction, we estimated time to 1-log RNA reduction using the Kaplan-Meier estimator comparing women starting/adding an INSTI in their regimen versus other ART. To compare groups with similar follow-up time, we also conducted a subgroup analysis limited to women with <14 days between baseline and follow-up RNA data.

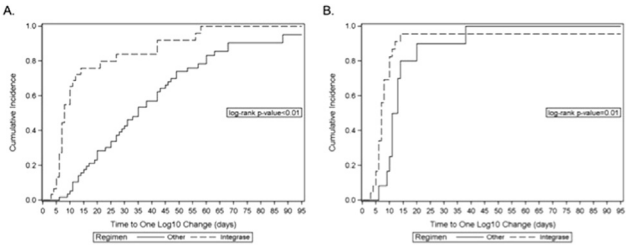
RESULTS: Maternal characteristics of 101 women from 11 U.S. clinics are shown in Table 1. 76/101 (75%) women were not taking ART at baseline. 39/101 (39%) women started/added an INSTI in their ART regimen. Among 90 women with a baseline HIV RNA permitting 1-log reduction, the median time to 1-log RNA reduction was 8 [IQR: 6, 14] days in the INSTI group versus 35 [IQR: 20, 53] days (p<0.001) in the non-INSTI ART group. In a subgroup of 39 women with first and last RNA measurements <14 days apart, median time to 1-log reduction was 7 [IQR: 6, 10] days in the INSTI group versus 11 [IQR: 10, 14] days (p=0.01) in the non-INSTI group. (Figure 1)

CONCLUSION: ART that includes INSTIs appears to induce more rapid viral suppression than other ART regimens in pregnancy. Inclusion of an INSTI may play a role in optimal reduction of HIV-RNA for HIV-infected pregnant women presenting late to care or failing initial therapy. Larger studies are urgently needed to assess the safety and effectiveness of this approach.

TABLE 1. Characteristics of 101 HIV-infected pregnant women from 11 US clinics post 20 weeks gestation at time of starting/including a new ART regimen, 2009-2015.
Categorical variables are expressed as N (%), and continuous variables are expressed as median (IQR).
*** Missing data, N=1**

	Integrase (N=39)	Other ART (N=62)	p-value
Race & Ethnicity			
White, non-Hispanic	5 (13)	11 (18)	0.47
White, Hispanic	4 (11)	6 (10)	
Black	28 (72)	45 (73)	
Other	2 (5)	0 (0)	
Parity*			
0	17 (44)	21 (34)	0.63
≥1	22 (56)	40 (65)	
Maternal Age (years)	29 (23, 34)	26 (23, 31)	0.33
Median Gestational Age (weeks)	33.6 (29.9-36.1)	27.5 (25.4-30.7)	<0.01
Body Mass Index (kg/m^2)	28.2 (24.4-35.0)	30.5 (26.6-35.3)	0.33
No ART at baseline	20 (51)	56 (90)	<0.01
Initial HIV RNA (log_{10})	4.3 (3.5-4.9)	4.1 (3.3-4.6)	0.17
(copies/mL)	21,278 (3,370-71,660)	13,015 (2,050-35,570)	
AIDS Diagnosis	23 (60)	20 (32)	<0.01

FIGURE 1. Cumulative incidence of time to 1-log_{10} change among A) 90 HIV-infected pregnant women from 11 U.S. clinics and B) a subset of 39 of the 90 HIV-infected pregnant women with baseline and follow up HIV RNA measurement of less than 14 days, stratified by drug regimen intervention.



22 Changes in the patterns and rates of term stillbirth in the USA following the adoption of the 39-week rule: a cause for concern?

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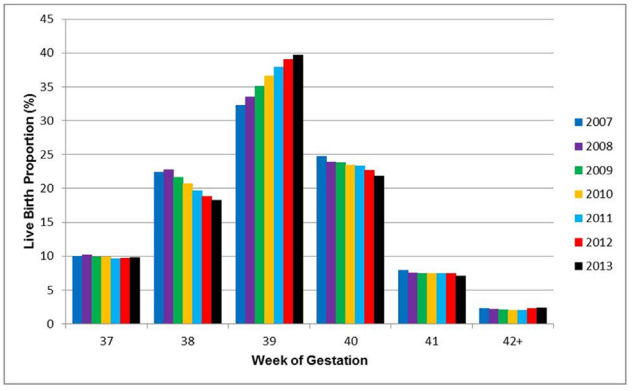
OBJECTIVE: Because of reported associations between early-term delivery and various neonatal morbidities, an obstetric guideline called "the 39-week rule" was formally implemented in 2010 throughout the USA. The rule restricts "non-indicated" planned delivery prior to 39 weeks of gestation. However, several publications have suggested that the rule, by increasing the mean gestational age of term delivery, might increase population rates of term stillbirth. The objective of this large study was to determine if implementation of the 39-week rule was associated with an increase in the USA rate of term stillbirth.

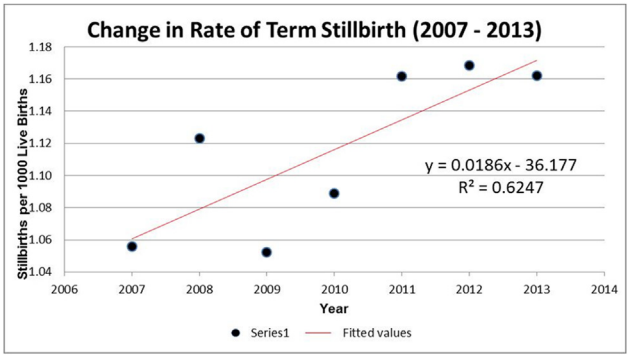
STUDY DESIGN: Sequential ecological study, using state data, of the patterns and rates of term live births and term stillbirths within the USA between 2007 and 2013, inclusive.

RESULTS: Usable datasets were obtained from 46 states. Between 2007 and 2013 there was a continuous decrease in the proportion of term deliveries occurring in the 37th and 38th weeks of gestation. Over the same interval there was a continuous increase in the rate of term stillbirth (slope: 0.0186/1000/year, 95% CI 0.002-0.035). When comparing the 2007-2009 period to the 2011-2013 period, the rate of USA term stillbirth increased from 1.103/1000 to 1.177/1000 (RR 1.067, 95% CI 1.038-1.096).

CONCLUSION: Between 2007 and 2013 in the USA, the implementation of the 39-week rule achieved its primary goal of reducing the proportion of term births occurring before the 39th week of

gestation. During the same period the rate of USA term stillbirth increased significantly. Assuming 3.5 million term USA births per year, more than 300 more term stillbirths occurred in the USA in 2013 as compared to 2007. This study raises the possibility that the 39-week rule may be causing serious unintended harm. Additional studies measuring the possible impact of the implementation of the 39-week rule on major childbirth outcomes are urgently needed. Pressures to enforce the 39-week rule should be reconsidered pending the findings of such studies.





23 Antibiotics and betamethasone therapy do not significantly alter the placental microbiome in chorioamnionitis affected pregnancies

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OBJECTIVE: Chorioamnionitis (IAI) is frequently associated with PTB. We have demonstrated that the placenta harbors a unique microbiome and have recently shown that the preterm placental microbiome is distinct and varies based infection. Here, we aimed to examine the differences in the placental microbiome based on clinically indicated therapy (i.e. antibiotics, betamethasone) for preterm birth and IAI.

STUDY DESIGN: This was a cross-sectional analysis of prospectively acquired subject samples from women who delivered between 32-36 weeks. Women who delivered preterm received antibiotics (n=23) and steroids (n=12) as clinically indicated, and all placentas were sent to pathology. Histologic gradation of IAI and funisitis was reported. This resulted in six nested spontaneous birth cohorts (n=9-15 subjects/cohort, Table 1). DNA was extracted from placental swabs collected immediately at delivery and subjected to whole genome shotgun (WGS) metagenomic sequencing. Filtered microbial DNA sequences (150 million/sample) were annotated and analyzed using MG-RAST and R.

RESULTS: The mean gestational age (GA) for spontaneous preterm infants was 35.1 weeks. We observed different placental microbiome communities among preterm subjects with severe IAI (p=0.07) and with antibiotic treatment (p=0.021). However, we did not find clear differences in the most abundant taxa between preterm subjects that received antibiotic treatment and those that did not (Fig A). Additionally, we found no significant impact on Mycobacterium (p=0.76), Mycoplasma (p=0.89), and Ureaplasma (p=0.52) species. Furthermore, when examining steroid treatment, we found no significant differences in microbial communities (p=0.33) (Fig B).

CONCLUSION: Our data support the premise that histologically severe chorioamnionitis is associated with a significantly altered placental microbiome. Interestingly, antibiotic treatment did not significantly further shape nor modify the microbial community in regards to abundant species nor pathologically relevant species. These data suggest that the association of inflammation and spontaneous preterm birth warrants additional investigation, and that the cumulative impact of IAI on the placental microbiome is not amenable to antibiotic therapy.

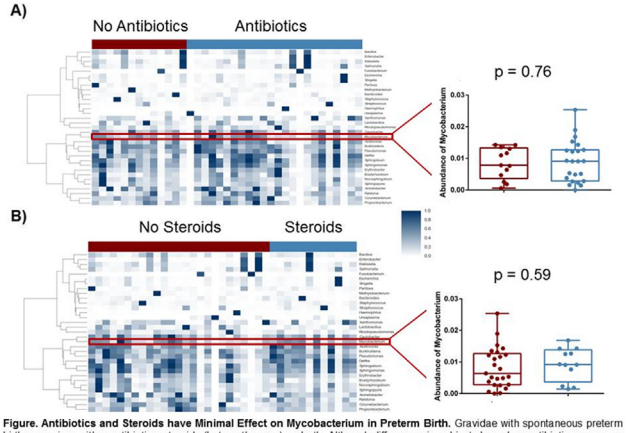

Figure. Antibiotics and Steroids have Minimal Effect on Mycobacterium in Preterm Birth. Gravidae with spontaneous preterm birth were given either antibiotics, steroids (betamethasone), or both. Although differences in subjects based on antibiotic usage was seen (p = 0.021), we did not see significant differences in the genus *Mycobacterium* in subjects that received antibiotics (A) or betamethasone (B). Statistics were determined by a t test.

Table 1. Cross-Sectional Cohorts

	Term/Preterm	Chorioamnionitis	Funisitis
Cohort 1	Term	No	No
Cohort 2	Term	Yes	No
Cohort 3	Preterm	No	No
Cohort 4	Preterm	Mild	No
Cohort 5	Preterm	Severe	No
Cohort 6	Preterm	Severe	Yes