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The impact of expedited third trimester viral load testing on the proportion of vaginal deliveries in HIV-positive pregnant women in the Dominican Republic

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Abstract

Objective: Advances in HIV treatment have led to a significant decrease in vertical transmission. Lack of adequate viral load testing capabilities inhibited the ability to follow national and international guidelines for obstetric care in the Dominican Republic (DR). The objective of this study was to determine if expedited third trimester viral load testing in HIV-positive pregnant women led to an increase in vaginal deliveries at a clinic in the DR, thus demonstrating the ability to follow national guidelines for obstetric delivery of HIV-positive women on antiretroviral therapy (ART).

Study Design: This study enrolled pregnant HIV-positive patients at a clinic in the DR October 2014-July 2015. Viral load testing was performed 34-36-weeks gestation and results were available within 48 hours. Demographic information, clinical factors, and obstetric outcomes were collected and compared to patients in a retrospective cohort, who delivered January 2012-December 2012 when expedited viral load testing was unavailable.

Results: Of the 20 women in the study, 17 (85%) had viral loads <1000 and seven women (35%) delivered vaginally. In the comparison retrospective cohort, of 41 women, three women (7%) had vaginal deliveries. Comparing the two groups, there was a statistically significant increase in vaginal deliveries from 7% to 35% (p=0.02) after expedited viral load testing was made available. All infants born in the study were HIV-negative.

Conclusion: The study with expedited viral load testing available had an increased number of vaginal deliveries of HIV-positive women on ART. The majority of these patients were on ART with HIV viral loads <1000, and access to viral load results allowed for providers and patients to plan for vaginal deliveries as indicated by national guidelines. These results reinforce the importance of access to timely viral load testing for pregnant women with HIV and support previous research demonstrating no increase in vertical transmission from mother to infant during vaginal delivery.

Keywords: *HIV, Vertical Transmission, Viral Load, Dominican Republic, Caribbean*

Introduction

The Caribbean region has the second-highest prevalence of human immunodeficiency virus (HIV) in the world after sub-Saharan Africa, with the Dominican Republic (DR) and Haiti accounting for nearly two-thirds of all new HIV cases in this area [1]. Currently, approximately 72,000 individuals are living with HIV in the DR, yielding a prevalence of 0.9% in adults [2]. Although much progress has been made, mother-to-child (i.e., vertical) transmission of HIV remains significant, with approximately 1,300 children below the age of 15 living with HIV in the DR [2,3].

Advances in HIV treatment and monitoring are changing the landscape of vertical transmission of this disease. Current guidelines from the United States and DR recommend that women infected with HIV receive antiretroviral therapy (ART) during pregnancy, because ART significantly decreases vertical transmission rates [4,5]. Before ART, Cesarean sections (C-section) were recommended for all HIV-positive women to decrease the risk of HIV transmission to the infant during delivery [6]. However, C-section carries significant risks including wound infection, infant respiratory problems, and a higher rate of maternal complications with future pregnancies (e.g.,

uterine rupture, placenta previa, placenta accreta, and bowel and bladder injury) [7]. As access to ART became widespread, studies demonstrated that pregnant patients on ART achieve a viral load low enough to decrease the risk of vertical transmission such that C-section and vaginal delivery carry the same vertical transmission rate [4]. Additionally, the DR has one of the highest maternal mortality rates in the region and the second highest C-section rate in Latin America [8,9]. International and Dominican guidelines now recommend that HIV-positive pregnant women who are on ART by the third trimester and meet certain criteria (e.g., HIV viral load less than 1000; negative syphilis, Hepatitis B, and Hepatitis C testing; fewer than two prior C-sections; no C-section in the past two years) should consider vaginal delivery in consultation with their obstetrician [4,5].

At the time of the study described herein, the DR had one viral load analyzer serving the entire country's population and was unable to support the testing demands. Thus, most HIV patients were either not monitored for viral load every six months, as recommended, or had their results returned months after testing, thereby decreasing clinical utility.

Located in the town of La Romana in the south-eastern region of the DR, Clínica de Familia La Romana (CFLR) is a non-profit primary care clinic that provides ambulatory services and houses an HIV clinic, in addition to providing care to HIV-positive pregnant women and their infants through a vertical transmission program. At the time this study was initiated, all HIV-positive pregnant women receiving care at CFLR were scheduled for delivery via C-section at 38 weeks gestation. Although national and international guidelines recommend considering vaginal delivery for women on ART with viral loads under 1000 at 34-36 weeks gestation, providers at CFLR were unable to follow these guidelines, because the in-country viral load testing program could not provide the required results in a timely fashion.

This study aimed to determine whether expedited viral load testing would be associated with an increase in planned vaginal deliveries in HIV-positive pregnant women in a vertical transmission program in the south-eastern DR (i.e., at CFLR).

Methods

This pilot study of HIV-positive pregnant women enrolled in a vertical transmission program at a primary care clinic, CFLR, and at its affiliated adolescent reproductive health clinic in La Romana in the south-eastern DR was performed from October 2014 through July 2015. All HIV-positive pregnant patients who were less than 36 weeks gestation and who were enrolled in CFLR's vertical transmission program were recruited and enrolled after providing written informed consent.

Demographic, clinical, and laboratory data were collected from patient medical records including the date of HIV diagnosis, current ART treatment and adherence, obstetric clinical history, expected date of delivery, planned and actual mode of delivery, maternal and infant outcomes, infant treatment regimen, maternal CD4 count, maternal complete blood count, and infant HIV PCR results at six weeks and six months post-partum. The mode of delivery was categorized as emergency C-section, elective C-section, or vaginal. Prior to initiation of the study, clinic physicians and staff were already aware of national guidelines for delivery options for HIV-positive pregnant women, so no additional education on these topics was necessary.

Whole blood specimens were collected from patients at 34-36 weeks gestation by trained CFLR phlebotomists. The samples were prepared and shipped overnight via FedEx to the New York Presbyterian/Columbia University Medical Center (CUMC) Clinical Microbiology Laboratory in accordance with specifications for the COBAS® TaqMan® HIV-1 Test, v2.0 and United States Category B infectious shipping regulations. Viral load testing was performed using the COBAS® TaqMan® HIV-1 Test, v2.0 in the CUMC Clinical Microbiology Laboratory and the results were uploaded within 48 hours from receiving the sample at CUMC onto a secure server for remote viewing by research staff at CFLR. Research personnel were available for questions and comments from staff and patients throughout the duration of the study. Research staff provided the HIV viral load results to the patient's medical team at CFLR, who independently utilized the results in the patient's care management and delivery planning and included the results in the referral paperwork that each patient brought with them to the hospital at the time of delivery. The obstetricians at CFLR were often the same providers performing the deliveries at the hospital. Data on the mode of delivery and maternal and infant outcomes were later extracted from the patient's medical record.

The mode of delivery and maternal and infant outcomes were compared to a historical cohort comprised of the clinic's vertical transmission program patients from a prior year during which timely viral load testing was not available. The historical cohort included obstetric HIV-positive patients cared for at CFLR and who delivered between January 1 and December 31, 2012 for whom HIV viral load results were not available during late pregnancy. Of the 55 patients who delivered in this time period, six patients were excluded due to insufficient recorded data and eight were excluded due to diagnosis with HIV at the time of their delivery.

The study protocol was approved by the Institutional Review Board of CUMC and by the "Consejo Nacional de Bioética en Salud" (CONABIOS), the ethical review board in the Dominican Republic.

Statistical Analysis

Analysis of the retrospective cohort data from 2012 was used to calculate a clinically meaningful vaginal delivery difference for the pilot group. Since the retrospective data from 2012 did not contain sufficient information (i.e. third trimester HIV viral load) to posit which women would have met clinical criteria for a vaginal delivery, we estimated that 41% of women in the retrospective cohort would have met clinical criteria for a vaginal delivery, given that they were (1) receiving appropriate suppressive ART (and would thus likely have a viral load less than 1000) and (2) had a parity < 2 (as a proxy for those who were less likely to have had a previous C-section, given a 50% C-section rate in the DR and since C-sections are the major exclusion criteria for vaginal deliveries). Given variability in patient and provider preference of delivery mode, we determined that a proportion of vaginal deliveries of 25% in the pilot study cohort (relative to 7% in the retrospective cohort) would reflect a clinically meaningful difference.

Table 1. Baseline characteristics, HIV viral load testing, mode of delivery, and infant HIV PCR test results for participants in the 2012 retrospective cohort and 2014 pilot cohort of HIV-positive pregnant women

	2012 Retrospective cohort (n=41)	2014 Pilot study cohort (n=20)
Maternal characteristics	Mean (SD)	
Age (years)	25.7 (6.3)	21.2 (4.0)
	N (%)	
HIV viral load testing performed at 34 to 36 weeks gestation	1 (2%)	20 (100%)
Mode of delivery		
Vaginal	3 (7%)	7 (35%)
Cesarean section	38 (93%)	13 (65%)
Infant Characteristics		
HIV PCR result at 6 weeks of age[a]		
Negative	39 (97.5%)	21 (100%)
Positive	0 (0%)	0 (0%)
Indeterminate	1 (2.5%)	0 (0%)
HIV PCR result at 6 months of age[b]		
Negative	7 (87.5%)	20 (100%)
Positive	1 (12.5%)	0 (0%)
Indeterminate	0 (0%)	0 (0%)

[a]At six weeks, there were N=21 infants in the pilot study cohort (one set of twins) and there were N=40 infants in the retrospective cohort due to loss to follow-up

[b]At six months, there were N=20 infants in the pilot study cohort (one infant passed away due to unknown reasons) and N=8 infants in the retrospective cohort (the remainder did not have 6-month HIV PCR results recorded in their clinical charts).

Table 2. 2014 pilot study cohort viral load testing and mode of delivery (N=20)

	HIV viral load <1000 copies/ml N=17 (85%)	HIV viral load ≥1000 copies/ml N=3 (15%)
	N (%)	
Vaginal delivery	6 (35%)	1 (33%)
Cesarean section	11 (65%)	2 (67%)

Descriptive statistics were used to characterize baseline characteristics, HIV viral load testing, mode of delivery, and infant HIV PCR test results. Fisher's exact test was performed to test for differences in the mode of delivery between the pilot study cohort and the retrospective cohort. All analyses employed two-tailed testing with a threshold of $p<0.05$ considered statistically significant. Data were analyzed using OpenEpi.

Results

Twenty women were recruited into the pilot study cohort during the nine-month study period in 2014-2015 and 41 women were included in the retrospective (2012) cohort. Mean (SD) age of women was 21.2 (4.0) years in the pilot cohort and 25.7 (6.3) years in the retrospective cohort (Table 1). HIV viral load testing was successfully completed at CUMC on all 20 patients in the pilot cohort at 34-36 weeks gestation, whereas in the retrospective cohort, one patient had an HIV viral load performed at 34-36 weeks gestation (Table 1).

Of the women in the pilot cohort, seven (35%) delivered vaginally and 13 (65%) delivered by C-section. In the retrospective cohort, three (7%) delivered vaginally and 38 (93%) delivered by C-section. In the pilot cohort, 17 (85%) had viral loads less than 1000 copies per mL (meeting viral load criteria for a vaginal delivery), and of those 17 women, six (35%) delivered vaginally (Table 2). Of the three women with elevated HIV viral loads, two had C-sections and the third woman arrived at the hospital in labor with a precipitous vaginal delivery. The deliveries were otherwise uncomplicated.

Compared to the retrospective cohort, the pilot study cohort where viral load testing and results were made available prior to 38 weeks gestation had a significantly higher proportion of vaginal deliveries (7% vs. 35%, $p=0.02$). The observed proportion of vaginal deliveries in the pilot study cohort (35%) was higher than the predicted proportion (25%) from pre-study calculated parameters. Although target enrollment was not achieved, the post-hoc power calculation using 20 participants revealed a power of 81%.

At six weeks of age, all 21 infants in the pilot study cohort (including one set of twins) had negative PCR HIV testing and 20 infants had negative PCR testing at six months of age (one infant passed away due to unknown reasons before the six-month time point) (Table 1). In the retrospective cohort, at six weeks of age, 39 infants had negative PCR HIV testing, one infant had an indeterminate result, and one infant did not have a result due to loss to follow-up. There are limited data available for the retrospective cohort infants at six months of age; however, the infant with the initial indeterminate result had a positive result at six months of age. This infant was born via C-section to a mother who was diagnosed with HIV during pregnancy and started on antiretroviral therapy at the 28-weeks gestation.

Discussion

Overall, the availability of expedited viral load testing and access to results was associated with an increased likelihood of vaginal deliveries in this vertical transmission program in the DR. Additionally, there was no associated increase in vertical transmission of HIV, which is consistent with findings of other studies [10].

Nonetheless, our study had several limitations. As discussed previously, in the power calculation, there was difficulty determining the expected proportion of vaginal deliveries in the pilot study cohort given limited data from the retrospective cohort. The sample size for the pilot study cohort (N=20) was significantly smaller than the prior cohort (N=41) due to the implementation of a prenatal vertical transmission program at the local public hospital, where many women deliver their infants, absorbing much of CFLR's patient load during the time the study was completed. Additionally, study time was decreased from 12 months to 9 months due to personnel limitations. Chart abstraction did not provide clear data on indications for C-section at the hospital, as hospital notes were not available. Due to patient loss to follow up and limitations in chart abstraction, there was missing data for infant HIV PCR results at six months of age. Finally, the statistical analysis performed to test for differences in delivery mode between the retrospective and pilot study cohort did not control for any additional variables that might have differed between the groups, due to limitations in data abstracted from the clinical charts.

Despite these limitations, having viral load testing performed and the results available in an expedited fashion provided women and their care team with the option of a vaginal delivery, in keeping with national and World Health Organization guidelines for HIV vertical transmission programs. Although the model used in this study (i.e., expedited shipping to an academic medical center in the United States) is expensive, findings from this study demonstrate the benefits of improved access to viral load testing equipment to evaluate HIV-positive patients, especially when it can dramatically alter management and avoid unnecessary abdominal surgery. In December of 2016, CFLR received a donation of a GeneXpert instrument for HIV viral load testing, in part, as a result of these study results. The clinic is now able to provide viral load testing on site, greatly reducing the time it takes to get results, both for pregnant women and for other HIV-positive patients. Although CFLR now has these capabilities, much of the DR still does not have access to timely viral load testing. As demonstrated by this study, increased access to and more efficient HIV viral load testing, analysis, and distribution of results could help to reduce the number of unnecessary C-sections in pregnant women with HIV in the DR.

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