Prenatal syphilis and adverse pregnancy outcomes in women with HIV receiving ART in Brazil: a population-based study

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Summary

Background We aimed to examine factors associated with prenatal syphilis, including prenatal care, and pregnancy outcomes of pregnant women with HIV in Brazil.

Methods Retrospective data were gathered from a national cohort of Brazilian women with HIV on antiretroviral therapy who became pregnant between January 2015 and May 2018. Prenatal syphilis was defined by clinical diagnoses with treatment or any positive syphilis laboratory result between 30 days before conception and pregnancy conclusion. Multivariable logistic regression models examined factors associated with prenatal syphilis risk and adverse pregnancy outcomes (including stillbirth, abortion, preterm delivery, small for gestational age, and congenital abnormalities). Receipt of recommended prenatal syphilis screening and adequacy of prenatal care were also evaluated.

Findings Among 2169 women, 166 (7.77% [95% CI: 6.5–8.8%]) had prenatal syphilis, of whom 151 (91%) had documented treatment. Prevalence of prenatal syphilis was higher among women of Black/*Pardo*/Indigenous race (13.7/7.7/8.3% vs. 5.8% in White women), those of younger age (median age 25.9 years vs. 27.6 in total cohort) and those with crack/cocaine use during/before pregnancy (20%). Of 1042/2169 women with prenatal care and screening data, 475 (46%) received inadequate prenatal care and only 301 (29%) received the recommended antenatal syphilis screening. Prenatal syphilis was not associated with adverse pregnancy outcomes (aOR 0.91 [0.64–1.30]).

Interpretation Prenatal syphilis was prevalent in this cohort of pregnant women with HIV. Prenatal syphilis was not associated with adverse pregnancy outcomes. Attention to syphilis prevention and treatment is especially needed in marginalised women.

Funding Brazilian Ministry of Health and United States' National Institutes of Health.

Keywords: HIV; Syphilis; Pregnancy; Prenatal; Birth outcomes

Introduction

Prenatal syphilis is associated with congenital syphilis (defined as an infant born to a mother with positive syphilis testing and lack of treatment or treatment response within 4 weeks of delivery, regardless of infectious symptoms) as well as other adverse pregnancy outcomes, including fetal loss, stillbirth, neonatal death, and preterm and low birth weight infants.[1,2] These outcomes are preventable with timely screening and treatment.[3] Despite generally high rates of prenatal

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Research in context

Evidence before this study

We conducted a search across PubMed and Google Scholar databases to evaluate data on prenatal syphilis and HIV. Search criteria included articles containing the terms "HIV," "prenatal syphilis," "syphilis," and "pregnancy." We also searched for articles focused on "syphilis," "pregnancy," and "Brazil." Given the recent resurgence of syphilis in the Americas and our study period, we focused on studies published since 2013. From these searches, 60 highly relevant articles were identified. Studies examining prenatal syphilis among women in Brazil to single-site cohort studies lacked data on women living with HIV, focused on HIV vertical transmission risk associated with prenatal syphilis, or lacked pregnancy outcome information. Studies among Brazilian women highlighted inequities in HIV and syphilis screening as well as variable adequacy in prenatal care.

Added value of this study

This nationally representative study of detailed pregnancy exposures and outcomes among women in Brazil is the largest observational study of prenatal syphilis in women living with HIV. We observed a prevalence of prenatal syphilis of 7.7% with the highest prevalence among particularly vulnerable women. While prenatal syphilis was not associated with adverse pregnancy outcomes, we observed a high prevalence of inadequate prenatal care among women in our study and more than 70% of all women failed to receive the recommended syphilis screening during pregnancy.

Implications of all the available evidence

The findings from our study contribute to the global epidemiologic data of prenatal syphilis in women living with HIV. Further efforts to improve the adequacy of prenatal care and syphilis prevention and screening during pregnancy among vulnerable populations, including women with HIV, are needed.

care in Brazil, rates of acquired syphilis (syphilis infection in an adolescent or adult), prenatal syphilis (syphilis infection in a pregnant woman), and congenital syphilis (vertical transmission of syphilis to an infant) have increased in recent years, with differences across country regions.[4,5] Timely screening, diagnosis, and treatment of syphilis as part of comprehensive prenatal care for pregnant women is critical for the prevention of congenital syphilis in newborns and other adverse pregnancy outcomes. Women with inadequate prenatal care are at highest risk of prenatal syphilis in Brazil.[6]

Many women with HIV in Brazil are burdened with both high social vulnerability and unmet reproductive health needs. In a study of more than 1000 women with HIV in Rio de Janeiro from 1996 to 2016, seroprevalence of syphilis was 11%.[7] Less is known about the epidemiology and consequences of prenatal syphilis in women with HIV. Maternal syphilis infection among women with HIV has been associated with older age, non-White race, alcohol use, and lack of prenatal care.[8] Maternal syphilis infection was also associated with a 2-fold increased risk of HIV vertical transmission, particularly *in utero* transmission due to placental inflammation.[8,9] However, information on the effects of prenatal syphilis on other adverse pregnancy outcomes and the results of prenatal syphilis infection in women with HIV receiving antiretroviral therapy (ART) is lacking. Further, no studies have examined the quality of prenatal care services and receipt of recommended syphilis screening among women with HIV who may be particularly vulnerable.

In this study, we aimed to describe the demographic and clinical characteristics of women with HIV with prenatal syphilis, to examine the receipt of recommended prenatal syphilis screening and to study the association between prenatal syphilis and adverse pregnancy outcomes in a retrospective observational cohort of Brazilian women with HIV.

Methods

Study population and design

We used national, comprehensive, retrospective clinical data on pregnant women with HIV and their birth outcomes collected by the Brazilian National Dolutegravir Cohort Study. Details of this cohort have been previously described.[10] To summarise, in response to the concern for potential neural tube defect risk associated with *in utero* dolutegravir exposure among infants born to women with HIV, public health leaders at the Brazilian Ministry of Health along with research collaborators from the National Institute of Infectious Diseases Evandro Chagas and the Caribbean, Central America, and South America network for HIV epidemiology (CCASAnet), conducted a national, retrospective, observational study of all pregnant women with HIV receiving dolutegravir or raltegravir and location-matched sample of pregnant women with HIV receiving efavirenz between January 2015–May 2018. Data sources included national Brazilian ART and HIV laboratory databases and live birth and death registries to identify women to include, followed by systematic data abstraction from medical records of pregnant women with HIV from HIV clinics, prenatal clinics, and obstetric hospitals by trained study personnel. Detailed chart review confirmed pregnancy details, outcomes, and periconceptional exposures, including coinfections such as syphilis.

For this analysis, we included all women with HIV captured through the Brazilian National Dolutegravir Cohort Study with a confirmed pregnancy, known pregnancy outcome (livebirth, stillbirth, or abortion), estimated gestational age (EGA) at delivery of livebirths, and weight at delivery for livebirths. Each woman contributed only one pregnancy though women with pregnancies of multiples (such as twins) were included.

Institutional review board and ethical approval for the study was obtained from the National Institute of Infectious Diseases Evandro Chagas (INI)-FIOCRUZ, the Brazilian National Research Ethics Commission (CONEP), and Vanderbilt University. Waiver of consent was obtained given the public health emergency response purpose of the study.

Exposure and outcome definitions

The primary exposure of interest in this analysis was prenatal syphilis, defined as either (1) clinical documentation of syphilis diagnosis and treatment or (2) positive syphilis screening test (including anti-treponemal antibody screening test, rapid plasma 6egain [RPR], or venereal disease research laboratory [VDRL] tests) between ≤30 days of the estimated date of conception (EDC) and 42 weeks gestation. Brazilian guidelines recommend treating pregnant women with a positive syphilis test regardless of the VDRL titre if there is no report of prior treatment or tests for comparison. As we did not have complete information on prior treatment and testing, we considered all women with any positive test to have prenatal syphilis. EDC was calculated by subtracting the estimated gestational age (EGA) reported from the prenatal ultrasound occurring in the first or second trimester (preferred method and used for 76% of women in the original cohort study), or as the first day of the woman's last menstrual period, or by subtracting an estimated gestational age obtained from a third-trimester ultrasound or at the time of delivery (if previous options unavailable). Women with conflicting EDC estimates were individually reviewed and the EDC was determined by panel review.[10] In this analysis, women whose EDC could not be calculated were excluded.

In Brazil, all PWH are recommended to be screened for syphilis yearly.[11] Screening for syphilis is recommended for all pregnant women as soon as they enter prenatal care, preferably during the first trimester.[12] If the initial test is negative, women are recommended to receive a second screening once more during the pregnancy in the third trimester. An additional test is recommended at delivery. For women who enter care in the third trimester, a single screening test is recommended. Syphilis screening in pregnant women is performed using a rapid anti-treponemal test which is followed by a non-treponemal test (e.g., VDRL) if positive. Given the current syphilis epidemic in Brazil, initiation of syphilis treatment with benzathine benzylpenicillin (a single dose of 2.4 million units intramuscularly for early syphilis and 3 weekly doses of 2.4 million units intramuscularly for late latent syphilis) is recommended in all pregnant women with a positive rapid anti-treponemal antibody test, regardless of RPR/VDRL titre.[12] In Brazil, empiric treatment with a single dose of intramuscular benzathine benzylpenicillin is recommended for sexual partners of all individuals diagnosed with syphilis, especially in cases of prenatal syphilis.[12] Following treatment, non-treponemal quantitative tests should be repeated monthly to assess for new infection and treatment response.[12]

We first examined the characteristics of women who did and did not receive the recommended syphilis screening during pregnancy per their timing of entry into prenatal care. Appropriate screening was deemed as: (1) at least one syphilis screening test during the first or second trimester and at least one syphilis screening test during the third trimester (if prior tests were negative) for women starting prenatal care before the third trimester, (2) at least one screening test for women entering prenatal care in the third trimester. Next, we assessed appropriateness of syphilis screening for women included in this analysis based on the adequacy of prenatal care. We used the adequacy of prenatal care utilization (APCU) index, which combines the timing of entry into prenatal care and the ratio of observed: expected number of prenatal visits as determined by Brazilian national guidelines,[12,13] to classify prenatal care as inadequate, intermediate, or adequate. Inadequate prenatal care was defined as: (1) first prenatal visit after EGA of 14 weeks (≥14w0d), regardless of the number of prenatal visits completed; (2) prenatal care initiation before EGA of 14 weeks (<14w0d) but <50% of the expected number of prenatal visits were completed during the pregnancy. Women with intermediate and adequate prenatal care included those who entered care before EGA of 14 weeks and with 50–79%, ≥80% of the completed to expected number of prenatal visits, respectively. To calculate the total number of expected prenatal visits based upon the timing of entry into care and EGA at pregnancy conclusion, we used definitions from the APCU criteria: one prenatal visit every 4 weeks for the first 28 weeks, every 2 weeks until 36 weeks, and weekly thereafter.[13] Women were excluded from the analysis if the appropriateness of syphilis screening or adequacy of prenatal care could not be determined due to missing information.

Given the rarity of some adverse pregnancy outcomes, a composite outcome including any adverse pregnancy outcome was used in a primary model that assessed its association with prenatal syphilis. We evaluated adverse pregnancy outcomes including stillbirths (foetal demise after 22 weeks gestation), abortion (foetal demise before 22 weeks gestation; presumed to be spontaneous as therapeutic abortions are illegal in Brazil), and among livebirths: preterm delivery (delivery

before week 37 gestation for single births), small for gestational age (defined as birthweight less than the 10th percentile based upon gestational age at delivery and sex[14]), and any congenital abnormalities. For analyses examining pregnancy outcomes, only singleton pregnancies were included.

Statistical approach

We described demographic and clinical characteristics at the time of EDC of pregnant women with HIV by prenatal syphilis diagnosis. For laboratory values, CD4 cell count at EDC within 180 days and HIV RNA within 90 days of EDC were used. Multivariable logistic regression models assessed demographic and clinical characteristics associated with prenatal syphilis and receipt of recommended prenatal syphilis screening. We included covariates in models selected *a priori* based upon hypothesised confounding relationships and key sociodemographic characteristics including age, year of EDC, race (dichotomised to Black/*Pardo*/Indigenous vs. White/All Others), education (dichotomised to $<$ or $\geq$ 8 years), HIV RNA below the limit of detection at EDC, any history of crack/cocaine use, residential zone (urban, suburban/periurban, or rural), and region (South/Southeast, Midwest, and North/Northeast). Lastly, we examined the association of our composite adverse pregnancy outcome with prenatal syphilis diagnosis. In addition to prenatal syphilis, the multivariable logistic regression model included potential confounders including selected *a priori* including maternal age, year, CD4 cell count, HIV RNA below the limit of detection, race, education, any documented history of cocaine use, residential zone, region of the country, receipt of ART after conception, and adequacy of prenatal care received.

For all multivariable models, continuous covariates were fit with restricted cubic splines with 3 knots, global statistical significance for continuous covariates was calculated using Wald tests, and results are presented as adjusted odds ratios comparing specific continuous levels with reference levels.[15] Multiple imputation with 20 replications were performed to account for missing demographic and clinical data, including gestational age at delivery and sex of infant for examination of small for gestational age among live births. We conducted a sensitivity analysis of the final multivariable model for adverse pregnancy outcomes which was restricted to complete cases only. Multiple imputation was not used for the assessment of receipt of recommended syphilis screening nor adequacy of prenatal care due to high rates of missingness. The imputation models used bootstrapping and predictive mean matching implemented with the aregImpute() function in the Hmisc R package.

All analyses were performed using R statistical software version 3.5.3, and analysis codes are available at http://biostat.app.vumc.org/ArchivedAnalyses.

Role of funding sources

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Study design, implementation, and analysis were jointly performed by investigators from the Brazilian Ministry of Health, INI–FIOCRUZ, and CCASAnet.

Results

Out of the complete list of women living with HIV with possible pregnancies exposed to dolutegravir, raltegravir, or efavirenz identified during the study period in the national ART registry (n = 3390), 2169 women had confirmed pregnancies with estimated dates of conception and pregnancy outcomes data (Fig. 1). In total, there were 166 women who met criteria for prenatal syphilis diagnoses (prenatal syphilis prevalence 7.7% [95% confidence interval: 6.5–8.8%]). Among them, 116 (70%) had documentation of anti-treponemal titre values at prenatal syphilis diagnosis. Of those with available initial titres, the median titre was 1:8 (interquartile range 1:2, 1:32). Among all 166 women with prenatal syphilis, 149 (90%) had record of receipt of treatment for syphilis. There were 17 women with only notation of clinical diagnosis without no supporting evidence of treatment nor positive syphilis test and who were considered as not having prenatal syphilis.

Overall, prenatal syphilis prevalence was higher among younger women, women of Black/*Pardo*/Indigenous race, and women with fewer years of formal education (Table 1). Prevalence was higher among women diagnosed with HIV during their pregnancy compared to those diagnosed with HIV before pregnancy. Overall, 16% of all women had no documentation of syphilis screening tests during pregnancy on medical record review; a higher proportion of women with prenatal syphilis had documentation of any and repeated syphilis screening during pregnancy. Prevalence of prenatal syphilis was also high among women with documented tobacco use, alcohol use, and substance use (including crack/cocaine use) before or during pregnancy. In the multivariable logistic regression model (Supplemental Table S1), younger age, Black/*Pardo*/Indigenous race (compared to all others), and crack/cocaine use before or during pregnancy remained statistically associated with increased risk of prenatal syphilis.

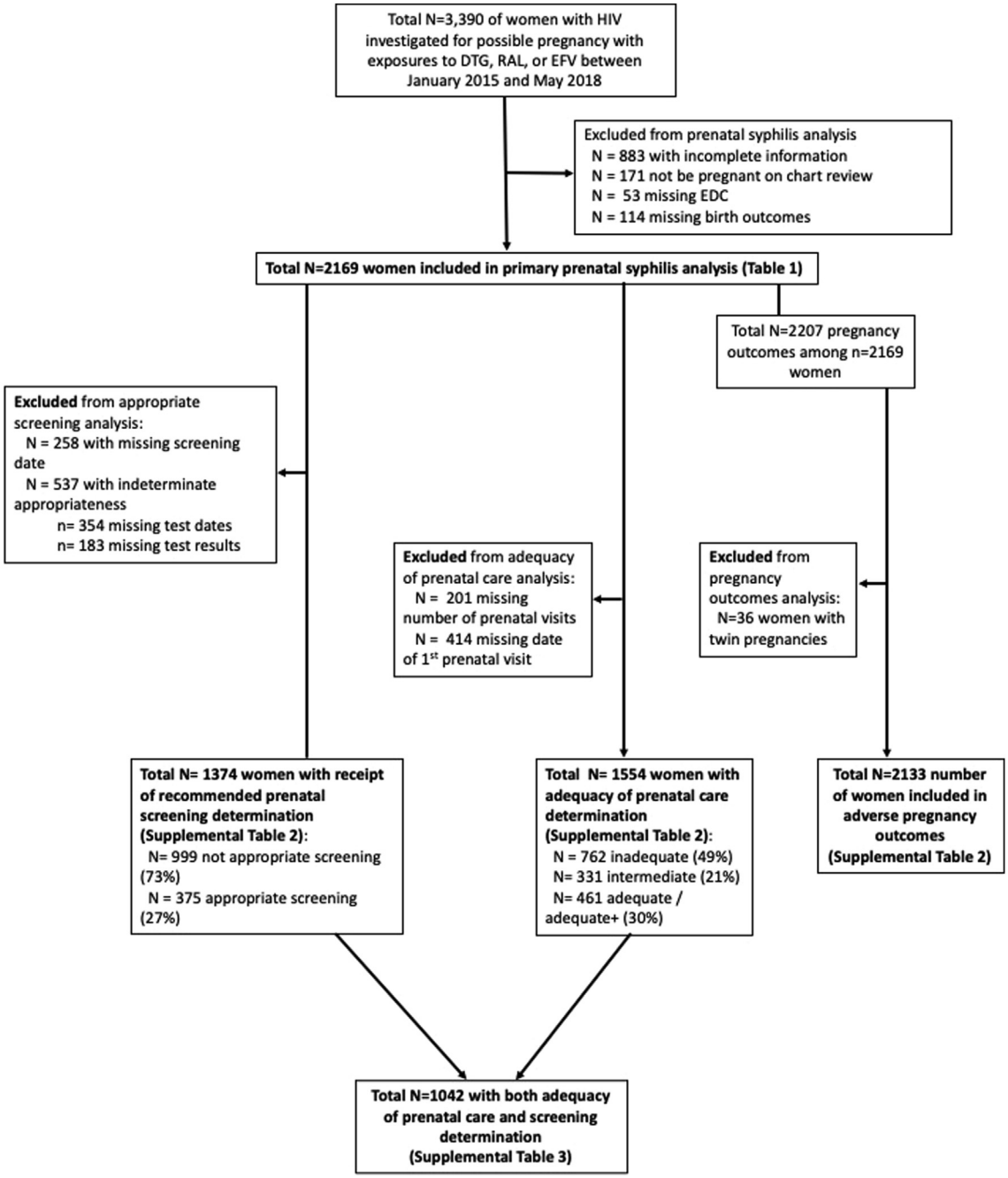

Fig. 1: Flow diagram of inclusion/exclusion criteria of analysis cohorts. Tables describing women included in each cohort noted. Abbreviations used: HIV: human immunodeficiency virus; DTG: dolutegravir; RAL; raltegravir; EFV: efavirenz; EDC: estimated date of conception.

Of the 2169 women originally included, receipt of recommended syphilis screening given timing of entry into prenatal care could be determined among 1374 women and adequacy of prenatal care could be determined for 1554 women (72%) (Fig. 1; Supplemental Table S2 includes details of cohorts). Overall, 73% (999/1374) of women did not receive the recommended number of syphilis screening tests based upon their timing of entry into prenatal care. A higher proportion of women without receipt of recommended syphilis screening included those of non-Black race, Midwest region, and pregnancy in more recent calendar years (Table 2). Of all women with prenatal care adequacy assessed, 762 (49%) met criteria for inadequate care.

	Women without prenatal syphilis (n = 2003)	Women with prenatal syphilis (n = 166)	All women (n = 2169)
Maternal age at conception (years), median (IQR)	27.7 (22.7–32.9)	25.9 (21.2–32.3)	27.6 (22.7–32.9)
Race[a], n (%)			
White	701 (35.1)	43 (26.1)	744 (34.4)
Black	227 (11.4)	36 (21.8)	263 (12.2)
Pardo	899 (45.0)	75 (45.5)	974 (45.0)
Asian	17 (0.9)	1 (0.6)	18 (0.8)
Indigenous	11 (0.6)	1 (0.6)	12 (0.6)
Unknown	143 (7.2)	9 (5.5)	152 (7.0)
Years of education[b], n (%)			
0–3 years	120 (6.4)	8 (5.2)	128 (6.3)
4–7 years	619 (33.0)	66 (42.6)	685 (33.8)
8–11 years	902 (48.2)	75 (48.4)	977 (48.2)
≥12 years	232 (12.4)	6 (3.9)	238 (11.7)
Region of residence[c], n (%)			
South & Southeast	1290 (64.4)	112 (67.5)	1402 (64.6)
North & Northeast	571 (28.5)	47 (28.3)	618 (28.5)
Midwest	142 (7.1)	7 (4.2)	149 (6.9)
Residential setting[d], n (%)			
Urban	1685 (92.5)	132 (91.0)	1817 (92.4)
Rural	105 (5.8)	8 (5.5)	113 (5.7)
Suburban/periurban	32 (1.8)	5 (3.4)	37 (1.9)
Timing of HIV diagnosis[e], n (%)			
Before pregnancy	1690 (84.4)	129 (77.7)	1819 (83.9)
Prenatal/postnatal period	274 (13.7)	34 (20.5)	308 (14.2)
Unknown	38 (1.9)	3 (1.8)	41 (1.9)
ART initiated before conception[f], n (%)	1308 (66.2)	94 (57.0)	1402 (65.5)
CD4 cell count at conception (cells/μL)[g], median (IQR)	554 (370–792)	519 (318–784)	551 (364)
HIV RNA below the limit of detection at conception[h], n (%)	674 (62.3)	42 (50.0)	716 (61.5)
Year of conception, n (%)			
2014	4 (0.2)	0 (0.0)	4 (0.2)
2015	11 (0.6)	0 (0.0)	11 (0.5)
2016	335 (16.7)	35 (21.1)	370 (17.1)
2017	1475 (73.6)	115 (69.3)	1590 (73.3)
2018	178 (8.9)	16 (9.6)	194 (8.9)
EGA at first prenatal visit (weeks)[i], median (IQR)	12.0 (8.4–17.0)	12.8 (9.0–19.3)	12.0 (8.4–17.3)
History of adverse pregnancy outcome prior to conception[j], n (%)	657 (32.8)	54 (32.5)	711 (32.8)
Total number of prenatal visits, median (IQR)	7 (5–9)	7 (5–9)	7 (5–9)
Total number of syphilis screening tests during pregnancy[k]			
0	340 (17.0)	8 (4.8)	348 (16.0)
1	909 (45.4)	47 (28.3)	956 (44.1)
2	539 (26.9)	54 (32.5)	593 (27.3)
3	215 (10.7)	57 (34.3)	272 (12.5)
Tobacco use before or during pregnancy, n (%)	372 (18.6)	56 (33.7)	428 (19.7)
Alcohol use before or during pregnancy, n (%)	323 (16.1)	51 (30.7)	374 (17.3)

(Table 1 continues on next page)

The most frequent cause of inadequate care was late initiation of prenatal care, whereby 657 (42%) women started prenatal care at or after the 14th week of gestation (≥14w0d). Prenatal syphilis screening and diagnosis and adequacy of prenatal care were concomitantly available in 1042 women (Supplemental Table S3). Receipt of recommended prenatal syphilis screening was more frequent among women with inadequate prenatal care (176/475, 37%) compared to women with intermediate (49/235, 21%) or adequate (76/332, 23%) prenatal. care. Similarly, diagnosis of prenatal syphilis was more frequent among women with inadequate prenatal care (59/475, 12%) compared to women who received intermediate (27/235, 8%) or adequate (27/332, 8%) prenatal care. Characteristics associated with receipt of recommended syphilis screening during pregnancy are shown in Table 3. In multivariable analysis (which adjusted for adequacy of prenatal care), women of Black/*Pardo*/Indigenous race, women who lived in the South and Southeast region of the country, women with detectable HIV RNA levels at conception, earlier calendar year of pregnancy, and any history of crack/cocaine use had greater odds of receipt of recommended syphilis screening testing during pregnancy. After accounting for demographic and clinical covariates, receipt of inadequate prenatal care remained strongly associated with receipt of recommended syphilis screening compared to receipt of intermediate or adequate/adequate plus prenatal care.

There were 2207 pregnancy outcomes among the 2169 women, which includes pregnancies with multiple foetuses (such as twins or triplets). In total, there were 2131 live births (96.6%), 22 stillbirths (1.0%), and 54 abortions (2.4%) observed (Table 4). The frequency of livebirths, stillbirths, and abortions among women with or without prenatal syphilis was similar. Of live births, the EGA at delivery was similar among women with prenatal syphilis compared to those without (39.0 weeks [IQR: 38.0–40.0] vs. 38.9 weeks [IQR: 38.0–39.4], respectively) and median birth weight at delivery was similar (3085 g [2782–3370] among women with vs. 3040 g [2755–3355] without prenatal syphilis). Of adverse pregnancy outcomes occurring among live births, preterm delivery was the most frequent, occurring in 21% of all pregnancy outcomes, followed by small for gestational age (9.8%) and presence of any congenital abnormality (5.1%). Frequencies of these adverse pregnancy outcomes were similar to slightly higher for those with prenatal syphilis. Of the 17 women with prenatal syphilis and without record of receipt of syphilis treatment, two women were recorded as not receiving treatment, of whom one delivered an infant small for gestational age. Of the 15 women with prenatal syphilis and missing (unknown) receipt of treatment, four women (27%) experienced adverse pregnancy outcomes: one had an abortion, one had a preterm delivery,

one had an infant with congenital abnormalities and which was small for gestational age, and one had an infant that was small for gestational age.

To examine whether prenatal syphilis was associated with the composite any adverse pregnancy outcome, we restricted analysis of pregnancy outcomes to singleton pregnancies (excluding 36 women with pregnancies with ≥2 foetuses). In total, 2133 pregnancy outcomes were included in this analysis (including 2089 outcomes with sufficient data on birth weight, gestational age at delivery and infant sex and 44 outcomes which were multiply imputed due to missing data). Among the pregnancy outcomes evaluated, 713 (34%) met the criteria of presence of at least one of stillbirth, abortion, preterm delivery, small for gestational age, or presence of any congenital abnormality. In unadjusted and adjusted models, prenatal syphilis was not associated with an increased odds of adverse pregnancy outcome (unadjusted OR: 1.03 [95% CI: 0.74–1.45], p = 0.86; adjusted OR: 0.91 [0.64–1.30], p = 0.61) (Supplemental Table S4).

	Women without prenatal syphilis (n = 2003)	Women with prenatal syphilis (n = 166)	All women (n = 2169)
(Continued from previous page)			
Substance use before or during pregnancy, n (%)	216 (10.8)	48 (28.9)	264 (12.2)
Crack/cocaine use before or during pregnancy, n (%)	140 (7.0)	35 (21.1)	175 (8.1)

Abbreviations used: IQR: interquartile range; ART: antiretroviral therapy; EGA: estimated gestational age. [a]Race missing for 6 women. [b]Education missing for 141 women. [c]South and Southeast regions includes the Brazilian states of Rio Grande do Sul, Santa Caterina, Paraná, São Paulo, Minas Gerais, Rio de Janeiro, and Espirito Santo; North and Northeast regions includes the Brazilian states of Acre, Amazonas, Pará, Rondônia, Tocatins, Amapá, Maranhão, Piauí, Bahia, Ceará, Rio Grande do Norte, Pernambuco, Paraíba, Alagoas, and Sergipe; Midwest region includes the Brazilian states of Mato Grosso, Mato Grosso do Sul, Goiás, and the Distrito Federal. [d]Residential setting missing for 202 women. [e]Timing of HIV diagnosis missing in 1 woman. [f]Timing of ART initiation missing in 29 women. [g]CD4 cell count closest to estimated date of conception ±180 days, CD4 cell count missing for 731 women. [h]HIV RNA closest to estimated date of conception ±90 days. Limit of detection: 40 copies/mL. HIV RNA missing for 1004 women. [i]Estimated gestational age at first prenatal visit missing for 438 women. [j]History of adverse pregnancy outcomes include previous stillbirth (fetal demise at or after 22 weeks EGA), congenital abnormality, abortion (fetal demise before 22 weeks EGA), preterm delivery (delivery before 37 weeks EGA), small for gestational age (birth weight <10th percentile for expected weight by EGA and sex). [k]Syphilis screening tests including rapid tests alone or with VDRL/RPR tests. Eight women with syphilis had no test events recorded in medical records but medical records included syphilis diagnoses and treatment during pregnancy.

Table 1: **Demographic and clinical characteristics of pregnant women living with HIV and with and without prenatal syphilis diagnosis during pregnancy.**

Discussion

In this large national, observational cohort of pregnant women with HIV in Brazil from 2015 to 2018, prenatal syphilis was frequent (prevalence 7.7%). Younger age, being of Black/*Pardo*/Indigenous race and having a history of crack/cocaine use were more prevalent among women with prenatal syphilis. Nearly half of pregnant women with HIV in this large cohort received inadequate prenatal care, as assessed by timing of entry into care and number of prenatal visits. Among women with complete screening and prenatal care data available, those with inadequate prenatal care had a higher prevalence of prenatal syphilis (12%) but were also more likely to receive recommended prenatal syphilis screening tests. Finally, adverse pregnancy outcomes were frequent in this cohort, particularly preterm delivery. Overall, 91% of all women with prenatal syphilis in this cohort had documentation of receipt of treatment for prenatal syphilis, and prenatal syphilis was not associated with increased odds of adverse pregnancy outcomes. However, disparities by age, education, and prior crack/cocaine use and risk of adverse pregnancy outcomes underscore the need for added care for vulnerable pregnant women with HIV.

Although a well-known and treatable disease, syphilis continues as a global health challenge, with recently increasing rates in the Americas in particular.[16–18] In the general Brazilian population, there was an increase in all syphilis indicators from 2005 to 2021.[19] Our national cohort study found a high prevalence of prenatal syphilis among women with HIV receiving ART in Brazil. While our study is unique in its focus on pregnant women with HIV, our findings reveal comparable risk factors associated with prenatal syphilis and similar syphilis prevalence observed in other studies among all pregnant women in Brazil during a similar period which have reported prevalence estimates ranging from 1 to 11%.[4,6,20] A study conducted in one HIV reference centre in southeast Brazil among 151 non-pregnant women with HIV found a syphilis prevalence of 10%.[21] Similarly, our observation of increased risk for prenatal syphilis among pregnant women of younger age, Black/*Pardo*/Indigenous race, fewer years of education, and with a history of illicit drug use mirrors risk factors among all pregnant women in the country.[4,6,22,23] These findings highlight persistent inequalities surrounding syphilis prevention. The association between social determinants of health and syphilis is not restricted to low- and middle-income countries. A recent systematic review included several countries across the world, including high-income countries, identified an association between congenital syphilis and factors such as young age, lower schooling, unemployment, low family income and unstable housing.[24] In the US, less healthy living conditions (a composite index based on education, housing, transportation, neighbourhood conditions, clean environment, healthcare access, and economic and social resources) have been associated with syphilis risk.[25] Although social inequities impact both HIV and syphilis epidemics, previous studies have shown that focusing on only women with HIV diagnosed with syphilis will be insufficient to curb rates of congenital syphilis in Brazil.[26]

Improving access to prenatal care, increasing the use of rapid tests for syphilis, and ensuring the availability of benzathine penicillin are key steps to reduce congenital syphilis in Brazil and other low- and middle-income

	Women with recommended syphilis screening during pregnancy (n = 375)	Women without recommended prenatal syphilis screening during pregnancy (n = 999)	All women (n = 1374)
Maternal age at conception (years), median (IQR)	26.9 (22.2–32.6)	27.5 (22.6–32.6)	27.4 (22.5–32.6)
Race[a], n (%)			
White	113 (30.3)	341 (34.2)	454 (33.1)
Black	58 (15.5)	111 (11.1)	169 (12.3)
Pardo	177 (47.5)	460 (46.1)	637 (46.5)
Asian	2 (0.5)	9 (0.9)	11 (0.8)
Indigenous	1 (0.3)	5 (0.5)	6 (0.4)
Unknown	22 (5.9)	71 (7.1)	93 (6.8)
Years of education[b], n (%)			
0–3 years	14 (3.9)	59 (6.4)	73 (5.7)
4–7 years	131 (36.8)	304 (32.8)	435 (33.9)
8–11 years	183 (51.4)	450 (48.5)	633 (49.3)
≥12 years	28 (7.9)	115 (12.4)	143 (11.1)
Region of residence[c], n (%)			
South & Southeast	272 (72.5)	634 (63.5)	906 (65.9)
North & Northeast	89 (23.7)	293 (29.3)	382 (27.8)
Midwest	14 (3.7)	72 (7.2)	86 (6.3)
Residential setting[d], n (%)			
Urban	309 (92.5)	839 (92.6)	1148 (92.6)
Rural	17 (5.1)	50 (5.5)	67 (5.4)
Suburban/periurban	8 (2.4)	17 (1.9)	25 (2.0)
Timing of HIV diagnosis[e], n (%)			
Before pregnancy	301 (80.3)	847 (84.9)	1148
Prenatal/postnatal period	70 (18.7)	132 (13.2)	202
Unknown	4 (1.1)	19 (1.9)	23
Year of conception, n (%)			
2014	0 (0.0)	2 (0.2)	2 (0.1)
2015	3 (0.8)	5 (0.5)	8 (0.6)
2016	92 (24.5)	154 (15.4)	246 (17.9)
2017	254 (67.7)	750 (75.1)	1004 (73.1)
2018	26 (6.9)	88 (8.8)	114 (8.3)
EGA at first prenatal visit (weeks) median (IQR)	13.4 (9.7–19.4)	11.6 (8.1–16.3)	12 (8.6–17.3)
History of adverse pregnancy outcome prior to conception[f], n (%)	124 (33.1)	329 (32.9)	453 (33.0)
Total number of prenatal visits, median (IQR)	7.0 (5.0–9.0)	7.0 (5.0–9.0)	7.0 (5.0–9.0)
Tobacco use before or during pregnancy, n (%)	83 (22.1)	196 (19.6)	279 (20.3)
Alcohol use before or during pregnancy, n (%)	82 (21.9)	159 (15.9)	241 (17.6)
Substance use before or during pregnancy, n (%)	67 (17.9)	100 (10.0)	167 (12.2)
Crack/cocaine use before or during pregnancy, n (%)	43 (11.5)	68 (6.8)	111 (8.1)

Abbreviations used: IQR: interquartile range; HIV: human immunodeficiency virus; EGA: estimated gestational age. [a]Race missing for 4 women. [b]Education missing for 90 women. [c]South and Southeast regions includes the Brazilian states of Rio Grande do Sul, Santa Caterina, Paraná, São Paulo, Minas Gerais, Rio de Janeiro, and Espirito Santo; North and Northeast regions includes the Brazilian states of Acre, Amazonas, Pará, Rondônia, Tocatins, Amapá, Maranhão, Piauí, Bahia, Ceará, Rio Grande do Norte, Pernambuco, Paraíba, Alagoas, and Sergipe; Midwest region includes the Brazilian states of Mato Grosso, Mato Grosso do Sul, Goiás, and the Distrito Federal. [d]Residential setting missing for 134 women. [e]Timing of HIV diagnosis missing in 1 woman. [f]History of adverse pregnancy outcomes include previous stillbirth (fetal demise at or after 22 weeks EGA), congenital abnormality, abortion (fetal demise before 22 weeks EGA), preterm delivery (delivery before 37 weeks EGA), small for gestational age (birth weight <10th percentile for expected weight by EGA and sex).

***Table 2*: Demographic and clinical characteristics of pregnant women living with HIV with and without receipt of recommended prenatal syphilis screening during pregnancy based upon timing of entry into prenatal care (n = 1374).**

countries worldwide.[27–29] Our multivariable results identified an apparent contradictory association between prenatal syphilis screening and adequacy of prenatal care whereby women with inadequate prenatal care were more likely to receive the recommended number of syphilis screening tests. This was likely related to the common scenario that only one syphilis screening test would be recommended for women who entered

antenatal care later in pregnancy, common in our cohort. However, neither late entry into prenatal care nor the receipt of only one syphilis screening test during pregnancy would be recommended. We also observed that women with detectable HIV RNA were more likely to receive recommended syphilis screening among other demographic differences, perhaps reflecting provider bias in the perception of syphilis risk. Indeed, our study population presented an overall high prevalence of inadequate prenatal care and a lack of receipt of recommended syphilis screening tests. Our results also revealed higher syphilis prevalence among women with inadequate prenatal care, parallel to epidemiologic trends among all pregnant women in the country.[30] A study by the Brazilian Ministry of Health used national surveillance data to investigate the adequacy of prenatal care and treatment of syphilis in more than 650,000 live births in state capital cities in the country in 2016.[22] Using a modified version of the composite index for adequacy of prenatal care,[13] the study found differences in rates of inadequate prenatal care across cities and observed that inadequate prenatal care was associated with younger maternal age, non-White race, lower education, and unpartnered marital status. These characteristics were also higher among women with prenatal syphilis in our study, highlighting the vulnerabilities linked to social determinants of health shared by many women regardless of their HIV status.[22] Recent public health efforts in Brazil have targeted improving prenatal care as well as improving syphilis and HIV screening, diagnosis, and treatment among pregnant women.[28,31–33] Increased screening and treatment of syphilis in male partners of pregnant women will be critical for reducing prenatal and congenital syphilis among women living with and without HIV.[34,35]

Finally, prenatal syphilis was not associated with increased odds of adverse pregnancy outcomes in our cohort. Prenatal syphilis has been associated with increased risk not only for congenital syphilis in infants but also for preterm delivery, vertical transmission of HIV, and early foetal demise and stillbirth.[1,36–39] Among women with prenatal syphilis, the risk of adverse pregnancy outcomes is highest among those with inadequate syphilis treatment during pregnancy.[35,36] While similar to recent nationally reported rates of treatment among women with prenatal syphilis in Brazil, in our cohort 90% of women with prenatal syphilis had documentation of receipt of any treatment, perhaps explaining the lack of association of prenatal syphilis and adverse pregnancy outcomes observed. The results of our study underscore the importance not only of syphilis screening and treatment for the prevention of adverse pregnancy outcomes, but also of the identification and interventions to reduce social and behavioural factors associated with the risk of syphilis during pregnancy, inadequacy of prenatal care, and adverse pregnancy outcomes generally, including substance use.

	Adjusted OR (95% CI)	p value
Age at conception[c]		0.942
15 years	1.05 (0.67–1.65)	
20 years	1.03 (0.83–1.26)	
25 years	Reference	
35 years	0.97 (0.77–1.23)	
45 years	0.96 (0.49–1.88)	
Race		0.042
White/Asian/Unknown	Reference	
Black/*Pardo*/Indigenous	1.34 (1.01–1.76)	
Years of education		0.688
≥8 years	Reference	
<8 years	1.06 (0.81–1.38)	
Region of residence[d]		<0.001
South & Southeast	Reference	
North & Northeast	0.38 (0.20–0.70)	
Midwest	0.56 (0.40–0.80)	
Residential setting		0.998
Urban	Reference	
Rural	0.98 (0.56–1.73)	
Suburban/periurban	1.01 (0.44–2.33)	
HIV RNA not below the limit of detection at conception[e]	1.16 (1.01–2.33)	0.045
Year of conception[f]		0.003
2014	1.98 (1.27–3.10)	
2016	Reference	
2017	0.71 (0.57–0.89)	
2018	0.51 (0.32–0.79)	
Crack/cocaine use before or during pregnancy	1.53 (1.01–2.33)	0.045
Adequacy of prenatal care received[g]		<0.001
Inadequate	Reference	
Intermediate	0.52 (0.36–0.77)	
Adequate	0.50 (0.36–0.70)	

Abbreviations used: OR: odds ratio; CI: confidence interval; aOR: adjusted odds ratio; HIV: human immunodeficiency virus; RNA: ribonucleic acid. [a]Multivariable analysis included multiple imputation with 20 replications to account for missing data including race, residential setting, and HIV RNA not below the limit of detection at conception. [b]Recommended prenatal syphilis screening in Brazil includes one test in the first or second trimester and one test in the third trimester for all women whose first prenatal care visit occurs during the first or second trimester and once for women whose first prenatal care visit occurs in the third trimester. [c]Age at conception modeled as non-linear, continuous covariate with restricted cubic splines, 3 knots. [d]South and Southeast regions includes the Brazilian states of Rio Grande do Sul, Santa Caterina, Paraná, São Paulo, Minas Gerais, Rio de Janeiro, and Espirito Santo; North and Northeast regions includes the Brazilian states of Acre, Amazonas, Pará, Rondônia, Tocatins, Amapá, Maranhão, Piauí, Bahia, Ceará, Rio Grande do Norte, Pernambuco, Paraíba, Alagoas, and Sergipe; Midwest region includes the Brazilian states of Mato Grosso, Mato Grosso do Sul, Goiás, and the Distrito Federal. [e]HIV RNA closest to estimated date of conception ±90 days. Limit of detection: 40 copies/mL. [f]Year of conception modeled as continuous covariate. [g]Defined using the Adequacy of Prenatal Care Utilization index, which incorporates the timing of prenatal care initiation by gestational month as well as number of prenatal care visits received while in care. Calculated the expected number of prenatal care visits according to gestational age at delivery based upon Brazilian prenatal obstetric care guidelines. The number of observed visits is then divided by the expected number of visits and classified into three categories: inadequate (<50% expected), intermediate (50–79% expected), adequate (≥80%). All prenatal care that began with the first visit after 14 weeks EGA considered inadequate.

Table 3: **Multivariable logistic regression model[a] for odds of receipt of recommended syphilis screening[b] among pregnant women with HIV (n = 1042).**

	Pregnancy outcomes of women without prenatal syphilis (n = 2039)	Pregnancy outcomes of women with prenatal syphilis (n = 168)	Pregnancy outcomes of all women (n = 2207)
Pregnancy outcome, n (%)			
Live birth	1970 (96.6)	161 (95.8)	2131 (96.6)
Stillbirth[a]	20 (1.0)	2 (1.2)	22 (1.0)
Abortion[b]	49 (2.4)	5 (3.0)	54 (2.4)
Multiple fetus[c], n (%)	68 (3.6)	4 (2.5)	72 (3.5)
EGA at birth (weeks)[d], median (IQR)	38.9 (38.0–39.4)	39.0 (38.0–40.0)	38.9 (38.0–39.4)
Birth weight (grams)[e], median (IQR)	3040 (2755–3355)	3085 (2782–3370)	3045 (2755–3359)
Preterm delivery[f], n (%)	405 (21.3)	34 (21.4)	439 (21.3)
Small for gestational age[g], n (%)	179 (9.7)	17 (11.0)	196 (9.8)
Any congenital abnormality, n (%)	96 (5.0)	11 (6.9)	107 (5.1)

Abbreviations used: EGA: estimated gestational age; IQR: interquartile range. [a]Stillbirth defined as fetal demise at or after EGA 22 weeks. [b]Abortion defined as fetal demise before EGA 22 weeks. [c]Multiple fetus includes fetus of twin or more pregnancy, multiple fetus status missing for 144 pregnancy outcomes. [d]EGA at birth for live births only, missing for 158 live births. N = 2049. [e]Birth weight was missing for 52 live births. N = 2079. [f]Preterm delivery defined as live birth occurring before 37 weeks EGA and only assessed for singleton pregnancies (live births of twins, triplets, etc., excluded), missing for 73 live births. N = 2060. [g]Small for gestational age defined as birthweight of live birth only below the 10th percentile for the Brazilian population as predicted by EGA at birth and sex (male or female), missing 134 lives births. Only assess in live birth outcomes from singleton pregnancies (live births of twins, triplets, etc., excluded). N = 1999.

Table 4: **Pregnancy outcomes of pregnant women living with HIV and with and without prenatal syphilis diagnosis during pregnancy.**

Strengths and limitations

This large cohort study of pregnant women with HIV from across Brazil has a number of unique strengths, including systematic abstraction of syphilis, behavioural, and pregnancy outcome data from medical records from antenatal care and hospital centres. As the original analysis focused on birth outcomes, the study data collected detailed information, including adverse pregnancy outcomes, such as preterm delivery, birth weight, and fetal demise. However, there are limitations to consider. Our study was limited to women with HIV engaged in HIV care and receiving ART (specifically first-line antiretrovirals of dolutegravir, efavirenz, or raltegravir) and did not include women not on HIV treatment, perhaps missing an especially vulnerable population at higher risk for adverse pregnancy outcomes or syphilis which may have introduced bias. Further, while our pregnancy outcome data included many details, we did not collect information regarding congenital syphilis diagnoses specifically, detailed congenital abnormalities beyond neural tube defects and other neurologic abnormalities, nor vertical HIV transmission. We collected syphilis diagnosis, treatment, and laboratory results from HIV and antenatal clinics but not hospital sites and were unable to evaluate screening and diagnosis at the time of delivery. Similarly, if a woman received syphilis screening and treatment at a clinic other than their HIV clinic or antenatal clinic, events may have been missed. Additionally, many women were missing details of syphilis screening, and it is possible those included in our analyses are not generalisable to all women. While most women included had documentation of syphilis treatment, details of the treatment, including number of doses received, were not collected. Thus, we could not assess adequacy of syphilis treatment. Information regarding male partner diagnoses and treatment of sexually transmitted infections including syphilis was also not collected. As we included receipt of treatment in the definition of syphilis for those women with a documented diagnosis but no test results available, it is possible that our rate of treatment is inflated. Finally, as an observational study, our data were still restricted by missingness, particularly in analyses of syphilis screening and adequacy of prenatal care, which may have biased our results. Women excluded from this analysis due to missing birth outcomes or other incomplete data may have different patterns of prenatal syphilis diagnoses, treatment, and outcomes than those for whom data were able to be collected. Finally, while this is one of the largest analyses of prenatal syphilis in women with HIV, our relatively low number of events (n = 166) resulted in small numbers for some subpopulations, introducing uncertainty into our estimates.

Conclusions

In this large, national cohort of pregnant women with HIV in Brazil, prenatal syphilis was frequent, particularly among vulnerable women also at risk for inadequate prenatal care and adverse birth outcomes. A preventable cause of adverse pregnancy outcomes when undiagnosed and untreated, prenatal syphilis remains an important public health focus in low- and middle-income countries worldwide as well as in high income countries.[40,41] Public health efforts in Brazil are working to improve access to prenatal care and syphilis screening and treatment and should include pregnant women with HIV in those interventions. Addressing adverse social determinants of health including substance use, poverty, access to prenatal care, and low education to improve pregnancy outcomes among vulnerable women is paramount in the fight against prenatal syphilis and improving birth outcomes.

Contributors

Study design and planning: Cohort design and study aims were developed by A Benzaken, F Fernandes Fonseca, VG Veloso, AE Miranda, BE Shepherd, JL Castilho, B Grinsztejn, VG Veloso, EM Jalil.

Data collection, analyses, and interpretation: Data collection was supervised by F Fernandes Fonseca, AMB Beber, and EM Jalil. Variable definition and dataset cleaning were led by EM Jalil, F Fernandes Fonseca, JL Castilho, BE Shepherd, A Kim, and S Tu. A Kim and S Tu had access to raw data. All statistical analyses were performed by A Kim, S Tu, and BE Shepherd. Figures and tables were prepared by A Kim and S Tu. All listed co-authors contributed to interpretation of results.

Manuscript preparation: JL Castilho, A Kim, S Tu, A Benzaken, F Fernandes Fonseca, EM Jalil, BE Shepherd, B Grinsztejn, AMB Beber, VG Veloso, AE Miranda were responsible for writing and editing. All co-authors read and approved the final version of the manuscript. JL Castilho had final responsibility of manuscript submission.

Data sharing statement

The Brazilian Ministry of Health and CCASAnet welcome interested investigators to collaborate with us for use of our data. Please visit https://www.ccasanet.org/for additional information.

Declaration of interests

All authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2024.100894.

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