BMJ Open

HIV-1 infection and pregnancy in young women in Brazil: socioeconomic and drug resistance profiles in a cross-sectional study

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ABSTRACT

Objectives: To describe socioeconomic and antiretroviral (ARV) drug resistance profiles among young pregnant women infected with HIV-1.

Setting: A public health antenatal programme responsible for screening ~90 000 pregnant women per year for nine different infectious diseases in Central Western Brazil.

Participants: 96 young pregnant women (15–24 years) infected with HIV-1.

Primary and secondary outcome measures: Standard interviews and blood samples were taken at the time of recruitment, at the first medical appointment after confirmation of diagnosis of HIV-1 infection, and before ARV prophylaxis initiation. Clinical and laboratory data were retrieved from medical files. HIV-1 *pol* gene sequences (entire protease/PR, partial reverse transcriptase/RT) were obtained from plasma RNA. ARV resistance mutations (CPR/Stanford HIV-1; International AIDS Society-USA databases) were identified.

Results: The median age was 21 years; most reported <8 years education; 73% were recently diagnosed. Approximately 20% (19/96) presented late for antenatal care (after 26 gestational weeks), while 49% reported ≥2 previous pregnancies. Possible heterosexual transmission by an HIV-1 infected partner (17%) and commercial sex work (2%) were reported. The median of CD4 cell count was 526 cells/mm^3; the median viral load was: 10 056 copies/mL in ARV-naïve (48/96) patients and 5881 copies/mL in ARV-exposed (48/96) patients. Two probable seroconversion cases during pregnancy were identified in adolescents. One mother-to-child transmission case (1.0%) was observed. Transmitted drug resistance among ARV-naïve patients was 9.3% (CI 95% 3.3% to 19.6%); secondary drug resistance among ARV-exposed patients was 12.5% (CI 95% 4.7% to 25.6%).

Conclusions: Despite high access to antenatal care, the low socioeconomic-educational profiles seen in these young HIV-1-infected women highlight the necessity of improved public health educational and preventive strategies regarding HIV infection and early unplanned pregnancy.

Strengths and limitations of this study

- Representative sample of HIV-1 infected pregnant young women attending an antenatal care programme that screens ~90 000 women per year;
- Assessment of drug resistance and mother-to-child transmission of potential risk among adolescents and young pregnant women;
- Other studies on larger groups of HIV-1 infected pregnant adolescent/young women from other settings in Brazil and abroad are important to better define this vulnerable population.

INTRODUCTION

The Brazilian AIDS epidemic is considered stable; however, in the past decade, a significant increase in AIDS cases in the younger population (15–19 years) was observed both among males (53.2%) and females (10.5%).[1] Adolescence is characterised by a series of physical, emotional and social modifications that influence health, especially factors associated with the start of sexual activities. Adolescents (10–19 years) and young adults (20–24 years) are considered highly susceptible to sexually transmitted infections (STIs), including HIV infection.[2] This vulnerability in the younger age is certainly associated with engagement in risky sexual behaviours such as early sexual debut, multiple sexual partners and lack of consistent use of condoms.[3] Young women may also be vulnerable to sexual violence and commercial sex with older men.[2]

In Brazil, during the past decade, 40% of HIV-1 infected pregnant women were in the age range of 15–24 years.[1] In the Central Western region, adolescents represented 26% of 54 139 pregnant women screened for HIV-1 infection during antenatal care.[4]

Compared to adults, younger HIV-1 infected patients had lower attendance in specialised clinical care, higher HIV-1 sequelae and difficulties in initiation and adherence to highly active antiretroviral therapy (HAART).[5] [6] Therefore, HIV infection and pregnancy association in young women raises a concern as long-term exposure to HAART started at early age, and low adherence may lead to increased selection of drug-resistant viruses. First-line combination drugs used for treatment in Brazil at the time of the study include: tenofovir-TDF+lamivudine-3TC +zidovudine-AZT. Mother–to-child transmission (MTCT) prophylaxis includes: lopinavir/ritonavir-LPV/r+AZT +3TC.[7] Drug resistance mutations may compromise future therapeutic options and MTCT drug prophylaxis.

In Central Western Brazil, antenatal care is provided free of charge by a comprehensive public health programme (Programme for the Protection of Pregnant Women-PPPW/Goiás State, Central Western Brazil). PPPW offers 'opt out' serological screening (∼90 000 women/year) for HIV-1/2, syphilis, hepatitis B and C, cytomegalovirus, toxoplasmosis, HTLV-1/2, rubella and Chagas disease, regardless of previous diagnosis for women from 246 municipalities at Goiás State. This is a feasible setting for cross-sectional studies among pregnant women. Prevalence of HIV-1 infection in this population has been recently estimated as 1.59/1000 (95% CI 1.27% to 1.96%).[4] In this context, this study aimed to describe in antiretroviral (ARV)-naïve and ARV-exposed young pregnant Brazilian women infected with HIV-1: socioeconomic variables, transmitted and secondary ARV resistance mutation profiles and pregnancy outcomes, such as MTCT.

METHODS

This study was delineated as a cross-sectional survey to describe socioeconomic, resistance mutation profiles and pregnancy-related outcomes among young pregnant women from Brazil. From 2008 to 2013, young pregnant women (<25 years) attending a local antenatal care programme with a positive result for HIV-1 infection were recruited at the time of the first medical visit after the diagnosis. Inclusion criteria were: HIV-1 infected pregnant women aged ≤24 years, ARV-naïve or ARV-exposed.

Sociodemographic information was obtained using a standardised questionnaire at the time of recruitment. Clinical and laboratory data were retrieved from medical files at the main local public HIV-1/AIDS reference hospital (Dr Anuar Auad Tropical Diseases Hospital, Goiânia, Goiás, Brazil). Written informed consents to participate in the study and to provide blood samples were obtained from all patients except for those aged younger than 18 years who had informed consents signed by one of the parents/legal guardian.

Blood samples were obtained at the time of recruitment. ARV-naïve patients had blood samples drawn before ARV-prophylaxis initiation. Plasma RNA (QIAamp

Viral RNA Mini Kit, Qiagen, Hilden, Germany) was used for genetic analyses in *pol* gene as previously described.[8] Transmitted drug resistance (TDR) rate among ARV-naïve patients was determined by the Calibrated Population Resistance tool (Stanford Surveillance Drug Resistance Mutations-SDRM). SDRMs and resistance profiles were defined by the Stanford HIV Drug Resistance Database and by the International AIDS Society-USA major mutation lists. All genotyping profiles obtained in this study were made available to the responsible clinician.

Descriptive analyses of the study variables were performed (Epi Info vs7, CDC, Atlanta, Georgia, USA). Categorical variables were presented as percentage values and continuous variables were analysed by the median value. Missing data were not included in the analysis.

RESULTS

During the study period, 96 young pregnant women infected with HIV-1 were enrolled: 35% (34/96) adolescents (15–19 years), 65% (62/96) within 20–24 years. Most patients were diagnosed during antenatal screening (69/96, 72%). For women with a former diagnosis (28.1%, 27/96), the median time since the previous diagnosis was 3 years (1–12 years range). The median gestational age at diagnosis or at enrolment was 18 weeks (range: 8–37 weeks) and 19% (19/96) started antenatal care after 26 weeks of gestation.

Among these patients, a low socioeconomic profile predominated: 28% (27/96) did not have a formal job, only 2% (2/96) self-reported as students, 18% (17/96) had <8 years of formal education, and 4% (4/96) were illiterate. Regarding HIV-1 acquisition risk, 17% (16/96) reported a known HIV-1 infected sexual partner, 2% (2/96) stated commercial sex work. Half of the participants (48/96) reported a stable sexual partner. Despite their young age, almost half of the participants (47/96) had at least two previous pregnancies (median number of previous pregnancies=2; range: 0–7).

The median of CD4+ T cell counts in this group was 526 cells/mm^3 (range: 82–1324 cells/mm^3); 30% (28/96) were in the CDC stages 2 and 3 (CD4+ T cell count<500 cells/mm^3). Half of the patients (48/96) were ARV-naïve. The ARV-exposed group included women who were previously exposed to an MTCT ARV prophylaxis and then discontinued it after delivery or women on continuous HAART. The median of plasma viral loads was 10 056 copies/mL (range: 299–750 000 copies/mL) among ARV-naïve participants and 5881 copies/mL (range: 157–507 108 copies/mL) in ARV-exposed patients. Viral loads higher than 100 000 copies/mL were detected in around 8% of ARV-naïve patients (4/48) and in 4% of ARV-exposed patients (2/48).

Two cases of probable seroconversion during pregnancy were identified in adolescents who were negative at the first trimester and became seropositive on retesting late in pregnancy. In our study group, one case of

HIV-1 MTCT was observed (1/96; 1.0%): the infected infant was born to a 23-year-old mother who had a late presentation to the antenatal programme, at 32 weeks gestation. Two days before delivery, maternal CD4 cell count was 714 cells/mm^3 and viral load was 5688 RNA copies/mL.

In ARV-naïve patients, TDR was identified in 9.3% (CI 95% 3.3 to 19.6) and among ARV-exposed participants, secondary drug resistance was 12.5% (CI 95% 4.7% to 25.6%). Single-class and dual-class resistance mutations were observed in ARV-naïve and ARV-exposed groups. Individual ARV transmitted and secondary resistance profiles among patients are depicted in table 1. GenBank accession numbers of sequences analysed in this study are: JN114114–JN114220, JN114222–JN114227, JN114235, JN662426–JN662437, KC249749–KC249766 and KJ658974–KJ659016.

DISCUSSION

This study population comprises a representative sample of young HIV-1 infected pregnant women attending a major Brazilian public health antenatal programme that screens ~90 000 women per year. Assessment of HIV-1 infection and mother-to-child transmission of potential risk was performed. Main characteristics included a moderate rate of both TDR and secondary drug resistance, low socioeconomic and educational level, risky sexual behaviours, including known HIV-1 infected sexual partners, commercial sex work and early exposure to ARV drugs. High-risk behaviours such as unprotected intercourse with multiple partners have been shown among adolescents, including those perinatally or behaviourally infected.[9] [10] This unfavourable combination of features in such a young population highlights failures in educational and preventive public health interventions for HIV infection.

Multiparity in young women indicates that improved policies for unplanned pregnancies at early age are highly needed. Previous studies demonstrated that most pregnancies in young HIV-infected women are unplanned and seropositivity is associated with higher previous pregnancy rates.[10] [11]

Late presentation to antenatal care reported among this population is also associated with increased risk for MTCT since it jeopardises retesting during pregnancy, which is important to identify recent seroconversion cases. Previous reports demonstrated that late presentation to antenatal care represents an important barrier for MTCT prevention and is associated with variables such as unplanned pregnancies and fear of HIV testing.[12] [13] HIV infection during pregnancy is associated with increased risk of MTCT and higher transmission risk to sexual partners.[14] HIV-1 testing programmes should be expanded to include at-risk, non-pregnant young women as suggested by a previous study among high-risk female adolescents seeking HIV testing in Brazil.[11] Ideally, HIV-1 diagnosis should precede

Table 1 Drug resistance mutation profiles of HIV-1 isolates obtained from Brazilian young pregnant women infected with HIV-1

GenBank n°	Age (years)	ARV status	CD4 count (cells/mm³)	Viral load (copies/mL)	Resistance mutations			Resistance level		
					PI	NRTI	NNRTI	Low	Intermediate	High
KC249761	22	Naïve	415	6227	L90M	M41L, T215C	–	FPV, LPV, ABC, DDI, TDF, AZT, D4T	ATV, IDV, SQV	NFV
KC249760	23	Naïve	532	21 458	L90M	M41L, T215D	–	FPV, LPV, ABC, DDI, TDF, AZT, D4T	ATV, IDV, SQV	NFV
JN114172	23	Naïve	524	<399	–	–	K103N	–	–	EFV, NVP
JN114216	24	Naïve	NA	2630	–	–	K103N, P225H	–	–	EFV, NVP
JN114197	15	Exposed	NA	44 378	–	–	M230L	–	EFV, ETR, RPV	NVP
JN114174	20	Exposed	1082	5577	T74S	–	–	NFV	–	–
KR559754	22	Exposed	225	19 076	–	M184V	E138Q	ABC, RPV	–	3TC, FTC
JN114142	22	Exposed	NA	NA	T74S	–	–	NFV	–	–
JN114145	22	Exposed	567	3629	–	M184V	K103N	ABC	–	EFV, NVP, 3TC, FTC

3TC, lamivudine; ABC, abacavir; ATV, atazanavir; AZT, zidovudine; D4T, stavudine; DDI, didanosine; EFV, efavirenz; ETR, etravirine; FPV, fosamprenavir; FTC, emtricitabine; IDV, indinavir; LPV, lopinavir; NA, not available; NFV, nelfinavir; NVP, nevirapine; PR, protease; RPV, rilpivirine; RT, reverse transcriptase; SQV, saquinavir; TDF, tenofovir disoproxil fumarate.

pregnancy since virological failure at delivery and MTCT are more likely in women diagnosed during pregnancy.[15]

Exposure to ARV drugs early in life was observed: more than half of the adolescents (20/34) had been previously exposed to ARV drugs. However, patients with high viral loads (500 000–750 000 copies/mL) were observed both among ARV-naïve and ARV-exposed groups, indicating high risk for both MTCT and sexual transmission. A previous study carried out in Haiti among adolescents and young patients receiving ARV treatment demonstrated that after 12 months more than half of the patients presented a detectable viral load, probably associated with low adherence and drug resistance.[16] High viral loads in ARV-exposed young women may reflect low adherence to ARV treatment, as previously reported in adolescents, possibly due to rebellious behaviour, collateral effects of ARV drugs and psychosocial factors such as depression.[6] Adolescents have shown higher virological failure after 6 months of HAART, presenting higher viral loads.[17] However, in our study, viral loads were highly variable and no data on adherence to ARV were available.

HIV-1 infection in adolescents and young adults may include both perinatal and sexual transmission cases since significant advances and broader paediatric access to antiretroviral treatment have reduced mortality rates in infected children.[2] Therefore, a growing number of perinatally infected children are now reaching adolescence and becoming sexually active.[18 19] Although most patients in this study reported heterosexual risk behaviour, perinatal HIV-1 infection, especially among adolescents, could not be excluded, even in recent diagnosed ARV-naïve patients, since maternal health status was not available and these could represent slow-progressor cases.

The moderate rate of TDR observed in this young group raises a concern regarding the efficacy of future HIV-1 MTCT prophylaxis and maternal treatment options. Dual-class resistance for the first-line combination drugs used for treatment and for MTCT prophylaxis was observed. Previous studies among ARV-naïve pregnant women from this setting reported absence of TDR in 2003 and the 9.3% TDR rate reported here suggests a rising trend.[20] Continuous TDR monitoring should be emphasised, especially with the new policy adopted by the Brazilian Ministry of Health of universal distribution of ARV drugs for all diagnosed cases of HIV-1 infection, regardless of CD4+ T cell counts.

Regarding ARV-exposed patients, a moderate rate of secondary drug resistance was observed, as previously demonstrated in this setting.[20] Temporary exposure to ARV prophylaxis for MTCT (from the 14th gestational week until delivery) was recommended in Brazil until 2013, a strategy that could have favoured the selection of ARV-resistant isolates. In Brazil, secondary resistance rates over 20% were previously reported in HIV-1 pregnant women exposed to ARV prophylaxis for MTCT.[21]

CONCLUSION

This study highlights the low socioeducational and economic profiles of highly vulnerable young HIV-1 infected pregnant women in Brazil. High viral loads and late presentation for antenatal care indicate higher risk for MTCT and sexual transmission. Furthermore, moderate levels of drug resistance in ARV-naïve and ARV-exposed pregnant women emphasise the need for continued drug resistance surveillance studies to assure effective MTCT measures and future treatment options. These findings, observed among an expressive population of pregnant women in a large country such as Brazil, represent important challenges to achieve the initiatives of the elimination of vertical transmission of HIV/AIDS in Latin America and the Caribbean. The profile of vulnerable HIV-1 infected young pregnant women can help delineate better public health strategies to promote improved educational and preventive measures for HIV infection and unplanned pregnancies as well as early diagnosis of asymptomatic cases and MTCT prophylaxis. Extended studies on larger groups of young HIV-1 infected pregnant women are needed to better define this vulnerable population.

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