Human immunodeficiency virus type 1 drug resistance in a subset of mothers and their infants receiving antiretroviral treatment in Ouagadougou, Burkina Faso

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Abstract

The emergence of HIV-1 drug resistance (HIVDR) is a public health problem that affects women and children. Local data of HIVDR is critical to improving their care and treatment. So, we investigated HIVDR in mothers and infants receiving antiretroviral therapy (ART) at Saint Camille Hospital of Ouagadougou, Burkina Faso. This study included 50 mothers and 50 infants on ART. CD4 and HIV-1 viral load were determined using FACSCount and Abbott m2000rt respectively. HIVDR was determined in patients with virologic failure using ViroSeq HIV-1 Genotyping System kit on the 3130 Genetic Analyzer. The median age was 37.28 years in mothers and 1.58 year in infants. Sequencing of samples showed subtypes CRF02_AG (55.56%), CRF06_cpx (33.33%) and G (11.11%). M184V was the most frequent and was associated with high-level resistance to 3TC, FTC, and ABC. Other mutations such as T215F/Y, D67N/E, K70R, and K219Q were associated with intermediate resistance to TDF, AZT, and 3TC. No mutation to LPV/r was detected among mothers and infants. The findings of HIVDR in some mothers and infants suggested the change of treatment for these persons.

Introduction

In 2015, the number of people living with HIV-1 worldwide was estimated at 36.7 million.[1] In Sub-Saharan Africa, it is still estimated that 620 000 new HIV-1 infections occurred in 2015.[1] The number of pregnant women infected with HIV in Africa in 2013 was estimated at 1.3 million.[2] Despite the 40% reduction of mother-to-child transmission (MTCT) of HIV-1 in the past five years, news pediatrics infections were estimated at 220 000 in 2014 and the majority were through MTCT.[3] In recent years, the hope of controlling the epidemic of HIV-1 is being thwarted by the emergence of HIV-1 drug resistance (HIVDR) to various antiretroviral (ARV) used for the treatment of HIV-1 infected patients. Factors leading to HIVDR may be related to the virus, HIV-1 infected persons, and the ARV drugs or to prevention program.[4] Emergence of HIVDR remains a major obstacle to the effectiveness of antiretroviral therapy (ART).[5] Previous studies have shown that the prevalence of HIVDR in Burkina Faso was 12.5% in patients with virologic failure in 2009 in Ouagadougou [6] and 20.4% in patients on HAART in 2011 in Bobo-Dioulasso and Ouagadougou.[7] Pregnant women harboring HIVDR might transmit these strains to their infants.[8] Prevention of mother-to-child transmission (PMTCT) reduces the risk of pediatric HIV-1 infection but does not completely prevent the transmission.[9-11] In addition, HIV-1 infected children in the frame of PMTCT can develop resistance to ARV administered.[12] Acquired HIVDR occurs due to incomplete suppression of viral replication during the administration of antiretroviral drugs to infants or by ingestion of maternal drugs through breast milk.[13] Thus, in the course of PMTCT, it is possible that mothers and their infants acquire HIVDR to ARV drugs used. Describing treatment failure and drug resistance in both mother and infant in PMTCT programs is highly relevant in a context where the pediatric formula of ARV is still limited. So, the objective of this study is to describe the HIVDR in mothers and their infants receiving ART for their best care in Ouagadougou, Burkina Faso.

Materials and Methods

Population study and collection of blood samples

It is a cross-sectional study that included 50 HIV-1 infected mother-child pairs followed up in PMTCT program at Saint Camille Hospital of Ouagadougou from August 2014 to December 2015. Blood sampling was done in mothers one year after delivery and in infants at 12 months after ART initiation for determination of clinical, immunological and virologic parameters. Whole Blood was collected in EDTA tubes and then centrifuged at 4000 rpm for 5 minutes. The plasma was collected into cryotubes and stored at -20°C until biological analysis.

Determination of CD4 cell counts and viral load of HIV-1

CD4 cells count and CD4 percentage were determined on fresh blood samples collected in EDTA tubes using BD

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Key words: HIV-1 drug resistance, MTCT, ART, Burkina Faso.

Acknowledgments: the authors wish to thank Saint Camille Hospital, CERBA/LABIOGENE and express their gratitude to the Italian Episcopal Conference (CEI) and the West African Economic and Monetary Union (WAEMU) (through the PACER2 program) for their financial support. The research was funded by an African Doctoral Dissertation Research Fellowship award offered by the African Population and Health Research Center (APHRC) in partnership with the International Development Research Center (IDRC).

Contributions: STS, data collection, analysis and interpretation of data and manuscript preparation; BVB, TRC, AZ, LT, analysis and interpretation of data; AKO, TMZ, data collection and manuscript preparation; DO, ATY, VP, revision of the manuscript; SA, SD, JS, final approval of the version; JS, conception and design.

Conflict of interest: the authors declare no potential conflict of interest.

Funding: the work was supported by APHRC grant, no. 2016-2018 ADF 007.

Received for publication: 17 August 2017.
Revision received: 7 November 2017.
Accepted for publication: 19 February 2018.

Journal of Public Health in Africa 2018; 9:767
doi:10.4081/jphia.2018.767

FACSCount (Becton Dickinson, San Jose, CA). HIV-1 viral load (VL) in mothers and in infants was determined using the Abbott Real-Time HIV-1 kit (Abbott Laboratories, USA) on Abbott m2000rt instrument according to manufacturer's instructions. In this study, we defined immunological failure in mothers as CD4 cells count below 350 cell/mm^3 and infants as <25 % according to WHO guidelines 2013.[14] Also, according to these guidelines, virologic failure (VF) was defined as plasma viral load above 1000 copies/mL after 6 months of treatment. But in this study, the ViroSeq kit used for sequencing recommended samples with viral load ≥2000 copies/mL.

Sequencing of HIV-1 and phylogenetic analysis

According to virologic failure criteria, 18 patients (10 mothers and 8 infants) were eligible for sequencing. Sequencing of HIV-1 was performed by using the ViroSeq HIV-1 Genotyping System v2.0 kit (Celera Corporation, CA, USA) on the ABI Prism 3130 Genetic analyzer (Applied Biosystems, California, USA) according to the manufacturer's instructions. This kit amplifies the *Pol* gene using seven (7) primers (A, B, C, D, F, G, H). The ViroSeq v.2.8 software was used for the correction of the sequences obtained in comparison with the reference sequence HXB 2. Subtypes were determined by local alignment from the drug resistance database of Stanford University (http://dbpartners.stanford.edu/RegaSubtyping/) and the National Institute of Health (http://vih.lanl.gov/content/sequence/BASIC BLAST / basic blast.html). Drug resistance mutations (DRM) associated with the HIVDR were determined from the latest list of mutations from a database of Stanford University (http://hivdb.stanford.edu), and a list of 2015 International AIDS Society (http://iasusa.org). Sequences were aligned by using the program ClustalX with MEGA 5.0 software. The algorithm of the Stanford University was used to classify HIVDR in high, intermediate and low.

Statistical analysis

The clinical data were analyzed by using the SPSS Statistics 21.0 software. Chi-square was used for the comparisons. Any value was considered statistically significant for P<0.05.

Ethical consideration

This study was approved by the Ethics Committee for Research Health of Burkina (Deliberation No. 2014-7-084). The free and informed consent of the mothers to participate in the study, anonymity, and confidentiality were observed.

Results

Demographics, clinical and biological characteristics of mothers and their children

Demographic and clinical data are summarized in Table 1. The median age was 37.28 years (IQR: 22-55) in mothers and 1.58 year (IQR: 1.2-1.75) in infants. The median CD4 cells count in mothers and in infants were 413.0 cell/µL (IQR: 11.0-907.0) and 491.46 cells/µL (IQR: 28-978) respectively. In infants, the median CD4 % was 32 % (11%-57 %). Immunological failure was observed in 24.0 % of mothers (12/50) and in 22.0 % (11/50) of infants. Also, 10 mothers (20.0%) and 8 infants (12.0%) presented virologic failure (viral load ≥ 2000 copies/mL).

HIV-1 genetic diversity in mothers and their infants

Sequences obtained were analyzed to determine the subtypes, DRM to non-nucleoside reverse transcriptase inhibitors (NNRTI), nucleoside reverse transcriptase inhibitors (NRTI) and protease inhibitors (PI). Subtype CRF02_AG was predominant (55.56%), followed by CRF06_cpx (33.33%) and G (11.11%) (Table 2). The subtype CRF02_AG was predominant (55.56%) in this study contrary to others study were the subtype CRF06_cpx was predominant.

HIVDR in mothers and infants

This study, identified resistance mutations to nucleoside reverse transcriptase (NRTI) inhibitors and to non-nucleoside reverse transcriptase inhibitors (NNRTI). No mutations of resistance were detected to protease inhibitors (PI). Among the muta-

Table 1. Clinical and biological characteristics of mothers and their infants.

	Mothers (n=50)	Infants (n=50)
Median age, years (IQR)	37.28 (22-55)	1.58 (1.2-1.75)
Median CD4 cells count, cell/µL (IQR)	413.0 (11.0-907.0)	491.46 (28-978)
Median CD4%, (IQR)		32 (11-57%)
Immunological failure, (CD4 cells count <350 cell/µL) %	12 (24.0)	
Immunological failure, (CD4% <25%)		11 (22.0)
Virologic failure, plasma viral load ≥2000 copies/mL, %	10 (20.0)	8 (16.0)
Treatment ART, %		
2 NRTI + 1 NNRTI	41 (82.0)	46 (92.0)
2 NRTI + 1 PI	7 (14.0)	4 (8.0)
3 NRTI	2 (4.0)	0 (0.0)
WHO clinical stage,%		
I	8 (16.0)	14 (28.0)
II	19 (38.0)	17 (34.0)
III	20 (40.0)	16 (32.0)
IV	3 (6.0)	3 (6.0)

IQR, interquartile range; ART, antiretroviral; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non- nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; WHO, world health organization

Table 2. Comparison of subtypes in present study with those found in previous studies in Burkina Faso.

Subtypes	Present study n=18 (2016)	Nadembega *et al.* (2006) n=29, %	Kagone *et al.* (2011) n=46, %	Sagna *et al.* (2015) n=17, %
CRF02_AG	55.56	31.0	38.6	35.3
CRF06_cpx	33.33	55.2	54.5	58.8
G	11.11	3.5		5.9
A		6.9	2.3	
CRF09_cpx		3.4		
CRF01_AE			4.6	
Total	100	100	100	100

tions identified, M184V was more predominant and was more frequent in mothers (27.78%) than in infants (22.22%). Other mutations such as T215F/Y and D67N/E were also more prevalent in mothers (16.67% and 11.11% respectively) than in infants (5.56% and 5.56% respectively) (Table 3). The drugs affected by these mutations were AZT (T215F/Y, D67N/E); 3TC (M184V, T215F/Y, D67N/E), FTC (M184V), ABC (M184V) and TDF (T215F/Y). Also, other DRM such as K70R (5.56%), K219Q (5.56%), T69D (5.56%), Y115F (5.56%) and K65R (5.56%) were detected with equal rates in mothers and were associated with resistance to (AZT, 3TC, TDF), 3TC, DDI, ABC and 3TC respectively. In contrast, Y115F (5.56%) and K65R (5.56%) were identified only in infants and conferred resistance to ABC and 3TC respectively. T69Sinsertion, V75M, and L210W were detected only in mothers but did not confer resistance to drugs used (Figure 1A).

In the NNRTI group, Y181C was more prevalent in infants (22.22%) than in mothers (5.56%) and conferred resistance to NVP and EFV. G190A and K101Q/E were more frequent in mothers (16.67% and 16.67% respectively) than in infants (5.56% and 5.56%) and conferred resistance to NVP and EFV. K103N was detected more in children (11.1%) than in mothers but did not confer resistance to ARV used. Other mutations such as P225H and 227L were identified only in mothers and conferred resistance to NVP (Figure 1B). In this study, we classified the resistance level in three categories: high, intermediate and low according to the Stanford University algorithm (http://hivdb.stanford.edu/). High-level resistance was observed for 3TC, ABC, NVP, and EFV in mothers and children at rates of 66.67%, 16.67%, 50%, 16.67% respectively and FTC only in 16.67% of mothers. Intermediate-level resistance was observed for AZT in 16.67% of mothers and 33.33% of infants, for TDF only in 33.33% of mothers and for 3TC only in 16.67% of children. In contrast, low-level resistance was observed for AZT in 16.67% of mothers and infants and for NVP only in 16.67% of infants (Figure 2).

Discussion

In this study, despite the limited number of patients, we showed the difference of HIV-1 genetic diversity and DRM in 18 patients (mothers and infants) with virologic failure. Subtypes CRF02_AG, CRF06_cpx and G were detected in 55.56%, 33.33% and 11.11% respectively.

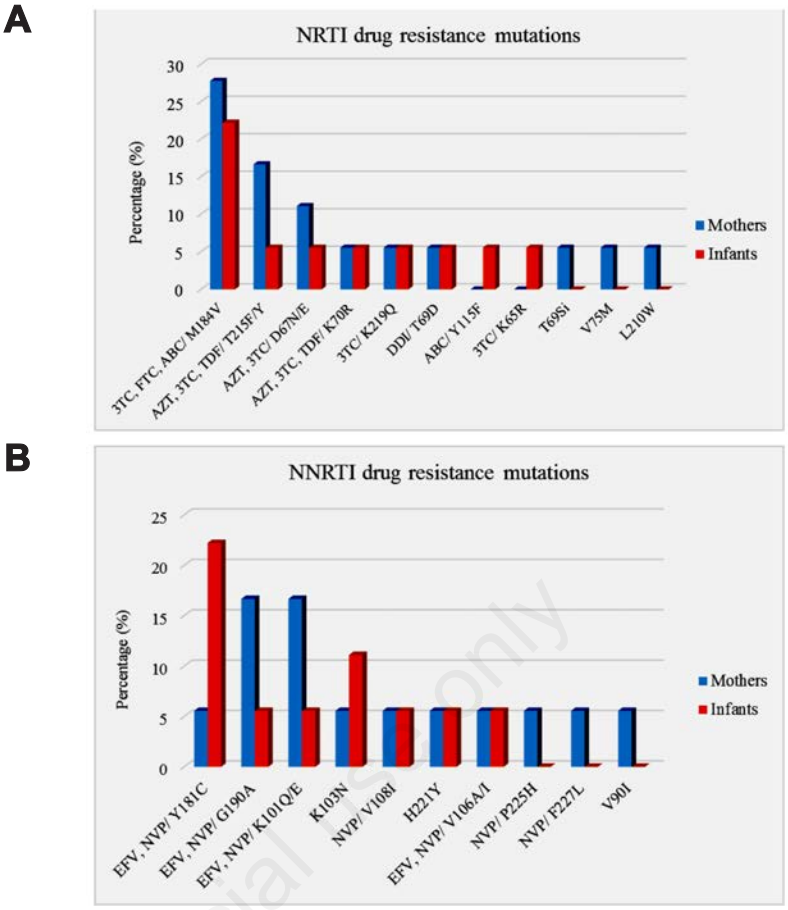

Figure 1. Drug resistance mutations to ARV used in mothers and infants (A) NRTI drug resistance mutations; (B) NNRTI drug resistance mutations. ABC, Abacavir; AZT, Azidovudine; 3TC, Lamivudine; DDI, Didanosine; EFV, Efavirenz; NVP, Névirapine; FTC, Emtricitabine; TDF, Tenofovir.

Table 3. Drug resistance mutations to NRTI and NNRTI.

Drug resistance mutations	Mothers (n=10)	Infants (n=8)
Nucleoside reverse transcriptase inhibitor (NRTI) mutations		
M184V	5 (27.78)	4 (22.22)
T215F/Y	3 (16.67)	1 (5.56)
D67N/E	2 (11.11)	1 (5.56)
T69D	1 (5.56)	1 (5.56)
K70R	1 (5.56)	1 (5.56)
K219Q	1 (5.56)	1 (5.56)
T69Si	1 (5.56)	0 (0.0)
V75M	1 (5.56)	0 (0.0)
L210W	1 (5.56)	0 (0.0)
K65R	0 (0.0)	1 (5.56)
Y115F	0 (0.0)	1 (5.56)
Non-nucleoside reverse transcriptase inhibitor (NNRTI) mutations		
Y181C	1 (5.56)	4 (22.22)
G190A	3 (16.67)	1 (5.56)
K103N	1 (5.56)	2 (11.11)
K101Q/E	3 (16.67)	1 (5.56)
V106A/I	1 (5.56)	1 (5.56)
P225H	1 (5.56)	0 (0.0)
F227L	1 (5.56)	0 (0.0)
H221Y	1 (5.56)	1 (5.56)
V108I	1 (5.56)	1 (5.56)
V90I	1 (5.56)	0 (0.0)

In this study, CRF02_AG was the most predominant contrary to others studies in Burkina Faso where CRF06_cpx was most represented.[7,10,14] Some studies showed that CRF02_AG and CRF06_cpx are the two most common CRF in West Africa with a predominance of CRF02_AG which is responsible for 50% of cases of HIV-1 infection.[15] Moreover, the prevalence of 5 to 15% for CRF06_cpx was reported in Niger, Togo, Benin, Mali, Ghana, and Nigeria.[16-20] In this study, DRM was observed to NRTI and NNRTI. No mutations had been observed to LPV/r, the only PI used. As reported in other studies,[10,21] M184V was the most frequent in this study and was associated with high-level resistance to 3TC, FTC, and ABC. Others mutations detected such as T215F/Y, D67N/E, K70R, and K219Q are associated with intermediate resistance to TDF, AZT, and 3TC. Mutation K65R, which was reported as a major mutation conferring high-level resistance to most of NRTI,[12,22] this mutation was associated with intermediate resistance to 3TC in this study. Mutations Y181C, G190A conferred high resistance to EFV and NVP in mothers and infants. Sagna *et al*. (2015)[10] showed also these mutations to confer resistance to NVP, EFV, and ETR in Burkina Faso. Other studies reported mutations G190A, Y181C that conferred high resistance to NNRTI in individuals with subtype C.[23,24] Some studies also found K103N and Y181C in individuals with subtypes A, B, C, F and CRF02_AG who developed resistance to NVP, ETR, and EFV.[23,24] As opposite to study of Sagna *et al*. (2015)[10] where K103N was associated to resistance to NVP and EFV, in this study this mutation was not associated to any NNRTI. All these mutations can be explained by some mechanisms such as rate of HIV-1 replication, errors of reverse transcriptase activity and the genetic recombination that contribute strongly to drug resistance in HIV-1 infected patients.[24,25] A high incidence of acquired HIV-1 resistance after a 1 year of first-line treatment has been reported in Cameroon and Togo, with rates of 46% and 24.5% respectively.[26,27] Also, a study in six sub-Saharan African countries showed that 70% of women with virologic failure after one year of treatment developed DRM to drugs used.[16] According to WHO recommendations in 2013, any person diagnosed HIV-1 positive should receive therapy regarding the lymphocytes T CD4 cell count.[28] At the Saint Camille hospital of Ouagadougou, Burkina Faso, HIV-1 infected women are followed within the framework of the PMTCT. In general, cases of treatment failure observed in HIV-1 infected patients are probably due to HIVDR or poor adherence.[4] Today, we observe the emergence of HIVDR to NNRTI, NRTI and PI making it difficult to fight against HIV-1.[21] So, HIV-1 infected mothers and infants in resource-poor settings may be particularly vulnerable to HIVDR due to limited monitoring and salvage options. Also, DRM could compromise the virologic response and confer resistance to the subsequent maternal or pediatric treatments that include non-nucleoside reverse transcriptase inhibitors (NNRTI), the main first-line treatment regimens in resource-limited settings, particularly in those initiating such treatment within 6 months after delivery.[29] This study was important because we identified some cases of HIVDR among mothers and infants with virologic failure. It is necessary to start a surveillance of HIV-1 drug resistance in mothers during PMTCT to reduce the spread in Burkina Faso.

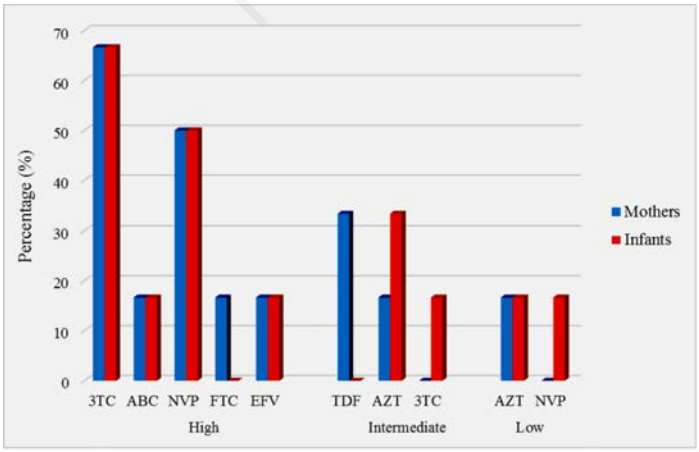

Figure 2. Level of resistance in mothers and infants: High, Intermediate and Low resistance.

Conclusions

This study showed HIVDR and DRM among mothers and infants with virologic failure and the findings allowed the change of the treatment of these patients to improve their care during PMTCT.

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