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Research Article

Transmitted Drug-Resistance Mutations and Early Clinical, Virologic, and Immunologic Outcome of Pediatric Antiretroviral Therapy in Northern Viet Nam, during 2010-2011

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Abstract

Introduction: Antiretroviral therapy (ART) was scaled up in HIV-infected Vietnamese children and adults as well. Few studies documented the association between drug-naïve resistant HIV-1 with treatment outcome, especially in children. This study aimed to determine the rate of drug-resistance mutations before initiating ART, and the treatment outcome after six months of ART.

Methods: During 2010 - 2011, 140 HIV-1 infected children were admitted at National Children Hospital Viet Nam. Of them, 116 were initiated first-line ART, their clinical profile, CD4+ T-cell counts, and HIV load after six months of ART were retrospectively collected. Their plasma before initiating ART was stored for analysis by 2012. Of 116 samples, 52 had the HIV-1 pol gene successfully sequenced to detect drug- resistance mutations.

Results: 18 children (29.0 ± 28.8 months) died, within an average of 1.6 ± 1.4 months of ART. Baseline WHO clinical stage 3-4 ($p<0.001$), and lower CD4+ T-cell counts ($p=0.03$) was associated with fatality. Stored plasma samples of 52 were sufficiently analyzed, six carried drug-resistance HIV-1. One of six was exposed to ART through prevention of mother-to-child transmission. Of RT-inhibition resistance, three had single mutant; one had K65R/Q151M / K101E/Y181C with six-month virological failure. Among PR-inhibition resistance, two had either M46L or M46L/L90M.

Conclusion: Transmitted drug - resistance mutations were found in 9.6% of 52 children. Six-month treatment outcome was induced by baseline clinical and immunological stage. Pre-treatment drug-resistance mutations might not associate with six-month mortality but induce risk of virological failure.

ABBREVIATIONS

HIV: Human Immunodeficiency Virus; ART: Antiretroviral Therapy; WHO: World Health Organization; AIDS: Acquired Immunodeficiency Syndrome; DRM: Drug-Resistance Mutations

INTRODUCTION

Globally, 2.1million children (<15 years of age) were infected with HIV by the end of 2016, and most (98%-99%) of them were from resource-limited settings [1]. An estimated coverage of antiretroviral therapy (ART) among children in need of ART was 43% [2]. The aim of ART is to suppress HIV to an undetectable level; this is the main approach in managing the clinical course of HIV infection [3]. Reports from low- and middle-income countries have demonstrated the benefits of pediatric ART [4-7]. ART has been proven to effectively reduce mortality, and change in causes of death in HIV-1-infected infants and children [8,9].

Since the first detection of HIV infection in Viet Nam in 1990 [10], estimated number of HIV-1 infected people increased to 254,000. By the end 2013, estimated number of children who were living with HIV was 7,200 [11]. From 2005 to the end of

2013, ART has been scaled up to 31 times, with 78,438 (66%) HIV-infected adults in need of ART, receiving therapy. Since 2006, ART has been used to treat HIV-1-infected children, as of the end of 2013; over 4,200 children were on ART [11]. As ART was scaled up rapidly, surveillance of transmitted drug-resistance mutations is necessary [12]. For past few years, several studies in HIV-infected adults revealed low rate of circulating resistant strains, and documented drug-resistance profile [13-17]. However, fewer studies about drug-resistance in HIV-infected Vietnamese children are available [18,19], and none of them reported the association of drug resistance with ART outcome. In Southeast Asia, other cohorts did establish treatment outcome, but limited concerning the impact of baseline drug-resistance mutation [20,21], or report from adult subjects [22].

Therefore, we conducted this study to describe transmitted drug-resistance mutations (DRM) proportion, and assess treatment outcome in HIV-infected Vietnamese children, after six months of first-line ART.

MATERIAL AND METHODS

This is an observational study; clinical data were collected retrospectively from database of routine care at Viet Nam National Children's Hospital.

Inclusion criteria

Children who were hospitalized and diagnosed HIV infection, from January 2010 to October 2011. For the purpose of drug-resistance description, baseline specimens those remained after complete blood count and/or $CD4^+$ T-cell counts would be stored at – 80°C upon analysis, by Oct. 2011. Totally, 140 children were admitted to the hospital, with 116 were initiated first-line ART during study period. Of 116 children, 52 blood samples were retrieved before initiating ART and successfully analyzed drug-resistance mutations. Other 64 blood samples which remained inadequate volume after routine hematology were unable to perform drug-resistance testing, and then were excluded from reporting result.

First-line ART was initiated in accordance with Viet Nam Ministry of Health's guideline version 2009. The regimen for HIV-1 infected children consisted of Zidovudine (AZT) and Lamivudine (3TC) in combination with Nevirapine (NVP). AZT was replaced by Stavudine (d4T) for children with a hemoglobin < 8 g/dl while NVP was replaced by Efavirenz (EFV) for children over 3 years of age (or >10 kg) who were receiving concurrent treatment for tuberculosis. Daily cotrimoxazole prophylaxis was given to all children, as recommended by the guideline. ART prophylaxis was given at the beginning of labour, the mothers got NVP 200mg + AZT 600mg + 3TC 150mg then AZT 300mg + 3TC 150mg every 12 hours until delivery; postpartum AZT 300mg + 3TC 150mg every 12 hours for 7 days. The infants got single dose NVP 6mg, immediately after birth + AZT 4mg/kg b.i.d. for 4 weeks [20]. The history of ART usage among the mothers was not recorded at the time of conducting study.

Percentages and absolute counts of $CD4^+$ T-cell were determined on a FACS Calibur (Becton Dickinson, US) using BD Multi Test reagents and Multi Set software (BD Immunocytometry Systems). Six-month immunological failure was defined as $CD4^+$ T-cell percentage <10% for children <5 years or absolute $CD4^+$ T-cell counts <100 cells/ml for children 5 to 12 years [20].

Plasma viral load (VL) was measured by using the Generic HIV Charge Virale test kit version 5.2 (Biocentric, France), with a detection limit of 300 copies/ml. Six-month virological failure was defined as having plasma VL above 1000 copies/ml [21].

Children who had stabilized clinical conditions without severe symptoms would be discharged, and visited the hospital every a month for drug distribution and clinical assessment. Children who required long time hospital care, and/or mortal case would be adjusted 6-month clinical assessment at latest record as possible.

Genotyping and resistant determination

HIV-1 RNA was extracted from 140µl plasma using the QIAamp Viral RNA mini kit according to the manufacturer's instruction. The HIV-1 *pol* protease (PR) and reverse transcriptase (RT) genes were amplified by nested RT- PCR. The primers used for RT region: DRRT1L and RTout in the first round and DRRT7L and DRRT6L in the second round. The primers using for PR region were DRPRO5 and DRPRO2L in the first round and DRPRO1L and DRPRO6L in the second round [13]. Sequencing reaction was done using the Big Dye Terminator v3.1 Cycle Sequencing Kit. Products from the sequencing PCR were purified using Sodium acetate and ethanol precipitation. Purified products were sequenced directly using an automatic ABI Prism 310 Genetic Analyzer (Applied Biosystems). The HIV-1 nucleotide sequences obtained from each child were analyzed for previously reported drug-resistance mutations using web resources forHIV-1 genotypic-resistance test interpretation [22], and the mutation panel from the International AIDS Society USA (IAS-USA), July 2014.

Statistical analysis

Pair wise comparisons were made in demographic, clinical features, virological, and immunological parameters between by-six-month survivors and fatal cases using Student's t-test, the chi-squared test or Fisher's exact test.

Ethics approval was obtained from Ethical committee of Viet Nam National Children's Hospital.

RESULTS

During January 2010 to October 2011, 116 children (57 males: 59 females) who fulfilled criteria were enrolled. Their age at ART start was 51.5 ± 35.8 months, 46.6% of them presented with WHO clinical stage 3-4. Baseline plasma of 52 children was available and successfully analyzed for DRM; six of them (11.5%) carried drug-resistant HIV-1 strains (Table 1).

By 6 months after initiating ART, of the 116 children, 18 (15.5%) had died. As described in Table 1, baseline WHO clinical stage 3-4 ($p<0.001$), was significantly associated with fatality. Among baseline opportunistic infections, Candida ($p=0.005$) and Pneumocystis ($p<0.001$) showed more association with death than other etiologies. In concordance with clinical condition, baseline $CD4^+$ T-cell counts of fatal cases were lower than survivors ($p=0.03$). Additionally, age of fatal cases were lower than average of those survivors (29.0 ± 28.8 *vs* 55.7 ± 35.6

Table 1: Baseline characteristics of HIV- infected children on antiretroviral therapy.

Characteristics	Total (n=116)	Alive (n=98)	Dead (n=18)
Gender, n (%)			
Male	57 (49.1)	50 (51)	7 (39.9)
Female	59 (50.9)	48 (49)	11 (61.1)
Age (months), mean ± SD	51.5 ± 35.8	55.7 ± 35.6	29.0 ± 28.8[a]
Parent status, n (%)			
At least one alive	106 (91.4)	88 (89.8)	18 (100)
Both dead	10 (8.6)	10 (10.2)	0 (0)
ART prophylaxis, prevention of mother to child transmission, n (%)			
No	107 (92.2)	91 (92.9)	16 (88.9)
Yes	9 (7.8)	7 (7.1)	2 (11.1)
WHO clinical stage, n (%)			
1 or 2	62 (53.4)	62 (63.3)	0 (0)
3 or 4	54 (46.6)	36 (36.7)	18 (100)[b]
Common clinical episodes, n (%)			
Oral Candidiadis	55 (47.4)	41 (41.8)	14 (77.8)[a]
Hives rash	41 (35.3)	39 (39.8)	2 (11.2)[a]
Herpes zoster	8 (6.9)	8 (8.2)	0 (0)
Recurrent pneumonia	24 (20.7)	19 (19.4.)	5 (27.8)
Pneumocytis pneumonia	12 (10.3)	3 (3.1)	9 (50)[b]
Pulmonary tuberculosis	8 (6.9)	6 (6.1)	2 (11.1)
Penicilliummarneffei infection	5 (4.3)	5 (5.1)	0 (0)
HIV encephalopathy	2 (1.7)	1 (1.0)	1 (5.6)
$CD4^+$ percent, mean ± SD	14,6 ± 14,1	14,8 ± 13,9	13,4 ± 15,3
$CD4^+$ counts (cells/µl), mean ± SD	414 ± 379	449 ± 388	221 ± 257[a]
Log_{10} viral load (n=84), mean ± SD	3,9 ± 2,3	3,9 ± 2,3	not available
Drug-resistance carriers (n=52)	6/52	5/38	1/14

[a] $p < 0.05$; [b] $p < 0.001$: Dead *vs* Alive

Table 2: Clinical endpoint in fatal cases (n=18) and six-month survivors (n=98).

Clinical episodes	Death, n (%)	Survivor, n (%)
Pneumonia [a]	13 (72.2)	3 (3.1)
Septicemia [b]	3 (16.7)	0
Pulmonary tuberculosis	1 (5.6)	4 (4.1)
HIV encephalopathy	1 (5.6)	0
Oral Candidiadis	0	1 (1.0)
Hives rash	0	2 (2.0)

[a] $p<10^{-7}$; [b] $p<0.001$

months, p=0.002). Of the 98 survivors, eight were in WHO clinical stage 3-4 at six months of ART, which showed an improvement, while 36/98 had severe baseline condition (Table 1). As detail, three had pneumonia, four presented pulmonary tuberculosis, and a child with oral candidiasis. Of 18 fatal cases, at end point, 13 children presented recurrent pneumonia, eight of 13 had unexplained wasting/malnutrition. Fatal cases were on ART for average 1.6 ± 1.4 months before developed lethal episode. Clinical presentation by six month of ART was described detail in Table 2. Paired $CD4^+$ T-cell counts were available in 92 children, which increased from 449 to 731 cells/µl ($p<0.001$). Of 92 children, nine (9.8%) still remained their $CD4^+$ T-cell counts as baseline.

Six-month plasma VL was available in 45 children, of them 30 (67%) had VL<1000 copies/ml. Fully virologic suppression was achieved in 24 children (55%) with viral load below limit of detection. As repeated plasma VL is needed to confirm treatment failure [20, 21], and viral suppressing could take 12 to 24 months to differentiate outcome [23]. Therefore, we combined plasma VL ≥ 1000 copies/ml and $CD4^+$ T-cell counts to confer early sign of treatment failure. There were 4/45 (8.9%) children whose plasma VL>1000 copies/ml and low $CD4^+$ T-cell counts, although they were still in WHO clinical stage 1-2.

Of 52 sequenced samples, RT inhibitors (RTI) associated mutations were found in four children (7.7%) and other two children had protease inhibitors (PI) associated mutations (3.8%), no child carried both RTI and PI resistant mutation. One DRM carrier (ID: DR84, Y181C mutation) exposed RTI drugs through PTMTC. In detail, the mother received AZT/3TC/NVP at labor and 3TC/AZT twice per day for seven days, the child got single dose of NVP at birth and two months of AZT. This child

Table 3: Characteristics of six drug-resistance carriers before and after six months of antiretroviral therapy.

ID	Age (years)	Drug resistance			ART at start	Before/after			
		PI	NRTI	NNRTI		WHO clinical stage	CD4+ %	CD4+ counts (cells/µl)	Viral load (copies/ml)
DR 84*	2	No	No	Y181C	AZT/3TCNVP	3/2	3/5.8	89/104	187108/474
DR 154	4	No	No	M230L	AZT/3TCNVP	2/1	16.5/ 49.7	215/1018	480301/NA
DR 172	3	No	K65R Q151M	K101E Y181C	d4T/3TC NVP	2/1	3.1/3.2	63/63	208193/1202
DR 190	3	No	L210W	No	d4T/3TC NVP	3/2	15.3/ NA	158/NA	NA
DR 92	2	M46L	No	No	AZT/3TCNVP	3/2	17/36.8	729/699	NA/386
DR 01	2	M46L L90M	No	No	d4T/3TC NVP	4/Dead	7.1/NA	57/NA	NA

d4T: stavudine; 3TC: lamivudine; AZT: zidovudine; NPV: nevirapine; NA: not available; PI: protease inhibitor; NRTI: nucleoside reverse-transcriptase inhibitor; NNRTI: non-nucleoside RTI; *exposed to antiretroviral therapy through prevention of mother to child transmission

was excluded from calculating of transmitted rate. Therefore, transmitted PI-resistance and RTI-resistance rate was 2/52 (3.8%) and 3/52 (5.7%), overall transmitted rate was 5/52 (9.6%).

Of four children with RTI resistance, two had non-nucleoside RTI (NNRTI) and one had nucleoside RTI (NRTI) resistant mutations, remain child had both NNRTI and NRTI resistance. Among the NNRTI resistance, Y181C was found in two children, and one remained child had M230L. Of two children with NRTI resistance, one had only L201W, one had multiple RTI resistance (K65R/Q151M-NRTI, and K101E/Y181C). Among PI resistance mutations, one child had M46L, one had M46L/L90M. Of all HIV strains, CRF01_AE were dominant subtype. By six months of ART, the child with M46L/L90M died, with WHO clinical stage 4.The child with multi RTI-resistance (ID: DR 172) had six-month VL = 1202 copies/ml, and CD4+ T-cell percentage= 3.2%, who was certainly in treatment failure. Detail of DRM profile and baseline characteristics of children who harbored resistant HIV-1 strains were shown in Table 3. All analyzed DNA sequences were submitted to Gene bank with accession number KJ541962 - KJ542063.

DISCUSSION

Current treatment guideline recommends ART initiation immediately in HIV-infected children, while children with severe HIV/AIDS symptoms would less observed nowadays. Here we described children were admitted to the hospital with requirement of clinical care, which might present nature course of HIV/AIDS. Thus, we could add more experiences about the disease for clinicians, researchers who needed.

A common feature of vertical HIV progression was obsessed in this study while average ages of 18 fatal cases were lower than those 98 survivors(p= 0.002). Other study also described vertical HIV infection progressed rapid in first year of life and less rapid in 2-5 years of age [24]. With availability of ART, this phenomenon would be less seen, but it would be helpful for clinical diagnostics of HIV-infected children who were not detected soon after birth.

As limitation of further VL testing at the time of study, combination of plasma VL ≥ 1000 copies/ml and CD4+ T-cell counts was used to suggest treatment failure. Although CD4+ T-cell counts were not routinely recommended [21], in such condition without sufficient VL testing, our method might alternatively define outcome. Relatively, this "combined failure" rate was lower than similar findings in Africa [25-28], Thailand [29, 30], and Vietnamese adult [31-38].

In this study, rate of 9.6% DRM was slightly higher than 7.6% children samples in 2004-2005 by other study from Southern Viet Nam [19]. Also, our RTI-resistance rate was higher than 6.2% of high-risk adults who tested in 2008, at same geographic regions [14]. As a weakness of the study with only 52 samples were analyzed DRM, sample size might not sufficient to predict trending of mutant rate in the HIV-infected population. We were also unable to define different outcome among children without drug-resistance testing, as the comparison was not made up at the time of conducting study.

Among detected mutants, Q151M was associated with long-term RTI failure [23]. Unfortunately, history of ART usage of the mother was not available; such remaining of mutant HIV strain was unusual to explain. As six DRM carriers were sampled at/ after two years old, detected resistant HIV strains might gain virological fitness and remained several years. Also, NNRTI-resistance mutations were more dominant, that suggest a persistence of these mutants among carriers.

CONCLUSION

In this study, transmitted drug-resistance mutations were found 9.6% of 52 HIV-infected children, by 2011. Children clinical stage 3-4 at ART start was mostly associated with the six-month mortality. Pre-treatment DRM might not associate with six-month mortality but induced risk of treatment failure.

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