Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.61, No.2(2021). p.94-9; DOI: 10.14238/pi61.2.2021.94-9

Original Article

Virologic and immunologic status of children with HIV-TB co-infections

Djatnika Setiabudi, Citra Cesilia, Almira Aliyannissa, Heda Melinda Nataprawira

Abstract

Background Studies about virologic and immunologic status of HIV children are lacking. Tuberculosis (TB) is the most common opportunistic infection in HIV patients and co-infection is associated with much worse prognosis.

Objective To describe the virologic and immunologic status of patients with HIV and TB co-infection, before and after HIV and TB treatment.

Methods A prospective study was conducted in HIV co-infected with TB patients in an Indonesian tertiary hospital between November 2016 - December 2018. Viral load and CD4 levels were performed at diagnosis and after 6 months of HIV and TB treatment.

Results Of 44 children hospitalized due to HIV, 15 newly diagnosed HIV cases had TB co-infection. Thirteen were included as subjects. Most patients (10/13) were under 5 years of age, with similar female and male proportions (7/13 *vs.* 6/13, respectively). All were diagnosed with stage 4 HIV. Six patients had respiratory problems at admission. First examinations revealed severe immunodeficiency (CD4+ <20%) in all patients, and high viral loads (>105 copies/mL) in most (9/13) patients. Despite good compliance to medications, 8/13 patients died before the sixth month follow-up. Deterioration of virologic and immunologic status was seen in 3/4 of the followed-up patients.

Conclusion Children with HIV-TB coinfections have severe immunodeficiency and high viral loads. Most such patients die before 6 months, while survivors experience virologic and immunologic status deterioration. Future study must take into account for HIV drug resistance investigation. **[Paediatr Indones. 2021;61:94-9 ; DOI: 10.14238/pi61.2.2021.94-9**].

Keywords: *HIV; children; Indonesia; poor outcome; TB co-infection*

Human immunodeficiency virus (HIV) infection remains a global problem, with almost 38 million people infected worldwide. Approximately 2.8 million (7.3%) of all HIV patients in the world are children and adolescents aged 0 to 19 years.[1] Tuberculosis (TB) is the most commonly found opportunistic infection in HIV patients. Patients with HIV infection have a 26-31 times greater risk of TB infection.[2] Children with HIV and active TB infection have a greater likelihood of dying within 1 year (15-20% *vs.* 7-8%)[3] and a lower success treatment rate (73.4% *vs.* 79.2%, respectively; P=0.127) compared to those without active TB.[4]

Indonesia has the fifth highest cases of HIV in Asian countries,[5] yet study on TB/HIV in Indonesian children is still lacking.[6] We aimed to describe the virologic and immunologic status of children with TB and HIV co-infection, before and after treatments.

From the Department of Child Health, Universitas Padjadjaran Faculty of Medicine/Dr. Hasan Sadikin General Hospital, Bandung, West Java, Indonesia.

Corresponding author: Djatnika A. Setiabudi, Department of Child Health, Universitas Padjadjaran Medical School/Dr. Hasan Sadikin General Hospital, Jalan Pasteur No.38 Bandung 40161, West Java, Indonesia. Email: djatnika_setiabudi@yahoo.com.

Submitted November 4, 2020. Accepted March 16, 2021.

Methods

A prospective cohort study was conducted in pediatric inpatients hospitalized due to HIV and/or TB/HIV co-infection in a tertiary hospital in Indonesia from November 2016 to December 2018. We documented characteristics of patients such as gender, age, parental HIV status, HIV stages, clinical presentation, and changes of viral load and CD4 after receiving ART and six months of anti-TB treatment. We diagnosed HIV by viral load in subjects aged less than 18 months, and by HIV serology in subjects aged 18 months or older, in accordance with WHO recommendations.[7] Tuberculosis was diagnosed based on clinical manifestations, tuberculin skin test (TST), microbiology, and/or histopathologic findings. Compliance to prescribed medications was assessed by medication record-keeping cards filled by parents or caregivers. HIV infection was classified according to the *WHO Classification System for HIV Infection* through assessment of clinical conditions and CD4 count.[7]

Anthropometric indices were estimated according to WHO standards for children aged under 5 years. In older children, nutritional status was calculated using body mass index (BMI) for age. Moderate malnutrition was defined as weight-for-height or BMI-for-age *z*-scores between -3 and -2, compared to the median of the reference population; severe malnutrition was defined as *z*-scores less than -3 SD.[8] TB investigation was performed on gastric aspirates in small children or sputum in children over 10 years. HIV diagnosis was determined by viral load examination for children under 18 months of age through real time PCR, and by serological test in children of older age.

Subjects were given first line anti-retroviral therapy (ART) in the form of fixed dose combinations. For children aged below three years old, a combination of abacavir (ABC) or zidovudine (AZT) + lamivudine (3TC) + lopinavir (LPV) were given. Those aged between 3 to 10 years old were given a combination of abacavir (ABC) + lamivudine (3TC) + efavirenz (EFV), while those above 10 years old received tenofovir (TDF) + lamivudine (3TC)/emcitarabine (FTC) + efavirenz (EFV).

For anti-TB regimens, GenXpert examination was performed before initiating medications. Those who showed sensitivity to rifampicin were given first line anti TB drugs (rifampicin, isoniazid, pyrazinamide, and ethambutol), depending on their own type of TB.

Parents or guardians provided written informed consent for participation. This study was approved by the Research Ethics Committee, Dr. Hasan Sadikin General Hospital Bandung.

Results

During study period, 44 patients were hospitalized due to HIV. We included fifteen patients who were newly diagnosed with HIV as subject. Five children died during the first hospitalization; of these, two died before obtaining the blood specimens. Thirteen patients were included in this study. Most (10/13) were under 5 years, and there were similar proportions of females and males (7/13 *vs.* 6/13, respectively). Most (10/13) were severely undernourished and had HIV-positive parents who died before the study period. HIV serological testing was carried out in two living parents, yielding positive results. One other parent refused to be tested.

Six of 13 children presented with respiratory distress, while others had prolonged fever, chronic diarrhea, pallor, and loss of consciousness. While all patients were also diagnosed with pulmonary TB, three had extrapulmonary TB (2 meningitis and 1 pleuritis TB) as well. TB diagnosis was established mostly by clinical symptoms and chest x-ray, since positive TST and acid-fast bacilli (AFB) stains only yielded positive results in 1 and 2 patients, respectively. Mycobacterium tuberculosis was found in two GeneXpert examinations, and both were still sensitive to TB standard regimens. The two meningitis TB children underwent lumbar puncture examination, with results that strongly supported the diagnosis. Baseline characteristics of subjects are shown in **Table 1**.

First examinations at the time of diagnosis revealed severe immunodeficiency (%CD4+ <20%) in all children, ranging from 0.27 to 18%. High viral loads (>10^5 copies/mL) were found in 9 children. However, we had one unexplained case in a 2-year-old patient, hospitalized for severe pneumonia and malnutrition. In this case, the child had positive HIV serology test and CD4+ count of 8 cell/mm^3 (%CD4+

Table 1. Baseline characteristics of pediatric patients with HIV/TB co-infection in 2016-2018

Characteristics	(N = 13)
Gender, n	
Male	6
Female	7
Age, n (%)	
<5 years	10
5 years	3
Nutritional status, n	
Severe undernutrition	10
Moderate undernutrition	0
Mild undernutrition	2
Normal	1
HIV stages, n	
Stage 1	0
Stage 2	0
Stage 3	0
Stage 4	13
Chief complaint, n	
Dyspnea	6
Chronic diarrhea	2
Prolonged fever	2
Pallor	1
Loss of consciousness	2
Mantoux test, n	
Positive	1
Negative	12
AFB stains, n	
Positive	2
Negative	11
Immunodeficiency status, n	
None	0
Mild	0
Advanced	0
Severe	13
Viral load, n	
Not detected	1
$<10^3$ copies/mL	1
10^4-10^5 copies/mL	2
$>10^5$ copies/mL	9

0.31%), but with undetectable viral load. The patient died within the first week of hospitalization, presumably due to severe pneumonia and the HIV.

Subjects' compliance was excellent, with prescribed ART and anti-TB drugs taken daily and regular visits to the HIV and *Directly Observed Treatment Short* (DOTS)-course clinics, as monitored by the card given to parents. Despite compliance, 8/13 children died before the second blood examination at the six-month follow up. Furthermore, three out of four children who survived up to 6-months had highly elevated viral load and decreased CD4+ levels, despite compliance to treatment regimens. **Table 2** shows the details of viral load and %CD4+ counts of all subjects before and after ART and anti TB treatment along with their 6- months survival outcomes.

Discussion

Here, we describe the characteristics, as well as virologic and immunologic status of subjects with HIV and TB co-infection, before and after 6 months of ART and TB treatments. Most newly-diagnosed, HIV-infected children were under 5 years of age, severely undernourished, and had HIV-positive parents who died before the study period. All patients were also diagnosed with pulmonary TB and had severe immunodeficiency. High viral loads were also found in most patients. By the six-month evaluation, almost all patients experienced poor outcomes. Eight children died and 3 of the 4 survivors experienced immunologic and virologic deterioration, namely, reduced CD4 counts and elevated viral load. These results were consistent with previous studies,[9-11] reflecting that TB is not only the most commonly opportunistic infection in HIV, but also one of the most important factors in predicting poor outcomes in HIV patients.[2,12]

To our knowledge, there has been only one descriptive study in Indonesia which reported on 50 HIV-infected children aged 0 to 12 years, of whom 27 (54%) were co-infected with TB, during an 8-year study period (2002-2010). In this study, most subjects were female with 3:1 gender ratio. Even though 20/27 children had severe immunodeficiency, viral load examination was not performed; 4/27 patients died.[9] Our results reported more HIV children (44) during shorter period (16 months) with 15 new HIV cases identified. Our subjects were of similar predominant age, but with different gender proportions. To our surprise, all newly HIV-diagnosed patients had pulmonary TB during hospitalization. Many patients died despite good compliance to medications.

The TB co-infection rate we found differed from the *Pediatric TB-HIV EuroCoord Study*, which reported that 5%, 63%, 21%, and 11% of TB/HIV cases occurred in Western Europe, Eastern Europe, Thailand, and Brazil, respectively.[10] Our number (100% co-infection rate) was also higher than those

Table 2. Virologic and immunologic status of patients and their 6 months outcomes

Subjects	Before ART and anti TB treatment		6-month survival outcomes	After ART and anti TB treatment	
	Viral load, copies/mL	CD4+ percentage		Viral load, copies/mL	CD4+ percentage
Patient 1	1,341,532	5.73	Died	N/A	N/A
Patient 2	3000	1.26	Died	N/A	N/A
Patient 3	93,609	3.2	Died	N/A	N/A
Patient 4	209,224	0.97	Died	N/A	N/A
Patient 5	189,335	18	Alive	288,400	4.56
Patient 6	456,700	3	Alive	154,500	4
Patient 7	108,650	8.45	Alive	243,000	7.3
Patient 8	75,000	9.89	Alive	254,000	5.43
Patient 9	Not detected	0.31	Died	N/A	N/A
Patient 10	292,060	12.95	Died	N/A	N/A
Patient 11	235,748	0.6	Died	N/A	N/A
Patient 12	303,000	1.28	Loss to follow up	N/A	N/A
Patient 13	107,500	0.27	Died	N/A	N/A

reported in a systematic review and meta-analysis of 47 studies, in which TB/HIV prevalence ranging from 2.93% to 72.34% (31.25% in African countries, 17.21% in Asian countries, 20.11% in European countries, 25.06% in Latin American countries, and 14.84% in the USA).[11]

Our subjects also had higher mortality rate (62%) compared to that of the *Pediatric TB-HIV EuroCoord Study*, which reported a 14.8% mortality rate (4 of 27 patients) and poor outcomes in 7 patients (5 did not complete treatment, 1 had recurrent TB, and 1 was lost to follow up). This differences might have been due to our patients' worse immunological and virologic status, as they had severe immunodeficiency and most had high viral loads (12/13 patients had >1,000 copies/mL, though one patient had undetectable levels). In contrast, only 52% of the *Pediatric TB-HIV EuroCoord Study* subjects had severe immunodeficiency.10

Our study result further strengthens the notion that TB/HIV co-infection can be difficult to manage, possibly due to a bidirectional interaction between TB and HIV. HIV infection increases the risk of progression to active TB and mortality associated with TB.[2] On the other hand, TB accelerates the course of HIV disease and increases the risk of other opportunistic infections.[2] The diseases affect each other's natural course and pathogenesis, which aggravates the TB/HIV epidemic.[13] The number of deaths from HIV-related TB has decreased since 2003, but there were still 300,000 deaths in 2017 due to TB, from a total of 940,000 deaths of HIV patients throughout the world.[14]

Other challenges lie in diagnosing TB in HIV-infected children. Definitive diagnosis is difficult to establish since TB and HIV in children have overlapping clinical manifestations, including fever, weight loss, and lymphadenopathy combined with persistent cough. Moreover, it is well-recognized that microbiologically-confirmed TB diagnosis is difficult to achieve in children due to the paucibacillary nature of childhood TB and the difficulty in obtaining specimens from children.[15] We, too, faced similar challenges. Positive TST was found in only one patient, AFB stains in two patients, and GeneXpert examination revealed *Mycobacterium tuberculosis* sensitive to rifampicin in two patients. Thus, TB diagnosis was established mostly by clinical symptoms and chest x-rays suggestive of TB, in accordance to WHO guidelines.[16] Lumbar puncture was performed in 2 patients suspected of having tuberculous meningitis, with results strongly supporting the diagnosis.

To our knowledge, our study is the first to investigate virologic and immunological status of HIV cases at the time of diagnosis and after 6 months of ART and anti-TB treatments. RNA viral load and CD4 counts are commonly used parameters to determine the status of HIV progression, as recommended by the WHO.[7] A previous study showed that detectable viral

load was significantly associated with opportunistic infections (OR=9.6), adherence (OR=0.195), and CD4 nadir (OR=1.102).17 However, another study reported that even though high RNA is the earliest predictor of clinical progression, CD4 has more prognostic power and is a better screening tool to select patients requiring ART.[18] We observed that generally subjects who died before 6 months follow up had higher viral load and lower CD4 count than those who survived.

Our study had several limitations. First, the sample size was small, so analysis was unfeasible, even though this was a prospective study. Second, selection bias may have occurred due to the relatively poor conditions of the children admitted into the hospital wards due to opportunistic infections. Our hospital is the largest referral hospital in the West Java province and, in general, accepts patients with severe conditions that could not be managed by other smaller hospitals. Third, there were limited ART options for children, especially if there was suspected resistance. Compliance to medications was good, as monitored through medication cards, but we still had concerns about possible resistance to HIV drugs. A recent study in 2018 reported that HIV drug resistance is an important challenge that needs to be addressed in treating children with HIV, as 16.2% of their patients had primary drug resistance to reverse transcriptase inhibitor.[19] This finding was due to the much higher risk (OR= 2.6) of pre-treatment antiretroviral drug resistant HIV in children whose mothers had HIV, due to the possibility of maternally-transmitted infection.[20] Finally, most patients were diagnosed at older than 1 year of age. Hence, several signs and symptoms of HIV infection may have gone undiagnosed during the first year of life.

In conclusion, this virologic and immunologic study in stage 4 HIV-infected children is the first to reveal severe immunodeficiency, high viral loads, and co-infection with TB. Most children die before 6 months and survivors experience deterioration of virologic and immunologic status. Future study must take into account HIV-drug resistance investigations.

Conflict of Interest

None declared.

Acknowledgments

We would like to thank the nurses and doctors at the Teratai HIV Clinic and Directly Observed Treatment Short-course (DOTS) Clinic of Dr. Hasan Sadikin General Hospital, Bandung, West Java, as the locations for taking monthly ART and anti-TB medications.

Funding Acknowledgment

This work was supported by the Academic Leaderships Grant (ALG) program of Universitas Padjadjaran (grant number 1390/UN6.C/Kep/PN/2014). The funders were not involved in data analysis or manuscript preparation.

References

1. UNICEF. Global and regional trends. 2018. [cited 2019 July 23]. Available from: https://data.unicef.org/topic/hivaids/global-regional-trends/.
2. Belay M, Bjune G, Abebe F. Prevalence of tuberculosis, HIV, and TB-HIV co-infection among pulmonary tuberculosis suspects in a predominantly pastoralist area, Northeast Ethiopia. Glob Health Action. 2015;8:27949. DOI: 10.3402/gha.v8.27949.
3. Ali SA, Mavundla TR, Fantu R, Awoke T. Outcomes of TB treatment in HIV co-infected TB patients in Ethiopia: a cross-sectional analytic study. BMC Infect Dis. 2016;16:640. DOI: 10.1186/s12879-016-1967-3.
4. Adejumo OA, Daniel OJ, Adebayo BI, Adejumo EN, Jaiyesimi EO, Akang G, *et al.* Treatment outcomes of childhood TB in Lagos, Nigeria. J Trop Pediatr. 2016;62:131-8. DOI: 10.1093/tropej/fmv089.
5. Infodatin. Situasi umum HIV/AIDS dan tes HIV. Jakarta: Pusat Data dan Informasi Kementerian Kesehatan RI; 2018. Available from: https://pusdatin.kemkes.go.id/ article/view/19042200004/situasi-umum-hiv-aids-dan-tes-hiv.html.
6. Pusat Data dan Informasi. Tuberkulosis. Jakarta: Kemenkes RI; 2018. Available from: https://pusdatin.kemkes.go.id/article/view/18101500001/infodatin-tuberkulosis-2018.html.
7. World Health Organization. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. 2016. [cited 2019 July 23]. Available from: http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf.
8. World Health Organization. Nutrition Landscape Information System (NLIS) country profile indicators: interpretation

guide. Nutr Landsc Inf Syst. 2010;1-51. Available from: https://apps.who.int/iris/handle/10665/44397.

9. Widyaningsih R, Widhiani A, Citraresmi E. Ko-infeksi tuberkulosis dan HIV pada anak. Sari Pediatr. 2016;13:55. DOI: 10.14238/sp13.1.2011.55-61.
10. Turkova A, Chappell E, Chalermpantmetagul S, Negra M Della, Volokha A, Primak N, *et al*. Tuberculosis in HIV-infected children in Europe, Thailand and Brazil: paediatric TB-HIV EuroCoord study. Int J Tuberc Lung Dis. 2016;20:1448-56. DOI: 10.5588/ijtld.16.0067.
11. Gao J, Zheng P, Fu H. Prevalence of TB/HIV co-infection in countries except China: a systematic review and meta-analysis. PLoS One. 2013;8:e64915. DOI: 10.1371/journal.pone.0064915.
12. Gupta RK, Lucas SB, Fielding KL, Lawn SD. Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis. AIDS. 2015;29:1987-2002. DOI: 10.1097/QAD.0000000000000802.
13. Gray JM, Cohn DL. Tuberculosis and HIV coinfection. Semin Respir Crit Care Med. 2013;34:32-43. DOI: 10.1055/s-0032-1333469.
14. World Health Organization. TB causes 1 in 3 HIV deaths. HIV/AIDS. 2018. [cited 2019 July 23]. Available from: https://www.who.int/hiv/mediacentre/ news/hiv-tb-patient-centred-care/en/.
15. Venturini E, Turkova A, Chiappini E, Galli L, de Martino M, Thorne C. Tuberculosis and HIV co-infection in children. BMC Infect Dis. 2014;14:S5. DOI: 10.1186/ 1471-2334-14-S1-S5.
16. Maher D. Chapter 3: Management of TB in the HIV-infected child. Int J Tuberc Lung Dis. 2006;10:1331-6.
17. Moolasart V, Chottanapund S, Ausavapipit J, Likanonsakul S, Uttayamakul S, Changsom D, et al. The effect of detectable HIV viral load among HIV-infected children during antiretroviral treatment: a cross-sectional study. Children. 2018;5:6. DOI: 10.3390/children5010006.
18. Korenromp EL, Williams BG, Schmid GP, Dye C. Clinical prognostic value of RNA viral load and CD4 cell counts during untreated HIV-1 infection - a quantitative review. PLoS One. 2009;4:e5950. DOI: 10.1371/journal.pone.0005950.
19. Chauhan CK, Lakshmi PVM, Sagar V, Sharma A, Arora SK, Kumar R. Primary HIV drug resistance among recently infected cases of HIV in North-West India. AIDS Res Treat. 2019;2019:1525646. DOI: 10.1155/2019/1525646.
20. Kityo C, Sigaloff KC, Sonia Boender T, Kaudha E, Kayiwa J, Musiime V, *et al*. HIV drug resistance among children initiating first-line antiretroviral treatment in Uganda. AIDS Res Hum Retroviruses. 2016;32:628-35. DOI: 10.1089/aid.2015.0215.