

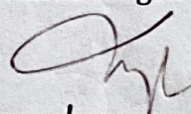
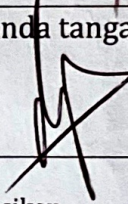


REKOMENDASI PERSETUJUAN ETIK

Nomor : 270/UN4.6.4.5.31/ PP36/ 2020

Tanggal: 13 Mei 2020

Dengan ini Menyatakan bahwa Protokol dan Dokumen yang Berhubungan Dengan Protokol berikut ini telah mendapatkan Persetujuan Etik :

No Protokol	UH20040193	No Sponsor Protokol	
Peneliti Utama	dr. Jamaluddin M, SpP	Sponsor	
Judul Peneliti	Efek Active Hexose Correlated Compound (AHCC) terhadap Respons Klinis dan Status Immunologi Pasien TB Paru dan TB Paru-HIV		
No Versi Protokol	1	Tanggal Versi	9 April 2020
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Tempat Penelitian	RSUD Labuang Baji Kota Makassar		
Jenis Review	<input type="checkbox"/> Exempted <input type="checkbox"/> Expedited <input checked="" type="checkbox"/> Fullboard Tanggal 13 Mei 2020	Masa Berlaku 13 Mei 2020 sampai 13 Mei 2021	Frekuensi review lanjutan
Ketua Komisi Etik Penelitian Kesehatan FKUH	Nama Prof.Dr.dr. Suryani As'ad, M.Sc.,Sp.GK (K)	Tanda tangan 	
Sekretaris Komisi Etik Penelitian Kesehatan FKUH	Nama dr. Agussalim Bukhari, M.Med.,Ph.D.,Sp.GK (K)	Tanda tangan 	

Kewajiban Peneliti Utama:

- Menyerahkan Amandemen Protokol untuk persetujuan sebelum di implementasikan
- Menyerahkan Laporan SAE ke Komisi Etik dalam 24 Jam dan dilengkapi dalam 7 hari dan Laporan SUSAR dalam 72 Jam setelah Peneliti Utama menerima laporan
- Menyerahkan Laporan Kemajuan (progress report) setiap 6 bulan untuk penelitian resiko tinggi dan setiap setahun untuk penelitian resiko rendah
- Menyerahkan laporan akhir setelah Penelitian berakhir
- Melaporkan penyimpangan dari protokol yang disetujui (protocol deviation / violation)
- Mematuhi semua peraturan yang ditentukan

The Active Hexose Correlated Compound (AHCC®) Effect on Clinical Outcome of Pulmonary Tuberculosis in HIV-Infected Patients

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Keywords:

TB-HIV, AHCC, clinical manifestations.

ABSTRACT

The complexity of tuberculosis (TB) treatment in HIV-infected patients is facing a challenge to both clinicians and patients. Active Hexose Correlated Compound (AHCC) is known to be beneficial for immunocompromised patients such as cancer patients. This study aims to explore the effect of AHCC to improve the clinical status of pulmonary TB in HIV-infected patients. All patients were followed up for clinical status and chest X-ray examination every three months after AHCC or placebo supplementation. After six months of placebo or AHCC supplementation, all clinical signs and symptoms were improved. None of the patients in both groups have cough and hemoptysis. Shortness of breath has well improved after 6 months of administrating AHCC compared to placebo which was 20%. Meanwhile, appetite has completely improved 100% after 6 months compared to placebo was still 32%. This was in line with the improvement in body weight (72% in placebo group vs 96% in the AHCC group). Meanwhile, nausea has not found in the AHCC group after 6 months compared to placebo has 8%. Also, vomiting was found 16% in the placebo group after 6 months dan no case in the AHCC group. Chest X-ray results showed improvement in both groups. In the sixth month, 80% in the placebo group was normal and 92% in the AHCC group. It is no different in acid fast bacillus (AFB) conversion between both groups. This study concluded that our findings after six-month AHCC 3 g/day supplementation lead to better clinical improvements in TB/HIV patients.



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1. INTRODUCTION

The complexity of treating tuberculosis (TB) in HIV-infected patients is a challenge for both health professionals and patients [1]. The proper assessment of antiretroviral therapy, possible drug interactions, and the patient's immunological status play an important role in the outcome of treatment. Active Hexose

Correlated Compound (AHCC) is known to be beneficial for immunocompromised patients such as HIV-infected patients. This topic will discuss issues related to the treatment of HIV-infected TB patients with AHCC supplement. Various studies have shown that AHCC supplementation has a positive effect on immune function in experimental animal and human subject. The mechanisms of AHCC include: (1) decrease of tumor formation; (2) increase of resistance to bacterial and viral infections; (3) increase of activity of natural killer (NK) cells; (4) improvement of dendritic cell function; (5) increase of T-cell proliferation; (6) changes in T-cell activity; and (7) changes in cytokine production [2], [3]. Clinical safety has been demonstrated in healthy patients and subjects [4]. Tuberculosis is an infectious disease that can affect the lungs (pulmonary tuberculosis) and other organs (extrapulmonary tuberculosis). Tuberculosis is caused by *Mycobacterium tuberculosis* which can spread through the air when an infected person expels the bacteria by cough [1]. According to WHO Global Tuberculosis Report in 2015, there were 1 million new TB cases per year in Indonesia, two times more than the previously predicted number [5]. In Makassar, the incidence rate for smear-positive cases is estimated to be 110/100,000 population, which is higher than the national incidence rate, 74/100,000 population. TB patients in Makassar were infected with various genotypes of isolates but EAI, T, H, and Beijing strains were observed as the dominant strains [6]. In 2015, there were approximately 2.1 million new cases of HIV infection worldwide which accounts for a total of 36.7 million people living with HIV [7]. Indonesia is currently one of the largest and fastest-growing HIV epidemics in the world. It is closely related to drug use and detention. HIV-related deaths in Indonesia increased by 427% from 2005 to 2013, while the number of people living with HIV (PLWHA) receiving treatment with antiretroviral therapy (ART) in 2013 remains the lowest in the Asia-Pacific region [1], [8]. HIV infects immune cells, attacking and destroying helper T lymphocytes, or T cells, which are essential for the immune system and immune response [9]. CD4+ counts drop dramatically in the late stages of HIV concurrently with the virus counts. If the patient is diagnosed with stage-4 HIV-related conditions (such as tuberculosis, cancer, and pneumonia), infected HIV case has become Acquired Immunodeficiency Syndrome (AIDS) [10].

All patients with TB, regardless of their perceived risk of HIV infection, should be offered an HIV test. In HIV coinfection, the clinical and radiographic presentation of TB may be atypical. Compared with the immune population, HIV-infected TB patients with active pulmonary TB are more likely to have a normal chest radiograph or have sputum smear-negative but culture-positive. Therefore, clinicians treating HIV-infected patients need to have a high suspicion for TB in symptomatic individuals [1]. In the guidelines released by WHO, it is strongly recommended to start antiretroviral therapy (ART) in all adults (> 19 years), pregnant women, breastfeeding mothers, and adolescents living with HIV regardless with any CD4+ count [5]. Drugs used to treat HIV infection are: (1) nucleoside and nucleotide analogs reverse transcription inhibitors (NRTIs); (2) non-nucleoside reverse-transcriptase inhibitors (NNRTIs); (3) protease inhibitors (PIs); and (4) fusion inhibitors [11]. It is recommended to use two NRTIs and one NNRTI or PI as the initial regimen [12]. Drug resistance is a challenge for the treatment of HIV-infected patients. Drug resistance is caused by mutations in the HIV-1 virus (IASUSA). Combinations of two or three drugs such as NRTIs and protease inhibitors can help control viral replication, restore immune function, and maintain health [13]. Furthermore, the patient should be using combination therapy (commonly called highly active antiretroviral therapy) exactly as prescribed. If adherence to the regimen is poor or not complete, HIV can quickly become resistant to drugs [14]. Active Hexose Correlated Compound (AHCC) is a compound produced and isolated from micelles of shiitake (*Lentinula edodes*), a fungus from the Basidiomycete family. AHCC is an alpha-glucan compound, derived from mushroom preparations and nutrient-rich supplements and the subject of a number of studies because of its potential to treat several diseases [15]. Alpha-glucan has the ability to stimulate the phagocytic system, increase the metabolism defense mechanism of the immune system in general, increases resistance to tumors, and significantly stimulates

defense reactions against infection [16], [17]. AHCC is an immune system modulating compound, which activates innate immunity by binding to natural pattern recognition receptors (PRRs), such as Toll-Like Receptors (TLRs). This bond effect on NK cell activity when induced by either the presence of an active tumor or infection caused by a virus to activate innate immunity by binding to natural PRRs, such as TLRs [18], [19].

The purpose of this study was to determine the effect of AHCC in improving the clinical status of HIV-infected pulmonary tuberculosis patients. This research will be carried out in Makassar with the Pulmonology Clinic/VCT of the Labuang Baji Regional General Hospital as the center. The collaboration will be carried out between doctors, nurses, and pharmacists to evaluate the effect of AHCC on the clinical status of tuberculosis in the treatment of HIV-infected patients.

2. METHODS

This Study is clinical research conducted at the Pulmonology/HIV Polyclinic of the Labuang Baji Regional General Hospital, Makassar, Indonesia with the approval of the Hasanuddin University Ethics permit (270/UN4.6.4.5.31/PP36/2020). All patients taking part in the study were given education before participating in the study by signing an informed consent form as a sign of agreement to follow the standard procedure in this study. The research scheme is designed to answer several research questions (1) Can AHCC treatment improve the clinical symptoms of TB-HIV patients that have been experienced by patients compared to placebo? (2) How do the chest radiographs of patients receiving AHCC supplements compared to placebo?

3. STUDY DESIGN

This clinical research will be centered at the Pulmonology/HIV Clinic, Labuang Baji Regional General Hospital, which is an associate Hospital of the Department of Pulmonology, FK-UNHAS. The Pulmonology/HIV Clinic at the Labuang Baji Regional General Hospital is one of the referral centers in Makassar. This study was a randomized, double-blind study in which AHCC would be administered for 6 months. Patients were divided into 2 groups, group 1 consisted of 25 TB-HIV patients who were given AHCC1 supplementation (Placebo), and Group 2 consisted of 25 TB-HIV patients who were given AHCC2 (original AHCC) in capsule form every 3 grams/day for 6 months. This randomization aimed to enroll HIV positives with a diagnosis of active TB who had converted without prior antiretroviral therapy. In the early stages, researchers will conduct treatment interviews; randomized subjects to receive either AHCC1 (placebo) or AHCC2 (original AHCC). Subjects will be monitored every month and every 3 months will be grouped with clinical symptoms experienced by patients starting from the beginning of the month of supplementation and chest X-ray examination from baseline, after 3 and after 6 months. All subjects will be started on antiretroviral therapy (ART) according to the Indonesian Ministry of Health guidelines.

3.1 Sample Criteria

Eligible patients for inclusion in this study were at least 18 years of age, those who were hospitalized and had been on TB treatment for three months but had not started their ARV therapy, agreed to use effective birth control methods throughout the study. While the exclusion criteria in this study were patients who had used a combination of anti-HIV drugs, were resistant to more than one drug used to treat TB.

3.2 Parameters and Statistics

For evaluation of effectiveness, only patients who completed all drug and supplement regimens were included. Follow-up must be carried out after the 3rd and 6th months by looking at the clinical course of the subject and examining a chest X-ray at the Radiology of the Labuang Baji Regional General Hospital,

Makassar. Measurement of the patient's subjective and objective clinical course (weight) was adjusted to the standard follow-up of clinical symptoms in the DOTS program of the Indonesian Ministry of Health.

This research is descriptive data so that the existing data is included in the SPSS version 21 program and will get an overall descriptive picture of the research results. Research results are prepared in the form of tables and graphs. In addition, the relationship between the variables to be analyzed using a non- parametric test.

4. RESULT AND DISCUSSION

In this study, 25 TB-HIV patients received AHCC (16 males and 9 females), and 25 TB-HIV patients received a placebo (21 males and 4 females). The average age of TB-HIV patients was 32.86 years (range 18-51 years, median 33 years) with the highest education being SMA/equivalent 58% and working in the private sector 64%. Many TB-HIV patients in this study also had a history of smoking 64%. The basic characteristics of TB-HIV patients in this study can be seen in Table 1. It is almost the same as in several studies which found more male TB patients. One of the reasons is because men are more often outside the house and smoke [1], [5].

Table 1. Characteristics in TB-HIV patient

Variable		n	%
Group	AHCC1/Placebo	25	50
	AHCC2/AHCC	25	50
Sex	Male	37	74
	Female	13	26
Age	< 25	6	12
	25-35	25	50
	36-45	16	32
	> 45	3	6
Education Level	Never	2	4
	Elementary	4	8
	Junior High School	6	12
	Senior High School	29	58
	College	9	18
Profession	No job	10	20
	Student	3	6
	Farmer	2	4
	Private sector	32	64
	Civil servant	3	6
Smoking	Yes	32	64
	No	18	36

TB coinfection often occurs in people with HIV-AIDS (PLWHA). People with HIV are about 30 times more likely to get TB than people who are not infected with HIV. More than 25% of deaths in people living with HIV are caused by TB. Clinical symptoms of TB in people living with HIV are often non- specific. Clinical symptoms that are often found are fever, cough with or without blood, shortness of breath, decreased appetite accompanied by significant weight loss (more than 10%) while HIV itself often causes

diarrhea [1], [5], [12]. In this study, these symptoms were the basis for the assessment plus the clinical symptoms that appeared or the effects that occurred when taking supplements such as other gastrointestinal disorders such as nausea and vomiting. The results of the evaluation of clinical symptoms in this study can be seen in Table 2 below.

Table 2. Clinical symptoms between before and after received AHCC vs placebo

Clinical symptoms TB-HIV	Month	Placebo			AHCC		
		0 n(%)	3 n(%)	6 n(%)	0 n(%)	3 n(%)	6 n(%)
Cough	Yes:	25 (100)			25 (100)		
	Persistent		0	0		0	0
	Improved		3 (12)	3 (12)		1 (4)	0
	Stop		22 (88)	22 (88)		24 (96)	0
	No	0			0		
Hemoptysis	Yes	3 (12)	0	0	3 (12)	0	0
	No	22 (88)	0	0	22 (88)	0	0
Fever	Yes	22 (88)	0	0	21 (84)	0	0
	No	3 (12)	0	0	4 (16)	0	0
Dyspnea	Yes	15 (60)	0	0	12 (48)	2 (8)	0
	No	10 (40)	15 (60)	20 (80)	13 (52)	22 (88)	0
	Improved	0	10 (40)	5 (20)	0	1 (4)	0
Loss of Appetite	Yes	20 (80)	3 (12)	8 (32)	22 (88)	7 (28)	0
	No	5 (20)	22 (88)	17 (68)	3 (12)	15 (60)	0
Weight Loss	Persistent	0	8 (32)	4 (16)	0	8 (32)	1 (4)
	Improved	0	17 (68)	18 (72)	0	10 (40)	24
	Worsened	25 (100)	0	3 (12)	25 (100)	7 (28)	0
Nausea	Yes	15 (60)	10 (40)	2 (8)	11 (44)	8 (32)	0
	No	10 (40)	15 (60)	22 (88)	14 (56)	17 (68)	0
Vomiting	Yes	2 (8)	4 (16)	1 (4)	5 (20)	0	0
	No	23 (92)	21 (84)	24 (96)	20 (80)	0	0
Diarrhea	Yes	5 (20)	5 (20)	1 (4)	4 (16)	4 (16)	0
	No	20 (80)	20 (80)	24 (96)	21 (84)	21 (84)	0

In this study, the clinical symptom that was measured objectively was the patient's weight (Graph 1 and 2). Bodyweight in TB-HIV patients before ATT/ARV treatment tends to decrease even up to 10%. We compared patient weight before and after 3 months and after 6 months of AHCC vs Placebo administration. Based on the graph below, the administration of AHCC after the 6th month gradually increased 100% compared to placebo after the 6th month, about 28% of the subjects experienced a varying decrease. Based on several studies that AHCC is a nutritional supplement that increases biological activity, stimulates the

phagocytic system, and plays a major role in improving the immune system [20].

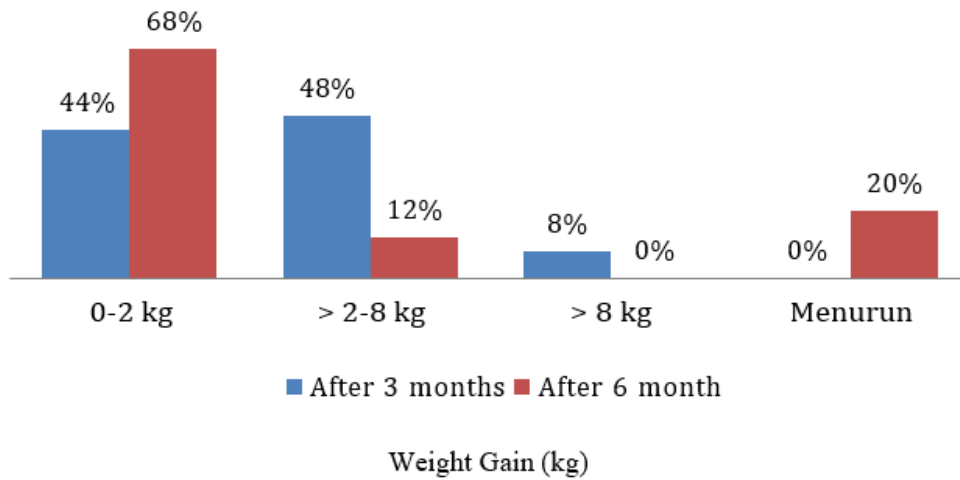


Chart 1. Improvement of weight gain in AHCC1 (Plasebo) supplementation

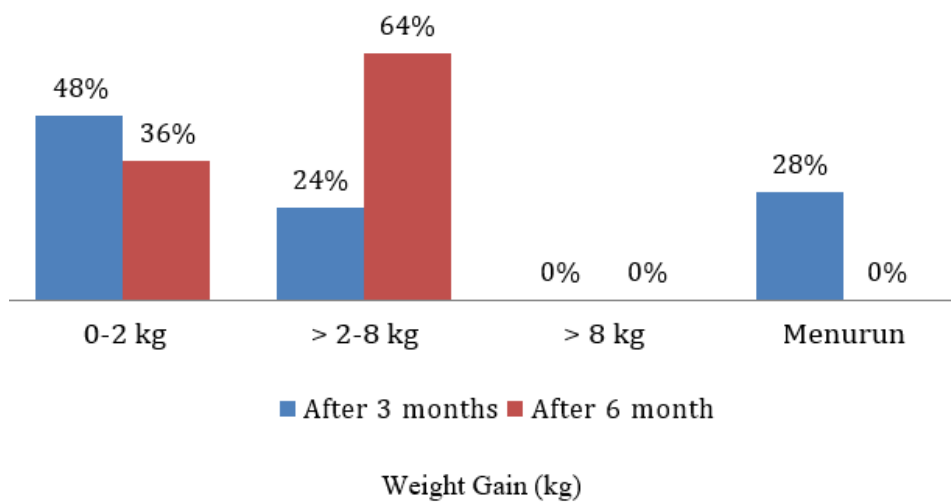


Chart 2. Improvement of weight gain in AHCC1 supplementation

4.1 Statistic analysis

4.1.1 Bivariate Test

Based on the non-parametric bivariate test, it was found that there was a significant correlation between supplementation in TB-HIV patients and weight gain in patients ($p < 0.05$) with a strong correlation.

Table 3. Correlation between supplementation and weight gain

Supplement	Weight	N	Mean Rank	P
(Placebo/AHCC)	Persistent	16	25.50	0,013
	Improved	27	22.26	
	Worsened	7	38.00	
Total		50		

Non parametric Test (Kruskal-Wallis)

Table 4. Non parametrik Correlation Test

Korelasi		Suplemen		Improvement of Weight gain
Spearsman's Rho	Suplement	Correlation Coeffisient	1.000	-0,281
		Sig. (1-tailed)		0,024
		N		50
Improvement of Weight gain		Correlation Coeffisient	-0,281	1.000
		Sig. (1-tailed)	0,024	
		N	50	

4.2 Multivariate Test

From the bivariate test, a multivariate test was then conducted on the relationship between AHCC2 (original AHCC) 3 g/day which is strongly suspected to have a significant relationship with the increasing body weight of TB-HIV patients. From the multivariate test conducted, it turned out that there was a non-significant relationship between the administration of AHCC supplements and weight gain.

Table 5. Multivariate Test

AHCC 3 gr	Regresion	df	S.E	Sig.	F	Exp (B)
	0,573	1	0,283	1.000	2.306	1.000
N=25						

4.3 Chest X-Ray

X-ray examination plays an important role in assisting the diagnosis of TB in HIV patient with negative smear [1]. In this study, all smear results were negative at the start of the study. In this study, we divided the chest X-ray images based on the radiological features of pulmonary TB, namely normal, minimal lesions, and extensive lesions. From Table 6 below, it was found that at the end of the 6th month of supplementation, it was found that TB-HIV patients who received AHCC had normal chest X-ray images 92% vs 80% placebo, minimal lesions 8% vs 20%, and both groups had no more extensive lesions.

Table 6. Chest X-Ray in AHCC (AHCC2) vs Plasebo (AHCC1)

TB-HIV Supplement	Radiology	Baseline		After 3 months		After 6 months	
		n	%	N	%	N	%
AHCC1	Chest X-Ray						
	Normal	0		18	72	20	80
	Extensive	16	64	0	0	0	0
	Minimal	9	36	7	28	5	20
AHCC2	Chest X-Ray						
	Normal	0	0	19	76	23	92
	Extensive	15	60	3	12	0	0
	Minimal	10	40	3	12	2	8

4.4 Statistic analysis

Based on the non-parametric test (Mann-Whitney) there was a significant relationship between the occurrence of shortness of breath in TB-HIV patients and the patient's chest x-ray ($p < 0.05$). Meanwhile, the relationship between cough and chest X-ray was not significant.

Table 7. Correlation between Dyspnea and Chest X-Ray

	Chest X-Ray	N	Mean Rank	Asymp.Sig. (2-tailed)
Dyspnea (Yes, No)	Minimal	19	39.00	0.000
	Extensive	31	17.23	
	Total	50		

5. LIMITATION OF THE STUDY

Several limitations found in this study are that there have been no previous studies of AHCC in TB-HIV so we have difficulty comparing the existing data. In addition, this research is clinical research that still requires supports to prove some of the things obtained from the results of this clinical research such as checking immunological status, other enzymes (peptides, adiponectins), and others needed to confirm the existing results.

6. CONCLUSION

Overall clinical symptoms in TB-HIV patients who received AHCC supplements of 3 grams/day were better than placebo. There is a significant correlation between the occurrence of shortness of breath and chest x-ray in TB-HIV patients. There was no significant relationship between AHCC supplementation and weight gain, but the tendency of patients receiving AHCC to increase overall body weight compared to placebo.

7. ACKNOWLEDGMENT

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