REVIWE ARTICLE

COMPARISON OF TRIPLE DRUG THERAPY VERSUS DOUBLE DRUG THERAPY FOR LYMPHATIC FILARIASIS : A SYSTEMATIC REVIEW

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ABSTRACT

Backgroud: Lymphatic filariasis is a parasitic infection caused by nematodes such as filaria Wuchereria bancrofti, Brugia malayi, and Brugia timori. These parasites can be transmitted through mosquito bites such as several species of mosquitoes, particularly Anopheles, Aedes, Culex, and Mansonia with geographical variations in the dominant vector identity. The main strategy used consists of community-wide mass drug administration (MDA) for the entire population at risk to stop disease transmission and prevent infectious morbidity. WHO recommends the use of annual medication in combination with the triple drug ivermectin therapy. Objective: To compare DEC and albendazole (IDA) versus the two drugs albendazole and diethycarbamazine or albendazole and ivermectin therapy.

Methods: The literature search was carried out independently by the researcher using the Sciencedirect, Pubmed, and Cochrane online databases without limiting the type of study or the year of publication. The keywords used in this study were combined with the Boolean operator, namely "AND" namely ((((Lymphatic filariasis) AND (albendazole)) AND (diethylcarbamazine)) AND (ivermectin)) AND (compare).

Results: where triple drug therapy was significantly better in reducing and clearing microfilariae and worm nests in patients with lymphatic filariasis compared to two drug therapy alone. However, side effects occur more frequently in the combination of three therapies. The average side effects were low, such as headaches, joint pain, fatigue, and nausea.

Conclusion: although it has relatively low side effects that occur in three drug combinations rather than two drug combination therapy, triple therapy combination therapy is more effective than two drug therapy in treating lymphatic filariasis disease.

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PRELIMINARY

Lymphatic filariasis is a parasitic infection caused by nematodes such as filaria Wuchereria bancrofti, Brugia malayi, and Brugia timori. Wuchereria bancrofti is responsible for more than 90% of infections that occur in tropical Asia, Africa, the Pacific islands, and in parts of the Caribbean and South America(1)(2). These parasites can be transmitted through mosquito bites such as several species of mosquitoes, particularly Anopheles, Aedes, Culex, and Mansonia with geographical variations in the dominant vector identity. Long-term infections can cause lymphatic system damage, characterized by severe swelling of the limbs (lymphedema) and then elephantiasis or scrotal lymphedema (hydrocele)(3). Lymphatic filariasis in addition to causing lymphedema (elephantiasis) and hydrocele, this disease also causes renal pathology that manifests as chyluria, and acute dermato lymphangio adenitis which causes regular fever(4). The World Health Organization (WHO) recommends mass treatment of entire populations once a year for years. The main strategy used consists of community-wide mass drug administration (MDA) to all populations at risk to stop disease transmission and prevent infectious morbidity(5). Treatment is a combination of two drugs of albendazole and a microfilarisidal drug (antifilaria), either diethyl carbamazine (DEC) or ivermectin. Albendazole is recommended for patients when DEC or ivermectin cannot be used(6)(7). An annual, single-dose, two-drug regimen (albendazole plus diethylcarbamazine (DEC) or albendazole plus ivermectin) for at least five years (according to the reproductive age of adult worms), covering at least 65% of the total population at risk to prevent transmission(8)(9). Recently, for specific settings, WHO has recommended the use of annual treatment with the triple therapy ivermectin, DEC and albendazole (IDA) combined with the dual therapy of albendazole and diethycarbamazine or albendazole and ivermectin(10)(11). The aim of this study was to compare the therapeutic efficacy of three drug therapy versus two therapeutic measures in treating lymphatic filariasis.

TRANSMISSION

Filariasis is transmitted by female mosquitoes from several genera, including Culex, Anopheles, Mansonia, and Aedes(12). The cycle of transmission begins when an infected female mosquito bites and deposits lymphatic filariasis larvae on the skin (Fig. 1).

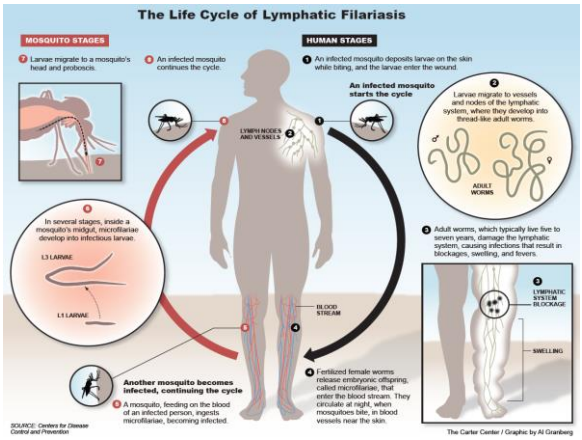

Figure 1. Life circle Lymphatic filariasis(13)

The larvae enter the bite wound and travel to the lymphatic vessels. Larvae develop for about 12 to 15 days in mosquitoes to become third stage infective larvae. The larvae enter the bite wound and travel to the lymphatic vessels. For 6 to 12 months, they become adult male and female worms in the lymph nodes, where male and female worms mate. The female worm then produces an early stage larva, called microfilariae (mf). During the 7 year life cycle, an adult female can release up to 10,000 offspring embryos (microfilariae) per day. Microfilariae (Mf) is carried by the natural lymph flow and introduced into the blood. When the human host is awake, Mf can survive permanently in the larger blood vessels. During sleep, however, they travel or migrate to the surface of the vessels, allowing them to be digested by biting mosquitoes at night. In mosquitoes, Mf undergoes several stages of molting and development. The larvae are ready to be transmitted from the carrier mosquito to humans in 10 to 12 days. Transmission in a community is influenced by several factors, namely the prevalence or number of infected people, the density of Mf in the blood of infected people, the density of carrier mosquitoes in endemic areas, characteristics that affect the growth and development of larvae and the

frequency of human contact with infected mosquitoes. Repeated mosquito bites over several months can cause lymphatic filariasis, thus indigenous people or long-term visitors living in endemic areas are at greatest risk(1)(14).

PATHOPHYSIOLOGY

In the human body, lymphatic vessels secrete circulating fluids and large molecules, such as proteins, from the extracellular spaces in almost every tissue of the body(8)(3). The lymph system is important for maintaining the correct extracellular fluid volume and clearing pathogens that have crossed the skin barrier and entered the extravascular compartment. The antigens, pathogens and invaders that ingest macrophages are transported afferently to the lymph nodes to undergo the process and uptake of additive immunity(15). After cleaning and filtering, the lymph fluid is returned to the blood vessel space. As a component of the adaptive immune system, T lymphocytes are programmed to recognize, respond to, and remember foreign antigens. The presence of a cell surface molecule known as CD4 or CD8 differentiates T lymphocytes. CD4 T lymphocytes, also called helper (Th) T cells, are productive cytokine producers(8). Cytokines are hormonal messengers in the immune system and are responsible for cell-mediated immune and allergic responses, so they are often classified as either pro-inflammatory (Th1 response) or anti-inflammatory (Th2 response). In patients with lymphatic filariasis, lymphatic vessel damage is mediated by a response to the presence of adult worms and the products released by these worms. Compounds secreted or secreted by live worms act on endothelial cells, causing lymph tissue, gradual loss of contractility of lymphatic vessels, unidirectional valve damage, and lymphangiectasis (pathological dilation of lymph vessels). Regardless of the treatment, lymph system damage can be permanent(16). Histologically, live Mf and adult worms rarely elicit an immune response. However, dead or dying Mf and adult worms are highly antigenic. Although the mechanism is not fully understood, the lymphatic filariasis antigen guarantees species survival by modulating the host immune system (Fig. 2) to support the anti-inflammatory response (Th2)(17). This response can be achieved by reducing the proinflammatory (Th1) response(17). As a result of weakening the immune system, the response to opportunistic pathogens and vaccines is severely reduced, such as tetanus toxoid, which can cause the disease to worsen, namely chronic lymphedema(18). Children born to infected mothers are more susceptible to contracting filarial infection(19)(20). In women treated with several cycles of antifilarial drugs before pregnancy, the incidence of children contracting lymphatic filariasis is reduced to less than 1%(21).). There is a hypothesis that placental antigen transfer modulates the infant's immune system, supporting the TH-2 response(17)(21).). Individual responses to the presence of adult worms and microfilariae vary as some develop clinical symptoms and others do not. The susceptibility, parasite load, and degree of cluster pathological changes in the family, suggest genetic polymorphisms play a role in lymph tissue remodeling, severity of lymphatic dysfunction, and degree of immune modulation(22).

EPIDEMIOLOGY

Classified as a tropical disease by the World Health Organization (WHO), this incurable condition affects more than 120 million people worldwide(8). Endemic disease in 73 countries, 1.1 billion people are at risk of being exposed to and contracting infectious diseases in tropical and sub-tropical regions of Asia, Africa, the western Pacific, and parts of South America and the Caribbean(2,4,23,24). In 1997, the World Health Assembly initiated a program aimed at the global elimination of lymphatic filariasis as a public health problem and by 2020 the world was clear of lymphatic filariasis based on the resolution WHA50(8)(25). The GPEFL is one of the fastest growing global public health programs in history. During the first decade, they focused on launching the Program, which included preparing guidelines based on available information, initiating programs in each WHO region where the disease is endemic and scaling up the program as quickly as possible(25)(26). Researchers have found that lymphatic filaria is associated with dermatitis, lymphedema, and elephantiasis on the limbs or

genitalia, which adversely affects personal and social life and limits work activities. By the end of 2011, 53 of 73 endemic countries had implemented mass drug administration, 12 of which had entered the surveillance stage. During 2000 to 2011, more than 3.9 billion doses of the drug were delivered to a cumulative target population of 952 million people(27). In 2011 World Health Organization (WHO) report confirms that it affects more than 120 million people living in 72 countries worldwide, and 39 African countries bear more than a third of the global burden of lymphatic filariasis(9)(28). Nigeria is the second endemic country in the world and also the country with the largest population at risk of lymphatic filariasis infection in the African continent (9)(4). A survey from the Federal Ministry of Health estimated that 20 million people in Nigeria are undergoing treatment for lymphatic filariasis. It states that this figure only represents about 20% of the population at risk. In addition, the Federal Ministry of Health's Nigerian Lymphatic Filarasis Elimination Program, with the assistance of the Carter Center, initiated a collaboration towards elimination of lymphatic filariasis in 2015 (29)(7)(9). In some communities as much as 5% of women can develop swelling of the limbs, and 50% of men can develop swelling of the genitals (hydrocele)(29)(30). The clinical severity and progression of the disease can lead to chronic health complications and disability, which may be accompanied by mental health problems and social stigma, while decreased productivity causes economic losses of nearly USD 1.3 billion per year(31). With several recent advances in diagnosis, pharmaceutical treatment options, and the establishment of the Global Program for the Elimination of Lymphatic Filariasis (GPEFL), WHO member countries were given a strategic plan consisting of 2 objectives, namely stopping the transmission and spread of lymphatic filariasis through mass drug administration (MDA). and alleviating suffering for those with chronic conditions associated with lymphatic filariasis(10)(32).

METHOD

Literature research is used as a reference in published articles which are carried out as an effort to enrich the following literature review. A review of published articles up to 9 October 2020 was involved in this literature review. The literature search was carried out independently by researchers using the Sciencedirect, Pubmed, and Cochrane online databases without limiting the type of study or the year of publication. The keywords used in this study were combined with the Boolean operator, namely "AND" namely ((((Lymphatic filariasis) AND (albendazole)) AND (diethylcarbamazine)) AND (ivermectin)) AND (compare). It is important to convey that researchers are trying to obtain good quality research evidence to support this literature review, namely a study using a randomized design to see the comparison between the combination of three drugs, albendazole, diethylcarbamazine, invermectin with two therapeutic drugs. Only studies published in English were included in the final review. All articles that met the inclusion criteria, even though they were published more than 10 years since this systematic review were carried out, were still used in the analysis to obtain a comprehensive picture. The data extracted from each research article includes: 1) the identity of the article (name of journal, name of researcher, and year of research), 2) country setting for the study, 3) sample size, 4) type of intervention given, 5) methodology and 6) study outcome. The inclusion criteria for research articles were articles containing: 1) lymphatic filariasis experienced in human subjects; 2) cases of lymphatic filariasis accompanied by therapeutic regimens; 3) original sources only; 4) contains a comparison of triple drug combination therapy as lymphatic filariasis therapy with a combination of two therapeutic drugs. The first step of a systematic review is to apply title / abstract filtering. The aim of this step is to remove all publications that do not discuss the comparison of triple therapeutic drug combinations with two therapeutic drugs in lymphatic filariasis. Search queries for conducting systematic reviews are shown in Table 1. In total 389 articles were

identified from the search and underwent a complete review (Figure 2).

Table 1. Search queries in conducting systematic reviews

Database	*Search queries*	Temuan
Crochane	((((Lymphatic filariasis) AND (albendazole)) AND (diethylcarbamazine)) AND (ivermectin)) AND (compare)	27
SienceDirect	((((Lymphatic filariasis) AND (albendazole)) AND (diethylcarbamazine)) AND (ivermectin)) AND (compare)	359
PubMed	((((Lymphatic filariasis) AND (albendazole)) AND (diethylcarbamazine)) AND (ivermectin)) AND (compare)	3

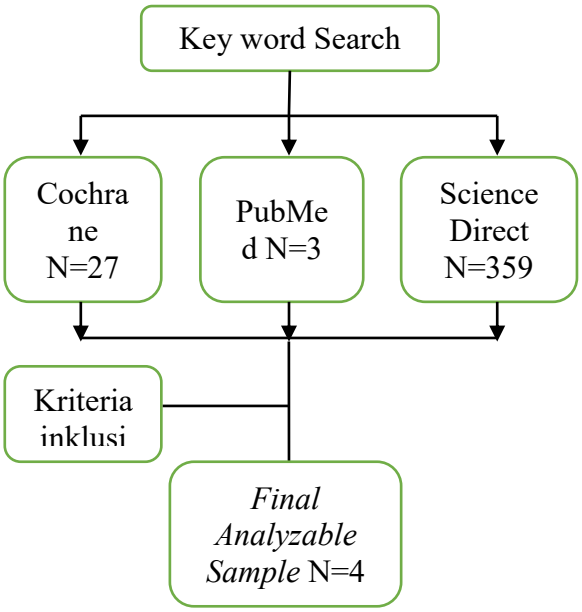

Figure 2. Identify data from article searches

RESULTS

The number of identified article search results was 389 articles. From these articles, 4 articles were used in the final study. The articles included in the final study came from several different countries. The article contains the results of a study using a combination of three drugs, namely albendazole (ALB), diethylcarbamazine (DEC), invermectin (IVM) compared to a combination of two drug therapies, namely albendazole (ALB) and ivermectin (IVM) or albendazole (ALB) and diethylcarbamazipe (DEC) for lymphatic filariasis therapy shown in comparison to the effectiveness of these treatment regimens. Thomsen's study (2016)(33) showed that a single dose of the triple combination ALB + DEC + IVM drug therapy resulted in almost total elimination of microfilariae at 36 hours and 7 days after treatment, and none of the patients experienced microfilaremia 12 months after treatment. Whereas the combination of the two single-dose therapies ALB + DEC resulted in a less specific decrease in microfilariae levels at 36 hours and 7 days, and 10 of the 11 patients continued to have mifillaremia at the 12 month time point. Twelve patients agreed to have blood drawn as additional blood samples (incidentally, 6 in each treatment group) and then examined for microfilaria 2 years after treatment. A total of 6

people who received 3 single drug treatment remained microfilariae at 2 years obtained p value = 0.047, compared with patients who received 2 drug therapy alone. ALB + DEC + IVM also resulted in a greater reduction in filarial antigen levels compared to DEC + ALB at 12 months. DEC + ALB + IVM also resulted in a greater reduction in filarial antigen levels compared to DEC + ALB at 12 months. However, this study also stated that patients treated with the three-drug regimen received more side effects than patients who received only two drug therapies, when the side effects of both objective and subjective groups were combined (9 of 12 (75%) in the group. 3 drugs and 7 of 12 (58%) in the 2 drug group). Side effects were mild to moderate in severity, started 8 hours after treatment, peaked at between 12 and 48 hours, and resolved 7 days later, except in 1 patient who had right inguinal tenderness on day 7. In King's study (2018)(34) used a sample of 182 patients, 172 (95%) evaluated at 12 months, 165 (91%) at 24 months, and 158 (87%) at 36 months after trial initiation. The triple drug regimen cleared micro filaremia in 55 patients (96%) at 12 months, at 52 (96%) at 24 months, and in 55 (96%)

Author	Publication Year	Method	Country	Sample	Intervention	Outcome
Thomsen et al(33)	2016	*Randomized*	Papua New Guinea	53 subject	Patients were stratified by sex and randomly assigned to 1 of the 2 treatment groups: DEC 6 mg / kg + ALB 400 mg or DEC 6 mg / kg + IVM 200 μg / kg + ALB 400 mg	Triple drug therapy (DEC + IVM + ALB) is safer and more effective than DEC + ALB for filariasis and has the potential to accelerate the elimination of lymphatic filariasis
King et al(34)	2018	*Randomized control trial*	Papua New Guinea	182 subject	Patients were randomized in a 1: 1: 1 ratio to a two-drug regimen of 6 mg diethylcarbamazine (Sanofi) per kilogram of body weight plus 400 mg of albendazole (GlaxoSmith-Kline) given once at the start of the trial, a two-drug regimen of 6 mg diethylcarbamazine per kilogram plus 400 mg of albendazole given at trial initiation and at 12 and 24 months, or a three-drug regimen of 200 μg ivermectin (Stromectol, Merck) per kilogram plus 6 mg diethylcarbamazine per kilogram plus 400 mg albendazole given once at trial initiation	These results suggest that a single dose regimen of three-drug ivermectin plus diethylcarbamazine plus albendazole is more effective at clearing microfilaria W. bancrofti from the blood than a single dose regimen of two-drug diethyl carbamazine with albendazole, which is the standard regimen used for mass drug administration for lymphatic filariasis elimination in outside sub-Saharan Africa. The frequency and severity of side effects after treatment with ivermectin plus dietylcarbamazine plus albendazole tends to be lower than for 2-drug therapy.

Bjerum et al(35)	2019	*Randomized, single blind*	Côte d'Ivoire	189 subject	Eligible individuals were randomized then divided into 2 groups reported in this study as follows: group 1 was given an IVM dose of 200 µg / kg (Merck & Co.) plus ALB 400 mg (GlaxoSmithKline) and group 2 was given IVM 200 µg / kg plus. DEC 6 mg / kg (Sanofi SA) plus ALB 400 mg	This study confirms that single-dose treatment with IDA IDA (IVM + DEC + ALB) is well tolerated and more effective against W. bancrofti larvae and adults than IA (IVM + ALB) and is comparable to 2 dose cycles of IA (IVM + ALB). . A greater overall cumulative reduction in MF within the first 2 years with a single dose of IDA (IVM + DEC + ALB) compared to 2 doses of IA (IVM + ALB) indicates better IDA effectiveness.
Dubray et al(36)	2020	*Cluster-randomized*	Haiti	5.998 (3.004 patients from five districts received IDA and 2,994 patients from five other districts received DA)	Each site was randomly assigned to receive an IDA regimen consisting of a single dose of IVM (200 µg / kg) + DEC (6 mg / kg) + ALB (400 mg) (5 regional sites) or an DA regimen consisting of a single dose of DEC (6 mg / kg) + ALB (400 mg) (5 areas)	The Haitian study reported that IDA was well tolerated in the lymphatic filariasis endemic community. The proportion of patients with side effects was significantly lower in people taking the IDA regimen than in people taking the DA regimen. IDA was well tolerated by study patients and was more effective at clearing Mf than DA.

at 36 months after trial initiation. In contrast, a single dose of the two drug regimen cleared microfilaremia in 18 patients (32%) at 12 months, at 31 (56%) at 24 months, and in 43 (83%) at 36 months. The three-drug regimen resulted in significantly greater microfilaria clearance at 36 months than the single-dose two-drug regimen (P = 0.02). The two-drug regimen given once a year for 3 years cleared microfilaremia in 20 patients (34%) at 12 months, at 42 (75%) at 24 months, and in 51 (98%) at 36 months. In patients receiving the three-drug regimen, microfilaria clearance at 36 months was better than the two-drug regimen given once a year for 3 years, with a difference of 2 percentage points (90% CI, - 10 to 6) (one-tailed P value for noninferiority, 0.004). In Bjerum's (2019) study(35) compared the combination therapy of Ivermectin, Diethyl carbamazine, Albendazole (IDA) with a combination of Ivermectin and Albendazole (IA) therapy. The IDA clearance rates at 6 and 12 months were significantly greater than those of IA (83% and 61% improvement, respectively) and showed greater microfilaria clearance at 24 months. IDA reduced mean individual Mf levels by more than 99% at 6 months, 98.9% at 12 months, and 93.2% at 24 months. Overall, there was an 81% greater reduction in microfilarial levels at 12 months compared to IA (incidence rate ratio [IRR], .19; 95% confidence interval [(CI), .12-.33; P <.0001). Cumulative microfilarial load (Mf) after administering a single dose of IDA for 24 months averaged 7.2 Mf / mL (783/109; total Mf at 6, 12, and 24 months divided by the total number of individuals examined at the same time points) versus 27.4 Mf / mL (3431/125) during the same period after 2 doses of IA, representing a 3.8-fold reduction in Mf levels with a single dose of IDA. IDA treatment disabled all worm nests detected in 74%, 81%, 79%, and 79% of patients at 6, 12, 24, and 36 months, respectively. Whereas IA treatment disabled all detected worm nests which accounted for 18%, 36%, 44%, and 40% of patients at 6, 12, 24, and 36 months respectively. Side effects that occur 24 hours after treatment. Of the patients in the IDA and IA groups 47% and 40% had side effects after treatment, respectively. No serious or severe side effects were observed. The frequency of mild and subjective (mild) side effects was similar between the 2 therapy groups, namely headache, joint pain, fatigue, and nausea being the most common symptoms. Saping effects (moderet) occurred in 5 patients (12%) after IDA and in 1 patient (2%) after IA (p value = 0.07). The patient's chance of having a (moderate) side effect increased by 23% for each incremental increase of the total 100 Mf / mL (odds ratio, 1.23; 95% CI, 1.09-1.43; P = 0.04) but all the effects of saping resolve within 2 to 3 days of initial therapy. Dubray's (2020) randomized study(36) in Haiti showed that significantly more participants who were Mf positive at baseline became Mf negative after IDA administration (Invermectin, Diethylcarbamazine, Albendazole) (94.4%, 34/36) than after DA administration (Diethylcarbamazine and Albendazole) (75.9%, 44/58) (P = 0.02). It was reported that two participants who were Mf positive as samples for IDA therapy had Mf counts of 3050 Mf / mL and 1383 Mf / mL. For the therapeutic safety study, this study demonstrated that 96.0% (5761/5998) of treated patients underwent a one-time examination during the 7-day follow-up period (2,917 IDA therapy and 2,844 DA therapy). Overall, 14.1% (812/5761) of patients assessed as having a treatment side effect reported at least one side effect during the week following treatment. The intracluster correlation coefficient for side effects is low (0.02). It is known that more patients who received DA (17.3%, 491/ 2,844) reported side effects compared to patients who received IDA (11.0%, 321/2917) (Table 3). The side effects reported were mostly mild, 88.7% (436/491) of all side effects in the DA group and 93.4%, (300/321) compared to all side effects in the IDA group. It was reported that more women reported side effects of therapy than men. Side effects that occurred more frequently occurred after treatment in positive micro filariasis patients, the comparison of side effects in people with microfilaremia had a low percentage difference,

namely on IDA treatment (34.1%,14/41) and on DA treatment (39.4%,26/66). For people with micro filaremia, the pre-treatment Mf count was significantly higher in people who experienced side effects after treatment compared to people without side effects (geometric mean: 20.98 Mf / mL vs. 8.81 Mf / mL, P = 0.002). The multivariable logistic regression analysis showed that after controlling for age, sex and infection status, the risk of experiencing side effects was significantly lower in patients receiving IDA compared to patients receiving DA.

CONCLUSION

The triple therapy combination is more effective than the two drug therapy in treating lymphatic filariasis. The therapeutic effectiveness can be seen in the final research article where triple drug therapy is significant in reducing and clearing microfilariae and worm nests in patients with lymphatic filariasis compared to two-drug therapy alone. There were fewer side effects from triple drug therapy than with two drug therapies. However, some studies say that the side effects are more in the combination of three therapies. The rate of side effects is low and can disappear two to three days after giving therapy. Some cases of side effects can rise to a moderate level but the percentage is small and no serious side effects have been reported after the administration of the three drug combination. Monitoring and supervision is needed in dealing with side effects that can be caused so as not to disturb the patient's comfort in continuing therapy.

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