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Literature Review

HIV AND MALARIA

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ABSTRACT

HIV/AIDS is a global problem involving industrialized and developing country including Indonesia. Malaria has killed millions of human beings almost 3 million people each year, whereas since 1999, nearly 36 million people in the world infected with HIV and 3 million more have died (Kakilaya, 2006). HIV infection increases the risk and aggravate malaria. In Africa in the area of malaria transmission intensities high and low, HIV aggravate malaria and improve case fatality at any age (Eline 2006). HIV is an RNA viruses whose hallmark is the reverse transcriptation of its genomic. Malaria is a protozoan disease transmitted by the bite of infected anopheles mosquito. Infection malaria can stimulate HIV replication and may cause faster progression of HIV disease.

Key words: *HIV, Malaria, infection, RNA, Progression*

ABSTRAK

HIV/AIDS merupakan masalah global yang meliputi industri dan negara berkembang termasuk Indonesia. Malaria telah membunuh jutaan manusia yaitu sekitar 3 juta orang tiap tahunnya, dimulai tahun 1999, 36 juta orang di dunia terinfeksi HIV dan lebih dari 3 juta telah meninggal[1]. Infeksi HIV dapat meningkatkan dan memperburuk malaria. Di Africa yang mana area transmisi malaria intensitasnya tinggi dan rendah, HIV memperburuk malaria dan meningkatkan kasus fatal di beberapa usia[2]. HIV adalah virus RNA yang ditandai dengan reverse transcriptation gennya. Malaria merupakan penyakit yang disebabkan oleh protozoa yang ditransmisikan oleh gigitan nyamuk anopheles yang terinfeksi. Infeksi malaria dapat menstimulasi replikasi HIV dan menyebabkan percepatan progesi penyakit HIV.

***Kata kunci**: HIV, Malaria, infeksi, RNA, perkembangan*

INTRODUCTION

HIV/AIDS is a global problem involving industrialized and developing country including Indonesia. The problem is growing increased rates pain and death. With respect to the decreasing immune from intervention HIV encourage micro growing organism one is a plasmodium malaria.

With technological progress digit HIV medicine supposed decline in pain in fact the pain remains high.

Malaria has been known for centuries, while the HIV in the last 2 decades. Malaria has killed millions of human beings almost 3 million people each year, whereas since 1999, nearly 36 million people in the world infected with HIV and 3 million more have died. Both of these diseases is expected to infect and kill a lot of people in the world because HIV was increased dramatically in countries with malaria are not controlled.[1]

HIV infection increases the risk and aggravate malaria. In Africa in the area of malaria transmission intensities high and low, HIV aggravate malaria and improve case fatality at any age.[2]

Has known that HIV reduce the number of lymphocytes, especially CD 4, so the immune response decline consequently micro an organism grows with fertile, one is malaria. Malaria while interference red blood cells and take glucose so happen deficiency nutrients that can result in immune deficiency. Malaria burdensome travel HIV infection being aids. On the basis of various fyl above necessary knowledge deep, mutual the relatedness of HIV and malaria so as to be done steps to reduce the rate in pain and death.

HIV

HIV aids first known in 1981 when acquired are sufferers by infection has opportunity without predisposing disorder of the immune system (Crowe, 2001; Fauci, 2005).Cause aids this is known as retrovirus divided into 2 groups namely human T lymphotropid viruses (HTLV) I and HTLV-II as "transforming retrovirus and human immunodeficiency viruses (HIV)-1 and

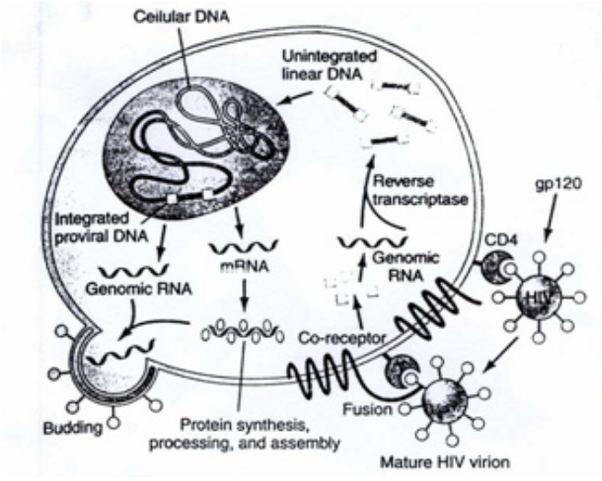


Figure 1. HIV replication cycle.

THE CYCLE OF HIV REPLICATION

HIV is the RNA virus that marked by a transcription inverted namely from RNA to DNA through enzyme reverse transcriptase. Started from the bonds protein gp120 receptor surface host namely molecules CD 4. Molecules CD4 is lymphocytes t that are responsible for helper T cells or induction the immune system. Cd4 expressed also at monocytes/macrophages and cells dendritic/langerhans. After the bond between gp120 with CD 4, gp120 will facilitate bond with co-receptor namely ccr5 and cxcr4. Bond with one or both these receptors will bring virus entering cells. Dendritic cell expressing receptors lectin type c different one of them is called dc-sign on surface that will make proteins gp120 HIV. Cell dendritic will facilitate binding virus T cell with CD 4+. After the ties it forms the surface virus will change, fusion to the cell membrane host would happen through penetration molecules gp 41 to a membrane plasma cells target. Capsule RNA viruses free and went into the cell target. Enzyme resvers transcriptase then catalyze RNA into double-strand DNA. DNA will hold translokation into the cell nucleus host and into the chromosome. Integration HIV this reactivated gene and produce provirus that may be latent or manifest at several levels genes expressions to a virus active. Next several levels activity cell host needed to start a transcription from proviral DNA into RNA or mRNA. MRNA HIV virus will be translation into protein were afterward subjected to modification through glicosilasion, miristilasion, fosforilasion, and division. The viral particles is formed of protein, enzyme, the genome RNA to membrane plasma of the host. Budding of virus happened through a special area in two layers of fat cell membranes host known as lipid rafts which will then be the outer layer of the virus.[3]

PATOFISIOLOGI AND PATOGENESE OF HIV

Sign of HIV is found immune deficiency caused by deficiency of lymphocytes t namely helper t cells or inductor T cells. CD4 that is part of t cells role as receptors of HIV. A co-receptor CD4 required to hold fusion and insert a virus hiv-1 into cells target for CCR5 and cxcr4. Although some mechanism responsible on decline and dysfunction immune T cells CD4+ have been demonstrated in vitro, currently it is not clear mechanism which most responsible on decreasing and impaired function in in vivo. When the number of T cells CD4+ declining the HIV have risk suffer hierograms disease opportunistic, several infections and a neoplasm (Fauci, 2005, O'neil, 2002).

Lysis of the virus and elimination directly caused by cellular immune response and humoral against viral is an important factor which contribute to the decreasing t cells are infected cd4 +. Allegedly that hiv infection cause chronic conditions of activity immune cells that cause elimination cd4 + uninfected. Mechanism is responsible for elimination cd4 + cell autoimmune and are not infected cell death.[4]

Lymphoid tissue constitutes the main hiv replication of the virus is also resulting in place lesions specific occurring imunodefisensi.[4]

TRANSMISSION OF HIV

HIV transmitted by contact heterosexual, homosexual, through blood and blood products, through mother to child is infected intra partum, perinatal or when breastfeeding. For research more than 20 years there is no evidence that HIV can be transmitted through the bite of an insect or propagated as mosquito.[3,5]

Like a capsule virus other all retroviruses inactive, easily into shape and not, is transmitted via air dust or smoke. Infection started having no direct contact through the tissue or body fluid from a source of infection.[6]

CLINICAL SYMPTOMS AND TREATMENT

The clinical and travel this disease correlated with cd4 number of cells. Divided into four degrees primary, namely infection where the virus in blood and proliferation quickly limfonodi, early deficiency immune/early (cell number CD4 > 500/μL), intermediate deficiency immune (CD4: 200–500/μL) and immune deficiency further/advanced (CD4 < 200/μL).[7]

Tabel 1. Clinical Stadium HIV WHO 2004 [3]

	Stadium 1 *asimtomatik*	**Stadium 2** *Mild disease*	**Stadium 3** *Moderate disease*	**Stadium 4** *Severe disease (AIDS)*
Weight	Tetap	BB ↓ 5–10%	BB↓ >10%	**HIV wasting syndrome**
A symptom of infection generally treatment and opportunistic infection according to the guideline and regulations	❖ Only limfa-denopati	❖ Wound around lips (angula cheilitis) ❖ Itchy (seborrhoea/ prurigo) ❖ Infection up track breathing, as sinusitis or otitis.	❖ Sprue (hairy leukoplakia) ❖ > 1 month • Diarrhea • Candidiasis vagina • Fever ❖ Infeksion of heavy bactery(pneumoni, infeksion muscle) ❖ TB lung in last year.	❖ Spure in esofagus ❖ > 1 month • Ulserasi herpes simpl ❖ Limfoma ❖ Kaposi sarcoma ❖ Ca cervix infasif ❖ Pneumocystis pneu ❖ TB ekstrapulmoner ❖ Meningitiscryptococcal ❖ Ensefalopati
ARV therapy	❖ Only if CD4 < 200	❖ Only if CD4 < 200 or limfosit total < 1200/mm3	❖ If CD4 not available start therapy. Start from CD4 < 350	❖ Further evaluation of patient for starting ARV.

ANTIRETROVIRAL THERAPHY OF HIV

Targets antiretroviral therapy (ARV) that inhibits bond with CD4 (in research) enzyme inhibit reverse trancriptase (*zidovudine, didanosine, zalcitabine, lamivudine, stavudine, foscamet*) a non-nucleoside reverse transcriptase inhibitor (*nevirapine*) termination of DNA (zidovudine, sintesa chain didanosine, zalcitabine, stop and budding assembly (viruses, interferon) hinder maturation protein virion core (a protease inhibitor: example saquinavir).[8]

It has proven that combination therapies more effective for viruses and impede progresivitation disease. Therapy for patients without major complications is d4T-3TC-NVP namely stavudine-lamivudine-nevirapine.[9]

MALARIA

Malaria is a disease due to protozoa that are transmitted through the bite of an infected anopheles mosquito. There were four genus infecting humans, a plasmodium namely *P. Tertian, P. Vivax, P. Ovale,* and *P. Malariae*. Infection began when a female an infected anopheles mosquito inoculation plasmodial sporozoites when suck the blood of humans. A microscopic malaria parasite would be taken quickly off the flow of blood to heart entering parenchyma liver and begin a period of asexual reproduction. Through a process of amplification (known as intrahepatic or preerytrocityc schizogony or merogony) a sporozoites can produce 10,000 until > 30,000 & merozoites. Liver swell will issue merozoites moving into the blood stream. Then went into the red blood cells and multiplication 6 until 20 times every 48–72 hours. Parasitic on sat reached–50/µL blood clinic symptom of infection this will seem (White, 2005). On *P. vivax* and *P. ovale* when phase intrahepatik not occurring cleavage immediately but is dormant between 3 weeks until a year or so before reproduction began, called hepaticae hypnozoit this condition allow parasitic adapted to climate change.[11,12] Upon entering blood flow merozoites entrance to erythrocytes and tropozoit be assisted by receptors surface erythrocytes specific during the early phases intra eritrosit notching the ring (ring forms) of four species parasitic looked same under a light microscope. As makin magnify tropozoit specific characteristic each species more real, pigment more visible, parasitic looked irregular or notching ameboid. After 48 hours the life cycle intraeritrosit (72 hours to *P. malariae* parasitic) has consume almost all hemoglobin and meet red blood cell (SDM), called schizont. Occurring splitting the nuclei of multiple and SDM shatterlng make 6–30 merozoites female that can mengivasi SDM new and cycle as above will recurring again. This disease in humans caused by any indirect effect of his invasion SDM, destructived by parasites phase asexual and reaction host. After cycle asexual (*P. Falciparum*) or immediately after out of liver (*P. Vivax. P. Ovale, P. Malariae*) some parasitic form morphology different namely sexual phases (gametosit) can anything to malaria. After sucked by the bite of an infected anopheles mosquito female, gametosit male and female form a zygote in intestines of mosquitoes. Which the zygote mature ookinet be entering and protected in the intestinal wall. Ookcyst formed from cleavage asexual continue to cleave to a sporozoites moving then migrate to hemolimf further to the salivary glands mosquito waiting inoculation into another human.[12]

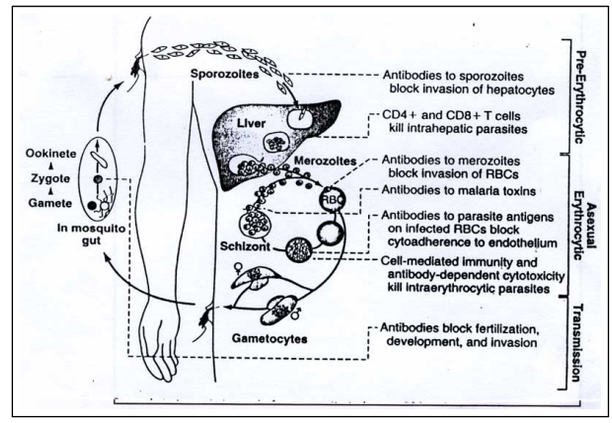
EPIDEMIOLOGY AND TRANSMISSION OF MALARIA

Malaria are found in tropic area. Africa, new guinea, Haiti dominant *P. Falciparum, P. vivax* more numerous in central America and parts of the south north Africa, middle east and zindian subcontinen. *P. Ovale* rare outside west african while *P. Malariae* found in many place.[12]

Malaria transmitted by several species mosquito anopheles. Transmission this is not happening in temperature under 160 c, or over 330 c and height of more than 2000 m. condition optimum is on moisture high with temperature between 20 and 300 c (White, 1996). An area that many obtained the gnat is marshes that deals with the high rate occurrence malaria. Stagnant water into one that support mosquito reproduction.[11]

Malaria can also occurring by sporadic in the non endemic. In example because of malaria latent relapse few months after traveling from the endemic. Sufferers as is generally not getting therapy complete or got kemoprofilaksis inadequate.[11]

Malaria also can be transmitted over blood transfusion, syringe or transplant organs. The incubation generally short having no stadium preeritrositik.[12]



Picture 2. The cycle of the transmission of malaria from the mosquito to humans.

Table 2. A manifestation of malaria clinics difficult because *P. falciparum*[3]

Signs	*Manifestations*
Major	
Unarousable coma / cerebral malaria	Failure to localize or respond appropriately to noxious stimuli; coma persisting for > 30 min after generalized convulsion
Acidemia/acidosis	Arterial pH < 7.25 or plasma bicarbonate level of < 15 mmol/L; venous lactate level of > 5 mmol/L manifests as labored deep breathing, often termed “respiratory distress”
Severe normochronic, normocytic anemia	Hematocrit of < 15% or hemoglobin level of < 50 g/L (< 5 g/dL) with parasitema of > 100,000/μL
Renal failure	Urine output (24h) of < 400 mL in adults of < 12 mL/kg in children; no improvement with rehydration; serum creatinine level of > 265 μmol/L (> 3.0 mg/dL)
Pulmonary edema / adult respiratory distress syndrome	Noncardiogenic pulmonary edema, often aggravated by overhydration
Hypoglycemia	Plasma glucose level of < 2.2 mmol/L (< 40 mg/dL)
Hypotension/shock	Systolic blood pressure of < 50 mmHg in children 1–5 years or < 80 mmHg in adults; core/skin temperature difference of > 10ºC
Bleeding / disseminated intravascular coagulation	Significant bleeding and hemorrhage from the gums, nose, and gastrointestinal tract and/or evidence of disseminated intravascular coagulation
Convulsions	More than two generalized seizures in 24 h
Hemoglobinuriaa	Macroscopic black, brown, or red urine; not associated with effects of oxidant drugs and red blood cell enzyme defects (such as G6PD deficiency)
Other	
Impaired consciousness	Obtunded but arousable
Extreme weakness	Prostration; inability to sit unaidedb
Hyperparasitemia	Parasitemia level of > 5% in nonimmune patients (> 20% in any patient)
Jaundice	Serum bilirubin level of > 50 mmol/L (> 3.0 mg/dL) if combined with other evidence of vital-organ disfunction

SYMPTOMS CLINIC

Malaria is one of the causes of fever in tropical countries. Early symptoms of malaria are non-specific, such as discomfort, headaches, tired, uneasy feeling in the stomach, muscle pain with heat is a symptom similar to some viral diseases. In some circumstances a very head aches, chest pain, abdominal pain, artralgia, myalgia or diarrhea may be due to other illnesses allegedly although headaches on malaria might be heavier. Nausea, vomiting and ortostatik hypotension often occurs as well. The classic symptoms of malaria, such as high heat, chills and stiffness that occurs on a regular basis appropriate intervals, relatively rare and is thought to be caused by *P. vivax* or *P. ovale*. Heat the irreguler on *P. falciparum* in patients with the declined immune and children often achieve above 40° C flutter, and sometimes accompanied by delirium. Seizures can also be caused by *P. falciparum* and is signified the presence of cerebral malaria.[12]

Found little physical examination teratology on patients without complication, malaria is hot malaise, anæmia light and in some cases spleen being palpable. Anemia more often resulted in children living in the transmission stable place that is resistant to partially parasitic chloroquin or other drugs. Enlarged spleen often resulted in patients in the endemic indicating the presence of infection repeated. Enlargement of the liver mild also found chiefly on small children. Mild jaundice associated with adults caused by *P. Tertian* and generally recovered after 1 to 3 weeks.[12]

MANAGEMENT

When a sufferers of an area that get malaria having symptoms heat, hapusan blood with drops thick and thin must be done to diagnose and determine species parasite that infects. Repet of hapusan blood to do at least every 12 to with 24 hours for two days, if hapusan first negative.As an alternative detection antigen or stick test assignment. Some medicines can be used orally and it depends on the sensitivity parasite that infects. Chloroquin is therapy options for malaria a tame *P. vivax*, namely *P. ovale*,

Table 3. Medicine which recomendation for antimalaria[12]

Drug	*Uncomplicated Malaria (Oral)*	*Severe Malaria[a] (Parenteral)*
Chloroquine[b]	10 mg of base/kg followed by 10 mg/kg at 24 h and 5 mg/kg at 48 h or by 5 m/kg at 12, 24, and 36 h (total dose, 25 mg/kg); for *P. vivax* or *P. ovale*, primaquine (0.25 mg of base/kg per day for 14 days[d]) added for radical cure	10 mg of base/kg by constant-rate infusion over 8 h followed by 15 mg/kg over 24 h *or* by 3.5 mg of base/kg by IM or SC injection every 6 h (total dose, 25 mg/kg)[c]
Amodiaquine[b]	15 mg of base/kg followed by 10 mg/kg per day at 24 and 48 h (total dose, 35 mg/kg)	–
Sulfadoxine/ pyrimethamine[b]	25/1.25 mg/kg, single oral dose (3 tablets for adults)	–
Mefloquine[b]	15 mg/kg followed 8-12 h later by second dose of 10 mg/kg	–
Quinine	10 mg of salt/kg q8h for 7 days combined with tetracycline[e] (4 mg/kg qid) or doxycycline (3 mg/kg once daily) or clindamycin (10 mg/kg bid) for 7 days	20 mg of salt/kg by IV infusion over 4 hf followed by 10 mg/kg infused over 2–8 h every 8 h
Quinidine gluconate	–	10 mg of base/kg by constant-rate infusion over 1–2 h followed by 0.02 mg/kg per min, with ECG monitoringg
Artesunate	In combination with 25 mg of mefloquine/kg, 12 mg/kg given in divided doses over 3–5 days (e.g., 4 mg/kg for 3 days or 4 mg/kg followed by 2 mg/kg per day for 4 days); if used alone or in combination with clindamycin or doxycycline, give for 7 days (usually 4 mg/kg initially followed by 2 mg/kg daily)	2.4 mg/kg IV or IM stat followed by 1.2 mg/kg at 12 and 24 h and then daily (or 2.4 mg/kg once daily)
Artemether	Same regimen as for artesunate	3.2 mg/kg IM stat followed by 1.6 mg/kg per day
Atovaquone-proguanil (Malarone)	For adults > 40 kg, each dose comprises 4 tablets (each tablet containing atovaquone 250 mg and proguanil 100 mg) taken once daily for 3 days with food	–
Artemether-lumefantrine	For adults š35 kg, each dose comprises 4 tablets (each tablet containing artemether 20 mg and lumefantrine 120 mg) at 0, 8, 24, 36, 48, and 60 h, taken after food	–

P. Malariae. Malaria on heavy anti arrhythmic quinidine gluconate replace quinine as malaria therapy in us. Discharging quinidine must with the monitor tight if there disritmia and to prevent from happening hypotension. Quinine safer than quinidine and has been much used in the world widely during malaria therapy heavy. In some area of chinese medicines derivable from artemesinin (artemether and artesunat) been first choice to malaria heavy.[12]

THE INFLUENCE OF HIV FOR MALARIA

Currently two health problems in africa HIV and malaria. Research on interaction between both still a little. HIV immunity so on could reduce malaria patients symptoms heavier. While malaria would accelerate HIV infection into AIDS (Chandramohan, 1998, Whitworth, 2005).

Immunologist mechanism will protect the infection. It can be achieved through destructive parasitic on phase preeritrositik in liver by of cytotoxic T cells and other mechanism that related. If this mechanism fail, parasitic will continue easily enter into the bloodstream, it will increase so that manifestation clinic was renewed and will overcome by an antibody in blood. T cells playing an important role in the immune response against malaria. CD4 cells will help production of antibodies against malaria and controls parasitemia by producing cytokines. On HIV with total CD4 decline will give effect on ability of body to form an immune response that is effective against malaria. Resulting from infection HIV in malaria will improve incident pain than healing, increase incident symptoms clinic compared infection asimtomatik, malaria and increase the weight compared light.[13]

THE INFLUENCE OF MALARIA FOR HIV

There is a possibility that cellular aktifasi resulting from infection pathogenic microorganisms will increase replication of the virus. Malaria is strong stimulators the immune system. Someone who exposed to malaria would increase the level of serum imunoglobulin, and occurring IgG acceleration of change. B cells activity excess this may be caused by some specific, the response to an antigen variant malaria and stimulation of non specific derivat a toxin or influential mitogen directly into b cells or through active T cells. The evidence active t cells that remains less strong than b cells but the inductions some immune response specific influence possible active helper t cells that recurs.[13]

There is evidence that function of T cells decline during acute phase episode malaria. Response proliferative are squeezed during acute episode of malaria. Malaria infections have an effect against HIV stimulated change T cells and and failure of function of cytotoxic T cells. Malaria infections also can undermine the placenta to make way for the transmission of HIV in utero.[13]

P. falciparum stimulates HIV replication through production of cytokines (IL-6 dan TNF-α) that is activated by lymphocytes. A study in Malawai, Africa shows that plasmatic viral loads HIV sufferers with higher on malaria compared with only HIV.[14]

THERAPY RESPONE AND INTERACTION OF MEDICINE

Therapy anti malarial will be effective on an individual that have had immunity against malaria. Estimated that response therapy will decline in individuals whose immunosuppressive because HIV infection and living on the transmission malaria stable. Recent observations estimate treatment with artemisin, sulfadoksin-pyrimetamine artemether-lumefantrine and less effective in people with with HIV. Interaction between an anti malarial drug and ARV most involving a protease inhibitor (PI) and nonnucleoside reverse transcriptase inhibitors (NNRTI). An anti malarial drug halofantrine, artemether lumefantrine and should not given by those with that off drugs PI (or NNRTI delavirdine) because will increase the risk toxicity. Among who wears NNRTI another (nevirapine or efavirenz) the lumefantrine and artemether concentration low will increase the risk failure therapy. Acquired also potential interaction between quinine and NNRTI or PI. However potential interaction between drugs is still needs far more research.[14]

Chloroquin commonly used as anti malaria caped inhibits the activity of antiviral namely interferon and beta alpha on experiment animals. Found also that chloroquine increase replication of the virus in mice tried.

Chloroquin often worn as chemotherapy malaria. (Kakkilaya, 2005) chloroquin have an effect immunosuppression and only effective in the central America and middle east. Prophylactic proper to malaria resistant chloroquin is mefloquin and doxycyclin (Rulf at, 1997). In one research farmakokinetik obtained mefloquin norvir lower levels in the blood up to 30%.[1]

Many patients HIV allergic to sulfonamide as pirymethamine-sulfadoxine (Fansidar). Granting doxycycline 100 mg/day for two days before traveling, during traveling and four after that have some benefits because besides can give prophylactic on malaria also in diarrhea and some other infections. Prevent mosquito bite, and diagnosis rapid and on complaint heat especially during and after passing to the regions with risk malaria is important for the hiv who travel.[14,15]

Combination therapy ARV has a great potential to lower hiv dealing with malaria. Prophylactic cotrimoxazol recommended for children and adults with HIV in africa and effective to relieve the symptoms clinic malaria.[2]

SUMMARY

HIV is an RNA viruses whose hallmark is the reverse transcriptation of its genomic. The hallmark of HIV disease is a profound immunodeficiency. Primarily, deficiency of the subset T lymphocytes, CD4, which serves the us primaries celullar receptor of HIV.

Malaria is a protozoan disease transmitted by the bite of infected anopheles mosquito. Four species of the genus a plasmodium cause malaria infection of human. These are *P. vivax, P. falciparum, P. ovale* and *P. malariae*. There are two cycles of a plasmodium life, sexual and asexual cycles which happen in human and female anopheles mosquito.

The association between the two infection has important implications. Malaria and HIV-1 are two most common infection in Sub-Saharan Africa, to a lesser extent, in other developing countries.

HIV-related immunosupression may increase malaria rates of infection and malaria clinical disease. Infection malaria can stimulate HIV replication and may cause faster progression of HIV disease. There are some anti malarias and drug interactions between antiretroviral drugs (ARV).

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