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THE IMPACT OF MALARIA ON HIV AND VISE VERSA: IS IT RISKY TO EGYPT WITH IMMIGRATIONS AND CLIMATIC CHANGES?

By

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Abstract

Undoubtedly, the world is facing a process of climate change, which has adversely impact human health in many different ways, such as increase the risk of arthropod-borne infectious diseases, psychiatric disorders, cancer and other diseases.

The impact of HIV on malaria is modified by such factors as the endemicity and malaria transmission stability. In areas with stable malaria transmission, HIV increases the malaria infection risk and clinical malaria in adults, especially those with advanced immunosuppression.

This reviewed the marked interactions between HIV and malaria infections, including during pregnancy.

Key words: Egypt, Malaria, HIV, Pathogenesis, Climatic changes, Immigrations, Risk, Review.

Introduction

Egypt is highly vulnerable to climate change, with projected increases in heat waves, dust storms, storms along the Mediterranean coast and extreme weather events. Stronger warming has been documented over the past 30years, with average annual temperatures increasing by 0.53 degree Celsius/decade, and the climate risks are and will impact today's younger generations (UNICEF, 2022).

HIV and malaria infections coexist in patients in many global parts due to geographic overlap of both diseases, especially in sub-Saharan Africa; about 40 million people are living with HIV and 350 million annual malaria episodes (Hewitt *et al,* 2006). The HIV increases the risk of malaria fever with development of clinical malaria, which increases HIV/AIDS replication (WHO, 2017).

Plasmodium species causing human malaria are *P. falciparum, P. malariae, P. ovale, P. vivax* and *P. knowlesi* CDC (2024). Most data on HIV interaction with malaria are derived from *P. falciparum*-endemic sub-Saharan Africa regions but, HIV spreads to endemic *P. vivax* areas, same important interactions was identified (Murillo *et al,* 2012).

Malaria incubation period in most cases varied between 7 to 30 days (CDC, 2022). However, in *P. vivax, P. ovale* & *P. malariae* can be months, or even years (Ashley *et al,* 2018). Moreover, Looareesuwan *et al.* (1993) in Thailand reported *P. falciparum* and *P. vivax* infections occurred after splenectomy in four patients, one non-immune and three partially immune. The clinical picture was uncomplicated in all the patients, but parasite clearance was delayed in the non-immune one. Zimmerman *et al.* (2004) reported that in most malaria-endemic regions mixed infections were involved by two or more *Plasmodium* species. Kim *et al.* (2019) in Korea reported that mixed *P. falciparum* & *P. ovale* malaria infections were undiagnosed or underestimated.

Immunity to malaria is characterized by an age-reduction in parasite burden, clinical pictures, and severe disease prevalence in endemic areas (Karp and Auwaerter, 2007). *P.*

falciparum infection and parasitemia are less severe among elders than in children, who were at diminished risk of natural immunity by HIV-related immunosuppression (Singh *et al,* 2011). These individuals were not immune to infect per se, as *Anopheles* vector bite develops malaria with parasitemia, but with limited severe clinical symptoms (Barry and Hansen, 2016).

Review and Discussion

Impact of malaria on HIV: In vitro, malarial antigens lead to T cell activation and HIV viral replication (Froebel *et al,* 2004). Malaria episode was associated with CD4 cell counts declines over time compared with HIV-infected patients without parasitemia (Mermin *et al,* 2006). Both HIV and malaria account for >2 million deaths globally every year and sub-Sahara pregnant women are the most vulnerable to HIV (WHO, 2016).

Viral load: Malaria infection is associated with a temporary rise of HIV viral load, although long term this didn't appear to hasten progression to AIDS (Hoffman *et al,* 1999). Franke *et al.* (2010) in Tanzania reported that increased in viral load were greatest in patients with fever, CD4 counts >300 cells/microL and in those with a parasite density >2000/microL with near doubling of HIV/RNA was between baseline and follow-up in malaria infected patients. In Malawi 348 patients without parasitemia have a baseline HIV viral load and followed up showed active malaria (Mungwira *et al,* 2018). This rise was temporary, with HIV viral load returning to baseline at two months after treatment of malaria. If viral loads were used to monitor response to antiretroviral therapy, testing should be delayed if the patient has had a recent malaria infection (Hoenigl *et al,* 2016). This transient increase in viral load would be predicted to have mild impact on long-term HIV progression, unless infections were frequent or remained occult and untreated, but from the public health standpoint, even a transient rise in HIV viral load at a population level could impact sexual transmission (Morgan *et al,* 2002).

HIV-related survival: The HIV-related survival rates in malaria-endemic to non-endemic countries was problematic due to the higher prevalence of additional healthcare problems found in these geographic regions that may also impact morbidity and mortality. Besides, there were few well-done studies in malaria-endemic areas to answer this question. However, studies from Uganda and Malawi found a 10-year survival rate after HIV infection that was comparable with rates reported in the developed non-endemic malaria-countries in the pre-potent antiretroviral therapy era (Nunn *et al,* 1997).

Impact of HIV on malaria: HIV impact on malaria examined the various malarial markers including susceptibility, infection prevalence and peripheral parasite burden, disease severity, and treatment response (Jaffar *et al,* 2004). Patients co-infected with HIV have a lower number of antimalarial antibodies, due to high infection prevalence. Among 18 HIV infected and 18 HIV uninfected Rwandan adults, mean antimalarial IgG antibody breadth across HIV-infected patients was lower than in across HIV-uninfected ones (83 versus 208 antigens, respectively); also overall IgG magnitude reactivity was lower in HIV-infected patients (Subramaniam *et al,* 2015).

Susceptibility: HIV serostatus and immunosuppression was associated with an increased risk of susceptibility to malaria infection was reported among many studies (Kublin *et al,* 2005). A cohort study conducted among 224 HIV-infected and 125 HIV-uninfected Malawi adults to assess whether HIV serostatus affected malaria incidence or not (Patnaik *et al,* 2005). HIV-1 seropositivity was significantly associated with the first & second episode of parasitemia. The first episode risk was inversely related to baseline CD4 cell count in HIV-1-infected patients. A retrospective study in Uganda on 1965 patients treated for a malaria episode by molecular genotyping showed that HIV-infected patients were at significantly higher risk to acquire new infections than HIV-uninfected ones over 28-day follow-up (Kamya *et al,* 2006).

A clinical trial study among Zambian 971 adults with uncomplicated malaria; HIV infection was in 33% with CD4 counts <300cells/microL were at increased risk for recurrent parasitemia, recrudescence, and new infection (Van Geertruyden *et al,* 2006).

Clinical malaria risk: The host immunity by CD4 cell counts showed that clinical malaria pictures were critical factor in HIV-infected patients (Francesconi *et al,* 2001). Also, HIV status increased the high parasitemia level risk (French *et al,* 2001). In a longitudinal surveillance among 600 Malawi HIV-infected patients, malaria blood smears were monthly examined and also if patient had any illness suggestive of malaria and his/her clinical malaria episodes was higher in patients with CD4 counts <200 cells/microL L than in those with relatively preserved CD4 counts (Laufer *et al,* 2006). Among 222 HIV infected and 237 HIV-uninfected patients in Uganda who had routine and sick clinic visits, the clinical malaria risk was significantly higher in HIV-infected patients than in HIV-uninfected ones; 16 versus 10% (Whitworth *et al,* 2000). This risk increased with advanced immunosuppression (6-fold high in patients with a CD4 count<200 cells/microL compared to those with a CD4 count >500 cells/microL), that parasitemia was more common in HIV-infected patients than HIV-uninfected ones; 12 versus 6% (Steketee *et al,* 1996).

Severity of malaria: There were conflicted reports as to whether HIV serostatus contributes to malaria severity or not (Grimwade *et al,* 2004). This was partly related to whether a patient lives in a region of stable or unstable malaria transmission. But, Butcher (2005) reported that increased risk of severe disease among HIV-infected patients with significant immunosuppression. These were reported: 1- A prospective cohort study in South Africa was undertaken to examine the HIV status effect and prior to history malaria on clinical expression of malaria infection (Cohen *et al,* 2005). The non-immune HIV-infected patients with immunosuppression significantly showed more severe malaria (13/36) than non-immune HIV-uninfected patients (9/75; odds ratio 4.15, 95% CI 1.57-10.97), 2- Among 660 Malawi adults with HIV in followed up 1 to 2 years, only three had severe malaria; all three had CD4 counts less than 200cells/ mm^3, 3- In France using a hospital database, 104 HIV-infected patients and 161 HIV-uninfected ones acquired malaria during travel (Mouala *et al,* 2009). HIV serostatus reported to be a risk factor for severe malaria only in patients with CD4 cell count of <350 cells /microL, & 4. Among 655 Mozambique children, and 68 adults with malaria, HIV children had more severe acidosis, anemia, and respiratory distress with risk of blood parasitemia and plasma *P. falciparum* histamine-rich protein-2 (PfHRP2), irrespective of the predictors for death with the renal impairment, acidosis, parasitemia, and plasma PfHRP2 concentration (Hendriksen *et al,* 2012).

Co-infection and spread of disease: A direct relationship occurred between height of plasma HIV viral load levels and probability of HIV transmission per coital act (Quinn *et al,* 2000). Co-infection led to a near one-log increase in load viral in chronic HIV - infected patients and HIV increases susceptibility to malaria infection (Saleem *et al,* 2022).

Using a mathematical model, the estimated the impact of HIV and malaria on each other in Kenya, and excess prevalence was 2.1% for HIV & 5.1% for malaria (Abu-Raddad *et al,* 2006). Since 1980, this disease interaction was responsible for 8500 excess HIV infections and 980,000 excess malaria episodes, and co-infection also facilitated the geographic expansion of malaria in other areas where HIV prevalence was high (Uneke and Ogbonna, 2009). However, not all malaria infections increase HIV viral load. In a longitudinal study of 27 Rwandan patients with HIV and malaria infection without change in viral load for one month after malaria treatment, included the undetectable ten patients with viral load <40 copies/mL (Subra-

maniam *et al*, 2014). The malaria effect on HIV was more or less regional specific, and prevalence of *Anopheles*-transmitting gametocytes was higher in HIV-infected patients with immunosuppression (CD4 counts <200 cells/microL) that added to implications in transmission of malaria (Shah *et al*, 2006).

Pregnancy: If malaria infection occurred during pregnancy, infection was more severe, hypoglycemia and respiratory complications were more common (White and Pukrittayakamee, 1993). The concurrent malaria & HIV are still two of the most deadly diseases of a major public health menace in the sub-Saharan Africa (Kwenti, 2018).

Placental malaria: It is characterized by accumulation of *P. falciparum*-infected RBCs in placental intervillous space causing adverse perinatal outcomes as stillbirth, low birth weight, preterm birth, and small-for-gestational-age neonates due to inflammatory responses expressed specific class of the variant surface antigens (Zakama and Gaw, 2019). With each pregnancy, immunity to placental malaria occurs and the prevalence of maternal and fetal complications declines associated with maternal production of antibody specific to chondroitin sulfate A (CSA) expressing parasites (Simon *et al*, 2021). In Malawi pregnant women with malaria from showed lower concentrations of CSA VSA IgG in HIV-infected ones compared to those who didn't have HIV (Crampin *et al*, 2002). Reduced antibody production correlated with lower CD4 T cell counts, leading them to suggest that impaired humoral immunity accounted for an increase in susceptibility to placental malaria in this patient population (Stephens *et al*, 2005).

Maternal health: In studies of HIV-uninfected and -infected pregnant women, dual infection with HIV and malaria was associated with an increased risk of higher parasitemia, maternal death, postpartum maternal anemia, and severe clinical disease compared to HIV-uninfected women (Ayisi *et al*, 2003).

Perinatal outcomes: Dual infection with malaria and HIV led to an increased risk of adverse perinatal outcomes, and increased infant mortality (Hochman and Kim, 2012): 1- There was relationship between maternal HIV infection, placental infected malaria, and infant mortality. 2- Of 138/2608(5%) pregnant women were HIV patients. In a multivariate analysis, neonatal mortality in infants born to mothers with both placental malaria and HIV infection was significantly greater than infants born to mothers with either infection alone. The co-infection with malaria and HIV was associated with increased risk of stillbirth (odds ratio 4.7, 95% CI 1.34-16.78) and preterm delivery (odds ratio 4.1, 95% CI 2.17-7.75). Each infection was independently associated with an increased risk of low birth-weight, low Apgar scores, and fetal growth restriction, and among 986 pregnant women in Zimbabwe, the prevalence of HIV and malaria infections was 8 & 15%, respectively (Ticconi *et al*, 2003). 3- Malaria and HIV infections were independently associated with an increased risk of stillbirth, preterm delivery, low birth-weight, very low birth-weight, low Apgar scores, and fetal growth restriction associated with increased risky complications (Villamor *et al*, 2005). 4- Malaria infection caused a temporary increase in HIV viral load in non-pregnant and pregnant adults that returned to baseline after antimalarial treatment, but an increase in viral load at delivery time results in an increase in HIV vertical transmission, as placenta is organ by which maternal fetal HIV transmission occurs, and disruption by malarial parasites increased mother-to-child HIV transmission (ter Kuile *et al*, 2004). WHO (2004) recommended that HIV-infected pregnant women should receive at least three courses of IPT to reach the same benefits that HIV-uninfected women appear to have with the standard two-dose regimen, and also to define the optimum dosing frequency, the amount of drug needed during pregnancy is still uncertain.

The intermittent preventive therapy: WHO (2013) recommended that pregnant women living in sub-Saharan Africa in areas of stab-

le malaria transmission receive intermittent preventative antimalarial therapy (IPT) to reduce placental malaria and its complications. The most commonly drug used for IPT in pregnant women is sulfadoxine-pyrimethammine (IPTp-SP; 1500mg sulfadoxine and 75 mg pyrimethamine) administered at specific intervals after quickening mother's recognition of fetal movement (Schultz *et al,* 1994), which showed that three or more IPTp-SP doses were associated with higher mean birth-weight and rare lower birth-weights than two doses of IPTp-SP (20% reduction in low birth-weight 95% CI 6-31).

Women in low transmission regions may take two doses given in the second and third trimesters. Women with HIV taking cotrimoxazole don't need additional SP as cotrimoxazole prevents malaria along with HIV-related opportunistic infections (Kapito-Tembo *et al,* 2011). But, an optimal dosing for HIV-infected pregnant women is still being sought, although the data bulk suggested that greater reduction in peripheral and placental parasitemia and a significant increase in mean birth-weight were achieved with monthly IPT rather than the standard two-course regimens (Ter Kuile and Steketee, 2007): 1- In Kenya of intense malaria transmission, monthly IPT was more efficacious in preventing placental malaria compared with a two-dose course among the HIV-infected women 25 versus 7% (Parise *et al,* 1998), 2- A randomized non-blinded Malawi study compared 2 doses of sulfadoxine-pyrimethamine versus monthly sulfadoxine-pyrimethamine administered during pregnancy in 266 HIV-infected and 1626 HIV-uninfected women (Filler *et al,* 2006). In HIV-infected cohort, the monthly regimen gave a significant reduction in the placental malaria incidence compared with the two-dose arm (8 versus 22%), & 3- Data from a randomized controlled study of monthly versus 2-dose SP therapy in HIV-infected Zambian women confirmed a dose-dependent benefit of SP in reducing maternal anemia, peripheral and cord blood parasitemia, infant prematurity, and low birth-weight (Gill *et al,* 2007). Many women who were randomized to two doses of SP actually only received one, which was far inferior in efficacy, suggested that monthly SP intermittent therapy caused the more effective strategy in reducing risk of inadvertent underdosing with the poor outcomes (White *et al,* 2014). Daily cotrimoxazole was as effective as SP to prevent clinical and placental malaria and HIV-infected pregnant woman on cotrimoxazole didn't additional IPT, as pregnant ones with the low CD4 count or clinical immunosuppression features must remain on cotrimoxazole during pregnancy (Klement *et al,* 2014). The pharmacokinetic study proved that the area under the curve (AUC) concentration for sulfadoxine was insignificant during pregnancy than in the postpartum state, but HIV status itself had little effect on pharmacokinetic parameters in the pregnant women (Green *et al,* 2007). WHO (2021) recommended that IPTp-SP for all pregnant ones in high to moderate transmission areas must start in 2nd trimester at each scheduled antenatal care visit to the delivery time, providing that doses given at least a month apart. All cases must decrease malaria incidence by using insecticide-treated bed-nets (Hamer *et al,* 2007).

Diagnosis: The clinician needs to be aware of a few caveats as to diagnosis of malaria, and HIV infections (Focà *et al,* 2012). In many world regions, malaria is diagnosed on the basis of fever alone, and medications are administered without confirmatory laboratory testing (Murphy *et al,* 2013). Conversely, if a diagnostic workup is pursued, a positive malaria smear may be mis-diagnosed as the cause for fever in an HIV-infected patient or HIV-uninfected ones when an alternative etiology being present, as malaria infection and bacteremia may coexist in the same patient (Andreoli *et al,* 2015). Thus, malaria diagnosis should be considered in all febrile patients who have traveled to or lived in malaria-endemic areas (Bronzan *et al,* 2007).

Babesia and *Theileria* infections are usually asymptomatic, except in immunocompro-

mised persons show malaria-like symptoms (Ayeh-Kumi *et al,* 2022). Microscopically, *Babesia* and *Theileria* trophozoite stages can be misdiagnosed with *Plasmodium falciparum* (Sojka *et al,* 2022). Babesiosis and tropical theileriosis were reported in Egypt (Michael *et al,* 1987; Selim *et al,* 2022).

Diagnosis of HIV: Two important factors are important to keep in mind when considering the diagnosis of HIV in malaria-endemic areas: 1- Co-infection with HIV and malaria was highly common with anemia particularly in pregnant women (Ssentongo *et al,* 2020). Fever fatigue, pharyngitis and myalgias were also the presenting symptoms of primary HIV infection (Pincus *et al,* 2003).

Efficacy of malaria treatment: HIV patients equally respond to the antimalarial treatment but, they are at risk for higher prevalence of infection. In Uganda and Malawi, treatment failure didn't associate with HIV serostatus (Byakika-Kibwika *et al,* 2007). But, molecular methods that explore the dynamics between the infection timing and viral evolution emerged as a promising approach (Moyo *et al,* 2015).

Treatment of malaria in HIV-infected patients was more or less the same as treatment of HIV-uninfected individuals (CDC, 2017). However, new infections incidence might be higher, and recrudescence of drug-resistant parasites occurred and careful follow-up was necessary (Sanders *et al,* 2011).

Drug interactions: Limited data do exist on pharmacokinetic interactions between antiretroviral therapy and antimalarial drugs. Potential interactions between combination of amodiaquine plus artesunate (AQ/AS), & HIV nonnucleoside showed reverse transcriptase inhibitor (NNRTI), efavirenz that was prematurely discontinued after the first two patients developed severe asymptomatic hepatotoxicity more than one month after the study completion (German *et al,* 2007). The aminotransferases must be monitored in the patients given drugs include these medications as insignificant drug-drug interactions were expected between antimalarial drugs, and maraviroc or raltegravir due tometabolizing enzymes and drug transport proteins (Pham and Flexner, 2011)

Effect of ART on *Plasmodium* species: In vitro and in vivo showed that HIV protease inhibitors (PIs) exert antiplasmodial effects on erythrocytic-stage parasites (Parikh *et al,* 2005). In the rodent parasite model, lopinavir and saquinavir inhibited the pre-erythrocytic stage of parasite development (Hobbs *et al,* 2009). Therapeutic interventions were directed at the pre-erythrocytic (intrahepatic) stage with the advantage of inhibiting the parasite while in low numbers and before infecting bloodstream (Lek-Uthai *et al,* 2008).

In general, first-line antiretroviral therapy (ART) regimens in malaria-endemic areas always include nonnucleoside reverse transcriptase inhibitors rather than the PIs. WHO (2015) recommended combination ART for all pregnant and breastfeeding women, with efavirenz-based ART as a first-line regimen and lopinavir-ritonavir as the alternative. To examine if lopinavirriton-avir give an additional antimalarial benefit, an open-label randomized controlled study in Uganda compared lopinavir-ritonavir with efavirenz-based regimens to prevent placental malaria among 391 HIV-infected pregnant women didn't show difference in placental malaria or birth outcomes, including low birth-weight, neonatal death or preterm delivery, the incidence of maternal malaria, or prevalence of asymptomatic parasitemia (Natureeba *et al,* 2014). In Uganda, recurrent malaria risk for childrden with HIV treated with artemether-lumefantrine was lower among those given lopinavir-ritonavir–based regimens than those given NNRTI-based regimens (28 versus 54%; hazard ratio 0.41; 95% CI 0.22-0.76). Treatment with lopinavir-ritonavir was associated with higher serum lumefantrine levels on 7^{th} day showed a longer duration of antimalarial protection with a greater number of serious adverse events in the lopinavirritonavir group (5.6 versus 2.3%), but more safety studies were needed (Achan *et al,* 2012).

Malaria prophylaxis: Trimethoprim-sulfamethoxazole prophylaxis reduced morbidity and mortality in HIV adults and children patients by preventing bacterial infections, diarrhoea, malaria, and *Pneumocystis jirovecii* pneumonia, despite high levels of microbial resistance (Church *et al,* 2015). Besides, this therapy is an inexpensive and broad-spectrum anti-microbial drug widely available globally (Kärpänoja *et al,* 2008). Other interventions means for malaria prevention by bednets and improving immune by initiation of ART were effective (Mermin *et al,* 2006).

Morbidity and mortality effect: Prophylaxis with trimethoprim-sulfamethoxazole (cotrimoxazole) decreases the rates of morbidity and mortality from malaria in HIV-infected adults and children, even in the high resistance rate areas (Kamya *et al,* 2007). Among more than 3300 patients began ART in Uganda or Zimbabwe, where co-administration of cotrimoxazole there was highly variations (Walker *et al,* 2010). Those received prophylaxis had a 26% risk reduction of a new malaria episode over followed up for 22 months. But in Uganda, trimethoprim-sulfamethoxazole prophylaxis was associated with a 46% reduction in mortality and lower malaria, diarrhea, and hospital admissions in 509 HIV-infected patients followed for two years as compared to 1522 HIV-uninfected household controls (Andrews *et al,* 2006). Also, Rungoe *et al.* (2010) in Denmark reported that children received SMX-TMP prophylaxis during induction therapy showed fewer febrile episodes, fewer days with fever needed IV antibiotic treatment, and fewer bacteremial episodes. All these interventions in the sub-Sahara were introduced sequentially after a five-month period of observation alone; ART was specifically given to patients with a CD4 count <250 cells/microL (Govindasamy *et al,* 2015). But, without harm in resource-rich countries, trimethoprrim-sulfamethoxazole discontinuation in patients attained a CD4+ T cell >200 cells/microL showed a significant negative clinical impact in malarial endemic areas. A randomized control study showed that the discontinuing safety of trimethoprim sulfamethoxazole in 836 Ugandan patients halted by Data Safety Monitoring Board after 116 days (Campbell *et al,* 2012). Kasirye *et al.* (2017) reported that the patients assigned to the discontinuation arm compared with those who continued prophylaxis had significant increased malaria rates (12% versus 0.4%) & diarrhea (25% versus 14%).

Effect on drug resistance: Trimethoprim-sulfamethoxazole wide spread use in the malaria-endemic countries as opportunistic infection prophylaxis raises the concern of exacerbating antifolate drug-resistant malaria, as in vitro malaria models antifolate resistance caused quickly under drug pressure and development of sulfadoxine-pyrimethamine resistance in endemic areas gave 99.5% prophylaxis efficacy prevented clinical malaria; no increase in parasite antifolate resistance mutations (Juma *et al,* 2019). Due to the large impact on HIV-related mortality and malaria morbidity and mortality, trimethoprim-sulfamethoxazole use prophylaxis must continue in patients with CD4+ T cell counts < 200cells/microL or in cases with the recurrent malaria history (Thera *et al,* 2005). To address the effect of drug pressure on developing parasitic antifolate drug resistance mutations, a randomized open-label study pr oved trimethoprim-sulfamethoxazole prophylxis for malaria (Salah *et al,* 2019).

Prevention: Use of insecticide-treated mosquito nets for the prevention of malaria in endemic areas, such as Africa, is one of the main goals of the "Roll Back Malaria" partnership but, the availability scaling-up of such netting, particularly for children and pregnant women, was slow (Miller *et al,* 2007). El-Tawdy *et al.* (2018) in Egypt reported that major tools for malaria prevention in pregnant women includes chemoprophylaxis and mosquito avoidance, advised to defer travel to areas where risk of malaria is high until after delivery, if feasible. Also, pregnant women in areas of medium and high malaria transmission, three doses of IPTp with sulfadoxine pyrimethamine rather than

two doses and sulfadoxine pyrimethamine was given at each scheduled antenatal care visit in the 2nd and 3rd trimesters (at 24 to 26 weeks, at 32 weeks, and at 36 to 38 weeks).

In Egypt, malaria risk existed in El Fayoum Governorate focal rural areas, and in the Nile River Delta, along the Suez Canal, the Northern Red Sea coast, part of Southern Egypt as rural areas near Aswan (Soliman and Aufy, 1989). Also, Glick (1992) reported scattered oases (Siwa Oasis and El-Gara Oasis). Cope *et al.* (1995) reported *Anopheles sergentii* as a new record of the malaria vector in the southern Nile Valley. Mikhail *et al.* (2009) mentioned the presence of *Anopheles sergentii, An. pharoensis*, *An. multicolor, An. detali, An. algeriensis, An. tenebrousus, An. superp ictus, An. tarkhadi, An. hispaniola, An. rhodesiensis*, *An. stephensi,* & *An. coustani.* Wassim (2014) reported by the secondary structure and sequence of ITS2-rDNA *Anopheles pharoensis* proved to be the important vector of malaria in Egypt.

Another risk factor was the environmental changes existed by the water-sources develped in the two projects as El Salam Canal (Hassan *et al*, 2003), and Toshka (Shoukry and Morsy, 2011), where El Bahnasawy *et al*. (2011) recorded *An. multicolor, An. sergentii* and *An. algeriensis* in Toshka. Also, El Bahnasawy *et al*. (2014) added that the endemicity of chloroquine resistant *P. falciparum* on the Egyptian-Sudanese border pave the way for its transmission mainly among African travelers and immigrants to Egypt.

El-Bahnasawy *et al.* (2010) in a military fever hospital identified 36 malaria patients 20 were recruited from Peace Keeping Mission Forces in Africa and 16 were from Cairo (37.4%), El-Sharkia (18.7%) and El-Fayoum (12.5%). *P. vivax* was among locally acquired patients (81.25%), and *P. falciparum* among patients back from Africa especially Sudan (100%), and endogenous (6.2%) from El Fayoum. Mohamed *et al*. (2014) in Zagazig found 18/300 (6%) malaria among travelers back either Egyptians or foreigners within two months of their arrival.

Dahesh and Mostafa (2015) in El-Fayoum Governorate reported malaria in 14/2044 persons (0.68%) of whom three had *P. falciparum* and six had *P. vivax*. All positive patients were Sudan males and most of them were merchants with trade activities in Sudan. The high imported cases were Abu Shanap, Aboxa (Ballona) and Kafr Aboud (Abshaway Center), but without Anopheline spp. but in Al Nazla *A. sergeni* and A. *multicolor* larvae were detected neither imported case nor traveler to Sudan. They added that Kafr Fazara greatly changed by using fine sand instead of clay in manufacturing red brick for prevention excavation of land.

Kandeel *et al.* (2016) reported on May-June 2014 an outbreak of 20 *P. vivax* and 1 *P. falciparum* cases by house-to-house surveillance visits, after several years of non indigenous cases. They launched emergency response for early cases detection, treatment, control of *Anopheles*, and public health education with inter-sectorial collaboration. All the malaria patients were from El-Sheikh Mostafa village, Edfu City, Aswan Governorate.

Al-Agroudi *et al.* (2018) by reviewing Almaza Fever Hospital cases declared that no true active malaria transmission, but imported cases and of *Anopheles* vectors abundaare a significant health problem.

Elgohary and Ibrahim (2022) reported a risky case of UN Peace keeping Forces back to Egypt with malaria complicated with splenic infarction. He was cured after splenectomy with condensed *falciparum* malaria treatment as well as platelets, human albumin and packed RBCs.

Conclusion and Recommendations

The world is currently facing a process of climate change, which may adversely impact human health in many different ways. Sub-Sahara Africa region shoulders the heaviest burden, with two countries; the Democratic Republic of Congo and Nigeria, which accounted for > 35% of the world malaria deaths. But, HIV and malaria co-infection most frequently occurs with *P. falciparum* due to ge-

ographic overlap distribution between malignant malaria and HIV infected patients.

The malaria co-infection is associated with a transient increase in HIV RNA. If viral loads are being used to monitor the response to antiretroviral therapy (ART), testing must be delayed for approximately two months if the patient shows a recent malaria infection.

HIV infection is associated with increased susceptibility, higher parasitemia, and the increased risk for recurrent malaria infection, especially in patients with CD4 counts<200 cells/microL.

Trimethoprim sulfamethoxazole (160mg trimethoprim & 800mg sulfamethoxazole daily), and the use of bed nets in HIV-infected patients with CD4 counts <200 cells/microL who are living in malaria-endemic areas was recommended (Grade 2A). Also, trimethoprim-sulfamethoxazole may be considered in patients with higher CD4+ T cell counts with a history of re-current malaria. Decision to institute trimethoprim-sulfamethoxazole prophylaxis for malaria patients with CD4 >200 depends on transmission intensity that varies geographically and seasonally.

Dual infection with HIV and malaria during pregnancy leads to adverse maternal and perinatal outcomes. A monthly sulfadoxine-pyrimethamine (1500mg sulfadoxine & 75 mg pyrimethamine) during pregnancy must start in the second trimester in moderate and high transmission areas were recommended (Grade 1B). HIV-infected patients on daily cotrimoxazole don't need to take sulfadoxine-pyrimethamine.

HIV testing in adults who present with clinical malaria in a region where natural immunity normally develops was suggested. But, an accurate diagnosis of malaria in the context of HIV co-infection is very difficult in endemic areas as an HIV-infected patient may have fever unrelated to malaria, even in a setting of a positive blood smear with low-level parasitemia may lead to a misdiagnosis and inappropriate therapy.

Treatment of malaria in HIV-infected patients is similar to treatment of HIV-uninfected ones. However, the incidence of new infections may be higher and recrudescence of drug resistant parasites may also occur, so careful follow-up is necessary.

Antiretroviral therapy decreases incidence of malaria and consequently particular attention should be paid to give ART to treatment the individuals living in the malaria-endemic areas, if resources are available.

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Recommendations for Egypt

Egypt is the third country to be awarded a malaria-free certification in the WHO Eastern Mediterranean Region followed by UAE, and Morocco, and the first since 2010. Globally, a total of 44 countries and one territory have reached this milestone (WHO, 2024).

Malaria is the most common cause of the splenomegaly and spleen rupture, albeit variably, a landmark of the malaria infection.

Malaria must be considered in febrile patients and/or those coming back from known endemic African countries; they show usually a normal WBC and few parasitemia. Bone marrow biopsy is a must for these patients. Combined therapy is recommended to treat them.

Anopheles (all arthropod-vectors) distribution and control plans must be re-evaluated.

Blood donors must not have any history of traveling to HIV and/or a malaria endemic area.

Travelers and/or employees to endemic areas must have feasible preventive measures, and chemoprophylaxis. When back from to must they should be clinical and laboratory examined for malaria/HIV.

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