



Malaria, sickle cell disease, HIV, and co-trimoxazole prophylaxis: An observational study



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ARTICLE INFO

Article history:

Received 19 September 2017

Received in revised form 27 January 2018

Accepted 29 January 2018

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:

Malaria

HIV

Sickle cell disease

Co-trimoxazole

Ghana

ABSTRACT

Objectives: This observational study recorded the malaria and sickle cell disease (SCD) profile of people living with HIV/AIDS (PLHA) and determined whether prophylactic co-trimoxazole (CTX) and the haemoglobin S (Hb S) allele influenced malaria episodes.

Methods: Sickling status, malaria episodes, and HIV type, as well as other data, were extracted retrospectively from the clinical records of 1001 patients attending the antiretroviral therapy clinic at Ridge Regional Hospital in Accra, Ghana between 2010 and 2015. Finger-prick capillary blood of returning patients ($n = 501$) was tested for the haemoglobin (Hb) level and malaria, after information on malaria prevention methods was obtained through the administration of a questionnaire.

Results: The use of insecticide-treated mosquito nets was low (22.8%). CTX prophylaxis showed no significant influence on the overall number of malaria episodes from 2010 to 2015; however, it did show a statistically significant relationship ($p = 0.026$) with the time elapsed since the last malaria episode. Even though 19% of participants possessed Hb S, it had no influence on malaria episodes.

Conclusions: Hb S did not influence malaria in PLHA. Further studies in Hb SS and Hb SC are needed, as there are suggestions of increased frequency and severity of malaria. The impact of CTX prophylaxis on this cohort will be insightful.

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1. Introduction

HIV impacts heavily on population health in Sub-Saharan Africa (UNAIDS, 2017). Out of the 5000 new infections each day, 64% occur in Sub-Saharan Africa (UNAIDS, 2017). The increase in availability of antiretroviral therapy (ART) has transformed HIV into a chronic disease that can be managed well, and this has been the major reason for the 48% decline in HIV-related deaths (from 1.9 million (1.7–2.2 million) in 2005 to 1 million (830 000–1.2 million) in 2016) (UNAIDS, 2017).

In Ghana, support and treatment for people living with HIV was introduced in 2003, in spite of the fact that the first case was reported in 1986 (NationalAidsControlProgram, 2010). The current triple ART is routinely supplemented with drugs to primarily or

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<https://doi.org/10.1016/j.ijid.2018.01.031>

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secondarily prevent opportunistic infections (NationalAidsControlProgram, 2010). Co-trimoxazole (CTX), which is a fixed-dose combination of the antimicrobials sulfamethoxazole and trimethoprim, is used to treat or prevent opportunistic infections (NationalAidsControlProgram, 2010; WHO, 2013; CDC-NIH, 2016). The added benefit of CTX prophylaxis in reducing the frequency of malaria has been established (Xavier et al., 1999; Jonathan et al., 2006). It has also been shown to be effective in treating chloroquine-resistant falciparum malaria in HIV-infected people (Manyando et al., 2013).

Sickle cell disease (SCD) is also common in Sub-Saharan Africa (Grosse et al., 2011). Across the continent, the SCD carrier state (Hb AS) prevalence is 25–30% (Bernadette and Matthew, 2008). In SCD, allelomorphic genes that are linked to haemoglobin (Hb) formation are abnormal and cause red blood cells to sickle when deoxygenated; the disease also causes endothelial dysfunction (Hebbel et al., 2004). Sickling of the red blood cells causes an increase in blood viscosity, which results in stasis and then hypoxia (Konotey-Ahulu, 1974). Infarction of the tissues occurs, and a vicious cycle of stasis and hypoxia is set into motion (Konotey-Ahulu, 1974). This results in an inflammatory response and the release of neuropeptides (Olatundun, 2010), thereby producing excruciating pain of the entire body, especially the joints (Konotey-Ahulu, 1974). This is known as sickle cell disease crisis and may be brought on by anything from being caught in the rain to infectious diseases including urinary tract infection, diarrhoea, and malaria (Konotey-Ahulu, 1974; Olatundun, 2010; Sanjay et al., 2015).

Co-endemicity of malaria, sickle cell disease, and HIV may result in interactions between them on the population level and in individual patients. Interactions between HIV and SCD have been documented (Owusu et al., 2014); SCD has been shown to reduce the progression of HIV to AIDS. Some cases of ART-induced sickling crises have been reported (Owusu et al., 2014; Lowe Selwyn et al., 2002). Studies that have looked at interactions between malaria and HIV have shown the effect of one disease on the progression of the other (Abu-Raddad Laith et al., 2006; Andrea et al., 2004). For instance, research in Kenya showed that co-infection may have contributed to the increase in HIV and malaria episodes between 1980 and 2007 (Abu-Raddad Laith et al., 2006). Other studies that have looked at drug interactions have found chloroquine to independently reduce the HIV-1 and HIV-2 viral load, and in combination with protease inhibitors to synergistically reduce the viral load (Andrea et al., 2004). However, mefloquine has been associated with an increased viral load and hence increased HIV transmission from mother to child; the explanation for this remains unclear (Raquel et al., 2014). Co-infection with other parasites such as helminths has been observed to complicate disease progression of both HIV and malaria (Emil et al., 2013; Emil et al., 2012). However, information on malaria, HIV, and SCD interactions is scarce.

The aim of this study was to look at malaria and SCD profiles of people living with HIV/AIDS (PLHA) who attended the ART clinic at Ridge Regional Hospital in Accra, Ghana and to determine whether the prophylactic intake of CTX influenced the frequency of malaria episodes, as well as the time elapsed from the last malaria episode over a 5-year period. The relationship between HIV, Hb S, and malaria was also determined.

2. Methods

2.1. Study site and population

Ridge Regional Hospital (now known as the Greater Accra Regional Hospital) is one of the four government hospitals in the Accra metropolis of the Greater Accra region of Ghana. This study took place before the ongoing upgrade of the hospital, when it was

a 191-bed hospital (Max et al., 2010). It is located in Osu-Klottey sub-metro on latitude 5.56268 and longitude -0.19897. It has an ART clinic that caters for the health needs of HIV patients. In line with the national policy, it also provides free access to antiretroviral (ARV) drugs, patient care, and prophylaxis (NationalAidsControlProgram, 2010).

2.2. Participant selection and study design

Patient file registration numbers of those who had attended the ART clinic of the Ridge Hospital for a minimum of 5 years were listed chronologically, and a random selection of files was extracted. The formula used for sample size calculation for the retrospective study was: $n = t^2 \times p(1 - p)/m^2$, where the standard value was 1.96 for the confidence level (t) at 95% and 0.05 for margin of error (m). The estimated malaria prevalence in Ghana (p) of 27.5% (MOH, 2014) was used. A minimum sample size of 306 was calculated to be required. However, taking into consideration the possibility that some patients may have died, relocated, or defaulted and that this would reduce those available for the prospective study, the minimum sample size was increased to 900. Retrospective data from the years 2010–2015 were extracted from the files. All HIV-positive patients at the clinic were included regardless of whether they were on ARVs or not.

During the time of the study in Ghana, ARV was initiated when the CD4+ cell count was less than 350 cells/ml and/or when patient was symptomatic with HIV infection at World Health Organization (WHO) clinical stage 3 or 4 (NationalAidsControlProgram, 2010). Pregnant women were put on ARVs at 14 weeks to prevent mother-to-child transmission, even if their CD4+ cell count was higher than 350 cells/ml. In general, CTX prophylaxis was also initiated regardless of CD4+ cell count or WHO stage, in accordance with WHO guidelines for malaria endemic areas at the time (WHO, 2016).

Data obtained from the medical history included HIV type, malaria episodes in the 5-year period, SCD status, CD4+ count (most recent), and whether the patient was on CTX prophylaxis. Demographic characteristics of the patients such as age, sex, and level of education were also recorded.

Out of the folders randomly selected for the retrospective study, patients who returned to the clinic during the data collection period (May 2014 to April 2015) were recruited to take part in the cross-sectional study of malaria screening and haemoglobin testing. Patients of all ages were included. Written informed consent was obtained from study participants. Information pertaining to malaria episodes and prevention methods was obtained through the administration of a questionnaire; this included questions on what the participant used to prevent mosquito bites, whether the participant had taken any antimalarials in the last 3 months, and when the participant last had malaria. Finger-prick capillary blood was dropped on a First Response[®] Malaria Ag *P. falciparum* (HRP2) malaria rapid diagnostic test kit (RDT). Patients who tested positive were referred to the attending physician for treatment. A few drops of blood were dropped on a Mission[®] Plus Hb haemoglobin testing system (AconLabs) to determine the participant's Hb level. Hb values were categorized as normal (>13 g/dl), mild anaemia (9.6–13 g/dl), moderate anaemia (8.1–9.5 g/dl), or severe anaemia (≤ 8 g/dl). Patients with an axillary temperature above 37.5 °C, reporting with myalgia, headache, and vomiting and other symptoms suggestive of malaria, were recorded as having malaria symptoms.

2.3. Statistical analysis

Data were entered into Microsoft Office Excel 2010 (Microsoft Corporation, USA), cleaned, and subsequently analysed statistically

using STATA 14 (StataCorp., USA). Odds ratios (OR) (with 95% confidence intervals (95% CI)) from logistic regression were used to assess possible associations between CTX and malaria episodes, as well as between Hb S and malaria, with adjustment for age, sex, last CD4+ cell count, and duration of ARVs. Primary outcomes were the frequency of malaria and the time from last malaria episode. Other outcomes included sickling status and anaemia status. A two-sided *p*-value of ≤ 0.05 was considered as statistically significant.

3. Results

Retrospectively, the medical histories of 1001 patients who attended the ART clinic were obtained from the files. Out of that study population, blood samples of 568 patients who returned to the clinic during the period of data collection were screened.

However, 67 were excluded from the study for reasons including inconclusive RDT results ($n=9$), no Hb level recorded ($n=23$), and no record or recollection of last malaria episode ($n=35$). Thus, a total of 501 results were included.

Frequencies and averages were significantly different between the two groups. The mean (\pm standard deviation) age of the 1001 participants was 38 (± 12) years, whilst this was 37 (± 13) years for the 501 patients (Table 1). The mean last CD4+ cell count was 311.1 (range 3–1507) cells/ml for the retrospective subjects and 622 (range 9–2107) cells/ml for the cross-sectional participants. The ratio of female to male participants in the retrospective subjects was 2.6:1 (725:276) and in those who returned to the clinic during the study period was 2.8:1 (376:135). The Hb S allele was present in 190 (19%) of the retrospective subjects and 25 (5%) of those who returned. Information from the patient files indicated that 163 (16.3%) of the retrospective subjects had both HIV-1 and -2; of

Table 1

Socio-demographic characteristics and patient history from the hospital files: retrospective and cross-sectional study (returning) patients

	Retrospective (<i>n</i> = 1001)	Cross-sectional (<i>n</i> = 501)	<i>p</i> -Value
Mean age (SD), years	38 (± 12)	37 (± 13)	0.02 ^a
Mean CD4+ cell count (range) (most recent), cells/ml	311.1 (3–1507)	622 (9–2107)	<0.05 ^a
Sex, <i>n</i> (%)			<0.05 ^b
Female	725 (72.4%)	376 (75%)	
Male	276 (27.6%)	135 (25%)	
Education, <i>n</i> (%)			<0.05 ^b
JSS-MSLC	254 (25.4%)	97 (19.4%)	
Sec/Tech	363 (36.2%)	247 (49.3%)	
Tertiary	141 (14.1%)	117 (23.3%)	
Primary	138 (13.8%)	25 (5%)	
No formal education	105 (10.5%)	15 (3%)	
Marital status, <i>n</i> (%)			<0.05 ^b
Single	444 (44.3%)	179 (35.7%)	
Married	300 (30%)	108 (21.6%)	
Divorced	105 (10.5%)	103 (20.6%)	
Cohabiting	67 (6.7%)	50 (10%)	
Child	41 (4.1%)	35 (7%)	
Widow/widower	34 (3.4%)	20 (4%)	
Separated	10 (1%)	6 (1.2%)	
Diabetes status, <i>n</i> (%) ^d			<0.05 ^b
Positive	45 (4.5%)	9 (1.8%)	
Negative	956 (95.5%)	492 (98.2%)	
Malaria episodes (2010–2015), <i>n</i> (%)			<0.05 ^c
0	515 (51.4%)	287 (57.3%)	
1	297 (29.7%)	98 (19.6%)	
2	154 (15.4%)	113 (22.6%)	
>2	35 (3.5%)	3 (0.6%)	
Duration of ARV (years), <i>n</i> (%)			<0.05 ^b
<1	192 (19.2%)	82 (16.4%)	
1–5	276 (27.6%)	197 (39.3%)	
6–10	359 (35.9%)	124 (24.7%)	
>10	150 (15%)	29 (5.8%)	
ARV-naïve	24 (2.4%)	69 (13.8%)	
Co-trimoxazole prophylaxis, <i>n</i> (%)			<0.05 ^b
Yes	766 (76.5%)	491 (98%)	
No	235 (23.5%)	10 (2%)	
Sickling status, <i>n</i> (%) ^d			<0.05 ^c
AA	744 (74.3%)	470 (93.9%)	
AS	155 (15.5%)	19 (3.8%)	
AC	67 (6.7%)	6 (1.2%)	
SC	17 (1.7%)	5 (1%)	
SS	18 (1.8%)	1 (0.2%)	
HIV type, <i>n</i> (%) ^d			<0.05 ^b
1	608 (60.7%)	251 (50.1%)	
1 and 2	163 (16.3%)	94 (18.8%)	
2	230 (23%)	156 (31.1%)	

SD, standard deviation; JSS-MSLC, Junior Secondary School-Middle School Leaver's Certificate; Sec/Tech, Secondary/Technical; ARV, antiretrovirals.

^a *t*-test.

^b Chi-square test.

^c Fisher's exact test.

^d Data obtained from the medical records.

those who returned, 94 (18.8%) had both HIV-1 and -2. As many as 230 (23%) retrospective participants and 156 (31.1%) returning subjects had the HIV-2 virus.

Amongst the returning participants, even though many (240; 47.9%) reported symptoms suggestive of malaria as indicated in the Methods section, only 40 (8%) tested positive for malaria (Table 2); the rest might have had disease of non-malaria origin. For the 501 participants, the questionnaire showed that 142 (28.3%) had had malaria less than 3 months prior to the study, yet 178 (35.5%) had taken antimalarials during that period. Only 32 (6.4%) of the participants had a normal Hb level; the rest had varying degrees of anaemia.

Logistic regression analysis between CTX prophylaxis and the most recent laboratory-confirmed malaria episode in returning participants showed a significant association (OR 1.17, 95% CI 1.03–1.97; $p=0.03$) (Table 3). No association existed between the frequency of confirmed malaria episodes in the last 5 years and CTX prophylaxis. Likewise, no association was observed between HIV and having SCD and parasitaemia in a multivariate model adjusting for age, sex, and last CD4+ count (OR 0.81, 95% CI 0.57–1.13) (Table 4).

4. Discussion

This study retrospectively determined the malaria and SCD profiles of 1001 PLHA at the ART clinic in Ridge Regional Hospital, Accra between 2010 and 2015. CTX prophylaxis did not seem to influence the frequency of malaria episodes in the 5-year period. However, amongst the 501 participants who returned during the cross-sectional study, CTX significantly increased the time elapsed since the last confirmed malaria episode. Hb S was not associated with an increased likelihood of having parasitaemia.

Most (91.8%) of the patients living with HIV conscientiously made the effort to protect themselves from mosquito bites by using long-lasting insecticide-treated nets (LLINs), a mosquito coil, and

mosquito repellent spray. However, LLIN usage was low (22.8%). The use of a mosquito coil and mosquito spray in this study was similar to that reported in studies performed in other areas of Ghana (Owusu et al., 2016; Hogarh et al., 2016). This is reflective of the preference and popularity of these products on the Ghanaian market. The mosquito coil and spray have not been shown to significantly reduce malaria incidence (Hogarh et al., 2016). In fact, they have been associated with acute respiratory infections (ARI) (Hogarh et al., 2016); yet, they have been observed to be preponderant in many communities in Ghana (Owusu et al., 2016; Hogarh et al., 2016; GHS, 2013). In spite of the fact that PLHA take action to protect themselves, there is the need for intensified counselling to encourage them to use scientifically proven methods like LLINs.

Prophylactic CTX in the returning subjects was observed to be associated with a lower likelihood of malaria episodes in recent times. This concurs with published work that has shown CTX prophylaxis, in controlling parasitic infections, to provide added benefit in terms of protecting against malaria (Manyando et al., 2013; Reithinger et al., 2009). However, the number of returning participants not on CTX prophylaxis was low; this may have influenced observations. Yet this was beyond the authors' control, since the guidelines in the country are to administer CTX prophylaxis regardless of CD4+ cell count or WHO stage (WHO, 2016), hence the observational nature of this study. In contrast, the results of the retrospective study did not show any statistically significant relationship between CTX prophylaxis and the frequency of confirmed malaria episodes in the past 5 years. Many studies conducted in Sub-Saharan Africa have shown that CTX significantly reduces the frequency of malaria infections (Jonathan et al., 2006; Manyando et al., 2013; Sophie et al., 2011), with the exception of one study performed in Ivory Coast, where CTX did not provide protection from opportunistic infections (Sophie et al., 2011). However, this previous observation was before the initiation of ARV when cellular immunity of the HIV-infected patients was poor (Sophie et al., 2011). In the present study, with the exception of 24 participants who were ARV-naïve, all other participants were on ARVs. Another possible explanation might be the presence of the dihydrofolate reductase (dhfr)/dihydropteroate synthetase (dhps) quintuple mutant in this population. This mutant has been suggested to affect the efficacy of CTX prophylaxis and its protection against malaria (Manyando et al., 2013). However, its presence in the study population was not investigated at this time.

Generally, the Hb S allele was present in 19% of study participants. This is similar to the average of 18.8% for Ghanaians observed previously (Grosse et al., 2011). The genotype that causes sickle cell anaemia, Hb SS, was not common in this study (1.8%). Hb SS has been suggested to increase the severity and frequency of malaria (Lucio, 2012). In this study Hb S in PLHA did not significantly influence malaria episodes; perhaps an assessment of a larger cohort of participants with Hb SS might have yielded observable results.

This article has provided insightful information on the intricacies of CTX prophylaxis and malaria in PLHA in a major health centre in the capital of Ghana, a malaria hyper-endemic country. It has looked at the possible influence of SCD on the ability of CTX to reduce malaria infections in PLHA and shown that it may not complicate the situation. This study is, however, subject to certain limitations. Potential confounders such as participant compliance with CTX prophylaxis could not be determined and this might have influenced malaria infection and the detection of any pattern. Another limitation was the unavailability of current viral loads and CD4+ cell counts of participants at each visit. This might have provided information on the immune status of the participants and also influenced susceptibility to malaria. Also a logistic regression analysis was done on participants with the Hb S

Table 2
Malaria prevention practices, parasitaemia, and haemoglobin levels in the cross-sectional study ($n=501$)

Variable	Frequency (%)
Malaria prevention practice	
Prevention of mosquito bites	
Mosquito coil	107 (21.4%)
ITN	114 (22.8%)
Mosquito spray	175 (34.8%)
Combination of all three	64 (12.8%)
None	41 (8.2%)
Antimalarials within the last 3 months	
Yes	178 (35.5%)
No	323 (64.5%)
Malaria history	
Last malaria episode	
<3 months	142 (28.3%)
3–6 months	84 (16.8%)
7–12 months	92 (18.4%)
>12 months	170 (33.9%)
Don't remember	13 (2.6%)
Malaria symptoms	
Yes	240 (47.9%)
No	261 (52.1%)
Tests	
Malaria RDT	
Positive	40 (8%)
Negative	461 (92%)
Haemoglobin level (g/dl)	
≤8 (severe anaemia)	16 (3.2%)
8.1–9.5 (moderate anaemia)	20 (4%)
9.6–13.0 (mild anaemia)	433 (86.4%)
>13.0 (normal)	32 (6.4%)

ITN, insecticide-treated net; RDT, rapid diagnostic test.

Table 3

Association between malaria episodes and co-trimoxazole prophylaxis

Variable	No CTX prophylaxis	CTX prophylaxis	Crude OR (95% CI)	p-Value	Adjusted OR (95% CI) ^a	p-Value
Confirmed malaria episodes in past 5 years (n = 1001)	235 (23.5%)	766 (76.5%)	0.23 (0.21–1.43)	0.18	0.41 (0.13–1.95)	0.25
Most recently confirmed malaria episode (n = 501)	10 (2%)	491 (98%)	1.05 (0.9–1.65)	0.12	1.17 (1.03–1.97)	0.03

CTX, co-trimoxazole; OR, odds ratio; CI, confidence interval.

^a Adjusted for sex, age, antiretroviral duration, and last CD4+ cell count.**Table 4**

Association between haemoglobin S (in people living with HIV/AIDS) and parasitaemia in the cross-sectional study

Category	Malaria (n = 40)	Crude OR (95% CI)	p-Value	^a Adjusted OR (95% CI)	p-Value
HIV with Hb S	18 (45%)	0.75 (0.24–1.32)	0.98	0.81 (0.57–1.13)	0.91
HIV without Hb S	22 (55%)	1.02 (0.57–1.44)	0.46	1.14 (0.82–1.34)	0.21

Hb S, haemoglobin S; OR, odds ratio; CI, confidence interval.

^a Adjusted for sex, age, antiretroviral duration, and last CD4+ cell count.

allele generally; a more detailed analysis on a larger pool of Hb SS and Hb SC specifically might yield interesting findings, since they have been observed to be susceptible to frequent and severe malaria. Detailed cohort studies are encouraged to investigate the interplay between HIV, SCD, and malaria in this geographical area.

In conclusion, some studies prior to this one have underscored the importance of CTX in decreasing malaria in PLHA. This study showed the influence of CTX in PLHA in spite of their SCD status, which is prevalent in this geographical area. Further research should include close follow-up of the cohort for a number of years and also study the alternative perspective of sickle cell patients who visit the sickle cell clinic and have HIV, to shed more light on the intricacies of malaria, SCD, and HIV.

Author contributions

The study was conceived and designed by EDAO, MPG, and PM. CB, NSAC, EAN, MPG, and PM contributed to data collection and analysis. All authors contributed to data interpretation. The article was drafted by EDAO with critique and revision from MPG, PM, KKG, and CB. All authors contributed to and approved the final manuscript.

Acknowledgements

We are indebted to Deborah Dadzie (Head of the Pharmacy Unit, ART Clinic, Ridge Hospital, Accra, Ghana), the Medical Director (Ridge Hospital), and the Director (NACP) for giving their consent for this work to be done. The patients and staff of the Ridge Hospital ART Clinic are also very much appreciated.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval: In this research, all human studies were approved by the Ghana Health Service (GHS-ERC: 02/03/14) and were therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from each participant of the prospective study before commencement. For the retrospective study on secondary data, permission was sought and approval was obtained from the ethics committee to waive informed consent from each patient, since some of them may have died, relocated, or defaulted and may therefore have been unavailable. Moreover, only routinely recorded patient information was extracted from the folders. However, for participants recruited to take part in the prospective study, informed consent

was sought from them to access their health records for the retrospective study. Written permission was also sought from the Director of the National AIDS Control Program (NACP) and the Medical Director of Ridge Regional Hospital.

Conflict of interest: None.

References

- UNAIDS. UNAIDS Data 2017. 2017 Available at http://www.unaids.org/sites/default/files/media_asset/20170720_Data_book_2017_en.pdf. (Accessed 24 Jan 2018).
- NationalAidsControlProgram. Guidelines for Antiretroviral Therapy in Ghana. Ghana. 2010 Available at http://www.ghananids.gov.gh/gac1/pubs/Guidelines_for_Antiretroviral_Therapy_in_Ghana_2010_NACP.pdf. (Accessed 20 Jan 2018).
- WHO. The use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children. WHO Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection.; 2013 Available at: <http://www.who.int/hiv/pub/guidelines/arv2013/December2014-ARV-supplement-chap8.pdf%5Cn> <http://www.who.int/hiv/pub/guidelines/arv2013/en/> (Accessed May 10, 2016).
- CDC-NIH. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Inf. AIDSInfo. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oip.pdf (Accessed June 16, 2016).
- Xavier Anglaret, Geneviève Chêne, Alain Attia, Siaka Toure, Sylviane Lafont, Patrice Combe, et al. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Cote d'Ivoire: A randomised trial. *Lancet* 1999;353(9163):1463–8. doi:[http://dx.doi.org/10.1016/S0140-6736\(98\)07399-1](http://dx.doi.org/10.1016/S0140-6736(98)07399-1).
- Jonathan Mermin, Paul Ekwaru John, Liechty Cheryl A, Willy Were, Robert Downing, Ray Ransom, et al. Effect of co-trimoxazole prophylaxis, antiretroviral therapy, and insecticide-treated bednets on the frequency of malaria in HIV-1-infected adults in Uganda: a prospective cohort study. *Lancet* 2006;367(9518):1256–61. doi:[http://dx.doi.org/10.1016/S0140-6736\(06\)68541-3](http://dx.doi.org/10.1016/S0140-6736(06)68541-3).
- Manyando C, Njunju EM, D'Alessandro U, Van Geertruyden JP. Safety and efficacy of co-trimoxazole for treatment and prevention of Plasmodium falciparum malaria: a systematic review. *PLoS One* 2013;8(2):e56916. doi:<http://dx.doi.org/10.1371/journal.pone.0056916>.
- Grosse SD, Odamé Isaac, Atrash HK, Amendah DD, Piel FB, Williams TN. Sickle cell disease in Africa: a neglected cause of early childhood mortality. *Am J Prev Med* 2011;41(6 Suppl 4):S398–405. doi:<http://dx.doi.org/10.1016/j.amepre.2011.09.013>.
- Bernadette Modell, Matthew Darlison. Global epidemiology of haemoglobin disorders and derived service indicators. *Bull World Health Organ* 2008;2008(6):480–7. doi:<http://dx.doi.org/10.2471/BLT.06.036673>.
- Hebbel Robert P, Raymond Osarogiagbon, Dhananjay Kaul. The Endothelial Biology of Sickle Cell Disease: Inflammation and a Chronic Vasculopathy. *Microcirculation* 2004;11(2):129–51. doi:<http://dx.doi.org/10.1080/10739680490278402>.
- Konotey-Ahulu FID. The Sickle Cell Diseases Clinical Manifestations. *Arch Intern Med* 1974;133(4):538–43.
- Olatundun Ilesanmi Oluwatoyin. Pathological basis of symptoms and crises in sickle cell disorder: implications for counseling and psychotherapy. *Hematol Rep* 2010;2(1):e2. doi:<http://dx.doi.org/10.4081/hr.2010.e2>.
- Sanjay Tewari, Valentine Brousse, Piel Frédéric B, Stephan Menzel, Rees David C. Environmental determinants of severity in sickle cell disease. *Haematologica* 2015;100(9):1108–16. doi:<http://dx.doi.org/10.3324/haematol.2014.120030>.
- Owusu EDA, Visser Benjamin J, Nagel Ingeborg M, Mens Petra F, Grobusch Martin P. The Interaction Between Sickle Cell Disease and HIV Infection: A Systematic

- Review. Clin Infect Dis 2014;. doi:<http://dx.doi.org/10.1093/cid/ciu832> pii: ciu83.
- Lowe Selwyn H, Prins Jan M, Johannes van der Lelie, Lange Joep MA. Does highly active antiretroviral therapy induce sickle cell crises?. AIDS 2002;16(11):1572–4.
- Abu-Raddad Laith J, Padmaja Patnaik, Kublin James G. Dual infection with HIV and malaria fuels the spread of both diseases in sub-Saharan Africa. Science 2006;314(5805):1603–6. doi:<http://dx.doi.org/10.1126/science.1132338>.
- Andrea Savarino, Lucia Mothanje B, Elena Rastrelli, Sergio Rutella, Caterina Golotta, Emmanuela Morra, et al. Anti-HIV Effects of Chloroquine: Inhibition of Viral Particle Glycosylation and Synergism with Protease Inhibitors. J Acquir Immune Defic Syndr 2004;35(3):223–32.
- Raquel Gonzalez, Meghna Desai, Eusebio Macete, Peter Ouma, Kakolwa Mwaka A, Salim Abdulla, et al. Intermittent Preventive Treatment of Malaria in Pregnancy with Mefloquine in HIV-Infected Women Receiving Cotrimoxazole Prophylaxis: A Multicenter Randomized Placebo-Controlled Trial. PLoS Med 2014;11(9). doi:<http://dx.doi.org/10.1371/journal.pmed.1001735>.
- Emil Ivan, Crowther Nigel J, Eugene Mutimura, Obado Osuwat Lawrence, Saskia Janssen, Grobusch Martin P. Helminthic Infections Rates and Malaria in HIV-Infected Pregnant Women on Anti-Retroviral Therapy in Rwanda. PLoS Negl Trop Dis 2013;7(8):1–9. doi:<http://dx.doi.org/10.1371/journal.pntd.0002380>.
- Emil Ivan, Crowther Nigel J, Rucogoza Aniceth T, Osuwat Lawrence O, Elizaphane Munyazesa, Eugene Mutimura, et al. Malaria and helminthic co-infection among HIV-positive pregnant women: Prevalence and effects of antiretroviral therapy. Acta Trop 2012;124(3):179–84. doi:<http://dx.doi.org/10.1016/j.acta-tropica.2012.08.004>.
- Meis Max, Lipke Virginia, Holmes William. Tuberculosis Infection Prevention and Control in Ghana. Available at: http://www.tbghana.gov.gh/sites/default/files/Trip_Report_TB_CAP_Ghana.Meis_Lipke_Girma_Holmes.April_2010.pdf (Accessed November 13, 2016).
- MOH. Anti-malaria drug policy for Ghana. 2014.
- WHO. Clinical guidelines: managing common co-infections and co-morbidities. Chapter 5. Available at: <http://www.who.int/hiv/pub/arv/chapter5.pdf?ua=1> (Accessed July 4, 2017).
- Owusu Ewurama DA, Vincent Buabeng, Samuel Dadzie, Brown Charles A, Grobusch Martin P, Petra Mens. Characteristics of asymptomatic Plasmodium spp. parasitaemia in Kwahu-Mpraeso, a malaria endemic mountainous district in Ghana, West Africa. Malar J 2016;15(1):38. doi:<http://dx.doi.org/10.1186/s12936-015-1066-8>.
- Hogarh Jonathan N, Philip Antwi-Agyei, Kwasi Obiri-Danso. Application of mosquito repellent coils and associated self-reported health issues in Ghana. Malar J 2016;15(1):61. doi:<http://dx.doi.org/10.1186/s12936-016-1126-8>.
- GHS. Report of the Ghana Urban Malaria Study. Available at: <http://www.jsi.com/Independent/Docs/GhanaUrbanMalariaStudy.pdf> (Accessed September 27, 2016).
- Reithinger R, Kampya MR, Whitty CJM, Dorsey G, Vermund SH. Interaction of malaria and HIV in Africa. Br Med J 2009;338:b2141. doi:<http://dx.doi.org/10.1136/bmj.b2223>.
- Sophie Desmonde, Patrick Coffie, Edmond Aka, Clarisse Amani-Bosse, Eugène Messou, François Dabis, et al. Severe morbidity and mortality in untreated HIV-infected children in a paediatric care programme in Abidjan, Côte d'Ivoire, 2004–2009. BMC Infect Dis 2011;11:182. doi:<http://dx.doi.org/10.1186/1471-2334-11-182>.
- Lucio Luzzatto. Sickle cell anaemia and malaria. Mediterr J Hematol Infect Dis 2012;4(1):e2012065. doi:<http://dx.doi.org/10.4084/MJHID.2012.065>.