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Review article

Effects of malaria/helminthic coinfections on cervical cancer progression among sub Saharan African women on highly active antiretroviral therapy: A scoping review

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ABSTRACT

In Africa, the HIV prevalence in rural areas has begun to reach levels estimated within urban settings, where women are also more at risk for both malaria and intestinal parasitic infections. The objective of this review is to assess whether concomitant infections with malaria and/or helminthic diseases have an impact on cervical disease progression in women on HAART.

This scoping review was conducted in August 2018. To conduct this scoping review, we searched the relevant studies in electronic databases such as PUBMED, Global Health, EMBASE, CINAHL and SCOPUS published in the year between 1960 and 2018 using the following search terms HAART AND malaria OR Helminth and Female OR women.

Eight studies qualified for this review. The literature underscores the need for women on HAART with multiple co-infections to use adjuncts to retain immune recovery and undetectable HIV viral load, to reduce risk of cervical disease progression. A trend for higher risk of CIN3+ in HIV+ women reporting recent malarial infection was observed in one study.

Given the public health impact of synergistic interactions between malaria and helminthic infections in HIV/HPV co-infected women on HAART, it is urgent that these interactions are elucidated.

1. Background

It is estimated that two-thirds of the 36.9 million people living with HIV/AIDS worldwide, reside in the sub Saharan Africa region, with a rising majority in rural areas.(Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO), 2009) In 2007, the World Health Organization (WHO) included Invasive Cervical Cancer (ICC) to stage "4" of the HIV/AIDS classification of its clinical staging and case definition of HIV for resource-constrained settings. (WHO Department of Immunization, Vaccines and Biologicals, World Health Organization; Geneva, 2007) In sub Saharan African women, ICC is the second most common cancer and leading cause of cancer death.(Arbyn et al., 2011) (Ferlay et al., 2010)

High risk Human papillomavirus (HR/HPV), a sexually transmitted infection (STI), has been shown to be present in 99.7% of cervical cancers worldwide.(Walboomers et al., 1999) Co-infections leads to greater HIV replication and disease progression through immune activation of cellular mechanisms, rendering the CD4 + T lymphocyte cells susceptible to HIV increased viral load.(Celum, 2004) (Mercader et al., 2001) Available data suggest that HIV-positive women with squamous abnormalities detected on their Pap smears have a significantly higher HIV viral load than women with negative Pap smears. (Cardillo et al., 2001) (Agaba et al., 2009) (Swende et al., 2012)

Three WHO global recommendations for cervical cancer primary

Abbreviations: HIV, Human immunodeficiency virus; HPV, Human Papilloma virus; HAART, highly active antiretroviral therapy; STI, Sexually transmitted Infections; IMCI, integrated management of childhood illnesses

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and secondary prevention are likely to have an impact on women in resource-poor settings. These include: firstly, offering HPV vaccine against HPV genotypes 16 and 18, (which have the greatest oncogenic potential, accounting for about 70% of all ICC(Muñoz et al., 2003)), to girls at ages 9–13 naïve to the targeted types; secondly, a "screen and treat" approach in resource poor settings, in which access to Visual Inspection with 3–5% acetic acid (VIA) or, if possible, HPV testing followed soon or immediately by treatment of detected precancerous lesions(WHO, 2014); and thirdly, the INSIGHT START Study Group et al., 2015 revision of its recommendations to embark on Highly-Active Antiretroviral Treatment (HAART) regardless of WHO clinical stage classification for HIV or CD4 count.(WHO (WHO, 2013) WHO issues new HIV recommendations calling for earlier treatment accessed on, 2016) Whilst in some European populations a positive association of HIV infection and ICC has been documented in women on HAART, (Franceschi et al., 2003) (Dal Maso et al., 2001) the picture is less clear in Africa due to conflicting evidence,(Franceschi et al., 2003) (La Ruche et al., 1998) (Hawes et al., 2003) (Adjorlolo-Johnson et al., 2010) (Odida et al., 2011) (Kahesa et al., 2008) which in turn suggests that there may be other risk factors at play.

The use of HPV tests for cervical cancer prevention is expected to reduce the frequency of screening and "once a woman has been screened negative, she should not be rescreened for at least 5 years, but should be rescreened within ten"(New WHO Guide to Prevent and Control Cervical Cancer [Internet], 2014). However, there is currently a paucity of evidence to support the adequacy of this guideline in HIV-infected women living in Sub-Saharan Africa, Asia and South America, where a meta-analysis of case-control studies have indicated substantially higher risks of cervical cancer among women in lower social class groups.(Parikh et al., 2003) In sub-Saharan Africa, co-infected HIV/HPV infected women living in rural areas are also at higher risk of malaria and helminthic diseases, all 'diseases of poverty',(Worrall et al., 2005) (Stevens, 2004) where inequitable access to HIV, cervical cancer, malaria and helminthic interventions increase the vulnerability of the poorest.(Worrall et al., 2005)

Helminthic infections may dampen the protective Th1 responses responsible for cell-mediated immunity against bacterial, protozoal, viral, and intracellular parasitic infections, whereas in a Th2 response, helper cells mediate antibody-dependent immunity against extracellular parasites including intestinal helminths.(Rafi et al., 2012) The polarizing of the immune response towards Th2 and the ensuing reduction of the Th1 response modifies responses to viruses, including hepatitis C virus(Farid et al., 2005) and STDs, which in turn increases susceptibility to HIV and hastens its progression by increasing HIV viral load. (Farid et al., 2005) (Lamb et al., 2005) (Marsh & Kinyanjui, 2006) This in turn may reduce the potency of some vaccines(van Riet et al., 2007) and lead to cervical disease progression.

Malaria is associated with strong CD4 cell activation and upregulation of Th1 pro-inflammatory cytokines.

Previous studies have shown evidence of pathological interactions between HIV and malaria, especially in areas where they are co-endemic.(Onyenekwe et al., 2007) (Nkuo-Akanji et al., 2008) (Diego et al., 2011) HIV infection has been reported to roughly double the risk of malaria parasitemia and increase the frequency and severity of clinical malaria.(Francesconi et al., 2001) (French et al., 2001) (Laufer et al., 2006) (Whitworth et al., 2000)Furthermore, a systematic review reported that clinical malaria incites HIV replication, which in turn hastens immune system decline and HIV disease progression to AIDS. (Flateau et al., 2011) (Reina & Potter, 2006) As a corollary, this may result in cervical disease progression.

In sub Saharan Africa, the four diseases converge disproportionately in rural areas, (Ivan et al., 2013) with a recent study in Kenya reporting that only 16% of women were uninfected by either or both *P. falciparum* and helminth infection at the time of delivery, with hookworms accounting for 36–46% of all helminthic infections.(Fairley et al., 2013)

The objectives of this scoping review are two-fold: firstly, it assesses whether there is an association between malaria and/or helminthic diseases coinfections and cervical disease progression in women who have initiated HAART; secondly, it outlines epidemiological, clinical research gaps that will need to be addressed to design programmes that enhance prevention of malaria and helminthic infection in women with HIV and HPV.

2. Methods

We conducted this scoping review based on a pre-defined search protocol that conformed to the criteria set out by the PRISMA statement (PRISMA statement, 2016) We chose a scoping review as a research format, which has been described as a process of mapping the existing literature or evidence base as appropriate, to address the research questions included in this study. We searched the relevant studies in the following electronic databases, PubMed, Global Health, EMBASE, CINAHL and SCOPUS were searched until August 2018.

2.1. Search terms

The following search terms were used HAART AND malaria or helminth AND Female OR Women. See Annex for full search term strategy

2.1.1. Inclusion criteria

Article selection criteria included any methodologically-sound clinic-based randomized-controlled trials (RCTs), meta-analysis/systematic reviews and observational studies. We excluded publications such as case reports, articles that did not include combination antiretroviral therapy or did not report data by HAART users.

All references of retrieved articles were further searched for identification of other potential articles. Articles were title-screened and then abstract-screened. Articles that appeared as relevant from the first screening were read in full.

2.1.2. Study selection

We considered the following four components (Population, Intervention, Comparison, Outcome - PICO) to assess and categorize studies to be included in this review.

2.1.2.1. Population. The population of interest is sub Saharan women infected with HIV-HPV and malaria or helminthic infections who are on HAART. In addition, studies in which HIV viral load/ CD4 count were used as proxies for cervical cancer progression were eligible.

2.1.2.2. Intervention. The intervention examined in this study is the administration of HAART.

2.1.2.3. Comparison. Various comparisons were explored on the episodes (or not) of malaria and helminthic infection in women on HAART versus women not on HAART.

2.1.2.4. Outcome(s). 1) Change in HIV viral load or/and immunological parameters, 2) cervical dysplasia or the progression of cervical disease, and 3) incidence/prevalence of malaria/helminthic infections.

3. Results

On August 23th, 2018 we retrieved 585 articles, of which 43 were duplicates. After title/abstract screening, 20 were eligible for full text screening. Finally, 8 studies were included for this review (see flowchart).

Table 1
Summary of studies included in the review.

First author, Year	Country	Study design & sample size	Main exposure(s) of interest	Main outcome(s) of interest	Main results and remarks
Anastos et al. (Anastos et al., 2010)	Rwanda	Observational prospective cohort study among 476 women co-infected with HIV and HPV	Malarial Infection in HIV-HPV infected women	Cervical Intraepithelial Neoplasia grade 3 (CIN3)	A trend for higher risk of CIN3 + in HIV + women reporting recent malarial infection was found; 710 HIV-infected and 226 HIV-uninfected Rwandan women
Ekwaru et al. (Ekwaru et al., 2013)	Uganda	3-year randomized trial to compare 3 different monitoring strategies for HIV + patients among 1094 receiving ART.	Opportunistic infections in HIV-infected women	HIV RNA viral load (VL)	Episodes of opportunistic infections, including malaria, among patients taking ART with undetectable VL were associated with elevation of HIV RNA VL to detectable levels and decline in CD4 T cell counts.
Polyak et al. (Polyak et al., 2016)	Kenya	Randomized non-inferiority clinical trial among 500 Antiretroviral-Treated HIV-1-Infected People	Cotrimoxazole Prophylaxis Discontinuation	Malaria morbidity/mortality in HIV infected individuals on HAART	Combined morbidity/mortality was significantly higher in the CTX discontinuation arm, driven by malaria morbidity. 97% of the cases of malaria were in the CTX discontinuation arm.
Lankowski et al. (Lankowski et al., 2014)	Uganda	Retrospective observational study Sample Size: 5379 HIV-infected adults on ART	Empiric deworming	CD4 Count	Deworming was not associated with significant difference in CD4 count in either the first year or after the first year of ART. During the first year of ART deworming was associated with a significantly greater rise in CD4 count.
Ivan et al. (Ivan et al., 2015)	Rwanda	Longitudinal study beginning $n = 1100$, final $n = 980$ (began with targeted $n = 500$; untargeted $n = 550$; last follow: targeted $n = 466$, untargeted $n = 513$)	targeted deworming (400 mg albendazole at any visit if women were helminth positive) on pregnant women who are on ART untargeted deworming (400 mg albendazole at each visit even if not helminth positive)	HIV progression, hemoglobin levels, and efficiency of deworming	For pregnant women on ART, ABZ therapy increases CD4 count and decreases viral load
Ivan et al. (Ivan et al., 2013)	Rwanda	Prospective cohort study; n = 980	Deworming every 12 weeks through targeted and untargeted treatment (with 400 mg albendazole) and malaria treatment; women received ART and nevirapine treatment to prevent mother-to-child transmission of HIV	Helminth and malaria coinfection in HIV positive pregnant women on ART	Helminth infections more common in rural than peri-urban areas, while malaria was more common in peri-urban areas. Higher levels of all infections were found among women with a CD4 count of < 350 cells per mm^3 and a detectable viral load.
Ivan et al. (Ivan et al., 2012)	Rwanda	Cross sectional study of 328 women	HIV-positive pregnant women attending antenatal health centers in Rwanda	Intestinal helminths and malaria dual infections	Subjects treated with a d4T, 3TC, NVP regimen had a reduced risk of *T. trichiura* infection (OR, 0.27; 95% CIs, 0.10–0.76; $p < .05$) and malaria–helminth dual infection (OR, 0.29; 95% CI, 0.11–0.75; $p < .05$) compared to those receiving AZT, 3TC, NVP. High prevalence of malaria and helminth infection among HIV-positive pregnant women.
Omoti et al. (Omoti et al., 2013)	Nigeria	Cross sectional study of 342 HIV infected adults	HIV -malaria co-infected adult patients with HAART	malaria parasitemia, CD 4 + cell counts and some haematological indices	There was a significant association between CD 4 + cell count and having significant parasitemia ($P < .0001$)

3.1. Study population

The sample size ranged from 342 to 5379 HIV-malaria/or helminthic diseases infected women and 476 HIV- HPV- malaria triple infected women on HAART. See Table 1.

3.2. Study design

Two studies were cross sectional, one was retrospective cohorts, two were RCTs and three were prospective cohort study designs.

3.3. Geographical location

Of the eight studies identified for the current review, one study each was carried out in Nigeria(Omoti et al., 2013) and Kenya(Polyak et al., 2016). The remaining studies were conducted in Uganda (2)(Ekwaru et al., 2013) (Lankowski et al., 2014) and Rwanda (4).(Ivan et al., 2015) (Ivan et al., 2013) (Ivan et al., 2012)

3.4. Co parasitic infections

3.4.1. Malaria infections

Only one study has been identified to explore the direct association between abnormal cytology in dually infected HIV-HPV women and malaria. In Rwanda, (Anastos et al., 2010) found that recent malarial infections had a significant positive association with CIN3+ in HIV +/HPV+ women, after adjusting for CD4 count, (OR: 3.3; 95% CI: 0.8–13.3). This was the first report of any direct evidence that malarial infections might contribute to the risk of cervical pre-cancer and cancer. (Swende et al., 2012)

Ekwaru et al. (Uganda, 2013) suggested that women on HAART with undetectable HIV viral load may still experience increased HIV viral load to detectable levels and decline in CD4 T cell counts during episodes of WHO Stage 3 or 4 illnesses and malaria. (Reina & Potter, 2006)This difference remained statistically significant (OR: 3.8; 95% CI: 1.73–8.39), after adjusting for the non-independence of repeated observations within an individual, gender, duration of HAART, age, Body Mass Index at baseline, first-line HAART regimen, HAART adherence preceding the interval and previous three month CD4 T cell count in 1094 HIV-1-infected adults.(Reina & Potter, 2006) Similarly, Omoti et al. (Omoti et al., 2013) in Nigeria observed a significant association between CD4+ cell count and significant parasitemia ($P < .0001$) and the odds of having malaria parasitemia increased with advancing clinical stage of HIV infection and this was statistically significant ($P = .002$, OR = 2.32) underscoring the importance of early HAART initiation to prevent a subsequent HIV viral load and as a corollary cervical disease progression. This study group included 342 HIV+ adults with HAART, although it is not known whether the viral load increased to detectable levels.(PRISMA statement, 2016)

Polyak et al. (Polyak et al., 2016) undertook a RCT conducted among adults on HAART with evidence of immune recovery (ART for ≥18 months and CD4 count > 350 cells/mm^3) to determine whether discontinuation of Co-trimoxazole (CTX) was non-inferior to continued CTX prophylaxis in decreasing morbidity for some diseases, including malaria. (van Riet et al., 2007) Despite having received HAART for a median of > 4 years and having immune reconstitution, adults who stopped CTX prophylaxis had significantly higher incidence of the combined morbidity/mortality endpoint, driven by malaria morbidity (IRR = 2.27, 95% CI: 1.52–3.38).(Rafi et al., 2012) These results, while not being able to assess the role of HAART in preventing malaria morbidity or mortality, show the importance of CTX treatment continuation in HIV patients in malaria-endemic contexts.

3.4.2. Helminthic infections

Two studies have shown how women seem to benefit most from empiric deworming. It is therefore possible that Albendazole (ABZ) therapy has a more significant effect on the immune system responsiveness of HIV-infected subjects in the presence of HAART. (Lankowski et al., 2014)reported that empiric deworming of HIV-infected individuals on HAART conferred no significant generalized benefit on subsequent CD4 count recovery, with a change in CD4 over time of 42.8; 95% CI: −2.1–87.7)in the first year on ART and − 9.9; 95% CI: −24.1-4.4 after the first year of ART.(Stevens, 2004) However, in a sub-analysis by gender, during the first year of ART deworming was associated with a significantly greater rise in CD4 count with an increase of 63.0; 95% CI: 6.0–120.1 in women.(Stevens, 2004) However, it is noted that the female study population differed significantly from males with respect to several important baseline characteristics in the model, including age, tuberculosis co-infection and baseline CD4 count. These favorable findings in women are congruent with (Ivan et al., 2015)) findings from a longitudinal study where antihelminthic therapy significantly reduced detectable viral load and increased CD4 counts and hemoglobin levels in 980 pregnant, HIV-infected women with helminth coinfections receiving HAART.(van Riet et al., 2007)

Two studies in Rwanda suggested a differential impact of certain HAART combinations on helminthic and the prevention of malaria infection. Ivan et al. (Ivan et al., 2013) undertook a prospective study on 980 pregnant patients recruited from health centers in rural and peri-urban locations in the central and eastern provinces of Rwanda. Certain HAART combinations, including the Tenofovir (TDF)- Lamivudine (3TC)- Nevirapine (NVP) (OR: 3.47; 95% CI: 2.21–5.45); Stavudine (D4T)-3TC-NVP (OR: 2.47; 95% CI 1.27–4.80) and (Zidovudine) AZT-NVP (OR: 2.60; 95% CI: 1.33–5.080) regimens, yielded higher helminth infection rates than the AZT-3TC-NVP regimen. HAART had no effect on the risk of malaria. (Walboomers et al., 1999)

This finding is contradictory to the Ivan et al. (Ivan et al., 2012) findings from a cross sectional study of 328 HIV-infected pregnant women, which demonstrated that specific HAART regimens, such as d4T, 3TC, NVP regimen had a reduced risk of *T. trichiura* infection (OR: 0.27, 95% CI: 0.10–0.76) and malaria–helminth dual infection (OR: 0.29, 95% CI: 0.11–0.75) compared to those receiving AZT, 3TC, NVP. (Whitworth et al., 2000)

4. Discussion

Indirect evidence on cervical dysplasia progression suggests an antihelminthic effect of certain HAART regimens (potentially including the indirect impact of Co-trimoxazole treatment on malaria) and of a deworming adjunct, increasing HAART effectiveness in women. This underscores the need to consider an adjunct in order to improve positive impact of HAART. Moreover, there is evidence that episodes of malaria among patients on HAART were associated with detectable HIV viral load levels or reduced CD4 count and an adjunct is needed to reduce malaria-related morbidity. The only study on HIV-HPV- malaria co-infected women found a statistically significant association between malaria and CIN 3+. The mechanisms by which malarial infections could increase the risk of CIN3+ are unknown, but might include additional challenges to the already compromised immune system of HIV + women. HIV, HPV and malarial infections are highly prevalent in vast areas of sub Saharan Africa, and any increased risk of CIN3+ associated with malaria could result in a substantial attributable risk, although the percentage of women on HAART is unknown.

4.1. Strengths and limitations

One strength of our review is the relatively large sample sizes of the included studies as well as their prospective nature, which would allow the causal criterion of temporality to be fulfilled. However, our findings should be seen in light of the scarcity of studies specifically exploring a direct association between malaria and/or helminthic disease and cervical disease progression. Furthermore, our interpretations inferences may be further restricted as literature suggests that the impact of

helminth infection on HIV-1 may be species-specific.(Brooker et al., 2009)

4.2. Clinical and public health impact

One main aspect to consider is that high endemic settings for malaria are also settings where women are more at risk for helminthic infections due to less access to fresh water, adequate sewage and general living and hygienic conditions. In rural areas with socio economic deprivation, HIV-infected women are also likely to be infected with concomitant malaria and helminthic infections. In a rural study in Nigeria, out of the 205 subjects examined, 51.9% of the cases harboured various parasites with helminthes.(Jegede et al., 2014)

Moreover, in these settings, other services such as family planning and antenatal care may also be scarce, with potential negative spirals, if women have more difficulties in preventing unwanted pregnancies. This problem is further compounded by less access to antenatal care and malaria prevention during pregnancy, leading to a higher risk of malaria and helminthic infections during pregnancy, resulting in a potential higher burden.

These findings, uncertainties and extreme vulnerabilities of socio-economically deprived HIV-HPV co-infected rural women reveal the need for further research, which would determine the benefits for an integrated cervical prevention management approach, coupled with enhanced malaria and helminthic infections targeting this population. This may build on the integrated TB/HIV prevention model already in place, premised on the known correlates of HIV disease progression and co-morbid infection.

4.3. Epidemiological and clinical research gaps

In order to determine the effectiveness of a triage-based secondary cervical cancer prevention program in HIV-HPV infected women on the basis of malaria and/or helminthic disease co-infection, there are some clinical and epidemiological research gaps which will need to be elucidated.

4.3.1. Malaria and severe abnormal cytology

Given that HIV, HPV and malarial infections are highly prevalent in vast areas of sub Saharan Africa, and any increased risk of CIN3+ associated with malaria could result in a substantial attributable risk, the mechanisms by which malarial infections could increase the risk of CIN 3+ need to be elucidated. Prospective studies should be undertaken to enhance cervical cancer prevention in HIV-malaria co-infected women.

4.3.2. Helminthic infections and cervical disease progression

The potential variable geographic distribution in the continent between different species of soil-transmitted helminths should be considered, and trials to evaluate species-specific effects are required along with the long–term clinical outcomes following deworming.

Prospective studies are necessary to explore the clinical impact that helminthic infections have on HIV and cervical disease progression in women initiating HAART at different levels of immunosuppression. These may test whether enhanced preventive services for malaria and other parasitic infections slow down progression of cervical disease. Furthermore, the epidemiological, clinical, and biological basis of the differential impact of HAART with deworming as adjunct in women as well as the antihelminthic effect of some ART combinations warrants further studies.

4.3.3. Concomitant malaria and helminthic infections

In light of the geographic and socioeconomic overlap of immune modulating malaria and helminnthic infections, their synergistic interactions on cervical disease progression in HIV-HPV infected women need to be elucidated.

4.3.4. Prophylactic vaccines

Determination of a tailored triage-based secondary cervical cancer prevention program for HIV- infected women on HAART will also depend on the efficacy of the HPV prophylaxis vaccine within this population. Studies should explore differences between levels of HPV 16/18 antibodies after administration of the vaccine among HIV infected women exposed to malaria/and or helminthic infections.

4.3.5. Public health impact of multiple concomitant infections

The prevalence of HIV, HPV, malaria and chronic helminthic infections should be characterized in sub Saharan Africa and their synergistic interactions in the post HAART era better elucidated to calculate the Population Fraction attributable to cervical disease progression. On the basis of this impact, the effectiveness of an integrated management for cervical cancer prevention, akin to the IMCI model advocated by the WHO should be assessed.

5. Conclusion

Our review underscores the need for better elucidation of the synergistic interactions between HIV-HPV and malaria/helminthic diseases. Given the extensive overlap in the geographic distribution of malaria, helminthic and HIV-HPV co-infections, even the currently scant evidence on synergistic interactions may have an enormous public health importance in sub-Saharan Africa, where malaria and multiple helminth species are also endemic.

Declaration

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Authors' contribution

SM: Conception of the study, coordination of the study, screening of studies, interpretation of the findings of included studies, writing and editing the paper, validation of the final version.

RR: Screening of studies, interpretation of the findings of included studies, writing and editing the paper, validation of the final version.

AD: Screening of studies, interpretation of the findings of included studies, writing and editing the paper, validation of the final version.

GA interpretation of the findings, writing and editing the paper, validation of the final version.

SH interpretation of the findings, writing and editing the paper, validation of the final version.

HM interpretation of the findings, writing and editing the paper, validation of the final version.

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Appendix A. Supplementary data

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