



Co-infections; Their Role in HIV Acquisition and Disease Progression

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Authors' contributions

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ABSTRACT

HIV/AIDS disease manifestations play critical roles on the host's immune response to infections especially cell-mediated immunity which is central in combating many other infections, allowing opportunistic pathogens that otherwise rarely infect humans, to cause disease. There is paucity of information to satisfactorily explain the geographical pathophysiological overlaps of malnutrition, bacterial, parasitic, and viral infections widespread in sub-Saharan Africa (SSA) where HIV burden is much higher than elsewhere. HIV and/or co-infections may worsen HIV related symptoms and outcomes, alter the presentation or/and increase viral virulence consequently, assisting the infectivity. Hence, co-infections are potential cofactors of HIV transmission in SSA. Most of currently published work often underplays co-infections resulting in misleading statistics and conclusions. A lot of studies have been done assessing single infections in isolation or independently yet in real life practical situation such solitary infections are rare. The prevalence of co-infections, how these in isolation or combination modify or modulate HIV transmission remains poorly described.

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1. BACKGROUND

The underlying reason behind the high HIV-1 prevalence in sub-Saharan Africa (SSA) remains elusive. Unlike in Europe and the United States of America where HIV is common among intravenous drug users and homosexual men [1-3], the African epidemic is more widely distributed across the general population with heterosexual penile-vaginal transmission as the main mechanism [4-6]. However, this observation is inconsistent with the low probability of heterosexual HIV transmission per coital act, as differences in sexual behaviour do not always translate to differences in HIV prevalence or incidence [7-10]. Long-term concurrent relationships may be more common in many parts of SSA, but national rates of concurrency do not also always correlate with burden of HIV [11-13]. Moreover, this heterosexual mode of transmission does not satisfactorily explain the relatively high proportion of HIV discordant couples common in the region who in some instances continue to bear children [14-17]. Thus, sexual contact with an infected person represents only a necessary, but not sufficient condition for transmission of HIV through sex.

Recently, studies have observed a synergistic relationship between HIV and co-infections, implicating them as possible cofactors for HIV acquisition and transmission [18-21]. In the absence of such cofactors that may increase per-contact transmission rates, HIV transmissions in industrialized countries have not developed into heterosexual epidemics. In addition to co-infections, current thinking of scientific literature has demonstrated that ecological factors are equally important in determining an individual's vulnerability to HIV infection and progression to AIDS [22]. This scenario is further complicated by immunogenetic factors where human genetic differences may introduce heterogeneity into the host immune responses consequently, affecting the outcome of the co-infection(s), disease progression and/or response(s) to treatment. The foregoing suggests that co-infections and malnutrition both common SSA may be central in fueling the HIV epidemic in this region.

2. BURDEN OF CO-INFECTIONS IN SSA

On average 74% Africans are exposed to two or more parasitic, bacterial and viral infections

whilst a good 26% grapple with six or more diseases including non-communicable diseases some of which are side effects attributed to intake of antiretroviral therapy (ART) [23-25]. Consequently, in such an environment, the potential for significant epidemiological, biological, immunological and clinical interactions between HIV and other common tropical pathogens is likely [22]. Co-infecting pathogens exist in a dynamic homeostatic balance with the host. Pathogenesis is due to the pathogen-triggered disturbance of this equilibrium and the effectiveness of the host's immune responses [26]. Relative to single pathogen infection, co-infections can alter the transmission dynamics, clinical progression and treatment outcomes [27]. Establishing the nature, burden and consequences of co-infections requires integrated monitoring and research of different infectious diseases. Unfortunately, at the moment such researches are rare. Hence, the need for HIV and co-infections including the respective immunogenetics research may not be over-emphasised especially for SSA where co-infections out-number single pathogen infections, a situation exacerbated by poverty and malnutrition.

3. MALNUTRITION AND IMMUNITY

The geographic and pathophysiologic overlaps of the malnutrition and HIV infection epidemics in SSA has led to the realisation that nutrition is essentially a gene-environment interaction science that complicates relationship between the health of the individual, their genome, and the life-long dietary exposure [28]. Studies have shown that 30% of SSA population is malnourished [21]. In that view, it implies that a significant proportion of patients who require ART in this region may be malnourished due to both HIV-associated wasting and/or inadequate nutrient intake [29]. Thus, HIV compromises the nutritional status of the infected individuals and in turn, malnutrition worsens the effects of the disease by weakening the immune system, consequently hastening disease progression and early mortality [30-32]. Studies have shown that the overall host malnutrition increases vulnerability to infectious and parasitic diseases [22,33,34]. For instance, zinc deficiency leads to impaired function of the innate and adaptive immune responses thereby; increasing susceptibility to bacterial, viral and fungal infections [35]. Furthermore, selenium deficiency

has been implicated in accelerated HIV disease progression [36]. Even more interestingly is the observation that vitamin D has been shown to play a fundamental role in improving anti tuberculosis (TB) immunity, reducing progression and severity of the infection [37,38]. Thus, the role of malnutrition in disease acquisition and progression cannot be over-emphasised.

4. BACTERIAL CO-INFECTIONS; MYCO-BACTERIUM

Overcrowding and psychosocial stress play critical roles in the acquisition of TB infection [39,40]. The emergence of HIV has exacerbated an already enormous burden of TB worldwide. Thus, infection with HIV significantly increases the risk of developing active TB. T-lymphocyte subset is important in the control of TB. Ironically, HIV depletes CD4+ T-lymphocytes contributing to the susceptibility of the co-infected persons to TB [41]. Co-infection with both HIV and TB, often described as 'a cursed duet', is increasingly becoming a major public health challenge with 70-80% of HIV infected patients in SSA also having TB [41-44]. This observation of most AIDS patients also being infected with TB reflects a large number of people receiving concurrent treatments in a population where drug-drug interactions due to anti-tuberculous drugs and ART are not well documented, a situation further complicated by use of herbs and botanicals common within these communities [45]. Risks for developing toxidermia are also high in such environments [46,47]. Consequently, the need for further research in this regard is important.

In Zimbabwe, about 1 200 000 people are HIV infected and there is unmet need for ART [48,49]. This backlog of access to treatment gives an unfortunate but unique opportunity to stratify HIV infected patients as ART naïve or experienced and thus inadvertently helping assess the side effects associated with treatment(s) with the naïve group acting as controls. There is also an urgent need to investigate the high mortality and morbidity observed among the ever growing population of HIV exposed uninfected (HEU) children who are now maturing to adults but are at high risk of contracting infectious diseases such as TB, bacterial *Pneumocystis jirovecii* and *Cytomegalovirus* pneumonias [50]. The causes of the increased morbidity and mortality from infections among HEU children are likely to be multifactorial, encompassing environmental, maternal, and health systems issues among

others. The increased burden of other infections seen among HEU raises the question of whether their poorly described relative state of immunodeficiency may contribute to their increased susceptibility to infectious diseases [51]. A genetic polymorphism in an innate immune protein with wide antimicrobial activities called mannose binding lectin is suggested to have evolved to enhance immunity against TB caused by *Mycobacterium africanum* among African populations [52]. However, the same polymorphism is currently believed to increase the risk of HIV infection and disease progression in the same population [53,54]. Thus, findings from immunogenetic studies of HIV cannot be extended to all co-infections. There is paucity of data regarding the immunogenetics of HIV/TB co-infections and how their co-existence may modify or modulate, host immune responses, HIV/TB acquisition, disease progression or response to treatment. An integrated and holistic approach in dealing with the two conditions is warranted also in view of the hepatotoxicity due to anti-TB drugs that limit treatment options of patients co-infected with HIV and TB [55].

5. HEPIC VIRUSES AND HIV INFECTION

Liver disease due to chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection is now emerging as an increasing cause of morbidity and mortality among HIV infected persons in developing nations [56-58]. The evolution and prognosis of patients co-infected with HIV and HBV or HCV is not well known not to mention the immunological, virological and biochemical including the elastographic responses. Studies have shown that baseline CD4+ T-lymphocyte count is an independent predictor of HBV decline, emphasizing the role of immune status in clearance of HBV [59]. Thus, inadequate immune responses towards the hepatitis viruses in co-infected individuals may lead to the development of cirrhosis and end stage liver disease [60]. Co-infection with HIV poses a greater risk of mortality than either HCV or HBV infection alone and is frequently associated with hepatitis flares following ART initiation [61]. Among HIV-positive individuals co-infected with HBV and/or HCV initiating ART, biomarkers of inflammation and coagulation have been shown to be associated with an increased risk of death [61]. Hepatitis virus-related liver disease substantially increases the mortality rate of patients with HIV on highly active antiretroviral therapy (HAART) and as a result management of these patients warrants special attention [62,63].

To this end, there is a need to evaluate the role of HBV co-infection on immunological, virological and clinical responses to lamivudine based ART commonly prescribed in this region. There are also challenges associated with differentiating the etiologies of liver disease of viral hepatitis from drug-related hepatotoxicity, fatty liver disease, including direct and indirect effects of HIV infection, increased bacterial translocation, immune activation, and the presence of soluble proteins that modulate the hepatic cytokine environment [64].

6. ONCOGENIC VIRUSES; HUMAN PAPILLOMA VIRUS (HPV)

Besides being the main tumor virus in gynaecological malignancies HPV has been frequently detected in other anogenital tumors such as vulva/vagina, anal and penis carcinomas [65]. Controversial reports on the detection of HPV in various other tumors on the heart, kidney, prostate, urinary bladder, oral cavity, larynx, esophagus, stomach, colon, liver, endometrium, ovary, breast, skin, lung, ocular surface and skin have been cited [66-72]. HIV infection has demonstrated an increased risk of developing some malignancies [73,74]. Mounting scientific evidence points to a strong association between HPV infection and HIV acquisition [75-79]. Thus, HIV infection has an immediate impact on genital tract immunity, as evidenced by the high risk of multiple new HPV detections immediately after HIV acquisition [80]. HPV clearance has been associated with subsequent HIV sero-conversion, suggesting that HPV prevention could be another tool for HIV prevention [81-84]. Ecological correlation between HIV prevalence and the increase of HPV18 and the decrease of HPV 45 in SSA [85] warrants the need to consider different national specific monitoring programmes for these co-infections. Due to the oncogenic activity of HPVs, it is clinically important to detect HPV infections and to accurately identify the particular HPV types associated with specific cancers. Zimbabwe is one of the countries hardest hit by the HIV pandemic with cervical cancer affecting 1 in 2000 women [86,87]. Despite the high prevalence of both HPV infections and cervical cancer among Zimbabwean women, the ability to test for HPV infection of the uterine cervix is limited by a lack of an easy and cheap detection method that does not require gynecological examination, a situation exacerbated by medical professionals' brain drain. It is sad to note that 91% of rural women had never had cervical screening and

81% had no knowledge of cervical screening tests [88]. HPV DNA testing recently emerged as a likely candidate to complement Pap cytology for primary screening and more successful for early cancer diagnosis. However, currently HPV screening, epidemiological surveillance and research are hampered by high cost of commercial kits currently available on the market. Accessibility could be improved through development of simpler test complemented by urine-based HPV assays, dried cervical samples or dried blood spots as opposed to serum or plasma. Immune genetic factors influencing the progression to cancers also remain poorly defined.

HPV clearance seems to be under host genetic influence. Immunogenetic research explores the relationship between susceptibility to infectious microorganisms and human genetics. Thus, behavioral, biological factors, immunological, including ethnic variation in host restriction genes may play roles in differential transmission of the HIV pandemic. There is substantial epidemiological evidence that host genetic factors such as human leukocyte antigens (HLAs) and closely linked genes of the major histocompatibility complex (MHC) as well as non-MHC factors such as cytokines/chemokines and their receptors/promoters are important determinants of susceptibility or resistance to infectious diseases including differential response to treatments. HLAs are central to the recognition and presentation of pathogens to the immune system and therefore are a fundamental part of the human immune system. In view of challenges associated with early cancer diagnosis, investigation of host genetic factors associated with high-risk HPV types such as TP53, Arg72Pro, RNASEL, Arg462Gln or CASP8, HLA-G polymorphisms, HLA class II alleles especially DQB1*0602 and DRB1*1501, HLA class II DRB1*13/DBQ1*0603 or adipoikines allows the identification of the proportion of individuals at risk of developing cancers [89,90,91,92,93,94,95-97]. Several studies on HLA and disease association with HIV have been reported in different ethnic populations yet little information is available on HIV infected individuals in SSA with special reference to the incidence of co-infections and association with HLA.

7. PARASITES AND HIV CO-INFECTIONS

Parasite-HIV co-infections and interactions are one of the neglected areas in HIV research.

Recent studies have shown that malaria and helminthic infections could disturb the balance of anti-HIV immune responses thereby positively contributing to HIV replication and accelerated progression to AIDS [22,33,98]. HIV and malaria interact synergistically, with regions of the world that are most affected by malaria also carrying a heavy burden of HIV. In view of this overlap in their global distribution, it is presumed malaria increases HIV viral load as much as 10-fold thereby increasing the HIV transmission dynamics of HIV-infected persons at the population level [99-102]. HIV infection has also been shown to impair the inflammatory response of innate effect or cells to malaria [103]. Malaria infection has been shown to be associated with strong CD4+ T-lymphocyte activation and up-regulation of pro-inflammatory cytokines thereby facilitating an ideal microenvironment for the spread of the virus among the CD4+ lymphocyte and for rapid HIV-1 replication [104].

Helminthic and HIV-1 co-infections are also common in SSA [22]. Thus, the convergent distribution of the HIV and helminthes infections is suggestive of a possible biologically plausible observation that persistent infection with helminthes may exacerbates the HIV epidemic in this region [105,106]. There is now great interest in incorporating deworming into control programmes for many major diseases such as HIV, TB or malaria [107]. Recent studies have shown that deworming HIV-infected persons results in a statistically significant increase in CD4+ T-lymphocyte counts implying that a simple, inexpensive but effective deworming medication like albendazole could allow HIV-infected people to delay uptake of ART [108-110]. *Schistosoma hematobium* which affects almost 200 million people in SSA has been shown to act as a co-factor for HIV transmission, whereby parasite lesions create open portals for HIV and inflammation in the genital area making transmission more efficient consequently, increasing the risk of HIV acquisition three-fold [111-115]. Helminthes induced chronic immune-activation; altered immune cell distribution, immune suppression, and strong T-helper-2 bias have also been shown to increase susceptibility to HIV, including enhancing its replication and facilitating faster progression to AIDS [116]. There is paucity of data regarding parasite(s) co-infection with HIV and how their co-existence may modify or modulate, host immune response, HIV acquisition, disease progression and/or response

to treatment in the background of a SSA population infested with a myriad of parasites.

Considering, the population specific differences in the frequencies of protective or susceptibility alleles and their influence on the disease outcome, it is of utmost importance to strengthen ongoing efforts towards defining largely unknown genetic propensity in our local population, particularly by recruitment of large cohorts of well categorized exposed uninfected individuals including rapid, long term non progressors and elite viremic controllers. Multi-parametric or modeling analysis of these potentially interactive immunogenetic variables in these cohorts may help to identify potential pathogen-host biological or immunological factors which will also undoubtedly lead to biomarkers that may have diagnostic and/or prognostic values. Further research is also needed to identify the role of predisposed risks not only to single pathogen infection but also more importantly in the presence of co-infections. Due to the multifactorial nature of the immune forces at play against HIV and co-infections, genome wide association studies (GWAS) on co-infected populations may provide a more informative approach compared to candidate gene association studies. However, literature on such studies remains very limited especially in Africa. In addition to the need for population based studies on co-infections, microbe-microbe interactions deserve further research efforts as well.

8. CONCLUSION

Determination of cellular, immunological including inflammatory profiles associated with different co-infections in both immunocompetent and immune compromised who are either ART naïve or experienced can be used as immunological markers to detect individuals at higher risk of developing a faster disease progression or therapeutic failure. Co-infections studies involving at least three different infections would generate a more coherent picture of the nature and consequences of such infections in terms of disease acquisition and progression, immune responses including response to therapy. This may be achieved through careful selection of cohort(s) and comparing groups with different co-morbidities alongside their respective immune response profiles to HIV, genetic susceptibility to infection. Interpretation of data derived from such studies is more likely to be able to predict disease acquisition and

progression. Further investigations of these interactions are needed to elucidate the role(s) of co-infections with the long term goal of providing “individualized medicine”, for a more effective patient management tailored according to patient’s immunogenetics, at the same time improving predictive capacity with respect to acquisition, disease prognosis and treatment outcome.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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