

Management of HIV Infected Patients with Active Buruli Ulcer in Tropical Regions in Africa, a New Therapeutic Challenge: A Review

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ABSTRACT

BU is endemic in tropical and sub-tropical regions mainly with high prevalence in sub-Saharan Africa, in particular in West Africa. Sub-Saharan Africa is also burdened with high HIV prevalence. Therefore, there is a significant potential for BU and HIV to occur in the same individual, and it represented a treatment challenge related to paradoxical reactions or IRIS onset. A study conducted in Cameroon reported that the mortality rate was higher among HIV-positive/BU patients compared to HIV-negative /BU patients (11% dying compared to 1%). We conducted this work based on review articles on HIV/BU co-infection to summarize information and guidance data to help health care practitioners for proper patients' management. It is becoming obvious that HIV infection have an effect on BU incidence mainly in Sub-Saharan Africa and its clinical presentation and treatment similar to tuberculosis. Based on TB/HIV and HIV/others microorganism s management experience and WHO expert in HIV and BU management guidance protocol, it is recommended to health practitioner. To actively screen all HIV/MU co-infected patients for tuberculosis, before commencing BU treatment and before starting ART. To start BU treatment before commencing ART and it should be provided for 8 weeks duration. The outcomes of *HIV/BU* co-infection management should be monitored and evaluated, taking account the drugs interactions between ART and antimicrobial agents. And the program for HIV, BU and TB control should work in a collaborative framework. As, HIV/BU co-infection becomes frequent in

Sub-Saharan Africa where both disease incidence is high. This represents a treatment challenge related to IRIS occurrence, optimal ART regimens, and when to start ART and antimicrobial treatment. Base on TB/HIV co-infection, the preliminary guidance protocol issue by WHO should be recommended, and further study should be initiated to show its efficacy and to give answers to unknown mechanism of IRIS in HIV/BU co-infection.

Key words: HIV/BU co-infection; Treatment; IRIS or paradoxical reactions

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INTRODUCTION

Buruli ulcer (BU) is an infectious and neglected skin disease caused by *Mycobacterium ulcerans*, which leads to large skin ulceration, joint and bone destruction and sometimes to disabilities^[1,2]. BU is endemic in tropical and sub-tropical regions in Africa, Asia, Australia, South America and the Pacific mainly with high prevalence in sub-Saharan Africa, in particular in West Africa^[3]. It predominantly affects children in rural areas^[4]. BU lesions are classified into 3 categories: category 1, which consist of lesions with a size of < 5 centimeters (cm) at the widest diameter; category 2, which consist of lesions with a size between 5 and 15 cm at the widest diameter, and category 3, which consist of lesions with size > 15 cm at the widest diameter, lesions at the critical sites and multiple lesions^[5]. There is an increasing recognition of BU/HIV co-infection as an important challenge for treatment of *Mycobacterium ulcerans* disease, mostly in sub-Saharan Africa (west and central Africa), regions also burdened with high HIV prevalence. Therefore, there is a significant potential for BU and HIV to occur in the

same individual. A study conducted in Cameroon reported that the mortality rate was higher among HIV-positive/BU patients compared to HIV-negative /BU patients (11% dying compared to 1%). This shows real difficulties to manage BU/HIV co-infected patients in these regions who mostly present IRIS or paradoxical reactions^[6,7]. Thus, we conducted this work based on review articles on HIV/BU co-infection to summarize information and guidance data to help health care practitioners for proper management.

METHODS

We have conducted a literature review, using, Pub-med, pub med central, Google scholar, Directory of Open Access Journals (DOAJ), WHO web site to collect recent articles on HIV/BU co-infection management including IRIS and paradoxical reactions occurrence. This literature review concerned scientific articles, WHO initial guidance consensus and recommendation on HIV/BU co-infection and experience on HIV/tuberculosis (TB) or other microorganisms co-infection management.

COMMENTS

Buruli ulcer has been reported in more than 30 countries worldwide, but rural communities and children in western Africa are mostly affected. Until 2004, surgical treatment has been the only treatment recommended by WHO^[8]. It consisted of wide excision margins reacting into the healthy tissue added to skin graft. Because, surgery is limited for majority of BU patients due to multifocal BU forms, to wide ulcerations and to the high cost of this surgery, medical treatment was recommended by WHO in 2004.

BU management in HIV negative patients

This current WHO protocol of BU^[9] combines streptomycin to rifampicin or moxifloxacin or clarithromycin added or not to surgery depending on the clinical category. This protocol is conducted as follows: Rifampicin at 10 mg/kg body weight by mouth daily for 8 weeks and streptomycin at 15 mg/kg body weight by intramuscular injection daily for 8 weeks (contraindicated in pregnancy). Although, moxifloxacin is active against both TB and BU and orally administered; it is not recommended in pregnancy or in children under 18 year-old, and has limited availability due to its high cost^[10]. For pregnant women treatment, in Benin a pregnant patient was successfully treated with a combination of rifampicin and clarithromycin^[11]. There were subsequently other reports of successful treatment with this combination. The recommendation, based on expert opinion, is therefore: rifampicin at 10 mg/kg body weight by mouth daily for 8 weeks and clarithromycin at 7.5 mg/kg body weight by mouth twice daily for 8 weeks^[11].

Despite the strict adherence of this protocol, paradoxical reactions appear sometime during or after initiation of the antimicrobial therapy, with new or multiple lesions.

These paradoxical reactions or inflammatory reconstitution immune syndrome (IRIS) usually, occurs 2 to 12 weeks after the initial antimicrobial treatment, although some may commence much later over 1 year after the end of treatment^[12-14]. Clinically, lesions may seem to worsen after initial improvement, new lesions may appear, sometimes on a different part of the body, and non-ulcerative forms, such as nodules (or swelling), plaque and edema, may ulcerate. Persistence of acid fast bacilli (AFB) in the lesions has been reported after the end of the treatment period, in both mice and human^[15-17], raising the question of *Mycobacterium ulcerans* (MU) being died or

only in a state of latency as reported for mycobacterium tuberculosis (MT). In addition, the study in mouse model histological analysis suggests that antibiotherapy leads to a shift in type of inflammatory infiltrate from neutrophils/macrophages-predominant to macrophages/lymphocytes-predominant, associated with the enhancement of MU phagocytosis^[16-19]. This immunological reaction is thought to be due to an exuberant reconstitution of the local immune response during the demise of MU bacilli under the influence of antibiotic therapy and mediated by immune-stimulators released from dying MU in areas of declining mycolactone concentration. And histologically, it is characterized by massive leucocytes infiltration of necrotic areas in surgically excised sample contrary to the acellular or scanty immune cell infiltrates observed in untreated MU infected skin lesions^[20,21]. To treat these paradoxical reactions, oral corticosteroids were used to minimize damage from severe reactions^[22,23]. Corticosteroids are potent immune-suppression and anti-inflammatory compounds, which act upon leukocyte circulation, function and migration to the site of infection and tissue damage^[24,25].

Management of patient with BU/HIV co-infection

Few studies were conducted on HIV/BU co-infection to see whether HIV is a risk factor for Buruli ulcer and what is the impact on its management^[26]. These studies showed contrasting results. In Ghana, the study conducted on 116 BU cases with HIV versus one of 116 controls did not show any association^[27]. But, in Benin, a significant association was found on 11 of 426 versus 2 of 613, $p = 0.003$. Another study initiated in Benin targeted the effect of HIV on BU severity. HIV testing was positive in 34 of 1511 BU patients and more than 70% of patients with HIV developed severe BU, compared with 50% of HIV-negative patients (OR 2.77, 95% CI, $P = 0.006$)^[28,29]. This work reported evidence suggestive of a high incidence of HIV infection in patients with BU compared with the general population.

In Cameroon, study conducted on 83 HIV-infected patients (adults and children) from 2008-2013 were compared to 376 HIV-negative patients admitted with BU diagnosis. HIV-positive patients had significantly more multiple BU lesions at the time of diagnosis compared to HIV-negative individuals (24% vs 11% respectively, $P = 0.004$). The proportion of patients with multiple lesions tended to be lower in the highest CD4 strata, but did not increase according to immunosuppression status (14%, 30% and 20%, respectively from highest to lowest CD4 strata; $p = 3$), in addition, HIV-positive patients were less likely to have a timely cure of BU, and wound closure time was negatively associated with CD4 cell count^[30]. In Zaire, a study conducted brought up the important issue of HIV/BU co-infection which could not be established and for which care was not available at that time, and the response of HIV/BU patients to rifampicin + streptomycin may lag behind compared with HIV-negative patients^[31].

It is becoming obvious that HIV infection has an effect on BU incidence mainly in Sub-Saharan Africa and its clinical presentation and treatment similar to tuberculosis. In tuberculosis, it is clearly known that the HIV/AIDS which lead to reduced CD4 helper T-cell activity, is a risk factor for tuberculosis, but immune protection mechanism in BU disease are not fully understood^[5,32]. In addition, IRIS or paradoxical reactions which is known to be common in HIV patient initiating ART with a variety of other microorganisms such as tuberculosis, *Cryptococcus*, *Mycobacterium avium* complex, etc..., may occur in HIV/BU co-infection patient during or after antibiotic and antiretroviral treatment (ART). It is unknown whether IRIS occurrence increase in HIV/BU co-infected patient or influenced by CD4 cell count base line level^[4,33]. A recent report in

Côte d'Ivoire revealed multifocal BU lesions developed in a HIV positive adult woman one month after BU antibiotic treatment added to ART at CD4 baseline of 51 cells/mm³^[34]. In HIV/TB co-infection, the incidence of TB associated IRIS increased in those start high active antiretroviral therapy (HAART) within 30 days of commencing TB treatment^[4,12]. This could be extrapolated to BU treatment in HIV-positive to explain the occurrence of IRIS in these patients. In fact, in tuberculosis the increased of TNF α level favored by lipopolysaccharides and other lipo-polysaccharides present in the cell wall, has been postulated as an initial step in the IRIS occurrence^[12]. Based on a large randomized controlled trial, it is recommended to delay ART till 5 weeks into antimicrobial treatment when managing HIV/Cryptococcus co-infection. And in TB/HIV co-infection, it is recommended that ART should be started 2 weeks into antimicrobial treatment. So, the optimal time to starting ART may depend on the specific co-infection and know interactions of some ART with the anti-microbial agents^[5,35].

This combined effect of IRIS associated with HIV on ART and the paradoxical reactions experienced in BU patients on antimicrobial treatment could possibly lead to real challenge for BU/HIV co-infection management^[5,12]. HIV infection may affect the outcome of BU treatment such as mortality, time to healing, recurrence rate and the incidence of paradoxical reactions or IRIS^[30].

The appropriate times to start ART in HIV patients with opportunistic infection has always been a dilemma to clinicians, since ART can trigger severe IRIS-like reactions when commence early. So, many questions rising should be answered to find the best way to manage HIV infection in patients with active BU, such as: when to start ART? What the optimal therapeutic regimens are? What are the potential interactions between ART drugs and antibiotic used to treat BU?

To give an answer to these questions, WHO Initiated a panel of experts in BU and HIV management to develop preliminary guidance principles for the BU/HIV co-infection management, based on review of available scientific evidence, current treatment experience, and global recommendations established for management of HIV infection and tuberculosis^[6]. These guidance principles suggested were as follow: (1) All BU patients should be offered quality provider-initiated HIV testing and counseling, and referred to health providers trained in HIV management where needed; (2) All HIV/MU co-infected patients should be actively screened for tuberculosis before commencing BU treatment and before starting ART; (3) For all patients with a CD4 cell count < 350 cells/mm³ or if the CD4 cell count is not available and the patient has advanced HIV disease (WHO clinical stages 3 or 4) cotrimoxazole preventive therapy (one 960 mg tablet daily) should be commenced immediately. In settings with highly prevalent malaria and/or severe bacterial infections, cotrimoxazole preventive therapy is initiated in all individuals regardless of CD4 cell count; (4) BU treatment should be commenced before commencing ART and provided for 8 weeks duration: The recommend combination is rifampicin 10 mg/kg daily up to a maximum of 600 mg/day plus streptomycin 15 mg/kg daily; Or an alternative regimen combining rifampicin 10 mg/kg daily up to a maximum of 600 mg/day to clarithromycin 7.5 mg/kg twice daily up to a maximum of 1,000 mg daily. This regimen should be used with caution due to the potential for significant drug interactions; (5) For antiretroviral therapy: If patients are already under ART then this should be continued; All patients with active BU who are HIV-positive and have a CD4 cell-count \leq 500 cells/mm³ or have WHO clinical stage 3 or 4, HIV disease should be offered ART; If CD4 count is not available, those in WHO category

2 or 3 BU disease should be offered ART; For eligible individuals, ART should be commenced as soon as possible after initiating BU treatment, preferably within 8 weeks, and as a priority in those with advanced HIV disease (CD4 < 350 cells/mm³ or WHO stage 3 or 4 disease); All children < 5 years of age should be commenced on ART within 8 weeks of BU treatment initiation. ART regimens should follow those recommended in the current consolidated guidelines for antiretroviral therapy. In fact, All children < 5 years of age should be commenced on ART as soon as possible within 8 weeks of the start of BU treatment. But, for children \geq 5 years of age, recommendations for the timing of ART initiation are the same as for adults^[10]; (6) The outcomes of HIV/BU co-infection management should be monitored and evaluated.

For proper use of these guidance principles some potential interactions between ART drugs and antibiotic used to treat BU should be known: (1) As recommended for TB/HIV patients on ART using rifampicin containing regimens, the non-nucleoside reverse transcriptase inhibitor (NNRTI) component of the ART regimen should be efavirenz, secondly, if this option is not available or appropriate then nevirapine can be used, but the lead-in dose of nevirapine should be omitted in the presence of rifampicin at the start of treatment^[6,36]; (2) Caution should be taken in the use of nevirapine particularly in patients with high or unknown CD4 cell counts at the ART initiation due to a potential increased risk of hypersensitivity and toxicodermia^[37]; (3) The levels of protease inhibitor (PI) medications are significantly reduced and toxicity is increased when they are used with rifampicin and therefore they are ideally avoided during BU antibiotic treatment^[6]; (4) Efavirenz can reduce clarithromycin levels by up to 39% and more significantly when co-administered with rifampicin^[38,39]. But, an alternative that avoids this interaction is rifampicin 10 mg/kg daily up to a maximum of 600 mg/day plus moxifloxacin 400 mg daily. In fact, fluoroquinolones have good in vitro activity against *M. ulcerans* and combined with rifampicin perform as well as rifampicin and streptomycin combinations^[40]. This has been successfully used in Australian non-HIV BU patients in Australia^[10]. moreover, moxifloxacin combined with rifampicin may have benefits in reducing the risk of rifampicin resistant TB if used in patients with undetected active drug sensitive TB^[10]; (5) And the use of tenofovir in HIV/BU co-infected patients being treated with streptomycin may increase the risk of renal toxicity^[41]. Therefore, patients should be monitored to detect any additional factors that may decrease renal function such as dehydration, and the use of non steroidal anti-inflammatory drugs.

The different programs for HIV, BU and TB control should work in a collaborative framework.

CONCLUSION

As, HIV/BU co-infection becomes more and more frequent in Sub-Saharan Africa where both disease incidence is high. This represents a challenge related to IRIS occurrence, how to find the optimal ART regimens, and when to start ART and antimicrobial treatment. Base on TB/HIV co-infection, the preliminary guidance protocol issue by WHO should be recommended, and further study should be initiated to show its efficacy and give answers to unknown mechanism of IRIS in HIV/BU co-infection.

CONFLICT OF INTERESTS

The authors declare that they do not have conflict of interests.

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