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Management of BU–HIV co-infection

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Abstract

BACKGROUND Buruli Ulcer (BU)–HIV co-infection is an important emerging management challenge for BU disease. Limited by paucity of scientific studies, guidance for management of this co-infection has been lacking.

METHODS Initiated by WHO, a panel of experts in BU and HIV management developed guidance principles for the management of BU–HIV co-infection based on review of available scientific evidence, current treatment experience, and global recommendations established for management of HIV infection and tuberculosis.

RESULTS The expert panel agreed that all BU patients should be offered quality provider-initiated HIV testing and counselling. In areas with high prevalence of malaria and/or bacterial infections, all patients with HIV co-infection should be started on cotrimoxazole preventative therapy. Combination antibiotic treatment for BU should be commenced before starting antiretroviral therapy (ART) and provided for 8 weeks duration. The suggested combination is rifampicin (10 mg/kg daily up to a maximum of 600 mg/day) plus streptomycin (15 mg/kg daily). An alternative regimen is rifampicin plus clarithromycin (7.5 mg/kg twice daily up to a maximum of 1000 mg daily) although due to drug interactions with antiretroviral drugs this regimen should be used with caution. ART should be initiated in all BU–HIV co-infected patients with symptomatic HIV disease (WHO clinical stage 3 or 4) regardless of CD4 cell count and in asymptomatic individuals with CD4 count $\leq$500 cells/mm^3. If CD4 count is not available, BU–HIV co-infected individuals with category 2 or 3 BU disease should be offered ART. For eligible individuals, ART should be commenced as soon as possible within 8 weeks after commencing BU treatment, and as a priority in those with advanced HIV disease (CD4 $\leq$ 350 cells/mm^3 or WHO stage 3 or 4 disease). All co-infected patients should be actively screened for tuberculosis before commencing BU treatment and before starting ART. Programmes should implement a monitoring and reporting system to document the outcomes of BU–HIV interventions.

CONCLUSIONS Knowledge of the clinical and epidemiological interactions between BU and HIV disease is limited. While awaiting more urgently needed evidence, current management practice of both diseases has been useful to build simple 'common sense' preliminary guidance on how to manage BU–HIV co-infection.

keywords antiretroviral therapy, Buruli ulcer, HIV, treatment

Introduction

Buruli ulcer (BU) is a necrotizing infection of skin and soft-tissue caused by *Mycobacterium ulcerans*. The disease pathogenesis is mediated through a potent exotoxin called mycolactone which is both toxic to tissues and impairs local and systemic immune responses to the infection (Guarner *et al.* 2003; Coutanceau *et al.* 2007).

BU is the third most common mycobacterial disease worldwide in immunocompetent people, with the greatest burden of disease in West and Central Africa (World Health Organisation 2014a). BU affects mainly children but can occur in all age groups, and commonly affects people in resource-limited remote areas with limited access to health care. Disease severity is described according to a WHO classification: Category 1 for single lesions <5 cm diameter, Category 2 for single lesions 5–15 cm diameter and Category 3 for single lesions >15 cm diameter, osteomyelitis, multiple lesions or lesions in a critical site (World Health Organisation 2012). Antibiotics are now the recommended first-line treatment (World Health Organisation 2012) but many challenges remain with respect to early diagnosis and initiation of treatment to reduce the morbidity, long-term disability and economic costs associated with the burden of disease (Stienstra *et al.* 2005; O'Brien *et al.* 2013a).

Areas of Africa endemic for BU are also endemic for HIV with adult HIV prevalence rates between 1% and 5%. Although there is a lack of information on the prevalence of BU–HIV co-infection, preliminary evidence suggests that HIV may increase the risk of BU (Johnson *et al.* 2008; Christinet *et al.* 2014; Yeboah-Manu *et al.* 2013). In the *Médecins Sans Frontières* programme in Akonolinga, Cameroon, the prevalence of HIV is approximately 3–6 times higher in BU treated patients than the regional estimated HIV prevalence (37% *vs.* 7% in women; 20% *vs.* 5% in men; and 4% *vs.* 0.7% in children; Christinet *et al.* 2014). Similar data have been reported from Benin, where patients with BU were eight times more likely to have HIV infection than those without BU (2.6% *vs.* 0.3%), and Ghana where HIV prevalence was 5 times higher in BU patients (5% *vs.* 0.9%; Raghunathan *et al.* 2005; Johnson *et al.* 2008).

There is an increasing recognition of BU–HIV co-infection as an important challenge for the management of BU disease in settings where the two diseases overlap (O'Brien *et al.* 2013a); however, guidance for the management of BU–HIV co-infection has been lacking. To address this issue, WHO recently issued preliminary guidance on the management of BU–HIV infection, but it was limited by the paucity of evidence and experience, and was largely extrapolated from the experience of TB/HIV co-infection, which may differ in terms of risks and benefits of recommendations (World Health Organisation 2012). Building on this work, this article summarises the conclusions of more recent guidance developed by a panel of clinicians and technical experts taking into consideration more recent evidence, preliminary data from ongoing management protocols and clinical experience in managing these two diseases (Tables 1 and 2).

Challenges in the co-treatment of BU–-HIV

HIV may affect the clinical presentation and severity of BU disease with a reported increased incidence of multiple, larger and ulcerated BU lesions in HIV-infected individuals (Johnson *et al.* 2002; Toll *et al.* 2005; Kibadi *et al.* 2010; Komenan *et al.* 2013; Christinet *et al.* 2014). It also appears that the presence and severity of BU may reflect the level of underlying immune suppression in an HIV-infected person. In the *Médecins Sans Frontières'* programme in Akonolinga, Cameroon, 79% of patients with category 2 or 3 BU lesions had a CD4 count ≤500 cells/mm^3; *vs.* 54% of those with category 1 lesions ($P = 0.019$) (Christinet *et al.* 2014) and the main lesion size was significantly larger with falling CD4 cell counts (Christinet *et al.* 2014). These findings need to be confirmed with further research.

There is minimal knowledge about the impact of HIV on BU treatment outcomes such as mortality, cure, recurrence, time to healing, long-term disability and the incidence of paradoxical reactions secondary to antibiotic treatment. Further data from Akonolinga, Cameroon suggested that in BU/HIV co-infected patients a CD4 cell count above 500 cell/mm^3 was associated with a reduction in the time needed to heal BU lesions by more than 50% compared to those BU/HIV co-infected patients with a CD4 count 500 cell/mm^3 or below (hazard ratio, 2.39; $P = 0.001$; 95% CI, 1.44–3.98), although HIV itself was not associated with differences in time to healing (Christinet *et al.* 2014). These findings need further confirmation in other settings.

BU–HIV co-infected patients often present with significant immunosuppression. 70% of patients in Akonolinga have CD4 counts ≤ 500 cells/mm^3 at BU diagnosis, and thus in need antiretroviral therapy (ART) (World Health Organisation 2013; Christinet *et al.* 2014). Data from this routine programme setting also suggest that mortality in BU patients was significantly higher in those with HIV co-infection than for those without HIV co-infection (11% *vs.* 1%, $P < 0.001$). Median CD4 cell count at baseline among the 8 deceased HIV-infected patients was 229 cell/mm^3 (IQR 98–378 cell/mm^3), death occurred early with a median time to death post BU diagnosis of 41.5 days (IQR 16.5–56.5 days) and none had received ART (Christinet *et al.* 2014).

There is uncertainty about the best way to manage HIV in patients with active BU, such as when to start ART, and what the optimal ART regimens are, given the potential for significant interactions between antiretroviral drugs and antibiotics used to treat BU. There is also a critical lack of information to know whether ART will influence the incidence and severity of paradoxical

Table 1 Considerations for drugs used to treat BU and HIV co-infection

	Potential concerns	Potential benefits
ARV drugs		
Efavirenz	Contraindicated in children <3 years of age Reduce clarithromycin levels Increased toxicity when combined with clarithromycin	Efavirenz levels remain therapeutic when combined with rifampicin Once daily administration
Nevirapine	Reduction in nevirapine levels when combined with rifampicin Twice daily administration Risk of hypersensitivity particularly at higher CD4 counts	Can be used in children <3 years of age
PI	Significant reduction in levels when combined with rifampicin. Some can be used with dose adjustments (double dose or increased boosting ritonavir dose), but with increased toxicity when combined with rifampicin	
Raltegravir	Limited data on safety and effectiveness when combined with rifampicin. Limited availability/high cost	
Tenofovir	Increased risk of renal toxicity when combined with streptomycin	Once daily administration
BU drugs		
Rifampicin	Significantly reduces levels of nevirapine and PI	Most effective drug for BU Oral administration
Streptomycin	Injectable agent Increased toxicity (renal and vestibular) Contraindicated in pregnancy	Most published evidence of effectiveness as companion drug to rifampicin in HIV-negative patients.
Clarithromycin	Reduced levels and increased toxicity when combined with efavirenz Twice daily administration	Oral administration Can be used in pregnancy
Moxifloxacin	Limited data on use in HIV positive patients Not recommended in pregnancy or children <18 years of age Limited availability/high cost	No interaction with ART drugs Once daily administration Oral administration Active against *M. tuberculosis*

PI, protease inhibitor.

reactions, and to guide the management of these reactions in HIV patients, especially those on ART.

Guiding principles for the management of BU–HIV co-infection

Buruli ulcer (BU) patients may represent a sentinel group of patients with a higher prevalence of HIV, and knowing the HIV status will affect treatment options and may influence mortality and BU outcomes. For these reasons, all BU patients should be offered quality provider-initiated HIV testing and counselling at their initial contact with the BU treatment centre. Those found to be HIV positive should be referred to health providers trained in HIV management. Ideally, this would be integrated within the BU treatment centres to facilitate timely ART initiation and avoid patient loss to follow-up that may occur when patients are referred to different centres. However, if HIV management in BU treatment centres is not possible, then referral to the nearest HIV treatment centre will be required. Good co-operation between the BU and HIV treatment programmes on a local, regional and national level should be established to ensure the highest standard of care for BU–HIV co-infected patients.

Combination antibiotic treatment for BU should be commenced before commencing ART for HIV to minimise pill burden and avoid drug interactions and side effects in the early stages of BU treatment, to allow the time needed for patient preparation for ART, and to follow the usual principle of HIV care to treat and stabilize any co-infections prior to commencing ART. Based on experience with excellent BU outcomes in non-HIV-infected populations (Chauty *et al.* 2007; Nienhuis *et al.* 2010; Sarfo *et al.* 2010), the recommended combination is rifampicin 10 mg/kg daily up to a maximum of 600 mg/day plus streptomycin 15 mg/kg daily. If this regimen is not tolerated, acceptable or available, then an alternative regimen is rifampicin 10 mg/kg daily up to a maximum of 600

Table 2 Guidance for the co-management of BU and HIV

Guidance	Basis for the Guidance
HIV Testing	
All BU patients should be offered quality provider-initiated HIV testing and counselling, and referred to health providers trained in HIV management where needed.	Best practice
Prophylaxis	
Cotrimoxazole preventive therapy (one 960 mg tablet daily) should be commenced immediately for all patients with a CD4 count <350 cells/mm^3 or if CD4 count is not available and the patient has advanced HIV disease (WHO clinical stages 3 or 4). In settings with highly prevalent malaria and/or severe bacterial infections, cotrimoxazole preventive therapy is initiated in all individuals regardless of CD4 cell count.	WHO Guidance for Cotrimoxazole prophylaxis
BU treatment	
Combination antibiotic treatment for BU should be commenced before commencing ART and provided for 8 weeks duration.	Based on WHO Guidance for ART initiation in TB co-infected patients
The recommend combination is rifampicin 10 mg/kg daily up to a maximum of 600 mg/day plus streptomycin 15 mg/kg daily.	Based on WHO guidance for BU treatment
An alternative regimen is rifampicin 10 mg/kg daily up to a maximum of 600 mg/day plus clarithromycin 7.5 mg/kg twice daily up to a maximum of 1000 mg daily. This regimen should be used with caution (see text).	Based on WHO guidance for BU treatment
Antiretroviral therapy	
If patients are already receiving ART then this should be continued.	Based on WHO Guidance for ART initiation in TB co-infected patients
ART should be recommended to all patients meeting the eligibility criteria as per the current WHO Consolidated guidelines for ART.	WHO Guidance for ART
If CD4 count is not available, those in WHO category 2 or 3 BU disease should be offered ART.	Expert opinion based on preliminary observational data
For eligible individuals, ART should be commenced as soon as possible after the start of BU treatment, preferably within 8 weeks, and as a priority in those with advanced HIV disease (CD4 < 350 cells/mm^3 or WHO stage 3 or 4 disease).	Based on WHO Guidance for ART initiation in TB co-infected patients
All children <5 years of age should be commenced on ART within 8 weeks of the start of BU treatment. ART regimens should follow those recommended in the current WHO consolidated guidelines for ART.	Based on WHO Guidance for ART initiation in TB co-infected patients and children
Tuberculosis	
All patients should be actively screened for tuberculosis before commencing BU treatment and before starting ART.	Best Practice
Monitoring and evaluation	
Programmes should implement a monitoring and reporting system to monitor and evaluate the outcomes of BU–HIV interventions.	Best Practice

ART, antiretroviral therapy.

mg/day plus clarithromycin 7.5 mg/kg twice daily (up to a maximum of 1000 mg daily); this was effective in observational studies in non-HIV-infected patients (Chauty *et al.* 2011). However, due to potential drug interactions with ART, this combination should be used with caution. At this stage, there is no evidence that the duration of BU antibiotic treatment needs to be prolonged beyond the standard recommended 8 week course for BU–HIV co-infected patients (World Health Organisation 2012).

As currently recommended for all HIV-infected individuals, a CD4 cell count should be determined for all BU–HIV positive patients to assess the level of HIV-associated immune suppression. If the CD4 cell count is equal to or less than 350 cells/mm^3, then prophylactic cotrimoxazole (960 mg tablet daily) should be commenced immediately to reduce mortality, morbidity and HIV disease progression (Suthar *et al.* 2012). If a CD4 count is not available and the patient has advanced HIV disease (WHO clinical stages 3 or 4) they should receive cotrimoxazole prophylaxis regardless of CD4 cell count (World Health Organisation 2006). In areas with high prevalence of malaria and/or severe bacterial infections, cotrimoxazole should be commenced regardless of CD4 cell count in all BU–HIV-infected patients and continued for life (World Health Organization 2014b).

If patients are already receiving ART, then this should be continued. All patients with active BU disease who are known or diagnosed as HIV positive but not on ART

should initiate ART if they have a CD4 cell count equal to or below 500 cells/mm^3, have advanced HIV disease (WHO clinical stage 3 or 4) or have other concomitant clinical conditions that meet the eligibility criteria for commencing ART consistent with current WHO recommendations (i.e. pregnancy, active TB, HIV/HBV co-infection with severe liver disease, HIV serodiscordant couples; World Health Organisation 2013). This aims to reduce HIV-associated mortality and morbidity, which is increased in patients with CD4 $\leq$ 500 cells/mm^3, and HIV transmission (World Health Organisation 2013). Programmatic evidence also suggests that mortality is increased in HIV-infected patients with BU if ART is not commenced (Christinet *et al.* 2014). Furthermore, as the immune system plays an important role in curing BU disease and in healing lesions, optimisation of immunity with ART may be important to combat BU disease and potentially improve treatment outcomes (healing times, cure rates, long-term disability and recurrence rates).

If a CD4 count is not available, those in WHO clinical stage 3 or 4 HIV disease should be initiated on ART. Preliminary evidence suggests that a high proportion of patients with category 2 and 3 BU disease are likely to have significant immunosuppression, and therefore in the absence of CD4 counts those with WHO category 2 or 3 BU disease should also be offered ART (Christinet *et al.* 2014). Those whose CD4 count is not available with WHO clinical stage 1 and 2 HIV disease and with WHO category 1 BU disease should not be offered ART.

Antiretroviral therapy (ART) should begin as soon as possible after the start of BU treatment, preferably within 8 weeks, and as a priority in those with advanced HIV disease (CD4 < 350 cells/mm^3 or WHO stage 3 or 4 disease). Patients with advanced HIV are at immediate risk of further life-threatening opportunistic infections and delay in ART initiation may result in significant HIV-associated morbidity and mortality (Lewden *et al.* 2014). This risk may further be increased by an increased risk of bacterial sepsis from secondarily infected BU lesions. In BU–HIV co-infected patients with CD4 $\leq$ 500 cells/mm^3 healing times are significantly more prolonged than among HIV positive individuals with CD4 > 500 cells/mm^3 (Christinet *et al.* 2014). Therefore, early reconstitution of immunity with advanced BU disease may be important. Furthermore, this recommendation also takes into account the fact that in routine programmes, there may be delays in ART initiation while patients wait for assessment, training and availability of ART after completing their BU treatment. Also, as patients may receive BU treatment a significant distance from ART centres, they may be lost to HIV care if ART initiation is delayed (Rosen & Fox 2011).

Patients with CD4 cell counts >500 cells/mm^3 should not commence ART until the CD4 count has fallen to or below 500 cells/mm^3 or other criteria for ART have been met (World Health Organisation 2013). In patients with CD4 cell counts >500 cells/mm^3, there is no evidence supporting reduced HIV-associated morbidity and mortality with ART initiation in BU patients. Furthermore, any potential benefit to BU treatment outcomes by early restoration of immune function following initiation of ART early during BU antibiotic treatment is possibly outweighed by the potential risks of increased side effects, pill burden and adherence difficulties. For patients with less advanced HIV disease (CD4 counts >500 cells/mm^3) and less advanced BU disease (WHO category 1) there is a risk of reduced BU treatment efficacy due to potential drug interactions, especially between efavirenz and clarithromycin, which favours the delay in initiation of ART. It is also possible that early initiation of ART will lead to an increased incidence of paradoxical reactions associated with immune reconstitution when combining BU antibiotic treatment and ART and this may lead to undesired consequences, especially if lesions are in sensitive areas (e.g. the face).

All patients should be actively screened for tuberculosis (TB) before commencing BU treatment and before starting ART (Getahun *et al.* 2011; World Health Organisation 2011). As most BU–HIV co-infected patients live in highly endemic areas for TB, there is an important risk of TB-co-infection. As HIV-infected patients have a higher risk of TB reactivation, especially when severely immunosuppressed, there is therefore a risk of co-existent active TB disease. Therefore, it is important to exclude active TB disease prior to commencing BU treatment, as BU treatment regimens are not adequate to treat active TB, which may result in TB-related mortality and morbidity and the development of drug resistant TB.

Finally, approaches to support adherence to drug treatments for BU and HIV should be integrated, and programmes should implement a monitoring and reporting system to monitor and evaluate the outcomes of BU–HIV interventions.

Antiretroviral treatment and BU treatment interactions

There are a number of important issues regarding the use of antiretroviral drugs in patients receiving antibiotic treatment for BU (Table 1). Firstly, 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 (Bonnet *et al.* 2013; World Health Organisation

2013). 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. Additionally, caution should be exercised in the use of nevirapine particularly in patients with high or unknown CD4 cell counts at initiation due to a potential increased risk of hypersensitivity and Stevens Johnson's syndrome (Shubber *et al.* 2013). Close monitoring during the initial weeks of therapy is recommended when nevirapine is initiated in these patients. An alternative, if available, is for an integrase inhibitor such as raltegravir to replace the nevirapine during the 8-week BU treatment (Grinsztejn *et al.* 2014).

There are concerns about significantly reduced levels of protease inhibitor (PI) medications and increased toxicity when they are used with rifampicin and therefore they are ideally avoided during BU antibiotic treatment. If the patient is already receiving a PI-based regimen, and is NNRTI-naïve and not infected with HIV-2, change the PI-based regimen to an NNRTI-based regimen using efavirenz. If the patient is not NNRTI-naïve or infected with HIV-2, then the recommended PI regimen to use is lopinavir (LPV)/ritonavir (RTV) at either double dose 800 mg/200 mg twice daily or standard LPV dose with increased dose of RTV (400 mg/400 mg), but this combination in higher doses is frequently associated with high levels of toxicity and requires close clinical and laboratory monitoring. Again an alternative, if available, is for an integrase inhibitor such as raltegravir to replace the PI during the 8-week BU treatment.

Efavirenz can reduce clarithromycin levels by up to 39% (Kuper & D'Aprile 2000) which likely further compounds the known significant reduction of clarithromycin levels when co-administered with rifampicin (Wallace *et al.* 1997; Alffenaar *et al.* 2010). Although the clinical consequences of these interactions are unknown, it could potentially lead to reduced effectiveness of the rifampicin/clarithromycin regimen for BU treatment, with secondary treatment failure and drug resistance. Increased toxicity is also reported when the 2 drugs are combined with 46% of patients reported to develop a rash (Bristol-Myers-Squibb 2010). Therefore, this combination should be used with caution. 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. Fluoroquinolones have good *in vitro* activity against *M. ulcerans* and combined with rifampicin perform as well as rifampicin and streptomycin combinations in the mouse model (Ji *et al.* 2006, 2007), have been successfully used in Australian non-HIV BU patients (Gordon *et al.* 2010; O'Brien *et al.* 2012; Friedman *et al.* 2013) and are included in WHO guidelines as an acceptable alternative agent (World Health Organisation 2012). Furthermore, 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 (O'Brien *et al.* 2013b), although this needs to be assessed against the potential risk of fluoroquinolone resistance developing in the less likely scenario of undetected rifampicin resistant TB being present. As experience using moxifloxacin in BU/HIV co-infection is limited, its use should be further studied and evaluated.

Finally, the use of the antiretroviral drug tenofovir in those being treated with streptomycin may increase the risk of renal toxicity. (Nelson *et al.* 2007) Therefore any additional factors that may decrease renal function (e.g. dehydration, use of non steroidal anti-inflammatory drugs) should be avoided and renal function closely monitored when using this drug combination.

Children

All children <5 years of age should be commenced on ART as soon as possible within 8 weeks of the start of BU treatment. For children ≥5 years of age, recommendations for the timing of ART initiation are the same as for adults. Efavirenz is not approved for clinical use in children <3 years of age. Therefore, in this age-group if initiating ART while on BU treatment with rifampicin, nevirapine should be used instead of efavirenz at a dose of 200 mg/m^2. An alternative is to use a triple NRTI ART regimen. If already on a PI-based ART regimen when commencing BU treatment with rifampicin, LPV/RTV can be continued but the dose of RTV should be increased to achieve a 1:1 ratio with LPV. Alternative options include either replacing the LPV/RTV with nevirapine at a dose of 200 mg/m^2 or using a triple NRTI regimen.

Pregnancy

Efavirenz is no longer contraindicated during the first trimester of pregnancy and can be used in ART regimens (World Health Organisation 2013). As streptomycin and moxifloxacin are not recommended during pregnancy, the preferred BU treatment regimen is rifampicin 10 mg/kg daily up to a maximum of 600 mg/day plus clarithromycin 7.5 mg/kg twice daily (up to a maximum of 1000 mg daily).

Research agenda

There are many important questions that need to be addressed to better understand the epidemiological, clinical and treatment implications of the interaction between BU

disease and HIV infection, such as an improved understanding of the burden of BU in HIV-infected patients and the relative risk of BU in HIV-infected *vs.* non-HIV-infected populations. Clinical questions that need to be answered include an improved understanding of the effect of HIV on BU disease patterns, severity and mortality rates stratified by levels of immune suppression, and an understanding of the effect of BU on HIV clinical disease.

More information is required to clarify the effect of HIV on BU treatment outcomes such as mortality, rate of healing, cure, recurrence and long-term disability. It needs to be determined if and which patients will benefit from ART during BU treatment looking at both BU and HIV treatment outcomes, and the optimal timing of ART commencement. Research is also required to explore the effectiveness and safety of drugs used for BU treatment in HIV-infected patients on ART. For instance, assessing the effectiveness and safety in HIV-infected patients of BU treatment regimens that combine rifampicin and moxifloxacin (O'Brien *et al.* 2013b) as well as investigating the pharmacokinetic, clinical and safety outcomes of rifampicin and clarithromycin regimens in patients receiving efavirenz. The incidence, severity, predictors (including ART), management and outcomes of paradoxical reactions during the antibiotic treatment of BU in HIV-infected patients, all need to be better characterised in order to better understand the role of immune reconstitution and its risks and benefits in co-infected patients. Finally, on an operational level, research is required to assess the integration of HIV diagnosis and treatment in BU treatment centres to determine best models of care for co-infected patients.

Important steps required to answer these questions include the development and implementation of a research agenda with WHO and groups experienced in HIV and BU care, and strengthening research capacity within BU treatment programmes (O'Brien *et al.* 2013a). This could potentially involve the implementation of prospective multicentric BU–HIV cohorts to improve the power of the research and allow the sharing of treatment experience.

Conclusions

There are many important challenges involved in the emerging clinical scenario of treating patients co-infected with BU and HIV. Scientific studies to guide practice are currently lacking and research into these issues is eagerly awaited. While awaiting more evidence, current practice for management of both diseases allows for simple 'common sense' preliminary guidance on how to respond when these diseases are combined.

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