Management of Buruli ulcer–HIV coinfection

Technical update

World Health Organization

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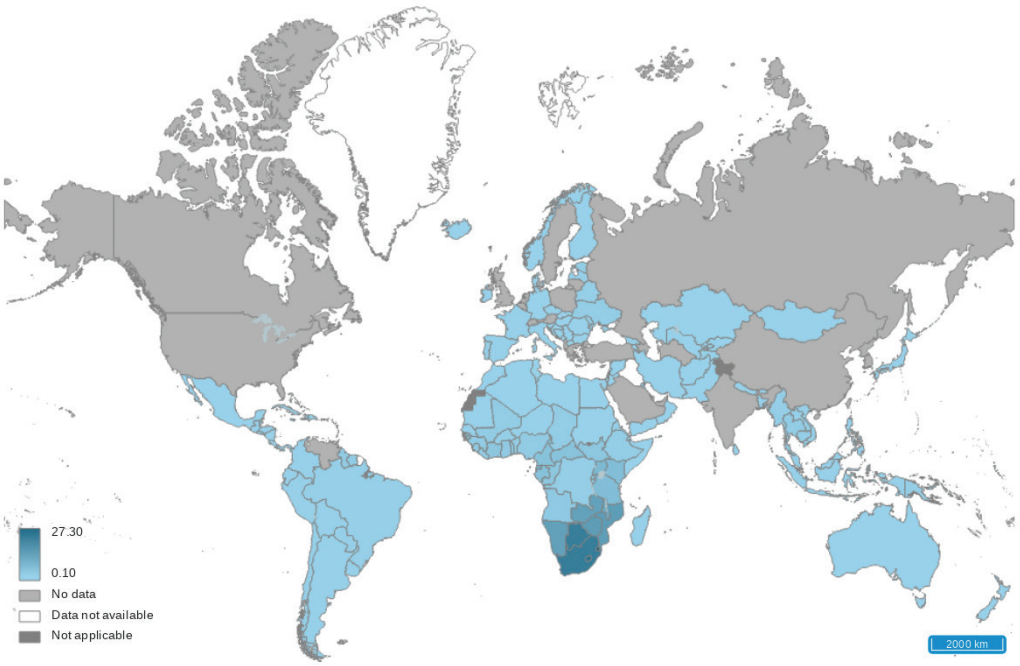
Key points

- All Buruli ulcer (BU) patients should be offered high-quality provider-initiated HIV testing and counselling.
- Combination antibiotic treatment for BU should be commenced before starting antiretroviral therapy (ART) and given for 8 weeks' duration. The recommended combination is rifampicin plus clarithromycin, although due to drug interactions this regimen should be used with caution when used with efavirenz. An alternative regimen is rifampicin plus moxifloxacin.
- Rapid ART initiation is recommended to all BU–HIV coinfected patients, regardless of clinical stage and CD4 cell-count.
- All BU–HIV coinfected patients should be actively screened for tuberculosis before commencing BU treatment and before starting ART.
- All BU–HIV coinfected patients with advanced HIV disease should be offered a package of care interventions including screening, treatment and /or prophylaxis for major opportunistic infections, rapid ART initiation and intensified adherence support interventions.
- Programmes should implement a monitoring and reporting system to monitor and evaluate the outcomes of BU–HIV interventions.

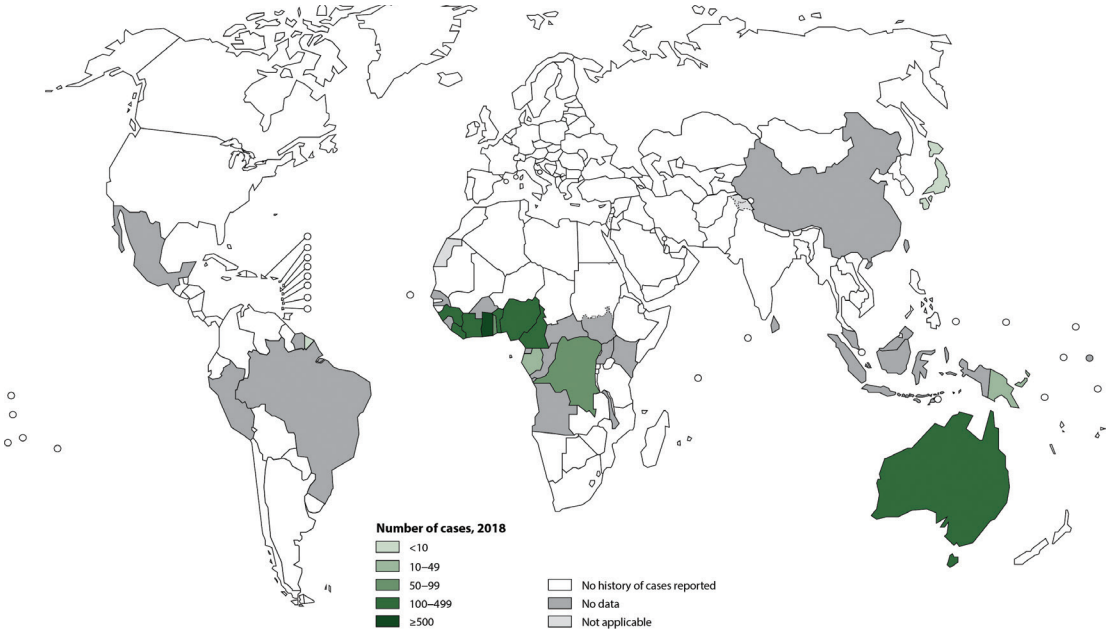
1. Background

Areas of Africa endemic for Buruli ulcer (BU), caused by *Mycobacterium ulcerans*, also have a high prevalence of human immunodeficiency virus (HIV), with adult prevalence rates between 1% and 5% (Maps). However, there is limited information on the prevalence of BU–HIV coinfection. Preliminary evidence suggests that HIV infection may increase the risk of BU disease (*1*–*3*). In the Médecins Sans Frontières project in Akonolinga, Cameroon, HIV prevalence was approximately 3–6 times higher among BU patients than the regional estimated HIV prevalence (*2*). Similarly in Benin and Ghana, BU patients were 8 times and 3 times respectively more likely to have HIV infection than those without BU (*1, 3*). Further study is needed to clarify this association and enhance knowledge about the prevalence of BU–HIV coinfection in endemic areas.

Prevalence of HIV among adults aged 15 to 49 (%)



Distribution of Buruli ulcer, worldwide, 2018



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 (*2–7*). Additionally in the Akonolinga project, the main lesion size was significantly increased with decreasing CD4 cell-count levels (*2*).

Little is known 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. The Akonolinga project reported that the mortality rate in BU–HIV coinfected patients treated for BU without antiretroviral therapy (ART) was significantly higher than for HIV non-infected BU patients (11% vs 1%, $P < 0.001$) (*2*). The median CD4 cell-count at baseline among the eight deceased HIV patients was 228.5 cell/mm^3 (IQR 98–378 cells/mm3); the median time to death from BU diagnosis was short (41.5 days, IQR 16.5–56.5 days). Additionally, in BU–HIV coinfected patients, ulcer healing took longer in those with CD4 levels below 500 cells/mm^3. These findings need further confirmation in other settings.

BU–HIV coinfected patients often present with severe immunosuppression: 22% of patients in Akonolinga at BU diagnosis had CD4 counts of < 200 cells/mm3; 48% had CD4 counts between 200 and 500 cells/mm^3 and were in urgent need of ART (*2, 8*). For patients with category II or III BU lesions, 79% had a CD4 count of ≤ 500 cells/mm3 compared with 54% of those with category I lesions, suggesting that the category of lesions may indicate the level of underlying immune suppression. In Ghana, 57% of BU–HIV coinfected patients presented with CD4 counts of < 200 cells/mm^3 (*3*). However, there is a lack of knowledge about how best to manage HIV infection in patients with active BU disease, including when ART should start and the optimal ART regimens.

There may be significant interactions between BU antibiotics and some antiretrovirals. For instance, dolutegravir (DTG) needs to be doubled-dosed when co-administered with rifampicin (*9*), while boosted protease inhibitors are generally not recommended for use in patients taking rifampicin because of significant reduction of their levels (*10*). Efavirenz is recommended over nevirapine in non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART regimens given the reduction in nevirapine levels when combined with rifampicin (*11*). However, efavirenz can reduce clarithromycin levels by up to 39% (*12*), which likely further compounds the known significant reduction of clarithromycin levels by rifampicin (*13*). Although the clinical consequence of this drug–drug interaction is unknown, it could lead to reduced effectiveness of the rifampicin and clarithromycin regimen for BU treatment, with secondary treatment failure and drug resistance. Increased toxicity is also reported when efavirenz and clarithromycin medicines are combined: 46% of patients are reported to have developed a rash (*14*).

There is also a lack of information to understand whether ART influences the incidence and severity of paradoxical reactions, and to guide the management of these reactions in patients on ART. Information on management of BU–HIV coinfection has been published in the international medical journal *Tropical Medicine & International Health* (*16*).

The World Health Organization (WHO) has issued preliminary advice on the management of BU–HIV coinfection. However, the process has been limited by the paucity of information upon which to base the guidance, and it is largely extrapolated from the experience of TB–HIV coinfection where significant differences in the risks and benefits of recommendations may apply (*17*). This technical update provides more recent advice 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.

2. Guiding principles of management

A. All BU patients should be offered high-quality provider-initiated HIV testing and counselling at their initial contact with the BU treatment centre.

B. Those found to be HIV-positive should be referred to clinicians trained in clinical management of HIV infection.

   a. Ideally, management should be integrated within the BU treatment centres to facilitate timely initiation of ART and avoid loss of patients to follow-up, which may occur during an external referral process for HIV care.

   b. If HIV management capacity in BU treatment centres is not possible, then referral to the nearest HIV treatment centre for care is recommended.

   c. Good cooperation between the BU and HIV treatment programmes at local, regional and national levels should be implemented to ensure the highest standard of care for BU–HIV coinfected patients.

C. Combination antibiotic treatment for BU should be commenced before initiating ART for HIV. The standard recommended 8-week duration of combination antibiotics for BU treatment should be given.

D. All patients with active BU who are HIV-positive should be offered ART regardless of clinical stage and CD4 cell-count. ART should begin as soon as possible, preferably within 2 weeks after the start of BU treatment.

E. For those BU–HIV coinfected patients with WHO clinical stage 3 or 4 HIV disease or those with a CD4 cell-count ≤ 350 cells/mm^3, prophylactic cotrimoxazole (one 960 mg tablet daily) should be commenced immediately. However, in settings of high prevalence of malaria and/or severe bacterial infections, co-trimoxazole prophylaxis should be commenced irrespective of CD4 cell-count.

F. All patients should be actively screened for active tuberculosis (TB) before commencing BU treatment and before starting ART. For those with symptoms suggestive of TB, this includes the use of Xpert MTB/RIF on sputum, and, if CD4 ≤ 100 cells/mm^3 or the patient is seriously ill (at any CD4 cell count), the use of LF-LAM on urine. In those without symptoms of TB, TB preventive treatment should be started according to local guidelines (*8*).

G. For those with a CD4 count < 200 cells/mm^3, it is recommended to screen with a cryptococcal antigen test and assess for danger signs of severe illness (*8*).

H. Approaches to support adherence to treatment for BU and HIV should be integrated.

I. A standardized monitoring and reporting system should be used to monitor the outcomes of BU–HIV interventions.

3. Recommended treatment for Buruli ulcer with HIV coinfection

3.1 Combination antibiotic treatment

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). However, clarithromycin and efavirenz interact to significantly reduce the dose of clarithromycin, potentially reducing its effectiveness and increasing the risk of toxicity (rash) (*18*). Rifampicin and clarithromycin should therefore be used with caution when combined with efavirenz.

3.1.1 *Alternative regimen*

Rifampicin 10 mg/kg daily (up to a maximum of 600 mg/day) plus moxifloxacin 400 mg daily. As experience using moxifloxacin in BU–HIV coinfection is limited, its use should be further studied and evaluated.

3.2 Antiretroviral therapy

3.2.1 *Regimens*

Important points regarding the use of ART medicines in patients receiving antibiotic treatment for BU:

a) Integrase inhibitors
   - A dolutegravir (DTG) based regimen is recommended as a preferred first-line regimen for adults, adolescents and children who are initiating ART. **See note on pregnancy below**.
   - However, due to a pharmacokinetic interaction with rifampicin, it is currently recommended that the dose of DTG should be increased to 50 mg twice daily when both drugs are used concomitantly.

b) Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
   - The preferred NNRTI component of an ART regimen should be efavirenz.[1] If this option is not available, then nevirapine (NVP) should be used as an alternative, but no lead-in dose of NVP is required in the presence of rifampicin at the start of treatment.[2]
   - Caution should be exercised in the use of NVP-containing regimens, particularly in individuals with high or unknown CD4 cell-counts at ART initiation, due to a potential increased risk of hypersensitivity and Stevens–Johnson syndrome. Close monitoring during the initial weeks of therapy is recommended when NVP is initiated in these patients.

c) Protease inhibitors (PIs)
   - Levels of the majority of PIs are significantly reduced when combined with rifampicin and should therefore be avoided during BU antibiotic treatment.
   - If the patient is already receiving a PI-based regimen, then the PI should be changed to DTG (with dose adjustment) as the preferred approach, or, if they are NNRTI-naive and not infected with the HIV-2 virus, the PI can be changed to an NNRTI-based regimen containing efavirenz. If neither of these options are possible, use the PI-based regimen of lopinavir (LPV)/ritonavir (RTV); adjusted doses (double-dose 800 mg/200 mg twice daily) can be considered. However, this regimen is associated with increased risk of toxicity and requires close clinical and laboratory monitoring.

[1] 400 mg or 600 mg per day of efavirenz are equivalent.

[2] If patients are unable to take EFV then, if available, the integrase inhibitor dolutegravir can replace the NVP.

d) Pregnancy
- Women and adolescent girls of childbearing age wishing to use DTG should be advised about the potential risk of neural tube defects in infants if used in the periconception period, and provided with reliable and effective contraception or an alternative ART regimen. However, DTG can be safely used in pregnant women after the first trimester and during breastfeeding periods.
- Efavirenz is no longer contraindicated during the first trimester of pregnancy.

e) Children
- All children should begin ART ideally within 2 weeks of the start of BU treatment.
- In children, DTG containing regimens should be used as the preferred first-line option. A raltegravir (RAL)-based regimen should be used as an alternative first-line regimen for infants and children for whom approved DTG dosing is not available.
- If DTG or RAL are not available, efavirenz can be used for children aged ≥ 3 years. As efavirenz is not approved for use in children aged < 3 years, an alternative is nevirapine at a dose of 200 mg/m^2. Another option, if already on a PI-based ART regimen when commencing BU treatment with rifampicin, is to continue LPV/RTV but increase the dose of RTV to achieve a 1:1 ratio with LPV.

3.2.2 *Rationale*

a) Reasons for performing HIV testing in all BU patients
- As BU may be increased in HIV-infected individuals, BU infection may indicate HIV coinfection.
- HIV coinfection can significantly impact BU management and treatment outcomes. Therefore, to optimize BU care, the HIV status of the patient needs to be determined.

b) Reasons explaining the criteria for, and timing of, ART initiation
- Patients with HIV are at risk of disease progression, and delay in ART initiation may increase HIV-associated morbidity and mortality. Preliminary evidence suggests that overall mortality is increased in HIV-infected patients with BU. This may be contributed to by an increased risk of bacterial sepsis from secondarily infected BU lesions (*2*).
- The immune system plays an important role in curing BU disease and in healing lesions. It has been found that, especially with CD4 counts of ≤ 500 cells/mm^3, healing times are significantly prolonged in HIV-infected patients (*2*). Therefore, early optimization 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). This also takes into account the reality that programming conditions may further delay the initiation of ART[1] ; it may be 3–4 months after BU diagnosis that ART will commence if ART initiation is delayed until BU treatment has been completed. Furthermore, as patients may receive BU treatment a significant distance from ART centres, they may be lost to HIV care if ART initiation is delayed.
- It is recommended that BU treatment be commenced before initiating ART to minimize pill burden and avoid drug interactions and side-effects in the early stages of BU treatment, to allow the time needed for ART patient preparation, and to follow the usual principle of HIV care to treat the coinfection before commencing ART.

[1] Delay can occur as patients wait for assessment, training and availability of ART after completing their BU treatment.

4. Research agenda

There are many important questions that need to be addressed with urgent scientific research to better understand the epidemiological, clinical and treatment implications of the interaction between BU disease and HIV infection. These include the following:

4.1 Epidemiology

Enhanced understanding of the burden of BU in HIV-infected patients and the relative risk of BU in HIV-infected compared with non-HIV infected populations..

4.2 Clinical

1. Improved understanding of the effect of HIV infection on clinical BU disease severity and mortality rates at stratified levels of CD4 cell-counts.
2. Understanding the effect of BU on HIV clinical disease.
3. Further clarifying whether the presence of BU disease and the clinical pattern of presentation reflect the level of HIV associated immunosuppression.

4.3 Treatment

1. Understanding the effect of HIV on BU treatment outcomes (rate of healing, cure, recurrence, long-term disability).
2. Understanding if and which patients will benefit from ART during BU treatment and the optimal timing of ART commmencement.
3. Improved effectiveness and safety of BU treatment in HIV-infected patients on ART. This includes assessing the effectiveness and safety in HIV-infected patients of BU–HIV treatment regimens such as the combination of rifampicin and clarithromycin in patients receiving efavirenz, the use of dolutegravir, and the use of rifampicin and moxifloxacin (*18*).
4. Improved understanding of the incidence, severity, predictors (including ART), management and outcomes of paradoxical reactions during the antibiotic treatment of BU in HIV-infected patients.

4.4 Operational

Assessing the integration of HIV diagnosis and treatment in BU treatment centres to determine best models of care for coinfected patients.

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