

# Management of Buruli ulcer–HIV coinfection

Technical update



World Health  
Organization

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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%.

However, there is a lack of information on the prevalence of BU–HIV coinfection. Further study is needed to clarify this association and enhance knowledge about the prevalence of BU–HIV coinfection in endemic areas.

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Technical update



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- Henry Asse  
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- Alexandra Calmy  
University of Geneva, Switzerland
- Annick Chauty  
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## Key learning points

- All Buruli ulcer (BU) patients should be offered high-quality provider-initiated HIV testing and counselling.
  - Cotrimoxazole prophylaxis should be commenced immediately for all HIV patients with a CD4 count  $\leq 350$  cells/mm<sup>3</sup>, or if CD4 count is not available and the patient has advanced symptomatic HIV disease (WHO clinical stage 3 or 4). In settings with high prevalence of malaria and/or severe bacterial infections, cotrimoxazole prophylaxis should be initiated in all individuals regardless of CD4 cell-count.
  - 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 streptomycin. An alternative regimen is rifampicin plus clarithromycin, although due to drug interactions this regimen should be used with caution.
- ALL BURULI ULCER (BU) PATIENTS SHOULD BE OFFERED HIGH-QUALITY PROVIDER-INITIATED HIV TESTING AND COUNSELLING.
- ART should be initiated in all BU–HIV coinfecting patients with advanced symptomatic HIV disease (WHO clinical stage 3 or 4) regardless of CD4 cell-count and in those asymptomatic individuals with CD4 count  $\leq 500$  cells/mm<sup>3</sup>. If CD4 cell-count is not available, BU–HIV coinfecting individuals with WHO 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<sup>3</sup> or WHO clinical stage 3 or 4 disease).
    - All BU–HIV coinfecting patients should be actively screened for tuberculosis before commencing BU treatment and before starting ART.
    - Programmes should implement a monitoring and reporting system to monitor and evaluate the outcomes of BU–HIV interventions.



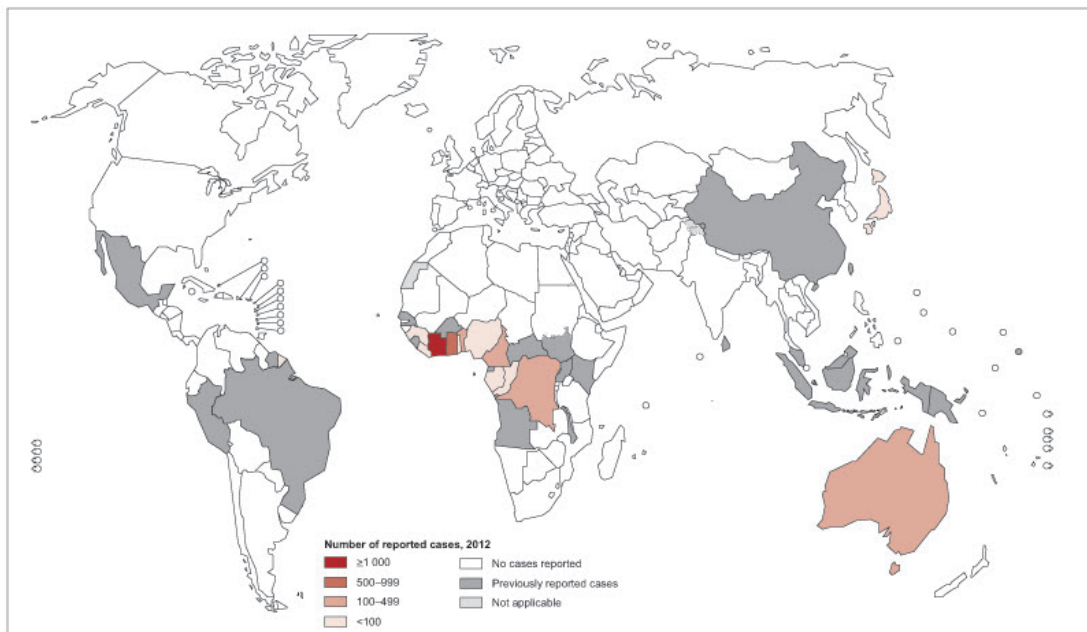
## Background

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% (Map<sup>1</sup>). However, there is a lack of 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 (3). Similarly

in Benin and Ghana, BU patients were 8 times and 4 times respectively more likely to have HIV infection than those without BU (1,2). Further study is needed to clarify this association and enhance knowledge about the prevalence of BU–HIV coinfection in endemic areas.

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 (3–6). Additionally in the Akonolinga project, the main lesion size was significantly increased with decreasing CD4 cell-count levels (3).

Distribution of Buruli ulcer, worldwide, 2013



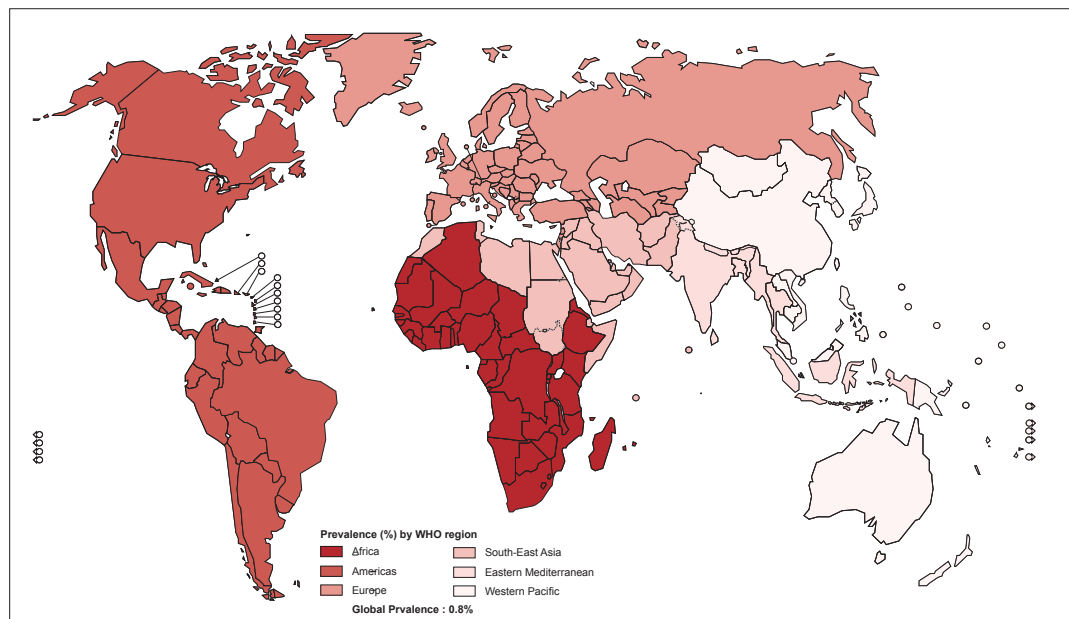
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Data Source: World Health Organization  
Map Production: Control of Neglected  
Tropical Diseases (NTD)  
World Health Organization





## Adult HIV prevalence (15–49 years), 2011, by WHO region



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

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%

BU–HIV coinfecting patients often present with severe immunosuppression: 22% of patients in Akonolinga at BU diagnosis had CD4 counts of  $<200$  cells/mm<sup>3</sup>; 48% had CD4 counts between 200 and 500 cells/mm<sup>3</sup> and required ART (3,7). For patients with category II or III BU lesions, 79% had a CD4 count of  $\leq 500$  cells/mm<sup>3</sup> compared with 54% of those with category I lesions, suggesting that the category of lesions may indicate the level of underlying immune suppression and thus the need for ART. However, there is a lack of knowledge about how best to manage HIV infection in patients with active BU disease, including who should be offered ART, when ART should start and the optimal ART regimens. There may be significant interactions between BU antibiotics and some antiretrovirals. For instance, boosted protease inhibitors are generally not recommended for use in patients taking rifampicin because of significant reduction of their levels (8). Efavirenz is recommended over nevirapine in NNRTI-based ART regimens given the reduction in nevirapine levels when combined with rifampicin (7). However, efavirenz can reduce clarithromycin levels by up to 39% (9), which likely further compounds the known significant reduction of clarithromycin levels by rifampicin (10). Although the clinical consequences of these drug–drug interactions are unknown, they could lead to reduced effectiveness of the rifampicin or clarithromycin regimen for BU treatment, with secondary treatment failure and drug resistance. Increased toxicity is also reported when these two

medicines are combined: 46% of patients are reported to have developed a rash (11). Additionally the use of tenofovir in those being treated with streptomycin may increase the risk of renal toxicity (12). 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 has recently been published in the international medical journal *Tropical Medicine and International Health* (13).

The World Health Organization (WHO) has issued preliminary guidance 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 (14). This technical update provides 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.

## 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 coinfecting 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. If available, a CD4 cell-count should be determined for all HIV-positive patients. However, if the CD4 cell-count is not available and the patient is symptomatic for HIV (WHO clinical stages 3 or 4), this should not delay the commencement of ART.
- E. For those BU–HIV coinfecting patients with WHO clinical stage 3 or 4 HIV disease or those with a CD4 cell-count  $\leq 350$  cells/mm<sup>3</sup>, prophylactic cotrimoxazole (one 960 mg tablet daily) should be commenced immediately. However, in settings of high prevalence of malaria and/or severe bacterial infections, cotrimoxazole prophylaxis should be commenced irrespective of CD4 cell-count.
- F. All patients with active BU who are HIV-positive and have a CD4 cell-count  $\leq 500$  cells/mm<sup>3</sup> or have WHO clinical stage 3 or 4 HIV disease should be offered ART.<sup>1</sup> 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<sup>3</sup> or WHO stage 3 or 4 disease).
- G. Patients with CD4 counts  $> 500$  cells/mm<sup>3</sup> should not commence ART until the CD4 count has fallen to or below 500 cells/mm<sup>3</sup> or other criteria for ART initiation have been met.

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<sup>1</sup> This also includes patients with other characteristics who meet the criteria for commencing ART (active TB, HIV–HBV coinfection, serodiscordant couples).

- H. If the CD4 cell-count is not available, those in WHO clinical stage 3 or 4 HIV disease should be offered ART commencing within 8 weeks of the start of BU treatment. For practical reasons, as because a significant proportion will have a  $CD4 \leq 500$  cells/mm<sup>3</sup> if tested, those with category II or III BU disease should also be offered ART commencing within 8 weeks of the start of BU treatment. Those in WHO clinical stages 1 and 2 and with WHO category I BU disease whose CD4 cell-count is not available should not be offered ART.
- I. All patients should be actively screened for active TB before commencing BU treatment and before starting ART.
- J. Approaches to support adherence to treatment for BU and HIV should be integrated.
- K. A standardized monitoring and reporting system should be used to monitor the outcomes of BU–HIV interventions.

## Recommended treatment for Buruli ulcer with HIV coinfection

### Combination antibiotic treatment

Rifampicin 10 mg/kg daily up to a maximum of 600 mg/day plus streptomycin 15 mg/kg daily.

### Alternative regimens

- a) 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) (15). This combination should therefore be used with caution.
- b) 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.

## Antiretroviral therapy

### Regimens

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



- a) Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
  - The preferred NNRTI-component of the ART regimen should be efavirenz. If this option is not available, then nevirapine (NVP) should be used, but no lead-in dose of NVP is required in the presence of rifampicin at the start of treatment.<sup>1</sup>
  - 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.

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<sup>1</sup> If patients are unable to take EFV then, if available, integrase inhibitors such as raltegravir can replace the NVP.

b) Protease inhibitors (PIs)

- Levels 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 if they are NNRTI-naïve and not infected with the HIV-2 virus the PI should be changed to an NNRTI-based regimen using efavirenz. If this is not possible, use the recommended PI-based regimen of lopinavir (LPV)/ritonavir (RTV) at adjusted doses [either double-dose 800 mg/200 mg twice daily or standard LPV dose with adjusted dose of RTV (400 mg/400 mg)]; but adjusted dose combinations are associated with increased risk of toxicity and require close clinical and laboratory monitoring.<sup>2</sup>

c) Nucleotide analogues

- The use of tenofovir (TDF) in those being treated with streptomycin may increase the risk of renal toxicity (12). 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.

d) Pregnancy

- Efavirenz is no longer contraindicated during the first trimester of pregnancy.

e) Children

- All children aged <5 years should begin ART within 8 weeks of the start of BU treatment.
- For children aged ≥5 years, recommendations for the timing of ART initiation are the same as for adults.
- Efavirenz is not approved for use in children aged <3 years. Therefore in this age-group:
- If initiating ART while on BU treatment with rifampicin, use nevirapine instead of efavirnez at a dose of 200 mg/m<sup>2</sup>. Alternatively use a triple NRTI ART regimen (AZT/3TC/ABC or AZT/3TC/TDF).
- If already on a PI-based ART regimen when commencing BU treatment with rifampicin, continue LPV/RTV but increase the dose of RTV to achieve a 1:1 ratio with LPV. Alternative options include replacing the LPV/RTV either with nevirapine at a dose of 200 mg/m<sup>2</sup> or with a triple NRTI regimen.

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<sup>2</sup> If available and appropriate, integrase inhibitors such as raltegravir can replace the PI.

## Monitoring of antiretroviral therapy

- a) Patients known to be HIV-positive or screened HIV-positive at initiation of BU treatment
- For patients with a CD4 count  $\leq 500$  cells/mm<sup>3</sup>, or with WHO clinical stage 3 or 4 HIV disease, commence ART as soon as possible after the start of BU treatment within 8 weeks, and as a priority in those with advanced HIV disease (CD4  $< 350$  cells/mm<sup>3</sup> or WHO stage 3 or 4 disease).
  - For patients with CD4 counts  $> 500$  cells/mm<sup>3</sup>, do not commence ART until the CD4 count has fallen to or below 500 cells/mm<sup>3</sup> or other CD4 independent criteria for ART initiation have been met.
  - If the CD4 count is not available, for patients in WHO clinical stage 3 or 4 HIV disease, commence ART within 8 weeks of the start of BU treatment. For practical reasons, and because a significant percentage of patients will have a CD4 count  $\leq 500$  cells/mm<sup>3</sup> if tested, also offer those patients with WHO category II or III BU disease ART commenced within 8 weeks of the start of BU treatment. Those in WHO clinical stage 1 and 2 HIV disease and in WHO category I BU disease whose CD4 count is not available should not be offered ART.
- b) Patients receiving ART when diagnosed with BU
- Continue ART treatment.
  - If the patient is receiving a regimen containing nevirapine, change the nevirapine to efavirenz if there is no contraindication to this antiretroviral. If this option is not available, continue the nevirapine.<sup>1</sup>
  - If the patient is receiving a PI-based regimen, then if NNRTI-naïve and not infected with HIV-2 the PI should be changed to an NNRTI-based regimen using efavirenz. If this is not possible or appropriate, use the recommended PI regimen of LPV/RTV at adjusted doses [either double dose 800 mg/200 mg twice daily or standard LPV dose with adjusted dose of RTV (400 mg/400 mg)]; but these adjusted dose combinations are associated with high levels of toxicity and require close clinical and laboratory monitoring.<sup>2</sup>
  - If the patient is taking TDF, and streptomycin is part of the BU treatment regimen, additional factors that may decrease renal function should be avoided and renal function closely monitored when using this drug combination.

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1 If available and appropriate, integrase inhibitors such as raltegravir can replace the NVP.

2 If available and appropriate, then the PI could be substituted for by integrase inhibitors such as raltegravir.



## 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 for explaining the criteria for and timing of ART initiation

- Patients with CD4 counts of  $\leq 500$  cells/mm<sup>3</sup> 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 (5).
- 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  $\leq 500$  cells/mm<sup>3</sup>, healing times are significantly prolonged in HIV-infected patients (5). 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<sup>1</sup>; it may be 3–4 months post 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.

- In patients with CD4 counts  $> 500$  cells/mm<sup>3</sup>, the potential benefit to BU treatment outcomes by early restoration of immune function following ART initiation early during BU antibiotic treatment is possibly outweighed by the potential risks of increased side-effects, pill burden and adherence difficulties. There is also a risk of reduced BU treatment efficacy due to drug interactions, especially between efavirenz and clarithromycin, which favour the delay in initiation of ART. Furthermore, it is possible that early ART initiation in patients with CD4 counts  $> 500$  cells/mm<sup>3</sup> will lead to an increased incidence of paradoxical reactions when combined with BU antibiotic treatment, which may lead to negative consequences, especially if

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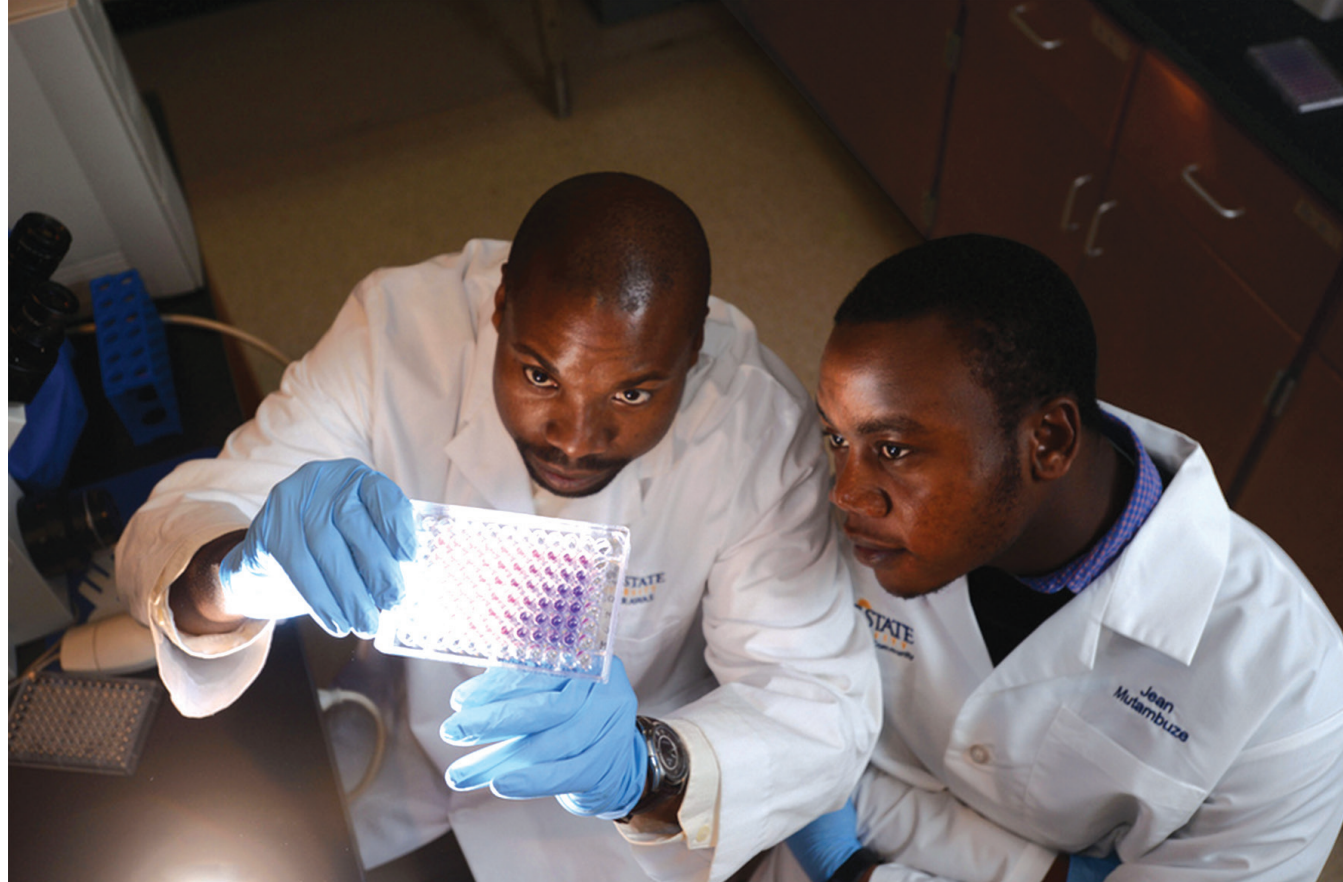
<sup>1</sup> Delay can occur as patients wait for assessment, training and availability of ART after completing their BU treatment.

lesions are in sensitive areas (e.g. the face). In addition, there is currently no evidence of mortality or morbidity benefits if ART is commenced in those with CD4 counts  $>500$  cells/mm<sup>3</sup>, and thus WHO guidelines do not recommend ART in this patient group unless they have advanced HIV disease (WHO clinical stage 3 or 4), are coinfectd with TB or HBV, or are an HIV-positive partner of a serodiscordant couple.

- Preliminary evidence suggests that patients with WHO category II and III BU disease are likely to have significant immunosuppression (79% of patients in the Akonolonga programme had a CD4 count of  $\leq 500$  cells/mm<sup>3</sup>); therefore in the absence of CD4 cell-counts it is preferable to start ART early (5).
- 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 co-infection before commencing ART.

BU MAY BE INCREASED IN  
HIV-INFECTED INDIVIDUALS

HIV COINFECTION CAN  
SIGNIFICANTLY IMPACT  
BU MANAGEMENT AND  
TREATMENT OUTCOMES



## 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:

### 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.

## 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.

## 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 commencement.
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 that combine rifampicin and clarithromycin in patients receiving efavirenz, rifampicin and moxifloxacin, and tenofovir and streptomycin (15).
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.

## Operational

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

THERE ARE MANY  
IMPORTANT QUESTIONS  
THAT NEED TO BE  
ADDRESSED WITH URGENT  
SCIENTIFIC RESEARCH

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