# Impact of Human Immunodeficiency Virus on the Severity of Buruli Ulcer Disease

## Results of a Retrospective Study in Cameroon

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## Introduction

Buruli ulcer (BU) is a necrotizing infection of skin and soft-tissue caused by *Mycobacterium ulcerans* and is the third most common mycobacterial disease worldwide in immunocompetent host after tuberculosis and leprosy. BU is considered a neglected tropical disease (NTD). M. ulcerans exact mode of transmission remains unknown but is associated with body's contact with slow flowing water.

Disease severity is described according to a WHO classification: Category 1 for single lesions < 5cm diameter, Category 2 for single lesions 5-15cm diameter, and Category 3 for single lesions > 15cm diameter, osteomyelitis, multiple lesions or lesions in a critical site.

The main burden of BU is in West and Central Africa (Figure 1). However this also corresponds to regions with high Human Immunodeficiency Virus (HIV) prevalence (Figure 1), and all 15 countries in West and Central Africa reporting BU cases have an HIV prevalence of 1-5%. Therefore there is a significant potential for BU and HIV to occur in the same individual.

The impact of HIV infection on the severity and prevalence of BU is unclear. Médecins Sans Frontières (MSF) implemented a BU treatment program with the Ministry of Health in Akonolinga, Cameroon. Since 2002, health workers were challenged by the clinical management of complicated HIV-BU co-infected patients. A retrospective study based on data collected in a MSF Buruli program in Akonolinga, Cameroon was performed.

The purpose of this study was to investigate HIV and BU interaction.

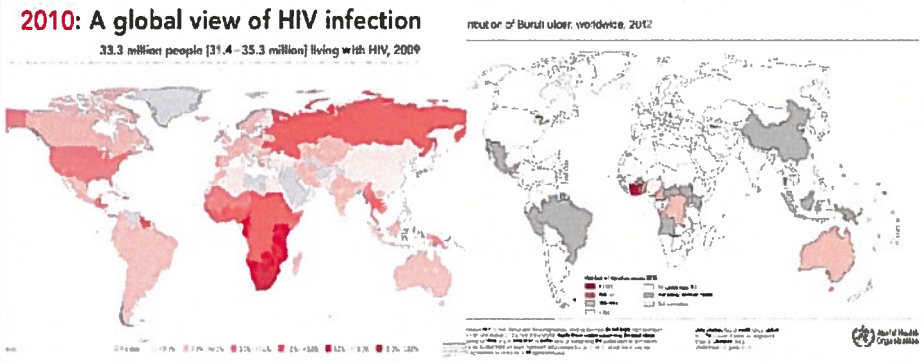


***Figure 1.*** Global distribution of HIV and BU estimated prevalence.

## Methods

Data were collected from January 1, 2002 to March 27, 2013. In order to investigate the association between the two infections, several analyses were retrospectively performed:

- HIV prevalence among BU patients was compared with regional HIV prevalence.
- Baseline characteristics of BU patients and mortality data were compared between HIV-negative and HIV-positive patients and according to CD4 cell count strata in the latter group.
- Buruli ulcer time-to-healing was assessed in different CD4 count strata
- Factors associated with BU main lesion size when entering care were identified.

Fisher's exact test was used to compare categorical variables, and the Kruskal-Wallis test was used for numerical variables. Survival analysis and Cox model were used for time-to-healing analyses and linear regression was used for BU main lesion size analyses.

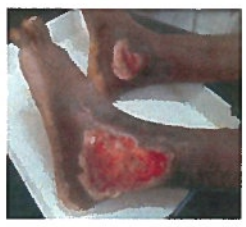

***Figure 2.*** Bilateral BU lesions on the ankles of a BU-HIV coinfected patient.

## Results

1130 patients with a first episode of BU were included in the analysis. The following graphs illustrate the main results.

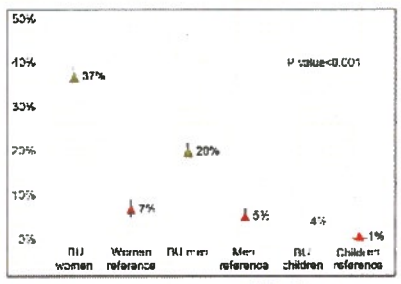


***Figure 3.*** HIV prevalence among BU patients is significantly higher than HIV estimated prevalence in referenced general population

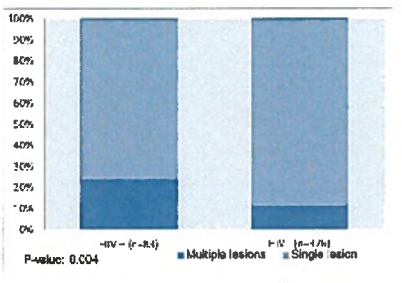


***Figure 4.*** Proportion of multiple BU lesions (severity criteria) is significantly higher among HIV+ than among HIV- populations

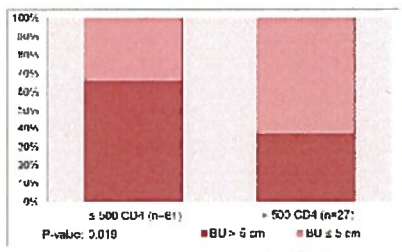


***Figure 5.*** Proportion of large BU lesions significantly higher among immunosuppressed HIV positive patients

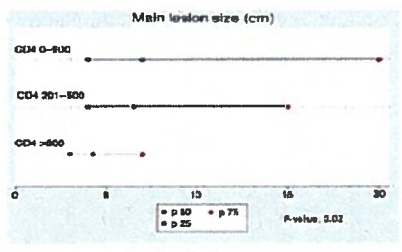


***Figure 6.*** BU lesion size significantly and gradually increases with immunosuppression among HIV positive patients

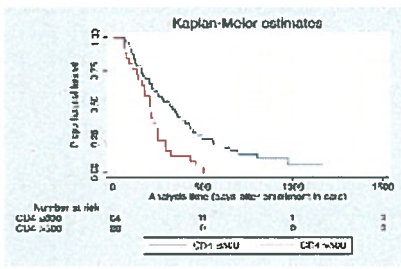


***Figure 7.*** Time to heal is significantly and independantly increased with immunosuppression among HIV positive patients
HR: 2.39 P =0.001 95% CI, 1.44–3.98

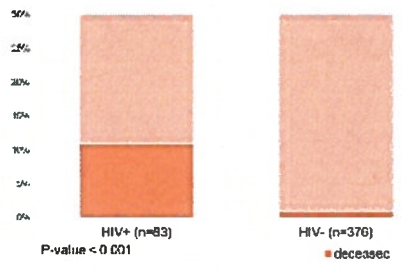


***Figure 8.*** Proportion of patients deceased among BU HIV+ coinfected population compared to BU HIV- population.

CD4 cell count median among the 8 deceased patients: 228.5 cell/mm3 (IQR, 98–378). None was on antiretroviral therapy (ART). Median time to death : 41.5 days (IQR, 16.5–56.5).

CD4 cell count < 500 cell/mm$^3$ significantly associated with a larger main BU lesion size (β-coefficient, −0.50; P = .015; 95% confidence interval [CI], −0.91–0.10) in the multivariable analysis.

**Based on the study's results, an expert panel organized by WHO agreed on guidance principles:**

**HIV Testing**

All BU patients should be offered quality provider-initiated HIV testing and counseling, and referred to health providers trained in HIV management if test positive.

**Antiretroviral therapy**

For eligible individuals, ART should be started 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).

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 antiretroviral therapy.

If CD4 count is not available, BU/HIV co-infected individuals with category 2 or 3 BU disease (lesions > 5 cm or multiple lesions) should be offered ART.

## Conclusions

The conclusions of the study reinforced the hypothesis that patients who are HIV positive are at higher risk for BU. It also showed that HIV-induced immunosuppression has a significant impact on BU clinical presentation and disease evolution. HIV-BU co-infected patients seem to be highly vulnerable with a high mortality rate despite relatively high CD4 cell count.

This study based on observed data collection revealed important new information regarding the clinical and epidemiological interactions between BU and HIV disease. It shows that well conducted operational research can impact WHO guidance for HIV-NTD, a field where it is difficult to conduct expensive clinical research because of the lack of interest and resources.

## Future proposals

To collect data in several observational cohorts of patients with BU in different countries and setting in order to further investigate the disease and its interaction with HIV infection. This will allow to strengthen the validity of the study results and to investigate other important aspects, such as the most adequate BU antibiotic treatment in the frame of an HIV infection, antiretroviral treatment and its introduction in the course of Buruli Ulcer disease.

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