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Management of Buruli ulcer / HIV coinfection: from operational research to WHO guidance.

Christinet V^{1,2,3}, O'Brien DP^{4,5,6}, Comte E²

1. HIV unit, University Hospitals of Geneva, Geneva, Switzerland 2. Médecins Sans Frontières, Geneva, Switzerland 3. Swiss Tropical and Public Health Institute, Basel, Switzerland 4. Manson Unit, Médecins Sans Frontières, London, United Kingdom 5. Department of Infectious Diseases, Barwon Health, Geelong, Australia 6. Department of Medicine and Infectious Diseases, Royal Melbourne Hospital, University of Melbourne, Australia.

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. 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.

BU is considered a neglected tropical disease (NTD). BU Conferences are organized regularly by the World Health Organization (WHO) to put together new scientific evidence. The impact of HIV infection on BU severity and prevalence remains unclear. Médecins sans frontières (MSF) implemented a BU treatment programme with the Ministry of Health in Akonolinga, Cameroon. Since 2002, health workers were challenged by the clinical management of complicated HIV-BU coinfecting patients. The retrospective study based on data collected in a MSF Buruli program in Akonolinga, Cameroon was performed.

2010: A global view of HIV infection

33.3 million people [31.4–35.3 million] living with HIV, 2009

Distribution of Buruli ulcer, worldwide, 2012

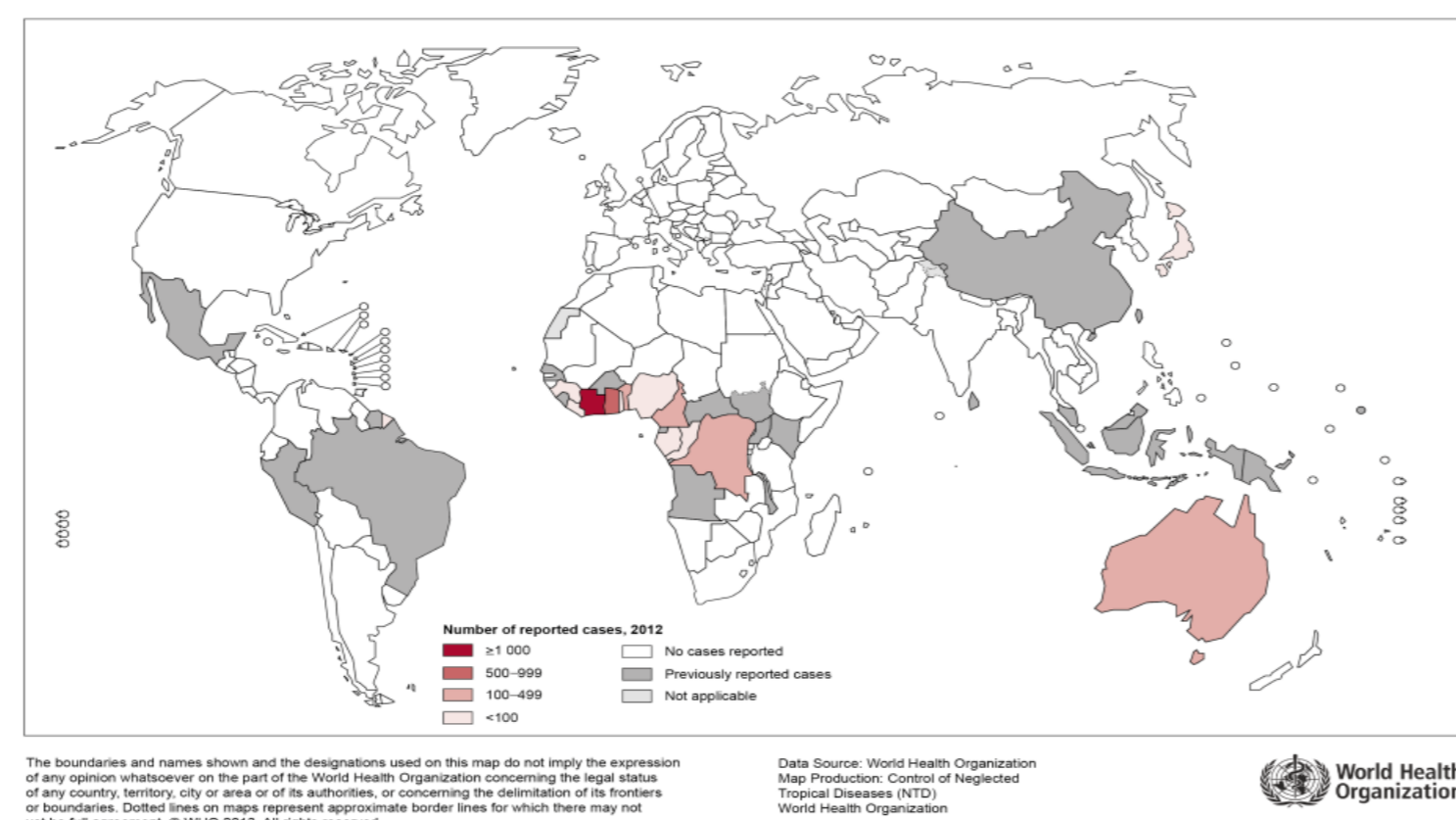


Figure 1. Global distribution of HIV and BU estimated prevalence.

Materials and methods

Data were collected from January 1, 2002 to March 27, 2013. Several analyses were 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.



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

Results

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

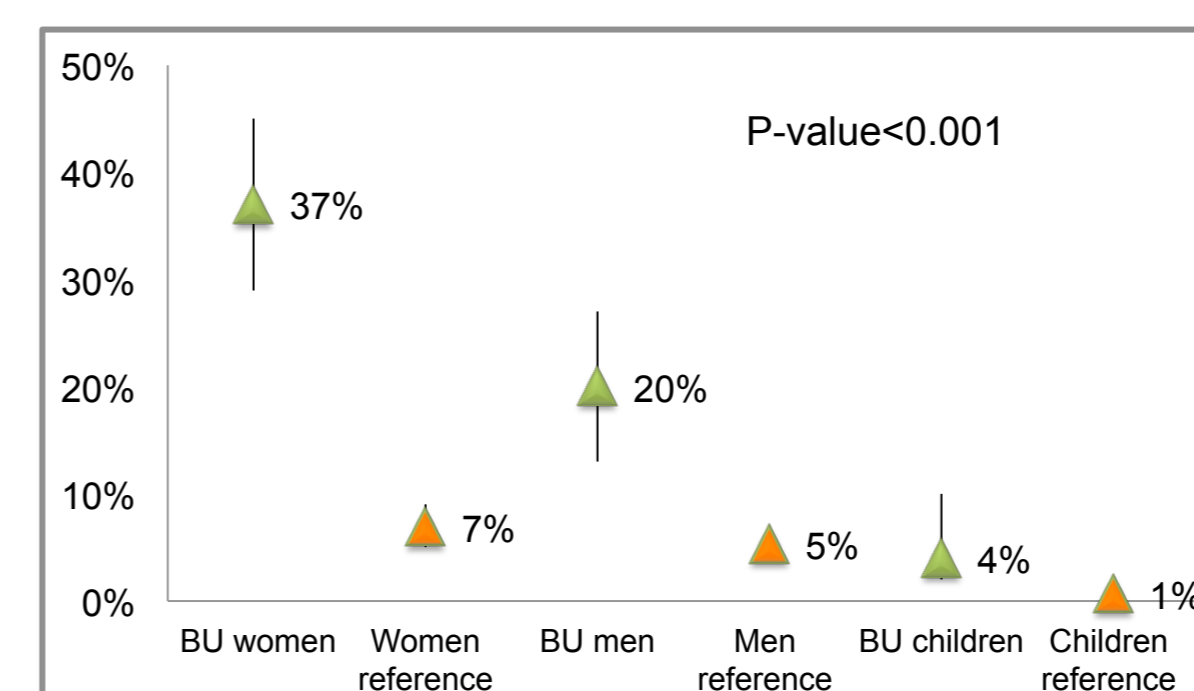


Figure 3. HIV prevalence among BU patients is significantly higher than HIV estimated prevalence in referenced general population

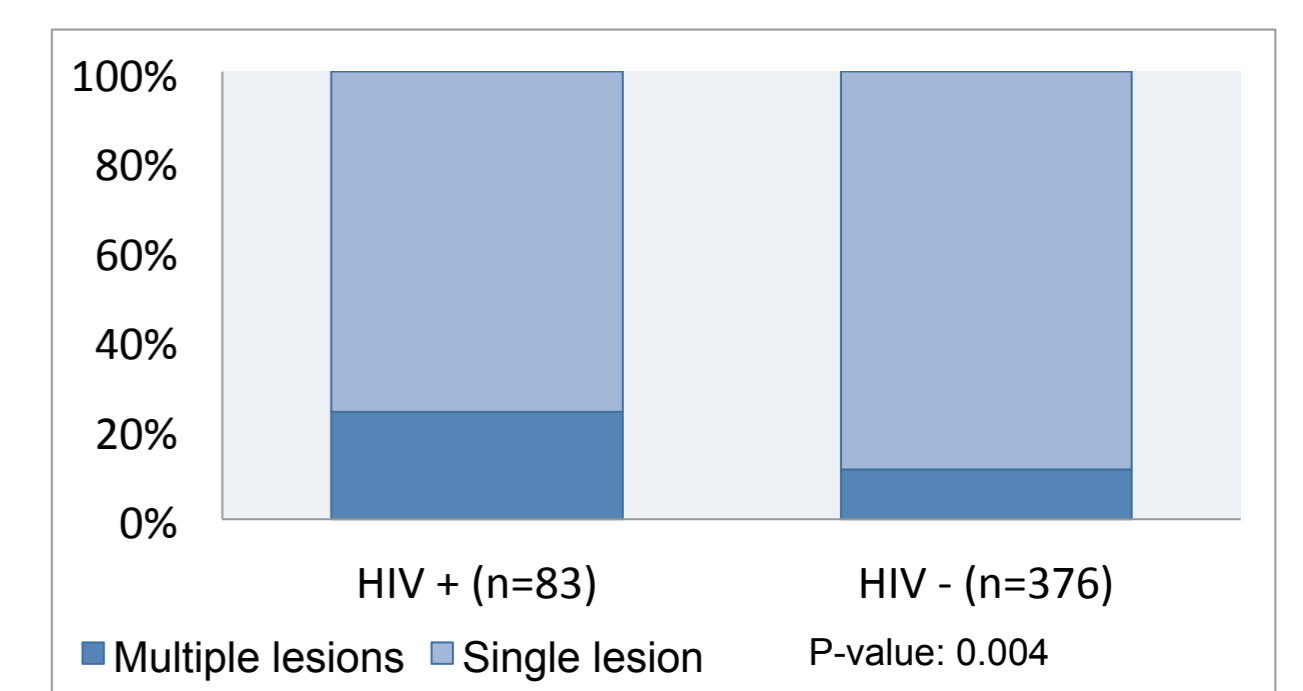


Figure 4. Proportion of multiple BU lesions (severity criteria) is significantly higher among HIV+ than among HIV- populations

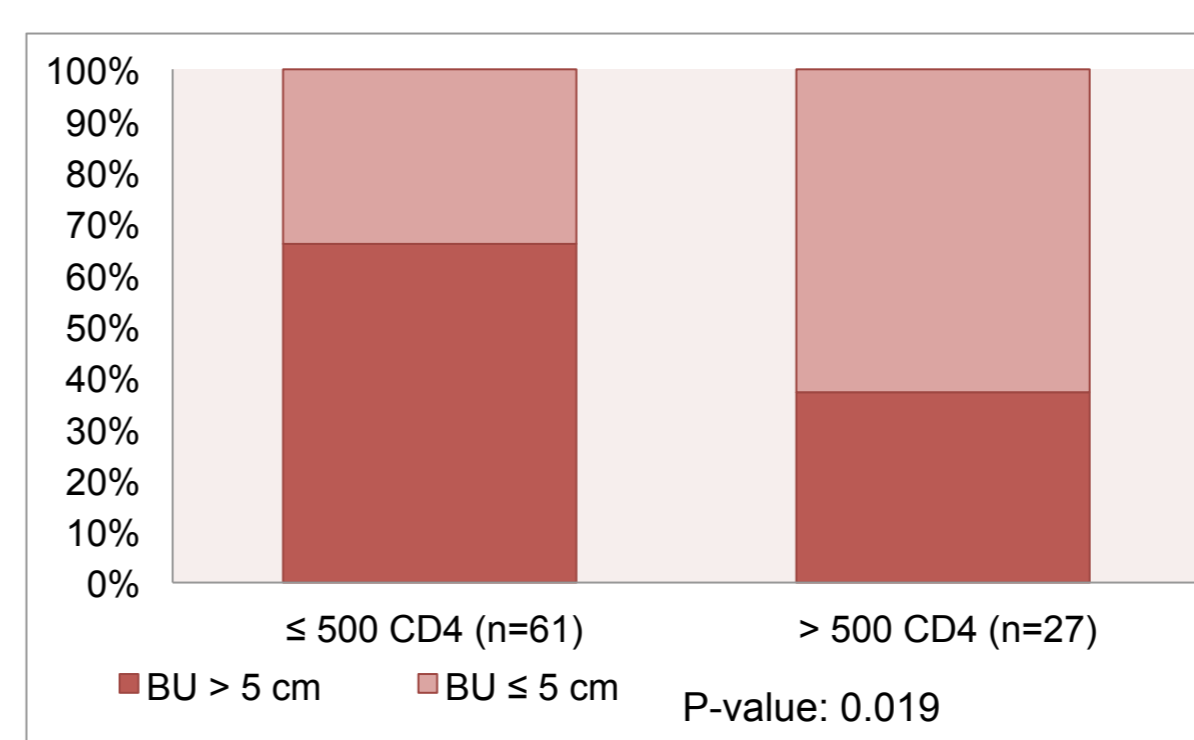


Figure 5. Proportion of large BU lesions significantly higher among immunosuppressed HIV positive patients

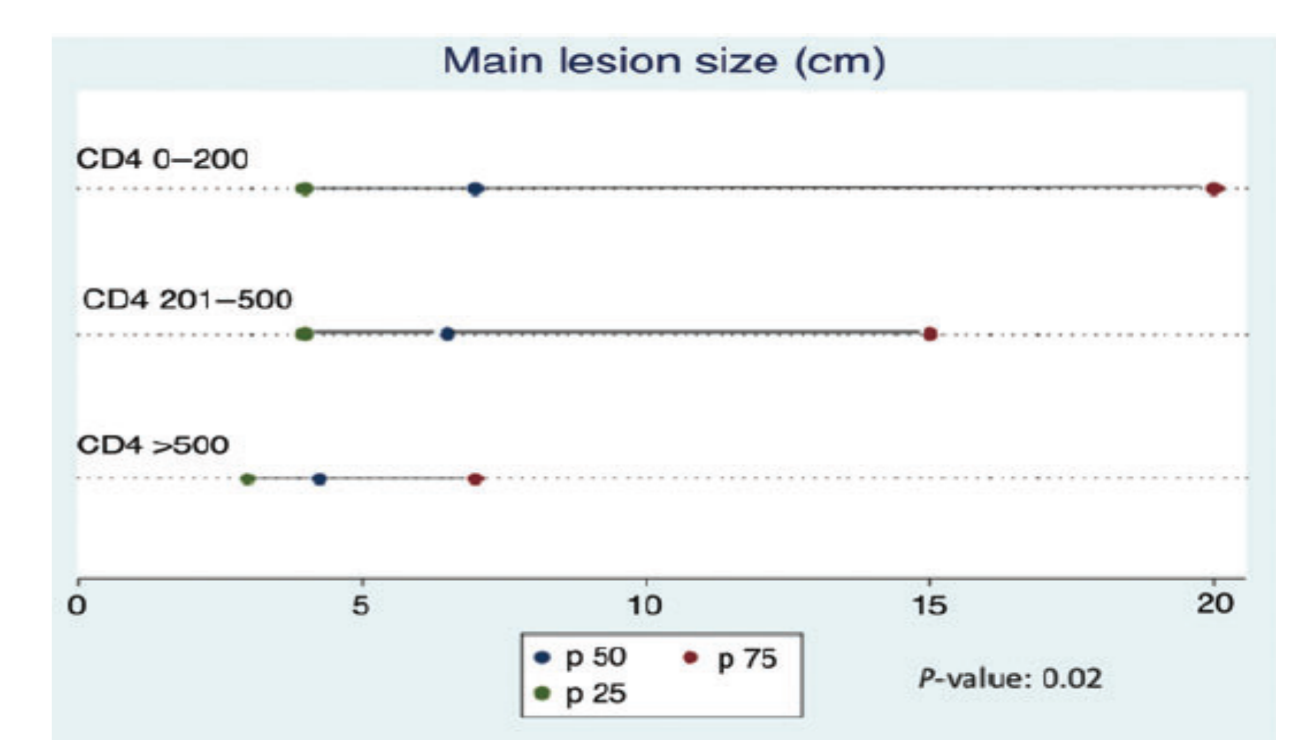


Figure 6. BU lesion size significantly and gradually increases with immunosuppression among HIV positive patients

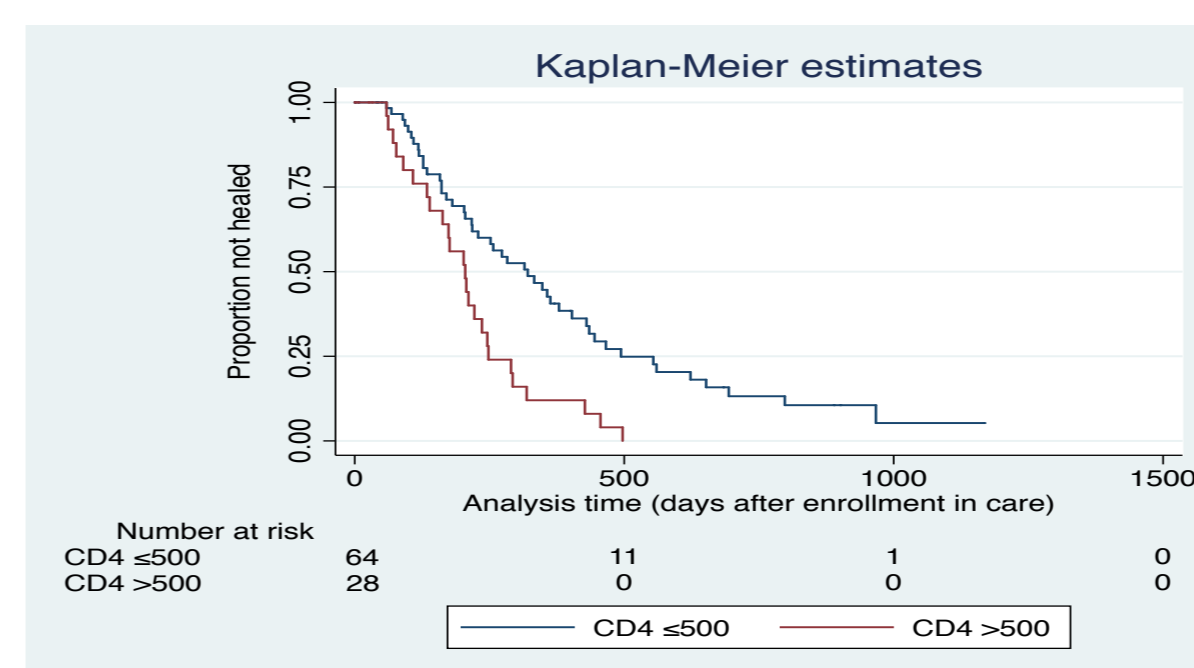


Figure 7. Time to heal is significantly and independently increase with immunosuppression among HIV positive patients

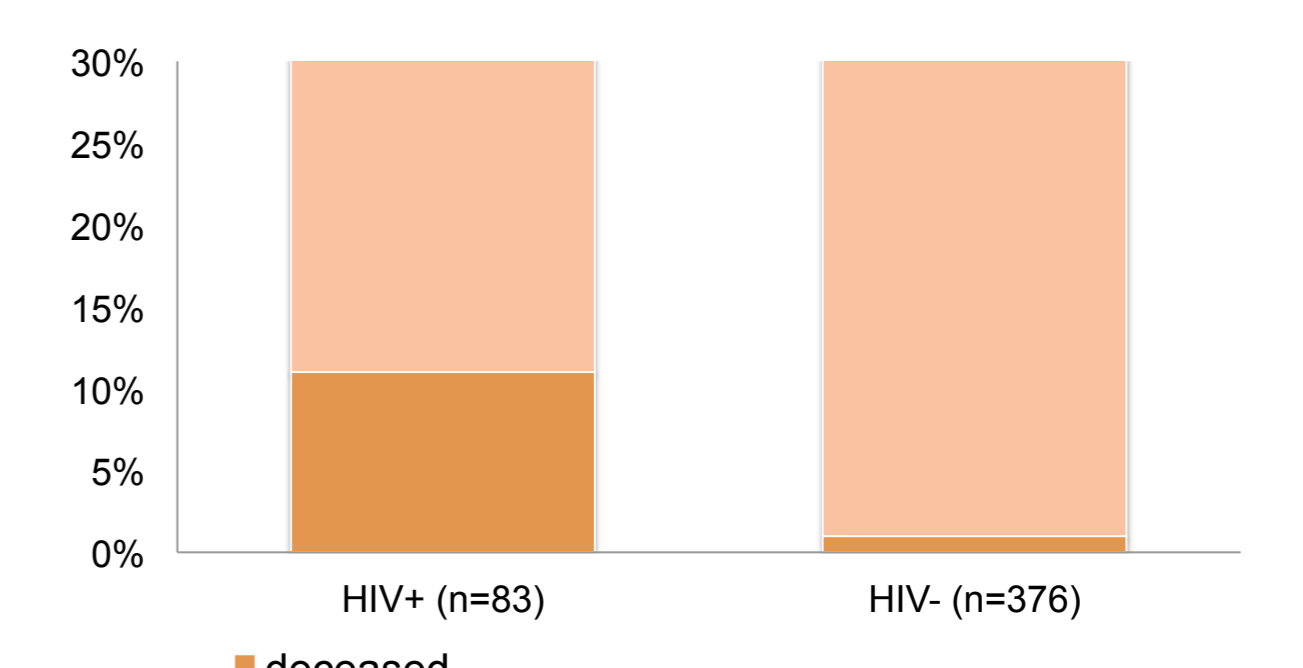


Figure 8. Proportion of patients deceased among BU HIV+ coinfecting population compared to BU HIV- population.

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

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 where needed.

Antiretroviral therapy

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/mm³ 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 coinfecting 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 coinfecting patients seem to be highly vulnerable with a high mortality rate despite relatively high CD4 cell count.

For several years, the intermediate analyses of the study were regularly presented at WHO conferences on BU. This has raised awareness on the interaction between HIV and BU infections among BU experts. These results were also presented in several HIV conferences. A panel expert on HIV-NTD was organized by WHO. This group developed a simple 'common sense' preliminary international guidance for the clinical management of BU/HIV coinfection. A symposium on HIV-NTD was held in HIV francophone conference in 2014.

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 elaborate an exhaustive literature review on the interaction between HIV and 5 NTD, in order to raise interest in this field and to define important questions that are remaining to establish a research agenda.
- To set up a NTD clinical care, teaching and research center in Akonolinga with a which will allow future observational research including on HIV and NTD interaction.