How MSF operational research in a neglected disease (Buruli ulcer) treatment programme can impact international management guidelines

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Introduction

The main burden of Buruli Ulcer (BU) is in West and Central Africa (Figure 1). However this also corresponds to regions with high 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 and BU-HIV coinfection is an important emerging management challenge for BU disease.

Despite this,there is little known about he interaction between BU and HIV. For example, is the prevalence of HIV increased in BU patients? Are there any clinical consequences of HIV infection in BU patients such as effects on disease presentation and severity. Does HIV effect outcomes on treatment such as mortality, time to healing, and cure rates? What are the management implications of HIV infection in BU patients such as when to start antiretroviral therapy and what are the optimum BU treatment regimens to use?

Limited by the paucity of scientific studies, guidance for management of this coinfection has been lacking. Therefore as a WHO initiative, a panel of experts in BU and HIV management were convened to develop guidance principles for the management of BU/HIV coinfection.

Here we describe how analysis of data from the BU treatment programme of Médecins Sans Frontières in Akonolinga, Cameroon provided some of the scientific basis for development of guidance principles for BU/HIV coinfection.

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

MSF-Akonolinga, Cameroon

•This was a BU treatment programme based in a District Ministry of Health Hospital.
•Prospective data was collected on all BU treated patients.
•The analysis included1130 patients with a first episode of BU treated from 1/1/2002 to 27/3/2013

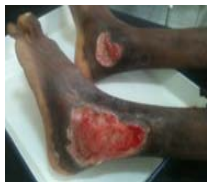


Figure 2. On the left an image demonstrating the increased severity of BU disease in HIV coinfected patients. On the right the BU pavillion in Akonolinga, Cameroon.

Results:

The prevalence of HIV in BU patients

	Female with BU ≥15yrs	Female regional (15-49yrs)	Men with BU ≥15yrs	Men regional (15-49yrs)	Children with BU <15yrs	Children regional	P-value
All BU patients	37% (52/141)	8%	20% (24/123)	4.7%	4% (5/114)	0.68%	<0.001
PCR confirmed BU patients	39% (34/87)	8%	17% (15/88)	4.7%	5% (4/73)	0.68%	<0.001

Figure 3: HIV prevalence in BU patients compared with mean HIV prevalence of local province (2004-2011) for adults and National HIV prevalence among 0-14yrs (UNICEF).

The effect of HIV on the clinical presentation.

	Single lesions	Multiple lesions	p-value
HIV + (n=83)	63 (76%)	20 (24%)	<0.01
HIV – (n=376)	333 (88%)	41 (11%)	

• HIV+ patients tended to have larger BU lesions: diameter 5.5 (IQR 3-12) *vs* 5.0 cm (IQR 2-9.5; *p*=0.12)
• A higher proportion of HIV+ patients had ulcerated lesions (93% *vs* 86%; *p*=0.12)

The effect of immunosuppression on the size of a BU lesion

	Cat 1	Cat 2/3	p-value
CD4<500	21 (55%)	40 (80%)	0.02
CD4>500	17 (45%)	10 (20%)	

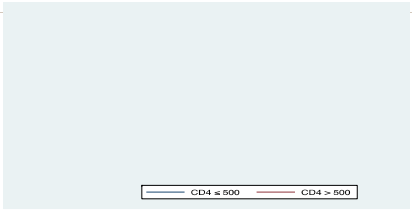
The level of immune suppression at diagnosis of BU/HIV patients

• 92/121 (76%) HIV+ patients tested since 2002 had CD4 data
• 20 (22)%: ≤200 cells/mm^3
• 44 (48%): 201-500 cells/mm^3
• 28 (30%): >500 cells/mm^3

The affect of HIV on mortality

• Mortality rate higher among HIV+ than HIV- BU patients [8/83 (11%) vs 5/376 (1%); p<0.001]
• Median CD4 cell count among the eight deceased HIV patients: 229 cell/mm^3 (IQR 98-378)
• Median duration until death: 41.5 days (IQR 16.5-56.5 days)
• None were on antiretroviral therapy

The effect of HIV immune suppression on time for BU wound healing



CD4>500 RR: 2.38, 95%CI 1.43-3.96; p<0.001

Recommendations of BU/HIV expert panel influenced by results from Akonolinga

•All BU patients should be offered quality provider-initiated HIV testing and counselling
•Combination antibiotic treatment for BU should be commenced before starting ART
•ART should be initiated in all BU/HIV coinfected patients with symptomatic HIV disease (WHO clinical stage 3 or 4) regardless of CD4 cell count and in those asymptomatic individuals with CD4 count ≤500 cells/mm^3
•If CD4 count is not available, those in WHO category 2 or 3 BU disease should be offered ART.
•Patients with CD4 ≥500 cells/mm^3 do not commence ART until CD4 has fallen below 500 cells/mm^3 or other criteria for ART have been met
•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).

Conclusions

An MSF programme focussed on the neglected tropical disease of BU, through clinical practice and study of observational data, allowed acquisition of important knowledge regarding the clinical and epidemiological interactions between BU and HIV disease. This was important in building simple 'common sense' preliminary international guidance for the management of BU/HIV coinfection

Acknowledgements

• MSF/MoH staff and patients Akonolinga, Cameroon
• MSF, Geneva: A. Antierens, L. Rossel, G. Alcoba
• Departments of NTD and HIV WHO: K. Asiedu, M. Vitoria.

Presented at WHO Buruli Ulcer Scientific Meeting, Geneva, Switzerland. May 23-35, 2015.