OPINION

Moxifloxacin for Buruli ulcer/HIV coinfected patients: kill two birds with one stone?

Daniel P. O’Brien¹,²,³, Eric Comte⁴, Nathan Ford⁵, Vanessa Christinet⁶ and Philipp du Cros¹

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Buruli ulcer is a necrotizing infection of skin and soft tissue caused by Mycobacterium ulcerans that results in significant morbidity and often long-term disability. It is endemic in West and Central Africa affecting regions similarly burdened by a high prevalence of HIV. According to the Médecins Sans Frontières programme in Akonolinga, Cameroon, the prevalence of HIV is approximately three to six times higher in Buruli ulcer-treated patients compared to the regional estimated HIV prevalence [1]. Similarly in Benin, patients with Buruli ulcer were eight times more likely to have HIV infection than those without Buruli ulcer [2]. HIV also affects the clinical presentation of Buruli ulcer disease with an increased incidence of multiple, larger, and ulcerated lesions [1,3]. Patients often present with severe immunosuppression, with 26% of patients in Akonolinga presenting with CD4⁺ cell counts less than 200 cells/μl, and in urgent need of antiretroviral therapy [1].

The treatment of Buruli ulcer has undergone a dramatic evolution in recent years, with antibiotics being shown to be highly effective in treating disease and preventing recurrences [4–7]. Combination antibiotics for 8 weeks are now the recommended first-line treatment [8].

Rifampicin and streptomycin is the most widely used combination, but increased toxicity [9], difficulties in administration, drug shortages [10], and impediments to decentralization of treatment that result from the use of injectable streptomycin have led to an increasing use of the oral combination of rifampicin and clarithromycin. This has been shown in mouse models [11] and observational cohorts to be effective [6].

Little is known about the optimal timing of antiretroviral therapy (ART) in HIV patients treated for Buruli ulcer, nor the optimal ART regimens to use. Nevertheless, recent WHO recommendations have followed those of tuberculosis/HIV (TB/HIV) and recommended ART be commenced in all HIV patients early during the course of Buruli ulcer antibiotic treatment [8]. As nevirapine and boosted protease inhibitors are not recommended for use in patients on rifampicin [12], many patients will be taking efavirenz (EFV) in the ART regimen. However, EFV can reduce clarithromycin levels by up to 39% [13], which likely further compounds the known significant reduction of clarithromycin levels by rifampicin [14]. Although the clinical consequences of these interactions are unknown, it could potentially lead to reduced effectiveness of the rifampicin/clarithromycin regimen.
for Buruli ulcer treatment with secondary treatment failure and drug resistance. Increased toxicity is also reported when the two drugs are combined with 46% of patients reported to develop a rash [15]. Finally, clarithromycin is given twice daily making adherence more difficult.

An alternative is moxifloxacin, which is more active against *Mycobacterium ulcerans* than clarithromycin in *vitro* [16], and in the mouse model shows equivalent efficacy in combination with rifampicin as both rifampicin/streptomycin and rifampicin/clarithromycin combinations [11]. Clinical experience in observational studies has shown it to be effective in combination with rifampicin for curing lesions and preventing recurrences [7,17]. It has high oral bioavailability, excellent bone and tissue penetration to reach the areas where the organism is active [18,19], and has the advantage of being administered only once daily. Although rifampicin is reported to reduce moxifloxacin serum levels by 25–30% [20], the maximal serum concentration after an oral 400 mg dose (3.2–4.5 μg/ml) [21] remains in excess of its reported minimal inhibitory concentration for *M. ulcerans* (0.5 μg/ml) [16], and should not reduce its effectiveness, as evidenced by its successful use combined with rifampicin treating *M. ulcerans* [7,17] and in human TB trials [22,23]. Finally, it does not interact with antiretroviral drugs. Therefore, it could potentially be effectively combined with rifampicin for treatment of Buruli ulcer/HIV-infected patients receiving ART while offering a number of advantages over the combination of rifampicin/clarithromycin. It will be important to perform further research to confirm the safety of rifampicin/moxifloxacin combinations for Buruli ulcer/HIV treatment, although it has been found that when moxifloxacin is added to TB regimens containing rifampicin, toxicity has not been increased [22,23].

Buruli ulcer/HIV-infected patients also live in areas highly endemic for TB and are likely to have high rates of TB infection. Buruli ulcer/HIV-infected patients, especially if significantly immunosuppressed, are therefore also likely to have an increased risk of developing active TB. If moxifloxacin were used in Buruli ulcer treatment regimens, a concern could be that if used in patients with active TB the organism could develop resistance against it and this would remove an important drug in current drug-resistant TB treatment regimens. Yet, this potential disadvantage in HIV populations is perhaps its greatest strength. First, moxifloxacin is active against dormant TB in *vitro*, and its activity is increased when combined with rifampicin [24]. It also has strong early bactericidal activity against active TB in *vitro* [25]. When combined with rifampicin for an 8-week Buruli ulcer treatment course, it may provide effective treatment of latent TB [24], as has been demonstrated with 2-month courses of rifampicin and pyrazinamide [26]. This would offer a significant advantage, as TB is the greatest killer of HIV-infected patients, and to try and minimize this, treatment for latent TB is strongly recommended for all HIV-infected patients [27]. Secondly, although of course it would be important to exclude active TB prior to commencement of, and during treatment with, moxifloxacin-based regimens [27], if active TB disease were present but undetected, then moxifloxacin would likely reduce the likelihood of rifampicin resistance developing during an 8-week treatment course [28], and thus help prevent the development of rifampicin-resistant TB. It would also be more likely to prevent rifampicin-resistant TB than the alternative agents given high rates of streptomycin TB resistance globally and the limited activity of clarithromycin against TB. Additionally, current experience suggests that the number of Buruli ulcer/HIV patients with active TB is low further minimizing the public health risk.

So, for HIV-infected patients with Buruli ulcer living in high-burden TB regions moxifloxacin has the potential to effectively and safely relieve the significant burden of Buruli ulcer disease while allowing the use of once-daily all oral antibiotic regimens that will aid adherence, reduce toxicity, and facilitate treatment availability in decentralized community settings. Additionally, it may kill two birds with one stone by potentially also providing life-saving eradication of TB infection or reducing the development of rifampicin-resistant TB disease. Therefore, we advocate for research to be urgently undertaken into the use of moxifloxacin combined with rifampicin to determine its effectiveness and safety as treatment for Buruli ulcer in HIV-infected adults on ART.

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**Conflicts of interest**

There are no conflicts of interest.

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