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Item Type	Article
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Citation	O'Donnell MR, Padayatchi N, Daftary A, Orrell C, Dooley KE, Rivet Amico K, Friedland G. Antiretroviral switching and bedaquiline treatment of drug-resistant tuberculosis HIV co-infection. Lancet HIV. 2019 Mar;6(3):e201-e204. doi: 10.1016/S2352-3018(19)30035-9.
Publisher	Elsevier
Download date	2025-04-28 19:13:31
Link to Item	https://pubmed.ncbi.nlm.nih.gov/30846058/

Antiretroviral switching and bedaquiline treatment of drug-resistant tuberculosis HIV co-infection

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Bedaquiline, a potent new therapy for drug-resistant tuberculosis, results in improved survival including in HIV patients with multidrug and extensively drug-resistant tuberculosis. In line with WHO recommendations, in South Africa and other low-income and middle-income settings, antiretroviral therapy is switched from generic fixed-dose combination efavirenz-containing regimens to twice-daily nevirapine with separate companion pills because of interactions between efavirenz and bedaquiline. Early data suggest a signal for low antiretroviral therapy adherence after this antiretroviral therapy switch. Mortality and other tuberculosis-specific benefits noted with bedaquiline treatment in multidrug and extensively drug-resistant tuberculosis HIV might be compromised by HIV viral failure, and emergent antiretroviral resistance. Programmatic responses, such as adherence support and dual pharmacovigilance, should be instituted; antiretroviral therapy initiation with fixed-dose combinations without bedaquiline drug interactions should be strongly considered.

Introduction

In 2006, an outbreak of extensively drug-resistant tuberculosis in patients with HIV in Tugela Ferry, in rural KwaZulu-Natal, South Africa drew unprecedented global attention because of severe early mortality[1] and the potential for transmission of an apparently untreatable strain of tuberculosis in a community with a high burden of HIV.[2] While the world's focus was on the emergence of this highly drug-resistant tuberculosis strain, the rapid mortality of the patients in Tugela Ferry (median survival 16 days from extensively drug-resistant tuberculosis diagnosis) was a result, at least in part, of their advanced and untreated HIV/AIDS (median CD4 count 63 cells per µL).[1]

Bedaquiline, a robust and effective new diarylquinoline antimycobacterial,[3] is the first new tuberculosis drug approved for the treatment of multidrug and extensively drug-resistant (MXDR) tuberculosis in more than 40 years.[4] An operational study of treatment for MXDR tuberculosis with bedaquiline-containing regimens in programmatic settings in South Africa has shown a three-times reduction in mortality over about 18 months compared with patients with older, injectable-based treatment regimens.[5] In this operational cohort, 1899 (70·8%) of 13 893 patients were co-infected with HIV and 11 729 (89·5%) of those patients were treated with antiretroviral therapy (ART).[5] In this study and others, the effect of bedaquiline introduction in the treatment of patients co-infected with HIV and MXDR tuberculosis, on HIV-specific factors such as ART adherence, CD4 T-cell count and HIV viral load were not reported.

Treatment of tuberculosis in patients on ART

About 13% of incident tuberculosis cases globally (or about 1·2 million cases) occur in HIV co-infected patients.[6] In South Africa, there are approximately 11 000 incident cases of MXDR tuberculosis (new and retreatment) in people with HIV each year.[6] One of the most common first-line ART regimens, in South Africa and other low-income and middle-income countries (LMICs), is a once-daily, fixed-dose, combination pill including the non-nucleoside reverse transcriptase inhibitor, efavirenz, with a dual non-nucleoside reverse transcriptase inhibitor, tenofovir disoproxil fumarate and emtricitabine backbone.[7] This fixed-dose combination is well tolerated, effective, and affordable.[7,8]

Bedaquiline is hepatically metabolised by the cytochrome p450 isoenzyme 3A (CYP3A) to its active M2 metabolite, which has reduced antimycobacterial activity but might result in a QT-prolonging effect.[9] However, efavirenz induces CYP3A, leading to reduced bedaquiline concentrations with coadministration.[4,9] In an AIDS Clinical Trials Group study of 30 healthy volunteers, coadministration of efavirenz with a single dose of bedaquiline led to an 18% reduction in the bedaquiline area under the curve.[10] A subsequent study used these data in pharmacometric models that accounted for bedaquiline's very long terminal half-life (5·5 months), and reductions in steady-state exposures were estimated to be around 50% with efavirenz coadministration.[11] In the same paper, lopinavir boosted with ritonavir, a potent CYP3A inhibitor, was estimated to decrease clearance of bedaquiline by 35% and its active M2 metabolite by 58%. Proposed model-based alternative dosing schemes might mitigate drug interactions, but the recommended regimens have not been tested prospectively to assess pharmacokinetics and safety or to evaluate costs.[11]

In response to these pharmacokinetic and modelling data, the primary WHO guidance is to change the ART regimen from efavirenz to nevirapine when bedaquiline is started (panel), because nevirapine has modest effect on bedaquiline concentrations.[12,13] Boosted protease inhibitors are discouraged in WHO guidance because there is concern that build-up of bedaquiline and toxic metabolites could lead to increased adverse effects, particularly cardiotoxicity.[13] In LMIC settings, extended-release nevirapine or nevirapine-based fixed-dose combinations are generally not available (likely due to the twice-daily dose) and therefore nevirapine-based ART regimens include three different medications and require twice-daily dosing.

Lancet HIV 2019; 6: e201–04

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Panel: **Recommendations for ART and bedaquiline**

2014 WHO recommendations for ART regimens for individuals on bedaquiline[12]

- Nevirapine with two NRTIs (eg, zidovudine with lamivudine or emtricitabine or tenofovir with lamivudine or emtricitabine)
- Triple NRTI (eg, zidovudine with lamivudine or emtricitabine, and abacavir); this option should only be used when others are not possible)

General considerations for WHO recommendations

- Avoid regimens with protease inhibitors
- Conduct monthly monitoring for QT interval prolongation
- Be aware of potential liver toxicity with nevirapine and bedaquiline
- These WHO recommendations might be superseded. Please consult current guidance

Proposed alternative recommendations for ART regimens for individuals on bedaquiline

- NRTI, no drug interactions anticipated; triple NRTI regimen not recommended
- Efavirenz, 50% reduction in bedaquiline with efavirenz anticipated; avoid coadministration, doubling of bedaquiline dose might mitigate drug–drug interaction, but has not been tested clinically and is costly
- Nevirapine, no drug–drug interaction; use with caution with high CD4, and pill burden, possibly less effective, consider monitoring hepatic function; monitor and support adherence
- Protease inhibitor, increased bedaquiline, might or might not be increased M2 metabolite, monitor QTc closely; higher QT possible, not confirmed in large studies
- Dolutegravir, no drug interactions anticipated; drug of choice where available, counsel sexually active female patients

General considerations for alternative regimens

- Adherence support and monitoring around tuberculosis and ART
- Be aware that increased pill burden and toxicity could make adherence more challenging
- Monthly sputum tuberculosis culture results and periodic HIV viral load to monitor treatment response
- HIV and tuberculosis sequencing to identify amplification of resistance on treatment.
- Conduct monthly monitoring for QTc interval prolongation

ART=antiretroviral therapy. NRTI=nucleoside or nucleotide reverse transcriptase inhibitor.

To date, ART switching has been primarily studied in the context of simplifying ART regimens (eg, changing to fixed-dose combination) to improve adherence[14] or the side-effect profile (eg, lipodystrophy).[15] However, switching from an efavirenz-based fixed-dose combination to a second-line ART regimen consisting of multiple pills given twice daily might negatively effect ART adherence.[14] In one meta-analysis, use of daily ART fixed-dose combinations was associated with 17% improved adherence compared with treatment with separate twice-daily pills (and a 9% absolute improvement in rates of HIV viral load suppression).[16] This adherence benefit with fixed-dose combinations has been reproduced in multiple populations and settings.[16,17] Many patients being treated for MXDR tuberculosis and HIV are taking eight or more medications and, therefore, adding to the pill burden might reduce overall medication adherence because of the increased regimen complexity and treatment fatigue.[18] Compared with efavirenz-containing regimens, nevirapine has been associated with higher rates of HIV virological failure in some, though not all, studies.[16,19] There was a reported pooled estimate of 15% increased risk of virological failure in another meta-analysis.[20] Neviripine has a more severe side-effect profile (rash and hepatotoxicity)[21,22] and has been associated with an increased risk for ART discontinuation.[22,23]

To understand these issues in more depth, we have begun a study of treatment adherence in patients co-infected with MXDR tuberculosis and HIV, initiating treatment with bedaquiline in those receiving ART in KwaZulu-Natal, South Africa. The PRAXIS study (NCT03162107) uses an electronic monitoring device (Wisepill RT2000) to measure real-time adherence to bedaquiline and ART.[24,25] We expect that qualitative interviews in the PRAXIS cohort might help to define the effect of ART switching on adherence behaviour.

Bedaquiline-containing regimens are associated with reduced mortality, quicker time to sputum culture conversion, and higher MXDR-tuberculosis treatment success, including in patients with HIV. However, it is important to also consider HIV-specific outcomes. If switching ART from an efavirenz fixed-dose combination to multiple-pill, twice-daily nevirapine-based regimens results in decreased adherence leading to worsened HIV viral control, then the overall benefit of bedaquiline might be compromised. Suboptimal ART adherence (whether because of increased pill burden or nevirapine-associated adverse drug effects) might also select for resistance to non-nucleoside reverse transcriptase inhibitors.

There are several programmatic responses that should be considered by tuberculosis and HIV programmes that treat patients with MXDR tuberculosis and HIV with bedaquiline-containing regimens. In addition to tuberculosis-related pharmacovigilance, commensurate levels of HIV-specific pharmacovigilance should be practiced. Adherence to HIV medications should be re-evaluated and supported, with specific attention to patient support and treatment literacy, especially when switching ART regimens. Research is needed to identify evidence-based interventions to improve adherence and support patients in dealing with dual stigma, depression, and other mental health issues including substance abuse.[26] Testing of alternative ART regimens is needed including more affordable fixed-dose combinations of nevirapine formulations. Increased bedaquiline dosing with efavirenz fixed-dose combinations should also be studied to determine if augmented dosing delivers appropriate bedaquiline concentrations without increased adverse effects. An additional consideration is that the estimated population prevalence of non-nucleoside reverse transcriptase inhibitor drug-resistance in previously untreated HIV infected patients is 10·1% in Southern Africa, just above the point where WHO guidance recommends considering a non-nucleoside reverse transcriptase inhibitor for first-line regimen.[27]

Dolutegravir, an integrase strand transfer inhibitor, is increasingly being championed as first-line ART globally.[28] Dolutegravir fixed-dose combination has also been

identified as a central component of a potential companion ART regimen for treatment of MXDR tuberculosis and HIV co-infection because it is well tolerated and, based on knowledge of drug metabolic pathways, there is a low theoretical risk of drug interactions. Generic dolutegravir-containing fixed-dose combinations will probably become available in the near future in South Africa. Ongoing trials are providing dolutegravir-based ART with bedaquiline-containing regimens, so preliminary pharmacokinetic data might be available soon.[28] However, we note the recent concerns raised by the Tsepamo study about the potential for increased risk of neural-tube defects in women who become pregnant while on dolutegravir,[29] which would require its provision to reproductive-age women to be accompanied with appropriate counselling and contraceptives.

Conclusion

Bedaquiline is a crucial advance in the treatment of MXDR tuberculosis. Operational roll-out in South Africa has been an unmitigated success especially given the substantial challenges associated with diagnosis, patient selection, and monitoring. However, enhanced attention to the HIV component of HIV-associated MXDR tuberculosis is important, to prevent adverse HIV-associated outcomes such as loss of virological control, emergence of drug resistance, and severe toxic effects that can erode gains noted with bedaquiline treatment. To sustain and extend this success, we caution against ART switches that substantively increase patient burden (eg, multipill, multidose regimens as presently required for nevirapine-based therapy). Pharmacovigilance, enhanced treatment support, and increased medication literacy, particularly around dual adherence to new drugs for multidrug-resistant tuberculosis and changes to ongoing ART must accompany treatment.[18] Development and testing of new companion ART regimens is urgently needed to maximise the benefits of bedaquiline in patients with HIV who have MXDR tuberculosis.

Contributors

All authors contributed to the writing and critical revision of the manuscript.

Declaration of interests

We declare no competing interests.

Acknowledgments

The PRAXIS Study was funded as part of the National Institutes of Health Grant #R01AI124413–01. Research reported in this publication was partly supported by the South African Medical Research Council. The funding bodies did not directly participate in study design and collection, analysis, or interpretation of data.

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