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The coming-of-age of bedaquiline: a tale with an open ending

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29 **Author contributions:**

30 LG made a substantial contribution to the conception of the manuscript, wrote the
31 manuscript, critically revised the manuscript for important intellectual content, gave final
32 approval of the current version to be published, and agrees to be accountable for all aspects
33 of the work in ensuring that questions related to the accuracy or integrity of any part of the
34 work are appropriately investigated and resolved.

35 FV made a substantial contribution to the conception of the manuscript, critically revised
36 the manuscript for important intellectual content, gave final approval of the current version
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42 LG is the co-Principal Investigator and FV is the Project Leader of two MSF-sponsored clinical
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45 **TEXT:**

46 Bedaquiline can probably be considered the biggest breakthrough of the last decades in
47 tuberculosis drug development. The first compound of a new anti-tuberculosis drug class,
48 diarylquinolines, bedaquiline binds the mycobacterial ATP synthase, inducing major
49 conformational changes and ultimately impacting the bacterial respiration pathway.[1, 2]
50 After being developed in 2005,[3] bedaquiline showed promising results in Phase II trials[4,
51 5], and was granted accelerated approval in 2012 by the FDA in the United States and
52 conditional approval in 2014 by the EMA in the European Union. In the following years, the
53 access to bedaquiline has progressively increased, from compassionate to programmatic
54 use,[6, 7] although at an insufficient pace. Between July 2015 and December 2019, 51,098
55 patients received bedaquiline worldwide: although remarkable, this figure only represents
56 11% of those who are estimated to need it according to the most recent recommendations
57 by the World Health Organization (WHO).[8]

58 In this issue of the *European Respiratory Journal*, Chesov and co-authors elegantly describe
59 the impact of the early years of programmatic bedaquiline implementation in the Republic
60 of Moldova.[9]. In this retrospective cohort study, consecutive adult patients diagnosed
61 with culture-confirmed pulmonary multidrug-resistant tuberculosis (MDR-TB) were
62 identified through a nationwide database. Overall, 2069 MDR-TB patients were included in
63 the study: 115 had received bedaquiline and 1954 had not. The study included patients who
64 started treatment between 2016 and 2018, a period during which bedaquiline was reserved
65 mainly for the most difficult-to-treat strains and for salvage treatment regimens:
66 consequently, most bedaquiline-treated patients in the cohort have a history of treatment
67 failure, positive sputum smear results and lung cavities at baseline, and harbour
68 fluoroquinolone-resistant strains. In order to select a comparable population, propensity

69 score matching was performed by age, sex, area of residence, presence of cavitary lesion,
70 HIV status, sputum smear positivity at baseline, fluoroquinolone resistance, previous history
71 of tuberculosis, and drugs included in the treatment regimen: this allowed the selection of
72 two groups of 114 patients with similar baseline characteristics. Remarkably, favourable
73 treatment outcome rates were higher in the bedaquiline-treated group using WHO
74 definitions (55.3% versus 24.6%) in all the cohort and TBnet definitions in the subgroup of
75 patients who had at least one year post-treatment follow-up available (43.5% versus 19.6%).
76 In addition, mortality rates were significantly lower in the bedaquiline-treated group.
77 Despite limitations due to its retrospective nature, missing data in some of the matching
78 variables, and potential unknown confounders not captured by propensity scoring, this
79 study gives an excellent example of the impact of bedaquiline as part of conventional MDR-
80 TB treatment regimens with a sound methodological approach. However, outcomes
81 achieved by bedaquiline-treated patients in the cohort are still far from optimal, as shown
82 by high rates of treatment failure (27.2% and 39.2%, according to WHO and TBnet
83 definitions). This finding, similar to results from previous studies performed in the same
84 region [10, 11], may have multiple explanations: bedaquiline was, in most cases (82%), not
85 part of the initial regimen and added subsequently to adapt to phenotypic drug
86 susceptibility testing (DST) results; when bedaquiline was added, it was usually not
87 accompanied by other effective drugs; bedaquiline was administered for a median of 34
88 weeks, and almost never for the full duration of treatment; finally, other important drugs,
89 such as clofazimine and delamanid, were used only in few cases due to limited availability in
90 the Republic of Moldova.

91

92 The study by Chesov et al. adds up to an already rich body of observational evidence
93 supporting the use of bedaquiline for MDR-TB[12]. Large, multinational cohort studies and a
94 meta-analysis of individual patient data have confirmed the efficacy of this drug.[13–16]
95 Similarly, initial safety concerns, in particular regarding QT interval prolongation, have been
96 progressively dispelled.[17–20] WHO recommendations include bedaquiline among the
97 “core drugs” of the individualized, conventional treatment regimen for MDR-TB, and
98 recently also as part of an all-oral shorter MDR-TB regimen.[21] Moreover, latest WHO
99 recommendations allow for increasing flexibility in establishing the duration of bedaquiline
100 treatment beyond 24 weeks and in combining it with other QT-prolonging drugs, like
101 delamanid.

102 Does this mean that the tale of bedaquiline is heading towards a happy ending?
103 Unfortunately, we cannot say for sure (yet). All these recommendations are based on
104 observational data, indirect comparisons (for the shorter regimen), and mostly very low
105 quality evidence.[22] Indeed, results of a Phase III clinical trial on bedaquiline are still
106 awaited, despite engagements by the manufacturer at the moment of provisional approval
107 by the FDA.[23] There are also reasons of concern that should not be underestimated. In the
108 last years, multiple reports have alerted on the selection of emerging drug resistance to
109 bedaquiline.[24–27] Fears of increasing resistance rates have led some groups to advocate
110 “restricting” the use of bedaquiline for fluoroquinolone-resistant strains.[28] In addition,
111 reliable DST for bedaquiline (and other new and re-purposed drugs) is currently lacking in
112 most medium- and high-incidence countries.[29, 30]

113 Ultimately, major breakthroughs, and reliable data on the risk of acquired drug resistance,
114 will only come from clinical research. Multiple clinical trials, summarized in the Table, are
115 currently planned or undergoing.[31] The development path of bedaquiline is now at a

116 crossroads leading to (at least) four main directions. First, bedaquiline may continue to be
117 assessed as part of all-oral regimens for rifampicin-resistant tuberculosis: these drug
118 combinations are tested as standardized options for all rifampicin-resistant strains (i.e. TB-
119 PRACTECAL), or as part of a strategy where regimens can be adapted to results of rapid
120 molecular testing for fluoroquinolone resistance (i.e. BEAT Tuberculosis). Second,
121 bedaquiline may be included in regimens which specifically target fluoroquinolone-
122 susceptible strains (i.e. STREAM Stage 2, endTB). Third, bedaquiline may be reserved for
123 fluoroquinolone-resistant strains, as part of combinations of new and re-purposed drugs
124 (i.e. endTB-Q). In all these cases, the overarching goal is to reduce the treatment duration of
125 such drug-resistant strains to 6 to 10 months, while preventing the selection of drug
126 resistance, not compromising the efficacy rates of conventional treatment, and hopefully
127 improving its safety profile. Finally, bedaquiline may be studied as a component of new
128 efforts to improve first-line treatment for rifampicin-susceptible tuberculosis by reducing its
129 duration to 2 to 4 months, as hinted by promising pre-clinical[32] and bactericidal activity
130 studies.[33] Regardless of the development path, randomized Phase III trials[34, 35],
131 including a sufficient sample size and an internal, dynamic control arm, are needed to
132 radically improve the evidence base for treatment of this disease.[36] Innovative trial
133 designs may help accelerate this process,[37, 38] but adequate funding and strong political
134 commitment are more critical than ever in these coronavirus disease 2019 (COVID-19)
135 times.[39]

136

137 Recent improvements in MDR-TB treatment with bedaquiline-containing regimens, as
138 shown by Chesov and co-authors,[9] are undeniable, and make a case for enhanced global
139 access to bedaquiline and other new and re-purposed drugs. However, this may only be the

140 beginning of the journey for bedaquiline. Strategic choices on priorities of clinical
141 development of this drug will shape its role in tuberculosis treatment in coming years. We
142 believe that these choices should be guided by the need to improve treatment outcome for
143 each patient, and that all development directions are worthy of being explored.
144 Implementation of bedaquiline-containing regimens based on high-quality evidence
145 expected from clinical trials, together with widespread DST capacity, rather than restricted
146 use for salvage therapy, may be the best way to prevent resistance and to ensure the grand
147 finale that this story deserves.

148 **Tables**

149

150 **Table.** Selection of main ongoing and planned Phase II/III clinical trials testing bedaquiline-
 151 containing regimens.

152

Trial	Phase	Control Arm	Experimental treatment duration (months)	Drug used in combination with bedaquiline in the experimental arm(s)	Clinicaltrials.gov identifier (reference)
<i>Drug-susceptible tuberculosis</i>					
CRUSH-TB	2	Yes	4	Z, Mfx, Rbt or Dlm	NA
SimpliciTB	2/3	Yes	4	Z, Mfx, Ptm	NCT03338621
TRUNCATE-TB	3	Yes	2-3	H, Z, E, Lzd	NCT03474198
<i>Rifampicin-resistant tuberculosis (regardless of susceptibility to fluoroquinolones)</i>					
BEAT Tuberculosis	3	Yes	6	Lzd, Dlm, Lfx or Cfz	NCT04062201
TB-PRACTECAL	2/3	Yes	6	Mfx, Cfz, Lzd, Ptm	NCT02589782
<i>Rifampicin-resistant, fluoroquinolone-susceptible tuberculosis</i>					
endTB	3	Yes	9	Z, Lfx or Mfx, Cfz, Lzd, Dlm	NCT02754765
STREAM Stage 2	3	Yes	9	H, Z, E, Lfx, Cfz, Pto	NCT02409290[40]
TB-TRUST	3	Yes	6-10	Z, Lfx, Cs, Cfz, Lzd	NCT03867136
<i>Rifampicin- and fluoroquinolone-resistant tuberculosis</i>					
BEAT-TB	3	No	6-9	Cfz, Lzd, Dlm	NA
endTB-Q	3	Yes	6-9	Cfz, Lzd, Dlm	NCT03896685
ZeNIX	3	No	6	Lzd, Ptm	NCT03086486

153 H = isoniazid, Rbt = rifabutin, Z = pyrazinamide, E = ethambutol, Lfx = levofloxacin, Mfx =
 154 moxifloxacin, Cfz = clofazimine, Lzd = linezolid, Dlm = delamanid, Ptm = pretomanid, NA =
 155 not applicable.

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