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Effectiveness of Bedaquilin (BDQ) for Drug-Resistant Tuberculosis (DR-TB) Treatment

Mita Restinia
2nd year PhD Student
Advisor: Professor Chung-Yi Li

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OUTLINE

01 Introduction

02 Research Question

03 Paper 1 & Paper 2

04 Comparison of the two papers

05 Discussion (Response to Comment)

Why I choose this paper?

- It could be potentially one of the topics for my dissertation to analyze the effectiveness and safety of antituberculosis for DR-TB.

Introduction

Bedaquiline is a diaryquinolone that **recommended** by the World Health Organization (WHO) as a group A prioritized drug in DR-TB treatment **since 2019 due to its effectiveness.**

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Groups & steps	Medicine	
Group A: Include all three medicines	levofloxacin *OR* moxifloxacin	Lfx Mfx
	bedaquiline[2,3]	Bdq
	linezolid[4]	Lzd
Group B: Add one or both medicines	clofazimine	Cfz
	cycloserine *OR* terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	ethambutol	E
	delamanid[3,5]	Dlm
	pyrazinamide[6]	Z
	imipenem–cilastatin *OR* meropenem[7]	Ipm–Cln Mpm
	amikacin (*OR* streptomycin)[8]	Am (S)
	ethionamide *OR* prothionamide[9]	Eto Pto
	p-aminosalicylic acid[9]	PAS

WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019

Guideline Treatment

Regimen	MDR/RR-TB fluoroquinolone susceptible	Pre-XDR-TB	XDR-TB	Extensive pulmonary TB	Extrapulmonary TB	Age <14 years
6-month BPaLM/BPaL	Yes (BPaLM)	Yes (BPaL)	No	Yes	Yes – except TB involving CNS, miliary TB and osteoarticular TB	No
9-month all-oral	Yes	No	No	No	Yes – except TB meningitis, miliary TB, osteoarticular TB and pericardial TB	Yes
Longer individualized 18-month	Yes[a]/No	Yes[a]/No	Yes	Yes	Yes	Yes
Additional factors to be considered if several regimens are possible	Drug intolerance or adverse events					
	Treatment history, previous exposure to regimen component drugs or likelihood of drug effectiveness					
	Patient or family preference					
	Access to and cost of regimen component drugs					

BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; CNS: central nervous system; MDR/RR-TB: multidrug- or rifampicin-resistant TB; TB: tuberculosis; XDR-TB: extensively drug-resistant TB.

[a] When 6-month BPaLM/BPaL and 9-month regimens could not be used.

Knowledge GAP

- **Bedaquiline** is recommended for treating drug-resistant TB since 2019.
- One of the reasons why patients do not want to complete the treatment is long duration of treatment and existing of adverse drug reactions
- Limited data its effectiveness **worldwide**.
- No evidence its effectiveness using longer treatment higher **6 months**.

Study Question of Interest

How is the effectiveness of **Bedaquiline** among DR-TB patients worldwide?

P1

American Journal of Respiratory and Critical Care Medicine
Volume 207 Number 11 | June 1 2023

Effectiveness of Bedaquiline Use beyond Six Months in Patients with Multidrug-Resistant Tuberculosis

Letizia Trevisi[1], Miguel A. Hernán[2], Carole D. Mitnick[1,3,4], Uzma Khan[5], Kwonjune J. Seung[1,3,4], Michael L. Rich[1,3,4], Mathieu Bastard[6], Helena Huerga[6], Nara Melikyan[6], Sidney A. Atwood[3], Zaza Avaliani[7], Felix Llanos[8,9], Mohammad Manzur-ul-Alam[10], Khin Zarli[11], Amsalu Bekele Binegdie[12], Sana Adnan[13], Arusyak Melikyan[14], Alain Gelin[15], Afshan K. Isani[16], Dmitry Vetushko[17], Zhenisgul Daugarina[18], Patrick Nkundanyirazo[19], Fauziah Asnely Putri[5], Charles Vilbrun[20], Munira Khan[21], Catherine Hewison[22*], Palwasha Y. Khan[23*], and Molly F. Franke[1*]; on behalf of the endTB Study Team

CATEGORY
RESPIRATORY SYSTEM
3/101

JCR YEAR	JIF RANK	JIF QUARTILE	JIF PERCENTILE
2023	3/101	Q1	97.5

P2

Pulmonology 27 (2021) 403–412

PULMONOLOGY

www.journalpulmonology.org

SPECIAL ARTICLE

Outcome of treatment of MDR-TB or drug-resistant patients treated with bedaquiline and delamanid: Results from a large global cohort

CATEGORY
RESPIRATORY SYSTEM
6/101

JCR YEAR	JIF RANK	JIF QUARTILE	JIF PERCENTILE
2023	6/101	Q1	94.6

Paper 1

Effectiveness of Bedaquiline Use beyond Six Months in Patients with Multidrug-Resistant Tuberculosis

[1]Department of Global Health and Social Medicine, Harvard Medical School, Boston, Massachusetts; [2]CAUSALab, Departments of Epidemiology, Harvard T.H. Chan School of Public Health, Harvard University, Boston, Massachusetts; [3]Division of Global Health Equity, Brigham and Women's Hospital, Boston, Massachusetts; [4]Partners in Health, Boston, Massachusetts; [5]Interactive Research and Development Global, Singapore, Singapore; [6]Field Epidemiology Department, Epicentre, Paris, France; [7]National Center for Tuberculosis and Lung Diseases, Tbilisi, Georgia; [8]Unidad de Tuberculosis, Hospital Nacional Dos de Mayo, Lima, Peru; [9]Instituto de Investigaciones en Ciencias Biomedicas, Universidad Ricardo Palma, Lima, Peru; [10]Interactive Research and Development, Dhaka, Bangladesh; [11]Médecins sans Frontières, Yangon, Myanmar; [12]Department of Internal Medicine, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia; [13]Indus Hospital and Health Network, Karachi, Pakistan; [14]Médecins sans Frontières, Yerevan, Armenia; [15]Zanmi Lasante, Port-au-Prince, Haiti; [16]National Core Research Group, Stop TB Partnership, Islamabad, Pakistan; [17]Republican Scientific and Practical Centre of Pulmonology and Tuberculosis, Minsk, Belarus; [18]Astana City Center of Phthisiopulmonology, Astana, Kazakhstan; [19]Partners in Health, Maseru, Lesotho; [20]GHESKIO, Port-au-Prince, Haiti; [21]Interactive Research and Development, Durban, South Africa; [22]Medical Department, Médecins sans Frontières, Paris, France; and [23]Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom

Miguel Hernan: Professor of Biostatistics & Epidemiology, Harvard T.H. Chan School of Public Health ; **Author Book "What If"**

Molly Forrest: Assoc Prof. in Depart. Epidemiology Harvard T.H. Chan School of Public Health

Objective Paper 1

To estimate the effect of three BDQ duration treatment strategies (6, 7–11, and >12 month) on the probability of successful treatment among patients receiving a longer individualized regimen for multidrug-resistant tuberculosis

Method

Study Design : observational cohort design

Framework: **A TARGET TRIAL EMULATION** was utilized to minimize common biases associated with treatment duration studies, such as immortal time bias and confounding by indication.

Database Used: endTB (Expand new drug markets for TB**)** observational study across **17 different countries** from 2015-2018 . This observational study encompassed **2,789 patients** diagnosed with rifampicin-resistant and multidrug-resistant tuberculosis

Method

Target Trial Emulation

- Find the protocol of TARGE TRIAL
- Clone data
- Censored
- IP weighting

Protocol of Target Trial

Khan *et al. BMC Infectious Diseases* (2019) 19:733
https://doi.org/10.1186/s12879-019-4378-4

BMC Infectious Diseases

STUDY PROTOCOL Open Access

The endTB observational study protocol: treatment of MDR-TB with bedaquiline or delamanid containing regimens

Uzma Khan[1*], Helena Huerga[2], Aamir J. Khan[3], Carole D. Mitnick[4,6,7], Catherine Hewison[5], Francis Varaine[5], Mathieu Bastard[2], Michael Rich[4,6,7], Molly F. Franke[4,6], Sidney Atwood[7], Palwasha Y. Khan[3] and Kwonjune J. Seung[4,6,7]

Protocol of Target Trial

Table 1. Protocol and Emulation of a Target Trial of Bedaquiline Duration Using Data from a Longitudinal Cohort of Patients Undergoing Treatment for Rifampicin-Resistant/Multidrug-Resistant Tuberculosis

Characteristics	Target Trial Protocol	Emulated Trial Using Observational Data
Eligibility	• Confirmed RR/MDR-TB • Initiated BDQ within the first month of MDR treatment • Completed 24 wk of BDQ within the first 27 wk of treatment • BDQ was likely to be effective at the end of Week 23 • Not treated in the Democratic People's Republic of Korea	Same
Treatment strategies	1. BDQ for 6 mo 2. BDQ for 7–11 mo 3. BDQ for ⩾12 mo • The content and duration of background regimen (i.e., other TB drugs included in the multidrug regimen) are determined on the basis of clinical judgment. • Participants can deviate from their assigned treatment arm (BDQ duration) for <2 wk for any prescribed reason (e.g., adverse event, out of stock). • Adverse events resulting in suspension of BDQ for ⩾2 wk are managed according to clinical judgment. • BDQ can be reinitiated after stopping when clinically indicated.	Same
Treatment assignment	Patients are randomly assigned to one of the three strategies and are aware of the strategy to which they are assigned.	Patients are assigned (via clones) to all the strategies compatible with their data at time zero

Protocol of Target Trial

Table 1. Protocol and Emulation of a Target Trial of Bedaquiline Duration Using Data from a Longitudinal Cohort of Patients Undergoing Treatment for Rifampicin-Resistant/Multidrug-Resistant Tuberculosis

Characteristics	Target Trial Protocol	Emulated Trial Using Observational Data
Follow-up	Follow-up starts in Week 24 of BDQ and ends at the end of treatment.	Same
Outcome	TB treatment success (i.e., cure or treatment completion). Those who die, who are lost from treatment, and in whom treatment fails are considered to have unsuccessful outcomes.	Same
Causal contrast	Intention-to-treat effect, per-protocol effect	Observational analogue of the per-protocol effect
Statistical analysis	Intention-to-treat analysis: probabilities of the outcome under each assigned strategy are compared via ratios and differences. Per-protocol analysis is the same, but patients are censored when they deviate from their assigned strategy, and potential selection bias is adjusted for using IP weighting.	Same per-protocol analysis, except that patient clones are used

Definition of abbreviations: BDQ = bedaquiline; IP = inverse probability; MDR = multidrug-resistant; RR = rifampicin-resistant; TB = tuberculosis.

Protocol of Target Trial

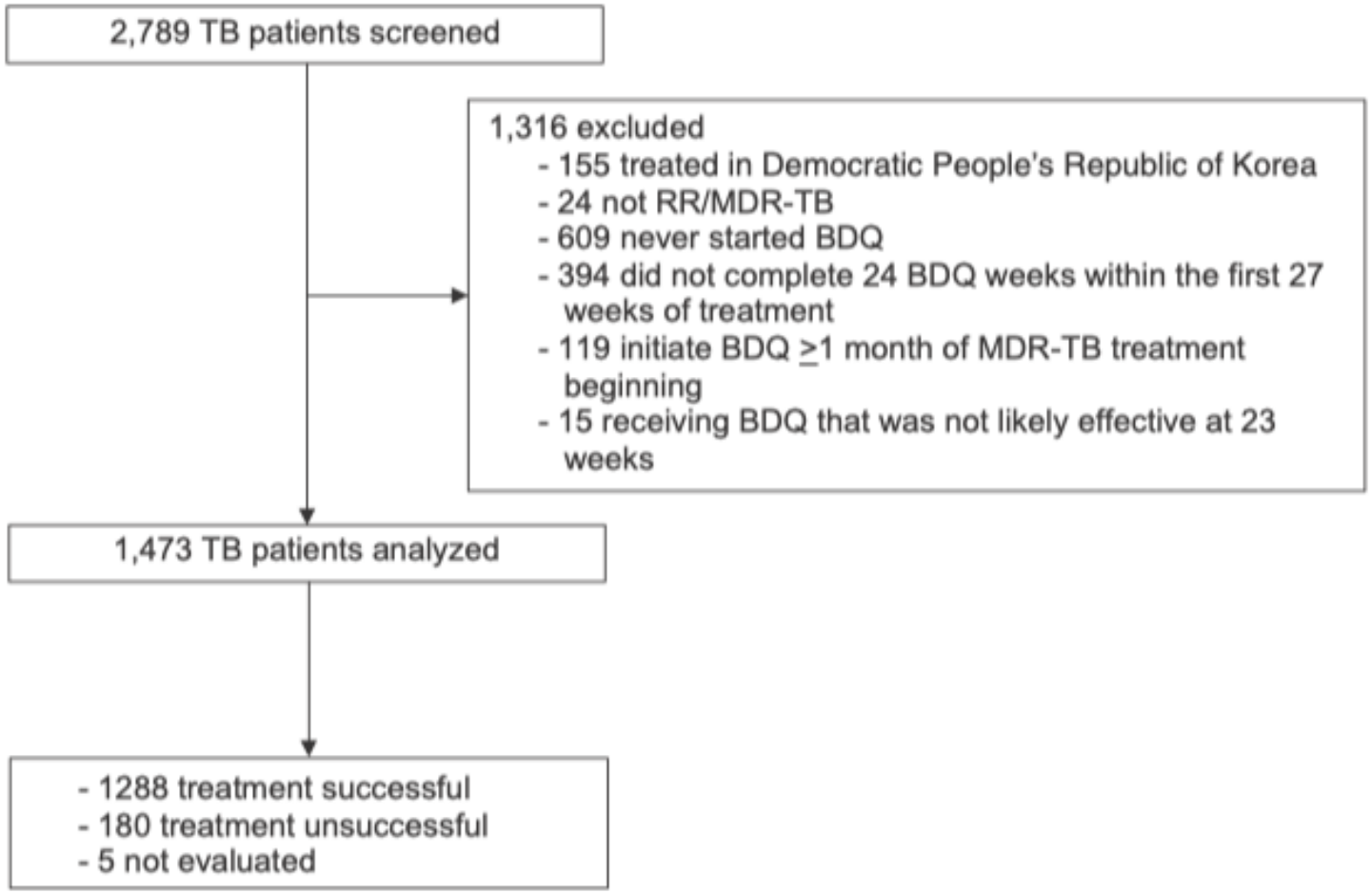
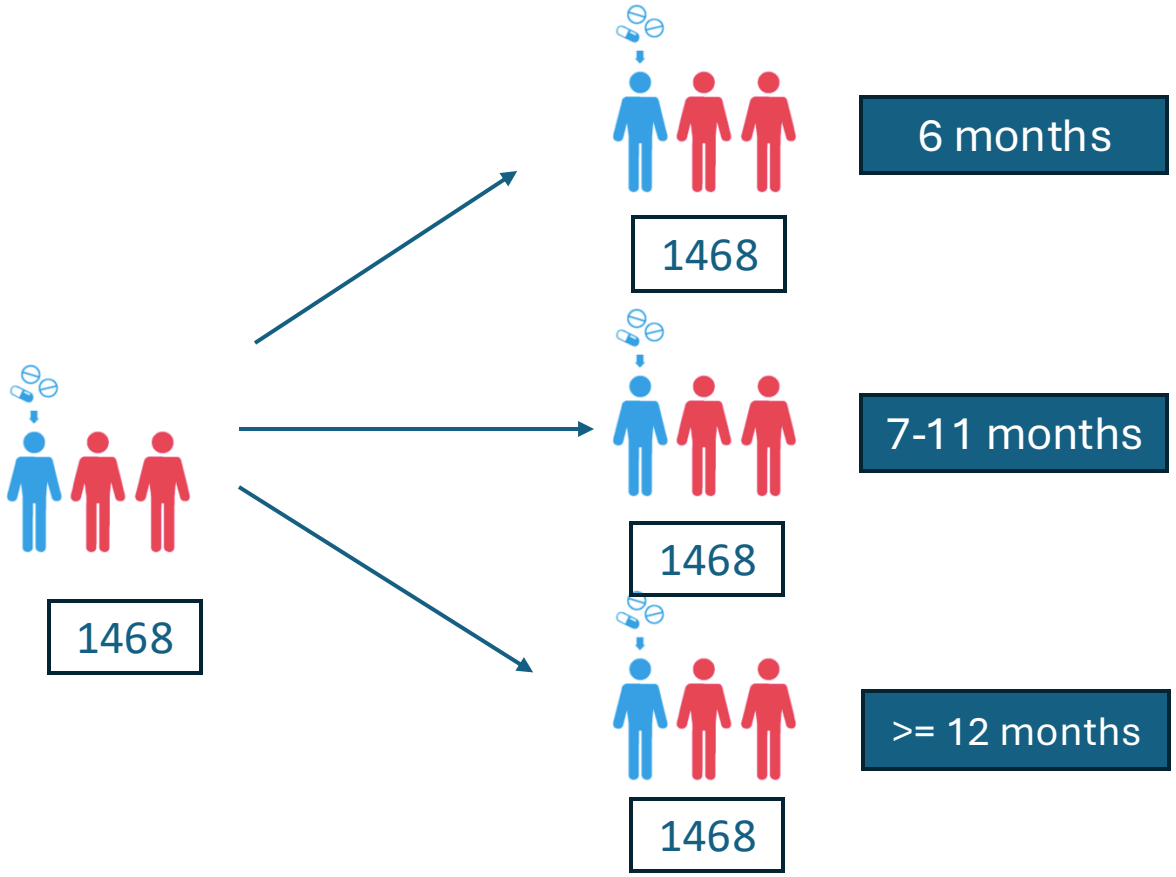


Figure 1. Flowchart of analysis inclusion, endTB (Expand New Drug Markets for TB) Cohort, 2015–2018. BDQ = bedaquiline; MDR = multidrug-resistant; RR = rifampicin-resistant; TB = tuberculosis.

Clone data

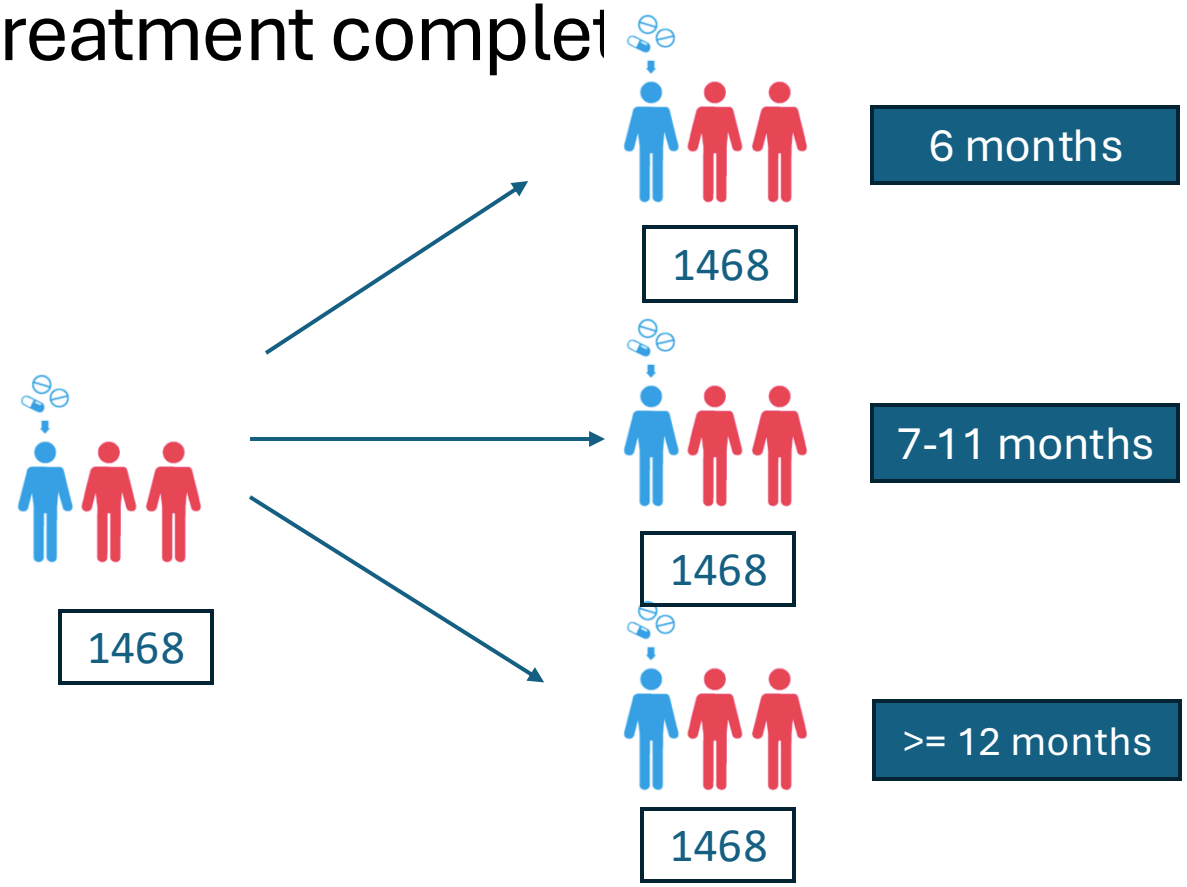


In this study, there is potential immortal time bias because longer treatment durations might appear more effective simply because patients must survive long enough to receive medication.

To avoids the **immortal time bias** that can occur if the treatment strategy is assigned on the basis of the observed duration of treatment.

Artificial Censoring

it occurs when patient data is removed from the analysis before treatment complet



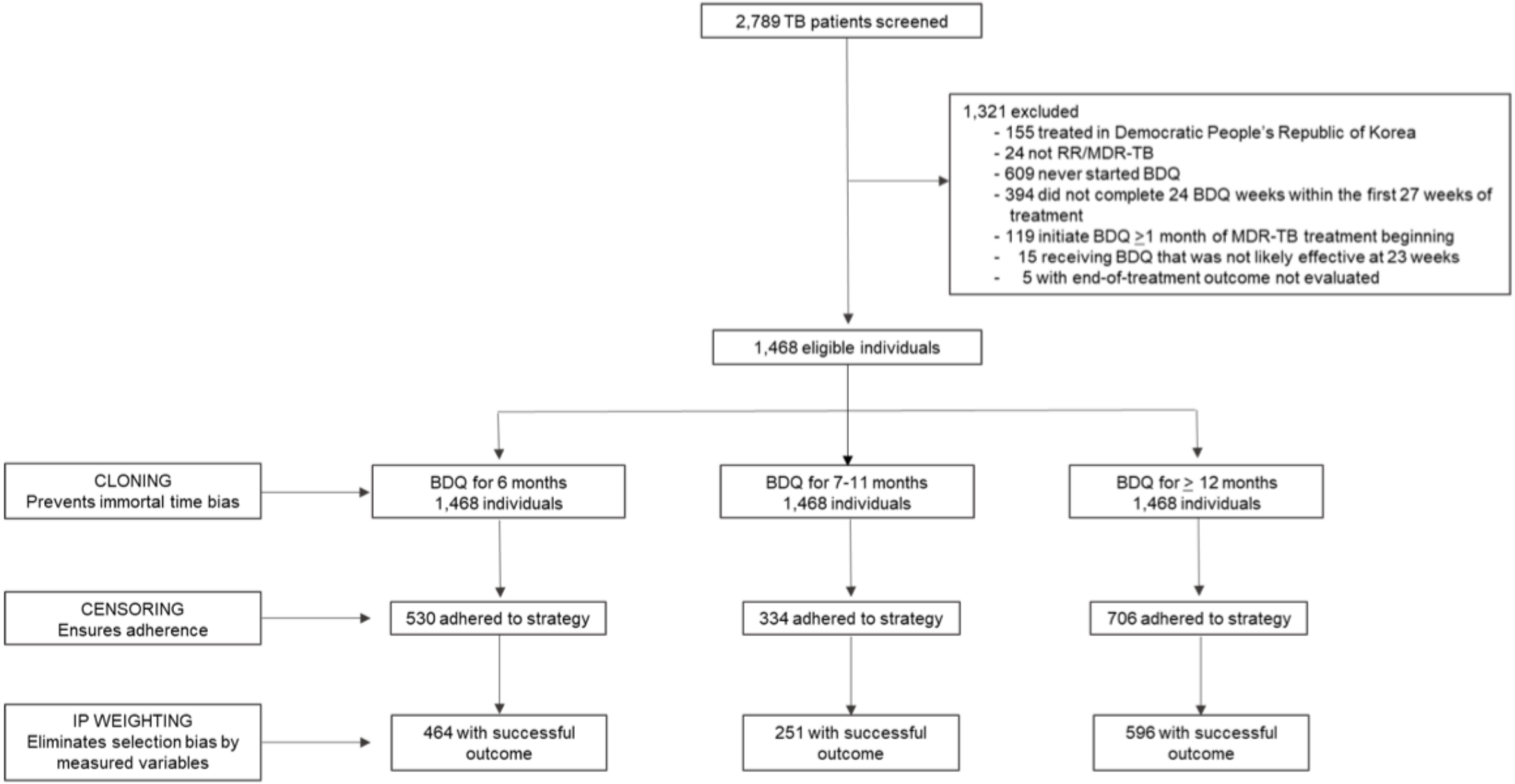
Each patient copy will be censored if/when it deviated from its assigned strategy. For example, clones assigned to the **strategy BDQ for 7–11 months were censored if they stopped BDQ for the first time before Month 7 or after Month 11** for a reason other than an adverse event.

IP Weighting

Artificial censoring → Introduce potential selection bias

So, IP weighting was used to adjust for potential selection bias. IP Weighting was conducting using logistic regression model for probability of treatment success among uncensored patients

Figure E1. Flowchart of the three-step approach, endTB dataset 2015-2018.



Abbreviations: TB = tuberculosis; RR = rifampicin-resistant; MDR = multidrug-resistant; BDQ = bedaquiline; IP = inverse probability.

Result: Baseline Characteristics

Table 2. Characteristics of 1,468 Patients Receiving Bedaquiline for at Least 24 Weeks, endTB (Expand New Drug Markets for TB) Cohort, 2015–2018

Characteristic	*n* (%)*	Missing [*n* (%)]
Assessed at treatment initiation		
Age at treatment initiation, yr, median (IQR; range)	34 (26–45; 10–78)	—
Female sex	531 (36.2)	—
HIV infection	95 (6.5)	1 (0.1)
Hepatitis C	139 (9.5)	3 (0.2)
Previous TB treatment with second-line drugs	1,181 (80.5)	—
Resistance profile		
RR/MDR-TB with FQ and injectable both sensitive	203 (13.8)	—
RR/MDR-TB without testing to FQ and injectable	77 (5.2)	—
RR/MDR-TB with injectable resistance, FQ sensitive	182 (12.4)	—
RR/MDR-TB with FQ resistance, injectable sensitive	402 (27.4)	—
RR/MDR-TB with FQ and injectable both resistant	554 (37.7)	—
Not tested for RR/MDR-TB	30 (2.0)	—
Assessed at 23 wk		
Complete data on adherence	1,294 (88.2)	—
Adherence rate > 80% among those with complete adherence ($n = 1,294$)	1,163 (89.9)	—
Positive sputum culture	78 (5.3)	13 (0.9)
Extensive disease	—	149 (10.1)
No cavitary disease, no smear 3+	460 (31.3)	—
Cavitary disease, smear <3+	845 (57.6)	—
No cavitary disease, smear 3+	4 (0.3)	—
Cavitary disease, smear 3+	10 (0.7)	—
BMI < 18.5 kg/m^2	448 (30.5)	7 (0.5)
Functional status	—	124 (8.4)
Fully active	726 (49.5)	—
Ambulatory	468 (31.9)	—
Capable of self-care	112 (7.6)	—
Limited self-care	27 (1.8)	—
Completely disabled	11 (0.7)	—
FQ	724 (49.3)	—
Likely effective†	494 (33.7)	—
Linezolid	1,323 (90.1)	—
Likely effective	1,278 (87.1)	—
Clofazimine	1,209 (82.4)	—
Likely effective	1,140 (77.7)	—
Cycloserine	831 (56.6)	—
Likely effective	266 (18.1)	—
Delamanid	311 (21.2)	—
Likely effective	309 (21.1)	—
Number of likely effective drugs, median (IQR; range)	4 (4–5; 1–9)	—

Result: Probability of Treatment Success

Use Clone Data

Table 3. Probabilities of End-of-Treatment Success under Several Bedaquiline Duration Strategies, endTB (Expand New Drug Markets for TB) Cohort, 2015–2018

	Unweighted Models			
	Unadjusted	Adjusted for Age and Sex	Baseline Adjusted*	Weighted and Baseline Adjusted*
BDQ Duration	Prob. of Treatment Success (95% CI)	Prob. of Treatment Success (95% CI)	Prob. of Treatment Success (95% CI)	Prob. of Treatment Success (95% CI)
6 mo	0.88 (0.85–0.90)	0.87 (0.85–0.90)	0.85 (0.81–0.88)	0.85 (0.81–0.88)
7–11 mo	0.75 (0.71–0.80)	0.75 (0.71–0.80)	0.77 (0.73–0.81)	0.77 (0.73–0.81)
⩾12 mo	0.84 (0.82–0.87)	0.84 (0.82–0.87)	0.86 (0.83–0.88)	0.86 (0.83–0.88)

Baseline adjusted: The model was adjusted for age (years; continuous), sex, cumulative adherence . 80% (binary, with missing counted as <80%), extensive disease (i.e., cavitary disease with a sputum smear result of 21 or 31), number of severe adverse events (binary: none vs. one or more), functional status (categorical: fully active, restricted in physically strenuous activity but ambulatory, ambulatory with full self-care vs. limited self- care, or completely disabled), body mass index , 18.5 kg/m2, culture result (positive or negative), number of drugs in the regimen (count variable), prescription of cycloserine, and prescription of the following drugs that were likely to be effective in the patient: fluoroquinolone, linezolid, clofazimine, and a second-line injectable.

Use Cloned Data

Result: Success Ratio and Success Difference

Table 4. Estimated Effectiveness of Several Bedaquiline Duration Strategies on Successful End-of-Treatment Outcome, endTB (Expand New Drug Markets for TB) Cohort, 2015–2018

	Unweighted Models			Weighted and Baseline Adjusted*
	Unadjusted	Adjusted for Age and Sex	Baseline Adjusted*	
BDQ Duration	SR (95% CI)	SR (95% CI)	SR (95% CI)	SR (95% CI)
6 mo	Ref.	Ref.	Ref.	Ref.
7–11 mo	0.86 (0.80 to 0.91)	0.86 (0.81 to 0.91)	0.91 (0.85 to 0.96)	0.91 (0.85 to 0.96)
⩾12 mo	0.96 (0.92 to 1.01)	0.97 (0.92 to 1.01)	1.01 (0.96 to 1.06)	1.01 (0.96 to 1.06)
	SD (95% CI)	SD (95% CI)	SD (95% CI)	SD (95% CI)
6 mo	Ref.	Ref.	Ref.	Ref.
7–11 mo	−0.12 (−0.17 to −0.07)	−0.12 (−0.17 to −0.07)	−0.08 (−0.13 to −0.03)	−0.08 (−0.13 to −0.03)
⩾12 mo	−0.03 (−0.07 to 0.008)	−0.03 (−0.07 to 0.009)	0.01 (−0.03 to 0.05)	0.01 (−0.03 to 0.05)

SR= Success ration; SD= Success difference;

There is no significant difference in the effectiveness of longer bedaquiline (BDQ) treatment durations compared to the standard 6-month treatment regimen

Do not Use Cloned Data

Result: Naive Analysis

Table 5. Naive Analysis: Estimated Effectiveness of Bedaquiline Duration on Successful End-of-Treatment Outcome, endTB (Expand New Drug Markets for TB) Cohort, 2015–2018

BDQ Duration	*n*	Successful Outcome [*n* (%)]	Adjusted SR (95% CI)
6 mo	538	470 (87.4)	Ref.
7–11 mo	272	215 (79)	0.93 (0.88–0.99)
⩾12 mo	658	603 (91.6)	1.09 (1.05–1.14)

There is significant difference in Success Ratio of >=12 month treatment durations compared to the standard 6-month treatment regimen

Strength and Limitation

Strength

- Large and Diverse Cohort
- Target Trial Emulation Approach
- Methodological approaches to control for biases, such as immortal time bias, selection bias, and confounding bias

Limitation

- Missing data: 10% of patients had missing data on extensive disease.
- Adherence data limitation: BDQ-specific adherence was not directly recorded; instead, overall TB regimen adherence was used.
- This study did not cover the potential side effect of BDQ, such as QT prolong

Conclusion

Main Findings:

6-Month Regimen:

- Adjusted success rate: **85%**
- Effective and comparable results in MDR-TB treatment.

Longer Durations:

7–11 Months: Success rate drops to **77% (SR: 0.91)**

>=12 Months: Success rate similar to 6 months at **86% (SR: 1.01)**

Clinical Insight:

- **No significant benefit from extending BDQ treatment beyond 6 months.**
- 6-month regimen may suffice for most patients with multidrug-resistant tuberculosis.

Recommendation: Prioritize a 6-month treatment duration, ensuring sufficient potency with companion drugs

Paper 2

Outcome of treatment of MDR-TB or drug-resistant patients treated with bedaquiline and delamanid: Results from a large global cohort

S. Koirala[a,*], S. Borisov[b,*], E. Danila[c,*], A. Mariandyshev[d], B. Shrestha[e], N. Lukhele[f], M. Dalcolmo[g], S.R. Shakya[h], S. Miliauskas[i], L. Kuksa[j], S. Manga[k], A. Aleksa[l], J.T. Denholm[m], H.B. Khadka[n], A. Skrahina[o], S. Diktanas[p], M. Ferrarese[q], J. Bruchfeld[r], A. Koleva[s], A. Piubello[t], G.S. Koirala[u], Z.F. Udwadia[v], D.J. Palmero[w], M. Munoz-Torrico[x], R. GC[y], G. Gualano[z], V.I. Grecu[A], I. Motta[B], A. Papavasileiou[C], Y. Li[D], W. Hoefsloot[E], H. Kunst[F], J. Mazza-Stalder[G], M.-C. Payen[H], O.W. Akkerman[I,J], E. Bernal[K], V. Manfrin[L], A. Matteelli[M], H. Mustafa Hamdan[N], M. Nieto Marcos[O], J. Cadiñanos Loidi[P], J.J. Cebrian Gallardo[Q], R. Duarte[R], N. Escobar Salinas[S], R. Gomez Rosso[T], R. Laniado-Laborín[U,V], E. Martínez Robles[W], S. Quirós Fernandez[X], A. Rendon[Y], I. Solovic[Z], M. Tadolini[aa,bb], P. Viggiani[cc], E. Belilovski[b], M.J. Boeree[E], Q. Cai[dd], E. Davidavičienė[ee,ff], L.D. Forsman[r], J. De Los Rios[gg], J. Drakšienė[p], A. Duga[hh,ii], S.E. Elamin[N], A. Filippov[b], A. Garcia[w], I. Gaudiesiute[i], B. Gavazova[jj], R. Gayoso[g], V. Gruslys[c], J. Jonsson[kk], E. Khimova[d], G. Madonsela[ll], C. Magis-Escurra[E], V. Marchese[M], M. Matei[mm,nn], C. Moschos[C], B. Nakčerienė[ee,ff], L. Nicod[G], F. Palmieri[z], A. Pontarelli[oo], A. Šmite[j], M.B. Souleymane[t], M. Vescovo[w], R. Zablockis[c], D. Zhurkin[o], J.-W. Alffenaar[pp,qq,rr], J.A. Caminero[ss,tt], L.R. Codecasa[q], J.-M. García-García[uu], S. Esposito[vv], L. Saderi[ww], A. Spanevello[xx,yy], D. Visca[xx,yy], S. Tiberi[F,zz], E. Pontali[AA], R. Centis[BB], L. D'Ambrosio[CC], M. van den Boom[DD], G. Sotgiu[ww], G.B. Migliori[BB,*]

Giovanni Battista Migliori

- Professor
- Managing Director at Istituti Clinici Scientifici Maugeri IRCCS

Director of the WHO CC, Editor of the UNION Journal IJTLD/OPEN, leading TB scientist and Global TB Network (GTN) Chair

Objective Paper 2

- The study aimed to **prospectively evaluate the effectiveness** of bedaquiline and/or delamanid-containing regimens in a large cohort of MDR-TB patients treated globally.

Method

2015

52 centers, 29 countries

2021

Observational, prospective study

Duration: Data collection twice a year (up to January 2021) from **Global Tuberculosis Network (GTN)**

Bedaquiline and/or delamanid

Treatment Outcome:

Successful

Unsuccessfull

The Global TB Network (GTN) is an international consortium dedicated to eliminating tuberculosis (TB)

Method

Patient Enrolment: Patients with MDR-TB, Include all age Recruitment started

Data collection:
Demographic data (age, sex, nationality)
Clinical status at diagnosis (e.g., pulmonary TB, presence of cavitary lesions)
Bacteriological data (sputum smear and culture results)
Treatment history
Adverse events and side effects
Treatment regimens and duration

Quality Control: The patients were managed according to **WHO and National guidelines**, under supervision of a coordinating team supervising the patients' clinical management and validation of data. **Investigators** were contacted by the coordinating centre to ensure accuracy after recoding and validation of the dataset before final analysis was conducted. Discrepancies were resolved by consensus.

Data Analysist: Data were analysed descriptively and Treatment outcomes were evaluated **only in patients who completed the prescribed treatment regimen.**

Result: Study Participants

52 centers from 29 countries

Table 1 Participating countries, estimated coverage and number of cases enrolled.

Countries	Estimated coverage[a] %	Cases enrolled N
Argentina	100	11
Australia[c]	100[e]	26
Belarus[b]	80	53
Belgium	60	3
Brazil	100	39
Bulgaria	100	17
Chile	100	1
China[c]	100[d]	5
Eswatini	100	41
Greece	100	6
India	100[e]	15
Italy[g]	80	40
Latvia	100	30
Lithuania[h]	100	160
Mexico[i]	100	11
Nepal[h]	100	125
Netherlands[b]	100	6
Niger	100	17
Paraguay	100	1
Peru	80	29
Portugal	100	1
Romania[c]	100[f]	7
Russian Federation[b]	100[j]	202
Slovakia	100	1
Spain[g]	100	8
Sudan	100	2
Sweden	100	19
Switzerland	100[d]	3
United Kingdom	10	4
Total 29	Range 10%–100%	Total 883

Legend:
[a] Countries' estimate of the national coverage of the aDSM project on new drugs;
[b] 2 centres;
[c] 1 centre;
[d] in the Province/Canton reporting;
[e] in the State reporting;
[f] in the Province reporting;
[g] 7 centres;
[h] 5 centres;
[i] 3 centres;
[j] in the 2 Oblasts reporting.

Result: Patients Characteristic

Table 2 Characteristics of 883 patients undergoing treatment with bedaquiline and delamanid in the cohort, including 477 who completed the prescribed regimen.

Variable	All patients (n = 883)	Patients with final outcome (N = 477)
Male, n (%)	602/883 (68.2)	333/477 (69.8)
Median (IQR) age, years	38 (28–49)	39 (30–50)
Foreign born n (%)	118/882 (13.4)	61/477 (12.8)
Diabetes Mellitus, n (%)	79/880 (9.0)	40/476 (8.4)
People living with HIV, n (%)	67/871 (7.7)	27/473 (5.7)
Thyroid disease, n (%)	25/795 (3.1)	17/399 (4.3)
Alcohol misuse, n (%)	186/879 (21.2)	112/475 (23.6)
Injecting drug user n (%)	48/880 (5.5)	30/475 (6.3)
Methadone user, n (%)	10/787 (1.3)	4/395 (1.0)
Previous anti-TB treatment, n (%)	544/880 (61.8)	329/474 (69.4)
Surgical therapy, n (%)	90/814 (11.1)	59/449 (13.1)
Pulmonary TB, n (%)	857/883 (97.1)	463/477 (97.1)
Extra-pulmonary TB, n (%)	72/882 (8.2)	39/476 (8.2)
Cavitary lesions, n (%)	523/831 (62.9)	295/448 (65.8)
MDR/RR-TB, n (%)	575/883 (65.1)	300/477 (62.9)
XDR-TB, n (%)	289/883 (32.7)	169/477 (35.4)
Other drug-resistance patterns, n*(%)	19/883 (2.2)	8/477 (1.7)
Median (IQR) number of reported drug-resistances	5 (3–7)	6 (4–8)
Bdq administration, n (%)	782/883 (88.6)	416/477 (87.2)
Dlm administration, n (%)	167/883 (18.9)	94/477 (19.7)
Median (IQR) months anti-TB treatment duration	–	18 (13–23)
Median (IQR) days Bdq administration	180 (168–264)	183 (168–363,5)
Median (IQR) days Dlm administration	168 (144–184)	168 (136–186)

TB: tuberculosis; IQR: interquartile range; Bdq: bedaquiline; Dlm: delamanid; MDR/RR-TB: multi-drug resistant /rifampicin-resistant tuberculosis; XDR-TB: extensively drug-resistant tuberculosis.

* Including 3 susceptible cases treated with second-line drugs due to AEs first-line drugs.

Result: Outcome

Table 4 Treatment outcomes of the 477 patients who completed the prescribed regimen including new anti-tuberculosis drugs.

Treatment Outcome	n/N (%)
Treatment success (cured + treatment completed)	344/477 (72.1)
Cured	281/477 (58.9)
Treatment completed	63/477 (13.2)
Died	38/477 (8.0)
Failure	20/477 (4.2)
Lost to follow-up	75/477 (15.7)

Bedaquiline and delanamid

Table 5 Treatment outcomes of the 383 patients treated with bedaquiline (but no delamanid) who completed the prescribed regimen.

Treatment outcome	n/N (%)
Treatment success (cured + treatment completed)	284/383 (74.2)
Cured	226/383 (59.0)
Treatment completed	58/383 (15.1)
Died	25/383 (6.5)
Failure	11/383 (2.9)
Lost to follow-up	63/383 (16.5)

Bedaquiline

Comparing both groups, the treatment success rates are similar (good enough for effectiveness), though failure rates were slightly lower in the bedaquiline-only group (2.9% vs. 4.2%). However, the lost-to-follow-up rate quite high in both groups, which might indicate adherence challenges.

Strength & Limitation

Strength:

- The number of countries participating (29) from all continents, a large sample size.
- The prospective design, and the accuracy of the information collected.
- the majority of countries/states/regions (24/29) provided data on all the consecutive patients treated with bedaquiline and dela- manid during the study period.

Limitation:

- Limited Pediatric and HIV Populations
- the impossibility of attributing the outcomes to a specific drug, as treatment regimens are inherently polypharmacological.

Conclusion

The study highlights that bedaquiline and or delamanid improves treatment outcomes for patients with multidrug-resistant tuberculosis (MDR-TB).

What I Have Learned and Can Improve:

1) We can emulate RCT using observational data (target trial emulation)
2) Adopt Target trial emulation using data from Indonesia
3) Utilizing the TB registry in Indonesia

Comparison Two Papers

No	Variables	Paper 1	Paper 2
1	Study objective	➢ To estimate the effectiveness of three duration treatment of bedaquiline (6, 7–11, and >12 month) on the probability of successful treatment	➢ To evalualte **the effectiveness** of bedaquiline and/or delamanid-containing regimens in a large cohort of MDR-TB patients treated globally.
2	Study design	Target Trial Emulation ★	Cohort, Retrospective
3	Study setting	17 Countries (EndTB database) (2015-2018)	Global TB Network, 29 countries and 52 TB centers (2015-January 2021)
4	Participants	All age of patients with **RR/MDR TB** treatment, completed bedaquiline at least 24 weeks	All of patients with **MDR TB**
5	Sample Size	2,789 participants ★	883 participants.
6	Outcome Measure	Successful or unsuccessful treatment	Successful or unsuccessful treatment

No	Variables	Paper 1	Paper 2
7	Statistical Analysis	➢ IP-Weight ➢ Logistic Regression Model	➢ Descriptive study
8	Selection Bias	Even there is a potential selection bias due to arti ficial censoring, but this study have provided IP weight to avoid this bias	None, no causal inference
9	Confounding Bias	IP weight have conducted to avoid confounding bias	-

Comment for Mita’s Paper 1

Commentor:

2nd Year PhD student

Chiu- Wen Chang (T88121015)

2025.03.19

Comment 1

- In pharmacoepidemiology studies, immortal time typically arises when the determination of an individual's treatment status involves a delay or wait period during which follow up time is accrued.
- The immortal time bias in the rate ratio resulting from misclassified or excluded immortal time increases proportionately to the duration of immortal time.

Q. In this study, it estimated a small decrease in the probability of successful treatment for 7–11 months compared with 6 months of BDQ. Do you think there is misclassification of treatment? How do you explain the impact?

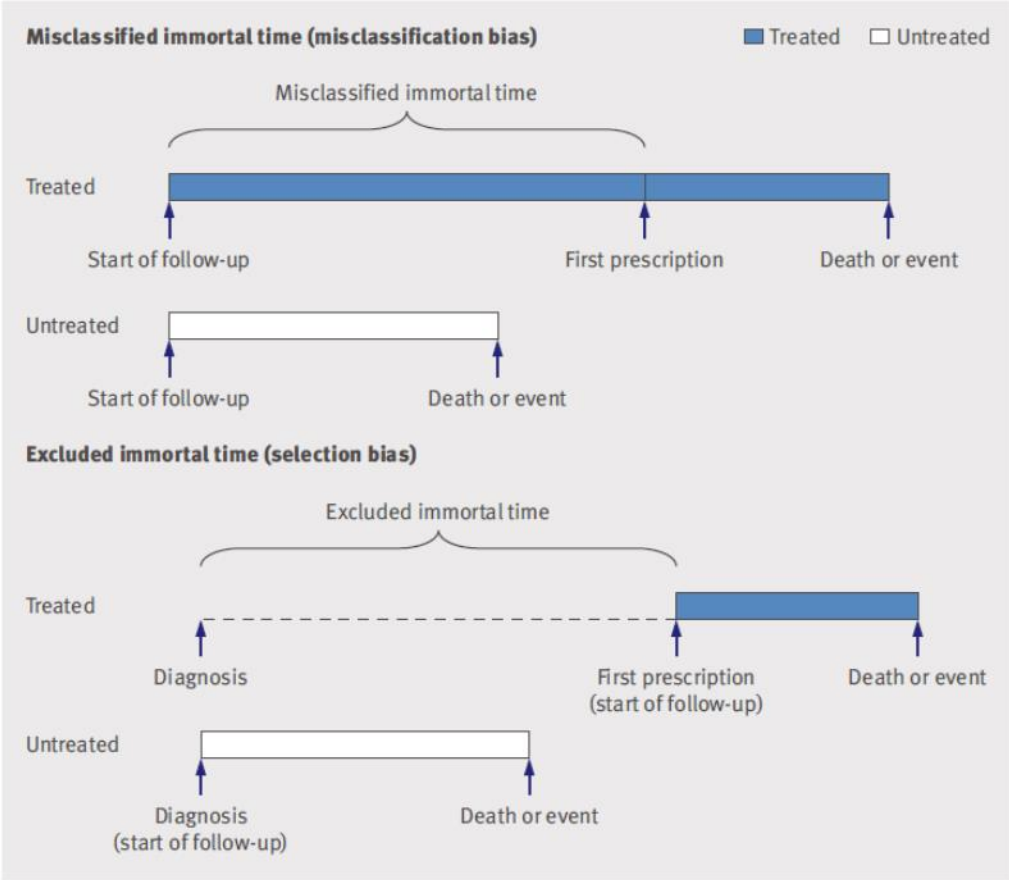


Fig 1 | Immortal time bias is introduced in cohort studies when the period of immortal time is either incorrectly attributed to the treated group through a time fixed analysis (top) or excluded from the analysis because the start of follow-up for the treated group is defined by the start of treatment and is, by design, later than that for the untreated group (bottom)

Comment 2

Table 2. Characteristics of 1,468 Patients Receiving Bedaquiline for at Least 24 Weeks, endTB (Expand New Drug Markets for TB) Cohort, 2015–2018

Characteristic	*n* (%)*	Missing [*n* (%)]
Assessed at treatment initiation		
Age at treatment initiation, yr, median (IQR; range)	34 (26–45; 10–78)	—
Female sex	531 (36.2)	—
HIV infection	95 (6.5)	1 (0.1)
Hepatitis C	139 (9.5)	3 (0.2)
Previous TB treatment with second-line drugs	1,181 (80.5)	—
Assessed at 23 wk		
Complete data on adherence	1,294 (88.2)	—
Adherence rate > 80% among those with complete adherence (*n* = 1,294)	1,163 (89.9)	—
Positive sputum culture	78 (5.3)	13 (0.9)
Extensive disease	—	149 (10.1)

Q2. The characteristics of participants, there are 80%(n=1,181) of previous TB treatment with second-line drugs. Could it influence the results?

Q3.There are 10%(n=149) of missing with extensive disease. Could it influence the results?

Feedback Comment 1 (Misclassification bias & Immortal time bias

- I agree that misclassification and immortal time bias is a potential issue in this study. **With an 89% adherence rate, around 11%** of patients did not fully comply with the treatment protocol, which could lead to misclassification bias.
- However, the study try to avoid immortal time bias by using statistical approach such as **cloning and censoring**, to provide more accurate comparison between treatment durations. As a result, the potential impact of misclassification **is minimized**, reducing its influence on the study's overall conclusions

Feedback Comment 2 (Previous TB Treatment)

The high proportion of previously treated patients could influence the results, particularly by lowering success rates due to resistance and disease severity. However, the study applied statistical **adjustments (IP Weighting) to control for confounding**. I believe it will reduce this potential bias and minimize the effect to outcome

Feedback Comment 3 (10% Missing Data)

- The 10% missing data on extensive disease could influence the results, particularly by underestimating disease severity and potentially biasing BDQ duration comparisons.
- However, in this study the authors have adjusted this problem using IP weighting to control confounding and make it balance comparison between three group. So, the impact to outcome will be minimial.

Comments to Paper 2
Takeshi
(T8813076)
1st Year PhD Student

Low coverage in the U.K.

- Why is the coverage in the U.K. so low (10%) compared to other countries/regions, which reported data for 80–100% of patients treated with bedaquiline and delamanid? **Does the value of including U.K. data outweigh the potential risk of bias (though could be small due to small *n*) in the overall results?**

Patient-centred outcomes

- The study reports on clinical outcomes such as culture conversion and treatment success, but how might the use of bedaquiline-containing regimens impact patients' quality of life and adherence to treatment? **What additional patient-centred outcomes should be considered in future studies?**

Feedback

"Low coverage in the U.K."

- The low UK data coverage (10%) may introduce bias due to underrepresentation, with only four cases enrolled, limiting statistical power. However, since this is a **descriptive study**, the researchers included UK data for geographic diversity and healthcare insights. Given the large cohort from 29 countries, the impact of this bias is minimal, with limited influence on overall conclusions.

Feedback; Patient-centred outcomes

- The impact of bedaquiline-containing regimens on patients' quality of life and adherence is truly important. Bedaquiline offers an all-oral, less toxic regimen, shorter duration treatment, potentially improving treatment adherence.
- However, prolonged BDQ use may also lead to adverse events like QT prolongation, (not frequent) which could impact patient well-being and willingness to continue treatment.

- Additional patient center we can consider: **quality of life, treatment adherence, incidence of adverse effect.**