

Overcoming challenges in TB care: from policy to practice

All-Oral Short Regimen as Future for RRTB Treatment Zhytomyr Experience

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МІНІСТЕРСТВО
ОХОРОНИ
ЗДОРОВ'Я
УКРАЇНИ

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- Zhytomyr is a region situated in the north of Ukraine with a total area of around 29,832 km² and a population of 1.2M with 58.5% living in urban area
- The administrative center is Zhytomyr, a city with 269 493 people located 140 km away from Kiev
- 23 districts
- Main cities are: Berdychiv (78,523 people), Korosten (65,503 people) Novohrad-Volynskyi (55,991 people), Malyn (26,934 people), Baranivka (11980 people).
- The northern part of the province is highly affected by the Chernobyl disaster: some of the towns and districts are devastated and are included in the Chernobyl zone



TB infrastructure :

- Zhytomyr TB dispensary - 440 beds - 3.69 beds/10.000 people (vs. 3.76/10.000 in Ukraine)
- 2 sanatoriums: one pediatric (240 beds) and 1 for adults (150 beds)
- 27 TB cabinets – most of them with 1 TB nurse+1 TB MD
- 30 laboratories level I and 1 level III
- 69 TB MD in the TB Dispensary and districts

Highlights of the epidemiological profile of Zhytomyr region

Categories (per 100,000)	2018	2019
Incidence of All Forms of TB	60.3	57.9
Incidence of HIV/TB Co-infection	9.7	8.6
Incidence of DRTB	17.9	12.9
Incidence of Relapse TB	16.2	10.6
Incidence of New and Relapse TB	76.5	68.6
Deaths from TB	10.8	8.7

Results of treatment of DRTB cases Zhytomyr Oblast, cohorts of 2016 and 2017

Outcome	2016 (%)	2017 (%)
Cured	45.9	45.6
Completed	5.9	5.8
Died	15.9	13.5
Lost to follow up	13.6	12.3
Failed	18.6	22.8

The Project

- March 2019: implementation of Operational Research “All-oral short-duration regimen with new and repurposed drugs for RRTB cases”
- Cornerstones:
 - Regimen with new and repurposed drugs for 9-12 months (Lfx-Bdq-Lnz-Cfz-Cs or Bdq-Lnz-Cfz-Dlm-Cs)
 - Early discharge to ambulatory care
 - Side effects management
 - Co-morbidities management
 - Psychosocial care

83 patients were proposed enrollment

7 (8%) refused

76 (92%) consented

76 (100%) had a GXP result

- 69 (91%) had MTB detected, 7 (9%) had MTB not detected
- 64 (93%) MTB+/RR+, 5 (7%) MTB+/RR-

76 (100%) initiated on OR regimen

- 54 (71%) on LFX
- 22 (29%) on DLM

72 patients had baseline LPA or DST result, 4 had no results

- 2 (3%) had no R or H resistance (DSTB)
- 23 (32%) had only H and R resistance (MDRTB)
- 22 (31%) had H, R, FQ and injectable resistance (XDRTB)
- 6 (8%) had H, R and FQ resistance (pre-XDRTB)
- 13 (18%) had H, R and injectable resistance (pre-XDRTB)
- 6 (8%) had RRTB

74 included in the analysis, 2 excluded because of Rif-Sensitivity by GX, LPA and DST

74 patients in the analysis:

- 53 (72%) on LFX
- 21 (28%) on DLM

- 8 (11%) died within 6 months
- 1 (1%) on DLM switched to ITR

65 (88%) remained on OR regimen

- 14 (21%) switched LFX to DLM
- 2 (3%) switched LZD to DLM
- 18 (28%) patients remained on DLM
- 31 (48%) remained on BDQ without DLM

64 (98%) had a baseline culture result, 1 (2%) had no baseline culture

- 54 (84%) had baseline positive culture
- 10 (16%) had baseline negative culture

- 1 is alive on ITR after 6 months, culture converted

65 (100%) are alive on OR after 6 months

- 54 culture converted at 6 months
- 10 remained negative at 6 months
- 1 had no baseline culture

Results

Table 1. Baseline characteristics of rifampicin resistant patients enrolled on all-oral short regimens including bedaquiline (and delamanid) in Zhytomyr, Ukraine between March and 30 July 2019.

Characteristic	Total n (%)		
	A. All patients n= 74	B. BDQ/LFX final regimen n= 37	C. BDQ/DLM final regimen n= 37
Demographic			
Sex, female	20 (27%)	11 (30%)	9 (24%)
Median age at initiation (IQR; range)	41 (34-53; 5-75)	45 (33-55; 5-75)	40 (36-47; 25-60)
Age ≤18 years old	2 (3%)	2 (5%)	0
Age ≤ 25 years old	6 (8%)	5 (14%)	1 (3%)
Married or lives with partner	32 (43%)	15 (41%)	17 (46%)
History of incarceration (past/present)	11 (15%)	3 (8%)	8 (22%)
BMI <18.5	24 (32%)	12 (32%)	12 (32%)
Comorbidities			
DM	5 (8%)	2 (6%)	3 (9%)
HIV	14 (20%)	7 (19%)	7 (20%)
HBV serology positive	1 (2%)	1 (3%)	0
HCV serology positive	10 (16%)	4 (13%)	6 (18%)
Hazardous drinking (Female: Audit≥8-13; Male:Audit≥8-15)	13 (20%)	5 (17%)	8 (24%)
Harmful drinking (Female: Audit>13; Male:Audit>15)	17 (27%)	7 (23%)	10 (29%)
Use of non-intravenous drugs	6 (8%)	3 (8%)	3 (8%)
Use of Intravenous drugs	3 (4%)	2 (5%)	1 (3%)
At least one other comorbidity**	39 (53%)	19 (51%)	20 (54%)

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	A. All patients n= 74	B. BDQ/LFX final regimen n= 37	C. BDQ/DLM final regimen n= 37
Tuberculosis related			
Prior TB treatment	35 (47%)	12 (32%)	23 (62%)
first-line	13 (37%)	8 (67%)	5 (22%)
second-line	16 (46%)	0	16 (70%)
unknown	6 (17%)	4 (33%)	2 (8%)
Extra-pulmonary disease	7 (9%)	5 (14%)	2 (5%)
Radiography: bilateral	55 (74%)	25 (68%)	30 (81%)
Positive baseline culture	54 (83%)	24 (75%)	30 (91%)
Drug resistance pattern			
H/S resistance	0	0	0
R resistance with H susceptibility	0	0	0
GXP RIF resistance only	6 (8%)	6 (16%)	0
Confirmed MDR	23 (31%)	18 (49%)	5 (14%)
Confirmed pre-XDR (FQ)	5 (7%)	0	5 (14%)
Confirmed pre-XDR (Inj)	13 (18%)	10 (27%)	3 (8%)
Confirmed XDR	23 (31%)	1 (3%)	22 (59%)
Unknown	4 (5%)	2 (5%)	2 (5%)

Results

Table 2. Outcomes at six months of rifampicin-resistant patients enrolled on all-oral short regimens including bedaquiline (and delamanid) in Zhytomyr, Ukraine between March and 30 July 2019

Population	N (%) at six months	Median days to outcome (IQR; range)
All RR-TB patients started on OR regimen (n=74)	8 (11%) died	42 (14.5-89.5; 1-138)
	0 LTFU	NA
	0 Failure	NA
	1 (1%) switched treatment	35
	65 (88%) alive on treatment	NA
	All patients alive on OR treatment with baseline culture positive (n=54)	54 (100%) converted

Results

Table 3. Culture conversion at six months of patients enrolled and alive on all-oral short regimens including bedaquiline (and delamanid) in Zhytomyr, Ukraine between March and 30 July 2019

Population	% of culture converted at six months	Median month to conversion (IQR, range)
All included (n =54)	100%	2 (1 - 2.9; 0.9 - 5.2)
Female (n=14)	100%	1.7 (1 - 2; 0.9 - 2)
Male (n=40)	100%	2.1 (1.2 - 3; 0.9 - 5.2)
Age ≤ 25 (n=3)	100%	1 (1 - 1.4; 1 - 1.4)
HIV positive (n=13)	100%	1.9 (1 - 2.3; 0.9 - 5.2)
HCV positive (n=9)	100%	2.9 (2 - 3.1; 1 - 3.1)
AUD/SUDa (n=13)	100%	2.3 (1 - 3; 1 - 3.9)
Harmful alcohol useb (n=8)	100%	2.1 (2 - 2.9; 0.9 - 5.2)
Extra-pulmonary TB (n=4)	100%	1.2 (1 - 3.3; 1 - 5.2)
XDR or pre-XDR FQ (n=23)	100%	2 (1 - 3; 1 - 3.9)

Results

Table 4. Incidence of relevant adverse events in patients enrolled on all-oral short regimens including bedaquiline (and delamanid) in Zhytomyr, Ukraine between March and 30 July 2019

Adverse event term	N (%) of patients*	Number of episodes	Time to occurrence of each episode in months (Median, IQR)	Median N (IQR) of episodes per person	Incidence of AE / 100 person-months
At least one adverse event	26 (35%)	38	3.8 (2 - 4.7)	1 (1 - 2)	9.4%
At least one serious adverse event	14 (19%)	15	3.1 (0.8 - 4.6)	1 (1 -1)	3.7%
Adverse event of special interest					
QtcF interval prolongation**	8	10	3.8 (1 - 4.6)	1 (1 -1)	2.5%
Hy's criteria for liver dysfunction	0	0	0	0	0.0%
Optic neuritis	1 (1%)	1	5.9	1	0.2%
Leading to permanent treatment change	1 (1%)	1	5.9	1	0.2%
Pregnancy	0	0	0	0	0.0%
Death	8 (11%)	8	1.4 (0.5 - 3)	1	2.0%

*74 patients included in this analysis so the denominator is 74

**> 450 for male; >470 for female

Results

Compliance with safety and efficacy threshold at six months for patients enrolled on all-oral short regimens including bedaquiline (and delamanid) in Zhytomyr, Ukraine between March and 30 July 2019

Threshold for continuation of the operational research regimens	Inclusion criteria	Result	Threshold met
<25 % of patients developing a serious adverse event	All patients initiating on OR regimen	19%	Yes
>60% of patients culture converted by six months	Patients with positive culture at baseline	100%	Yes