endTB in Lesotho

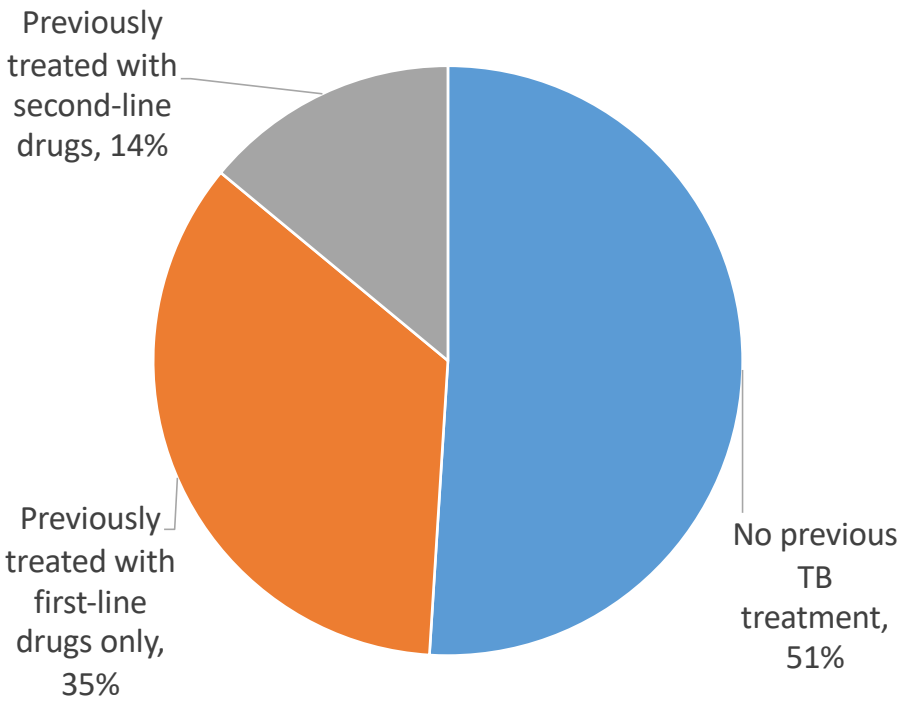
Questions

- What types of patients are treated with new and repurposed TB drugs?
- What are the characteristics of MDR-TB patients that affect the prescription of new and repurposed TB drugs?
- What are the outcomes of regimens using new and repurposed TB drugs?
- What are the lessons learned for routine care of MDR-TB with new and repurposed TB drugs?
- What are the national plans to expand access to new and repurposed TB drugs?

MDR-TB in Lesotho

- Lesotho has the highest TB incidence in the world, and there is a high rate of HIV co-infection (71%). This is similar to other countries in the southern African region.
- 6.5% of incident TB cases are estimated to have RR/MDR-TB in Lesotho.
- Bedaquiline, delamanid, linezolid and clofazimine have been introduced in Lesotho starting in October 2015 through endTB.

Lesotho patients are less chronic than other countries



- The first endTB patients in Lesotho were chronic patients, just like in other countries.
- Patients who were switched to new TB drugs because of toxicity to standard MDR-TB drugs are very common (~47%)
- Patients with new diagnoses of MDR-TB were increasingly common.

Lesotho patients are less resistant, but more complicated than in other countries

Resistance pattern	N (%)
RR/MDR-TB without evidence of resistance to FQ or injectable	174 (81%)
Pre-XDR, resistance to any injectable	5 (2%)
Pre-XDR, resistance to any FQ	20 (9%)
XDR-TB	10 (5%)

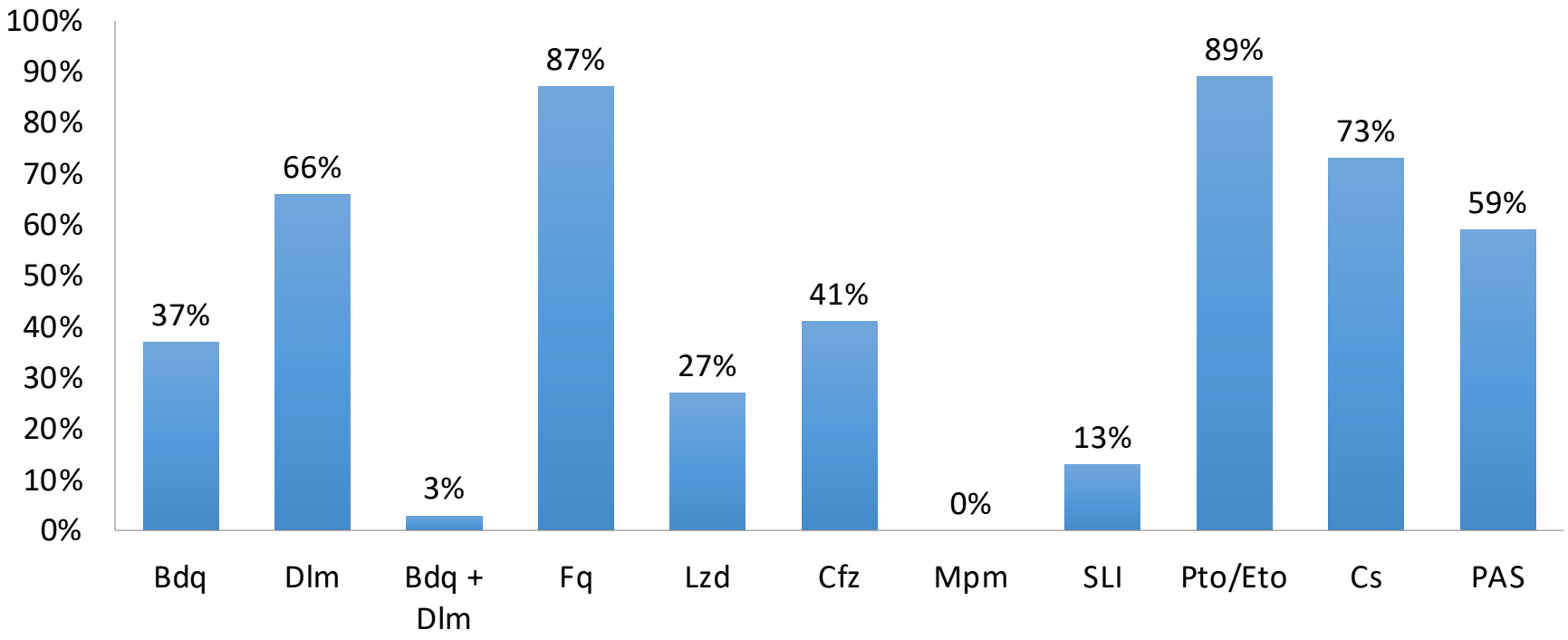
- Patients need new TB drugs because they cannot tolerate standard TB drugs, not because they are highly resistant.
- Pre-existing conditions make treatment complicated (e.g. kidney injury, baseline peripheral neuropathy, depression, elevated liver enzymes).
- A standard regimen is not possible; clinicians need a wide variety of therapeutic options.

Lesotho has a high rate of HIV co-infection and other pre-existing conditions

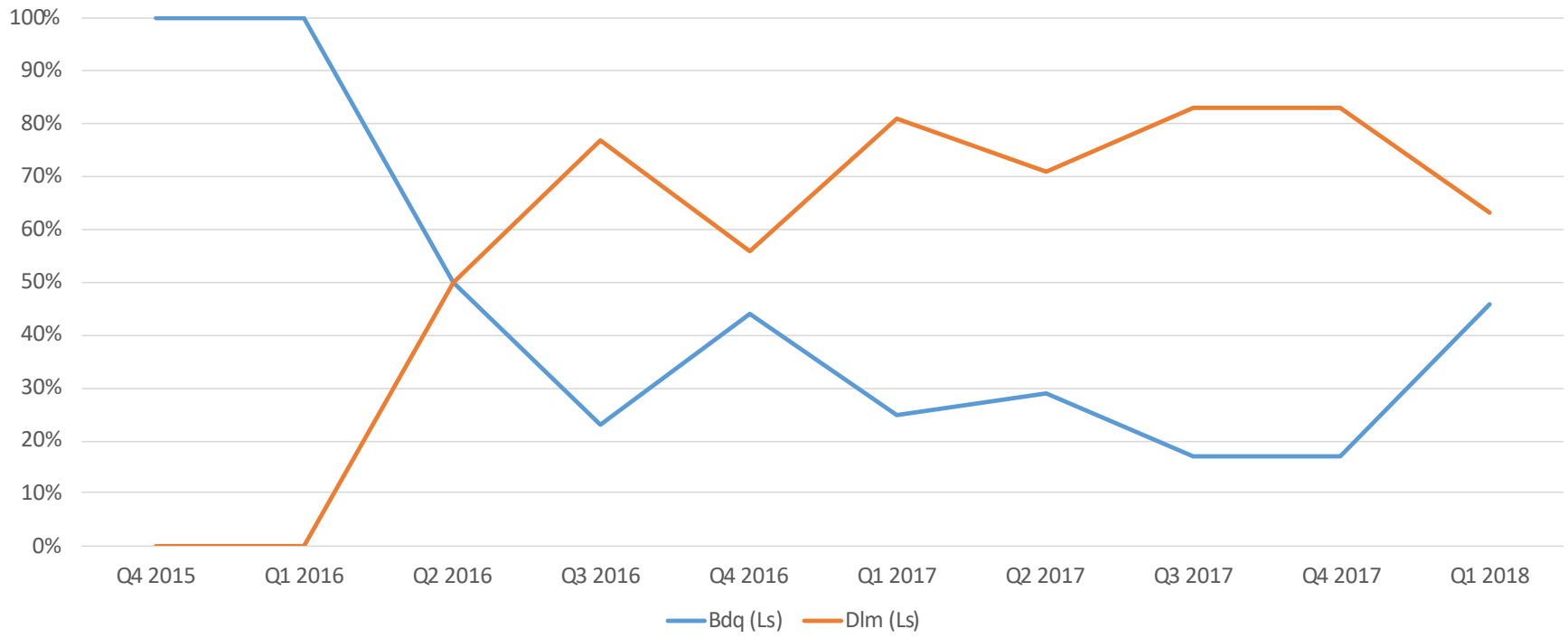
Baseline characteristics	N = 215
Median age in years (min, max)	42.0 (17.0, 88.0)
Male gender	134 (62%)
HIV co-infection	172 (80%)
Diabetes (type I or II)	8 (7%)
Hepatitis C	0 (0%)
Hepatitis B	14 (7%)
Body mass index < 18.5	97 (49%)

- Bedaquiline can still be used with ART, but EFZ should be switched to NVP because of interactions.
  - Integrase inhibitors are also a good option to avoid interactions.
- Delamanid has no clinically significant interactions with ART than bedaquiline.
- No "washout" period is required.

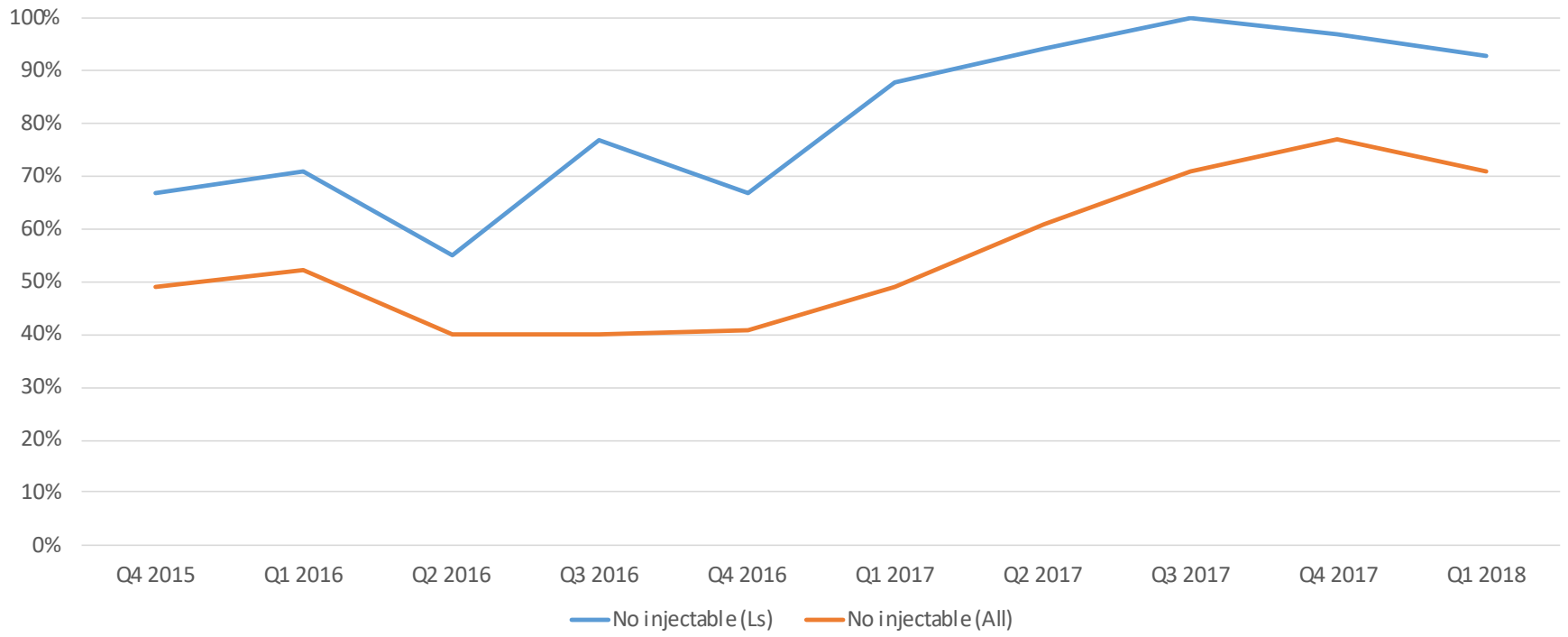
Most commonly prescribed drugs in endTB patients



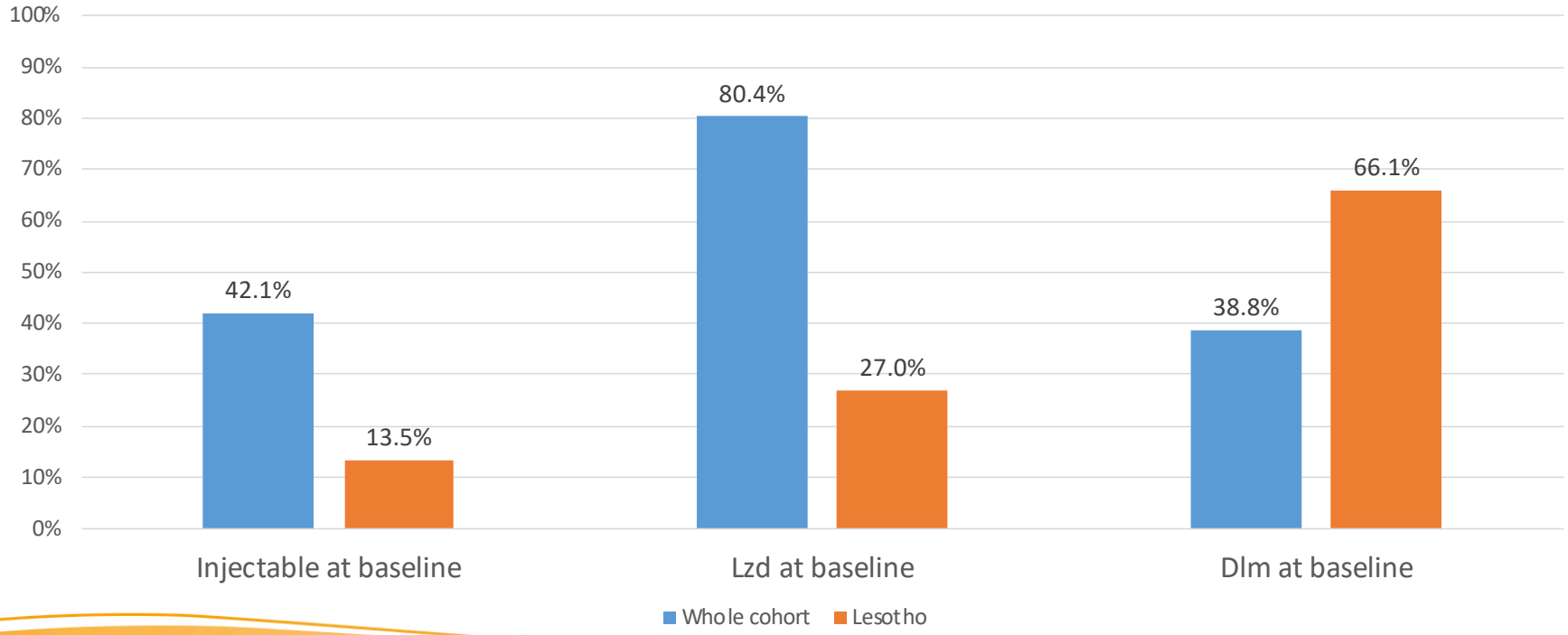
Dlm usage consistently higher than Bdq



Injectable-free regimens have become universal



Delamanid prescription is higher, but injectables and linezolid prescription is lower in Lesotho



Both Bdq and Dlm are commonly used more than 24 weeks

- Bedaquiline, delamanid, linezolid and clofazimine are used for as long as the responsible physician deems necessary.
- In general, bedaquiline and delamanid are better tolerated than linezolid, which often must be dose-reduced or suspended before the end of treatment.

Pre-existing anemia complicates use of linezolid

	Median Hb (g/dL)	Q1 (g/dL)	Q3 (g/dL)
Total cohort	12.5	11.0	13.8
Lesotho	10.5	8.7	12.7

- Median baseline hemoglobin is significantly lower in Lesotho compared to the entire cohort (Q3 cutoff is close to the overall median Hb).
- Linezolid can still be used in anemic patients, and can actually improve anemia caused by disseminated TB, but these patients need to be monitored closely.

Six month culture conversion (N=30)

Culture-positive patients enrolled between October 1, 2015 – February 28, 2017

Variable	Total n (%)	Converted by 6 months		p-value
		Yes	No	
Culture positive at baseline	30 (100%)	23 (77%)	7 (23%)	--
HIV serostatus				
Positive	22 (73%)	19 (86%)	3 (14%)	0.06
Negative	8 (27%)	4 (50%)	4 (50%)	
Baseline smear status				
Positive	15 (50%)	11 (73%)	4 (27%)	1.00
Negative	15 (50%)	12 (80%)	3 (20%)	
XDR TB (N=29 w/ 2nd line DST results)				
Yes	5 (17%)	3 (60%)	2 (40%)	0.27
No	24 (83%)	20 (83%)	4 (17%)	
Baseline body mass index (N=28)				
<18.5 kg/m²	15 (54%)	9 (60%)	6 (40%)	0.08
≥18.5 kg/m²	13 (46%)	12 (92%)	1 (8%)	

Treatment outcomes (N=42)

Patients enrolled between October 5, 2015 – June 30, 2016

Outcome	N (%)
Cured	26 (62%)
Completed	1 (2.4%)
Died	13 (31%)
Lost to follow-up	1 (2.4%)
Not evaluated	1 (2.4%)

23% mortality among HIV-positive participants compared with 71% mortality among HIV-negative participants (p=0.02)

Lessons learned from Lesotho (1)

- New TB drugs bedaquiline and delmanid have radically changed MDR-TB treatment.
  - Allowed patients to avoid potential serious toxicity from injectables and other standard MDR-TB drugs.
  - Injectable-free regimens are already the norm for new MDR-TB patients.
- Toxicity of new and repurposed drugs exists and can be challenging but is easier to monitor and manage than what is required for standard MDR-TB drugs.
  - Monitoring for linezolid toxicity (e.g. bone marrow toxicity) is the most important, especially in the face of TB-related anemia, but still manageable.

Lessons learned from Lesotho (2)

- Treatment with new TB drugs can achieve excellent outcomes in patients with high rates of HIV, malnutrition, anemia.
  - Delamanid has important advantages in the southern Africa region because of the lack of interactions with ART.
  - Extended duration of bedaquiline and delamanid is well tolerated and safe.
  - No standard MDR-TB regimen can be sufficient for all patients. Clinicians need a wide variety of options to respond to pre-existing conditions.
- Social, economic risk factors (e.g., extreme poverty, history of mining work) still important to address in order to improve outcomes.

Plans to expand access to new and repurposed drugs

- Lesotho MDR-TB guidelines is currently under revision. There is a general agreement on:
  - Injectable-free regimens for all MDR-TB patients.
  - Operational research on novel shorter regimens for selected patients.
- Ongoing discussions with partners (GFATM, WHO, GDF) about:
  - Forecasting the increased use of new and repurposed drugs.
  - Need for additional funding for drug procurement and operational research.