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**Table 4: Limitations of Clinical Trials Designed to Estimate Xpert Impact on Patient Outcomes**

Study	Design							Conduct	Health System Weaknesses				
	Study Population Not Exclusively a WHO Priority Population (reason)	Restricted to Outpatients	Not a Randomized Trial	No Blinding to TB Diagnostic used	Higher Rates of Empiric TB Treatment in Microscopy Arm	Not Powered to Detect a Morbidity or Mortality Difference	Anticipated Morbidity or Mortality Difference Possibly Too Large (i.e., possibly underpowered)	LTFU of Enrollees Restricted Key Outcome Ascertainment	% of Study Enrollees Not Knowing their HIV status	% of HIV-positive Enrollees on ART (ART coverage)	High LTFU of Microbiologically-Confirmed TB Patients before TB Treatment <sup>j</sup>	High LTFU of TB patients during TB Treatment	
TB-NEAT <sup>9</sup>	✓	(40% HIV - negative)	✓	X	✓	✓	X	✓ <sup>a</sup>	✓ <sup>b</sup>	<1% <sup>i</sup>	26%	✓	✓
XTEND <sup>10,29</sup>	✓	(50-55% HIV-negative)	✓	X	✓	✓	X	✓ <sup>a</sup>	X <sup>c</sup>	21-27%	33%	✓	NA
Brazil Stepped Wedge <sup>11,21</sup>	✓	(90-92% HIV-negative)	✓	X	✓	X	✓	N/A	✓ <sup>d</sup>	>50%	NA	NA	✓
Zimbabwe RCT <sup>14</sup>	X	(100% HIV-positive)	✓	X	✓	X	X	✓ <sup>a</sup>	✓ <sup>e</sup>	0%	100%	NA	NA
South Africa CRT <sup>12</sup>	✓	(40-41% HIV-negative)	✓	X	✓	✓	✓	N/A	NA	18%	NA	NA	✓
Uganda Pre-post <sup>13</sup>	✓	(24% HIV-negative)	X	✓	✓	✓	✓	N/A	✓ <sup>f</sup>	0%	NA	NA	✓
SA ICU trial <sup>15</sup>	✓	(70% HIV-negative)	X	X	✓	✓	✓	N/A	X <sup>g</sup>	15%	31%	NA	NA
Pre-Post trial, Indonesia <sup>16</sup>	X	(100% DR TB suspects)	✓	✓	✓	X	✓	N/A	✓ <sup>h</sup>	NA	NA	✓	NA

Abbreviations: “✓”, stated study limitation applies to this study; “X”, study limitation does not apply; WHO, World Health Organization; TB, tuberculosis; LTFU, loss to follow-up; HTC, HIV testing and counselling; NA, not available; N/A, not applicable, SA, South Africa; SOC, standard of care; DR, drug resistant

<sup>a</sup> See text for discussion

<sup>b</sup> 20% loss to follow-up (LTFU) of culture-confirmed TB cases.

<sup>c</sup> Although LTFU before TB treatment was 16% among microbiologically confirmed TB patients, investigators ascertained vital status of nearly all study enrollees (+99%) by study end.

<sup>d</sup> High incidence of LTFU (about 16% in both SOC and intervention phase)

<sup>e</sup> 17% (70/424) of ART enrollees LTFU before 6 months.

<sup>f</sup> 7% of study enrollees (32/477) LTFU before study end.

<sup>g</sup> Less than 4% were LTFU at 90 days.

<sup>h</sup> Missing data on 2<sup>nd</sup> line treatment initiation was very high both pre-Xpert (52.4%) and post-Xpert (31.0%). Based on available data, missing data on TB treatment initiation seems equivalent to LTFU before second-line TB treatment initiation. Overall missing data (probable LTFU) before second-line TB treatment was 42% (267/634) among rifampicin resistant cases.

<sup>i</sup> Study enrollees were offered HIV testing and counseling at study enrollment.

<sup>j</sup> Data points are presented in Table 3