Azithromycin for management of HIV-associated chronic lung disease in African children (BREATHE trial): A randomised controlled trial

Rashida Ferrand

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

BRTI
Biomedical Research and Training Institute

Background and trial hypothesis

- HIV-associated chronic lung disease (HCLD) in children in Africa is common despite antiretroviral therapy (ART) and is associated with poor lung function and substantial morbidity.[1]
- HCLD in the ART era affects small airways and may be a consequence of repeated respiratory tract infections and/or chronic immune activation.[2]
- Trial hypothesis: Azithromycin (AZM) improves lung function and morbidity through preventing respiratory tract infections and controlling systemic inflammation.

1. Rylance J et al AIDS 2016; 30:2795-2803; Githinji L et al Clin Infect Dis 2020;70:483-490
2. Desai SR et al; Clin Infect Dis 2018; 66:274-281; Attia EF et al JAIDS 2020

Methods

- **Trial design** Individually randomized, placebo-controlled, double-masked trial (ClinicalTrials.gov: NCT02426112)[1]
- **Trial population** Children with HIV aged 6-19 years on ART (for >6 months) with chronic lung disease (Forced Expiratory Volume 1 second (FEV1) z-score <-1 and no reversibility) in Malawi and Zimbabwe
- Randomized to once-weekly AZM (weight-based dosing) or placebo for 48 weeks
- **Primary outcome** Mean FEV1 z-score at 48 weeks
- **Secondary outcomes** **A**cute respiratory exacerbations (ARE)
  Mortality, hospitalisations, infections

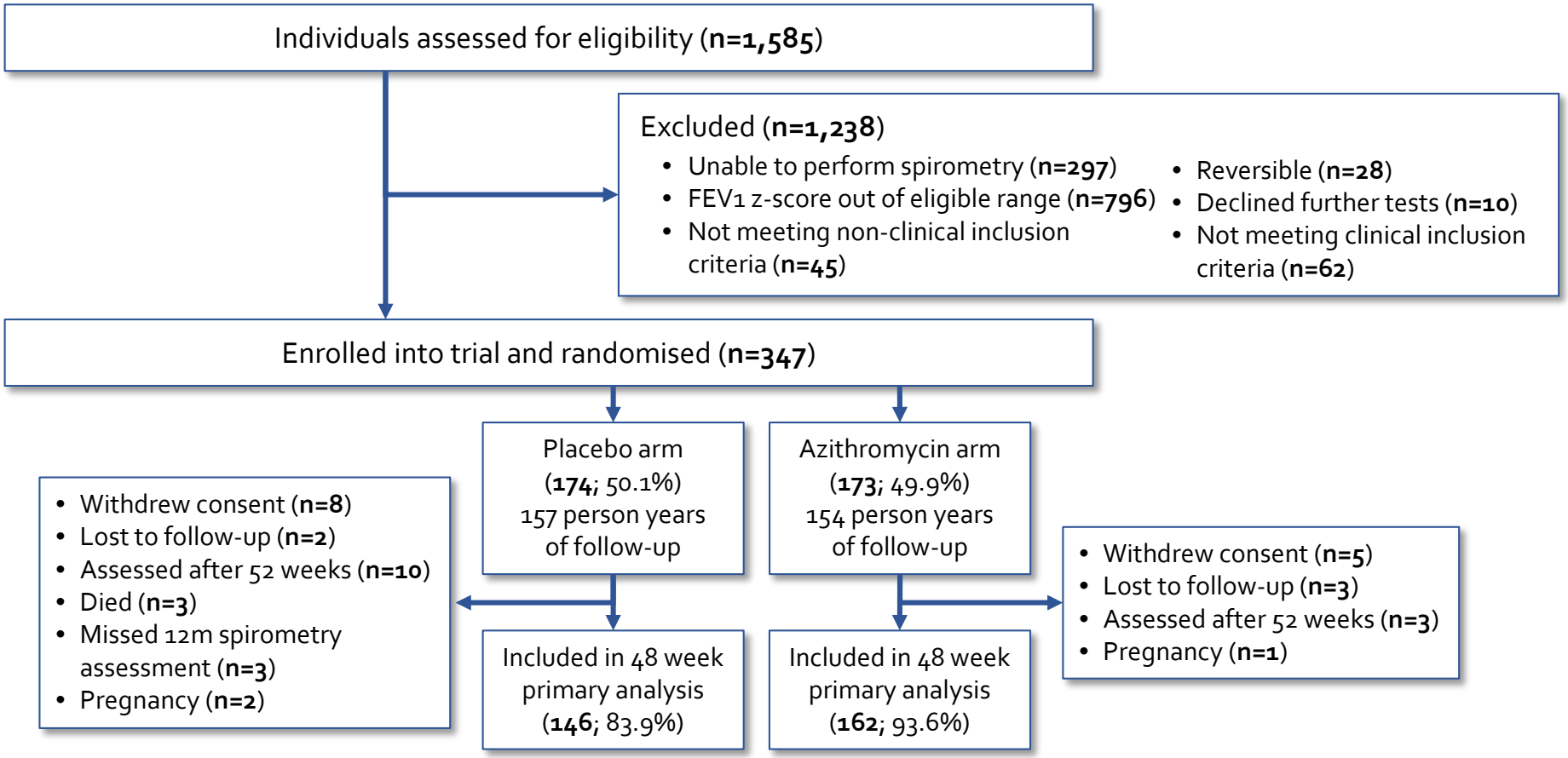
ARE: new or worsening respiratory symptoms +/- symptoms and signs of an infection

[1]Gonzalez-Martinez C et al. Trials. 2017;18:622

Statistical methods

- **Continuous outcomes**
  - Linear regression with fixed effect for trial arm
  - Robust standard errors to allow for heteroscedasticity
  - Adjusted for site, baseline FEV1 z-score
  - Further adjusted for variables associated with missingness at primary endpoint
- **Time-to-event data**
  - Cox regression with robust standard errors to allow for multiple events
- All comparisons adjusted for key variables imbalanced at baseline (age, sex, log10 baseline HIV viral load)

Trial flowchart



Baseline characteristics by arm

Characteristic		Placebo arm (50.1%)	AZM arm (49.9%)
Site 1		69.5%	69.4%
Age (years)		15.8 (SD 3.2)	14.7 (SD 3.2)
Female sex		90 (51.7%)	80 (46.2%)
Age at diagnosis years*		8.31 (IQR 5.20 – 11.07)	7.18 (IQR 3.49 – 9.90)
Age at ART start yrs†		8.86 (IQR 6.70 – 11.67)	8.16 (IQR 5.04 – 11.22)
Duration on ART years†		6.40 (IQR 3.92 – 8.24)	5.94 (IQR 3.79 – 8.96)
HIV VL<1000 copies/ml‡		94 (54.0%)	100 (58.5%)
Median CD_4 count (cells/mm^3)		549.5 (IQR 325 – 779)	601 (IQR 417 – 784)
ART Regimen§	NNRTI	131 (75.3%)	127 (73.4%)
	PI	42 (24.1%)	46 (26.6%)
Cotrimoxazole‡		156 (90.0%)	157 (90.8%)

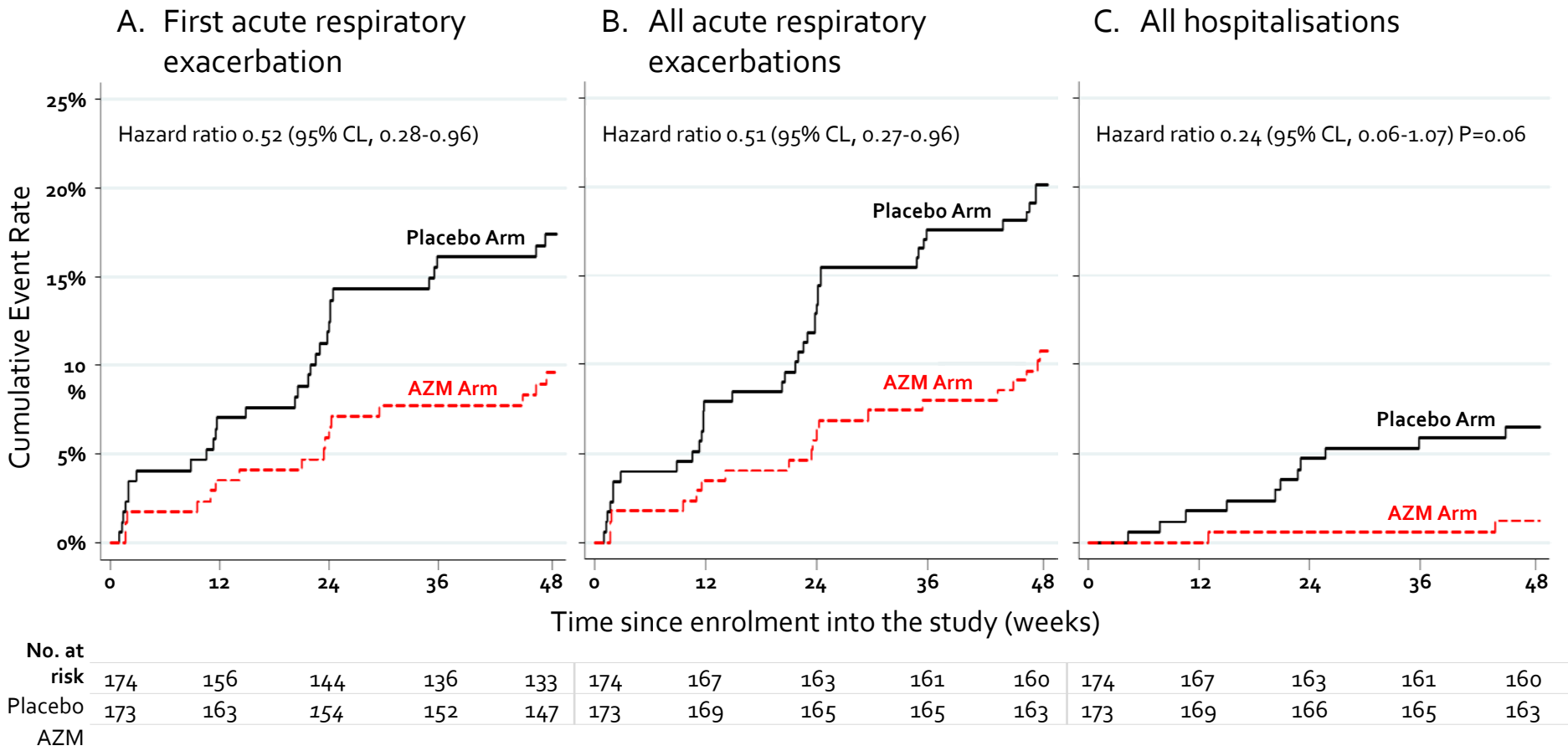
Missing data: *n=16; †n=11; ‡n=2; §n=1

Effect of the intervention on FEV1 z-score

Outcome	Placebo	AZM	Adjusted mean difference (95% CI)	P-value
Primary outcome: FEV1 z-score measured at 48 weeks (n=308)	-1.95 (SD 0.91)	-1.90 (SD 0.90)	0.055 (-0.100, 0.209)	0.48
Stratified by sex (P=0.29 for interaction)				
Males	-1.91 (SD 0.93)	-1.82 (SD 0.89)	0.134 (-0.078, 0.346)	0.21
Females	-1.99 (SD 0.90)	-2.00 (SD 0.89)	-0.032 (-0.255, 0.191)	0.78

Ferrand RA et al *JAMA Netw Open.* 2020;3(12):e2028484

Intervention effect on secondary outcomes



No. at risk															
Placebo	174	156	144	136	133	174	167	163	161	160	174	167	163	161	160
AZM	173	163	154	152	147	173	169	165	165	163	173	169	166	165	163

Effect of the intervention on rare event outcomes

Outcome	Placebo arm	Azithromycin arm
Death	3/1.54 Rate 1.95 per 100py	0/1.57 Rate 0.00 per 100 py
Malaria	2/1.54 Rate 1.30 per 100py	1/1.57 Rate 0.64 per 100 py
Salmonella typhi and non-typhi infections	0/1.54 Rate 0.00 per 100 py	0/1.57 Rate 0.00 per 100 py
Gastroenteritis	2/1.54 Rate 1.30 per 100py	1/1.57 Rate 0.64 per 100py

Adherence and Adverse events

- <3 doses missed on average: 67.2% in placebo vs 73.4% AZM arm

Adverse event	Placebo arm	Azithromycin arm
Drug-Related	21	50
DAIDS grade 1-2	21	50
Not drug-related	72	46
DAIDS grade 1-2	56	44
DAIDS grade 3	12	2
DAIDS grade 4/5	4	0

Respiratory flora and antimicrobial resistance

- Nested Case-control study comparing CLD+ with control group (CLD-ve): CLD-ve defined as FEV1 *z*-score >0, no respiratory symptoms or known heart or lung disease. Controls frequency-matched for site, age and ART duration

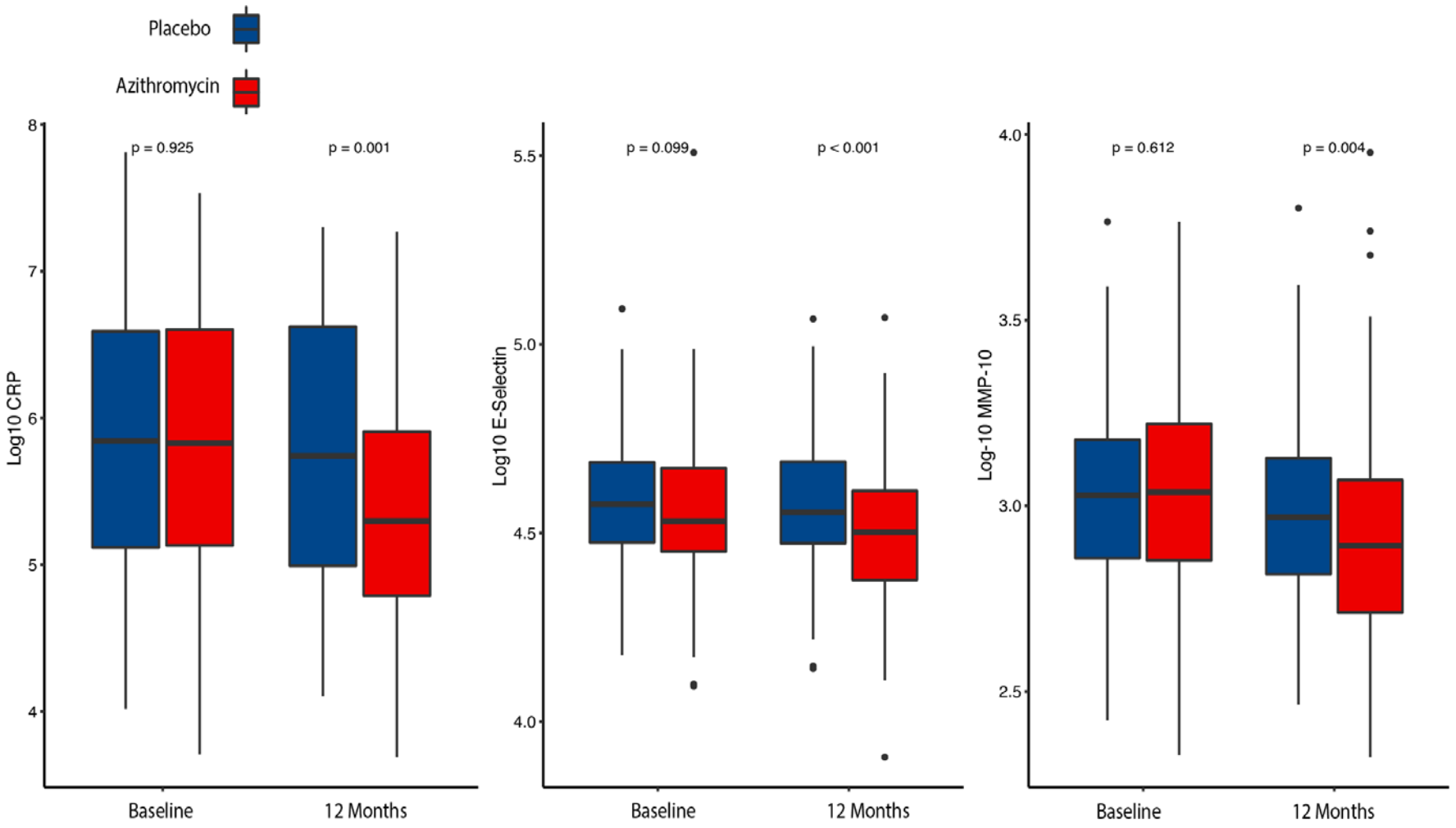
Bacteria isolates on nasopharyngeal swabs	CLD+ (n= 336)	CLD- (n=74)	P-value
S. pneumoniae	154 (46%)	19 (26%)	0.008
S. aureus	77 (23%)	9 (12%)	0.164
H. influenzae	40 (12%)	4 (5%)	0.576
M. catarrhalis	49 (15%)	2 (3%)	0.012
≥ 1 bacterial species	226(67%)	29(39%)	<0.001

- *S. pneumoniae* non-susceptibility to penicillin:

CLD+ve: 36% [53/144] vs CLD-ve: 11% [2/18], p=0.036

Abotsi R et al, manuscript under review

Markers of immune activation



Hameiri-Bowen D et al, manuscript in preparation

Conclusions

- This is the first trial of an intervention to address HCLD in children
- After 48 weeks treatment, there was no evidence of an effect of AZM on FEV1 Z-score (primary outcome) but participants in AZM arm had lower incidence of acute respiratory exacerbations and hospitalisations
- Azithromycin is safe in this population, as expected
- Azithromycin is an effective intervention in reducing morbidity associated with HIV-associated chronic lung disease in children and adolescents
- Investigation of impact of azithromycin on antimicrobial resistance and anti-inflammatory activity ongoing

Acknowledgements

- **BREATHE TRIAL TEAM**: **Jon Odland, Grace McHugh,** Trine Andreassen, Regina Abotsi, Tsitsi Bandason, Dan Hameri- Bowen, Jessica Chikwana, Liz Corbett, Felix Dube, Carmen Gonzalez, Tore Gutteberg, Trond Flaegstad, Trym Flygel, Katharina Kranzer, Edith Majonga, Slindile Mbhele, Brewster Moyo, Hilda Mujuru, Lucky Ngwira, Mark Nicol, Andrea Rehman, Sarah Rowland-Jones, Robina Semphere, Vicky Simms, Evegeniya Sovarashaeva, Helen Weiss, Louis-Marie Yindom
- James Rylance: Liverpool School of Tropical Medicine
- University of Tromso
- Harare Children's Hospital, Zimbabwe
- Queen Elizabeth's Hospital, Malawi
- Biomedical Research and Training Institute
- University of Zimbabwe
- Malawi-Liverpool-Wellcome Programme
- University of Cape Town
- University of Oxford
- Trial participants

The Research Council of Norway

Programme for Global Health and Vaccination Research – GLOBVAC