Next gen PrEP at CROI 2016

Peter Godfrey-Faussett
Senior Science Adviser

Thanks to Jared Baeten for original slides and apologies for editing them

UNAIDS

Vaginal Rings, Rectal Gels and Intramuscular Injections – next gen PrEP

- **ASPIRE**
- **RING**
- **MTN 017**
- **ÉCLAIR**
- **Maraviroc**

MTN
microbicide trials network

ASPIRE
A Study to Prevent Infection with a Ring for Extended Use

A Phase III Trial of the Dapivirine Vaginal Ring for HIV-1 Prevention in Women

The MTN-020/ASPIRE Study Team

CROI 2016, Boston, USA

MTN-020/ASPIRE

- MTN-020/ASPIRE was a multi-center, randomized, double-blind, placebo-controlled phase III trial of a vaginal matrix ring containing the non-nucleoside reverse transcriptase inhibitor dapivirine.

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MTN-020/ASPIRE and IPM/RING

- MTN-020/ASPIRE was a multi-center, randomized, double-blind, placebo-controlled phase III trial of a vaginal matrix ring containing the non-nucleoside reverse transcriptase inhibitor dapivirine.
- The IPM/RING study was a multi-center, randomized, double-blind, placebo-controlled phase III trial of a vaginal matrix ring containing the non-nucleoside reverse transcriptase inhibitor dapivirine

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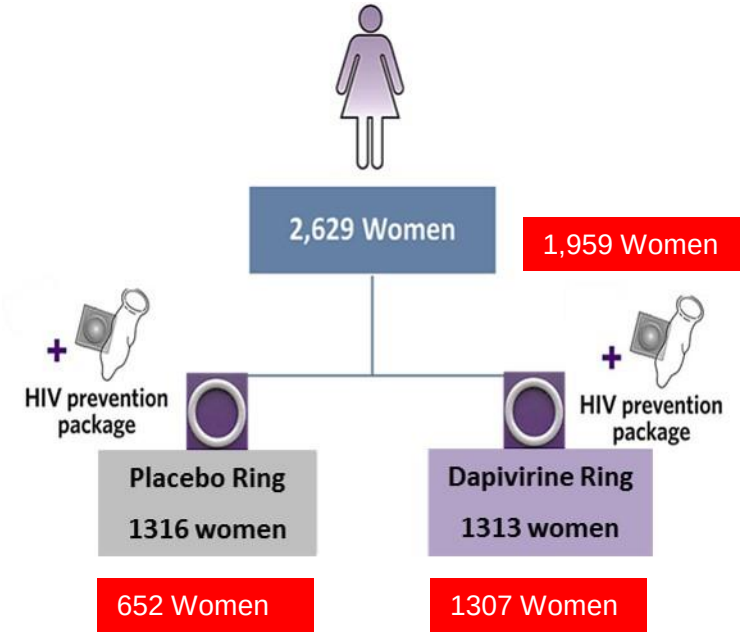
Trial Design

- At enrollment, women were randomized 1:1 to dapivirine:placebo.
- Women were counseled to wear the ring continuously, and a new ring was provided at scheduled monthly visits.
- Follow-up was for a minimum of 1 year.
- All received a comprehensive package of HIV-1 prevention services.



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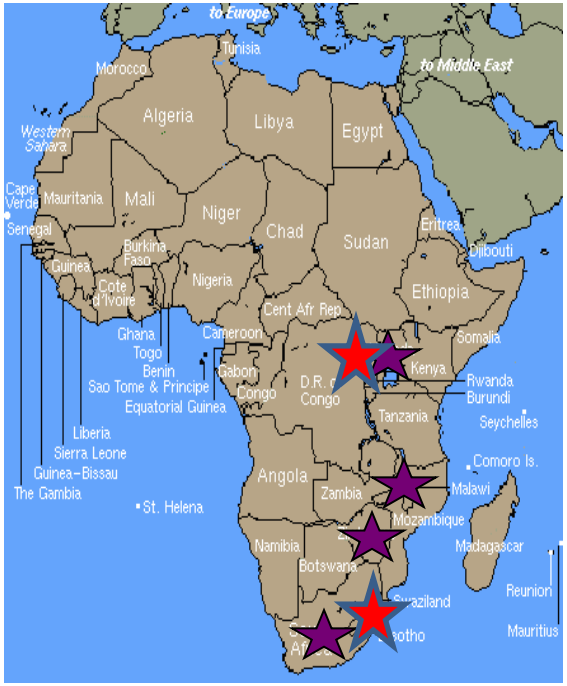
Participants



- Between August 2012 and June 2015, a total of 2629 women were enrolled and followed across 15 sites in 4 countries: Malawi (10%), South Africa (54%), Uganda (10%), & Zimbabwe (26%)
- Participant characteristics were balanced between the arms and defined a population at risk for HIV-1:
  - Median age was 26 years (IQR 22-31)
  - Less than half (41%) were married
  - Nearly all (>99%) reported a primary sex partner & 17% reported more than one partner in the prior 3 months
  - Nearly half did not use a condom with their last sex act

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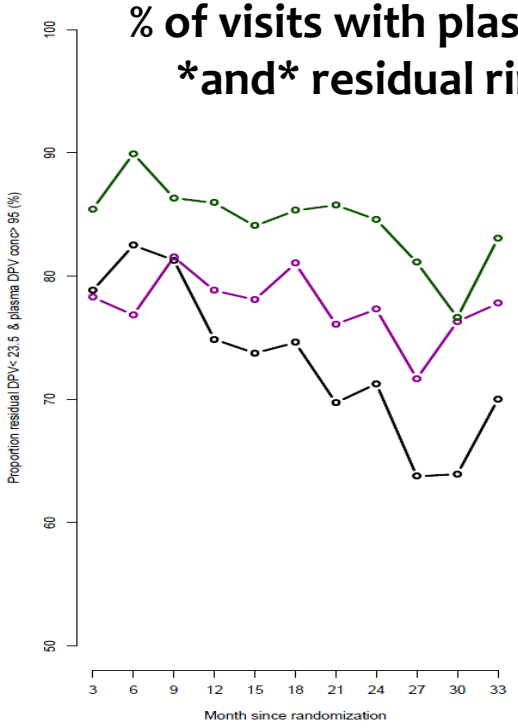
Adherence

- Dapivirine was detected in 82% of plasma samples at concentrations >95 pg/mL.
  - Detection increased during the first year of use and stabilized thereafter.
  - Two study sites were identified early in the study as having lower detection of dapivirine compared to other sites, as well as lower retention.
- In the subset of visits where returned rings were available, 84% contained <23.5 mg of dapivirine, and dapivirine levels in plasma and in returned rings were generally correlated.
  - However, high residual dapivirine levels were observed for some visits with plasma dapivirine concentrations >95 pg/mL

Age and Adherence

- Adherence measures were statistically significantly lower among women 18-21 years compared to women >21 years

% of visits with plasma dapivirine >95 pg/mL *and* residual ring dapivirine <23.5 mg



Age 27-45

Age 22-26

Age 18-21

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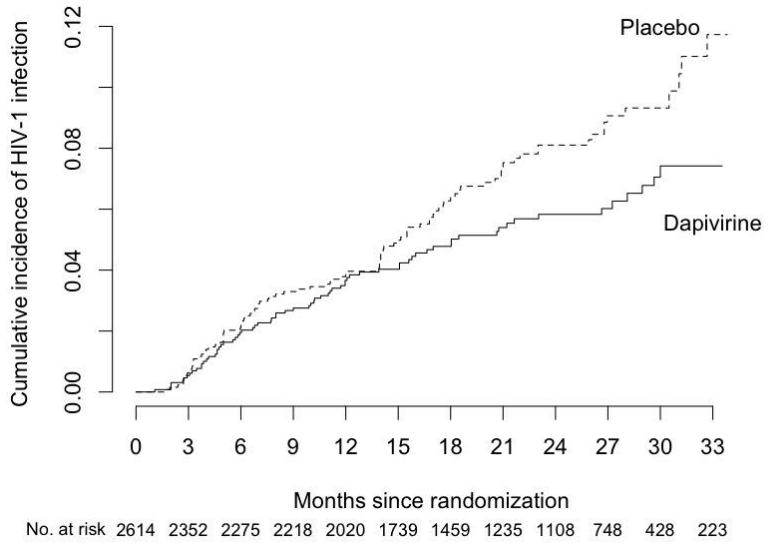
HIV-1 Protection

Overall, women in the dapivirine vaginal ring arm had a 27% reduction in the rate of HIV-1 acquisition, compared to placebo.

Primary HIV-1 effectiveness intention-to-treat analysis (15 sites)				
	Dapivirine		Placebo	
# HIV-1 infections	71	77	97	56
HIV-1 incidence, per 100 person-years	3.3	4.1	4.5	6.1
HIV-1 protection effectiveness 95% CI, p-value	27% (1, 46) p=0.046		31% (1,52) P=.04	



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Subgroups

- In subgroup analyses – by country, education, marital status, STIs at baseline, number of sexual partners, and partner knowledge of study participation – HIV-1 protection was similar to the overall findings.
- However, HIV-1 protection differed significantly by age, with women ≥25 years demonstrating substantial HIV-1 protection while those <25 years of age no statistically significant reduction in HIV-1 incidence:

	Age <25	Age ≥25
HIV-1 protection effectiveness (95% CI)	10% (-41,43)	61% (32, 77)
Interaction p-value	p=0.02	

	Age <22	Age ≥22
HIV-1 protection effectiveness (95% CI)	15% (-60,55)	37% (3,59)
Incidence in placebo	8.2%	5.5%

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Conclusions

- In the placebo arm of this study, HIV-1 incidence was >4% per year (>6% in those aged 22-26; **>8% in <22**). Effective, safe prevention options are needed for women at risk of HIV-1.
- Our results, with those of The Ring Study, provide confirmatory evidence that an antiretroviral vaginal ring can protect against HIV-1.

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Vaginal Rings, Rectal Gels and Intramuscular Injections – next gen PrEP

- **ASPIRE – dapivirine ring has some efficacy, complex interaction with adherence, age and biology**
- **RING – highly consistent with ASPIRE, most at risk women, least protected**
- **MTN 017 – most of 187 men prefer pills to rectal gel (1% TDF)**
- **ÉCLAIR – long acting injections are painful but may be acceptable**
  - **106 men given oral and then injections of cabotegravir 2 x 2ml every 3/12 vs 21 placebo**
  - **1 dropped out, 11 SAE in oral phase, so 94 men injected, 59% c/o pain (10% severe), 7% fever**
  - **Drug released quicker than expected, so 2/12 proposed**
  - **Despite pain and fever, men preferred it to daily pills**
  - **Moving forward for efficacy study (1 seroconversion on treatment, 1 after completed with no drug remaining)**
- **Maraviroc – HPTN 069 – may (or may not) be a good choice for future PrEP**
  - **406 MSM, 28% black, 20% no college edu**
  - **MVC; MVC+FTC;MVC+TDF;TDF+FTC**
  - **22% had STI during FU and 5 seroconversions (4 on MVC; 1 on MVC+TDF); Incidence 1.4%**
  - **67 had some SAE, generally mild and no difference between arms**
  - **Some suggestions from floor that MVC doesn't work as well as expected in explant models, and may increase GALT targets – no such evidence in this trial**

Moving forward with PrEP – Choices for everyone at substantial risk

- **SA sex worker implementation – plus insurance covered PrEP**
- **HOPE studies – open label studies of dapivirine ring focusing on younger women**
- **ÉCLAIR – 2 monthly injections for MSM**
- **? Maraviroc – expanding choice of anti-retrovirals**

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Why are people living with HIV still dying of tuberculosis?

Tuberculosis and HIV have been seen as intertwined since the earliest report of AIDS more than 30 years ago.[1] Despite the remarkable success of the expansion of access to antiretroviral therapy, deaths due to HIV-related tuberculosis remain common. WHO estimated the number of such deaths to be 0·4 million in 2014.[2] This number is not straightforward to estimate. The more clinicians test for tuberculosis in patients with advanced HIV, the more patients with tuberculosis they find.[3] Yet the introduction of more sensitive diagnostic tools has not reduced mortality.[4] For years pathologists have highlighted that many patients dying with HIV infection do so either from or with tuberculosis, and that the diagnosis of tuberculosis had often not been made ante-mortem.[5,6] Epidemiologists show that in adults found in random population samples from Africa and Asia with respiratory samples from which *Mycobacterium tuberculosis* can be cultured, a substantial proportion deny having any symptoms that would make a clinician consider a diagnosis of tuberculosis.[7,8] Pragmatists have therefore proposed that to reduce mortality, we should consider giving patients with

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Empirical TB treatment in advanced HIV disease: Results of the TB Fast Track trial

Alison Grant, Salome Charalambous, Mpho Tlali, Suzanne Johnson, Susan Dorman, Christopher Hoffmann, Aaron Karat, Anna Vassall, Gavin Churchyard, Katherine Fielding

London School of Hygiene & Tropical Medicine; Aurum Institute; Foundation for Professional Development; Johns Hopkins University School of Medicine

THE AURUM INSTITUTE

FPD

JOHNS HOPKINS MEDICINE

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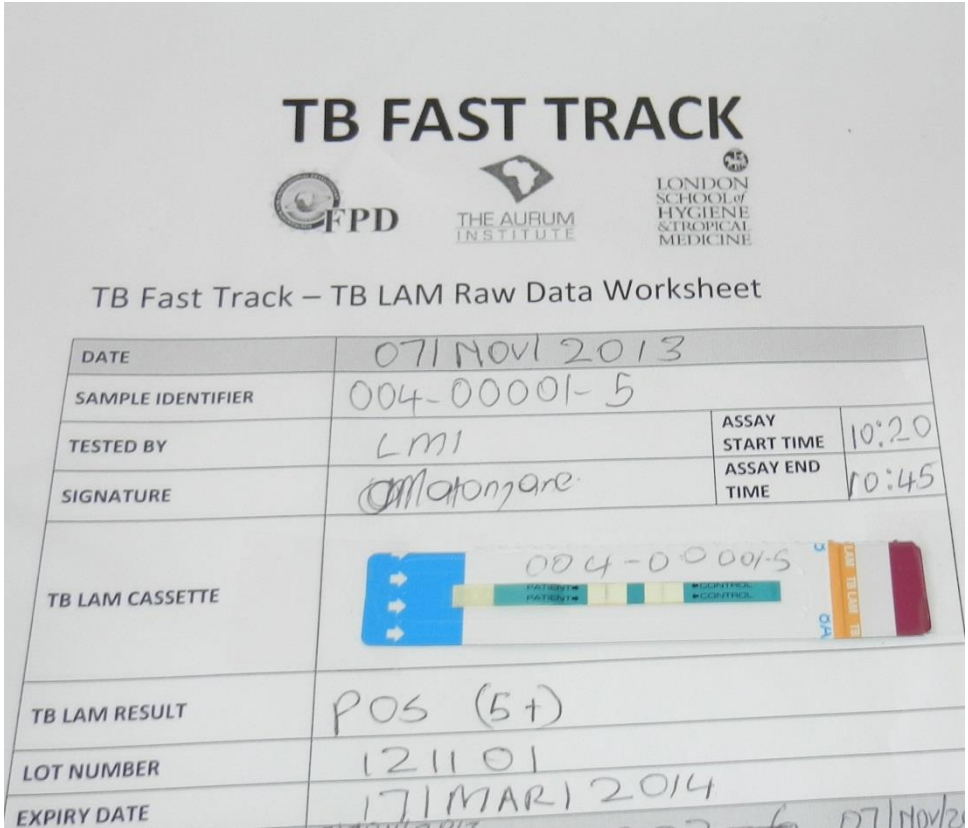
TB risk assessment

- Positive urine LAM test OR
- BMI <18.5 OR
- Haemoglobin <10 g/dl



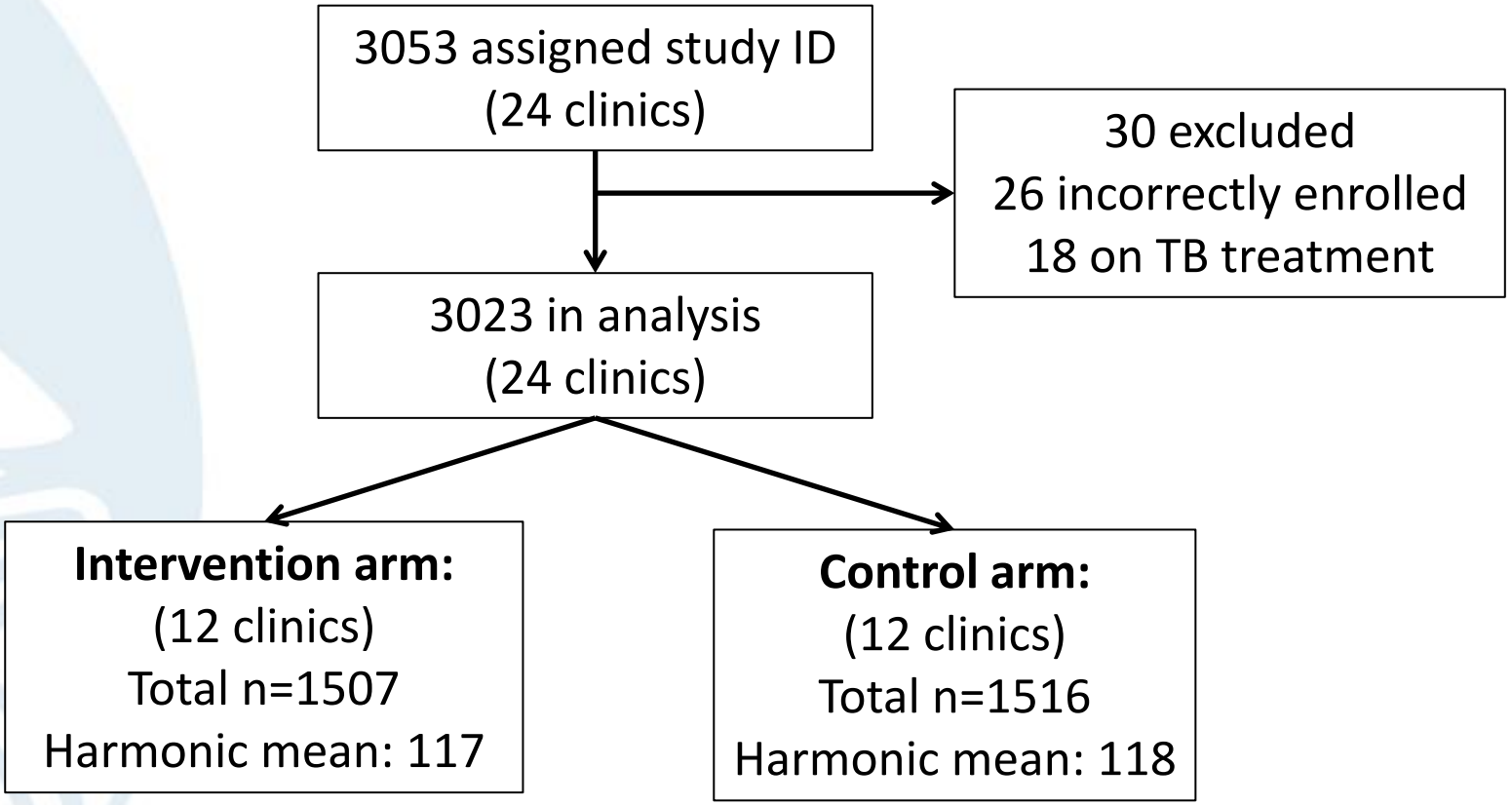
TB FAST TRACK

FPD THE AURUM INSTITUTE LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

TB Fast Track – TB LAM Raw Data Worksheet

DATE	07 Nov 2013		
SAMPLE IDENTIFIER	004-00001-5		
TESTED BY	LMI	ASSAY START TIME	10:20
SIGNATURE	Malongare	ASSAY END TIME	10:45
TB LAM CASSETTE	004-00001-5		
TB LAM RESULT	POS (5+)		
LOT NUMBER	121101		
EXPIRY DATE	17 MAR 2014		

Results: trial profile



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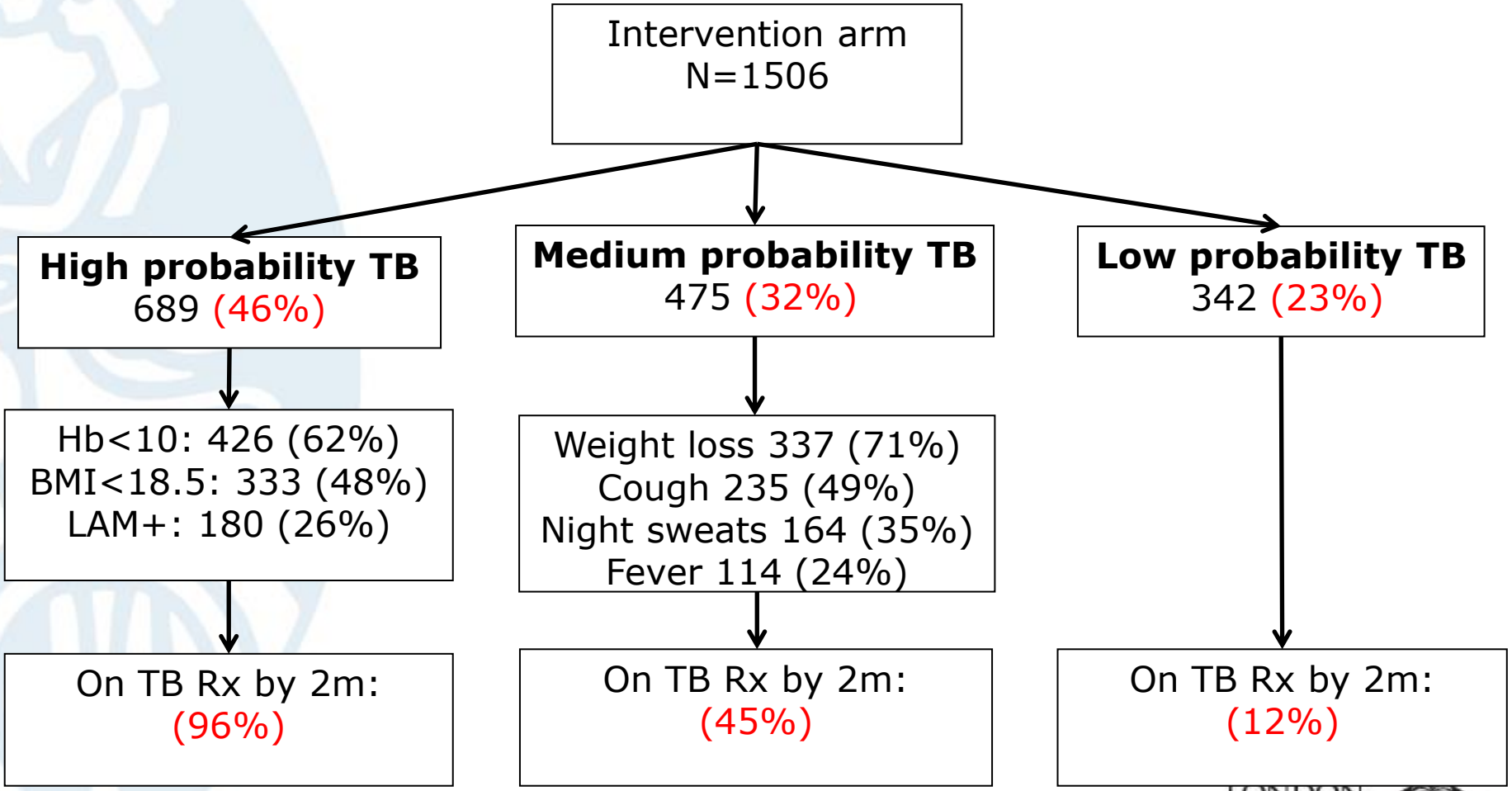
How did the risk assessment work?



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Primary outcome: mortality at 6 months

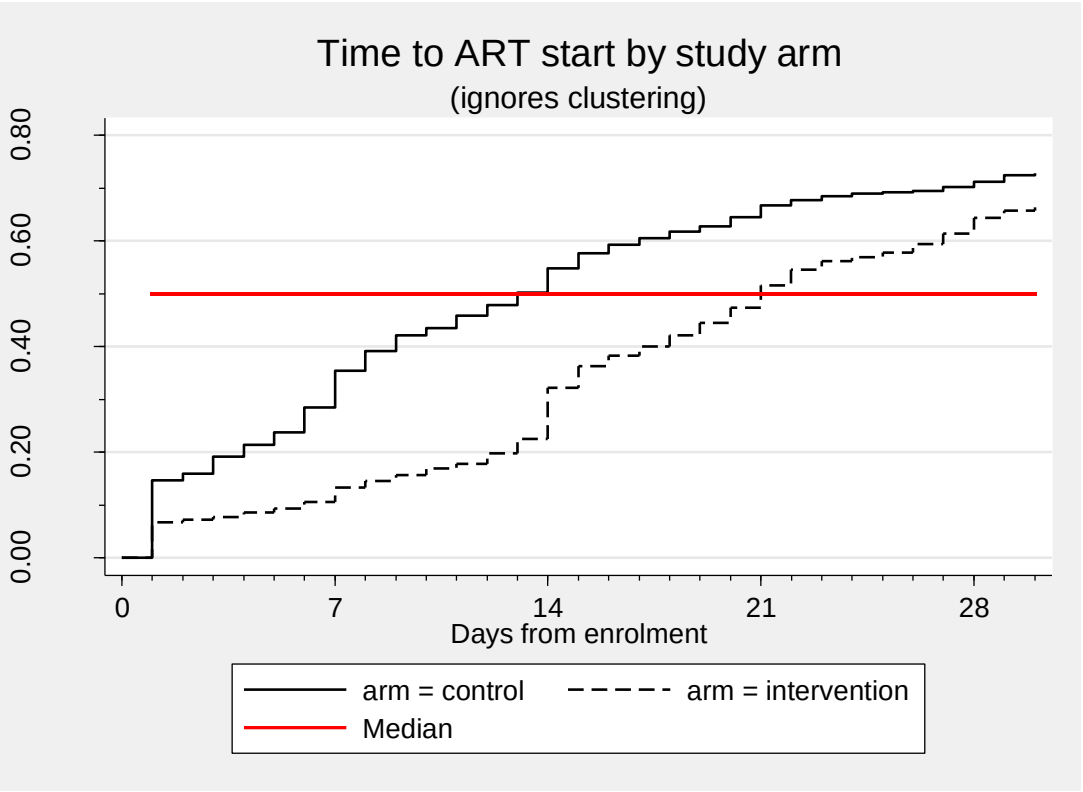
	Events/pyrs	Rate / 100pyrs	Unadjusted RR (95% CI)	Adjusted RR* (95% CI)
Intervention	134/704	19.0	0.92 (0.67-1.26)	0.87 (0.61-1.24)
Control	151/699	21.6	1	1

*Adjusted for age, gender, BMI, CD4, taking IPT, symptoms, TB tests in last 6m & previous TB; P=0.43

Secondary outcome: time to ART start

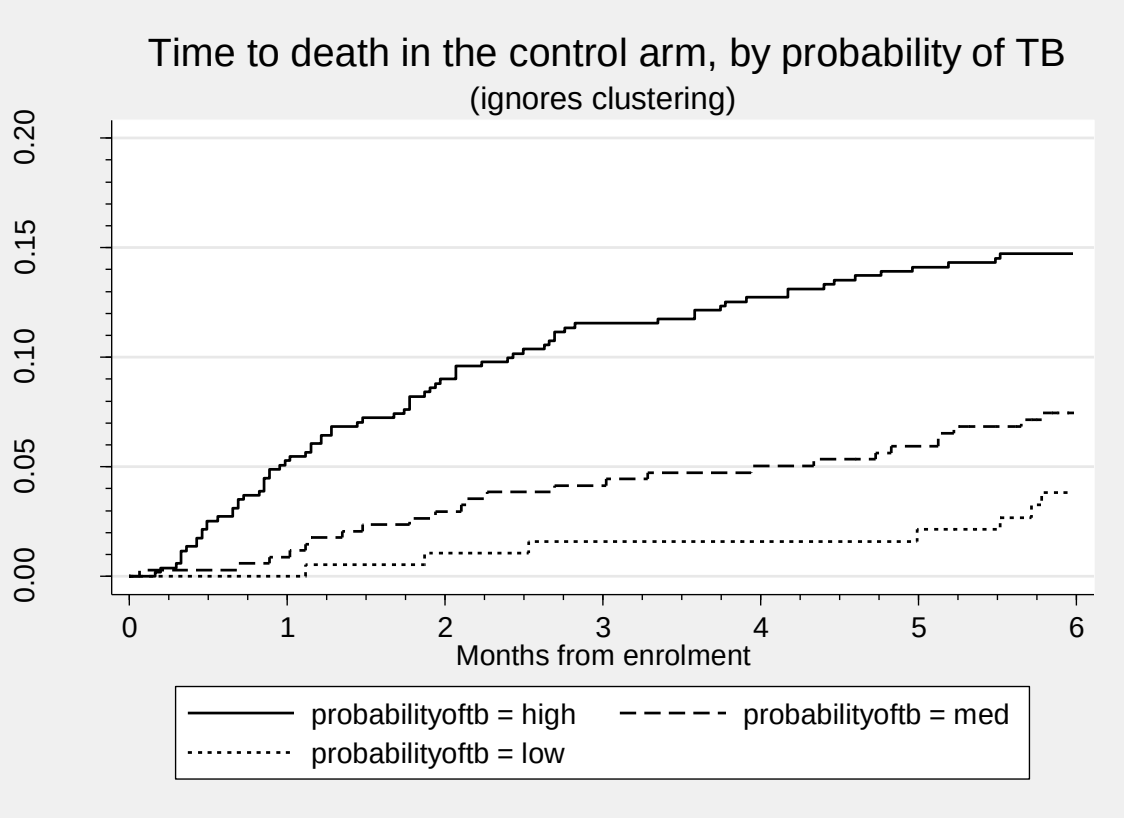
	starting ART in 30 d, n/N	%	Unadjusted RR (95% CI)	Adjusted* RR (95% CI)
Intervention	1001/1507	66.4%	0.89 (0.76-1.03)	0.91 (0.79-1.05)
Control	1104/1516	72.8%	1	1

*adjusted for age, gender, BMI, CD4, taking IPT, symptoms, TB tests in last 6m & previous TB; P=0.17



LAM / BMI / Hb identified high mortality risk

- Control arm participants (N=1040)
- Survival by algorithm probability (assigned retrospectively)
- High risk comprised positive urine LAM OR BMI <18.5 OR Hb<10



Conclusions

- Risk assessment using primary care-friendly tests can identify people at highest risk of mortality
- Our strategy of targeted empirical TB treatment did not reduce mortality at 6 months
- Effective interventions needed for people at high risk
  - rapid, sensitive, point-of-care TB diagnostic tests
  - prompt ART start likely to be important

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