Advanced HIV care and COVID-19 Learning Series 2

Session 4: Non-tuberculous bacterial infections in advanced HIV disease - time for an adapted approach?

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"Christ's Love in word and deed"

Disclosures

- Received honoraria from GSK for Subject Matter Expertise Technical Advice
- Received honoraria from MSD for Subject Matter Expertise Technical Advice

We should routinely use additional prophylactic antibiotics in people with advanced HIV disease

“FOR”

We know bacterial disease is a major problem in patients with advanced HIV disease in Africa – but hard to diagnose!

- People with AHD frequently have severe bacterial infections
  - including bloodstream, respiratory, central nervous system, gastrointestinal infections
- Severe bacterial infections are estimated to cause more than one third of hospitalizations among adults and children living with HIV worldwide

- AHD burden of mortality & morbidity from severe bacterial infections is poorly studied in Africa largely because appropriate diagnostic facilities are lacking. This lack is unfortunately not only also true for studies – but also diagnostic confirmation in daily routine is close to impossible !!
- Cotrimoxazole prophylaxis protects against some but not all severe bacterial infections
  - WHO recommends lifelong cotrimoxazole prophylaxis for PLHIV regardless of CD4 cell count in settings where severe bacterial infections or malaria are highly prevalent
- Immediate ART reduces risk of severe bacterial infections (O'Connor, Jemma, et al.)
  - Early ART has wider impact than that on bacterial infection but- reduction of bacterial infection may account for some of the survival benefit we have seen with *early* ART

Support for the proposition's rationale comes from Mordor…

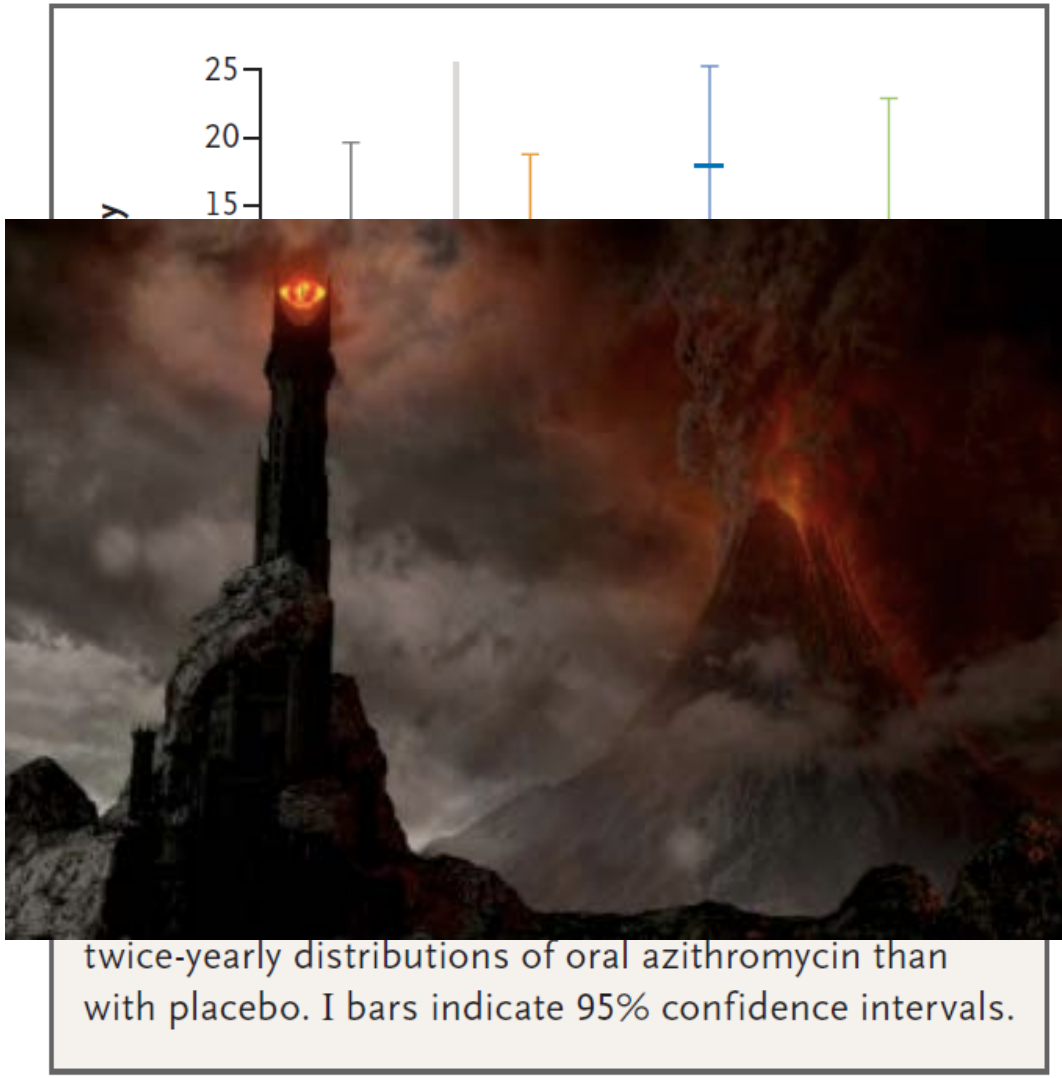
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Azithromycin to Reduce Childhood Mortality in Sub-Saharan Africa

J.D. Keenan, R.L. Bailey, S.K. West, A.M. Arzika, J. Hart, J. Weaver, K. Kalua, Z. Mrango, K.J. Ray, C. Cook, E. Lebas, K.S. O'Brien, P.M. Emerson, T.C. Porco, and T.M. Lietman, for the MORDOR Study Group*

- The MORDOR study found bacterial prophylaxis with Azithromycin was reducing mortality in children in a trial in Tanzania, Niger and Malawi



twice-yearly distributions of oral azithromycin than with placebo. I bars indicate 95% confidence intervals.

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The Shire in the Warm Heart of Africa

Effect of Mass Treatment with Azithromycin on Causes of Death in Children in Malawi: Secondary Analysis from the MORDOR Trial

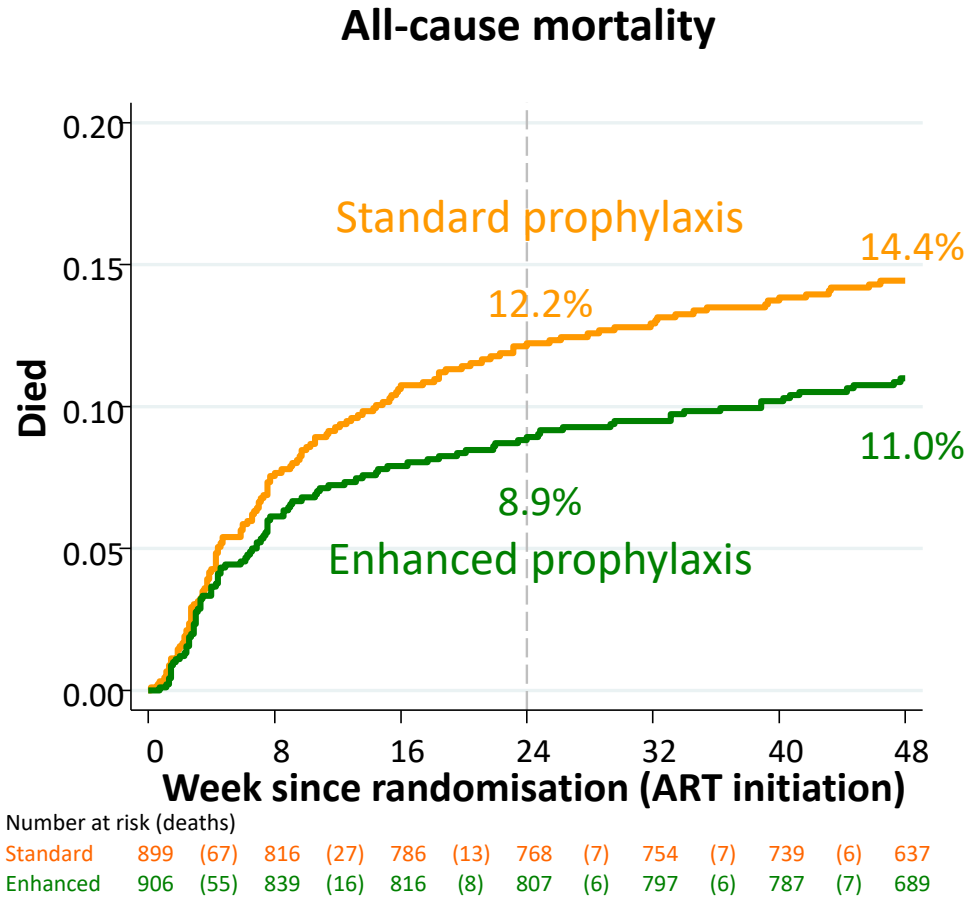
John D. Hart,[1*] Khumbo Kalua,[2] Jeremy D. Keenan,[3] Thomas M. Lietman,[3] and Robin L. Bailey[1]

"An effect of azithromycin on respiratory and gastrointestinal infections, including on a background of HIV exposure or infection, leading to a reduction in the rate of pneumonia and diarrhea as immediate causes of death, is certainly plausible. "

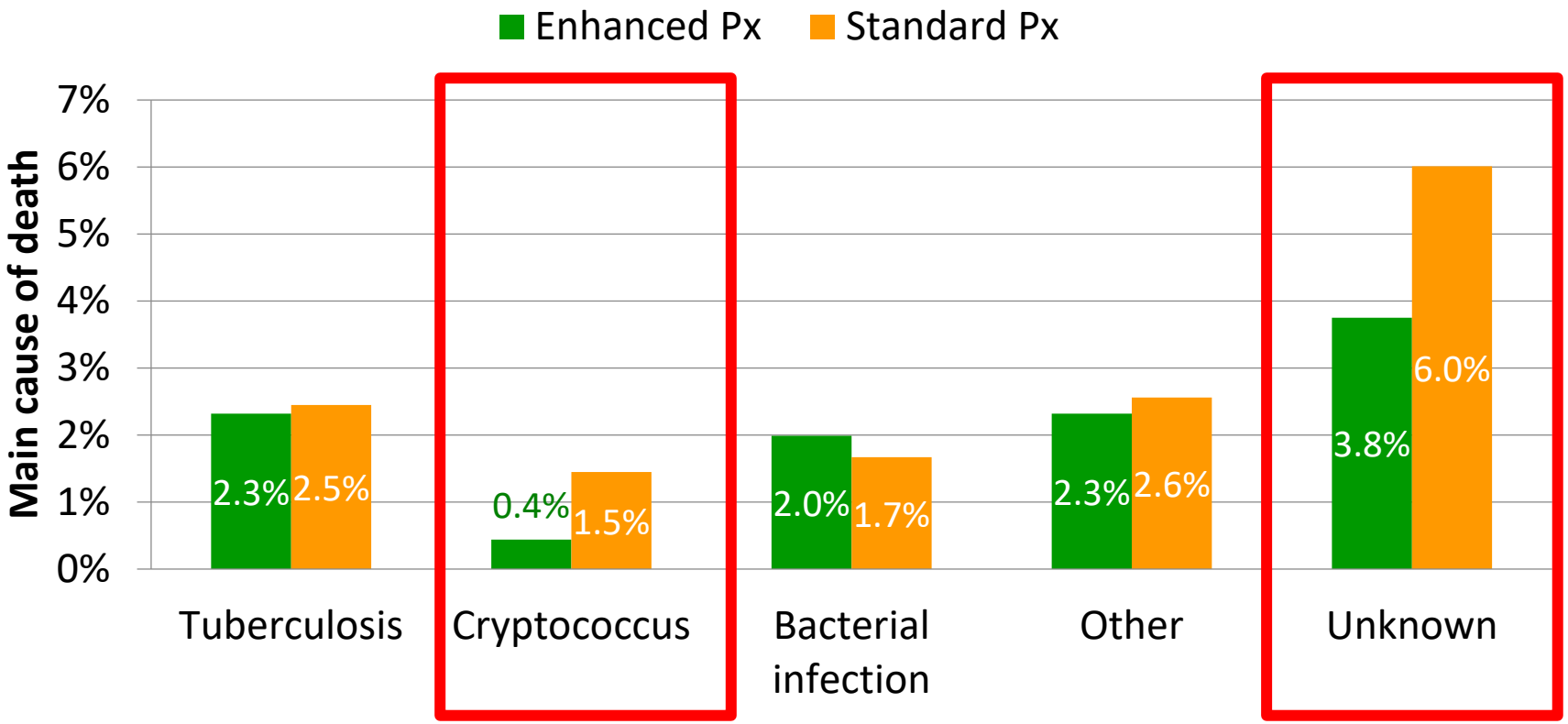
Let us simply look at the REALITY...(Hakim et al 2017)

- What was done: Patients received a **bundle** of prophylaxis beyond CPT
  - Fluconazole Prophylaxis
  - Tuberculosis preventive Therapy (INH/Vit. B6)
  - Albendazole
  - Azithromycin for 5 days

- Significant survival benefit from enhanced **bundle** of anti-microbial prophylaxis
- Rate of death with enhanced prophylaxis was lower than that with standard prophylaxis



- Enhanced prophylaxis reduced deaths from cryptococcosis and unknown causes ($P < 0.05$) but **not** tuberculosis, SBI, potentially azithromycin-responsive infections, or other causes ($P > 0.3$)
- Lack of impact on bacterial infections raised questions about using 5 days of azithromycin within enhanced prophylaxis particularly given concerns about antimicrobial resistance
- But: a third of all deaths from unknown causes occurred within the first 4 weeks after ART initiation and many occurred at home, making it say that azithromycin had no role in reducing undiagnosed SBIs causing these early deaths.
- **So, lack of evidence for effect should not be confused with evidence for lack of effect**



Shall we conclude to stop TPT as there was no reduction in mortality?

Let us look at the REALITY…(Hakim et al 2017)

If you order a **bundle** – you expect to get a bundle. If the order is changed you may be in for disappointment:

- Causes of death were multifactorial – because these were very sick patients
- So most had several secondary causes adding to mortality
- Many patients died at home/had unclear cause of death
- That is why we do not really know what part of the bundle prevented the death…

Development of antimicrobial resistance is a risk…

- We acknowledge risk of resistance development and its general increase globally
  - But no studies have shown this to happen in individuals receiving 3-5 days of azithromycin
  - In the real world Azithromycin is frequently dished out as part of part of *Helicobacter* treatment in patients with questionable gastric ulcers, for upper respiratory tract infection in patients who may well have viral causes and lately for almost anybody with COVID infection – whether symptomatic or not…
  - Let us try to get that right first – because for the short-term use in a selected patient population of AHD we have at least some data…and these patients are very vulnerable and at high risk of death!

REALITY package and azithromycin

- Azithromycin may modulate the inflammatory milieu through reductions in subclinical infections, enteropathy, and microbial translocation, or through direct immunomodulatory effects
  - well recognized that inflammation can drive mortality independent of immuno-suppression
- Theoretically, azithromycin has additional benefit for prevention of MAC and toxoplasmosis, however their epidemiology in Africa is not well described and no studies exist on the benefit of prevention of these infections in Africa
- REALITY enhanced antimicrobial prophylaxis was cost-effective
- REALITY could not distinguish between individual contributions of INH, fluconazole, azithro and albendazole to the mortality and morbidity benefits from enhanced antimicrobial prophylaxis.
- **Therefore, we should not take antimicrobial prophylaxis out of a package until we have more evidence - on potential effects or side effects like resistance development**

Conclusion

- Cotrimoxazole Preventative Therapy and TB Preventative Therapy are the undisputed basis of anti-microbial prophylaxis for patients with AHD
- Additional to this, azithromycin and albendazole as given in the REALITY trial should be given to adults with AHD when CD4 <100 cells/microL
  - plus fluconazole pre-emptive treatment based on positive CrAg screening (and exclusion of CM)

- **We have the evidence from a very strong "bundle intervention trial" – and we should not have the hubris to pick and choose only what pleases us in REALITY !**
- **I therefore urge you to clearly vote FOR prophylactic antibiotics for this very vulnerable patient population where potential antibiotic resistance in the future needs to be balanced against an imminent risk of early death today**

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Thank you *Zikomo*

- Prof Joep van Oosterhout, Partners in Hope
- Dr Tom Heller LIGHTHOUSE