

# Updates on reducing mortality in advanced HIV, 2019

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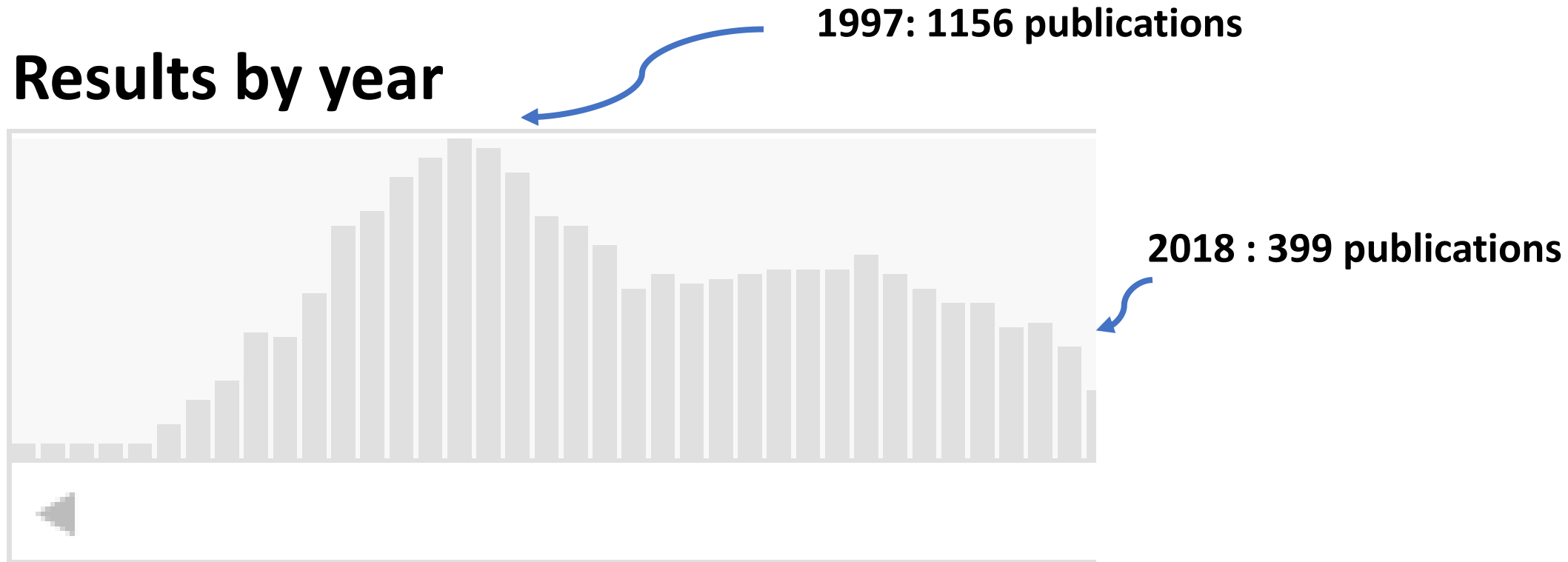
# Objectives

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- 1. Provide new data related to treatment and prevention of infections in advanced HIV**
- 2. Provide updates on ART in advanced HIV**

No disclosures

# Publications on opportunistic infections in HIV in PubMed



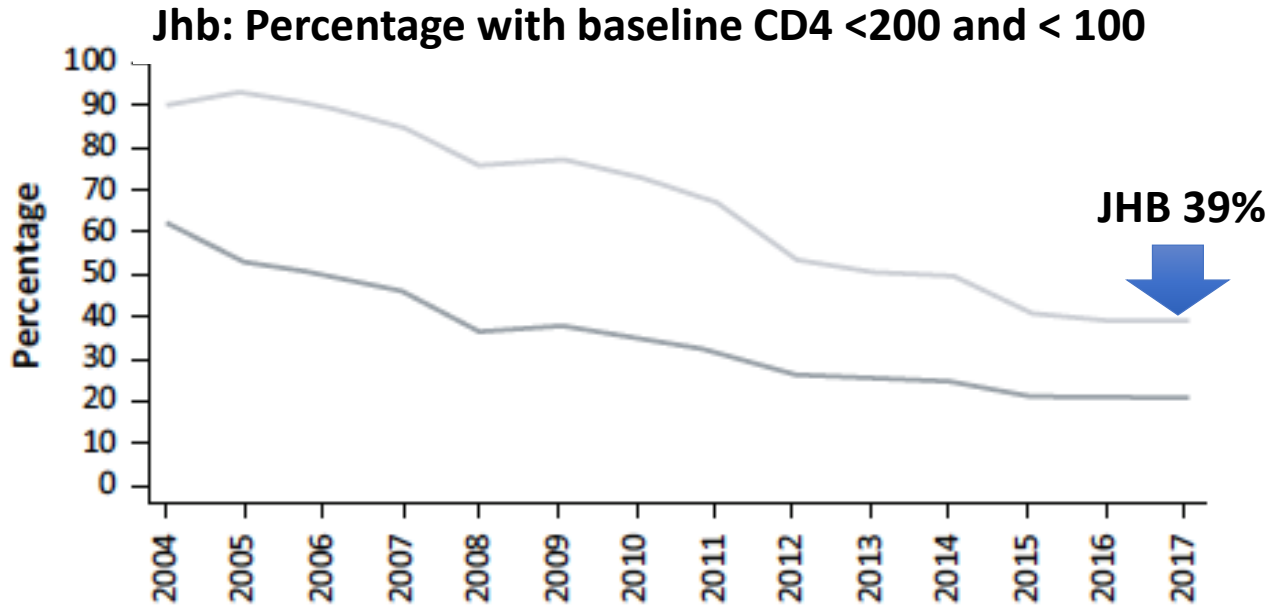
Pubmed search: August 18, 2019

# South Africa: What proportion now have CD4 < 200 at ART start?

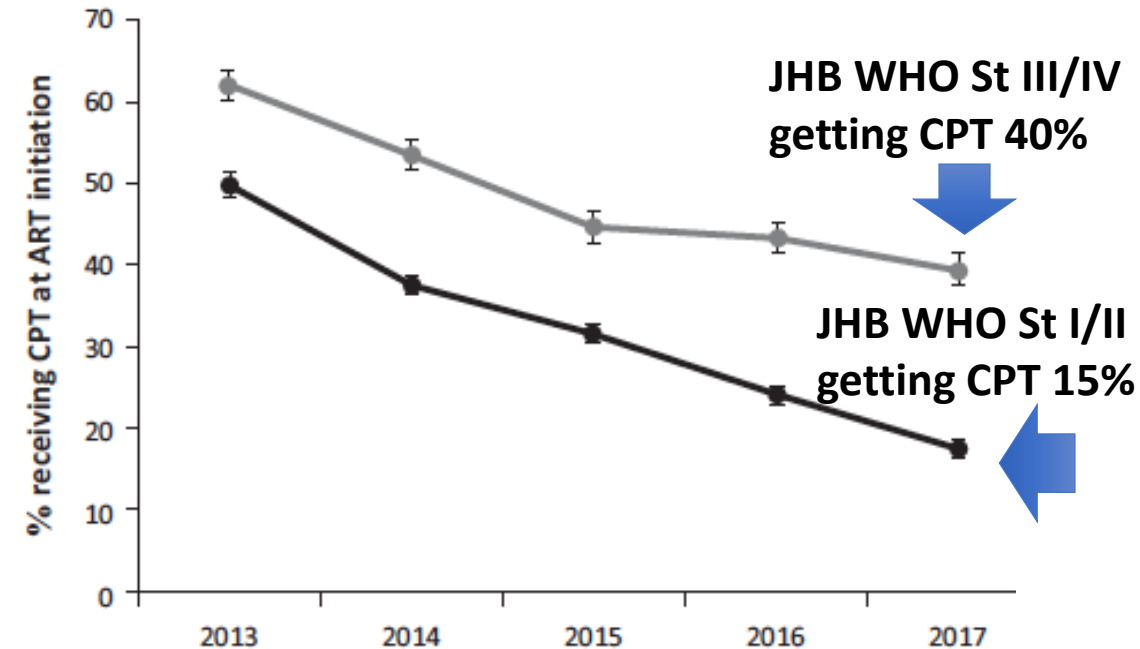
Routine data from TIER.NET analyzed from JHB and Mopani district, Limpopo

**Results:**

- For years the percent of patients initiating ART w/ advanced HIV has fallen slowly
- However the proportion initiating at CD4 < 200 in 2017 remained high: **JHB 39%, Mopani 35%**
  - Low CD4 at ART start linked w/**older age, male gender, hospital initiation**
  - In JHB: 20% had CD4 <100 at ART start
- Of note, the use of cotrimoxazole prophylaxis in advanced HIV has declined
  - Patients with CD4<200 + WHO Stage I or II (vs. WHO stage III/IV) less likely to receive CTX



**Jhb: Cotrimoxazole delivery by WHO stage to patients with CD4 < 200**



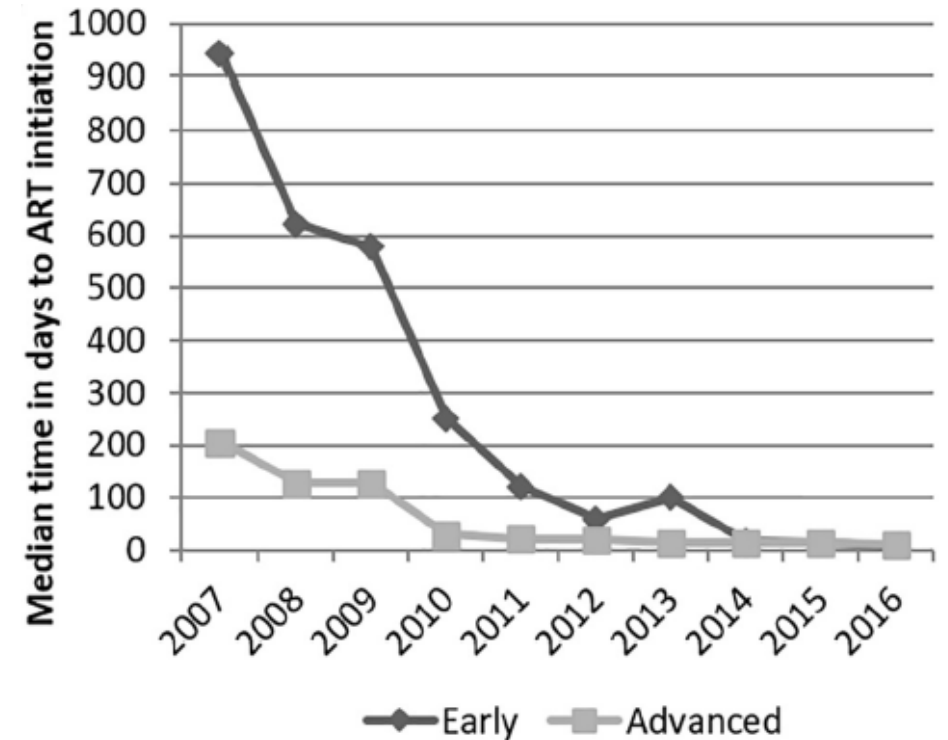
# Zimbabwe: Proportion starting ART with CD < 200 remains high

Cohort study (2007-16) at Epworth Clinic, Zimbabwe

## Results:

- N=16,007 ART naïve (62% female, med. age 33)
- Delay prior to ART initiation has declined significantly for all patients from >100 days to 2 weeks.
- Over 10 year look-back, proportion with adv. HIV has declined very slowly to 40%
  - **Risk factors for advanced disease at ART initiation: (1) male gender, (2) older age and (3) unmarried**
- 12 m after ART start, those with advanced HIV had higher mort. vs early stage (5% vs 0.5%) ( $P=0.001$ )

Zimbabwe: Delay before ART initiation has markedly declined for early and advanced HIV



# Case

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- 50 yo HIV+ man comes to hospital with 2 months of cough and weight loss and, more recently, fever.
- He was diagnosed with HIV in 2007 and his initial CD4 count was 378 cells/mm<sup>3</sup>, he did not initiate ART and fell out of care.
- Seen in a private clinic 2 weeks ago, sputum sample not taken. Given amoxicillin-clavulanate with no improvement

# Case

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## Exam

- HR 126, RR 32, Temp 38.5, BP 95/53, O2 96% RA
- Unable to stand without help, + oral thrush, no rash, no LAN, crackles throughout R lung

# Urine LAM in clinics to help diagnose TB in HIV patients

- MSF study in 6 facilities in Malawi + Mozambique
- Ambulatory HIV (+) with symptoms concerning for TB
- 1<sup>st</sup> visit: urine LAM, microscopy, sputum Xpert MTB/RIF, sputum culture, and x-ray

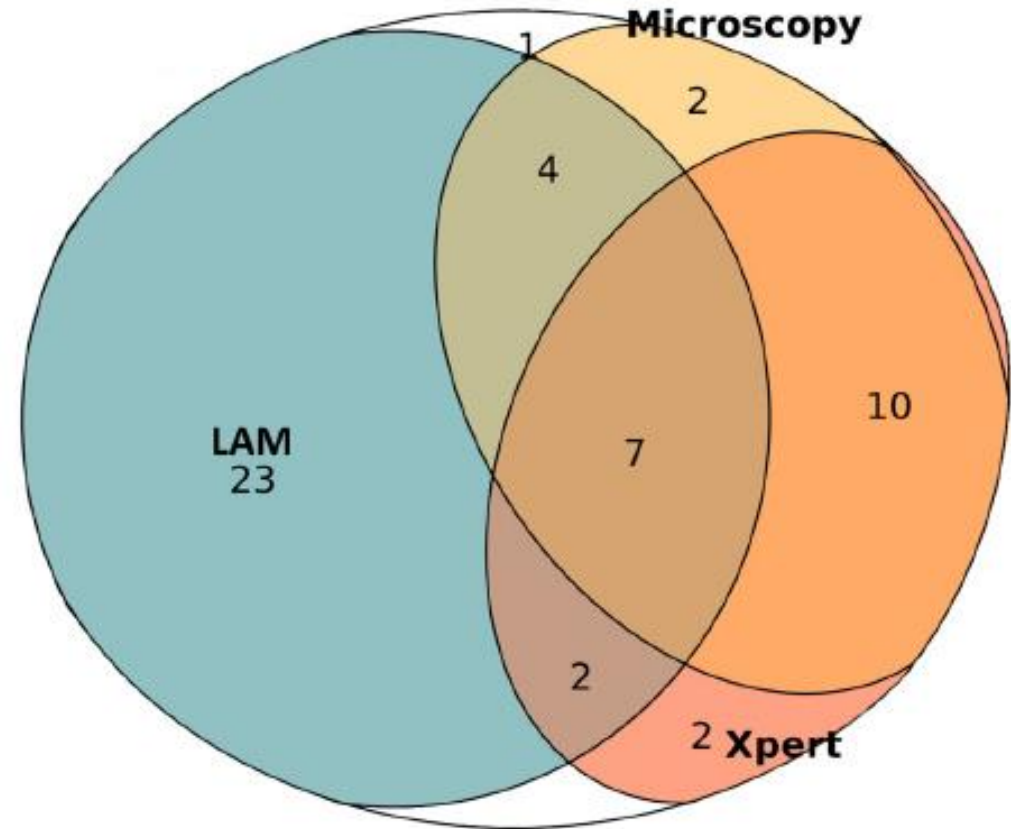
## Results :

- N=456, median CD4 50. Diagnosed TB: 45% = 205/456
  - Urine LAM (+) at any cutoff in 82% of TB patients
  - Microscopy positive in 34% of TB patients
  - Xpert positive on sputum in 40% of TB patients
    - Many patients with difficulty providing sputum, not always staff in place to manage sputum samples

**50% with lab-confirmed TB diagnosed only thru LAM.**

**In this real world-study, LAM detected otherwise “missed” cases in those with CD of 100 - 199**

**Case detect of TB with various tools among HIV (+) with CD4 of 100-199 c/mm<sup>3</sup>**



# LAM has good sensitivity for TB in advanced HIV but some false + tests

- Thai study among HIV (+) with CD4<200 and suspected TB.
- Patients underwent multiple tests for TB including Alere Determine LAM
- LAM graded according to band intensities on scale of 1-4 (from light to dark)

## Results :

- N=280 enrolled, med. CD4 33
  - Microbiologically confirmed TB found in 25% of patients, and confirmed or probable in 50%
- LF-LAM test able to detect 75% of TB cases in Thai adult patients with advanced HIV
  - Most sensitive when CD4<50 but detects half of TB cases in patients with CD4 100-199
- Specificity is 76%; can be positive in other diseases incl. MAC

## False positives with Alere LAM in NTM disease

Patient	Band		Cryptococcosis <sup>a</sup>	PCP <sup>a</sup>	Other Infection
	Intensity	MAC <sup>a</sup>			
1	4+	Yes	No	No	...
2	4+	Yes	No	No	...
3	4+	Yes	No	No	...
4	4+	Yes	No	No	...
5	4+	Yes	No	Yes	...
6	2+	Yes	No	No	...
7	1+	Yes	No	No	...
8	4+	No	Yes	No	...
9	2+	No	Yes	Yes	Bacterial pneumonia
10	1+	No	Yes	Yes	...
11	1+	No	Yes	No	Bacterial pneumonia
12	1+	No	Yes	No	...
13	1+	No	Yes <sup>b</sup>	No	...
14	1+	No	No	Yes	...
15	1+	No	No	Yes	...
16	1+	No	No	Yes	Bacterial pneumonia
17	1+	No	No	No	<i>Mycobacterium kansasii</i>
18	1+	No	No	No	Histoplasmosis
19	1+	No	No	No	Lymphoma
20	1+	No	No	No	No proved OI <sup>c</sup>

# Case

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## Exam

- HR 126, RR 32, Temp 38.5, BP 95/53, O2 96% RA
- Unable to stand without help, + oral thrush, no rash, no LAN, crackles throughout R lung

# If this is TB, how many WHO danger signs present?

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- A) One
- B) Two
- C) Three
- D) Four
- E) None

# Case

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## Exam

- HR 126, RR 32, Temp 38.5, BP 95/53, O2 96% RA
- Unable to stand, + oral thrush, no rash, no LAN, crackles throughout right lung

### **WHO Danger Signs:**

- Cannot stand
- Temp >39C (102)
- RR > 30
- HR > 120

# Sepsis syndrome in advanced HIV

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- Ugandan study of preserved samples of consecutive patients w/ sepsis (N=336, 84% HIV +, med. CD4 61)
- Quantitative PCR tool used (TaqMan Array Card)

## Results :

- 96% rec'd antibiotics, 11% rec'd anti-TB agents
- Most frequently detected possible pathogens in HIV-infected:
  - cytomegalovirus (CMV) (46%)
  - **TB (22%)**
  - ***Streptococcus pneumoniae* (10%)**
  - ***Plasmodium* spp (6%), E. coli (4%), C. neoformans (2%)**
- 27% died in hospital,
  - In MV analysis linked with mortality was (+) TB qPCR (aOR 4.6,  $p < 0.01$ ) and CMV viremia (aOR 3.2,  $p < 0.01$ )
- Unclear if CMV is independently caused excess mortality; frequently identified w/ 2<sup>nd</sup> pathogen



# Case

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## Data

- WBC 8.5, Hb 7.8, PLT 298
- EKG: Sinus tachycardia
- Urine obtained for LAM assay

He is unable to provide a sputum sample

# Prospective study of acutely ill HIV-infected patients with suspected TB, Cape Town

- HIV patients admitted coughing for any duration and  $\geq 1$  WHO danger sign
- N=332 (median CD4=107)

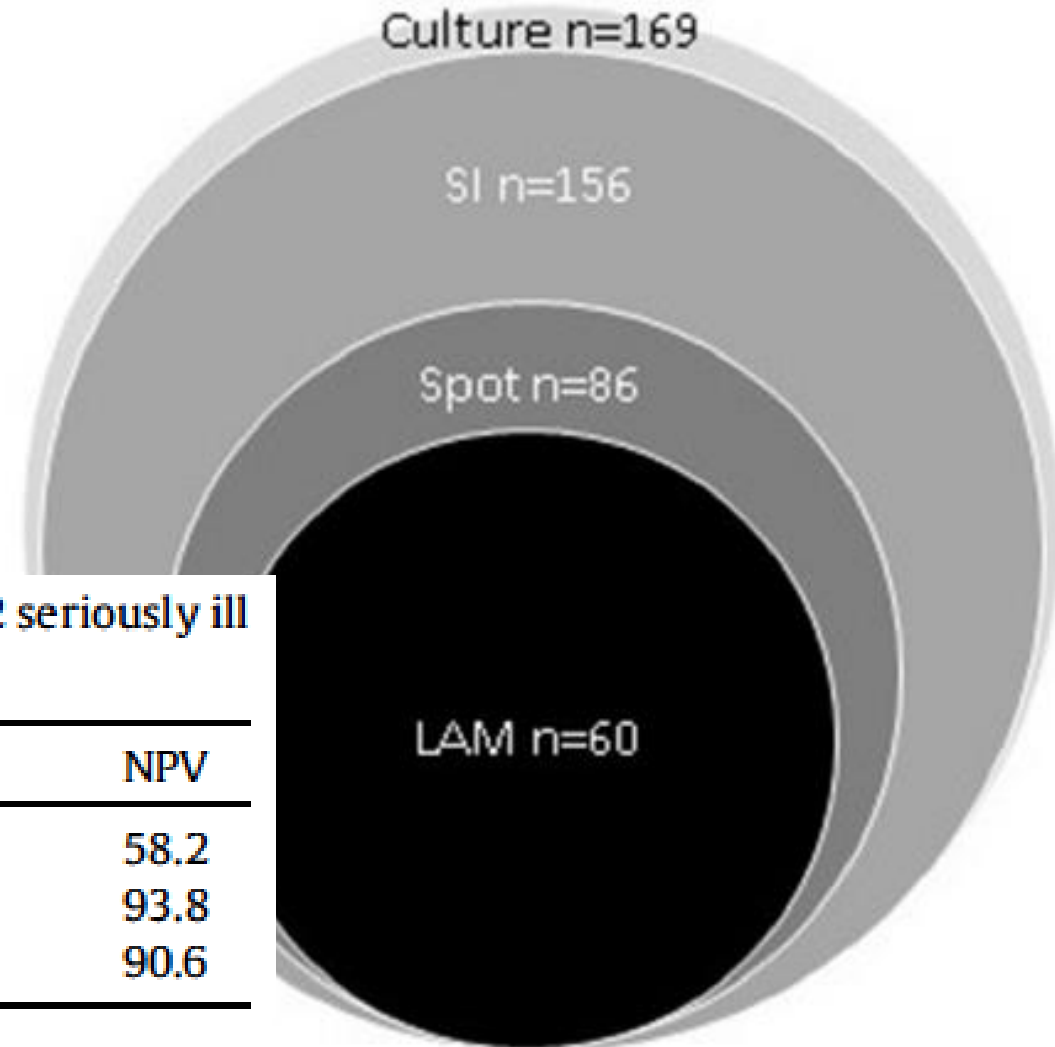
## *Accuracy of urine LAM, Xpert spontaneous sputum & Xpert induced:*

Diagnostic accuracy of LAM, Xpert Spot, and Xpert SI in a cohort of 332 seriously ill HIV-infected patients with a prevalence of tuberculosis of 51%.

Test	Sensitivity	Specificity	PPV	NPV
LAM	35.5	93.3	84.5	58.2
Xpert Spot <sup>a</sup>	92.9	97.8	97.5	93.8
Xpert SI <sup>b</sup>	90.5	94.5	94.4	90.6

<sup>a</sup> Only 27% of 332 patients able to spontaneously produce sputum

<sup>b</sup> Performance characteristics includes both spontaneous +induced sputum

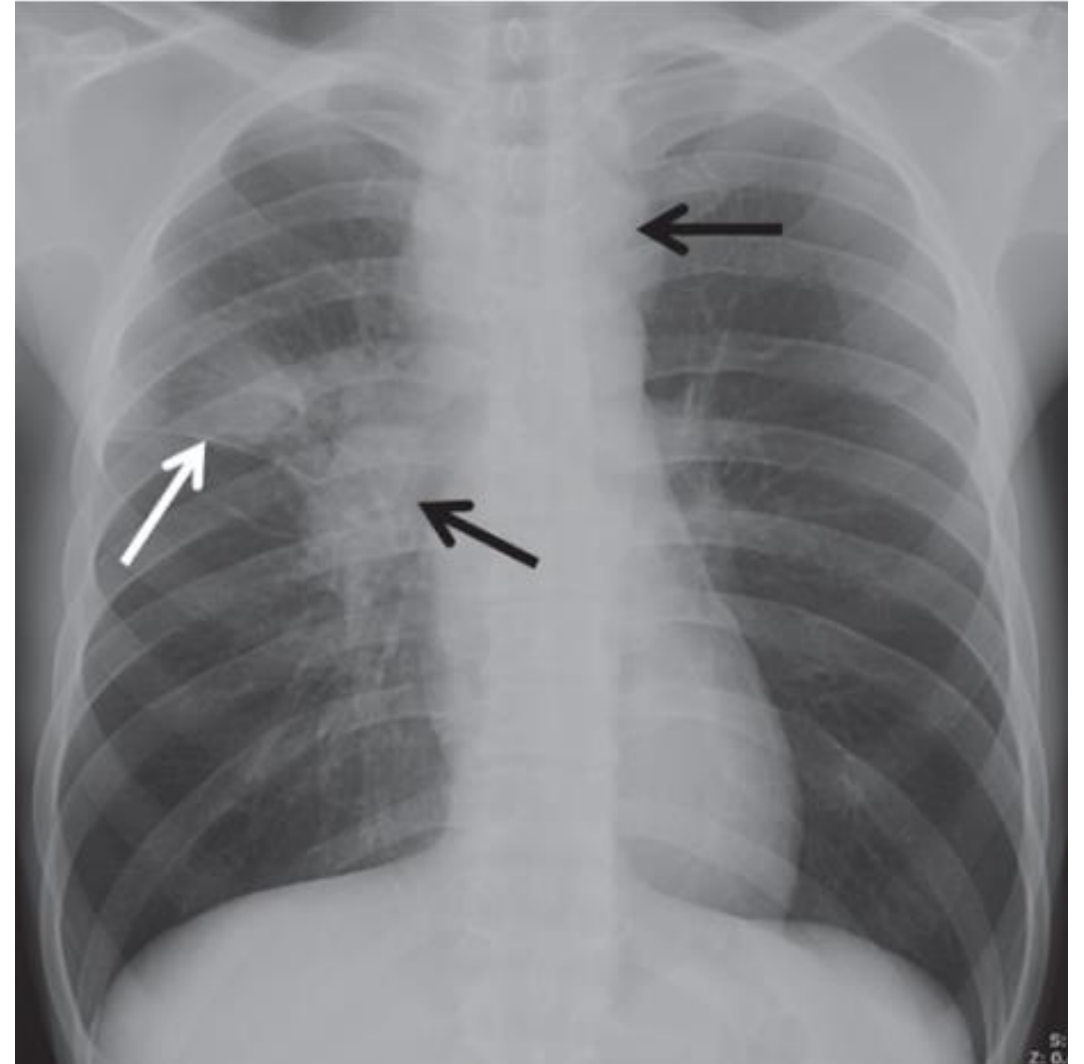


# Case

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## More data :

- Urine LAM weakly positive +1
- Hilar and mediastinal adenopathy and right upper lobe infiltrate



# Risk factors for mortality in patients admitted with HIV + TB

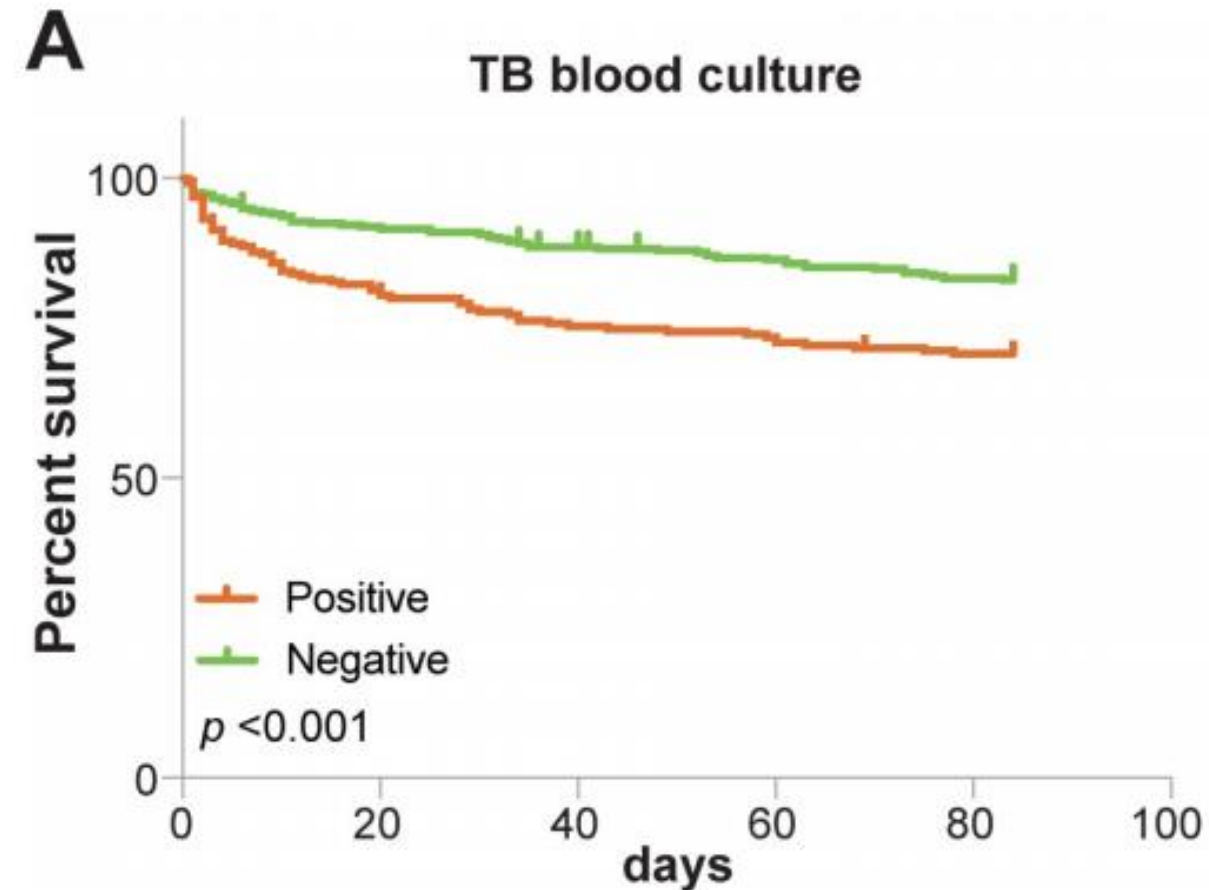
- Hospitalized patients with HIV-associated TB have case fatality rates between 11% and 32%.
- Same study but not limited to patients with danger signs. N=576 with HIV associated TB in hospital

## Results:

- TB therapy started within 48 hrs in 85% but 12 wk. mortality high at 22%

## Risk factors for mortality:

- Presence of MDR-TB – 10% of cohort
  - 2/3 did not get MDR-TB therapy initially
- Disseminated tuberculosis as suggested by + LAM
  - MTb cultured in blood in 53% of those who died, 36% of those who survived ( $P=0.002$ )
  - Urine LAM and Urine Xpert performed well for diss. TB
- Elevated lactate / sepsis syndrome



# Risk factors for mortality in HIV patients admitted with TB

## Demographic factors:

1. Is the patient male? Yes: add 9 points
2. Is the patient aged 55 years or older? Yes: add 7 points

## HIV factors:

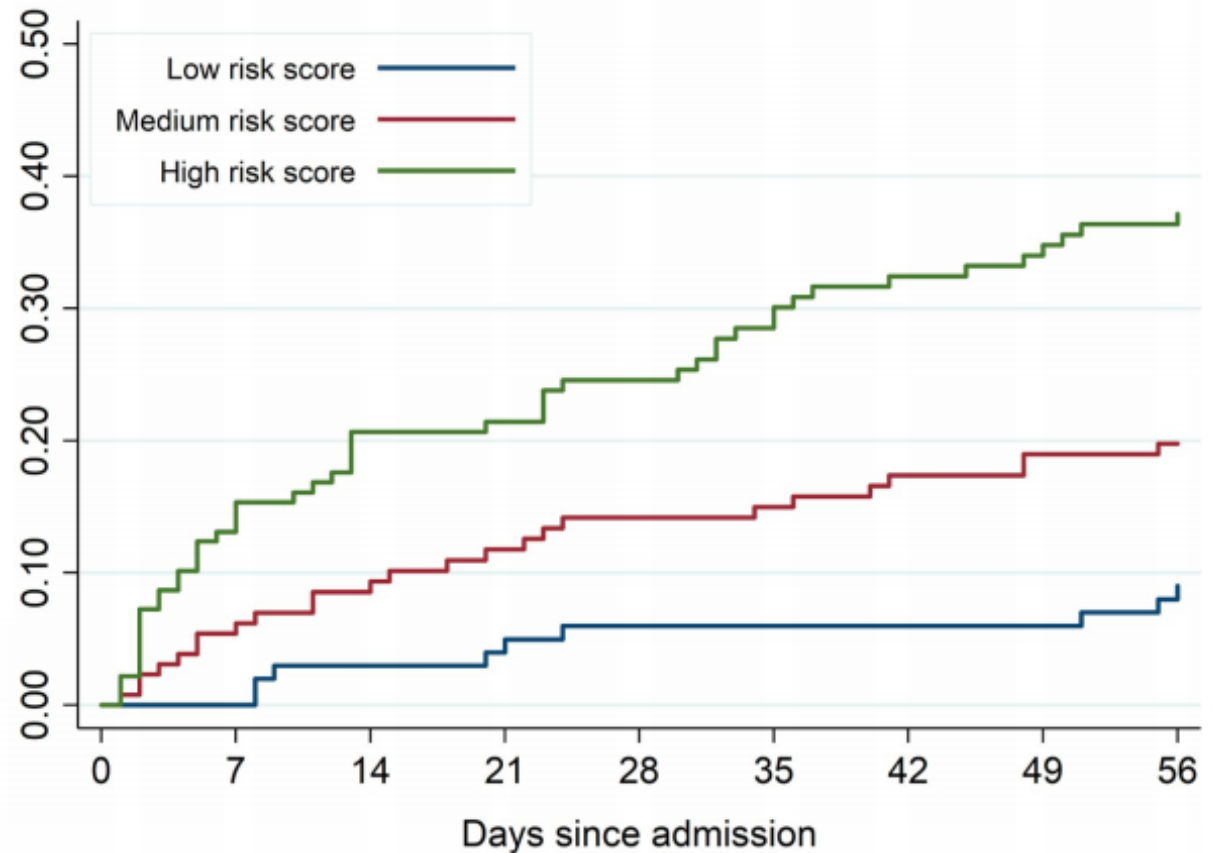
3. Is the patient currently taking antiretroviral therapy? Yes: add 6 points

## Clinical presentation and TB diagnosis:

4. Is the patient unable to walk unaided? Yes: add 7 points
5. Does the patient have severe anaemia (haemoglobin <80g/l)? Yes: add 7 points
6. Is the patient positive on urine TB-LAM testing? Yes: add 6 points

**Total points (min 0. max 42):**

## Survival in patients with high, medium and low scores



## **Advanced HIV with fever and WHO danger signs consider:**

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### **WHO Danger Signs:**

- HR>120
- Temp>39
- RR>30
- Can't walk

### Early studies include:

- Urine LAM
- Xpert OR Xpert Ultra, *if necessary with induction*
- Chest x-ray
- Serum CrAg
- (Blood culture if available)

### Interventions include:

- Empirical antibiotics w/ *S. pneumoniae* and enteric GNR activity (e.g. 3rd generation cephalosporin)
- If LAM, Xpert or x-ray suggestive very early TB therapy

### Before discharge:

+/- HIV viral load

# Case

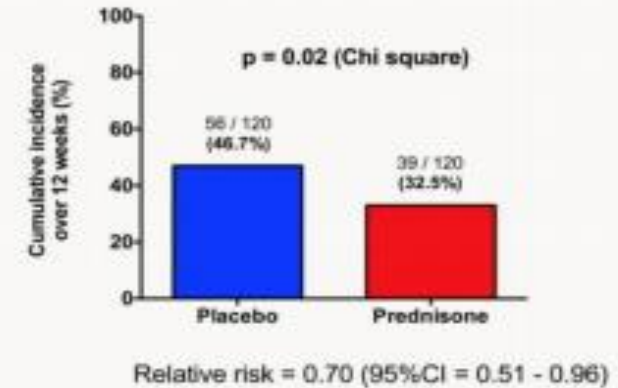
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- Stable after 1 week on standard TB therapy and started on cotrimoxazole prophylaxis.
- Normal renal function, hepatitis B surface Ag and CrAg negative. CD4 cell count is 48.
- What ART regimen would you start and when?
- Would you start steroids at the same time as ART?

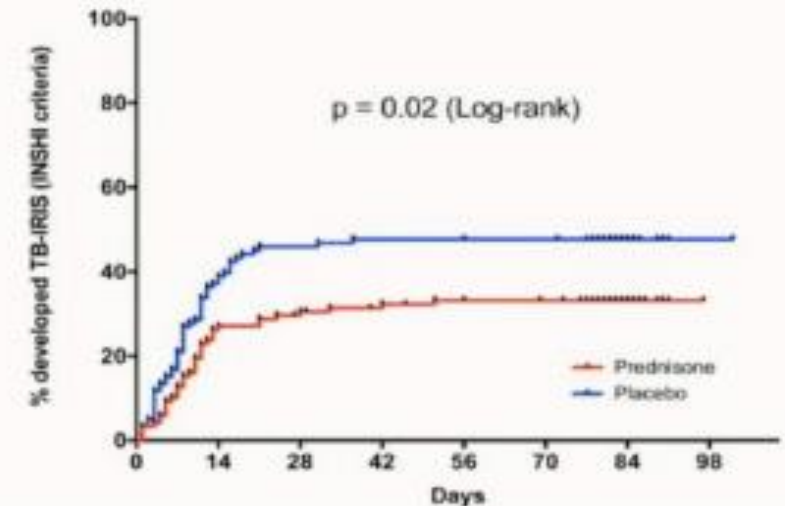
# Impact of corticosteroids in preventing IRIS in HIV-associated TB

- RCT in Cape Town of prednisone vs. placebo in TB among HIV-infected at high risk for IRIS
  - N= 240
  - **CD<100** + ART naïve on TB therapy
  - Prednisone 40 mg/day for 2 wk; then 20 mg/day for 2 wk vs. placebo **at start of ART**
  - Risk of TB IRIS lower in prednisone group: 33% vs 47%, RR 0.7
  - No diff. in mortality, infections, cancer.
  - Fewer hospitalizations in prednisone arm

Primary endpoint: Paradoxical TB-IRIS



Time to TB-IRIS event



# Start corticosteroids with ART to reduce IRIS in patients with HIV/TB coinfection?

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- A) Yes but attempt to rule out cryptococcal disease and KS first
- B) No
- D) Not sure, dude

# What ART to initiate and when?

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- A) TDF / FTC / EFV within 2 wks
- B) TDF / FTC / EFV at 2 months
- C) TDF / 3TC / DTG 50 mg daily within 2 wks
- D) TDF / 3TC / DTG 50 mg with DTG given bid at 2 months
- E) TDF / 3TC / DTG 50 mg with DTG given bid within 2 wks

# Initial ART with CD4 <200 and hi VL: INSTIs vs bPIs vs NNRTI

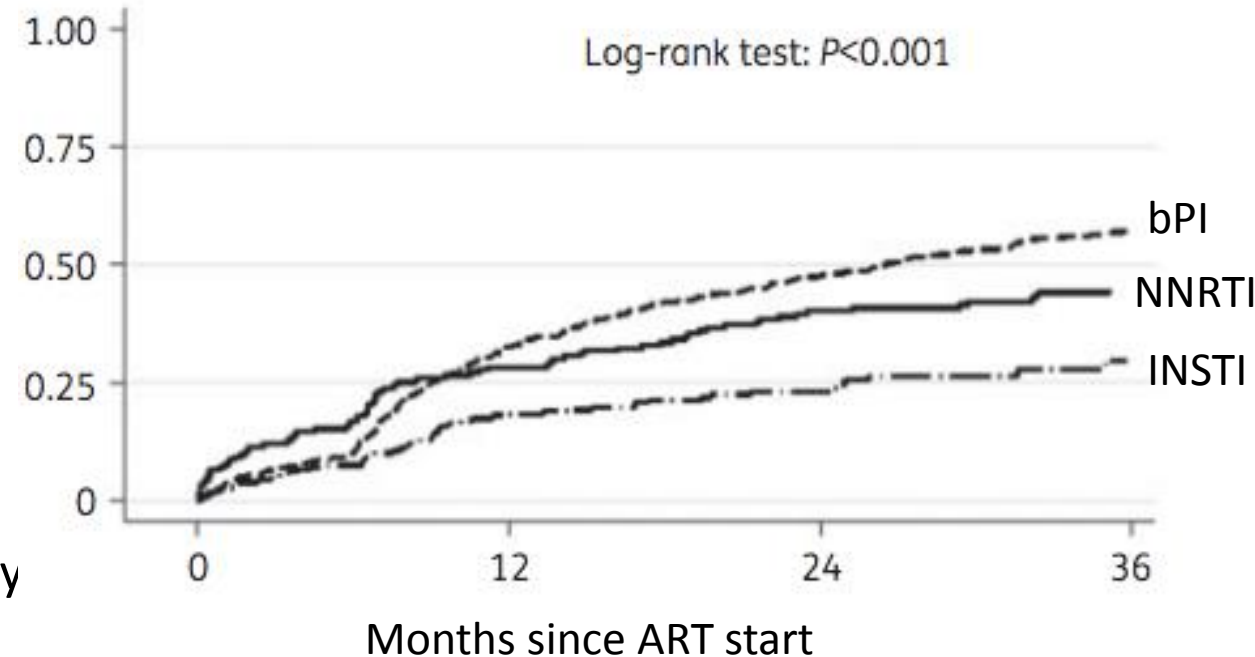
ICONA: Prospective study of HIV (+) Italians starting ART  
Eligible if CD4<200 at ART start and viral load > 100,000

**Results:** 1195 patients fulfilled the inclusion criteria:

- 1/2 started bPI: 48% DRV/r, 29% ATZ/r, 20% LPV/r
- 1/3 with an InSTI: 50% DTG, 26% EVG/c, 24% RAL
- 1/5 with an NNRTI: 94% EFV
- Treatment failure, a combination of several undesirable outcomes, was most common with bPIs, driven by toxicity related stoppage

Treatment failure independently associated with starting ART with a bPI vs. NNRTI ( $P=0.001$ ) and starting ART with NNRTI vs. an INSTI ( $P=0.03$ ).

**Treatment failure = VF + discontinuation + death**



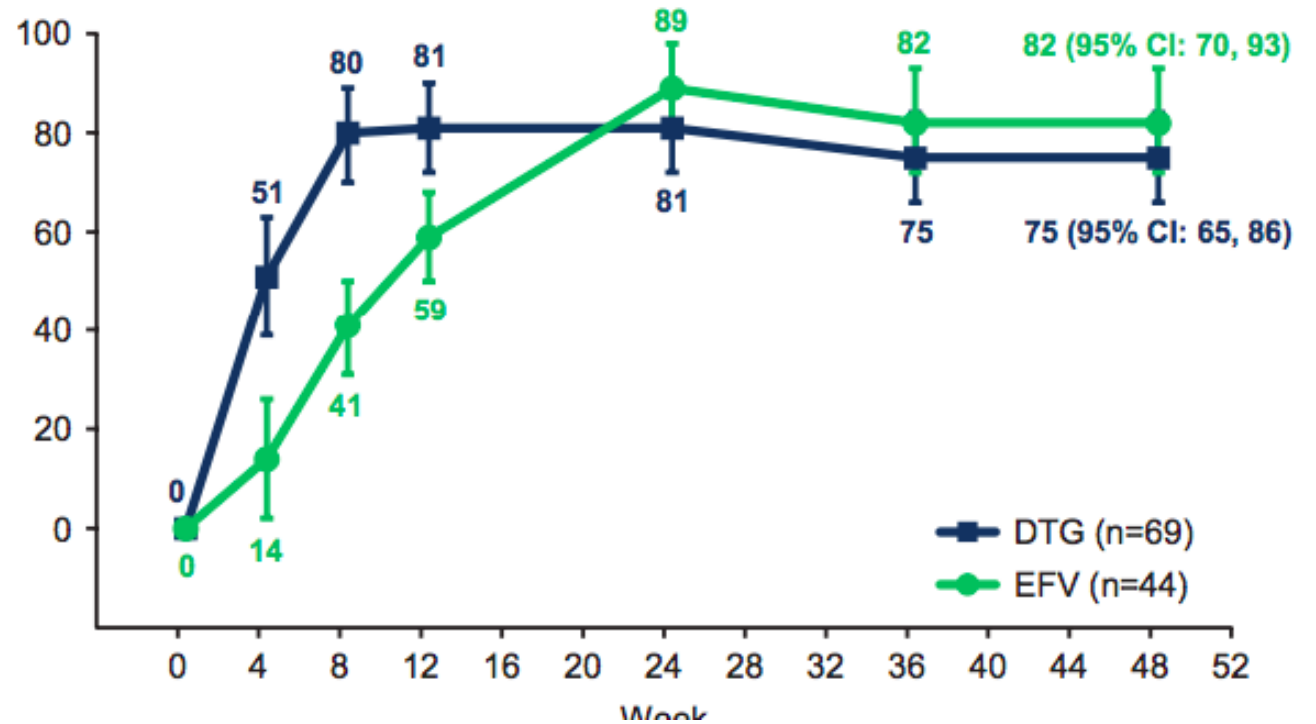
# DTG-based ART vs EFV-based ART in HIV/TB coinfection

- Open-labeled trial comparing EFV-based ART and DTG-based ART in patients naïve to ART with TB
- Patients in DTG arm rec'd 50 mg BID

## Results:

- N=113, median CD4 <250 cells
- Wk 48 virologic response rates 75% (65–86%) for DTG and 82% (70–93%) for EFV
- DTG non-responses driven by non treatment related discontinuations (n = 10 lost to follow-up).

48 week viral load <50 copies DTG-based and EFV-based ART



# Programmatic outcomes in Botswana with DTG in HIV/TB

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- Studies suggest rifampicin decreases DTG blood concentrations substantially
- Programmatic outcomes in HIV/TB coinfection in patients receiving DTG-based regimens, Botswana

## Results

- Among patients on DTG-based ART regimens, 91% achieved favorable TB treatment outcomes.
- DTG-based ART: **44% received qd** and 53% BID
- DTG-based ART associated with favorable TB treatment outcome (aOR= 1.56; 95% CI = 1.1, 2.3)
- Virologic suppression (VL<400) during TB treatment:
  - *DTG 50 mg QD: 298/322 (93%)*
  - *DTG 50 mg BID: 352/390 (90%)*
- Caveat: Programmatic study -- missing VL data removed (not considered as a virol. success or failure)

# Common ART adjustments during rifampicin-based TB therapy

*Assuming rifabutin is not available*

Existing ART	Change to :	Dose	Notes
Nevirapine	<b>Efavirenz</b>	600 mg/day	
LPV/r standard dose	<b>High dose LPV/r</b>	Two tabs twice daily	Poorly tolerated
Dolutagravir (DTG)	<b>Adjusted dose DTG</b>	50 mg twice daily	May not be critical
Tenofovir alafenamide (TAF)	<b>Tenofovir disoproxil fumarate (TDF)</b>	300 mg/day	
Atazanavir/r	<b>High dose LPV/r</b>	Two tabs twice daily	Poorly tolerated

# Case

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- He runs out of ART and TB therapy shortly after discharge
  - He had to go to a rural area of KZN to help his mother
- 6 months later he presents to the hospital with headache, and “not acting like himself”
- LP reveals:
  - Cell count 200 cells
  - 52% lymphocytes, 40% polys, 8% monocytes
  - Elev. protein, depr. glucose, CrAg (-) and bacterial GS (-)
  - Normal opening pressure
- What is the test of choice to confirm the diagnosis?

# Test of choice to confirm diagnosis?

- A) India Ink
- B) Fungal culture
- C) Bacterial culture
- D) XPERT MTB/Rif
- E) XPERT Ultra

# Addition data on XPERT Ultra in diagnosis of TB-meningitis (TB-M)

- Prior prospective study: Xpert Ultra improves TB-M detection in CSF with 95% sensitivity (21/22 cases)
- With Xpert Ultra, category of “trace positive” introduced to report positivity for IS6110 and/or IS1081 genes
  - Trace positive does not provide info on RIF resistance
- In Uganda, one hospital has introduced Xpert Ultra for CSF identification of *M. tuberculosis*, w/o centrifuge

## Results:

- All patients had definitive or probable TB-M
- CSF samples showed protein >45 mg/dl, low glucose <2.2 mmol, lymph. predominance and all CrAg (-)
- **Xpert Ultra detected TB in 7/11 patients, including 2 whose CSF was (-) by routine Xpert and culture**
- **4/11 definite/probable cases undetected by Xpert Ultra**

Xpert MTB/RIF	Xpert MTB/RIF Ultra	MGIT <sup>b</sup> (no. of days)
Low	Low	7
Low	Low	9
Very Low	Very Low	NG
Very Low	Trace	13
ND	Very Low	NG
ND	Trace	NG
ND	Trace	17
ND	ND	12
ND	ND	NG
ND	ND	NG
ND	ND	NG

In 11 cases of definite/probably TB-M: Xpert Ultra improves detection of *M. tuberculosis* in CSF

# Xpert MTB/Rif and Xpert Ultra

	Xpert MTB/Rif	Xpert Ultra*
<b>Sensitivity, HIV (+) persons with pulmonary TB</b>	77%	90% Lower specificity than Xpert
<b>Gene targets</b>	rpoB gene	rpoB gene IS6110 gene IS1081 gene
<b>Chamber size</b>	25 ul	50 ul
<b>Limit of detection</b>	112 cfu/ml	15 cfu/ml
<b>Trace positive result</b>	Not available	Indicates presence of IS6110 and/or IS1081 gene  Trace + provides no information on rif resistance

**\* Xpert Ultra recommended by WHO as the test of choice for TB - meningitis (2017)**

# Case

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- The patient improves on anti-tuberculosis therapy and corticosteroids
- After 6 weeks he restarts ART with TDF/FTC/EFV with no development of IRIS.
- The patient reports high adherence but after 6 months the viral load is 10,300 c/ml and CD4 122 cells/mm<sup>3</sup>
- He is referred for adherence support and told to continue TDF/FTC/EFV.
- A second viral load is not performed until 6 months later and is 12,100 c/ml and the CD4 is 77 cells/mm<sup>3</sup>

# Second-line ART switch delay in patients with advanced HIV results in excess mortality

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Retrospectively enrolled patients who failed 1<sup>st</sup>-line ART (2 VL > 1000 copies) in SA private sector cohort

## Results:

- N=5748 (53% female, median age 40, CD4 < 200 in 48%)
  - **Time to confirmation of virologic failure was typically >6 months**
- After 1<sup>st</sup>-line virologic failure there were 421 deaths overall, 78% of them in patients with CD4<200
- When CD4<200, timing of switch matters: **early switch <30 days** after confirmed virologic failure reduced death: **HR 0.78** (95% CI: 0.68-0.90)

# CD4 count low in SA at the time of 1<sup>st</sup>-line ART failure

South African patients managed in the Aid for AIDS cohort, a private sector managed care program

Year	Number with virol. failure	Proportion with CD4 < 200
2012	2233	50%
2013	689	53%
2014	677	45%
2015	688	46%
2016	1263	46%
2017	198	43%

***P=0.041*** for time trend suggests a slow improvement

Unpublished data

# Case

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- Our patient was changed eventually to TDF/3TC + LPV/r, double dose (2 tabs BID)
  - Received double-dose LPV/r until completion of TB therapy
- CD4 count now 222 cells/mm<sup>3</sup>
- The patient asks if cotrimoxazole prophylaxis can be stopped.
- The current VL is undetectable has been for >12 months.

# **A few updates on OI prevention strategies**

# Cotrimoxazole preventative therapy (CPT) in SA

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2014 WHO guidelines:

- **CPT indicated for adults (incl. pregnant) with a CD4 count  $\leq 350$  cells/ $\mu\text{L}$  or WHO stage 3/4**
  - Where prevalence of malaria high, WHO recommends CPT for all patients with HIV regardless CD4 count

National SA HIV Guidelines (2015) also recommended stopping CPT once  $\text{CD4} \geq 350$  on 2 occasions

SA Nat Essential Medicine List Subcommittee (2019):

- Benefit of CPT unclear when  $\text{CD4} > 200$  and  $\leq 350$  in countries such as SA without large malaria burden

SA HIV Clinician Society recs: stop CPT when  $\text{CD4} > 200$

**New SA ART clinical guidelines (2019): stop CPT when  $\text{CD4} > 200$**



# Case

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- Cotrimoxazole prophylaxis was stopped
- The patient is doing well on LPV/r (standard dose) + TDF/3TC and viral load remain undetectable
- CD4 cell count remains  $<350$  cells/mm<sup>3</sup>

# DHHS update, 2019: No MAC prophylaxis in most with HIV

**DHHS: “Primary prophylaxis for MAC (eg, azithromycin 1200 mg/week) who immediately initiate ART no longer recommended, regardless of CD4 count.”**

ART-era (1998-2014) study N=157 w/ HIV and CD4 <50

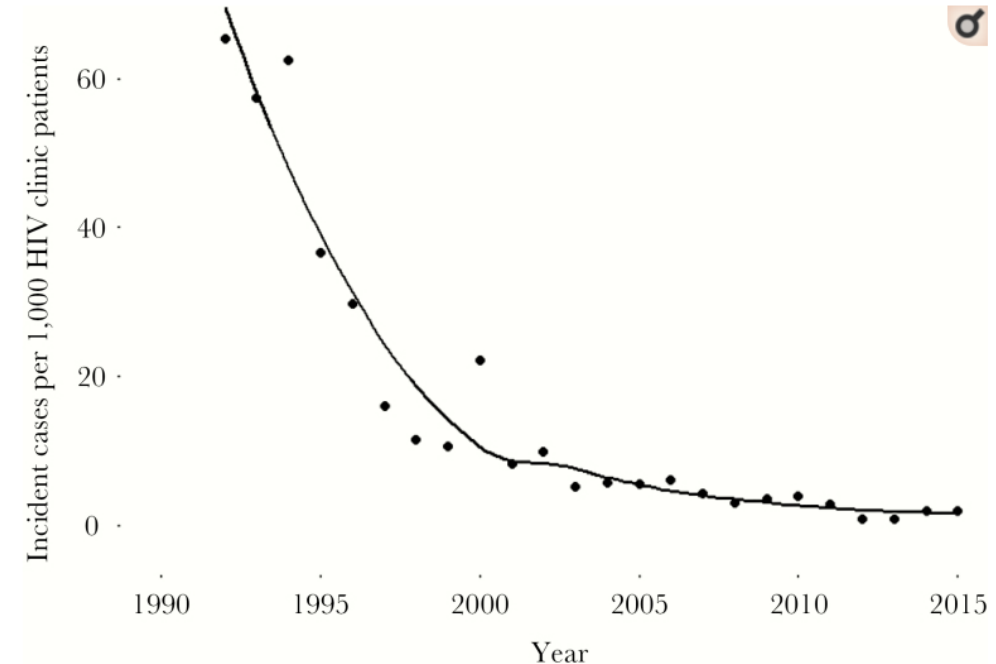
- Study compared incidence of MAC within 12 months after the first CD4 count <50 between 33 participants who received prophylaxis and 122 who did not

**3.4 / 100 person-years in those on prophylaxis**

**0.8 / 100 person-years in those not on prophylaxis**

**However in US, MAC prophylaxis remains indicated if:**

- CD4<50 and not receiving ART



**MAC incidence declined rapidly after introduction of combination ART in 1995-96**

# One month of prophylaxis to prevent HIV-associated TB

Trial conducted in SA, comparing in HIV(+):

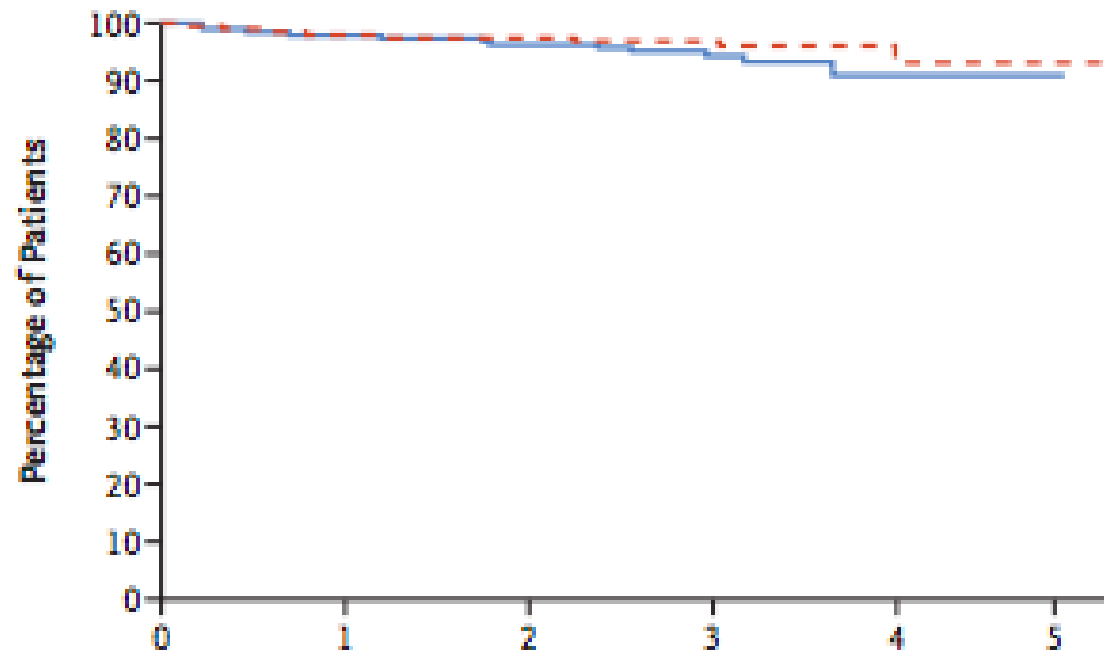
1 month of daily rifapentine 600 mg/day + INH 300 mg/day

versus 9 m of INH alone

## Results:

- N=3000 enrolled based on residence in hi prevalence area or + LTBI test, followed 3.3 yr
  - 54% women; median CD4+ 470, 1/2 on ART
- Primary end point reported in 2% in the 1-month group and 2% in the 9-month group,
- Serious adverse events occurred in 6% in 1-month group and 7% in 9-month group (P=0.07).
  - 1 case of rifampicin-resistant TB in each group

Freedom from Primary End Point in Patients with CD4+ Count of  $\leq 250$



**Primary endpoint: Incidence of TB**

**or death -- no difference in TB or death**

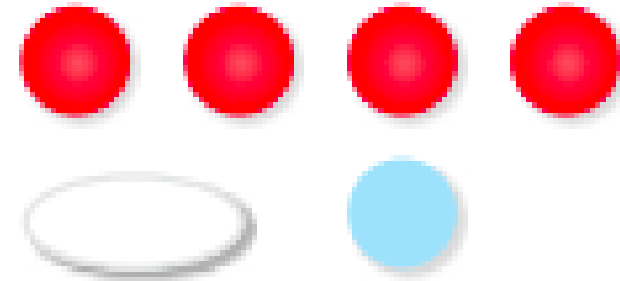
- **The % completing treatment higher in 1-m group vs. 9-m group (97% vs. 90%, P<0.001)**

# Access to rifapentine remains poor

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- Rifapentine was developed in the 1960s and the drug is off patent
- But access is limited globally because of high price and lack of registration in most countries.
- High price charged by Sanofi -- the main producer – remains a barrier.
  - Recently Sanofi registered the drug in SA (2018)
- In early 2019, a generic producer (India) applied for prequalification from the WHO
- **But activism is needed from nurses, doctors, pharmacists for access to key drugs like: rifapentine, rifabutin and 5FC/flucytosine**

**1HP**



**Thank you.**