Approach to the critically ill patient with advanced HIV in low resource settings

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why You should be this guy….

…instead of that guy…

USFR, Guinea-Conakry

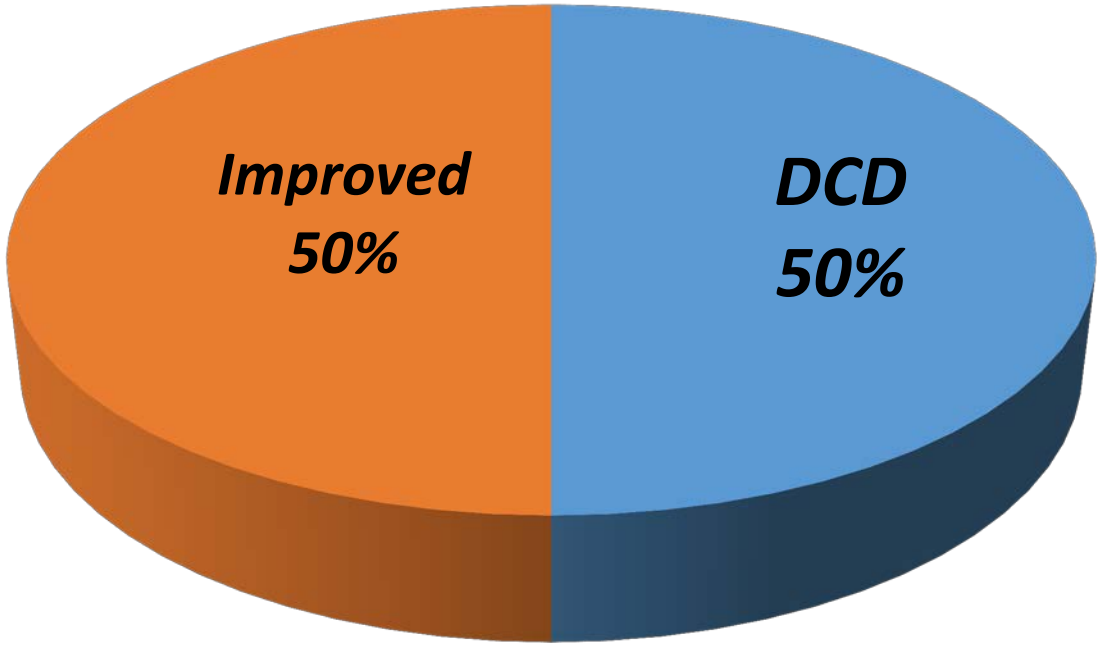
- ✓ *1 childhood safari to Kenya*
- ✓ *Read Heart of Darkness*
- ✓ *2 years experience in Infectious diseases department in Germany*

- ✓ *just built*
- ✓ *30 beds, 4 (level 2) ICU beds*
- ✓ *10 nurses, 4 national doctors, 1 nurse supervisor*

Mission: treat advanced HIV cases

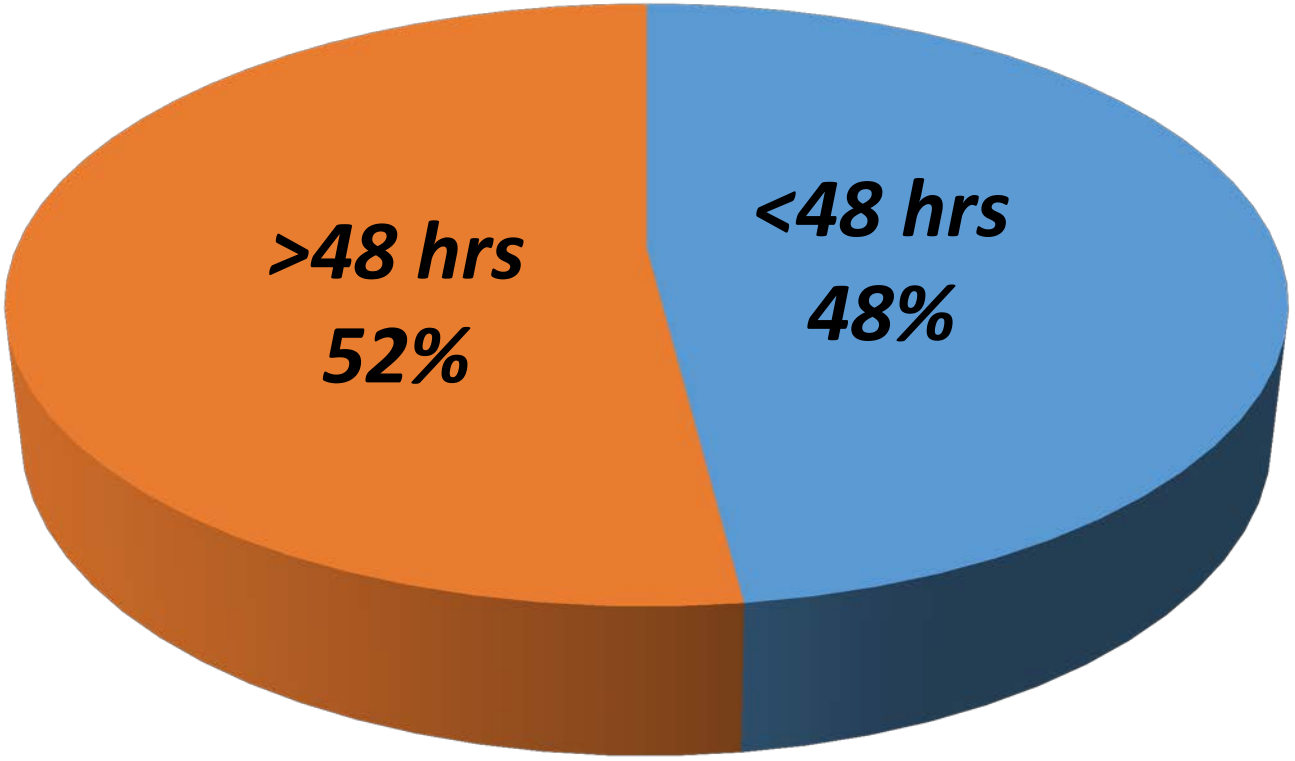
What could go wrong??

Mortality USFR during first two months of activity



n=50

Deceased patients by length of stay
11/16-12/16

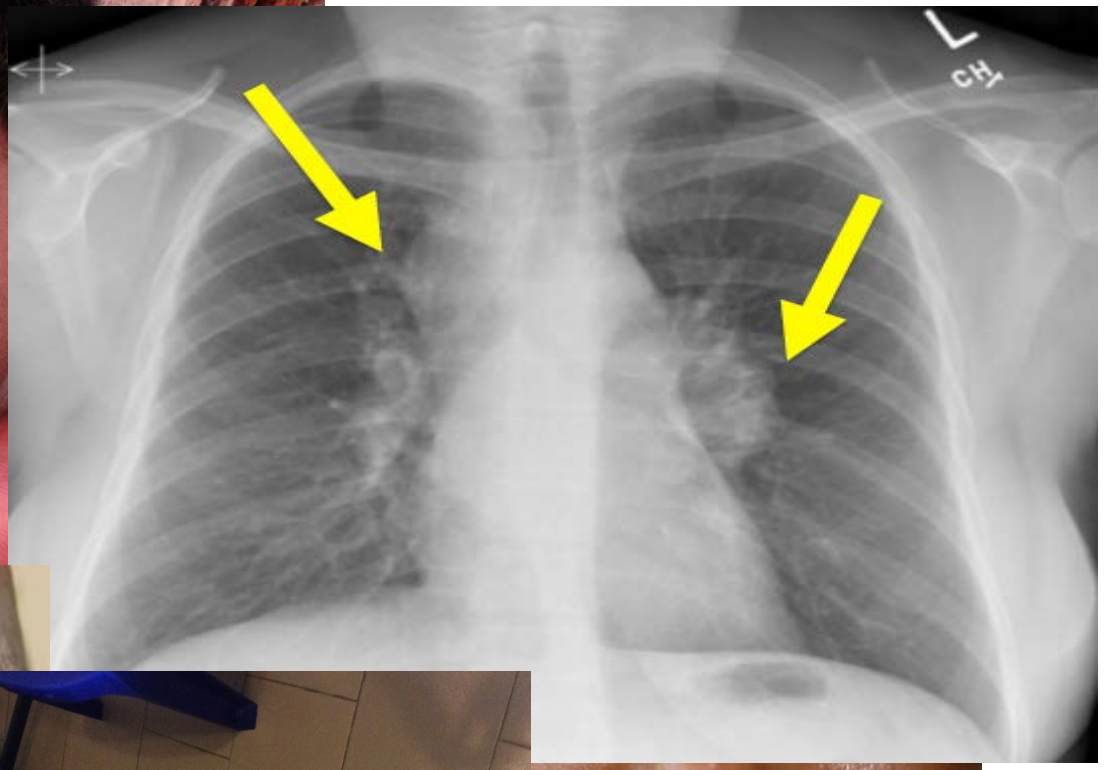


n=25

Whats going on

A readymade Definition

„A critically ill patient with advanced HIV is a patient with (advanced immunosupression) and one or more life-threatening (opportunistic) infections“


L
CH

Three boxes for three problems…

Clinical

Danger signs?

- Coma
- Heart rate>120/min
- Resp. rate >30/min
- Unable to walk unaided
- Malnutrition
- Any neuro signs????

Presenting complaint(s)

- For how long?
- Where(CNS,chest,abdo)?
- How many levels?

Establish and maintain diagnostic algorythms

- RDTs (Malaria, LAM,CRAG, Xpert, Glucose)
- bloods
- CXR
- Ultrasound
- Lumbar puncture

Organisation

Establish and maintain treatment algorythms

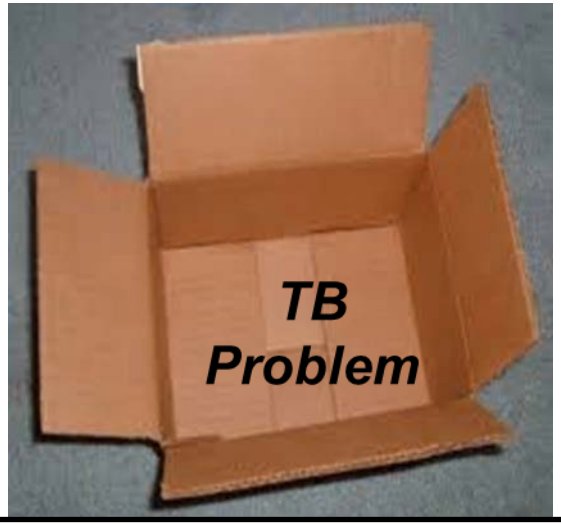
- Shock
- CPR
- Seizures
- Hypoglycaemia
- Transfusion

History

XRAY
Ultrasound
LP

Could this be TB?
Actively look for TB in ALL NEW patients

Examination



LAM
Xpert
(Smear)
culture

Is this patient already on TB treatment?

- How was TB initially diagnosed
- For how long has the patient been treated
- Why is he not improving
  - Recently started ARVs?
  - adherence?
  - Resistance?
  - Alternative diagnosis?

Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis

Rishi K. Gupta[a], Sebastian B. Lucas[b], Katherine L. Fielding[c] and Stephen D. Lawn[d,e]

- 3200 autopsies
- 43% (95% CI 38.0–48.3%) of facility based HIV related adult deaths
- Cause of death in >90% of cases
- 50% undiagnosed at death

AIDS 2015, **29**:1987–2002

How do we diagnose anything?

- History
- Examination
- Tests
  - Bedside
  - Laboratory
    - Blood
    - Sputum
    - Urine
    - Other fluids and tissues
  - Radiology
    - X-ray
    - USS

WE ASK YES OR NO QUESTIONS

Diagnostic accuracy studies

	Has disease	**Doesn't have disease**
Test +ve	True positive A	False positive B
Test -ve	False negative C	True negative D

Sensitivity A/(A+C)

Specificity D/(B+D)

PPV

NPV

Likelihood ratios

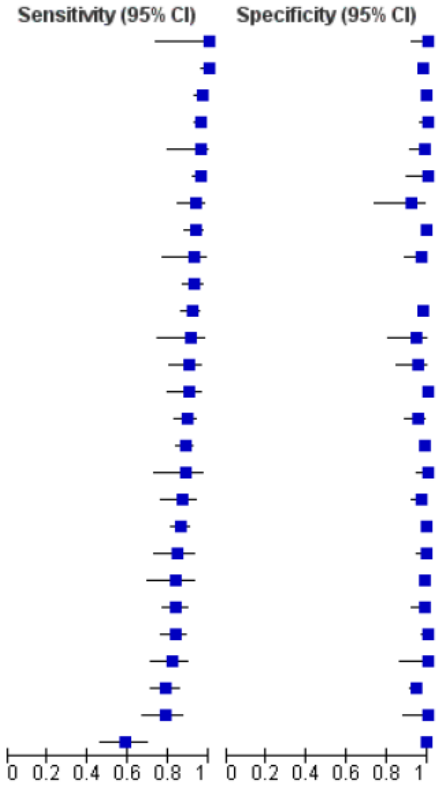
GeneXpert

- Detects MTB DNA
- PCR Amplification

- Detects Rif resistance
- Can stay + during treatment

Figure 5. Forest plots of Xpert sensitivity and specificity for TB detection, Xpert used as an initial test replacing smear microscopy. The individual studies are ordered by decreasing sensitivity. TP = True Positive; FP = False Positive; FN = False Negative; TN = True Negative. Between brackets are the 95% CI of sensitivity and specificity. The figure shows the estimated sensitivity and specificity of the study (blue square) and its 95% CI (black horizontal line). Xpert specificity could not be estimated in one study.

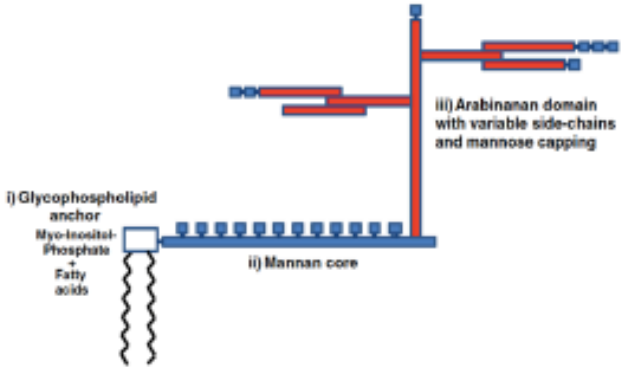
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Malbruny 2011	12	0	0	46	1.00 [0.74, 1.00]	1.00 [0.92, 1.00]
Boehme 2011e	101	16	0	671	1.00 [0.96, 1.00]	0.98 [0.96, 0.99]
Boehme 2011b	171	3	6	825	0.97 [0.93, 0.99]	1.00 [0.99, 1.00]
Boehme 2010b	201	0	8	101	0.96 [0.93, 0.98]	1.00 [0.96, 1.00]
Ciftci 2011	24	1	1	59	0.96 [0.80, 1.00]	0.98 [0.91, 1.00]
Boehme 2010e	179	0	8	35	0.96 [0.92, 0.98]	1.00 [0.90, 1.00]
Bowles 2011	60	2	4	23	0.94 [0.85, 0.98]	0.92 [0.74, 0.99]
Boehme 2010c	136	1	10	185	0.93 [0.88, 0.97]	0.99 [0.97, 1.00]
Miller 2011	27	2	2	58	0.93 [0.77, 0.99]	0.97 [0.88, 1.00]
Friedrich 2011	117	0	9	0	0.93 [0.87, 0.97]	Not estimable
Boehme 2011f	136	5	12	234	0.92 [0.86, 0.96]	0.98 [0.95, 0.99]
Ioannidis 2011	29	2	3	32	0.91 [0.75, 0.98]	0.94 [0.80, 0.99]
Teo 2011	56	2	6	42	0.90 [0.80, 0.96]	0.95 [0.85, 0.99]
Hanif 2011	54	0	6	146	0.90 [0.79, 0.96]	1.00 [0.98, 1.00]
Marlowe 2011	116	4	14	82	0.89 [0.83, 0.94]	0.95 [0.89, 0.99]
Boehme 2011a	203	4	26	303	0.89 [0.84, 0.92]	0.99 [0.97, 1.00]
Zeka 2011	31	0	4	68	0.89 [0.73, 0.97]	1.00 [0.95, 1.00]
Scott 2011	58	3	9	104	0.87 [0.76, 0.94]	0.97 [0.92, 0.99]
Boehme 2011c	201	2	32	669	0.86 [0.81, 0.90]	1.00 [0.99, 1.00]
Rachow 2011	49	1	9	101	0.84 [0.73, 0.93]	0.99 [0.95, 1.00]
Boehme 2010d	36	3	7	215	0.84 [0.69, 0.93]	0.99 [0.96, 1.00]
Boehme 2010a	123	1	24	68	0.84 [0.77, 0.89]	0.99 [0.92, 1.00]
Boehme 2011d	121	0	24	144	0.83 [0.76, 0.89]	1.00 [0.97, 1.00]
Helb 2010	67	0	15	25	0.82 [0.72, 0.89]	1.00 [0.86, 1.00]
Theron 2011	111	19	30	320	0.79 [0.71, 0.85]	0.94 [0.91, 0.97]
Moure 2011	61	0	17	29	0.78 [0.67, 0.87]	1.00 [0.88, 1.00]
Lawn 2011	42	2	30	320	0.58 [0.46, 0.70]	0.99 [0.98, 1.00]



Sensitivity 89%

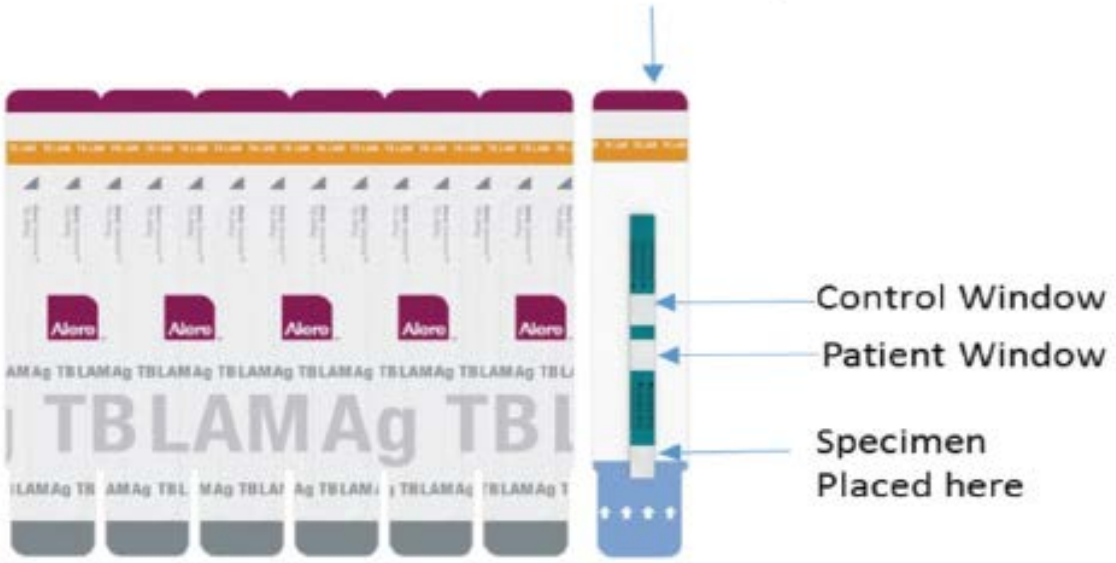
Specificity 99%

Urine LAM



- LAM = Lipoarabinomannan
- *MTB* cell wall polysaccharide

A



B

Alere Determine™ TB LAM Ag

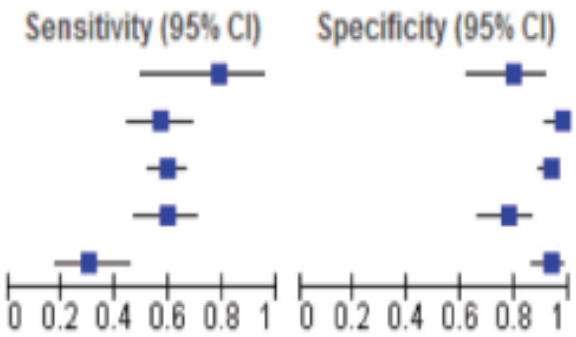
Reference Scale Card

- Hold the card alongside the patient window and read the result
- If the result line is hard to define refer to the package insert
- Store the card in the kit pouch away from direct light and heat
- Do not use the card beyond the expiration date

Figure 12. Forest plots of sensitivity and specificity of LF-LAM for diagnosis of active TB in HIV positive patients with CD4 count ≤ 100 cells/μL, microbiological reference standard

LAM_DX_MicroRef_CD4<100 Grd2

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Andrews 2014	11	7	3	27	0.79 [0.49, 0.95]	0.79 [0.62, 0.91]
Lawn 2014	41	2	31	81	0.57 [0.45, 0.69]	0.98 [0.92, 1.00]
Nakiyingi	116	12	80	176	0.59 [0.52, 0.66]	0.94 [0.89, 0.97]
Peter 2012	44	16	30	55	0.59 [0.47, 0.71]	0.77 [0.66, 0.87]
Peter and Theron 2014	14	5	32	76	0.30 [0.18, 0.46]	0.94 [0.86, 0.98]



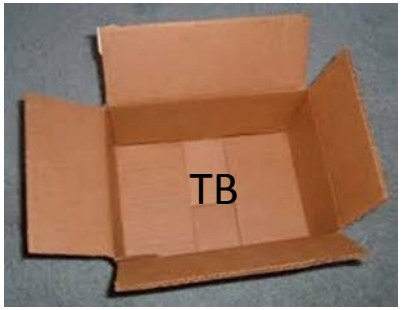
Pooled sensitivity was 56% (98%CI, 41-70%)
pooled specificity was 90%

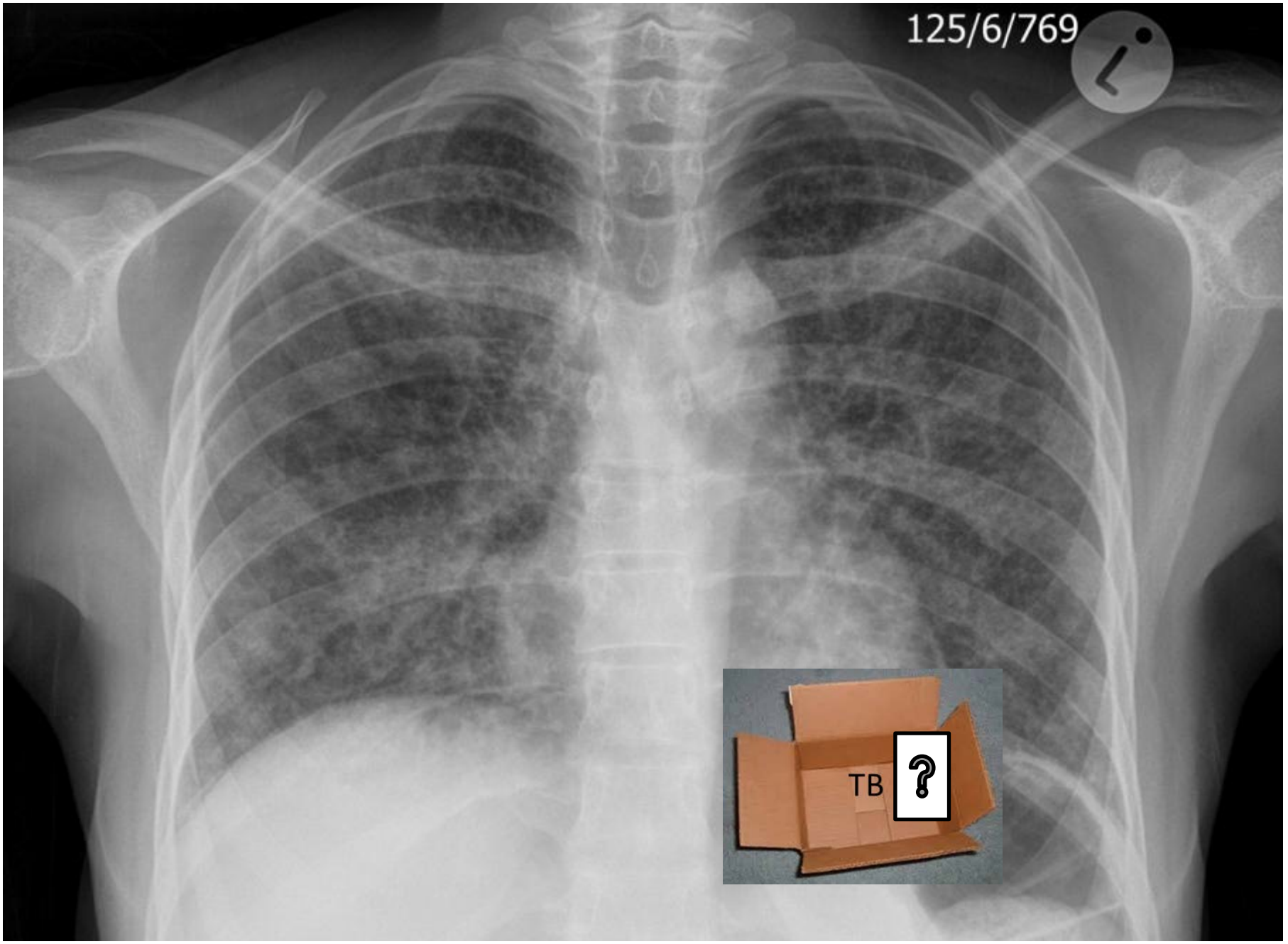
…lets see a patient

- 26 year old woman
- Diagnosed with HIV this admission
  - ART naïve, CD4 = 17
- Presents with:
  - Fevers, night sweats
  - shortness of breath for 3 weeks

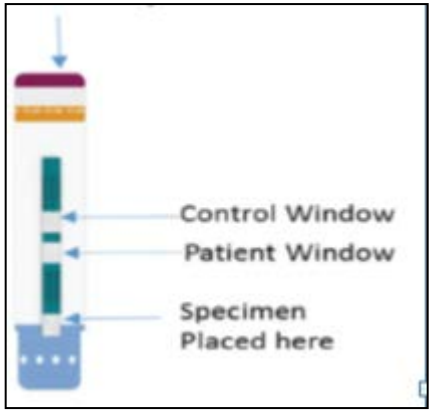
Examination:

- RR 40
- saturation 82% on room air
- Temp 37^{7}
- No lymphadenopathy
- Chest clear on examination

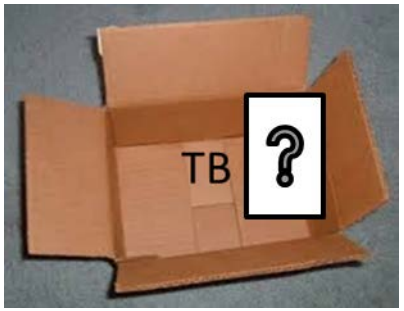



125/6/769
TB
?

negative



negative



So can we rule out TB??????

All tests say “no“ but can we trust this “no“???

Diagnostic tests

	Has TB	**Doesn't have TB**
Test +ve	True positive A	False positive B
Test -ve	False negative C	True negative D

Sensitivity = $A/(A+C)$

Negative predictive value = $D/(C+D)$

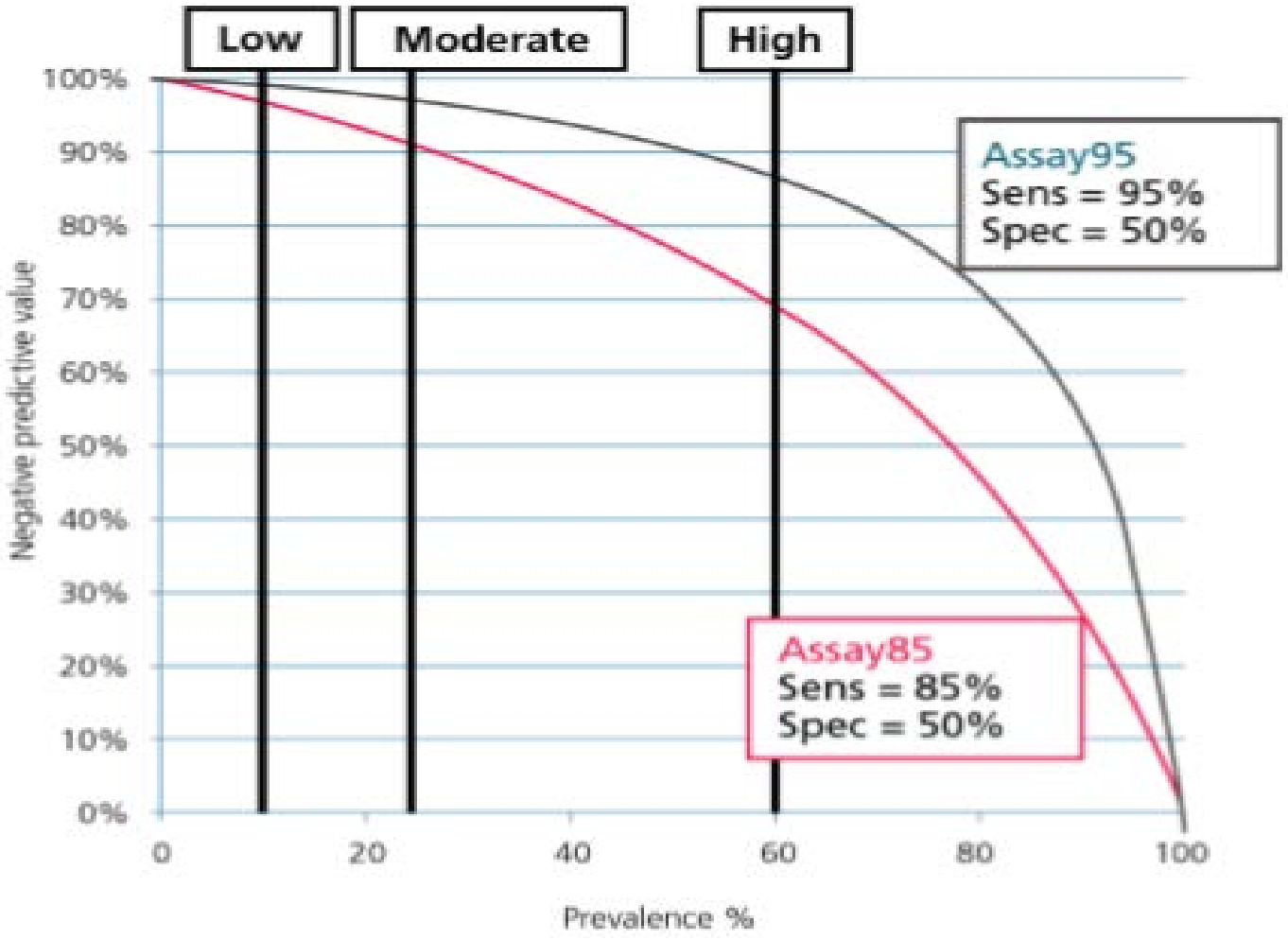


FIG. 6: Negative predictive values as function of prevalence. Prevalence of PE for "low"-, "moderate"- and "high"-pretest-probability groups shown.

Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis

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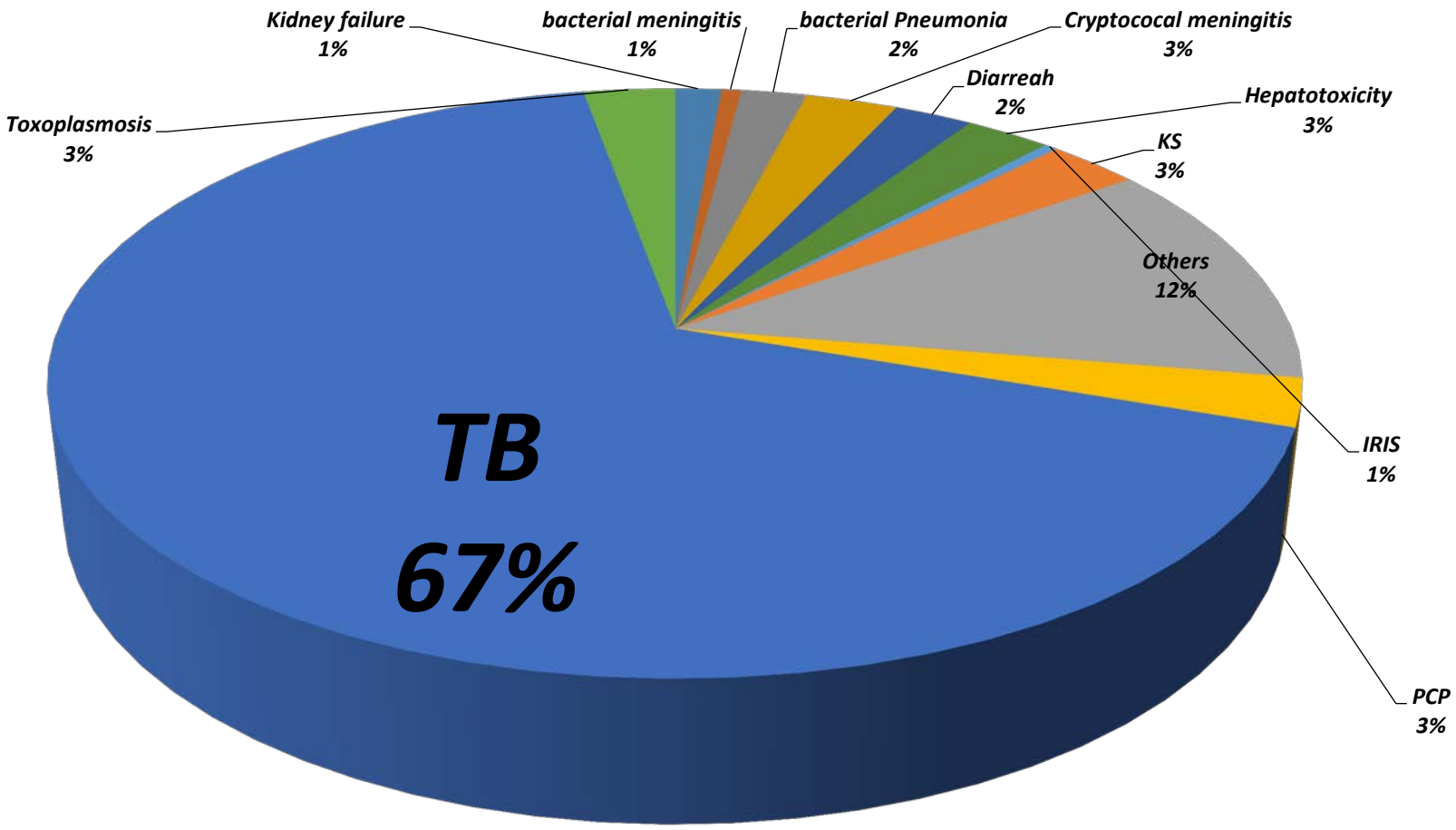
- 50% undiagnosed at death

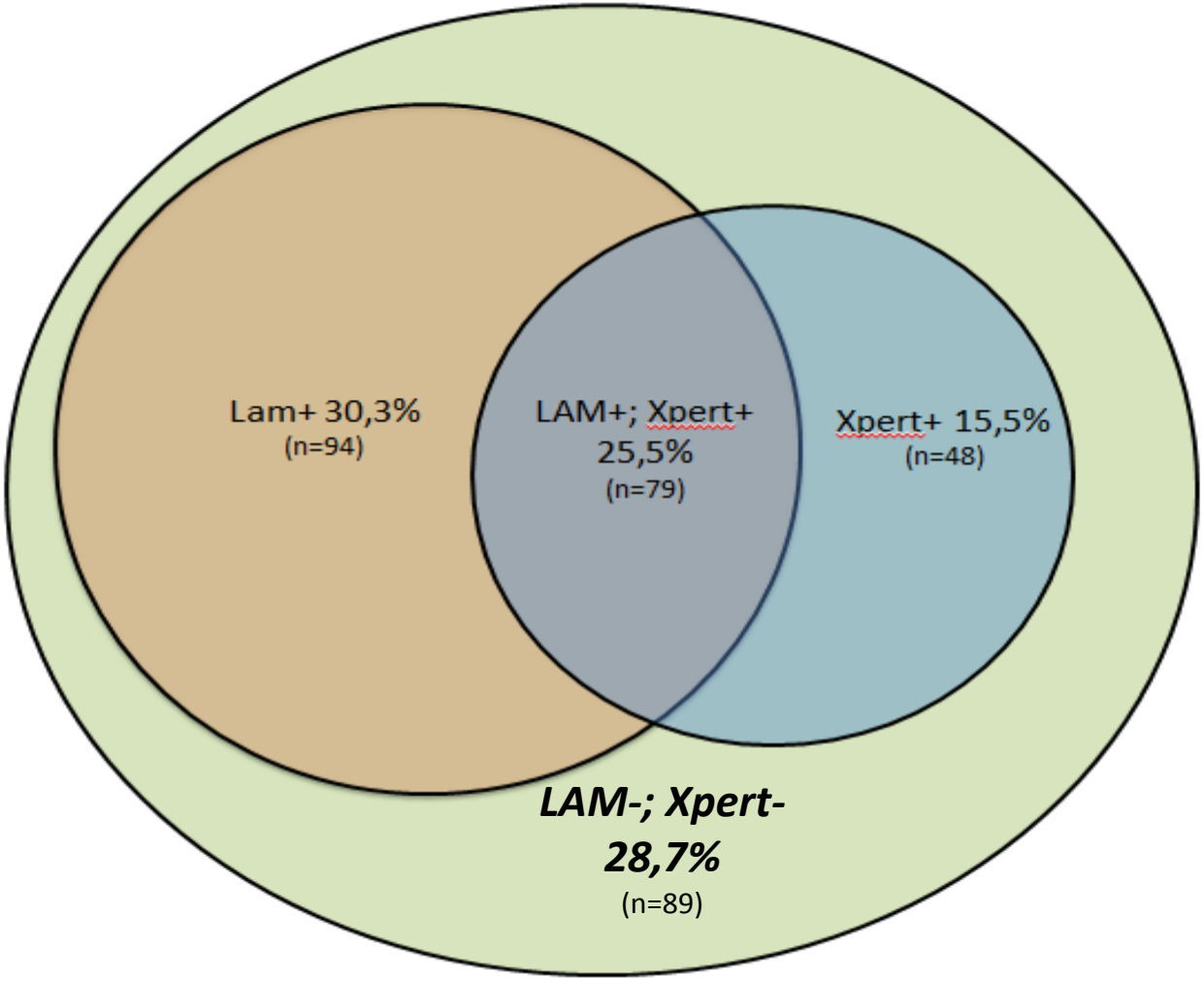
AIDS 2015, **29**:1987–2002

……..it could always be TB……



USFR patients from 11/16-11/17 n= 547

TB cases USFR 11/17-11/18 (n=310)



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UNRESOLVED ISSUES

Potential utility of empirical tuberculosis treatment for HIV-infected patients with advanced immunodeficiency in high TB-HIV burden settings

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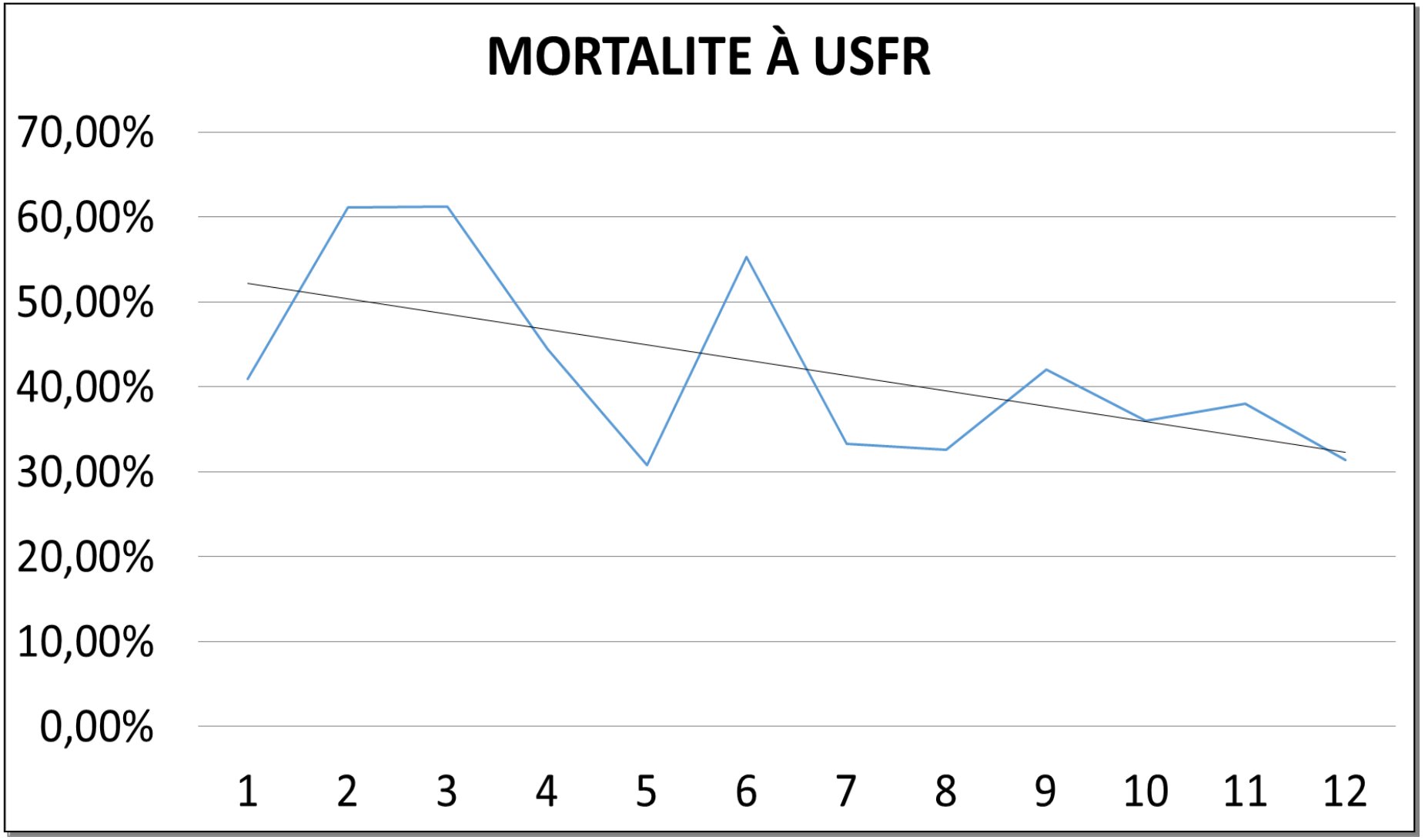
……Ideally……


MORTALITE À USFR
70,00%
60,00%
50,00%
40,00%
30,00%
20,00%
10,00%
0,00%
1
2
3
4
5
6
7
8
9
10
11
12

KEY MESSAGES

- Organize standard algorythms
- Test agressive
- If necessary treat agressive+ empirical
- Become serious HIV Nerd+ make everybody else become one too

“DONT EVER EXCLUDE TB“

Vielen Dank für die Aufmerksamkeit

Questions..???

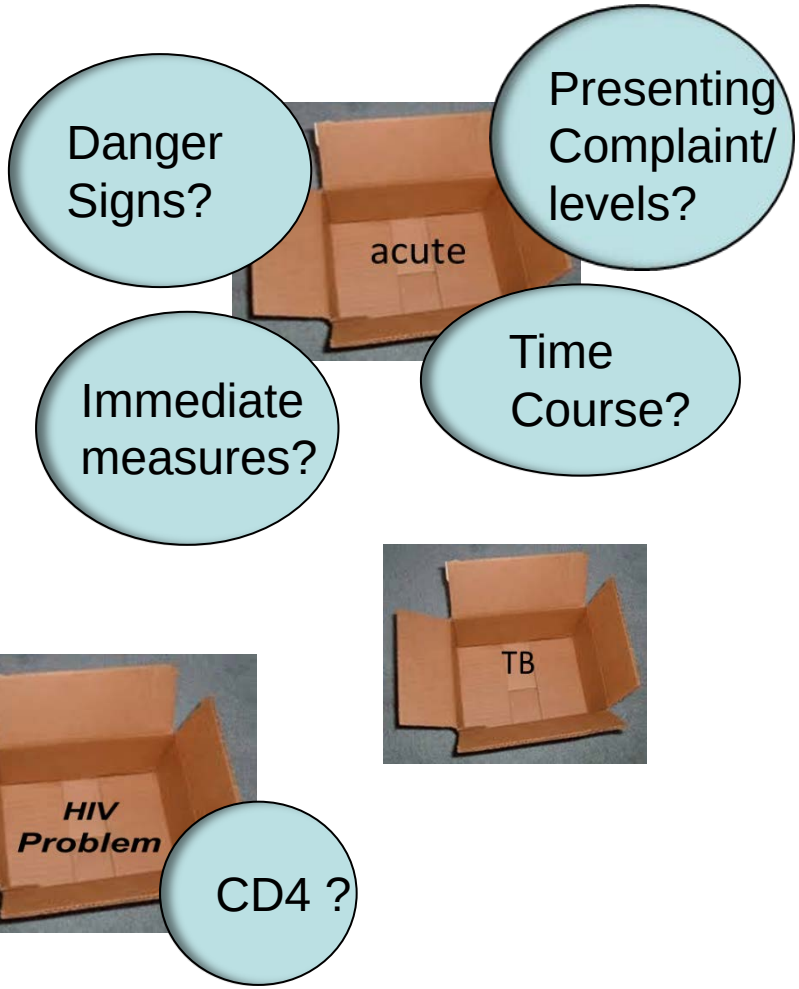
…or……

Practice Session

Case study

26 year old man,HIV diagnosed this admission:

- Presents with:
  - Seizures
  - Confusion
  - Fever
- Examination
  - RespRate 36, saturation 87%
  - RR 90/40, HR 110/min
  - Bilateral crepitations
  - Meningism



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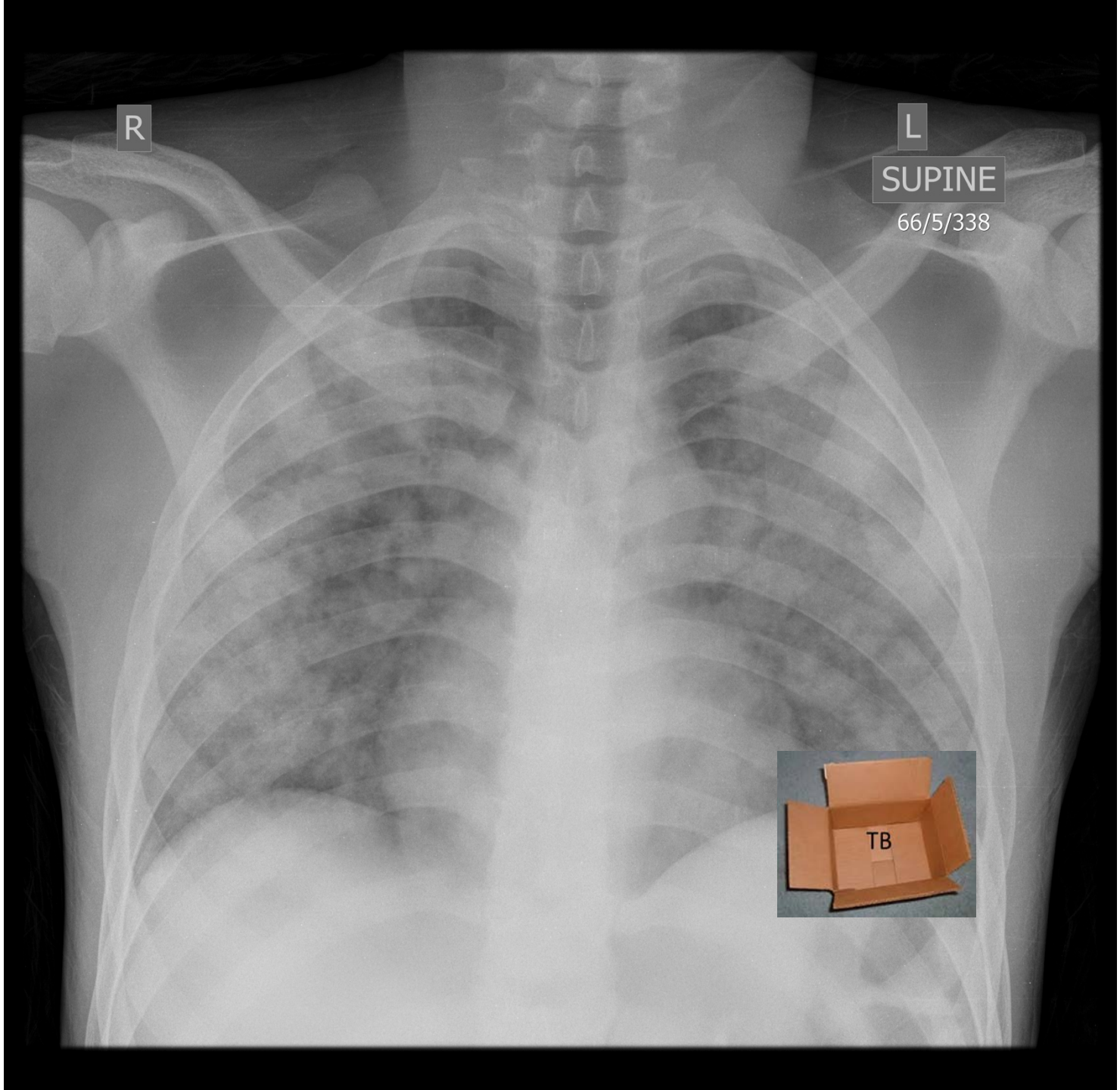

R
L
SUPINE
66/5/338
TB

Additional tests?

- Xpert negative
- Lam positive
- sCRAG negative

LP: WBC 120 (10% Neutrophiles), Pandy++,
Glucose 10 mg/dl, CRAG-

Differential diagnosis

- Disseminated TB: pulmonary, TBM
- Pneumocystis pneumonia plus another infection cause of meningitis
- Bacterial pneumonia plus meningitis, bacterial or other cause

how will you treat this patient?

- Advanced disease, respiratory and neurological danger signs

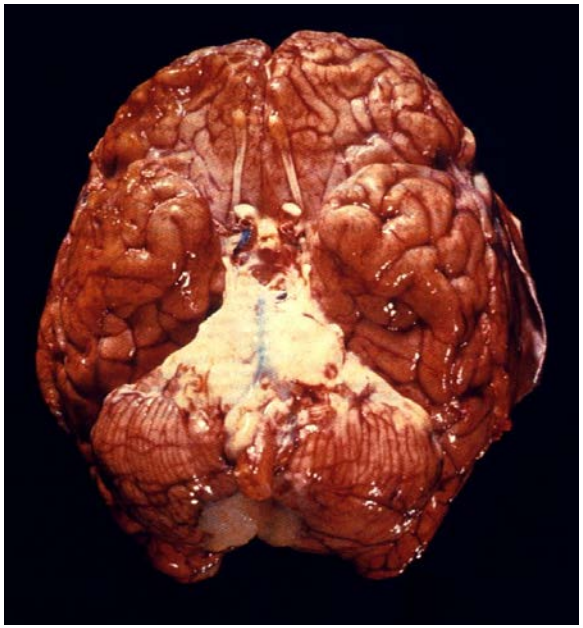
Empiric treatment:

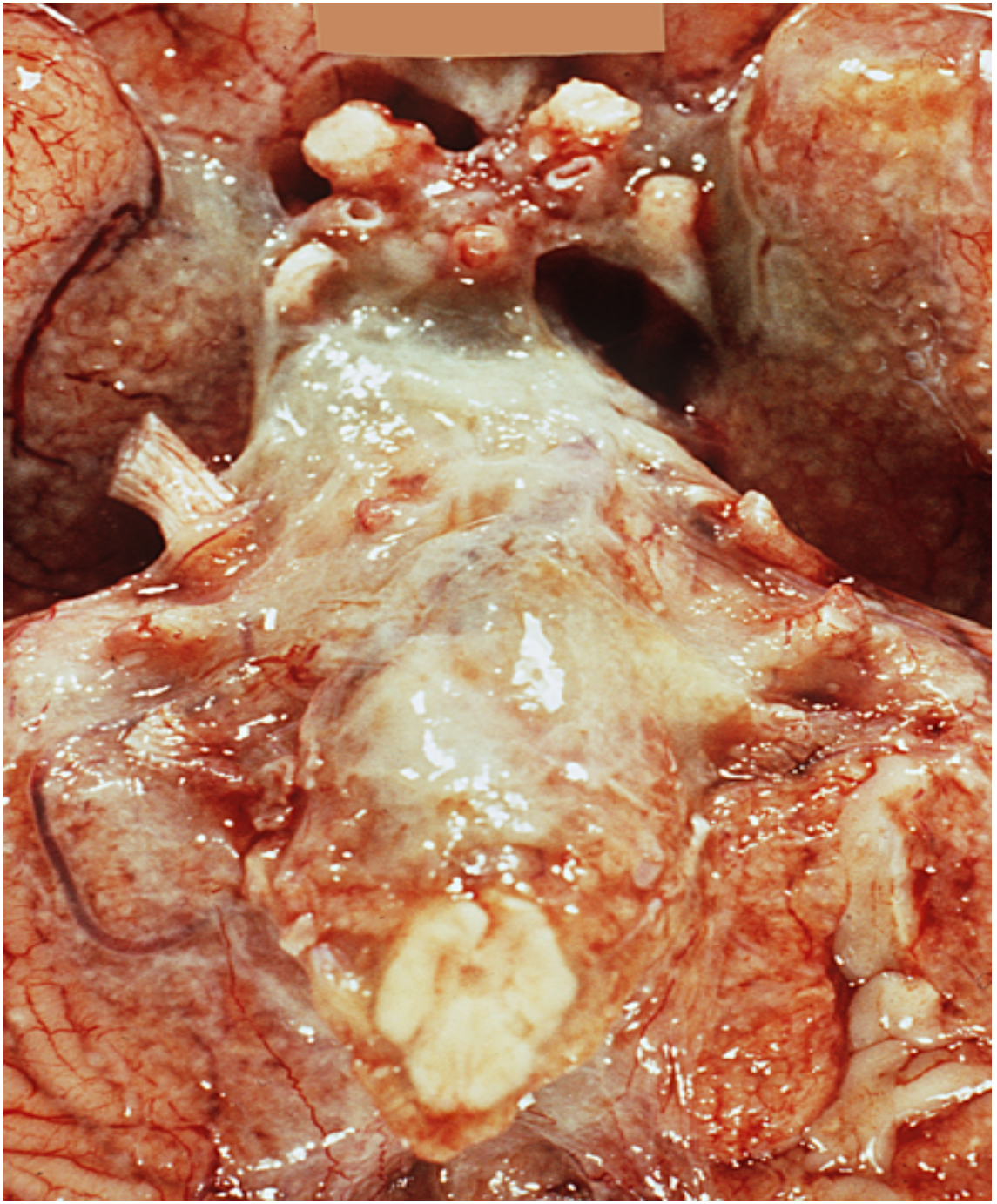
- TB – treat for TBM
- Pneumocystis pneumonia
- Crypto ruled out
- Antibiotics?

TB Meningitis

- Common cause of meningitis in countries with high HIV/TB prevalence
- CNS involvement is 5 x higher in HIV positive pts with TB
- Mortality 30-70%; neurological sequelae in 25%

TB meningitis: pathology

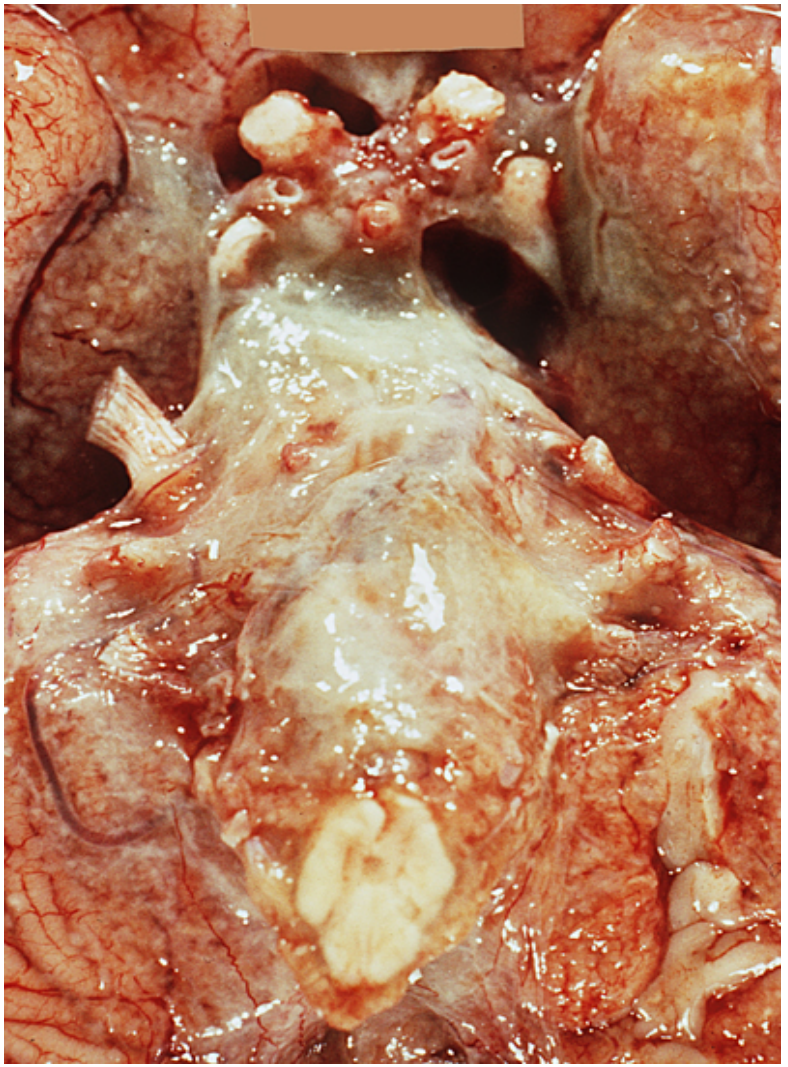




TB meningitis: pathology

- Dense gelatinous exudate - most florid around base of brain

- cranial nerve palsies from inflammation surrounding nerves
- Vasculitis
- hydrocephalus



Treatment:

Some guidelines prolong the continuation phase:

- 2 months of RHEZ
- 7 -10 months of RH (South Africa: 7 months)

Optimal regimen/duration is active research area:

- Watch out for new evidence
- High dose rifampicin?
- Quinolones?

Corticosteroids for TB meningitis

- Improved survival for HIV negative patients with TBM
- Trend for improved survival in HIV positive pts
- Recommended for all patients irrespective of HIV status

- Studies used intravenous dexamethasone

- Most resource-poor, high prevalence countries use oral prednisone:

  1.5mg/kg/day x 4 weeks

  then 0.75mg/kg/day x 2 weeks

Prognosis

- High mortality – 20-50% *with* treatment

- Neurological impairment amongst survivors - 20-30%:

  cranial nerve palsies hemiparesis

  seizures blindness

Prognosis worse:

- more severe disease at presentation: decreased consciousness, focal neurology