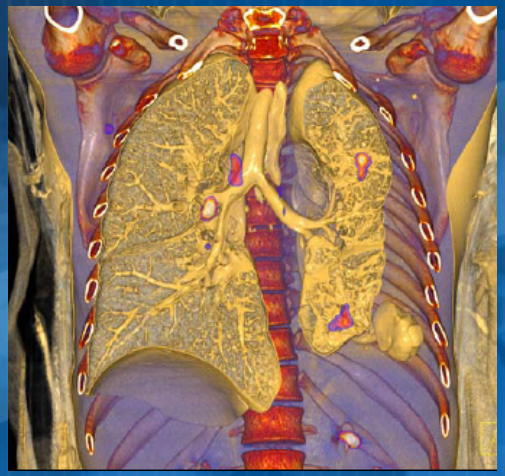
Assessing Tuberculosis Response to Therapy



Mike Sathekge, PhD

Nuclear Physician-in-Chief

100
1908 - 2008

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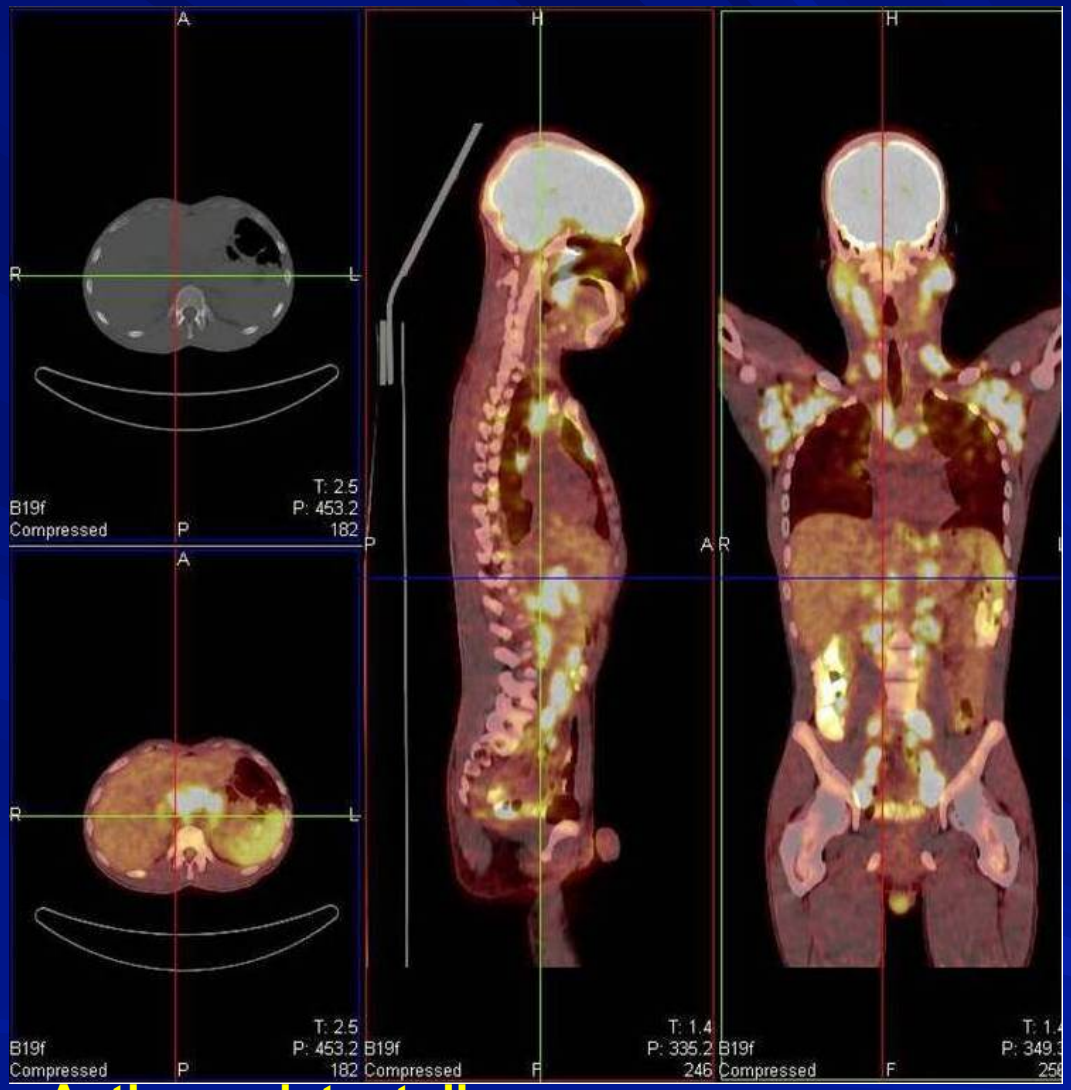
16th ISORBE Congress: University of Pretoria
Pretoria, South Africa. 21-23 March 2013

FDG PET/CT: HIV &TB



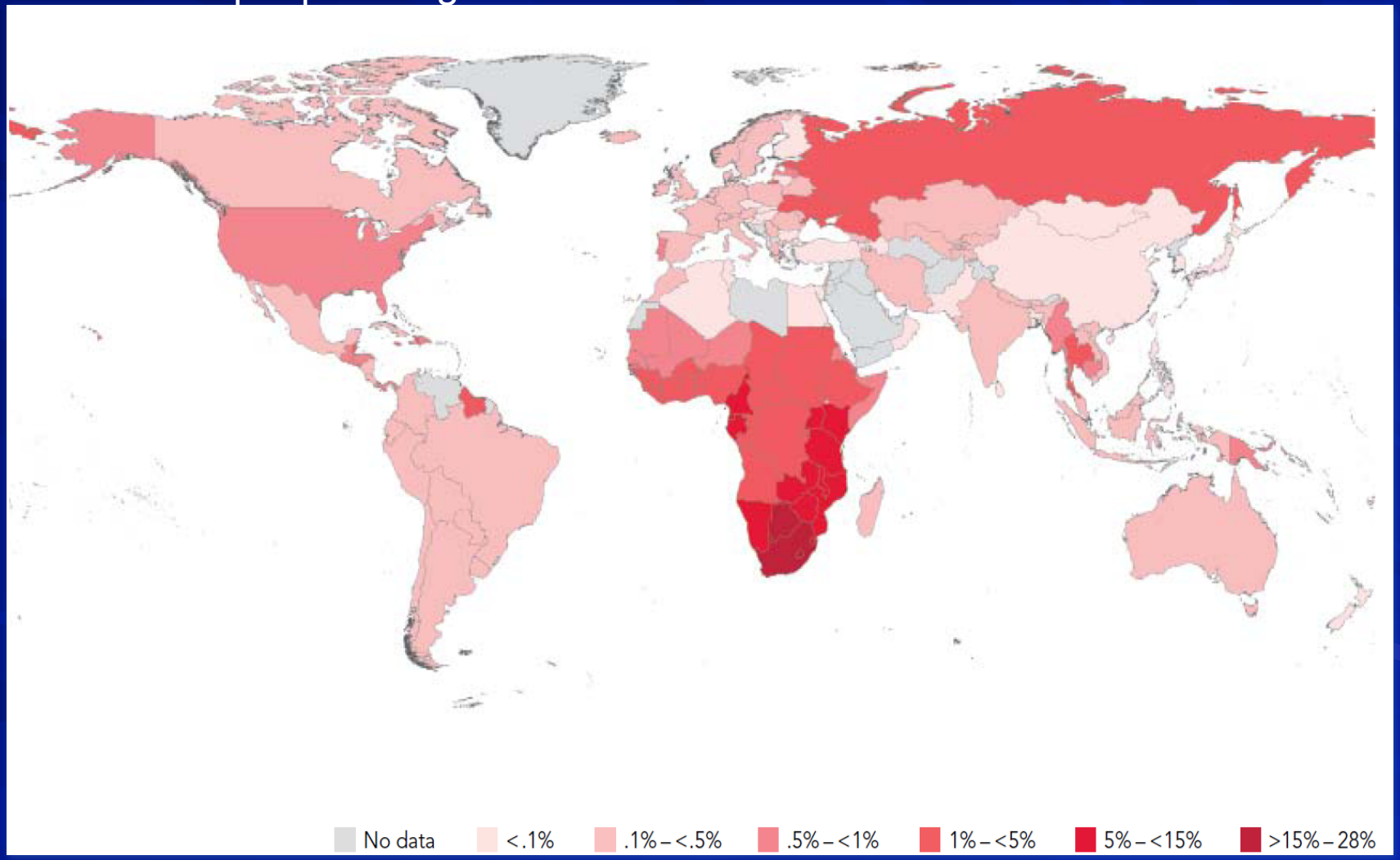
- Active vs latent disease
- Monitoring of Response to anti-TB Rx
- Guide to Duration of antimicrobial therapy
- Prognosis
- Drug Development & new biomarkers

TB Iceberg

How Big?

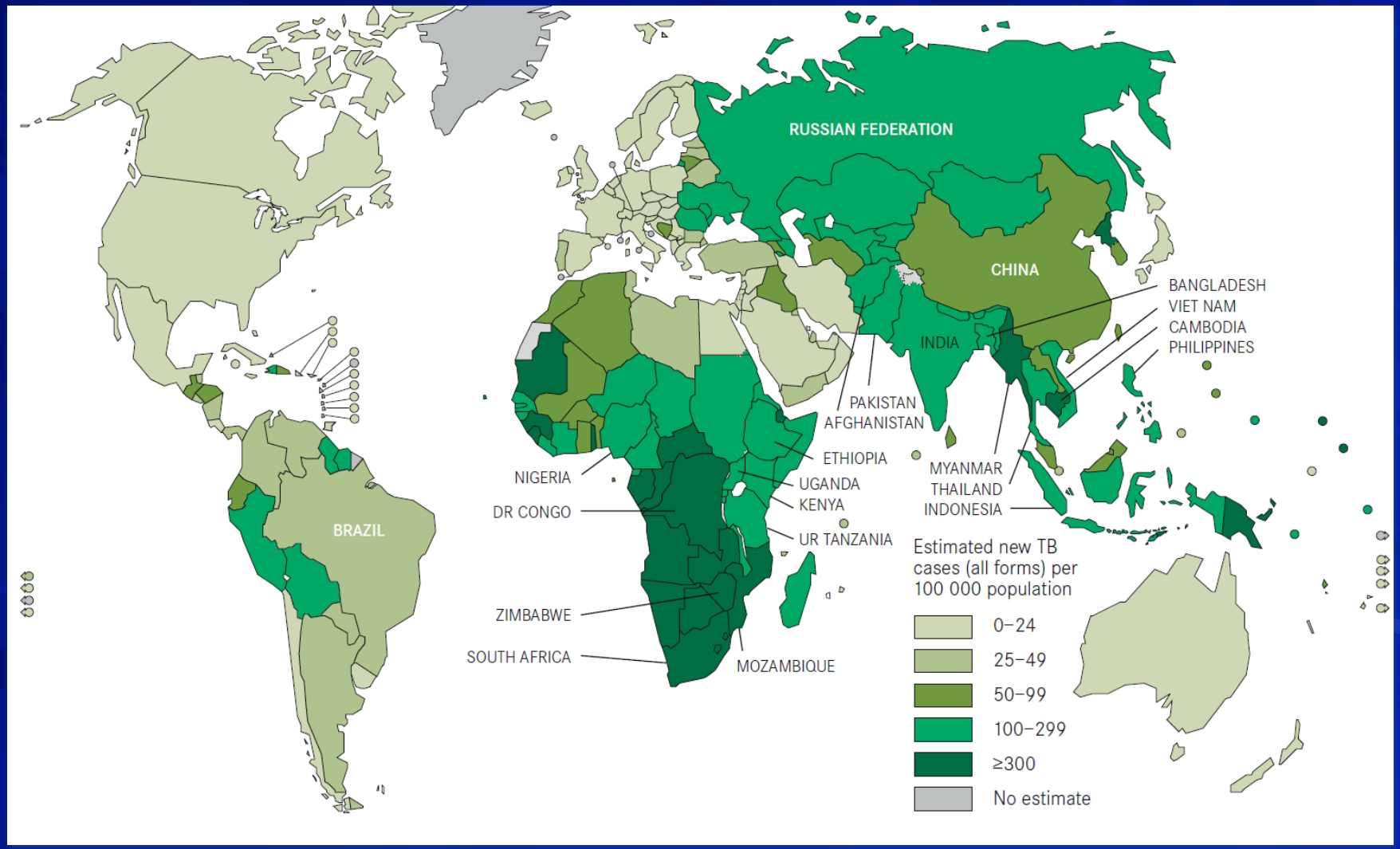
Global prevalence of HIV, 2009

33.3 million people living with HIV **22.5** million in Sub-Saharan Africa



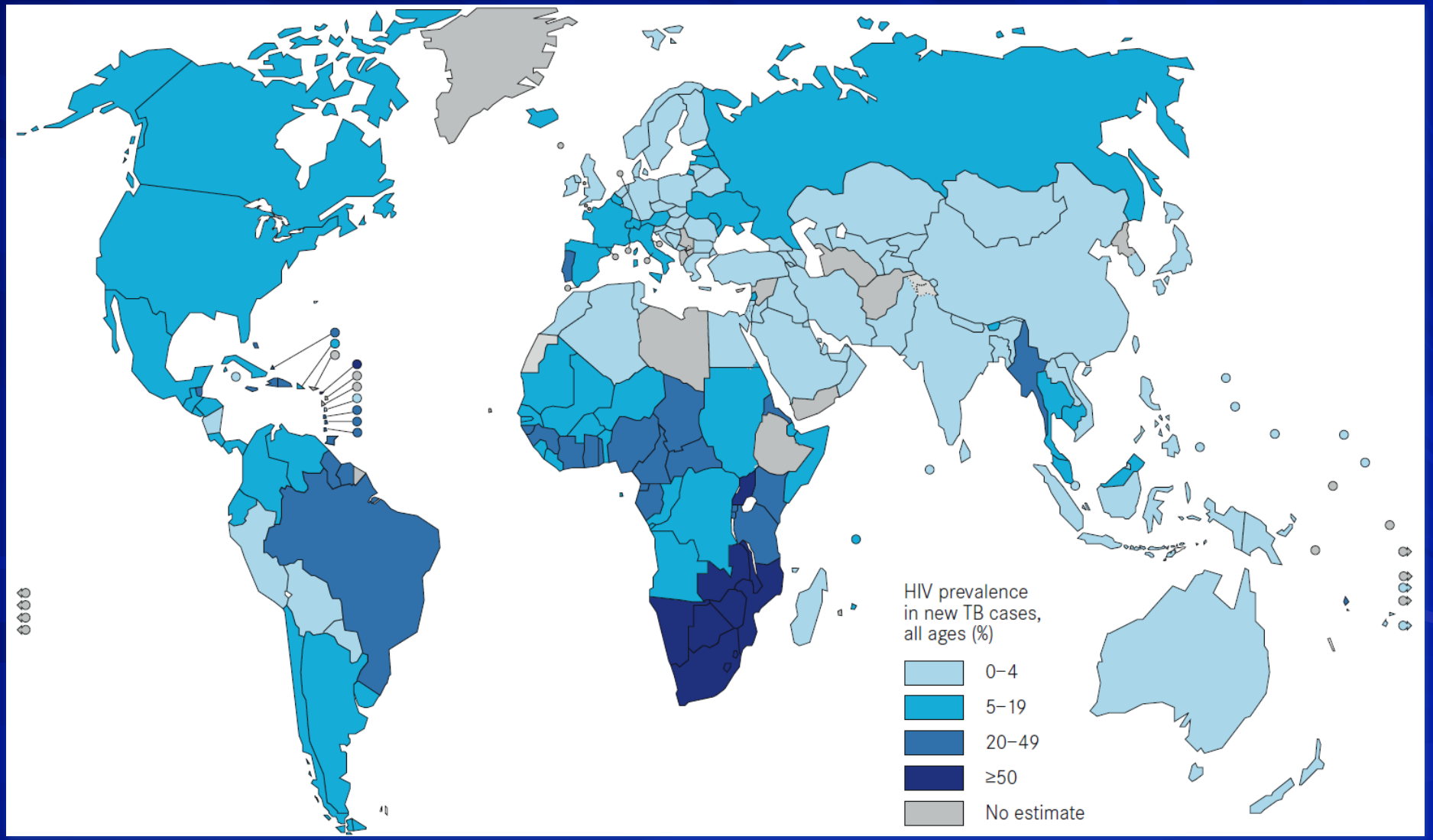
Estimated TB incidence rates, 2010

8.8 million incident cases of TB, **1.1** million deaths from TB among HIV-negative people



Estimated HIV prevalence in new TB cases, 2010

Challenge of TB cases in HIV positive people & **350 000** deaths from HIV-associated TB



Global & South African TB and HIV epidemics

HIV

- **Globally:**
  33.3 million HIV +ve
- **South Africa:**
  5.6 million HIV +ve

TB

- **Globally:**
  8.8 million cases of TB
- **South Africa:**
  461 000 cases of TB

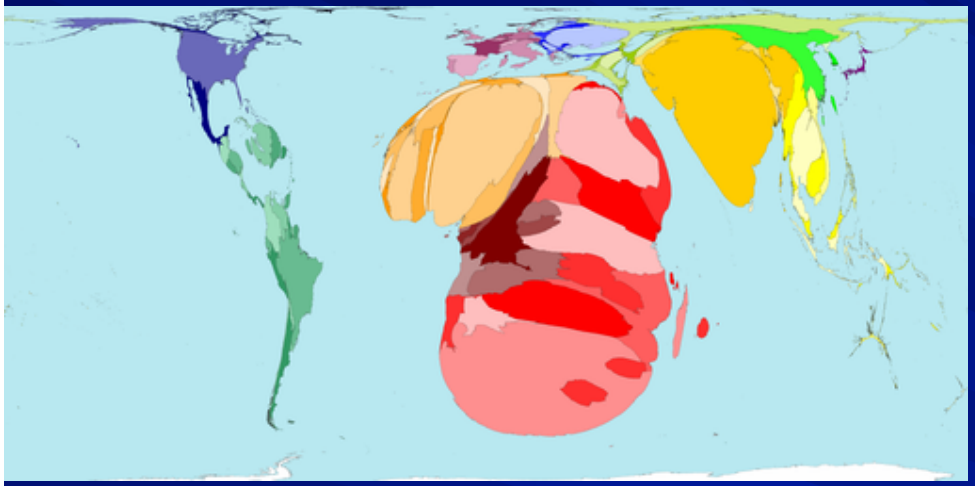
TB - HIV co-infection

- **Globally:**
  1 368 000 cases & 350 000 deaths
- **South Africa:**
  ~336 000 cases (HIV-TB co-infection = 73%)

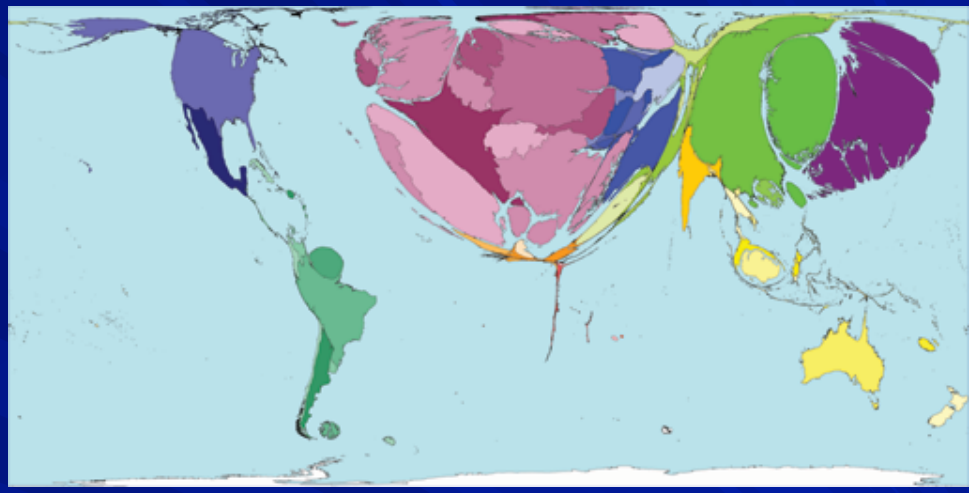
WHO Report 2009: Global Tuberculosis Control

UNAIDS 09 AIDS Epidemic Update

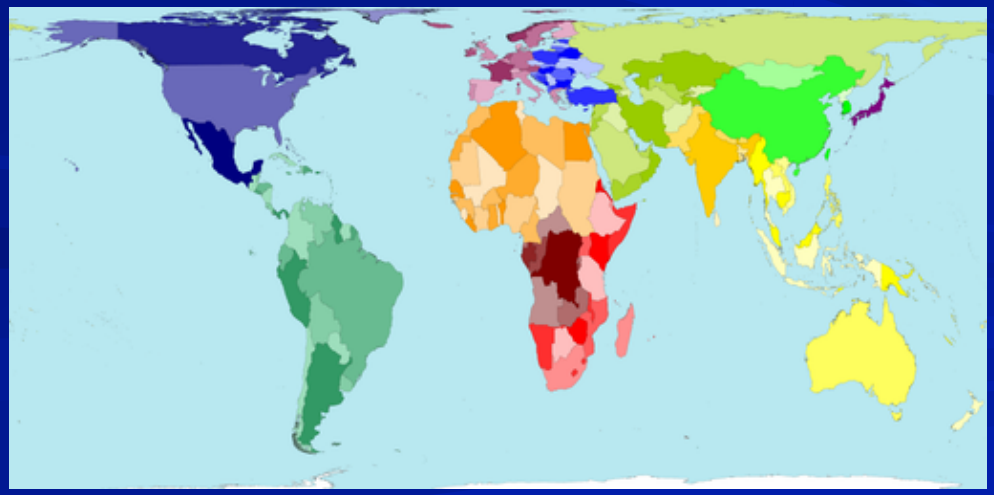
HIV/AIDS



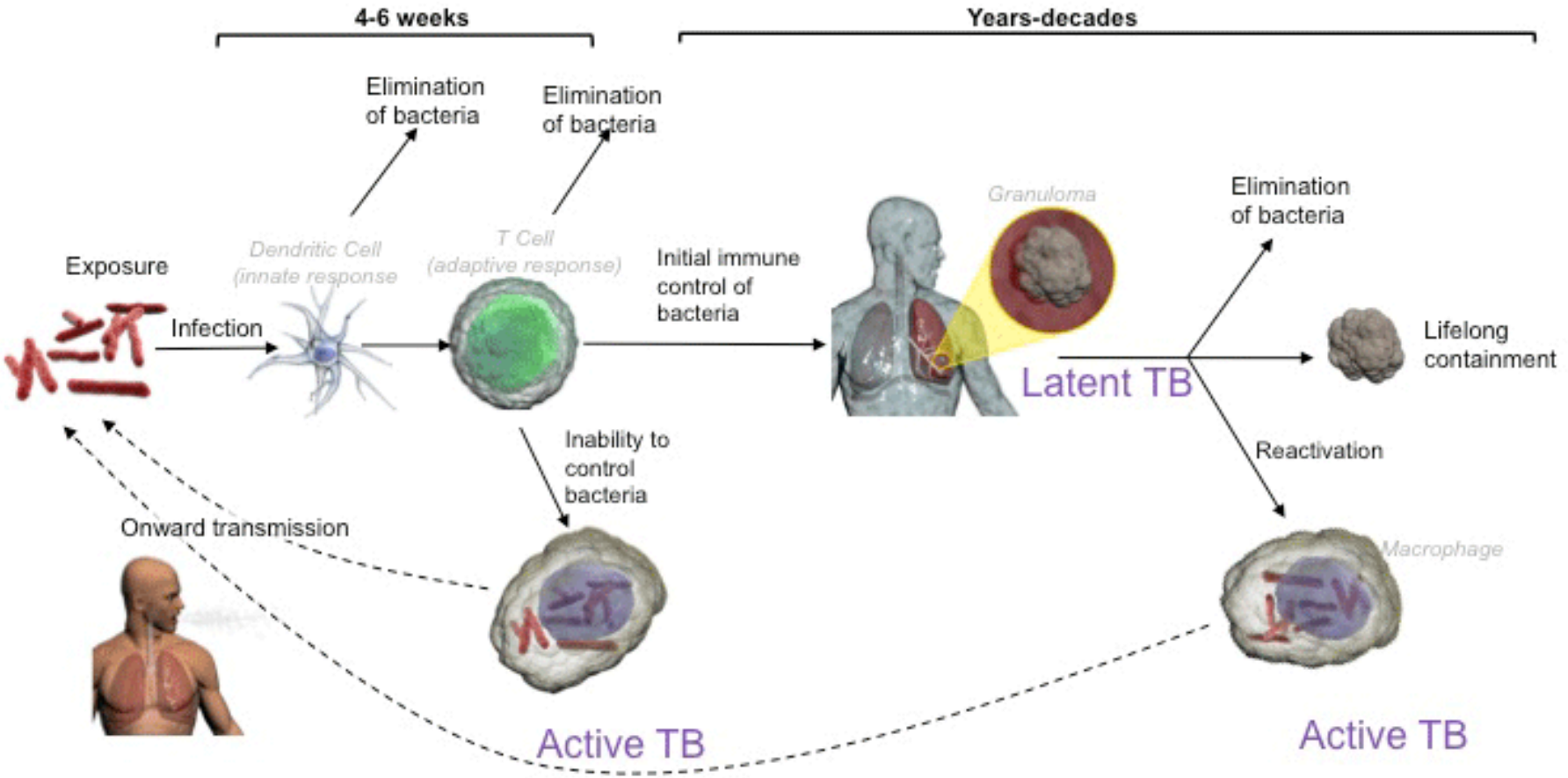
Science Growth



Normal Land Area



Natural history of TB infection



Why harmonise & integrate TB and AIDS care?

- TB commonest first presentation in HIV+ patients
- Efficient way of identifying patients for ART
- TB-HIV co-infected patients have high mortality
- Treating TB properly reduces AIDS-related deaths
- TB-HIV co-infected often present when CD4 counts are ±200 - indicating need to start ART
- Treating HIV/AIDS reduces incidence of TB

Mortality rates lower when ART integrated with TB treatment

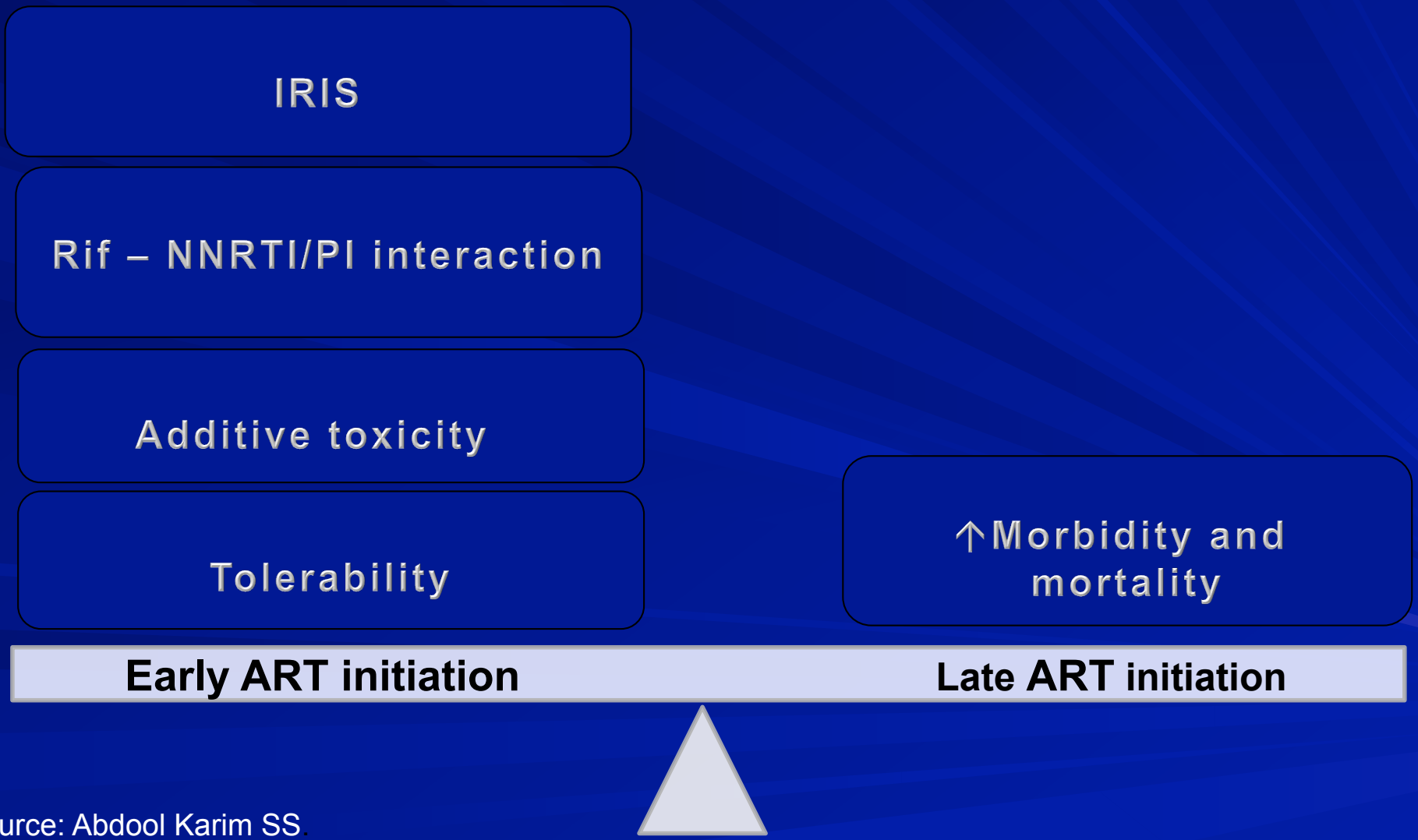
	Combined Integrated Treatment Arms n = 429	Sequential Treatment Arm n = 213
Number of deaths	**25**	**27**
Person-years of follow-up	467	223
Mortality rate (per 100 person-years)	**5.4**	**12.1**

Hazard Ratio: 0.44 (95% CI: 0.25 to 0.79); p = 0.003

56% lower mortality with integrated TB-HIV treatment

Source: Abdool Karim SS, et al. New Engl J Medicine 2010.

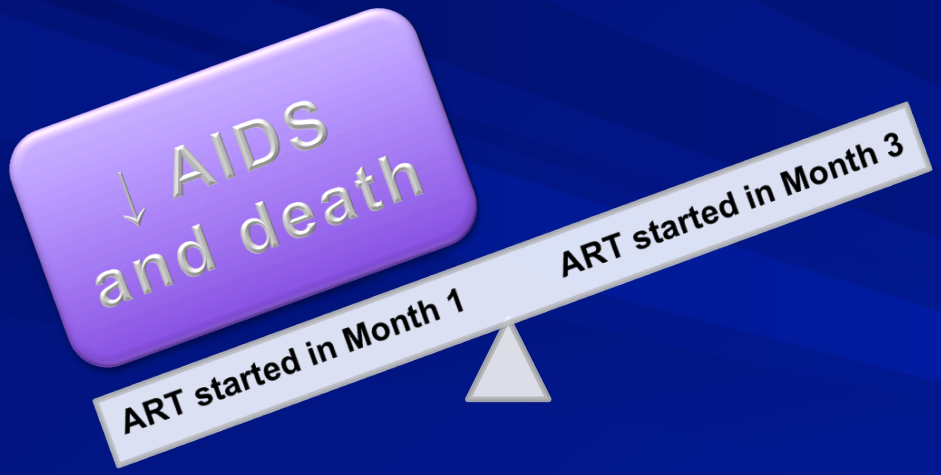
Balancing the risks and benefits of early vs late ART in TB patients



Source: Abdool Karim SS.

Immediate ART for patients with CD4<50 but at month 3 when CD4 > 50

For CD4 count <50 cells/mm^3



ART started in month 1 has:
68% lower AIDS /death rate overshadows
- 5-fold higher risk of IRIS
- ↑ in drug switches

For CD4 ≥50 cells/mm^3

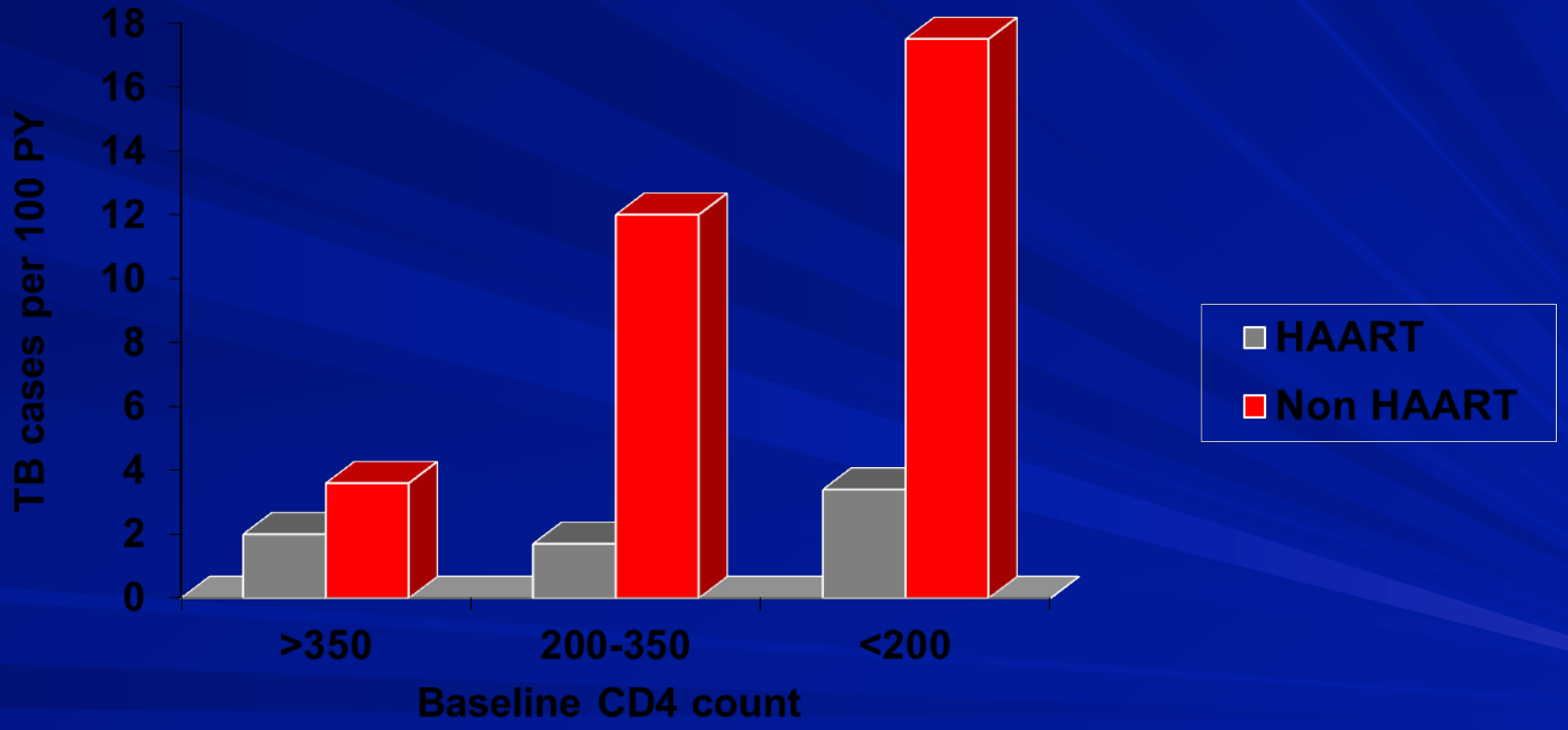
ART started in month 1 has:
No discernable benefit in AIDS /death rate
- 2-fold higher risk of IRIS
- ↑ drug switches

Optimal timing of ART initiation in TB-HIV treatment harmonisation

- Findings support integration of TB and HIV treatment
- Recommend:
  - *Patients with CD4+ counts <50 cells/mm^3:*
    - Early ART initiation as soon as possible after TB treatment initiation (within month 1)
  - *Patients with CD4 counts ≥ 50 cells/mm^3:*
    - ART initiation can be deferred to start of the continuation phase of TB treatment (Month 3)
    - Decision on early or late initiation: use clinical judgement of capacity to manage IRIS & toxicities

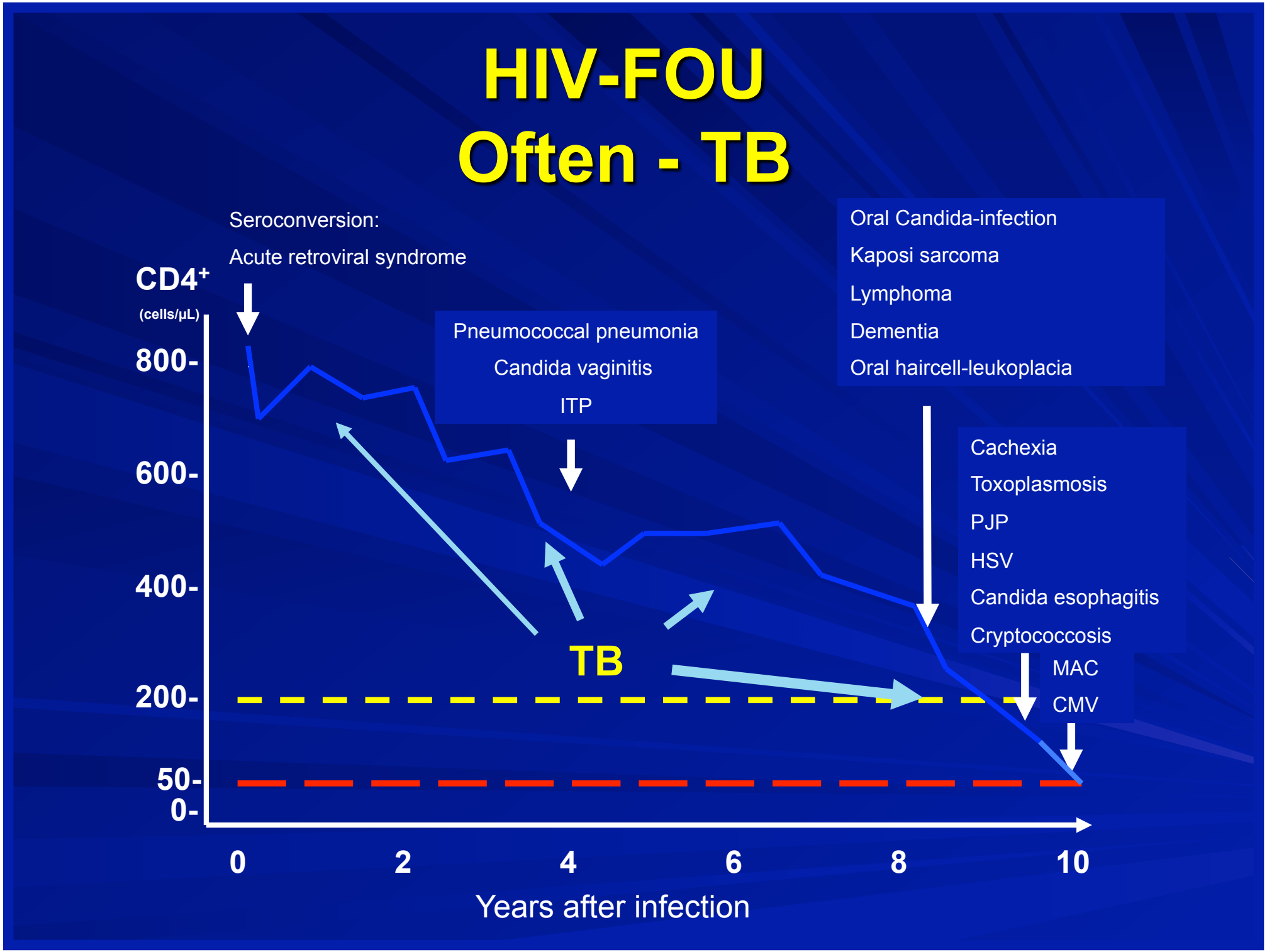
Source: Abdool Karim SS, et al. New Engl J Medicine 2010.

Effect of ART on incidence of TB

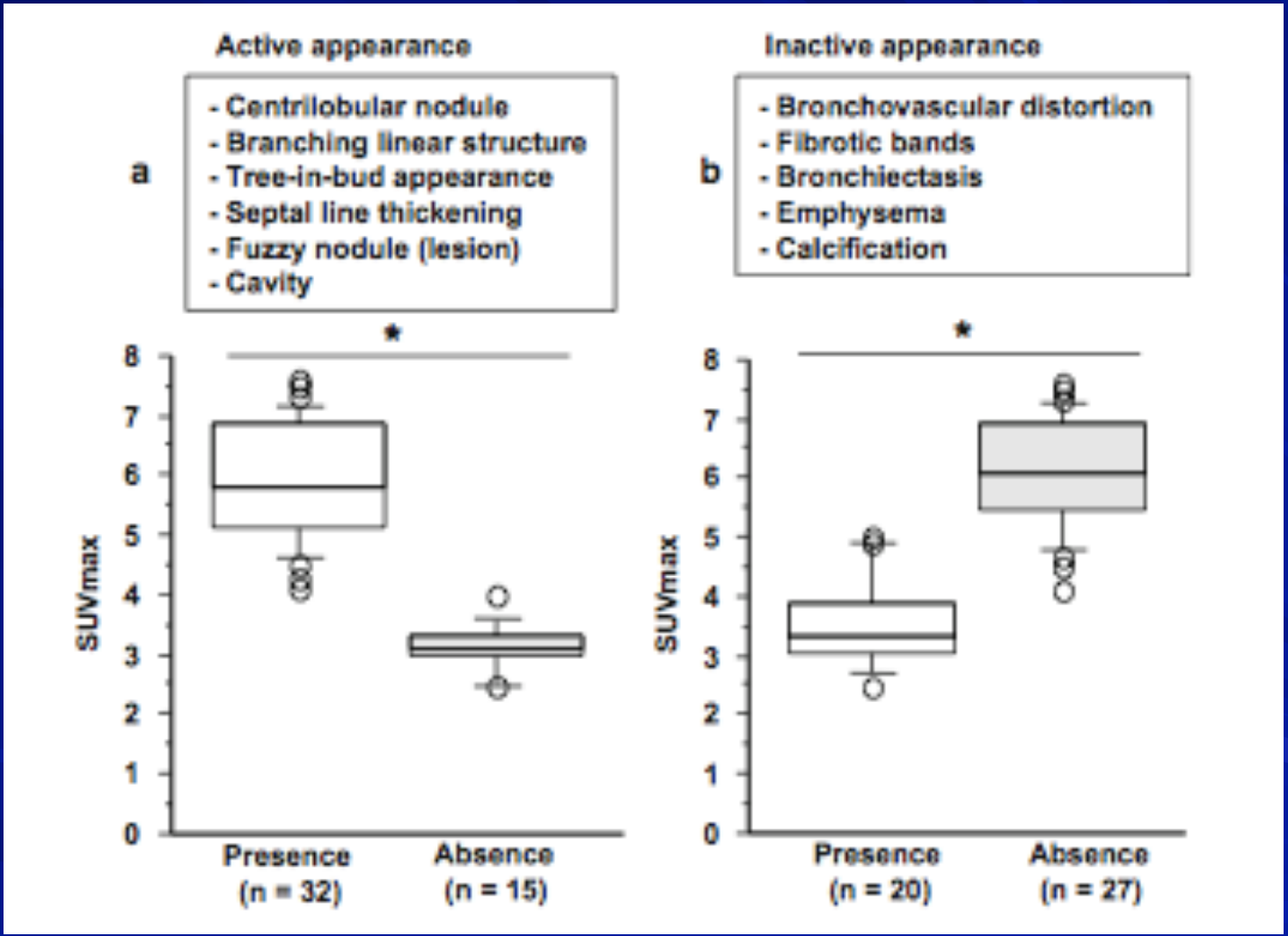


Data from AIDS clinic in Cape Town, South Africa Source: Badri, Lancet 2006

HIV-FOU Often - TB



Active vs Nonactive

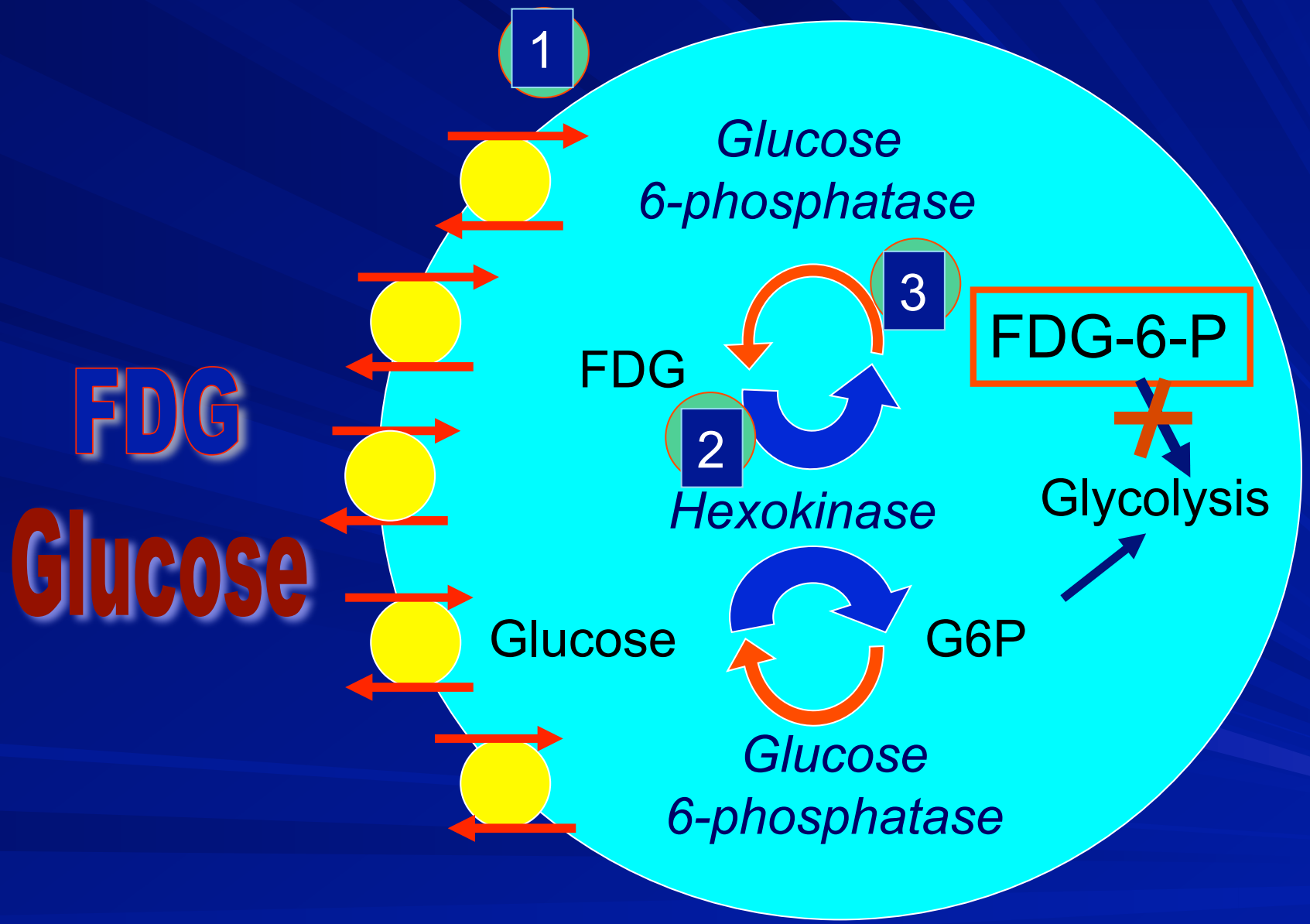


Source: Demura Y, et al. EJNMMI 2009.

Active vs Nonactive

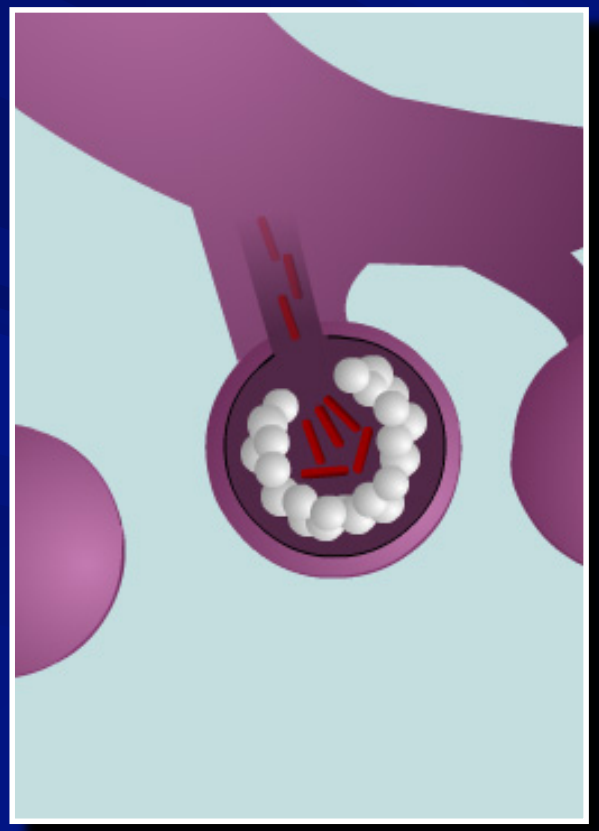
Tree-in-bud pattern

Justification for FDG in Therapy Response



Neoplastic Cells vs Infection/Inflammation

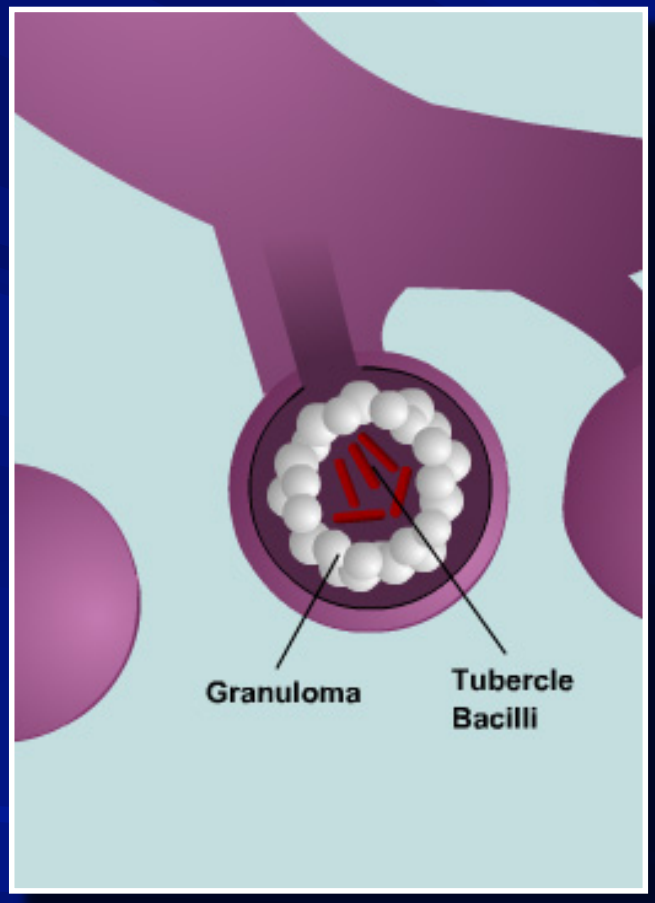
Active TB Disease



Granuloma breaks down and tubercle escape and multiply

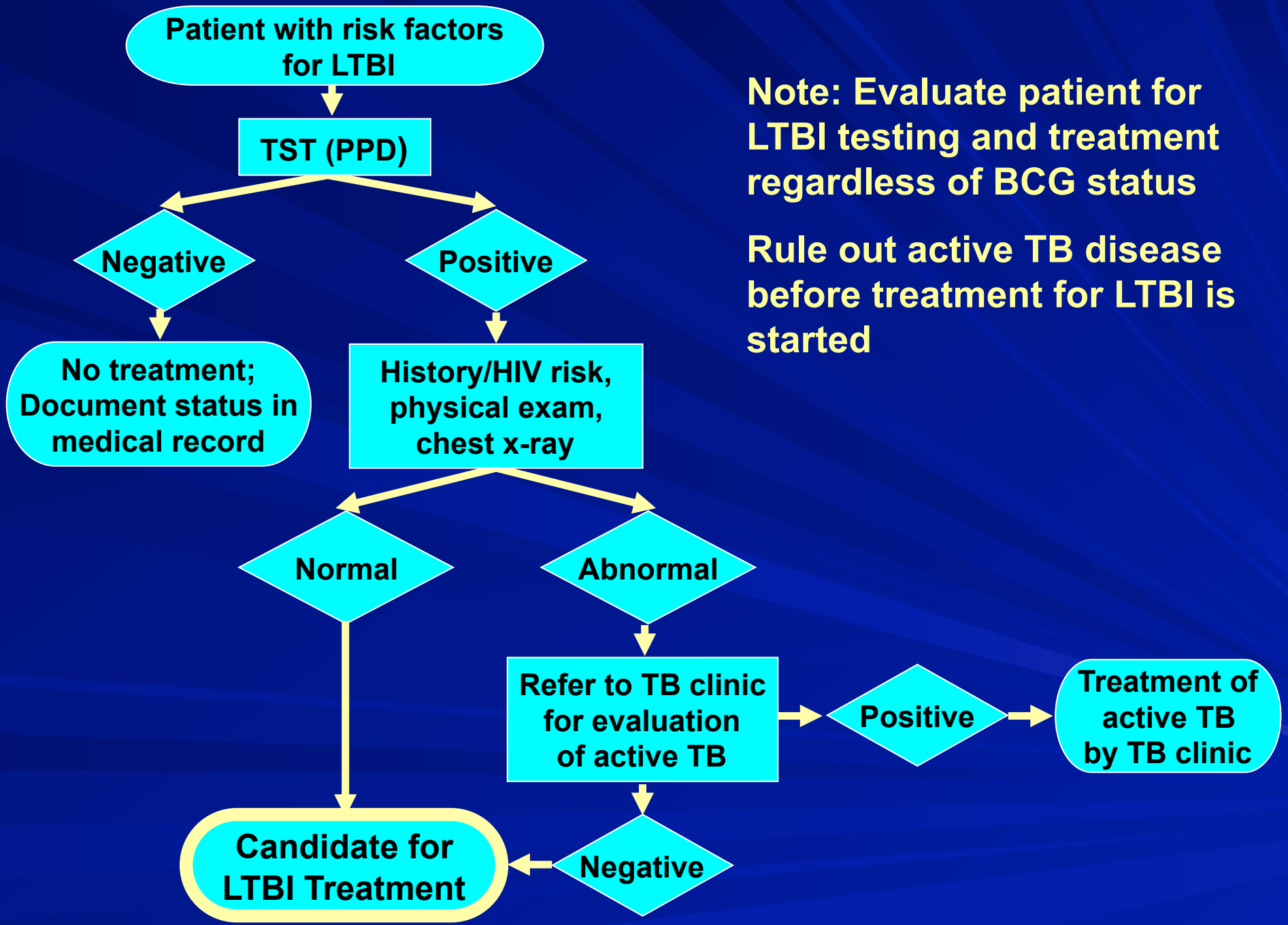
- Tubercle bacilli in the body
- Usually positive skin test
- Infectious (before treatment)
- Symptoms of TB
- Chest x-ray usually abnormal
- Sputum smears and cultures usually positive
- An active “case” of TB

Latent TB Infection (LTBI)



- Tubercle bacilli in the body
- Usually positive skin test
- NOT infectious
- No symptoms
- Normal chest X-ray
- Sputum smears and cultures are negative
- Not a “case” of TB

Flow Chart for Latent TB Infection (LTBI) in Primary Care



Note: Evaluate patient for LTBI testing and treatment regardless of BCG status

Rule out active TB disease before treatment for LTBI is started

Current Treatment for LTBI

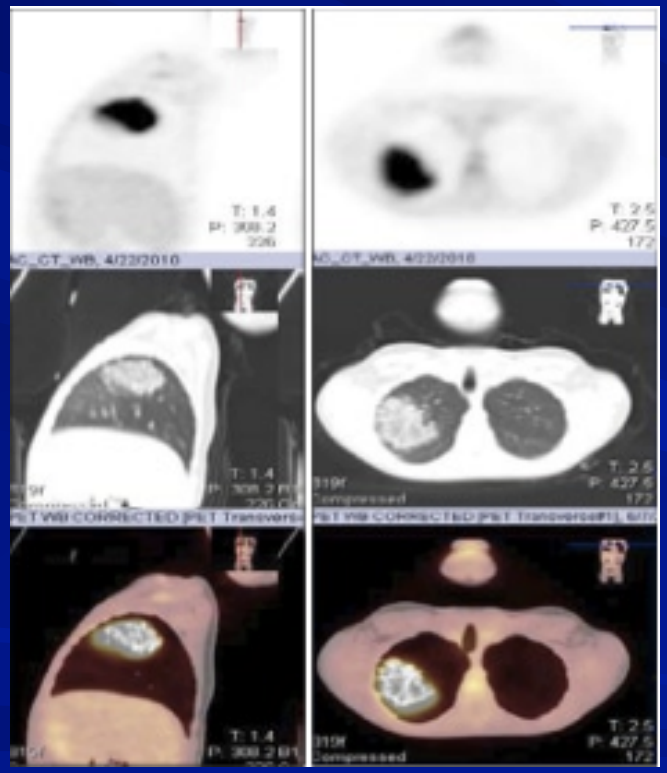
Preferred Regimen

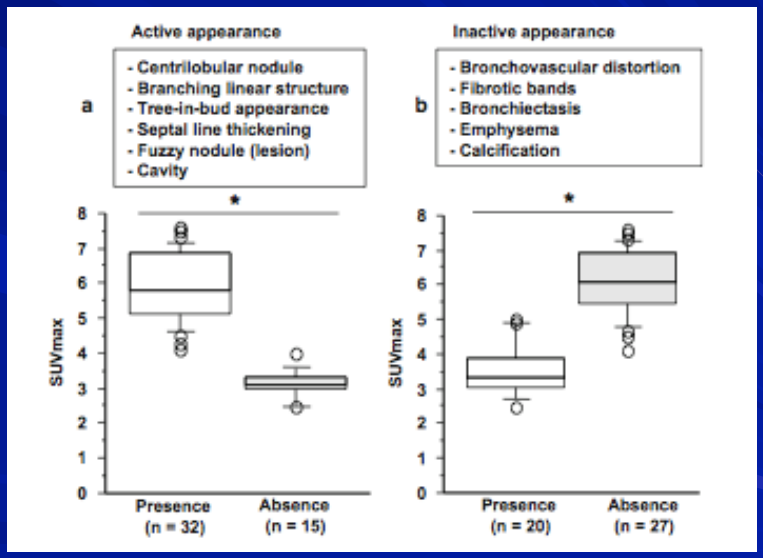
Drug	Dose	Frequency	Duration
Isoniazid (INH)	300 mg	Daily	9 months

A minimum of 270 doses must be administered within 12 months

Original Article

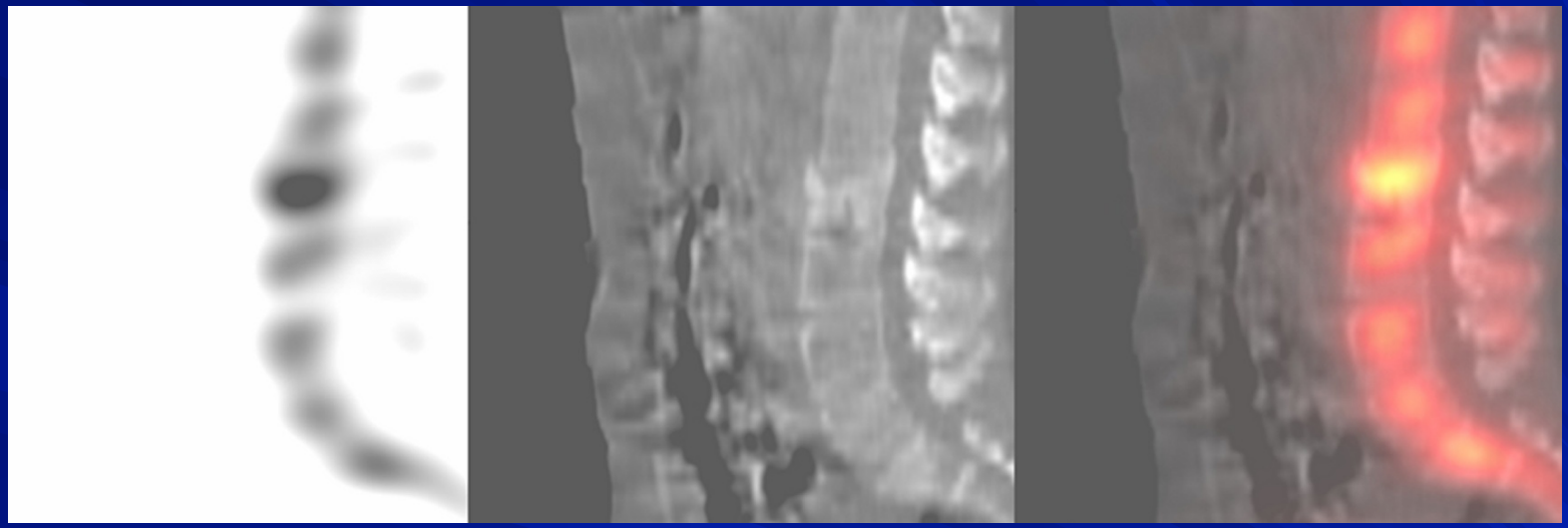
Positron emission tomography in the prediction of inflammation in children with human immunodeficiency virus related bronchiectasis



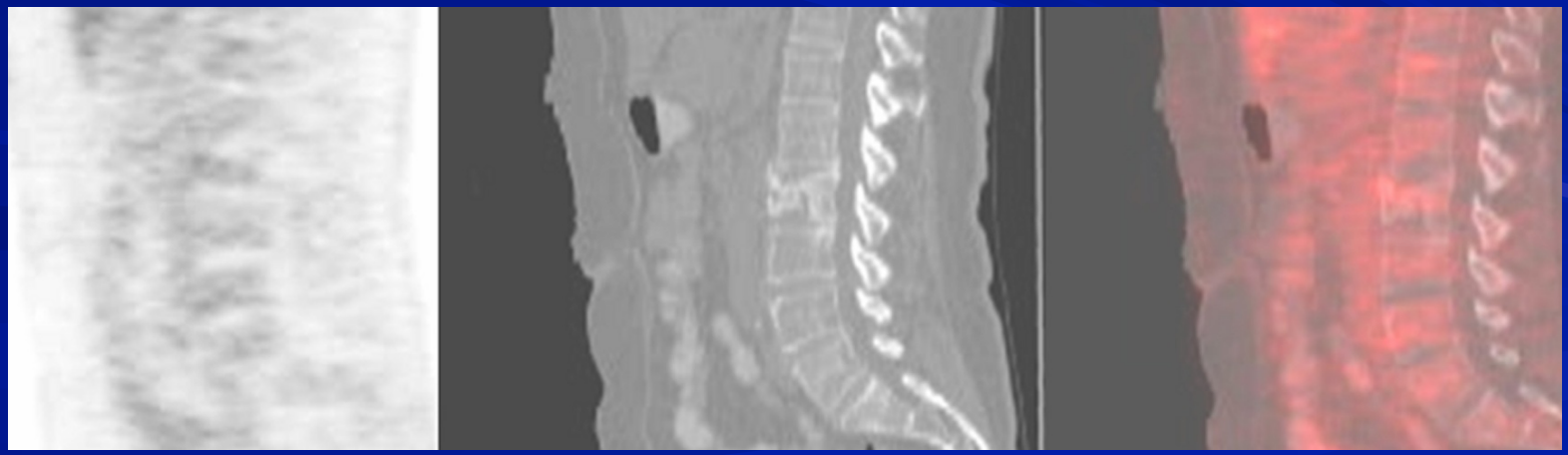


L-3 Compression Fracture
(3 months old)

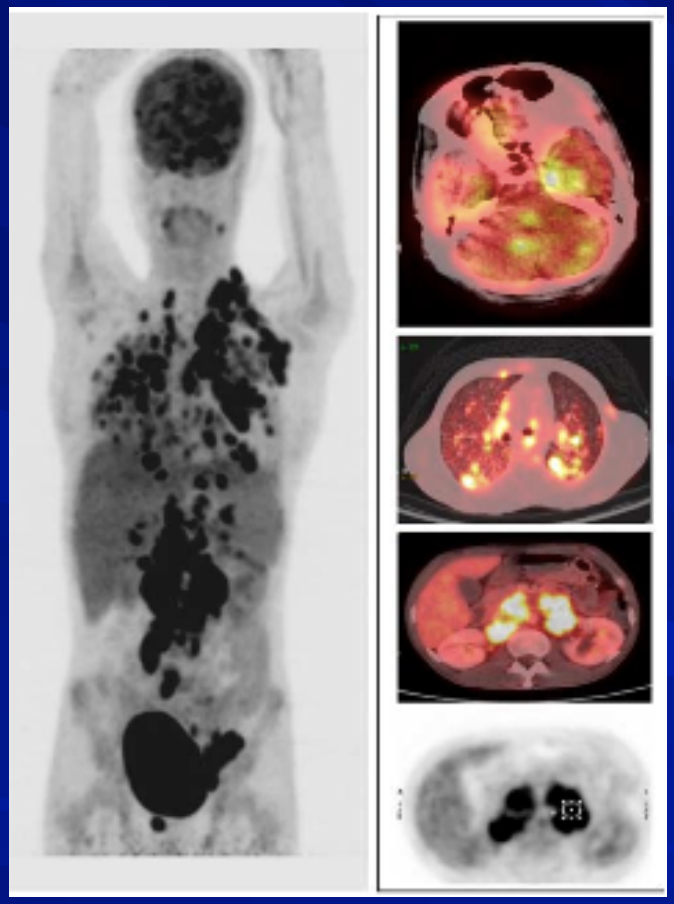
SPECT/CT



PET/CT

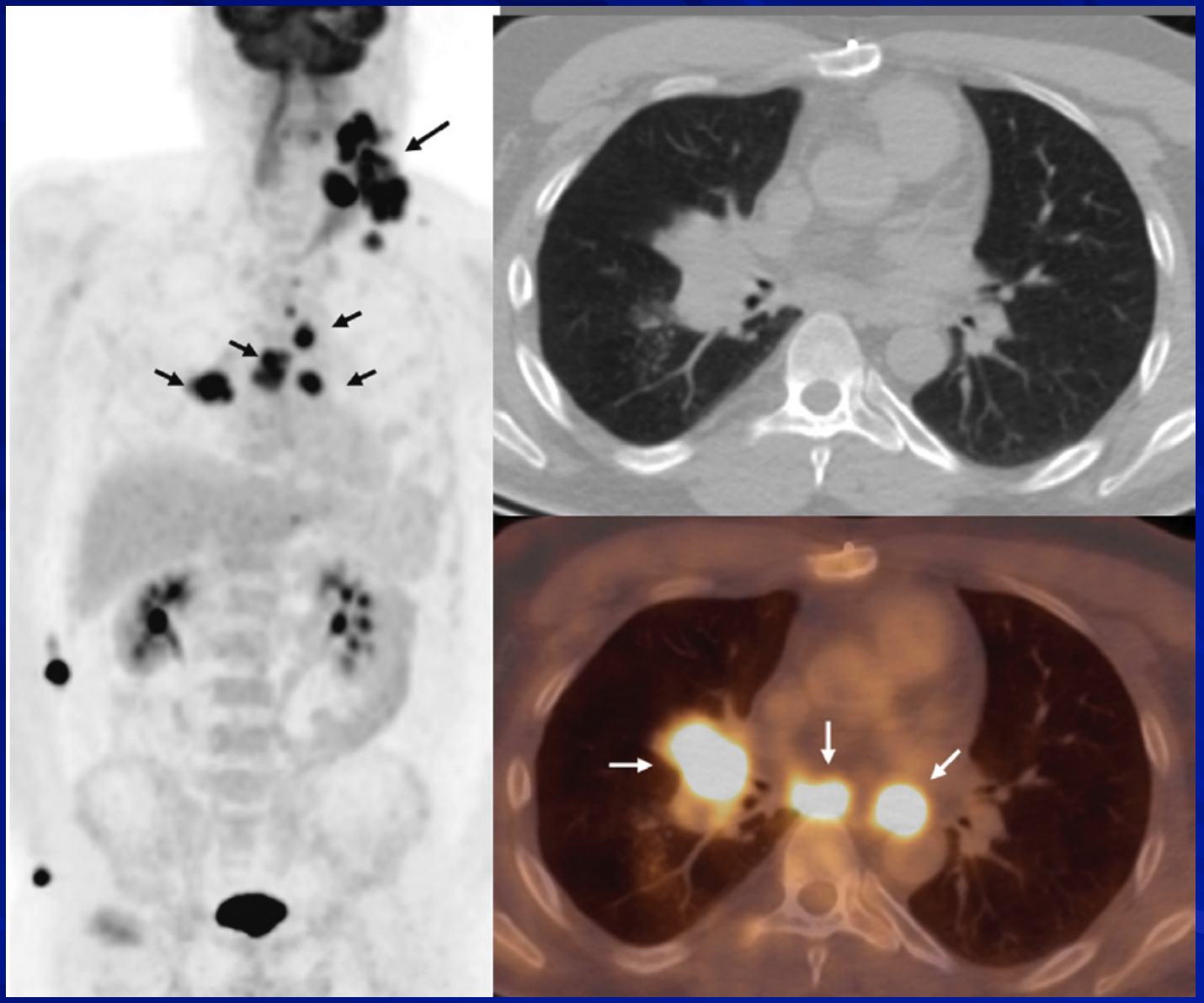


Disseminated tuberculosis infection: a ‘super’ 18F-FDG PET/CT appearance



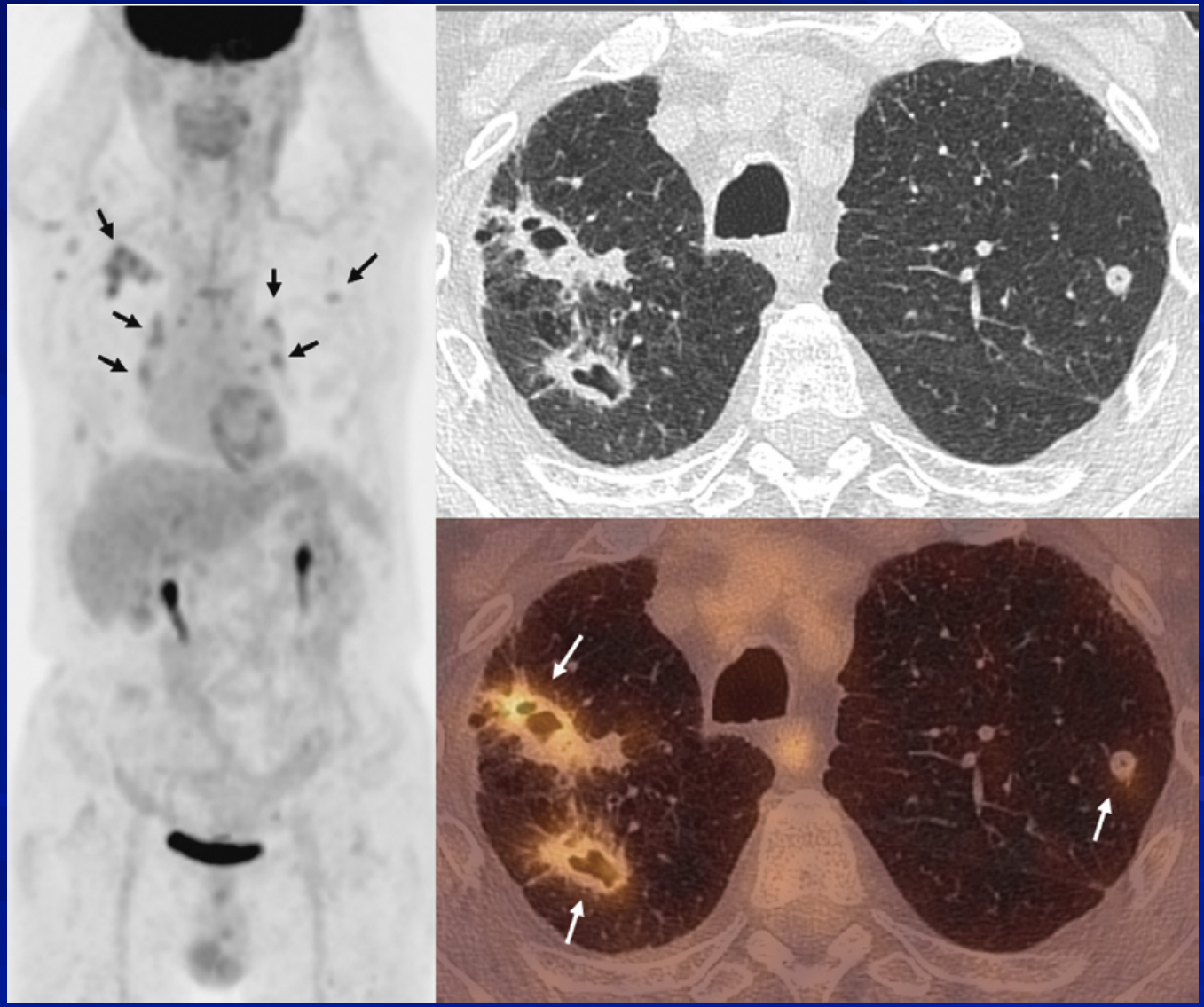
The case illustrates the usefulness of 18F-FDG PET/CT in mapping active tuberculous lesions which can be used for baseline study

Nordin et al. EJNMMI. 2009

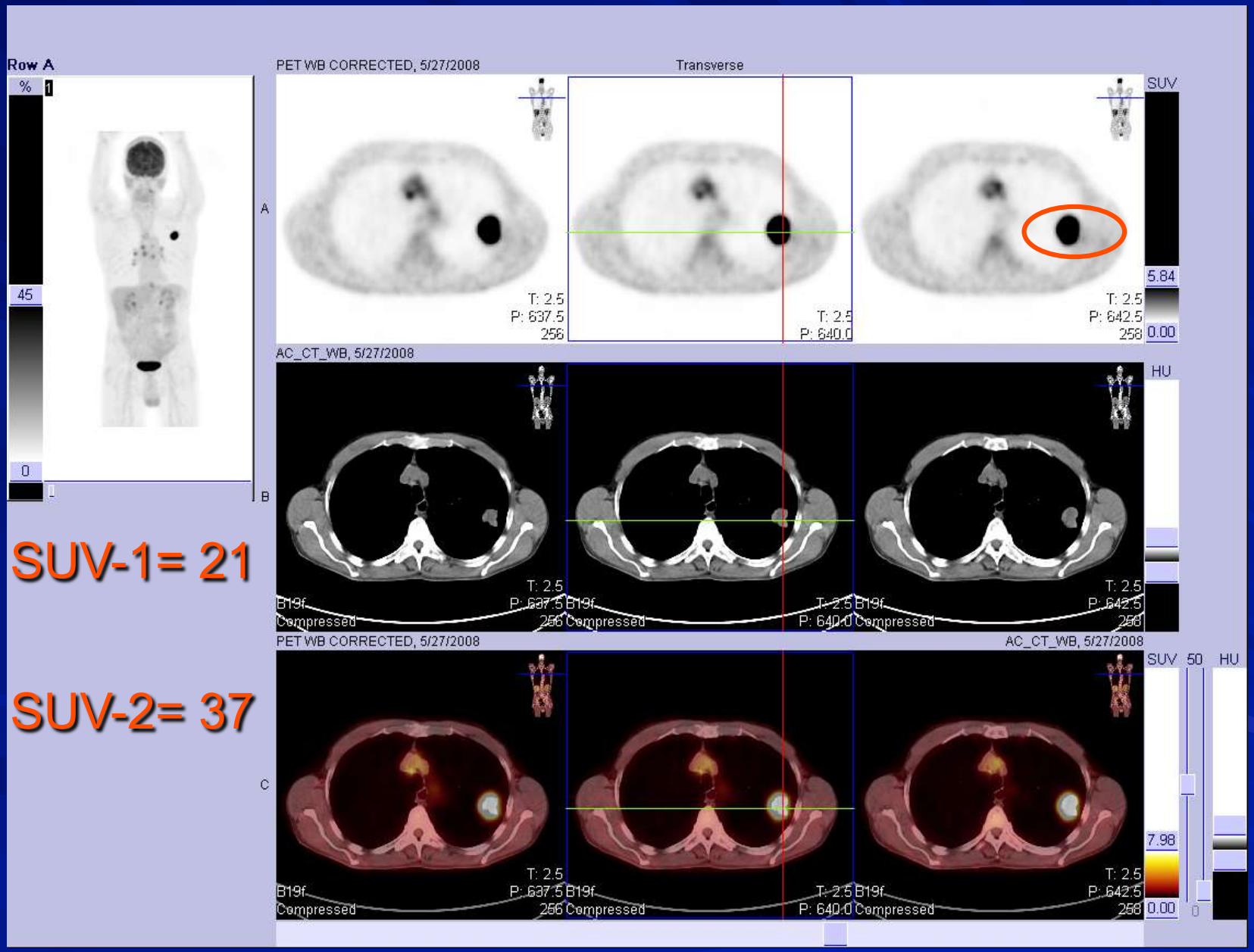


Lymphoma vs TB
Especially in Upcoming Countries

Cancer vs TB: Pattern



TB or Cancer?


Row A
PET WB CORRECTED, 5/27/2008
Transverse
SUV
5.84
0.00
AC_CT_WB, 5/27/2008
HU
PET WB CORRECTED, 5/27/2008
AC_CT_WB, 5/27/2008
SUV 50 HU
7.98
0.00
SUV-1= 21
SUV-2= 37

Dual time-point FDG PET/CT for differentiating benign from malignant solitary pulmonary nodules in a TB endemic area

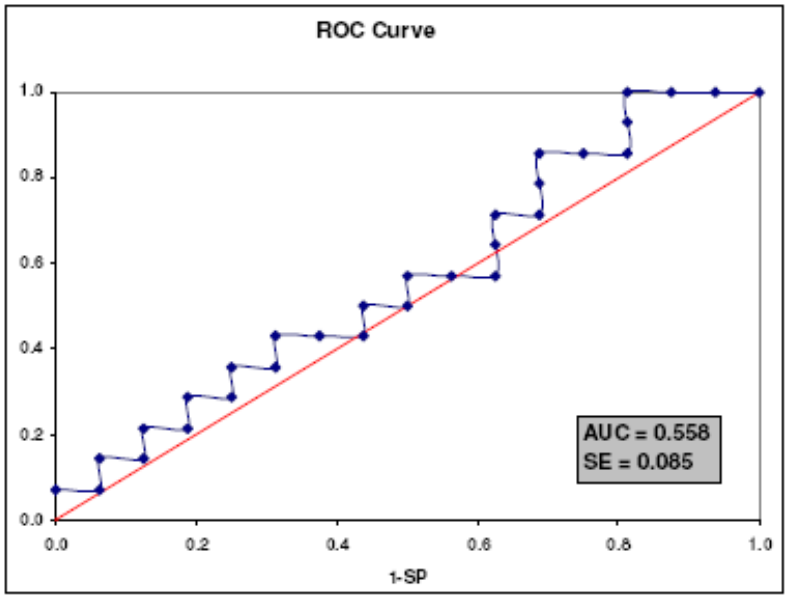


Fig. 2. ROC curve (AUC = area under the curve; SE = standard error; S = sensitivity; SP = specificity).

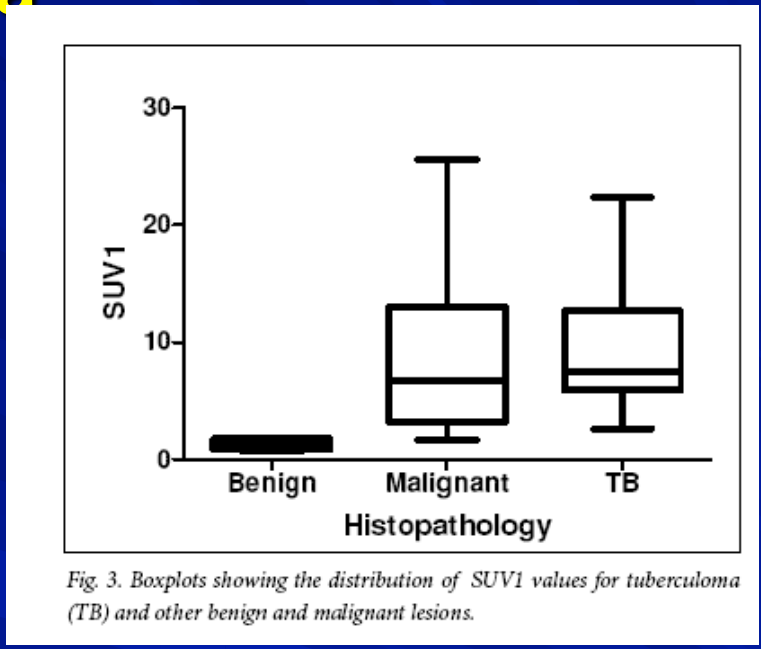
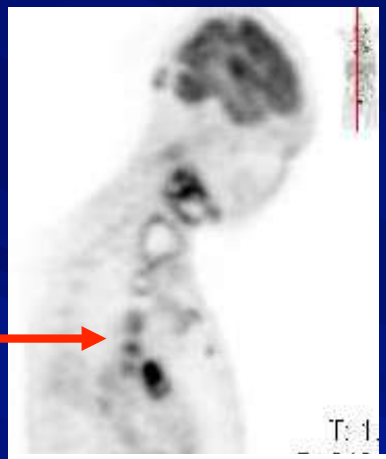


Fig. 3. Boxplots showing the distribution of SUV1 values for tuberculoma (TB) and other benign and malignant lesions.

"Hence FDG-PET is unable to distinguish malignancy from TB and therefore cannot be reliably used as a tool to reduce futile biopsy/ thoracotomy in these patients."

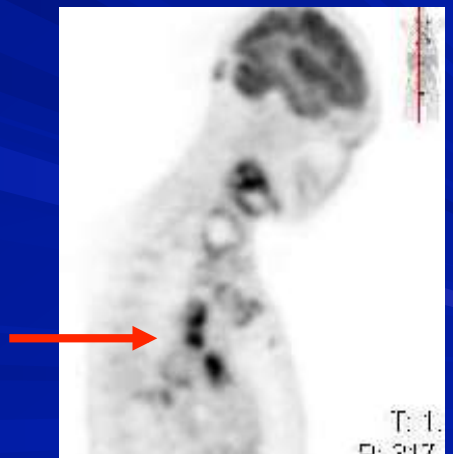
Sathekge et al. SAMJ. 2010

Triple Phase in TB



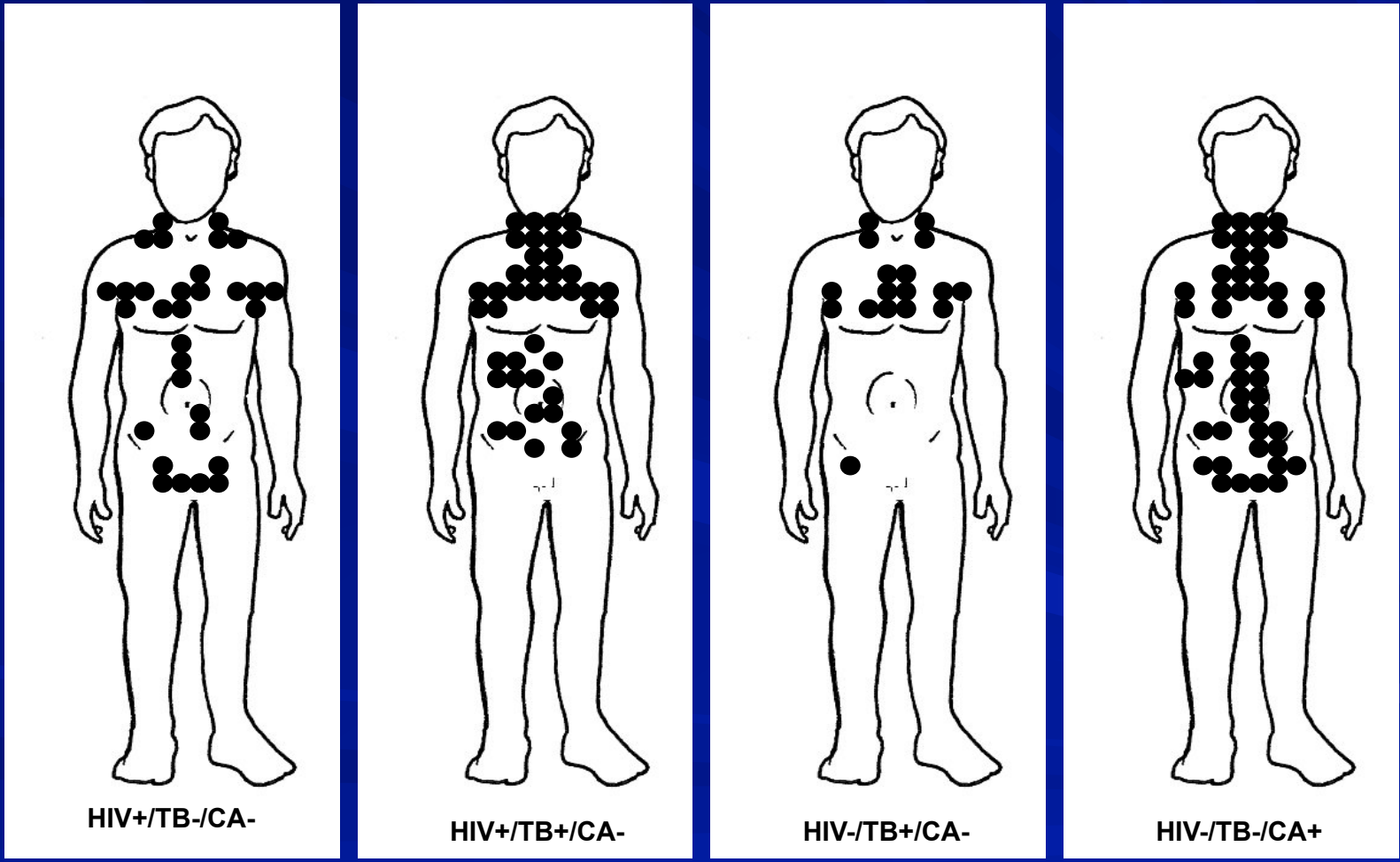
60 min p.i

120 min p.i



240 min p.i

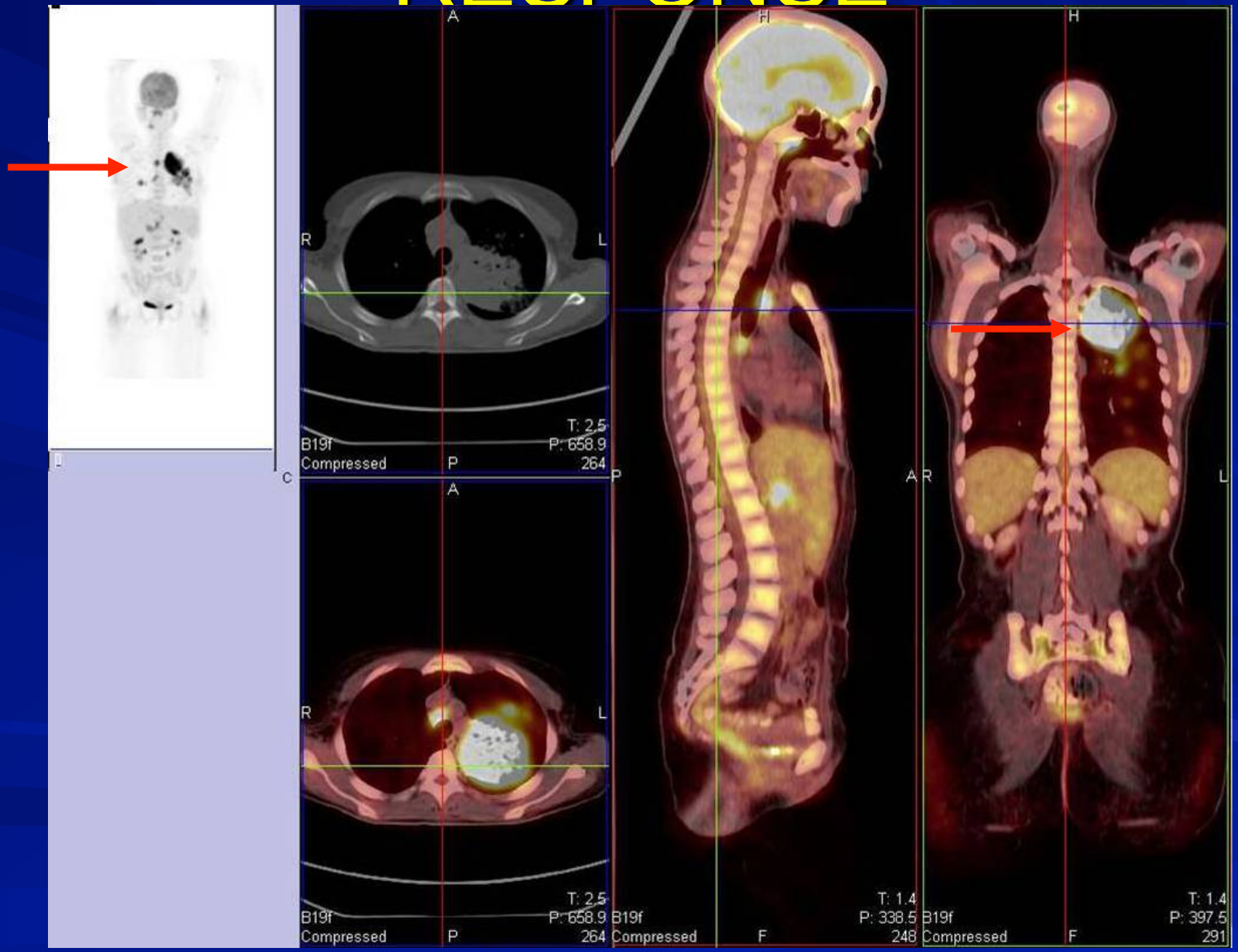
FDG UPTAKE IN LYMPH NODES OF HIV+ AND TUBERCULOSIS PATIENTS: IMPLICATIONS FOR CANCER STAGING



Sathekge et al., Q J Nucl Med

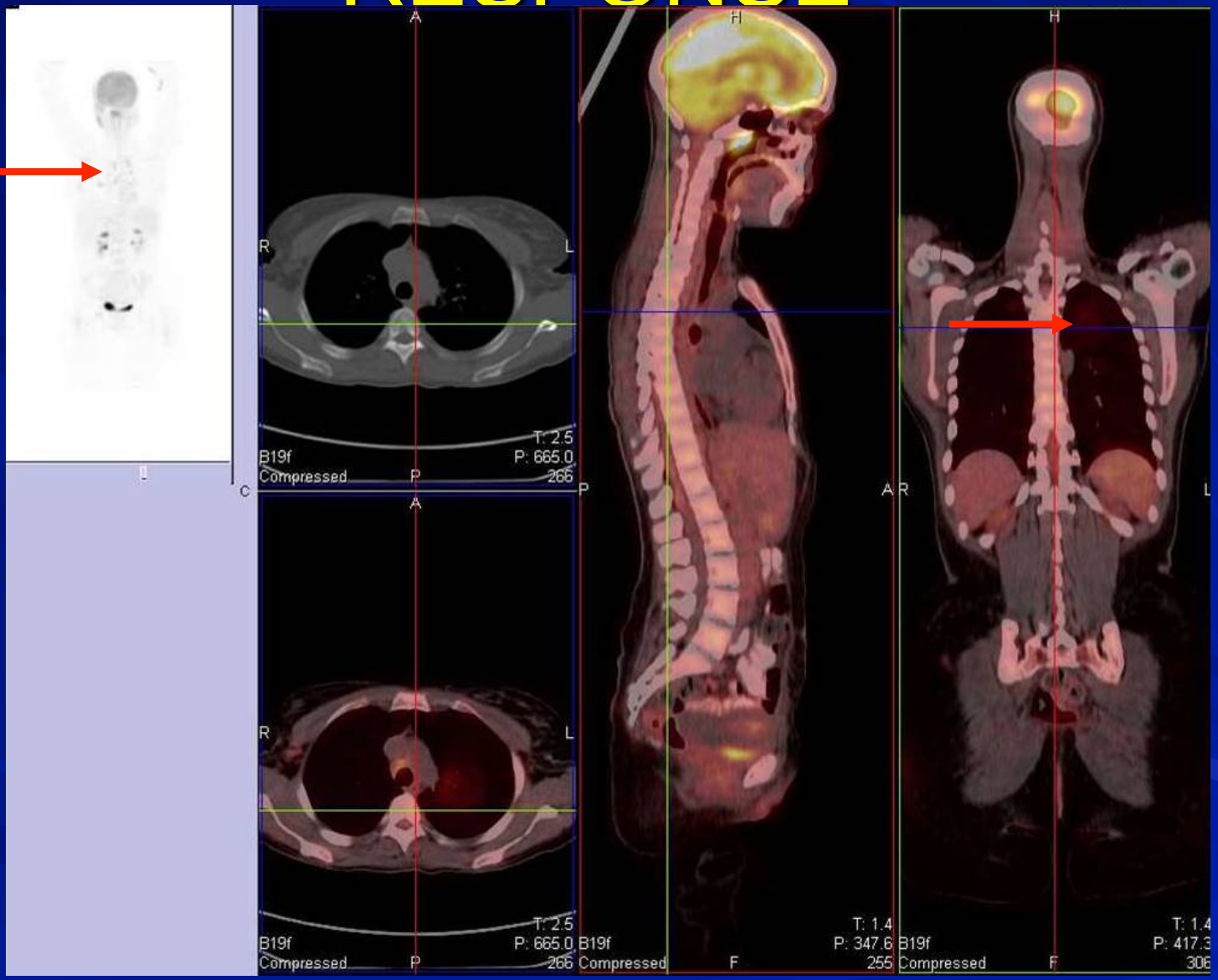
Duration of TB Treatment

TB: MONITORING THERAPY RESPONSE



BEFORE THERAPY

TB: MONITORING THERAPY RESPONSE



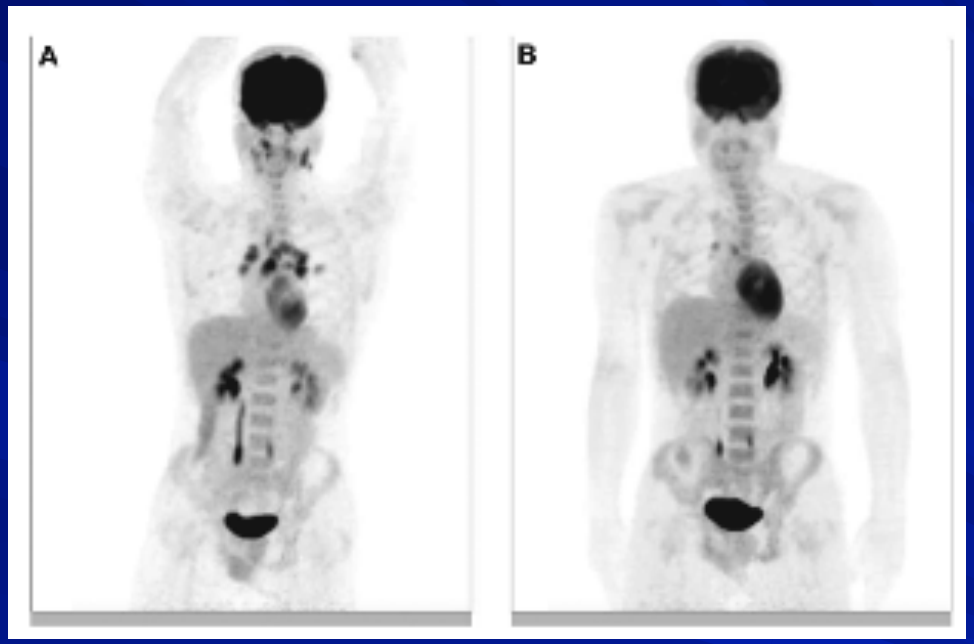
AFTER THERAPY

F-18 FDG PET/CT Studies in Patients Receiving Treatment for Tuberculosis: A Six Month Follow-Up Study

- After 1 month ?
- After 6 months;
- FDG uptake normalised in only 5/31
- Improved in the majority of cases (65%)
- 4 cases with a mixed pattern.
- 3 patients had residual LN uptake.

A. Ellmann, A. Du Plessis, L. Nolan, D. Kriel, G. Walzl, J. Warwick;
Stellenbosch University, Cape Town, SOUTH AFRICA.

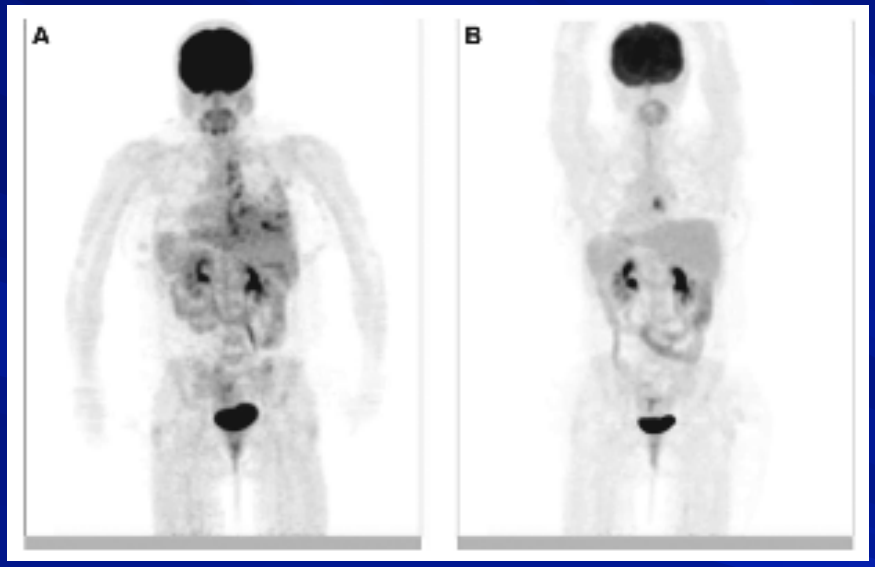
18F-FDG PET/CT in tuberculosis: an early non-invasive marker of therapeutic response



18F-FDG PET-CT whole-body maximum intensity projection in an 18-year-old man. A. Before anti-tuberculosis treatment, showing multiple lesions of intense FDG uptake in the neck and the thorax. B. All pathological foci have clearly de- creased after 1 month of anti-tuberculosis treatment. 18F-FDG PET/CT = 18F-fluoro- deoxyglucose positron emission tomography/ computed tomography.

Martinez et al. INT J TUBERC LUNG DIS 2012 16:1180–1185

18F-FDG PET/CT in tuberculosis: an early non-invasive marker of therapeutic response



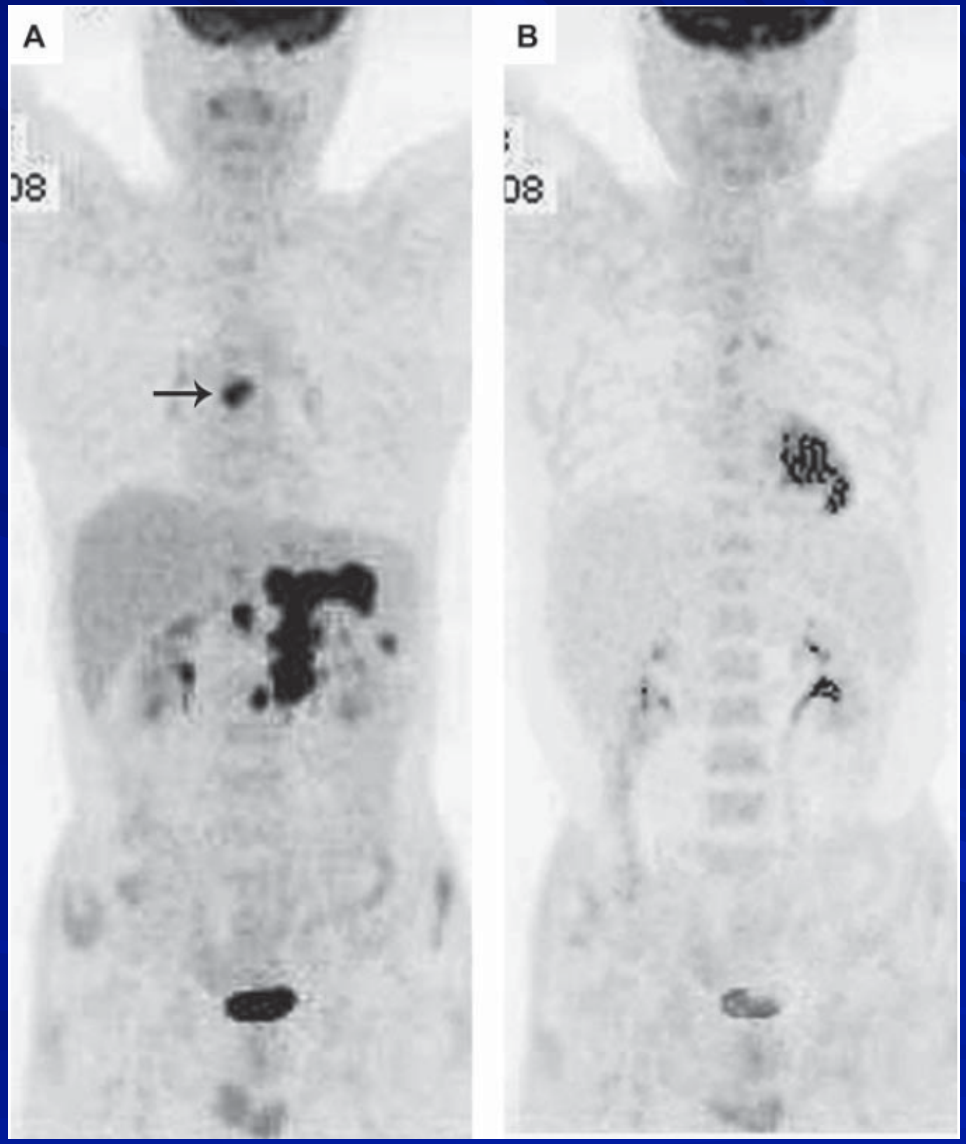
18F-FDG PET-CT whole-body maximum intensity projection in a 35-year- old woman with multidrug-resistant tuberculosis before (A) and after (B) 1 month of anti-tuberculosis treatment. Regression of pulmonary and lymph node pathological foci were observed at the first PET-CT. 18F-FDG PET/CT = 18F-fluorodeoxyglucose positron emission tomography/computed tomography.

Table 1 Characteristics of the 21 patients at M0 and M1

Patient	Sex	Age years	Past history of TB	Quanti-FERON test IU/ml	Diagnosis of TB	Site of TB on PETscan	SUV_{max} M0	SUV_{max} M1	% variation SUV_{max}
1	Female	30	No	>10	Microscopy and culture	Pulmonary, lymph node (mediastinal, portal-hepatic)	14.9	9.2	−38
2	Female	32	No	>10	Histology	Lymph node (para-aortic), ovarian	15.5	5.5	−64
3*	Male	62	Yes	None	Histology	Pulmonary, lymph node (mediastinal, hilar)	5.3	5.7	+7
4	Male	47	No	1.41	Histology	Lymph node (para-aortic, pelvic)	5.7	4	−30
5	Female	84	No	0.35	Histology	Bone	11.1	5.3	−52
6	Male	71	No	None	Histology	Lymph node (cervical, axillary, mediastinal, hilar)	10.5	3.8	−64
7	Male	48	No	0.35	Histology	Pulmonary, lymph node (cervical, mediastinal, hilar, pelvic)	11.3	8.2	−27
8	Male	21	No	>10	Clinical	Lymph node (cervical, pelvic)	10.6	6.1	−41
9	Female	36	No	>10	Histology	Pulmonary, lymph node (mediastinal, hilar)	16	11.9	−26
10	Male	18	No	None	Microscopy and culture	Pulmonary, lymph node (cervical, mediastinal, hilar)	8.6	4.8	−44
11	Male	37	Yes	>10	Microscopy and culture	Pulmonary, lymph node (mediastinal, hilar)	6.8	6	−12
12†	Female	30	No	5.08	Microscopy and culture	Pulmonary, lymph node (mediastinal)	9.6	13.4	+40
13	Female	35	Yes	>10	Microscopy and culture	Pulmonary	3.1	2.9	−7
14	Female	35	Yes	>10	Clinical	Lymph node (axillary, mediastinal, pelvic)	5.6	2.9	−48
15	Female	74	No	>10	Clinical	Lymph node (para-aortic, pelvic)	14.9	3	−80
16	Female	48	No	>10	Microscopy and culture	Lymph node (cervical, axillary, mediastinal)	12.3	11.6	−6
17	Female	36	No	>10	Histology	Ovarian	5.9	1	−83
18	Female	30	No	>10	Clinical	Pulmonary, lymph node (axillary, mediastinal, portal-hepatic)	5.5	5.4	−2
19	Female	35	No	5.11	Microscopy and culture	Pulmonary, lymph node (hilar)	6.4	1	−84
20	Female	44	No	>10	Histology	Lymph node (cervical, axillary, mediastinal), ovarian	7.2	5	−31
21	Female	80	Yes	2.39	Microscopy and culture	Pulmonary, lymph node (mediastinal, hilar, portal-hepatic)	7.1	5	−30

*Patient with lymphoma.
†Patient with multidrug-resistant tuberculosis.
M0 = Month 0, before commencement of anti-tuberculosis treatment; M1 = first month after initiating anti-tuberculosis treatment; TB = tuberculosis; SUV_{max} = maximum standardised uptake value.

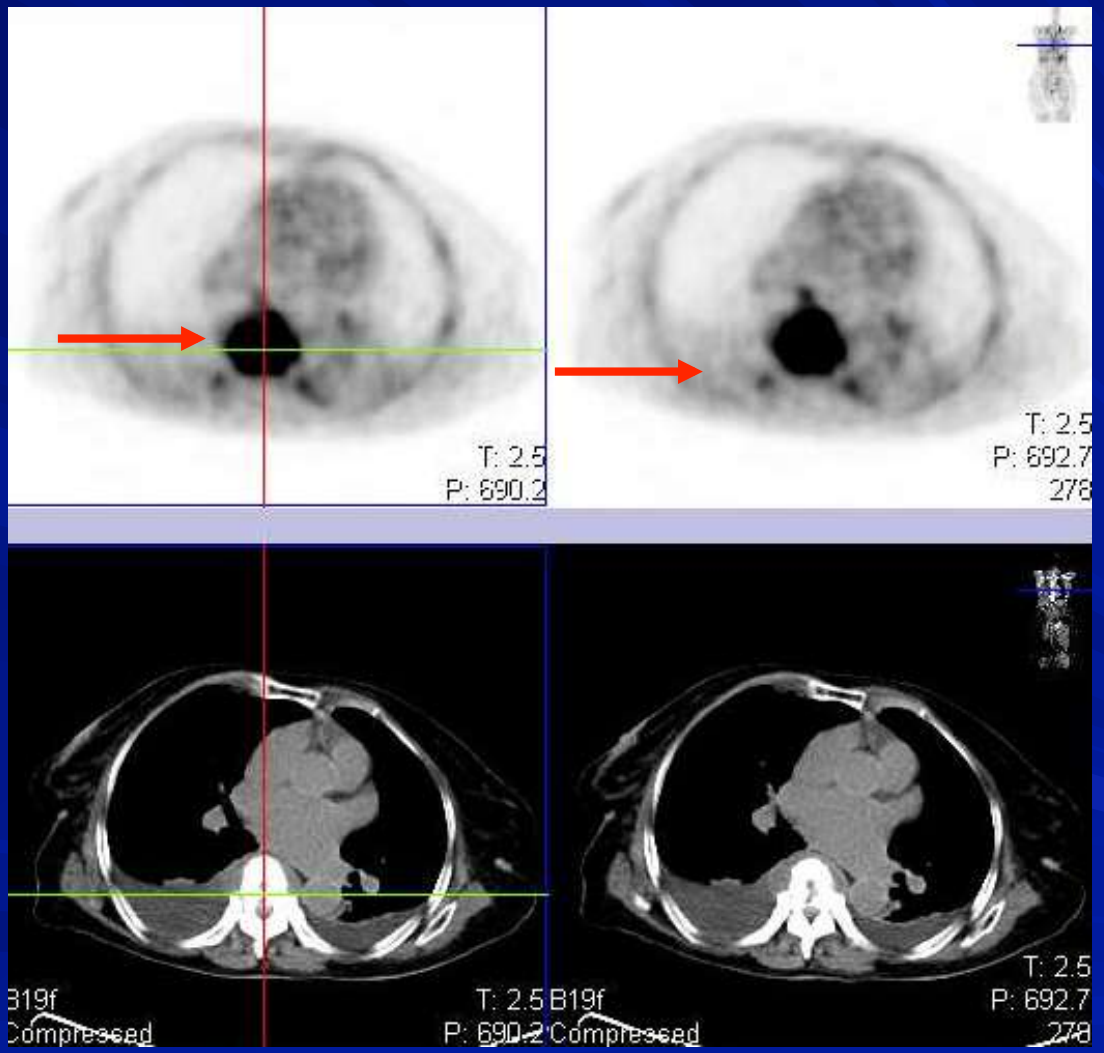
Treat for how long?



6m vs 9m vs 12m

Extrapulmonary TB & Rx

FDG PET best for EPTB



Negative Effusion in TB Spine

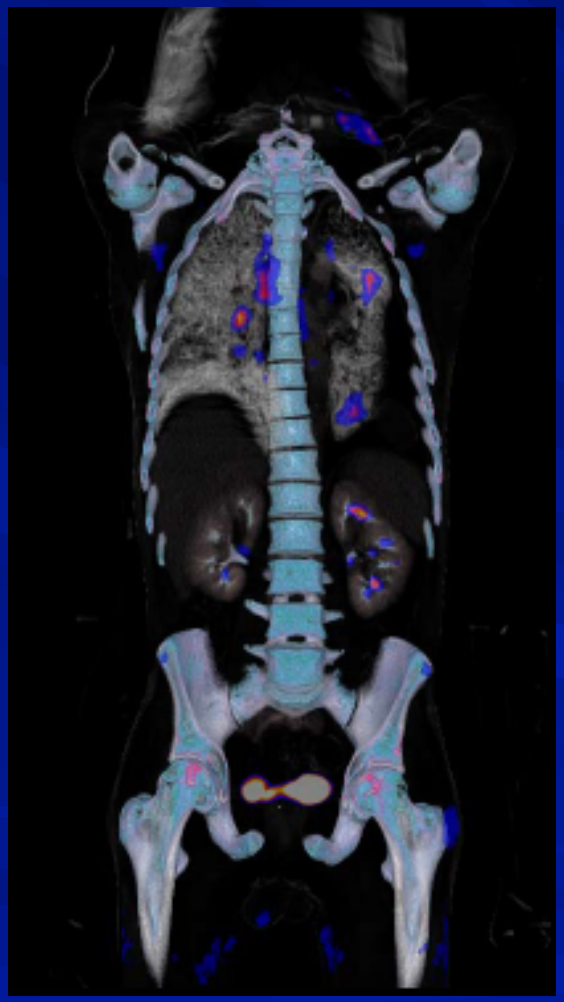
Source: Sathekge M, et al. NuKlear Medizin 2010.

FDG PET IMAGING IN EXTRAPULMONARY TB TREATMENT

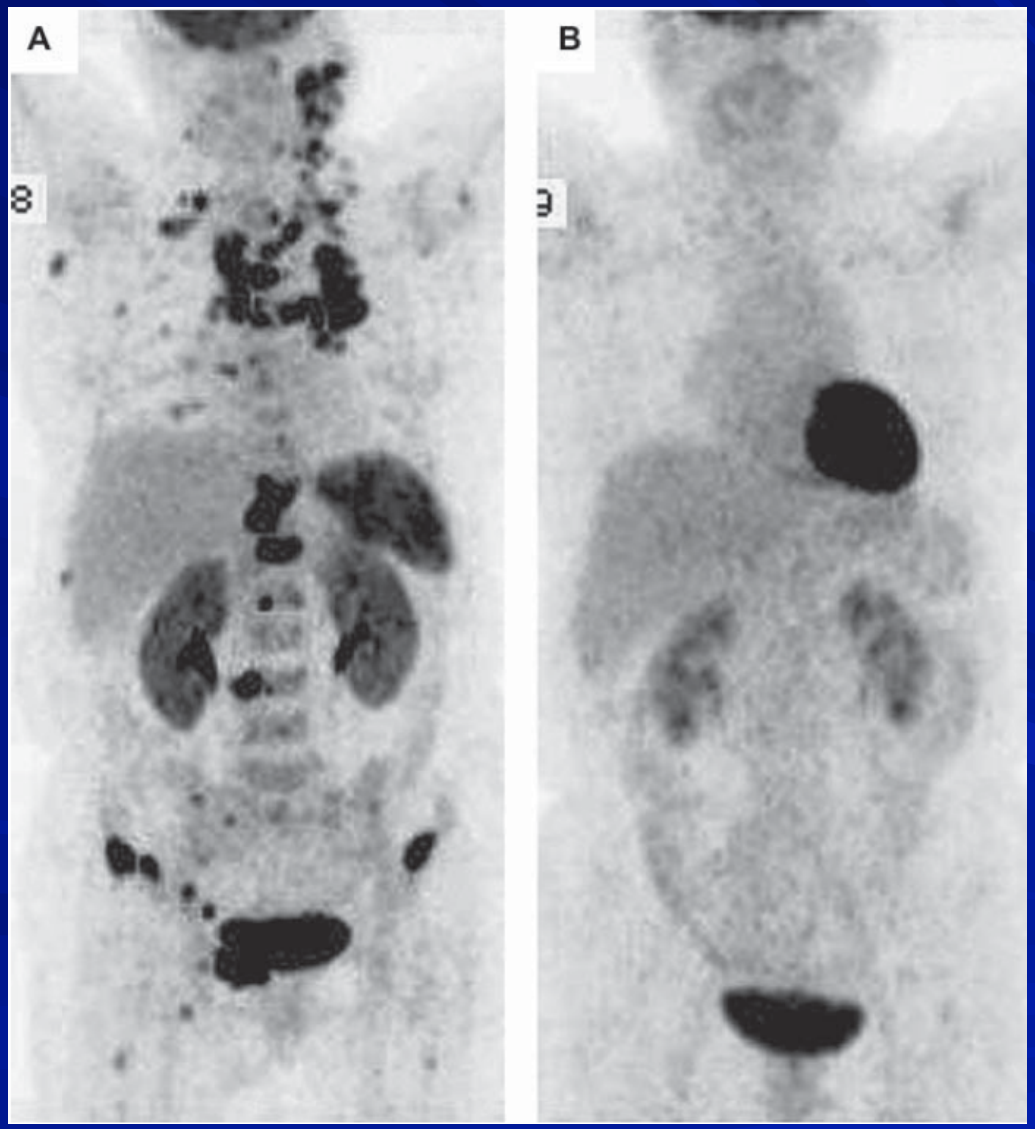
- PET vs CT
  - PET demonstrated 50% more lymph nodes than CT
  - PET & CT were equal for lung
  - PET was inferior to CT for pleural involvement

Sathekge et al., Nuklearmedizin 2010

TB lymphadenitis



Reliable Monitor for EPTB



Source: Tain G, et al. Acta Radiologica 2010.

Prognosis
Responder vs Nonresponder

MDR TB

- > 450,000 cases identified every year
- 150,000 deaths/year from a disease that could and should be curable
- **MDR TB is MAN MADE**
  - -Mismanagement of Fully susceptibleTB or INH resistant TB
  - -Poor quality of drugs
  - -Drugs shortages→ erratic supply
  - - Patients not taking drugs correctly
- **XDR TB** results from failure to properly manage MDR TB

MDR TB Management

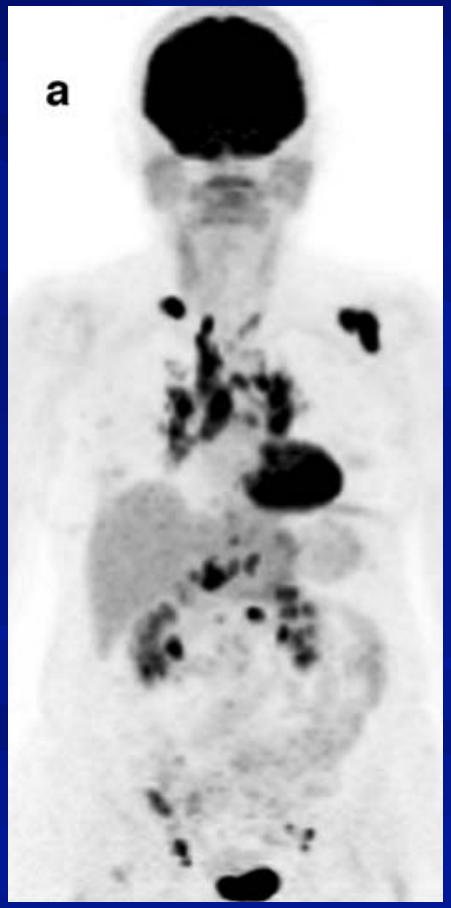
- Treatment should be individualized and based on drug susceptibility studies
- Patient to receive all the drugs to which the infecting M.TB is susceptible. When available drugs need to be given iv
- If there is past history of TB and drugs previously received are known, give at least 3 drugs (bactericidal) never used before
- If drug susceptibility still unknown give at least 3 bactericidal drugs, but no Rifampin or Isoniazid
- Treatment for 2 years following bacteriologic conversion
- DOT mandatory
- Well structured and strict follow-up
- Surgery in selected cases

Management of MDR TB

- Prolonged Hospitalization
- Significant psycho-social issues
- Requires increased number of drugs
- Poor tolerance to the drugs
- Increased drug- associated toxicity
- Long term Follow-Up is necessary
- Increased health care costs

Biopsy proven multiple site sarcoidosis in one patient: before and after corticosteroid treatment

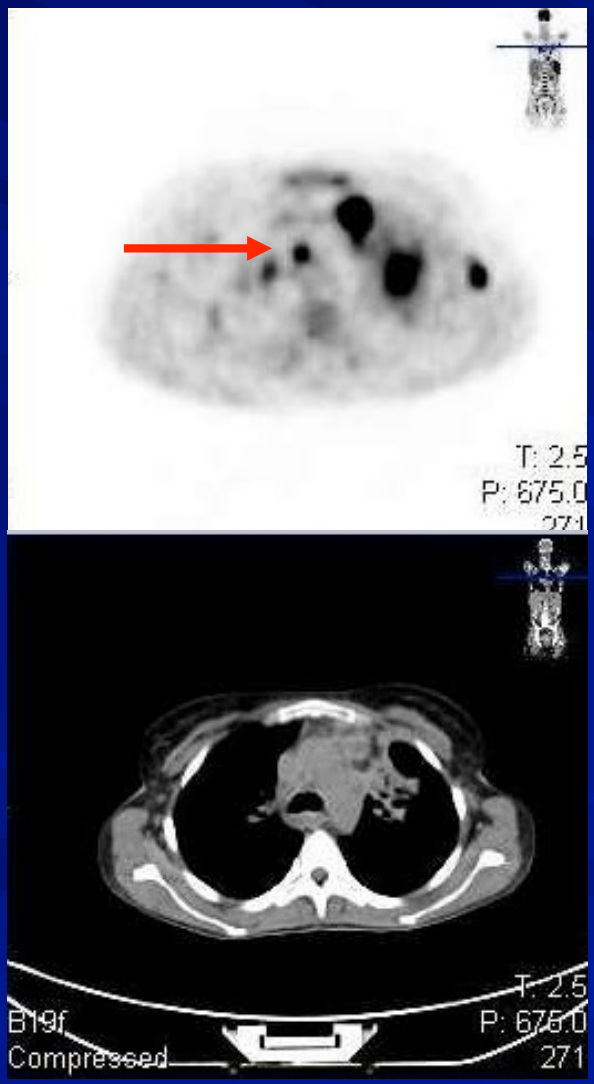
FDG-PET baseline



FDG-PET after CS treatment

Braun, EJNM 2008;35: 1537-1543

MDR TB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Compressed
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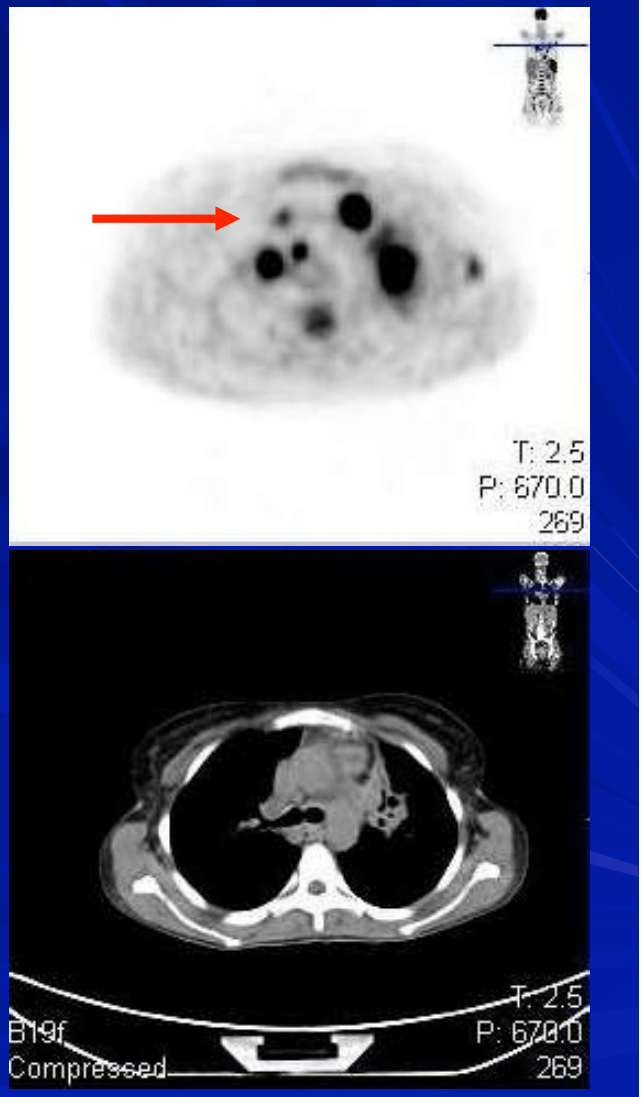
P: 675.0
271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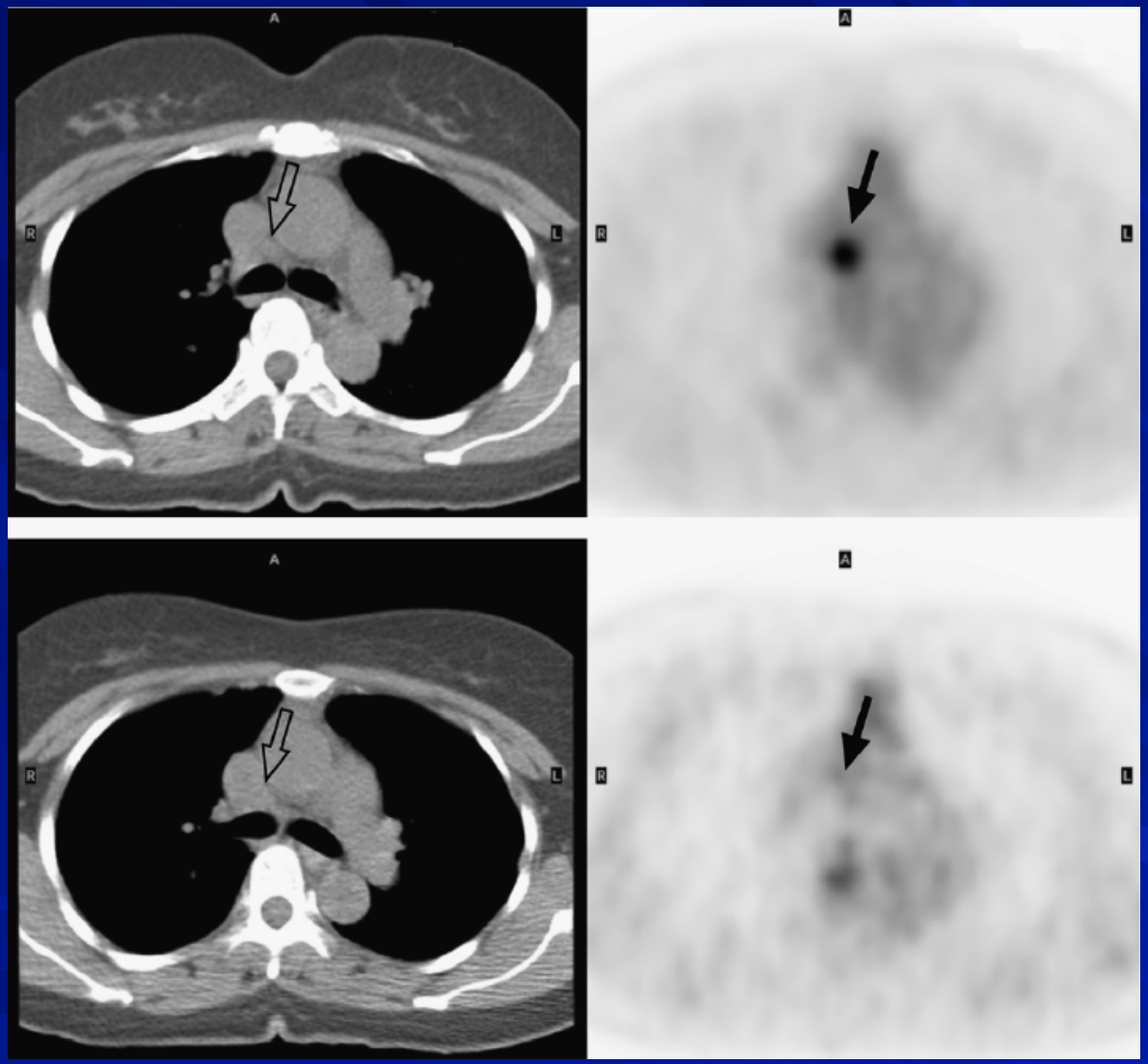
Good Therapy Response



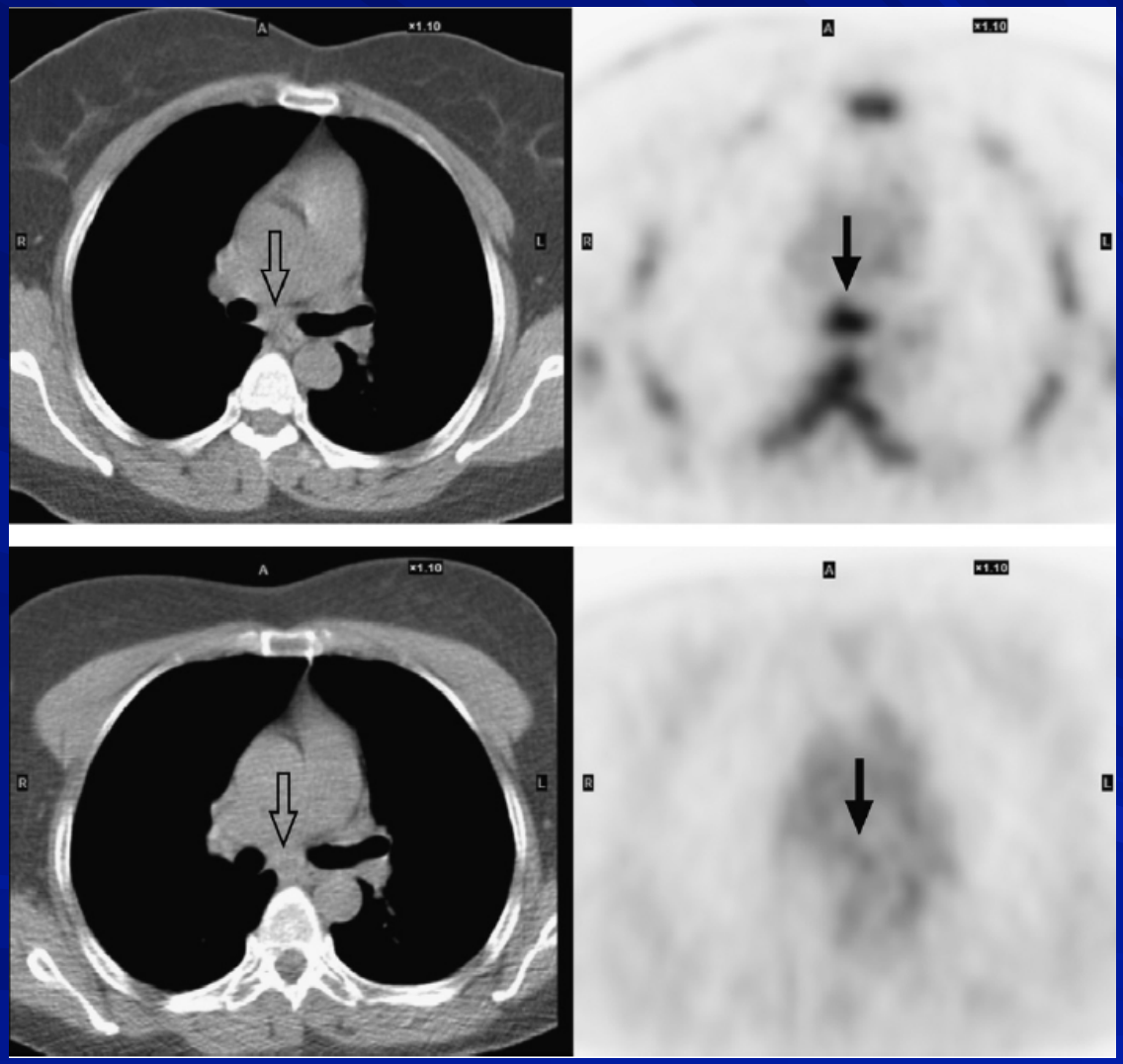
SUV = 5.5

SUV = 1.8

Mediastinal tuberculous lymphadenopathy post-chemo-radiotherapy Persistently enlarged mediastinal lymph nodes on CT with metabolic PET response

Source: Hoymer A, et al. Tuberculosis 2007.

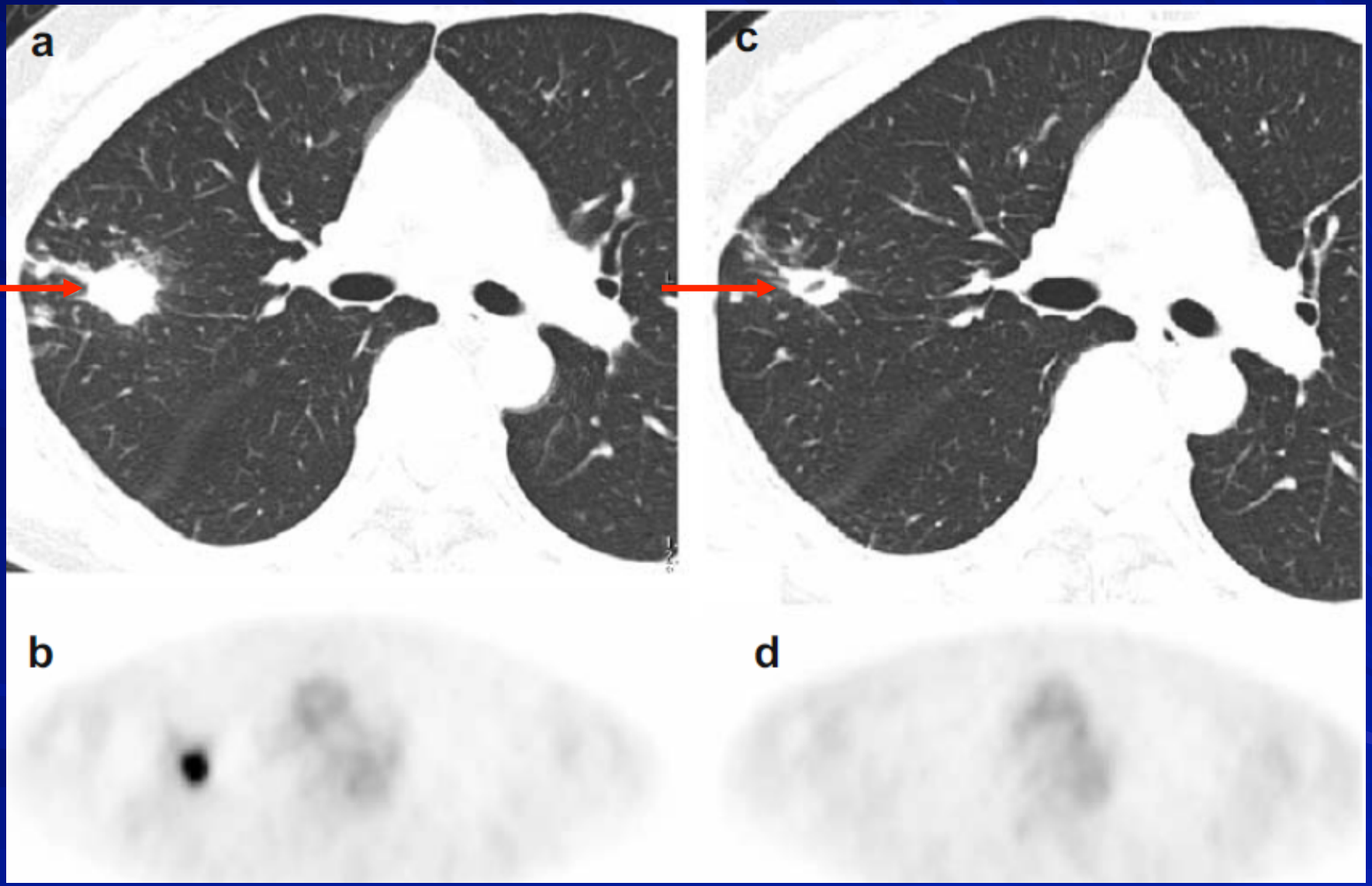
Persistent CT Abnormality



SUV = 5.2

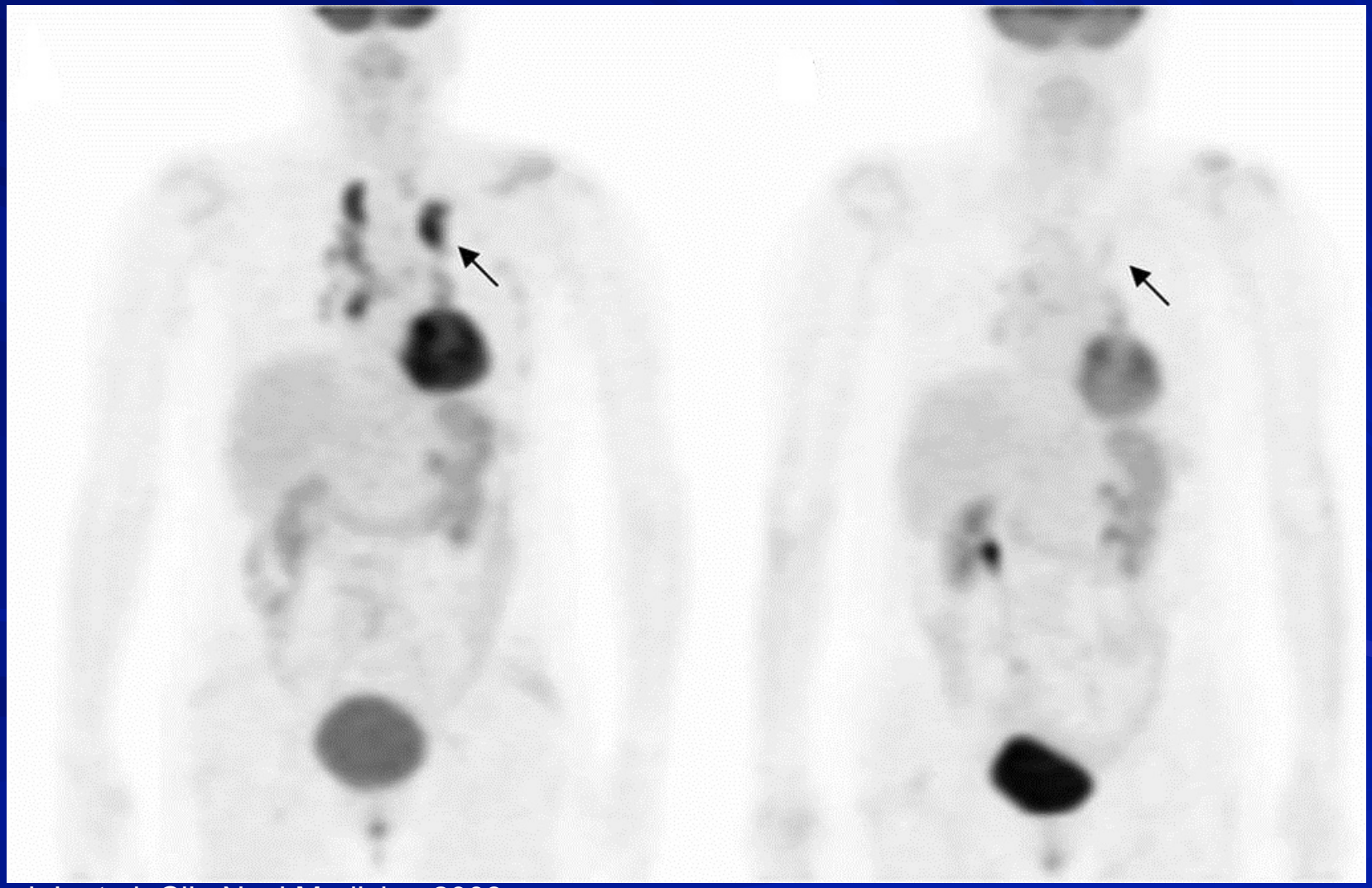
SUV = 1.9

FDG Superior to Some Biomakers & CT



Source: Demura Y, et al. EJNMMI 2009.

Confirmation of clinical response when in doubt



Source: Park I, et al. Clin Nucl Medicine 2008.

Use of ^{18}F-FDG PET to Predict Response to First-Line Tuberculostatics in HIV-Associated Tuberculosis

Mike Sathekge[1], Alex Maes[2,3], Mpho Kgomo[4], Anton Stoltz[5], and Christophe Van de Wiele[6]

[1]Department of Nuclear Medicine, University of Pretoria, Pretoria, South Africa; [2]Department of Nuclear Medicine, AZ Groeninge, Kortrijk, Belgium; [3]Department of Morphology and Medical Imaging, University Hospital Leuven, Leuven, Belgium; [4]Department of Internal Medicine, Louis Pasture Hospital, Pretoria, South Africa; [5]Department of Infectious Diseases, University of Pretoria, Pretoria, South Africa; and [6]Department of Nuclear Medicine, University Hospital Ghent, Ghent, Belgium

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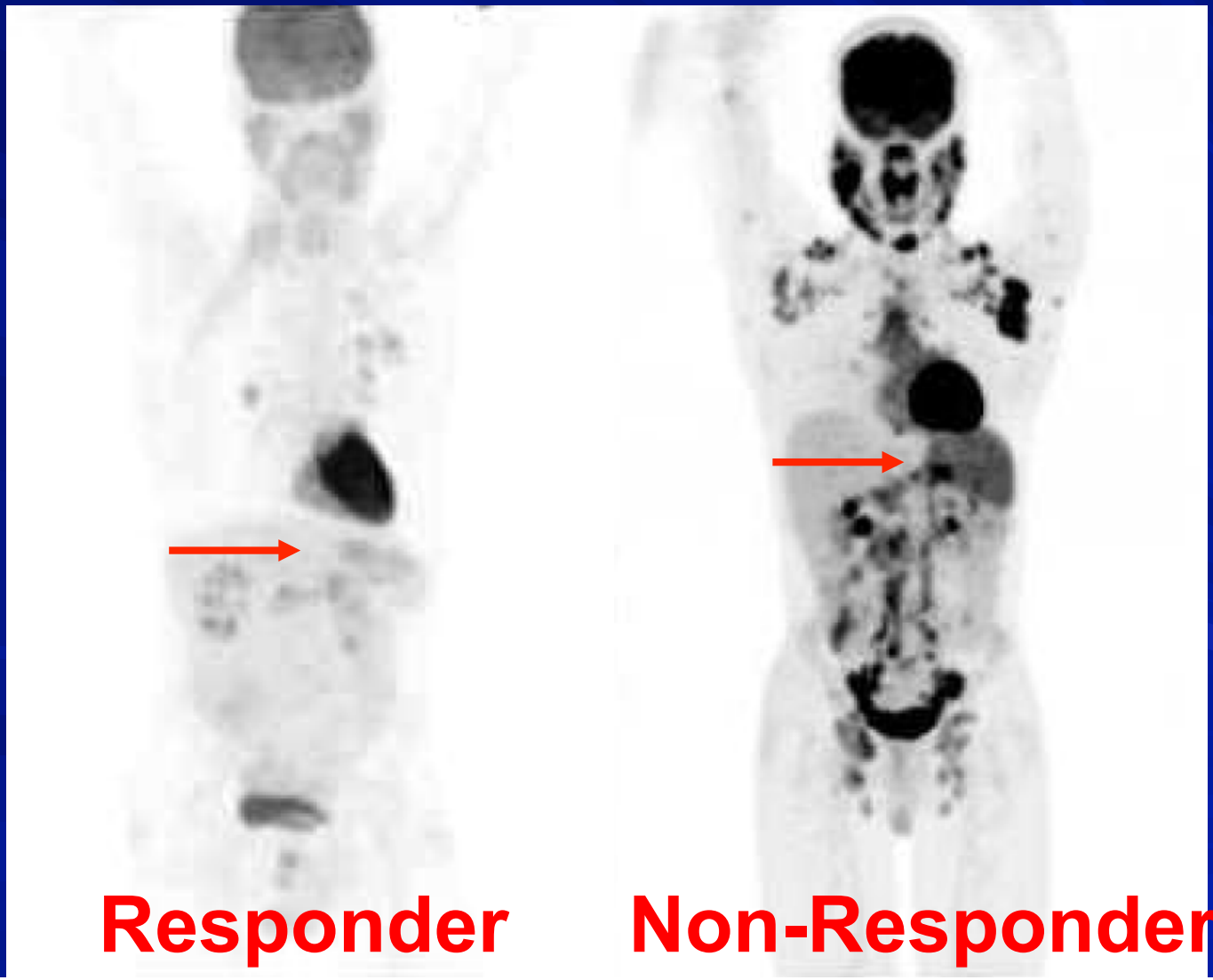

Responder **Non-Responder**

Use of ^{18}F-FDG PET to Predict Response to First-Line Tuberculostatics in HIV-Associated Tuberculosis

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THE JOURNAL OF NUCLEAR MEDICINE • Vol. 52 • No. 6 • June 2011

^{18}F-FDG PET/CT as a Sensitive and Early Treatment Monitoring Tool: Will This Become the Major Thrust for Its Clinical Application in Infectious and Inflammatory Disorders?

In the June 2011 issue of *The Journal of Nuclear Medicine*, Sathekge et al. (*1*) examined the reliability of ^{18}F-FDG PET/CT in differentiating tuberculosis-infected HIV patients who respond to anti-Koch therapy from those who do not respond. The authors reported that at 4 mo there was an excellent sensitivity, specificity, and negative predictive value and a modest positive predictive value. Such an observation is important, because shifting to alternative regimens is a crucial and defining step in patients who have multidrug-resistant and extensively drug-resistant tuberculosis.

NEWS

SNMMI Press Releases

Back to Archives

May 24, 2011

PET Scans Predict Effectiveness of Treatment for Multidrug-Resistant Tuberculosis in HIV Patients

Reston, Va. –With the deficiencies in knowledge of tuberculosis—as well as in the practices, programs and strategies used to combat the disease and co-infection with human immunodeficiency virus (HIV)—the spread of multidrug-resistant (MDR) tuberculosis poses a major problem for the health care community. Research in the June issue of *The Journal of Nuclear Medicine*, however, shows that the use of 18F-FDG positron emission tomography (PET) scans can help to determine earlier if treatment for tuberculosis is working or if the disease is MDR.

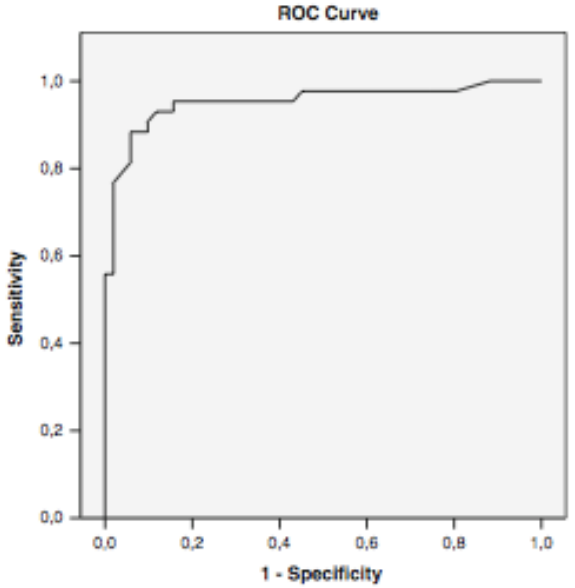


Fig. 1 ROC curve analysis of SUVmax of involved LN basins for separating responding LN from nonresponding LN to TB treatment (AUC 0.952) A SUVmax cut-off value of 4.5 yields a sensitivity and specificity of 95 % and 85 %

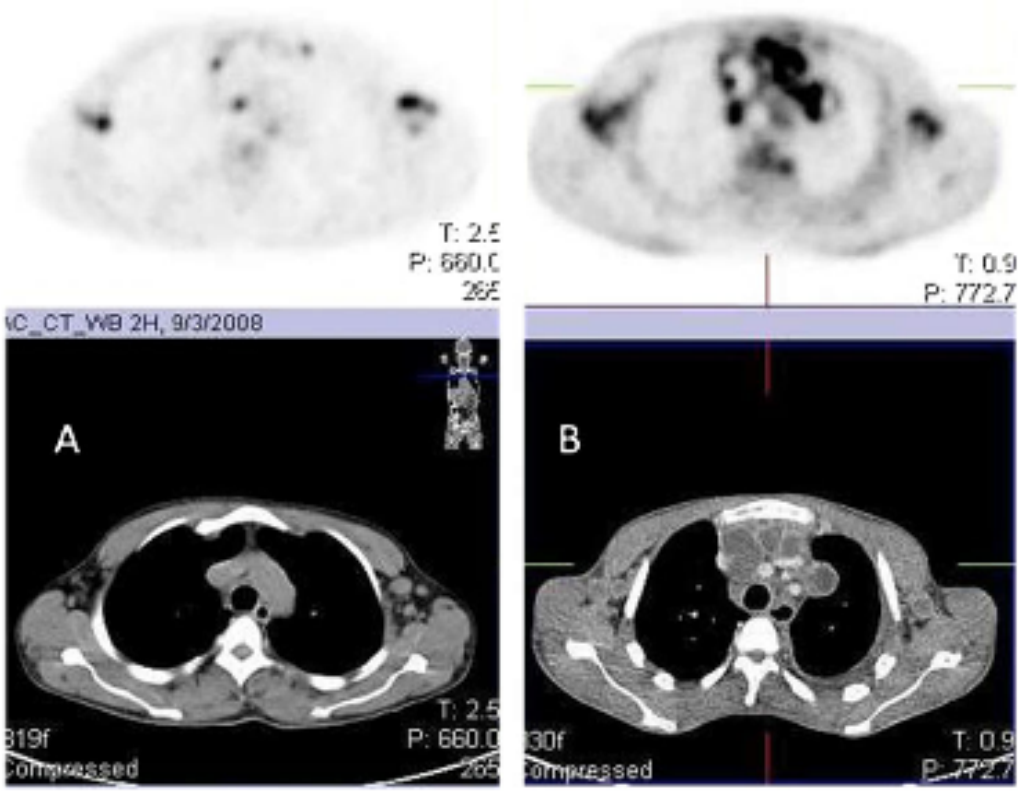
Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-012-2115-y

ORIGINAL ARTICLE

Tuberculous lymphadenitis: FDG PET and CT findings in responsive and nonresponsive disease

Mike Sathekge · Alex Maes · Yves D'Asseler · Mariza Vorster · Harlem Gongxeka · Christophe Van de Wiele

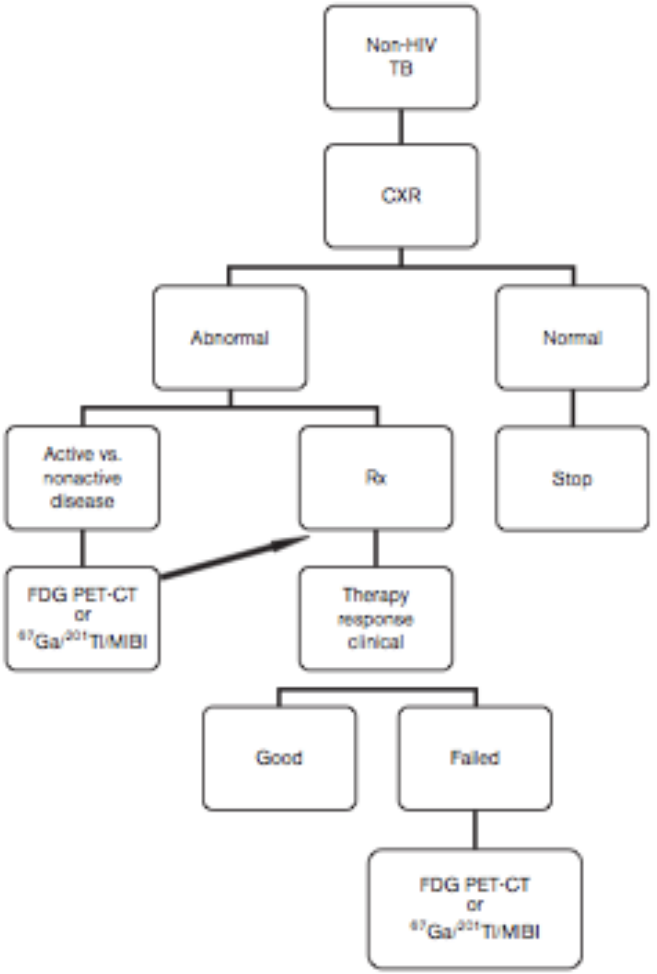
Fig. 3 PET/CT findings in (**a**) a responder with basins of homogeneous involved LNs and (**b**) a nonresponder with basins of involved LNs displaying central attenuation and peripheral rim enhancement



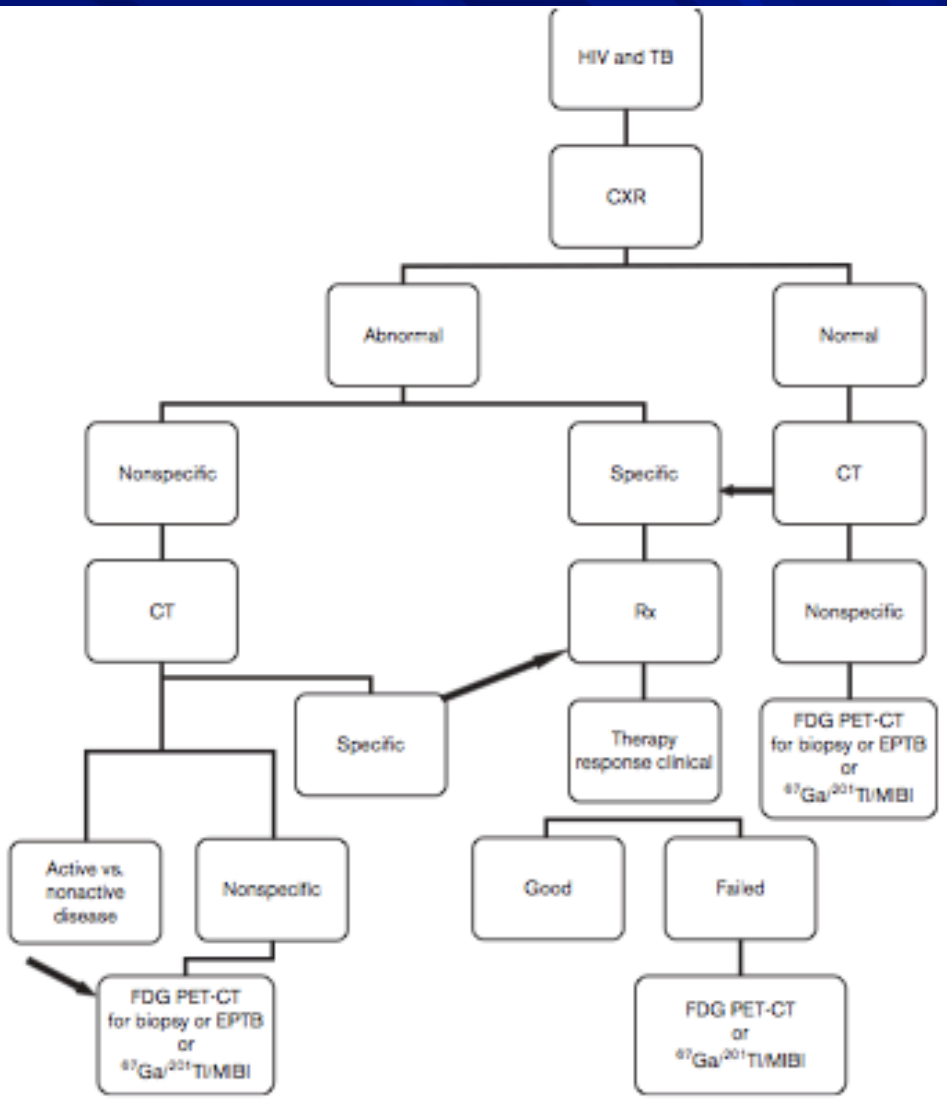
Nuclear medicine imaging in tuberculosis using commercially available radiopharmaceuticals

Mike Sathekge[a], Alex Maes[b,c], Yves D'Asseler[d], Mariza Vorster[a] and Christophe Van de Wiele[d]

Nuclear Medicine Communications 2012, 33:581–590

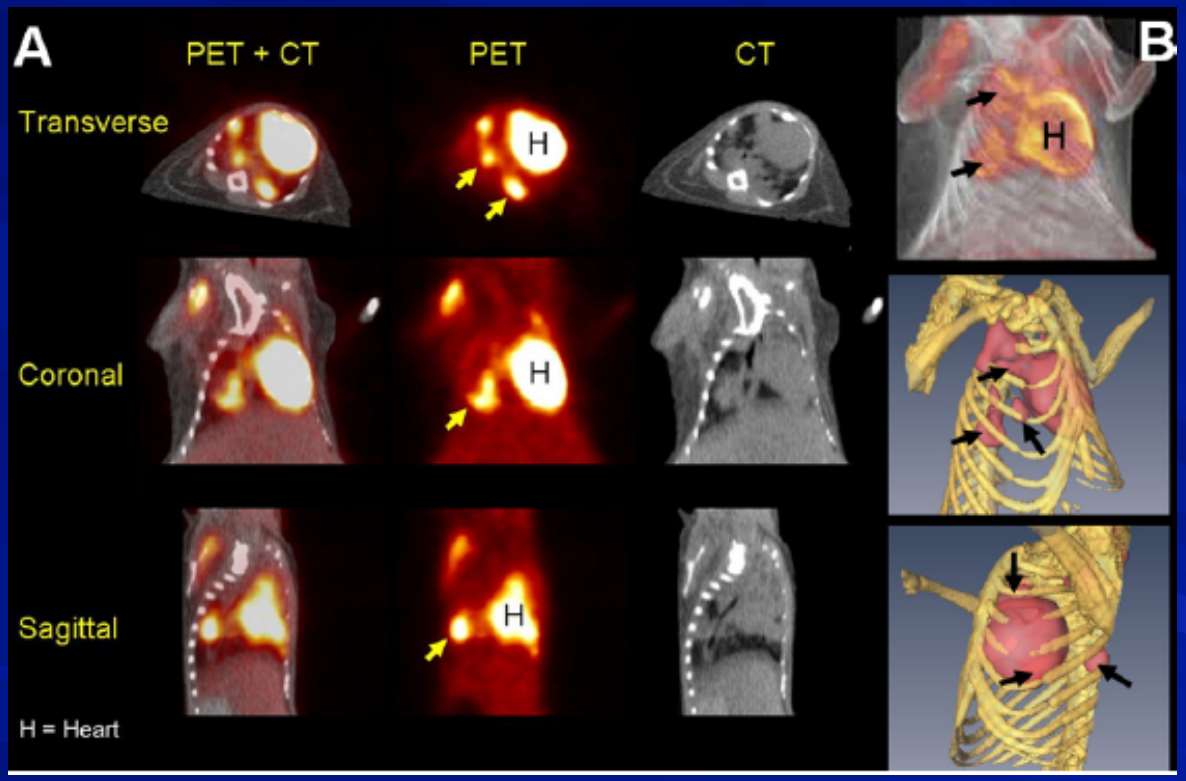


Algorithm for the evaluation of immunocompetent patients suspected of having tuberculosis. CT, computed tompgraphy; CXR, chest radiographs; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; HIV, human immunodeficiency virus; MIBI, methoxyisobutylisonitrile; Rx, treatment; TB, tuberculosis.

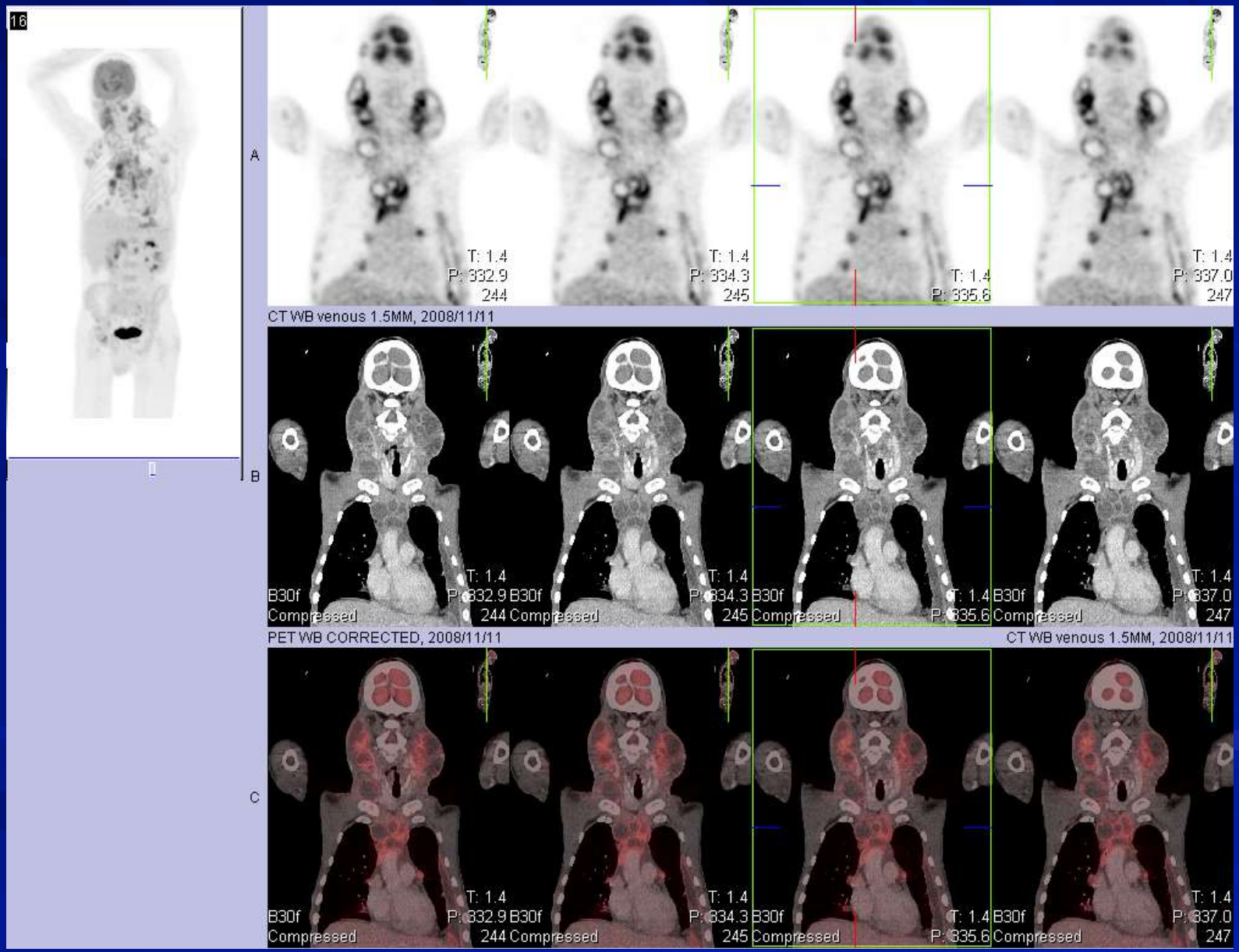


Algorithm for the evaluation of immunocompromised patients suspected of having tuberculosis. CT, computed tompgraphy; CXR, chest radiographs; EPTB, extrapulmonary tuberculosis; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; HIV, human immunodeficiency virus; MIBI, methoxyisobutylisonitrile; Rx, treatment; TB, tuberculosis.

FDG PET: Drug Deveoplment & Validation of New Biomarkers



Source: Davis S, et al. ANTIMICROBIAL AGENTS AND CHEMOTHERAPY 2009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CT WB venous 1.5MM, 2008/11/11
B30f
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PET WB CORRECTED, 2008/11/11
CT WB venous 1.5MM, 2008/11/11


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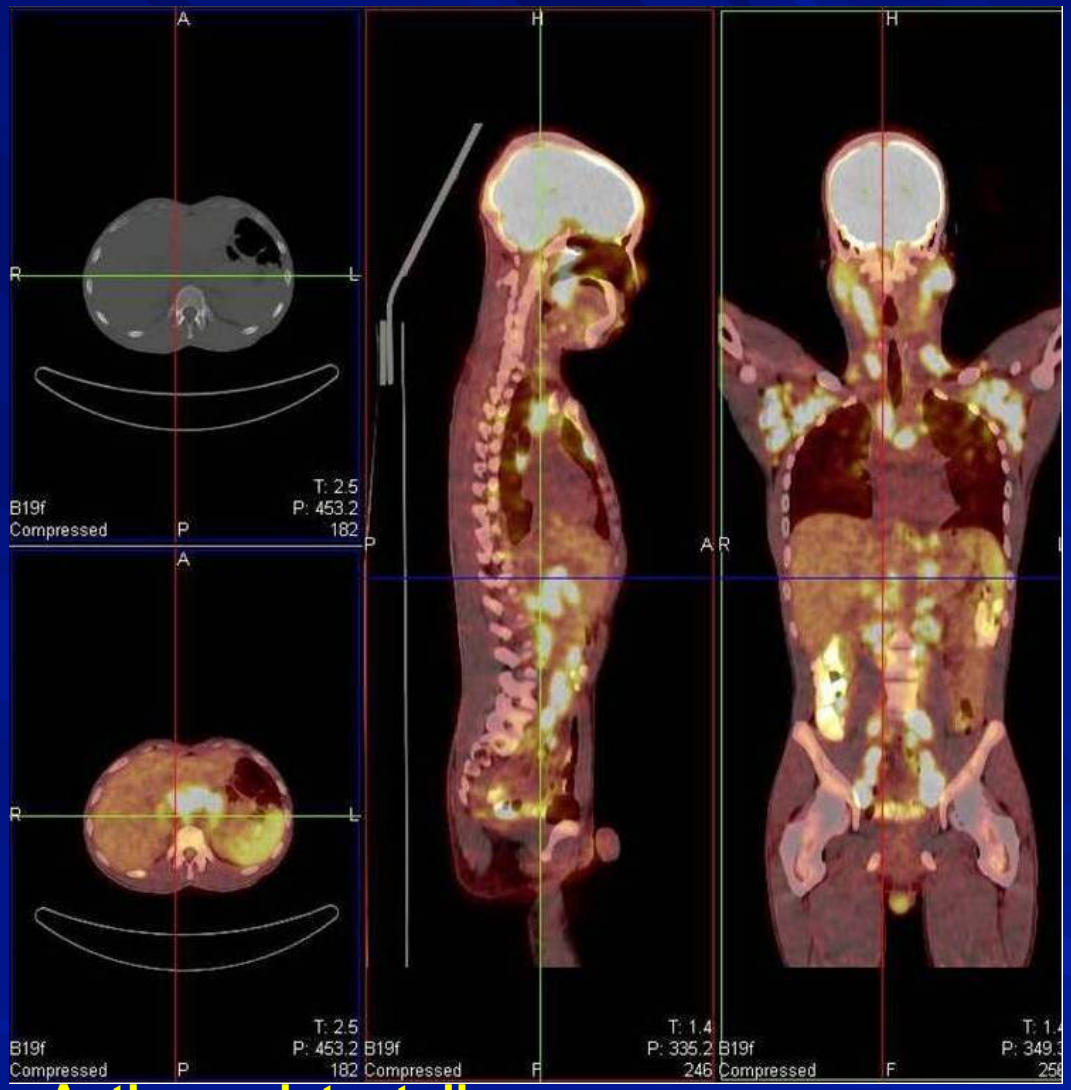
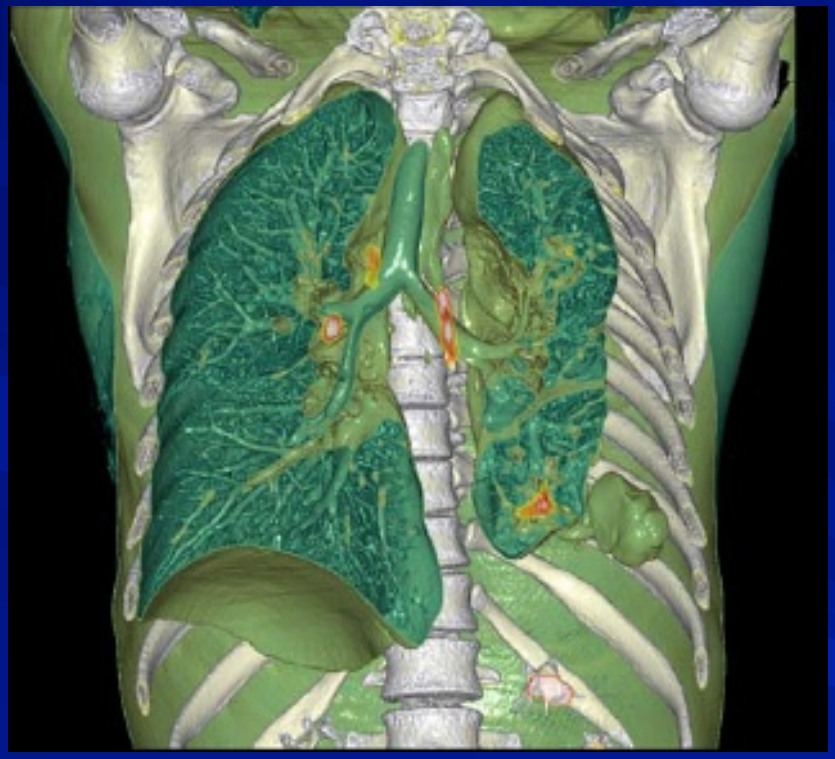
FDG PET/CT: HIV &TB



- Active vs latent disease
- Monitoring of Response to anti-TB Rx
- Guide to Duration of antimicrobial therapy
- Prognosis
- Drug Development & new biomarkers

Internationally: Selected Front Cover Image



Delivering the Ultimate Power in Molecular Imaging Siemens 2010

Sathekge M & UP