CORSO EDUCAZIONALE

GRUPPO LINFOMI IN PAZIENTI CON IMMUNODEFICIT

Milano, Best Western Hotel Madison
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# Ruolo della PET nei Linfomi correlati a HIV

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# Disclosures of Name Surname

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| **Gilead Sciences** | | | | | **X** | | |
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# The problem of FP FDG-Avid Nodes in PLWH

| Etiology | Mechanism | Clinical Context |
|---|---|---|
| **Immune deficiency-related lymphoid hyperplasia** | **Chronic immune activation** | **Any CD4 count, unsuppressed VL** |
| **Unsuppressed HIV viremia** | **Direct viral-driven glycolysis in lymphoid tissue** | **High VL, ART-naive (1)** |
| **Tuberculosis/MAC** | Granulomatous inflammation, high metabolic activity | Low CD4 (<200 cells/µL) (4) |
| **Toxoplasmosis, CMV, cryptococcosis** | Opportunistic infection-related inflammation | Severely immunocompromised (3) |
| **IRIS (Immune Reconstitution Inflammatory Syndrome)** | **Post-ART hyperinflammation; SUV and total glycolytic activity significantly higher in IRIS vs non-IRIS** | **Early ART initiation, CD4 <100 (5)** |
| **Sarcoidosis/granulomatous disease** | Inflammatory macrophage uptake | Can occur at any HIV stage (6) |

*1- Tawakol A et al. JAMA Cardiol 2017*
*3- NCCN Clinical Practice Guideline 2019*
*4- Esmail H. et al. Nat. Med. 2016*
*5- Hammoud DA et al. Clin Infect Dis 2019*
*6- Ceriani L et. Ann Oncol 2016)*

Non-malignant causes of lymphadenopathy are more common in patients with **higher viral loads and lower CD4+ T-cell counts**, meaning the population with the highest lymphoma risk also has the highest false-positive rate (*Reid E et al. J Natl Compr Can Netw 2019*)

# Arterial and Lymph Node Inflammation Associate with Distinct Inflammatory Pathways in HIV

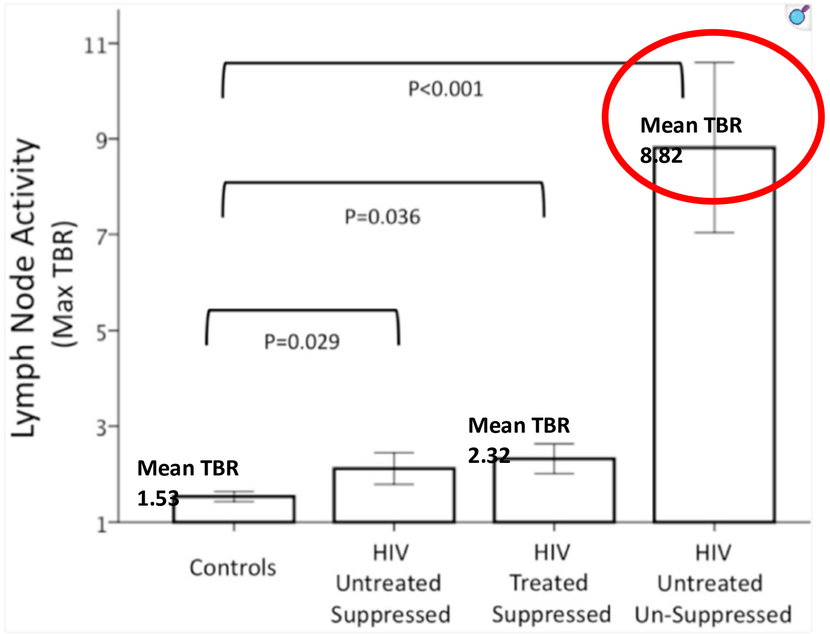
*Tawakol A et al. JAMA Cardiol 2017*

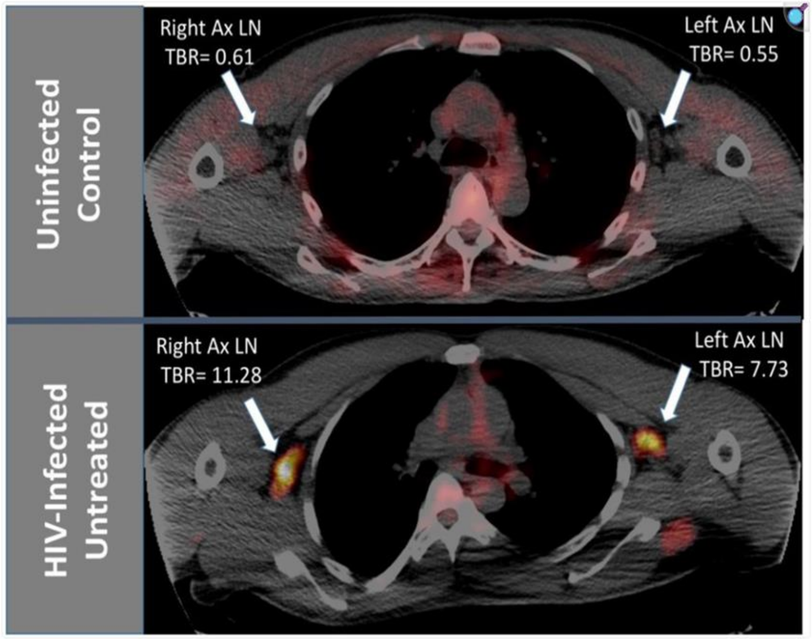
**Conclusion**

In un-suppressed HIV + patients inflammation lymph node activity can be very high (SUVmax up to 12-15)

**Population**

- 74 pts; **45 HIV+ and 29 HIV- (ctrls)**
- 18-F FDG PET/CT in all pts
- Viral load (CD8+ T cells; CD4+ T-cell activation CD4/CD8 ratio)
- **LN metabolic activity: T/BKG (SUVmax LN/SUVmax SVC)**



# Can we distinguish FP from TP adenopathy in PET scan ?

# PET/CT in the Evaluation of Lymphoma in Patients With HIV-1 With Suppressed Viral Loads

Gohsen E et al 2008

**Population**

- 7 pts (6 NHL) HIV+ underwent PET/CT.
- 16 PET/CT scans (5/16 staging, and 10/16 for treatment response and follow-up)
- 1 pt referred for suspected lymphoma.
- PET/CT findings were compared with concurrent clinical, immunologic, histological and virological data.

TABLE 1. Summary of Virological, Immunological, and PET/CT Findings

| Patient | Sex, Age | Viral Load | CD4 (Cells/μL) | Indication for PET/CT | Anatomic Distribution of PET/CT Lesions | PET/CT (+/+, −/+, or +/−), Outcome |
|---|---|---|---|---|---|---|
| 1a | M, 31 | 10,760 | 92 | Staging | Active enlarged LN (neck, axillae, hilar, retroperitoneum, inguinal), extranodal orbit, lungs, omentum, kidney, and marrow | +/+, TP |
| 1b | | 180 | 187 | Response | FDG normal, CT residual pneumonitis | −/+, TN |
| 2a | M, 35 | 1300 | 356 | Staging | Active enlarged LN in neck, medistinum, axillae, porta hepatis; extranodal in skeleton | +/+, TP |
| 2b | | <50 | 474 | Response | FDG normal, CT residual | −/+, TN |
| 2c | | 21,000 | 348 | Follow-up | Active LN (neck, axillae, mediastinum, inguinal) CT abundant, normal-sized LN | +/−, FP |
| 2d | | 7900 | 316 | Follow-up | Progression of LN and now active spleen; CT all normal-sized LN | +/−, FP |
| 2e | | 53,000 | 352 | Follow-up | Slight improvement of PET; CT normal | +/−, FP |
| | | | | | Retroperitoneal mass and enlarged subdiaphragmatic LNs | +/+, TP |
| | | | | | Active enlarged mediastinal LNs | +/+, TP |
| | | | | | FDG normal, CT residual | −/+, TN |
| | | | | | Active enlarged axillary LNs | +/+, TP |
| | | | | | FDG normal, CT residual | −/+, TN |
| | | | | | FDG normal, CT residual | −/+, TN |
| | | | | | Pharynx and neck active enlarged LNs, bone | +/+, TP |
| 6b | | LDL | 142 | Response | Progression to sinus, spleen, enlarged peritoneal LNs, and more bone lesions | +/+, TP |
| 7 | F, 42 | 84,000 | 380 | Suspected lymphoma | Abundant active axillary, inguinal LNs, spleen; CT normal-sized nodes | +/−, FP |

LDL indicates lower than detection level; NA, not available; TP, true positive for active lymphoma; TN, true negative; FP, false positive for lymphoma.

## Results

- **PET+/CT+** in 12/16 scans (75%) confirmed as **TP**
- **PET+/CT-** in 4/16 (25%) defined as **FP**
- **PET-/CT+** in 5/16 scans (31%) defined as **TN**

# Clinical features and $^{18}$F-FDG PET/CT for distinguishing of malignant lymphoma from inflammatory lymphadenopathy in HIV-infected patients

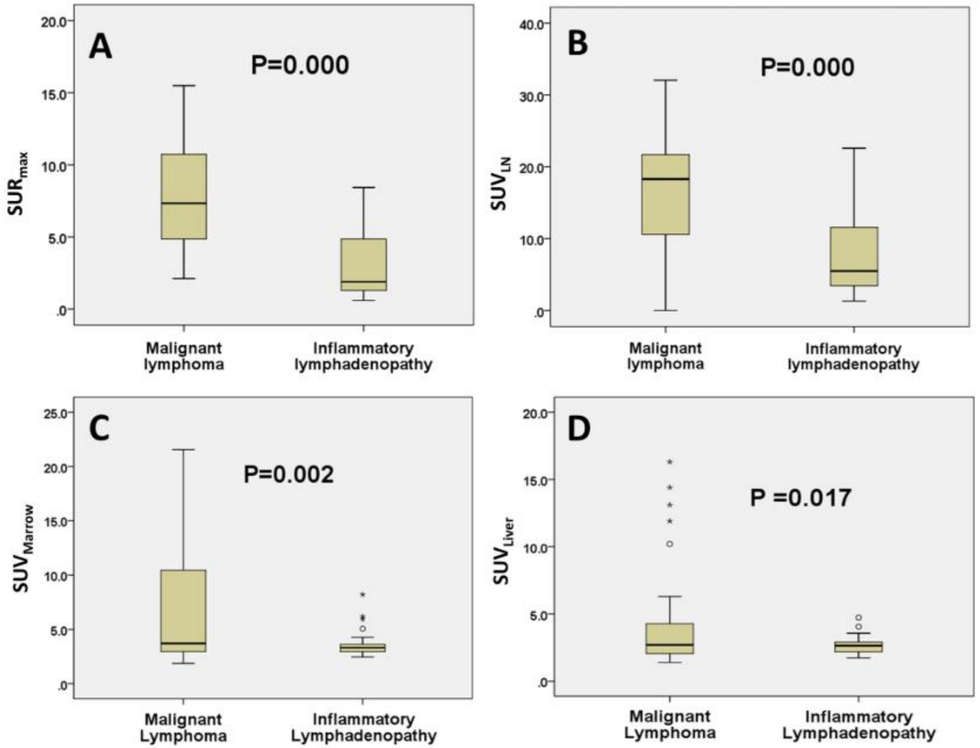
*Cheng D. et al. BMC Infect Dis 2022*

**Population**

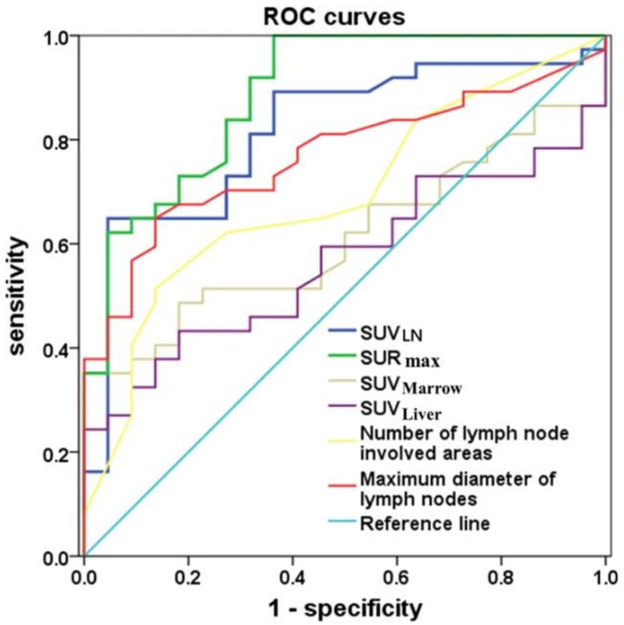
- 59 HIV+ pts underwent PET/CT.
- **37/59 HIV associated lymphoma**
- **22/59 with HIV associated inflammatory lymphadenopathy as controls.**
- $SUV_{max}$ of disease,
- **$SUV_{max}$ of only LN ($SUV_{LN}$)**
- **$SUV_{max}$ liver/ratio ($SUR_{max}$),**
- Optimal cut-off by ROC curve

## Results

- **AUC: 0.888 for SURmax (P < 0.001) and 0.815 for SUVLN (P < 0.001),.**
- **Best cut-off: 3.1 for SURmax and 8.0 for SUVLN**




Association between lymphoma status and PET parameters established by using a gradient-based segmentation method. The correlations are shown for $SUR_{max}$ (**A**), $SUV_{LN}$ (**B**), $SUV_{Marrow}$ (**C**) and $SUV_{Liver}$ (**D**)




**Conclusions**

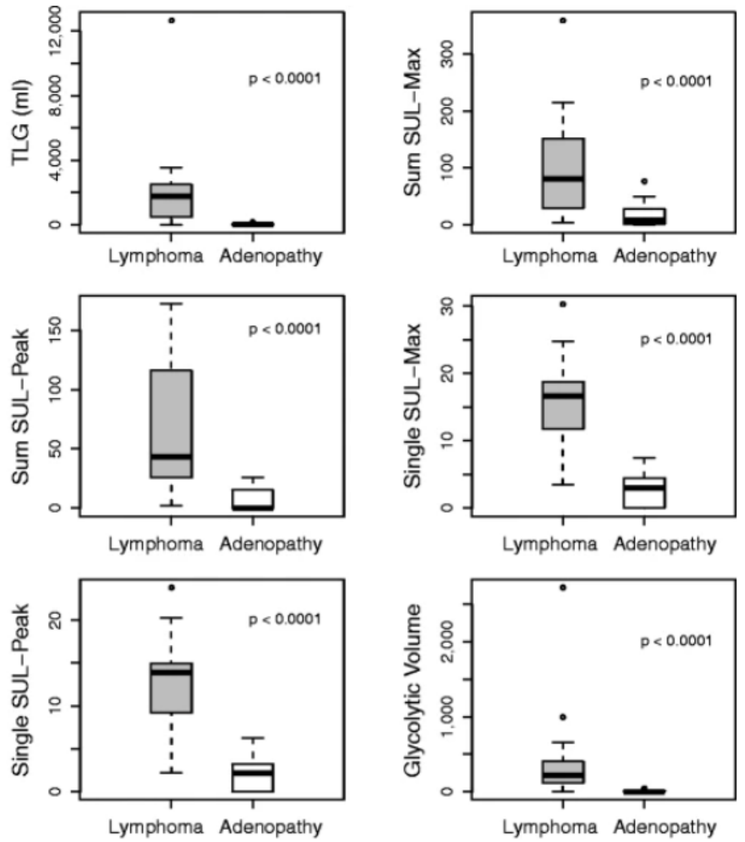
- Using the **cut-off point of 3.1 $SUR_{max}$ or 8.0 $SUV_{LN}$** can discriminate malignant lymphoma vs inflammatory lymphadenopathy.

# Differentiation of HIV-associated lymphoma from HIV-associated reactive adenopathy using quantitative FDG PET and symmetry

*Mhalanga JC Eur J Nucl Med Mol Imaging 2014*

- 41 PET/CT studies in HIV+ pts
- 19 lymphoma,
- 22 reactive adenopathy

| Metric | Cut-off | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | AUC |
|---|---|---|---|---|---|---|
| Single SUL-Max | 7.8 | 89 | 100 | 100 | 92 | 0.971 |
| TLG | 173 | 89 | 100 | 100 | 92 | 0.964 |
| Single SUL-Peak | 6.6 | 84 | 100 | 100 | 88 | 0.964 |
| Glycolytic volume/MTV | 53.8 | 84 | 100 | 100 | 88 | 0.957 |
| Sum SUL-Peak | 23.8 | 84 | 95 | 94 | 88 | 0.935 |
| Sum SUL-Max | 28.4 | 84 | 82 | 80 | 86 | 0.904 |
| Summed CT nodal size | 82.6 | 58 | 68 | 61 | 65 | 0.671 |
| Single nodal visual score, reader 1 | 3.5 | 84 | 32 | 52 | 70 | 0.581 |
| Sum nodal visual score, reader 1 | 23.5 | 53 | 64 | 56 | 61 | 0.576 |
| Nasopharyngeal region SUL-Max | 4.0 | 42 | 73 | 57 | 59 | 0.443[a] |



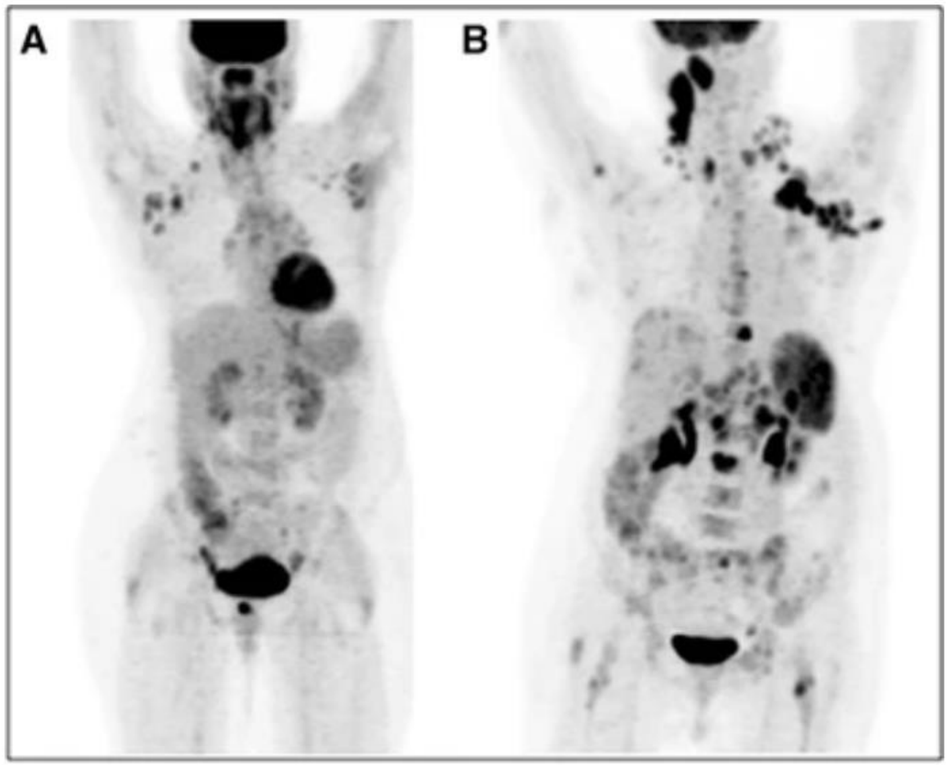
## Differentiation of HIV-associated lymphoma from HIV-associated reactive adenopathy using quantitative FDG PET and symmetry

*Mhalanga JC Eur J Nucl Med Mol Imaging 2014*

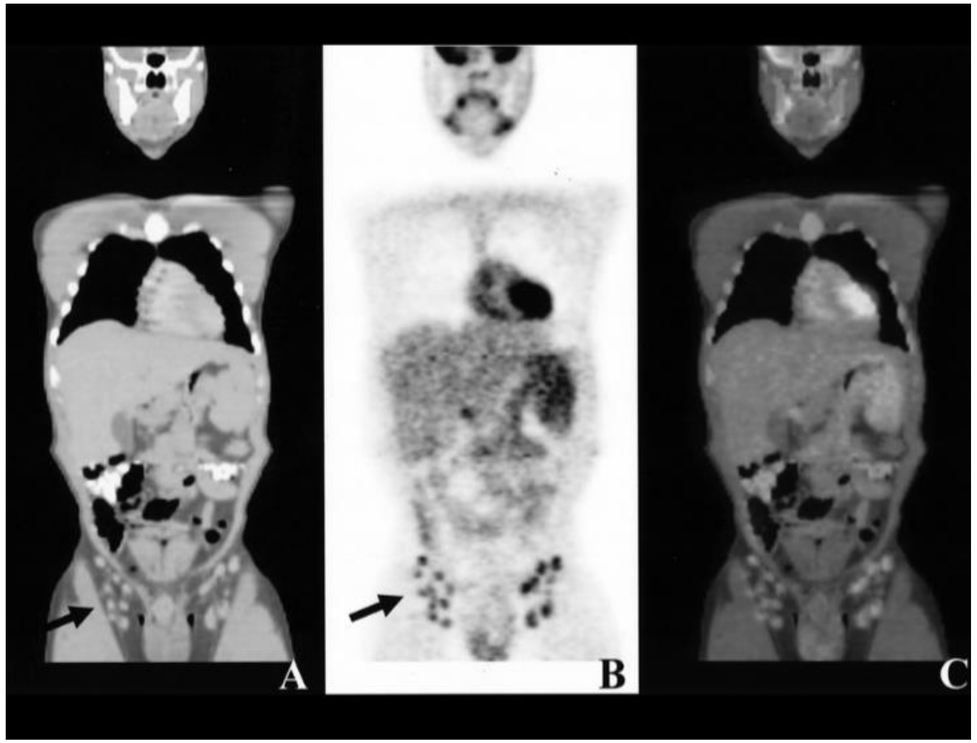
| HIV patient group | Reader 1 | | Reader 2 | |
|---|---|---|---|---|
| | Symmetry score 0 | Symmetry score 1 | Symmetry score 0 | Symmetry score 1 |
| Reactive adenopathy | 3 | 19 | 2 | 20 |
| Lymphoma | 18 | 1 | 17 | 2 |

**Conclusion**

Visual reading for **asymmetrical vs symmetrical** nodal uptake distribution: **accuracy 90.4**



| Feature | Reactive HIV nodes (FP) | Lymphoma |
|---|---|---|
| **Distribution** | Symmetric, diffuse | Asymmetric, focal |
| **SUV** | Moderate (can overlap) | Often very high |
| **Nodes** | Multiple small/medium | Dominant bulky nodes |
| **Necrosis** | Rare | Possible |
| **Viral load** | Often high | Variable |
| **CD4** | Often preserved | Often low (but not always) |
| **ART effect** | Improves uptake | No improvement |




*Bhargava P et al Clin Nuc Med 2006*

## FP lymph node PET: Take Home Message

- In HIV patients nodal FDG uptake can reflect immune inflammation not lymphoma
- High viral load + preserved CD4 counts → clinical setting for FP uptake
- FDG distribution and clinical data → useful to avoid/reduce FP results

# Role of PET in differentiating PCNSL vs Toxoplasmosis

- PCNSL: incidence of 5‰ (mostly DLBCL)
- Cerebral toxoplasmosis: up to 30%
- Sign and symptoms overlapped
- **MRI: first line imaging**

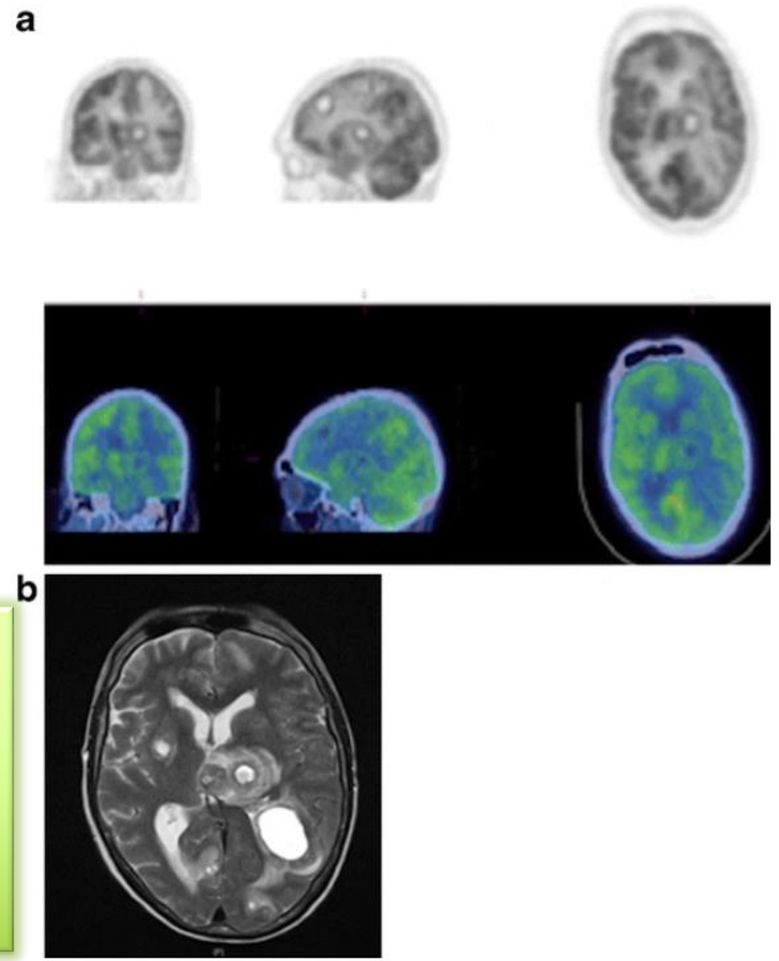
# $^{18}$F-FDG PET/CT in HIV-related central nervous system pathology

*Lewitschnig S. et al. Eur J Nucl Med Mol Imaging 2013*

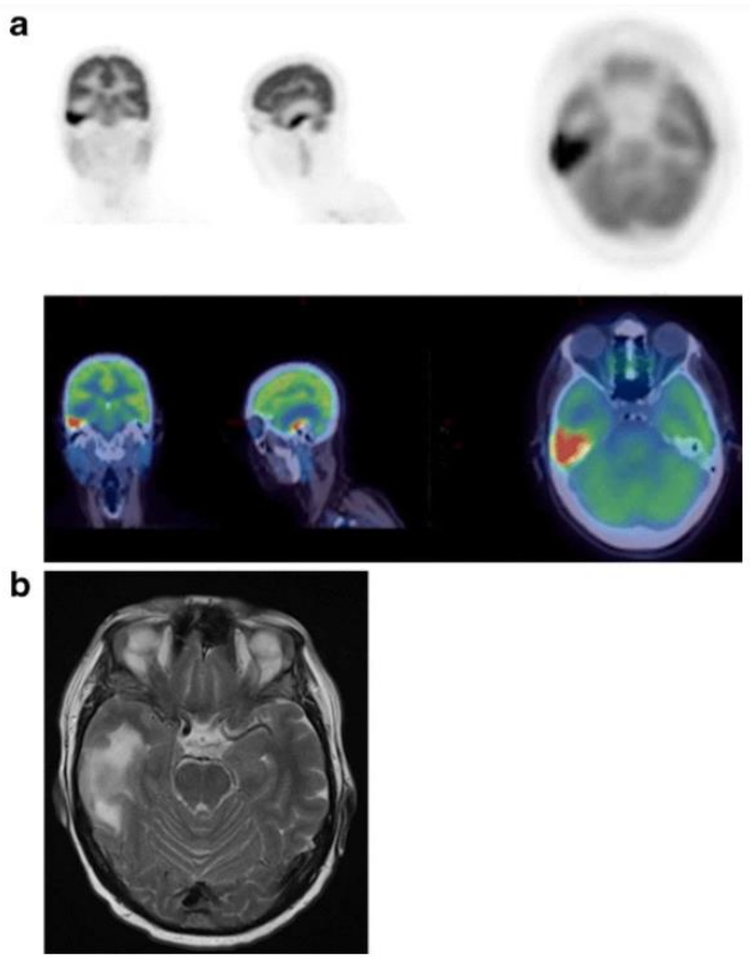
- 25/29 brain PET/CT performed to differentiate infection from malignant causes of cerebral pathology
- 10/11 toxoplasmosis correctly identified
- 5/5 PCNSL correctly identified

**Results**

- **Toxoplasmosis lesions: mean SUVmax: 3.5** (range 1.9 - 5.8) lower than cortex uptake
- **Lymphoma lesions: mean SUVmax 18.8** (range 12.4 - 29.9) higher than cortex uptake




Toxoplasmosis

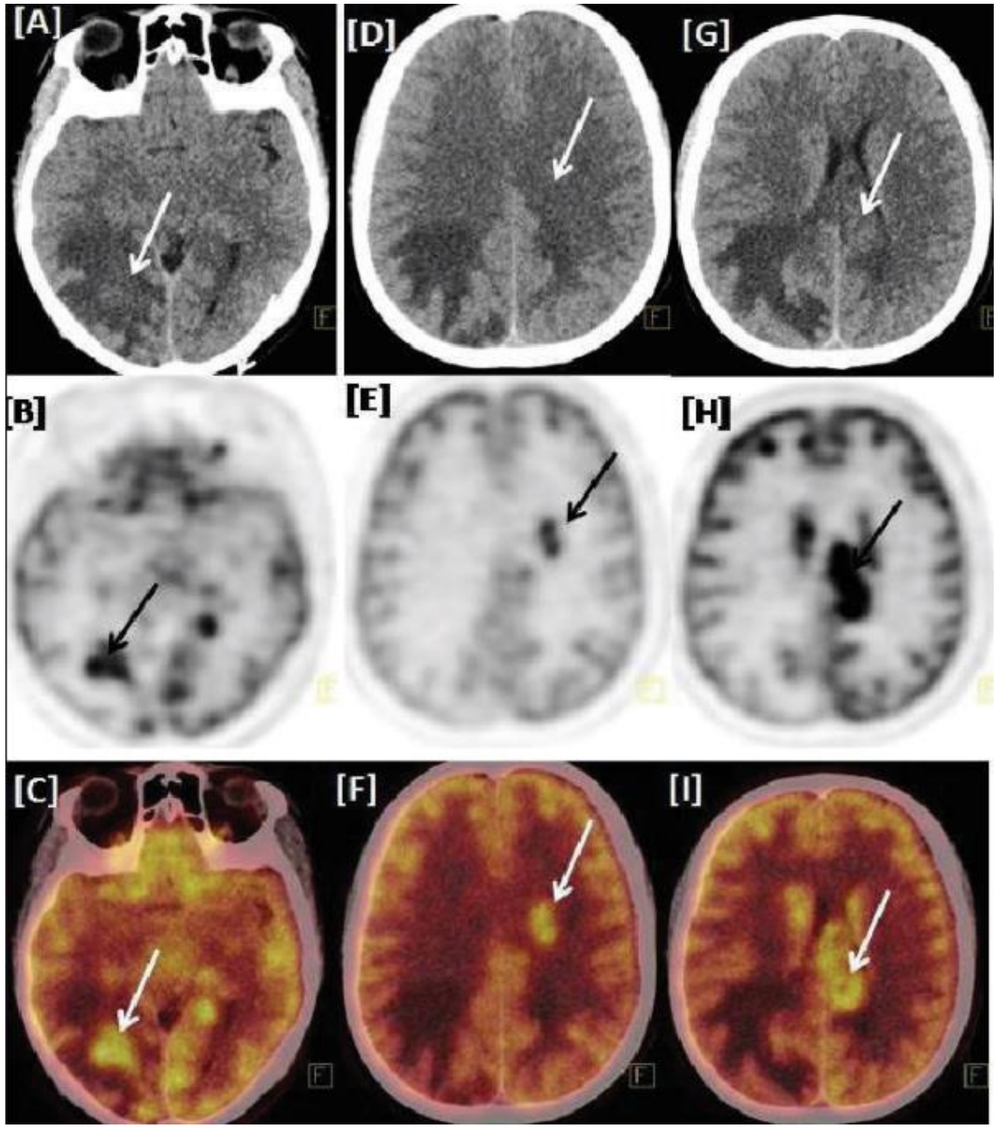



Lymphoma

- SNMMI/EANM guide
  imaging: **pooled sen**
  **PPV, and NPV all >8**
  characteristically hig
  homogeneous uptak
  toxoplasmosis typica
  low uptake (*Arbizu J J*

- **Stereotactic brain b**
  **gold standard** for de
  FDG-PET supports bu
  tissue confirmation.

## Take home messages




**Multifocal Toxoplasmosis**

*Mukherjeer A. et al. Medicne 2017*

# PET in staging HIV related Lymphoma (HL, DLBCL, BL, PCNSL)

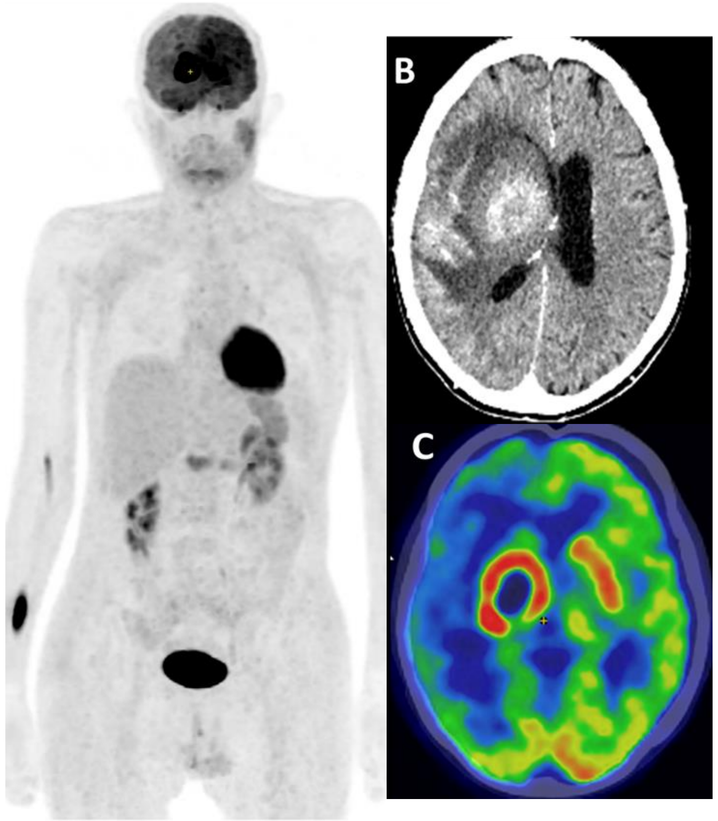
- **Recommended as preferred imaging technique**
- Higher sensitivity than ceCT, especially for EN disease (BL)
- **Useful in PCNSL to exclude extracranial localisations**
- **Possible FP (immune deficiency-related lymphoid hyperplasia and non-suppressed HIV infection)**

*(2024 EHA-ESMO GGLL Hubel et al 2024)*
*(NCCN Version 3.2026; B-Cell Lymphoma)*
*(NCCN Version 1,2026; Hodgkin Lymphoma)*

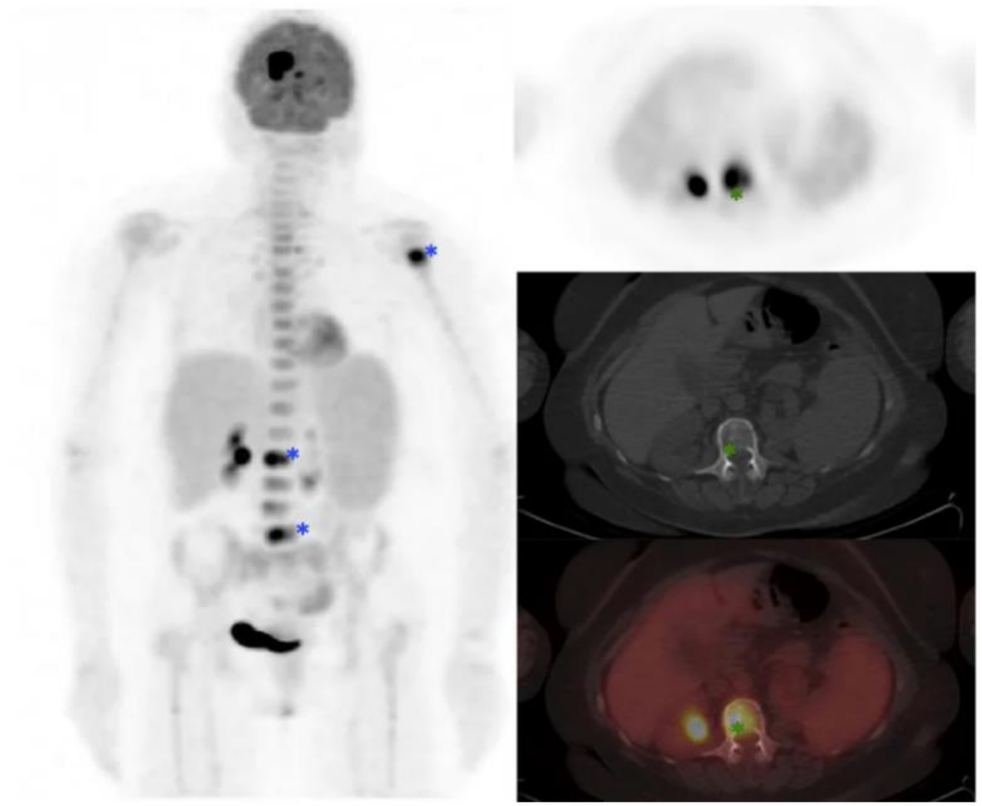
# PET in PCNSL staging

- **FDG-PET/CT recommended:** for all PCNSL, **including HIV-related**, to exclude extracranial lymphoma (about 8% of presumed PCNSL in PLWH).

*Übel et al Ann Onocol 2024*
*Ferreri AJM et al Ann Oncol 2024*
*Eyre TA Ann Oncol 2025*
*Suh CH Neuro Oncol 2024*
*Kaulen LD Blood 2026*
*Mohile NA et al Neuro Oncol. 2006*




*Fondazione IRCCS San Gerardo dei Tintori - Monza*



*Bertaux M et al J Neuro-Oncol 2020*

# Interim PET in HIV related lymphoma

- i-PET/CT is prognostic in **HIV HL** and **should be used for response assessment with the 5-point Deauville scale and Lugano criteria**
- i-PET/CT results must be **interpreted cautiously in HIV HL** when used to escalate treatment, and FDG-avid lesions of uncertain significance should be re-biopsied rather than acted upon directly **given the higher false-positive rate in PLWH**
- **Currently, i-PET** (after 3-4 cycles) is considered a standard **in DLBCL** immunocompetent patients and has a strong prognostic value (DS 5; ΔSUVmax ≥ 70%) but **no consistent data are available to recommend it in PLWH**
- **In BL (low/intermediate IPI) , PET during treatment to modulate the therapy regimen**

*(2024 EHA-ESMO GGLL Hubel et al 2024)*
*(NCCN Version 1,2026; Hodgkin Lymphoma)*

# EoT PET in HIV related lymphoma

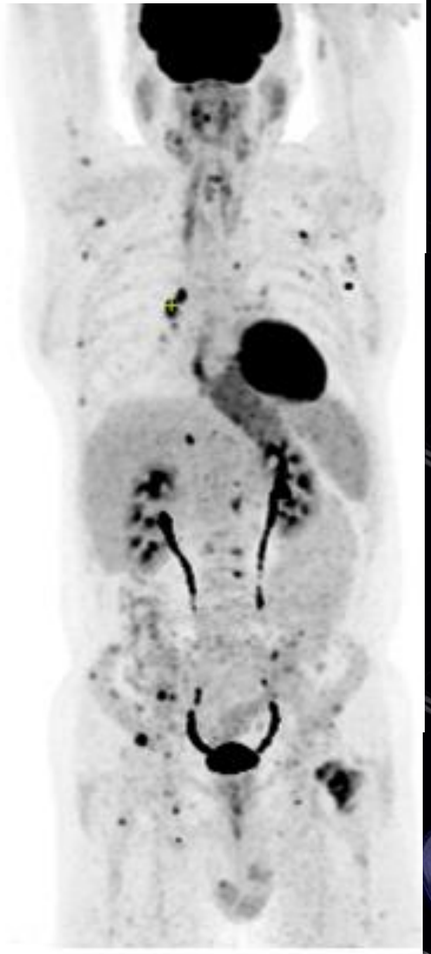
- **EoT FDG–PET/CT is the standard for response assessment in HIV lymphoma, with criteria identical to the HIV-negative setting (Deauville 5-point scale; Lugano Criteria).**

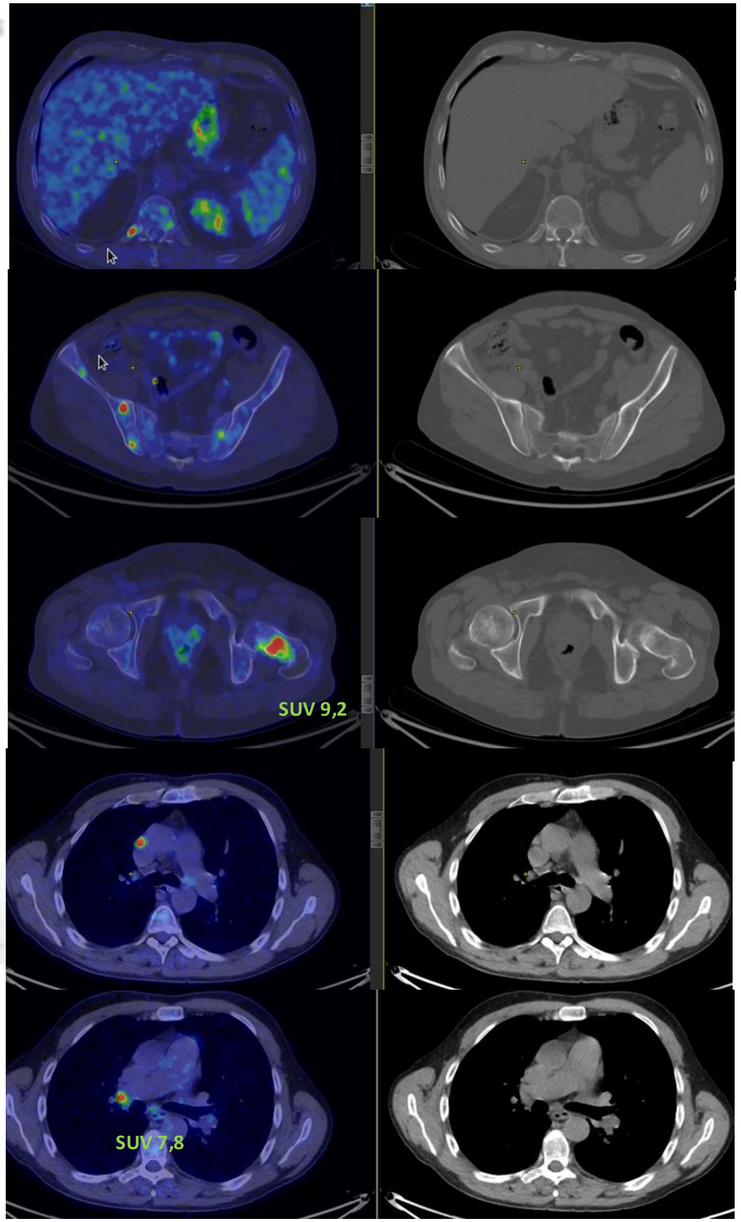
- **Higher false-positive rate in PWH at EoT** due to immune deficiency-related lymphoid hyperplasia, opportunistic infections, and non-suppressed HIV viremia; this **lowers the positive predictive value** of EoT PET compared to the general population.

- **Biopsy confirmation is required** for FDG-avid residual lesions at EoT when there is clinical doubt or when a positive result would change management (e.g., initiate salvage therapy or RT).

*(2024 EHA-ESMO GGLL Hubel et al 2024)*
*(NCCN Version 1,2026; Hodgkin Lymphoma)*

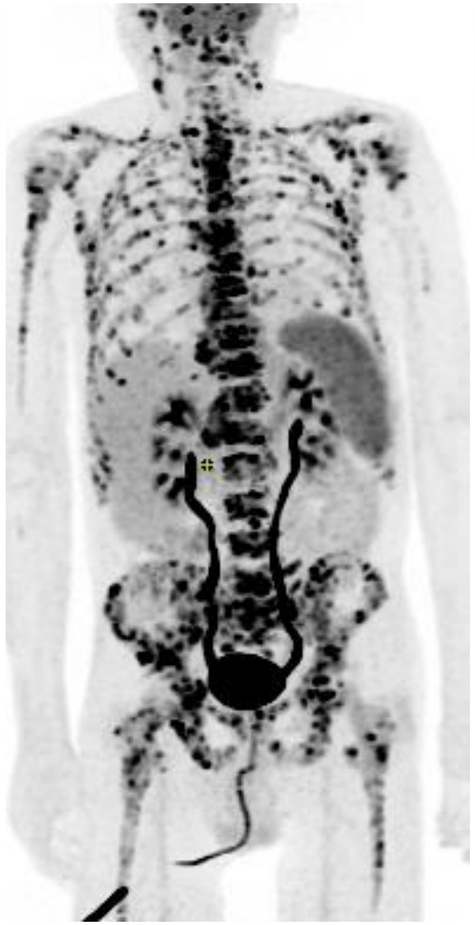
# Alcuni Casi Clinici



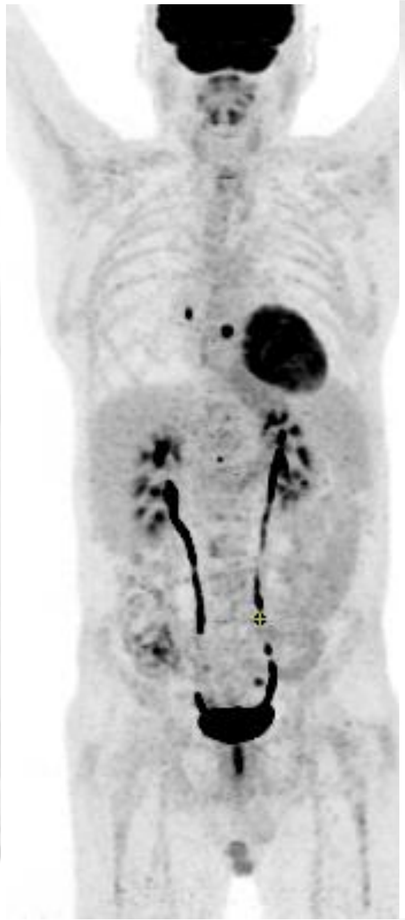



10/01/2025 EoT PET
**Nodal and diffuse BM disease**

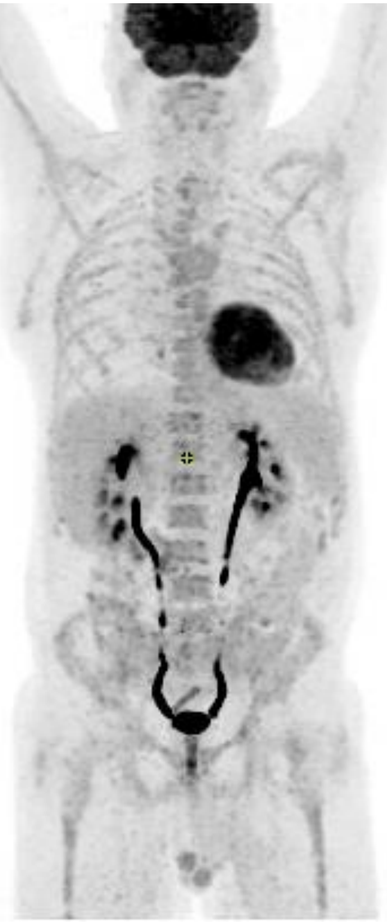
→ **BOM neg; no symptoms**



09/06/2025
BEGEV x 2 – **DS5-PMD**



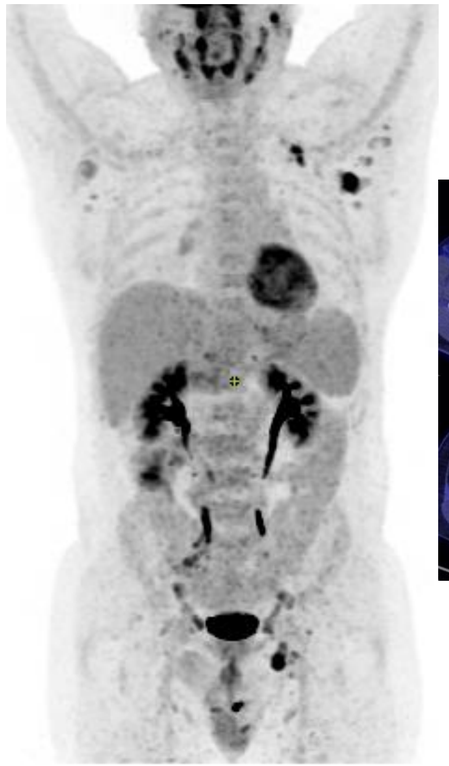
05/08/2025
Pembro-GVD x 2
**DS5-PMR**

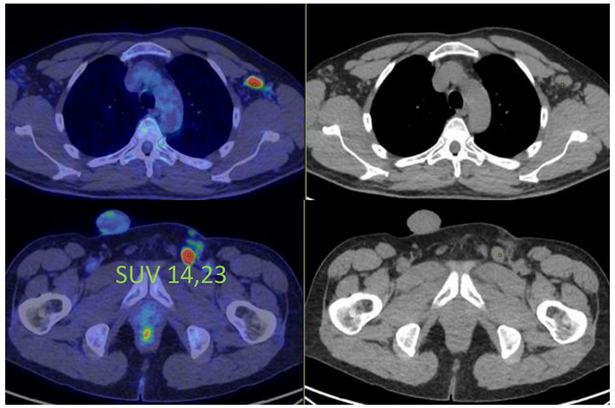


22/09/2025
Pembro-GVD x 4
**DS2-CMR**

## HODGKIN LYMPHOMA

Male 51 yrs
stage IV (BV-AVD x6)
PET-2: CMR

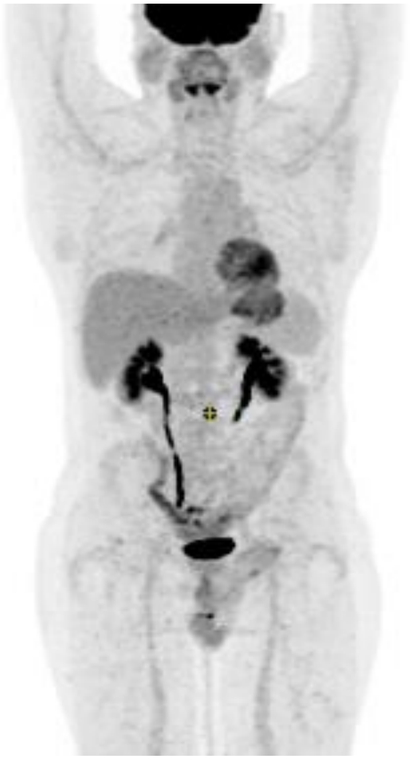




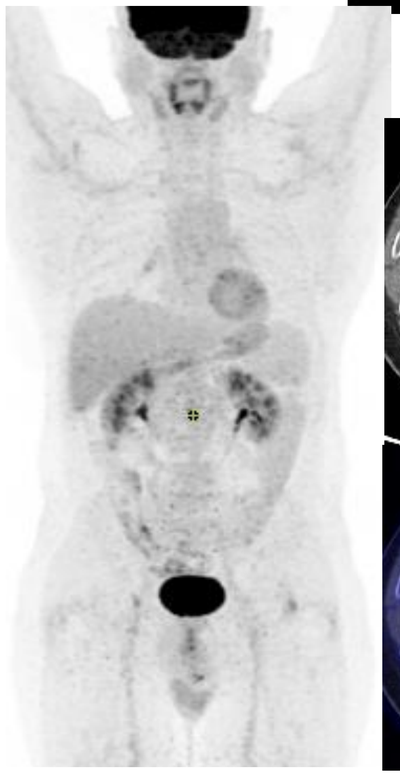

18/11/2023
Baseline PET

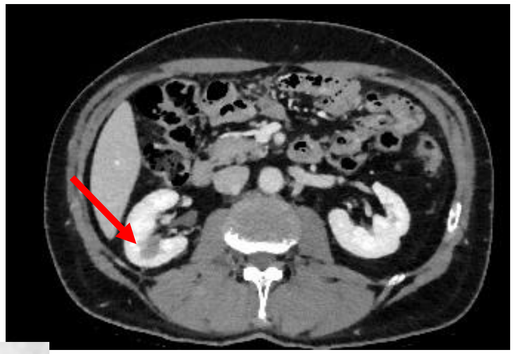
# DLBCL

Male 59 yrs
Stg III
R-CHOP x 6

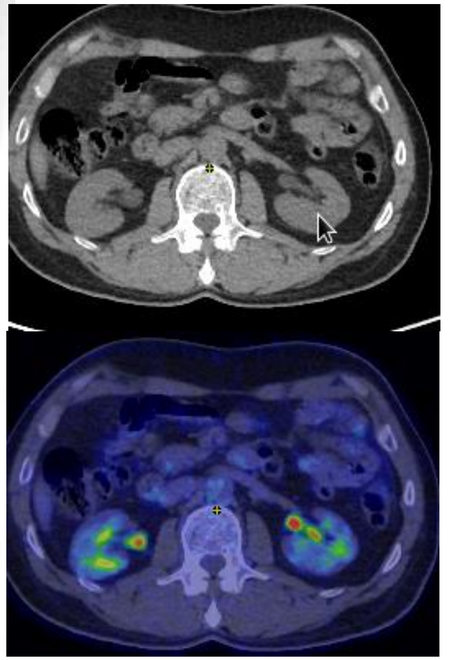


01/07/2024 EoT PET
**CMR**



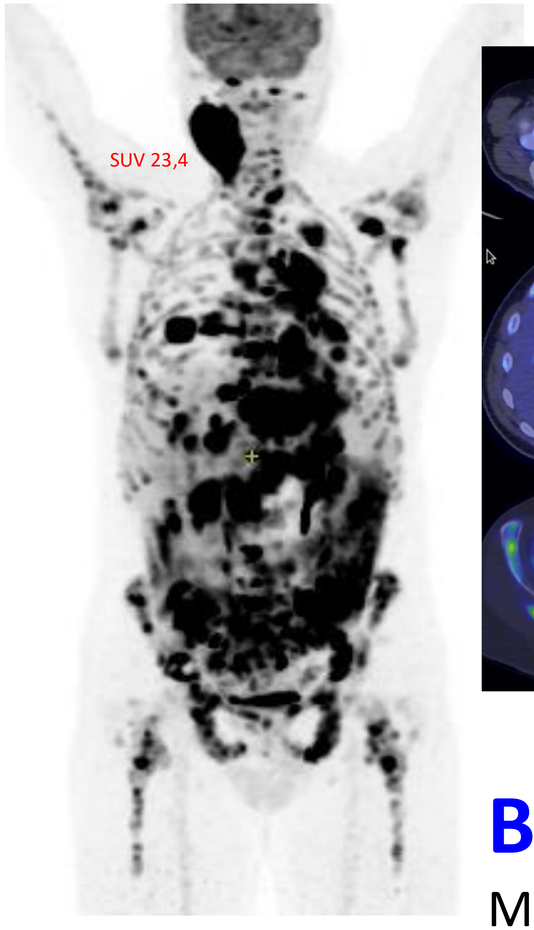


08/01/2026

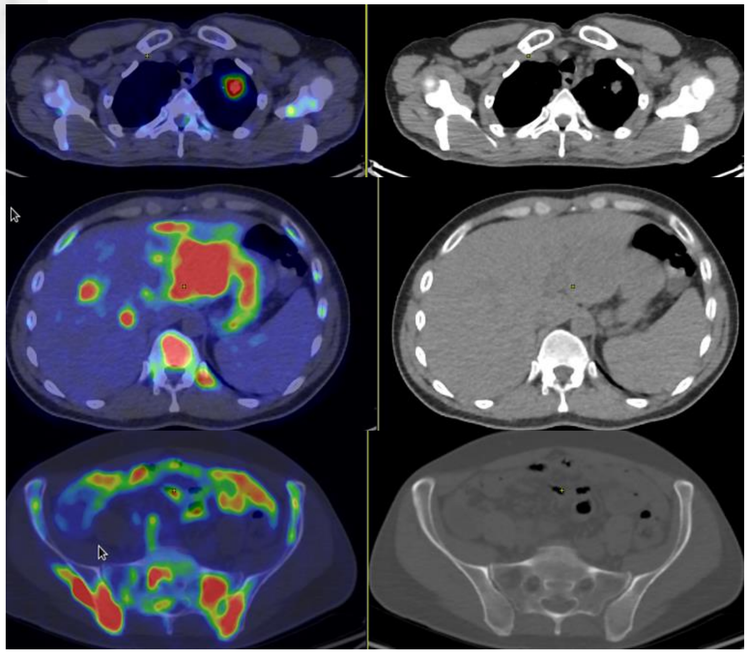


26/01/2026 – Followup PET
**CMR maintained**

**MRI abdomen 25/02/2026: no neoplastic lesions**

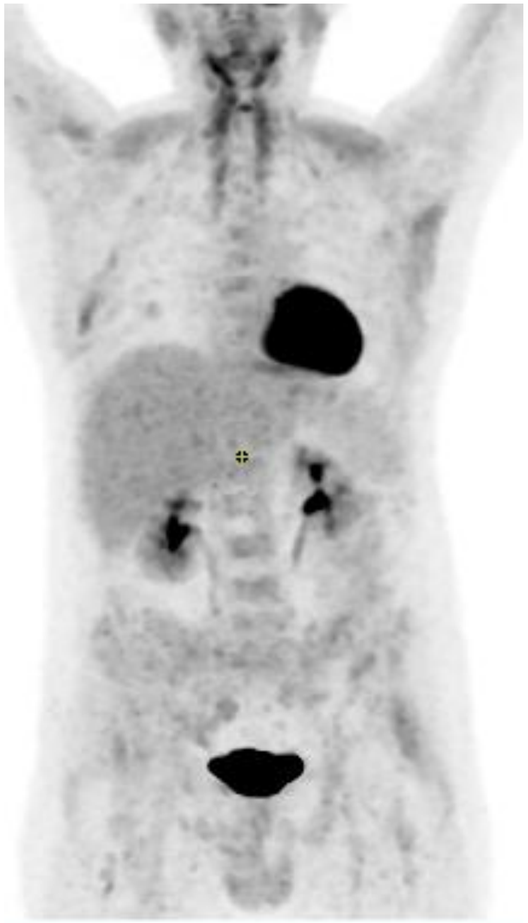



26/09/2024
Baseline PET

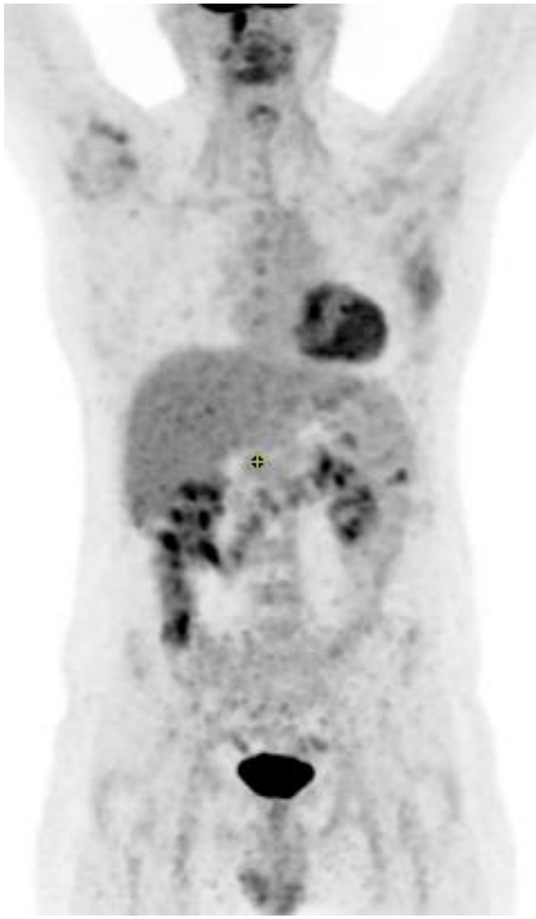


# BURKITT LYMPHOMA

Male 45 aa
BL stage IV
GMALL treatment regimen



20/12/2024
After 2 cycles **DS1-CMR**



19/09/2025
EoT **DS1-CMR**

**CR @ 12/04/2026**

# PET prognostic value in HIV related Lymphoma

| Study (Year) | Population | Study Design / Method | PET Parameters | Key Results | Main Conclusion |
|---|---|---|---|---|---|
| **Rubinstein et al., 2023 (AMC 085)** | **41 HIV-HL** | **Phase 1/2 trial**; BV + AVD | Response evaluation with PET | **100% CR in completers; 2-year PFS 87%** | **PET response; BV-AVD is highly effective and well tolerated in HIV-HL** |
| **Louarn et al., 2022** | **109 HIV-HL** | **Prospective** cohort; baseline PET (PET1) and interim PET (iPET) | Total Metabolic Tumor Volume (TMTV) | **TMTV > 527 cm³ → 2-year PFS 71% vs 91%** | **High baseline TMTV independently predicts worse prognosis** |
| **Ferreri AJS et al. 2021** | **20 HIV HG/BL** | **Prospective** Phase II | PET and CT Response | **2/20 FP pts at PET** | **Biopsy of residual PET lesion required** |
| **Gastwirt et al., 2019 (update)** | **55 HIV-DLBCL** | **Prospective**; response-adapted strategy | Interim PET (Lugano criteria) | **No significant PFS difference between PET− and PET+** | **Limited prognostic reliability of interim PET** |
| **Lawal et al., 2018** | **160 HL patients (57 HIV+)** | **Retrospective** comparative (HIV+ vs HIV−) | SUVmax, SUVmean, MTV, TLG, IPS | **No significant differences between HIV+ and HIV− groups** | **Quant. PET parameters and IPS are comparable regardless of HIV status** |
| **Press et al., 2016 (S0816)** | 336 HIV-negative HL (**13 HIV+**) | **Phase II trial**; PET-adapted therapy | PET2 (Deauville score) | **Overall 2-year PFS 79%; 64% in PET+** | **Interim PET useful to guide response-adapted therapy** |
| **Minamimoto et al., 2013** | **24 HIV NHL (11BL; 13 DLBCL)** | **Retrospective** | Interim PET | **OS higher in PET− (932 vs 454 days)** | **Interim PET predicts overall survival** |
| **Okosun et al., 2012** | **23 advanced HIV-HL** | **Multicenter study**; interim PET (after 2–3 cycles ABVD) | Qualitative interim PET | **2-year PFS: 100% (PET−) vs 50% (PET+)** | **Negative interim PET strongly predicts treatment success** |
| **Dunleavy et al., 2010** | **33 HIV-DLBCL** | **Phase II study**; SC-EPOCH-RR | Interim PET after 2 cycles | **Good negative but poor positive predictive value** | **PET (NPV) useful to rule out failure, less reliable to confirm it** |

# First Extensive Analysis of $^{18}$F-Labeled Fluorodeoxyglucose Positron Emission Tomography–Computed Tomography in a Large Cohort of Patients With HIV-Associated Hodgkin Lymphoma: Baseline Total Metabolic Tumor Volume Affects Prognosis

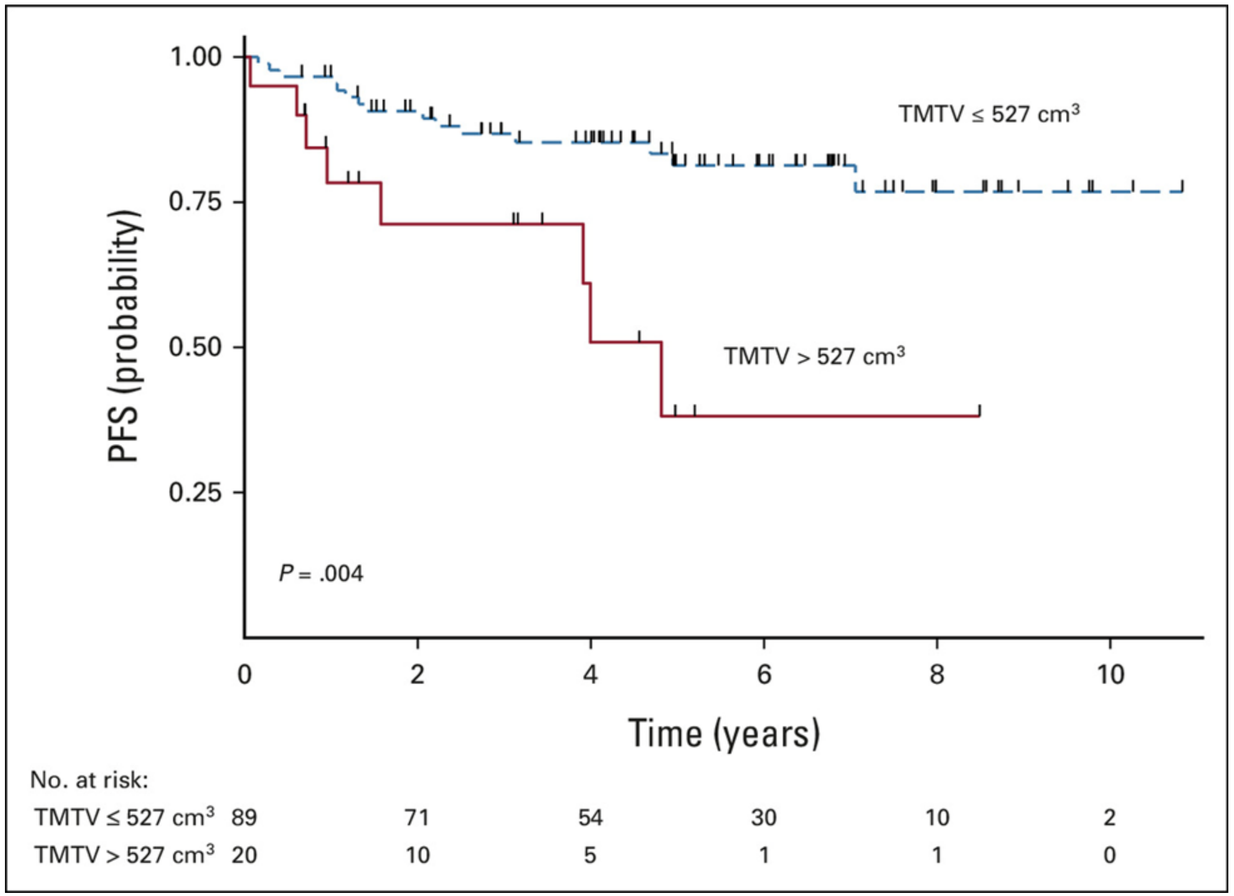
*Louarn N et al J Clin Oncol 2022*

**Population**

- 109 HIV-HL pts prospectively enrolled
- 73% advanced stage (III/IV)
- Baseline and i-PET (104 iPET centrally reviewed)
- ABVD regimen

**Results**

- Median follow-up: 6.7 years
- 12 relapsed (11%); 13 died (12%).
- Optimal MTV threshold: **527 ml**
- 5-yrs PFS and OS: 75.1% and 86.1%.
- **2-yrs-PFS: 71% vs 91% (*P* = .004)**



# Response-Adapted Therapy in HIV-Associated Diffuse Large B-Cell Lymphoma: Updated Results of a Prospective Phase II Study of Short-Course-EPOCH-RR

*Gastwirt JP et al Blood 2019 (Abst)*

## Population

- **55 untreated HIV-associated DLBCL**
- Stage III/IV: 84%
- IPI i/h: 71%
- CNS: 11%
- BM: 11%
- Median CD4: 210 cells/ml

- EPOCH every 21 days; rituximab on days 1 and 5 (SC-EPOCH-RR) min. 3, max 6 cycles
- Baseline and i-PET: **response according DS**

## Results

- 64%  PET-negative after 2 cycles;
- **5-year PFS: PET- 73.4% vs PET+ 62.7% (p = 0.14)**
- **5/13 relapsed pts were i-PET-**

Figure 1: Freedom From Progression (FFP) for All Treated Patients

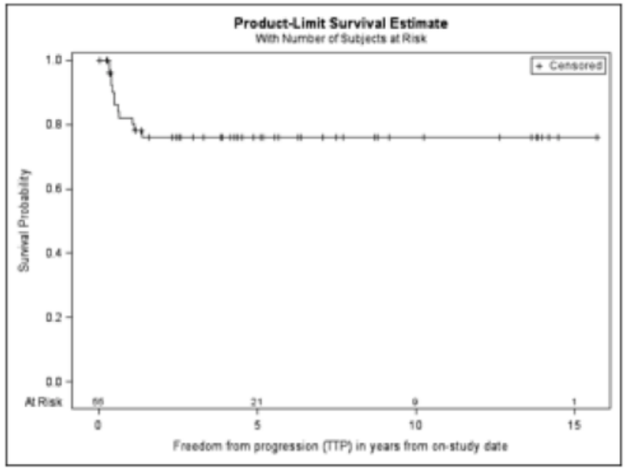



Figure 2: Progression Free Survival (PFS) for All Treated Patients

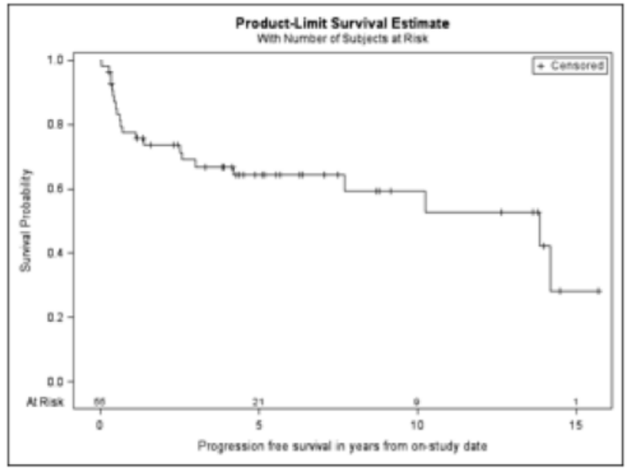



Figure 3: FFP based on Interim PET Response per Lugano Criteria

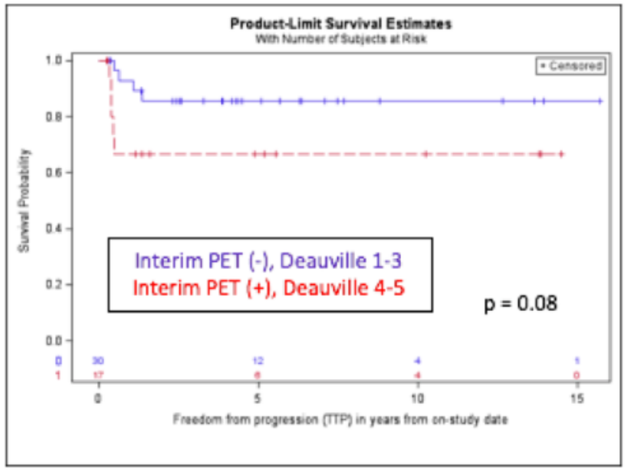
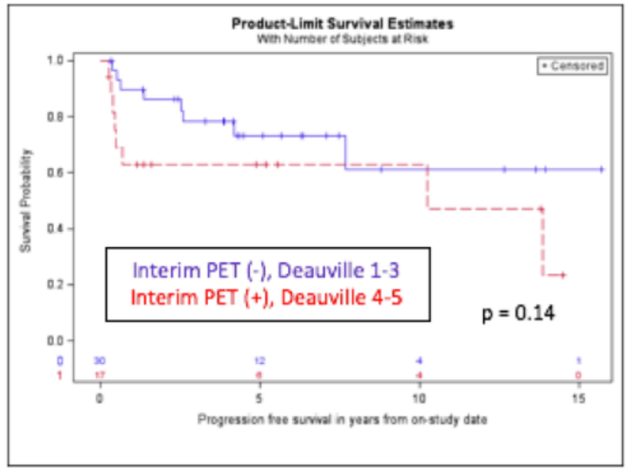



Figure 4: PFS based on Interim PET Response per Lugano Criteria



# Take home messages

- **Staging PET/CT retains its diagnostic value, similarly to immunocompetent patients. In PCNSL, PET/CT is recommended to exclude extracranial localisation.**
- **Interim PET/CT (i-PET/CT) has prognostic value in HIV-HL. No clear evidence supporting the utility of i-PET in DLBCL. Useful in BL with low/intermediate IPI**
- **End-of-treatment PET (EoT PET) is the standard of care for response assessment in alla HIV-related lymphoma**
- **Beware the clinical/virological/on course ART status of the patient as related to FP results.**
- **No clear evidence supporting the role of quantitative PET parameters (SUVmax, MTV, TLG) as prognostic factors.**

# Grazie per l'attenzione