PUO in late stage HIV:
a system based approach

Clues from history
Clues from examination
Clues from standard tests
Work-up
Empirical treatment
What is a PUO?

- Few consultants in ID can define PUO for you and get it correct
- Prolonged fever
- Basic investigations have drawn a blank
  - These now include standard cultures, chest X-Ray and USS abdomen
- For HIV
  - Also tests you would expect to get back within 5-7 days (e.g., CRAG, CMV-PCR, induced sputa etc) have also drawn a blank

Classic PUO

- T >38.3°C for ≥4 weeks. No diagnosis after >2 OPD visits or >3d as in-patient with –ve standard tests

PUO is important in HIV

- Presentation in 2-3% (≤10% pre-HAART)
- Around 2/3rd have a CD4 count <50 cells/mm³
  - Around 60% result from infection
- Morbidity is significant as prolonged hospital stay is common
- Occasional mortality without diagnosis being reached
- Multiple aetiologies may exist but HIV alone will NOT be the cause
PUO is important in HIV

- Presentation in HIV patients is often atypical compared to HIV uninfected
- Presentation in those with CD4 <50 cells/mm³ is often atypical compared to those with higher CD4 counts
- Focal disease is less common and drug-related hypersensitivity and fever more
- Investigations may yield atypical results so experience is necessary in interpretation

Causes of PUO in late stage HIV

- **Common:**
  - TB
  - MAI
  - Lymphoma

- **Less common:**
  - PCP
  - Salmonellosis
  - Syphilis
  - CMV
  - Cryptococcus
  - IRIS

- **Rare UK:**
  - Histoplasmosis
  - Penicilliosis
  - Leishmaniasis
  - Bartonellosis
  - Coccidiodomycosis
  - Toxoplasmosis
  - Castleman’s disease
  - Haemophagocytic syndrome
Also must include the ‘classical’ causes

- **Standard bacterial disease:**
  - Endocarditis
  - Deep abscess/osteomyelitis
- **Connective tissue diseases:**
  - SLE, rheumatoid disease, Still’s disease, PAN, Giant cell arteritis
- **Sarcoidosis**
- **Solid tumours**
  - Renal cell carcinoma, hepatoma, colonic
  - Leukaemias, malignant histiocytosis, myeloma
- **Endocrine:**
  - Thyroiditis
- **Tropical infections**
  - Amoebic liver abscess
  - Brucellosis
- **Factitious fever**

PUO in late stage
HIV: a system based approach

**Clues from history**
Clues from examination
Clues from standard tests
Work-up
Empirical treatment
Clues from the history

• How long have they had a fever?
• What other symptoms do they have?
  • How has the illness evolved?
• What past history is there of note?
  • What do they get up to?
  • Where were they born?
  • Where have they been?

Clues from the history

• Any relevant contacts?
• Have antibiotics improved things?
• Are they taking their HAART?
• Are they taking their prophylactic drugs?
• Have they recently started drugs?
  • What is the CD4 count?

• What clues can you gleam?
Above all

- Record all complaints, even if they disappeared before admission
- Always go back and ask again
- Speak to the relatives/partner
- Consider anything and everything as potentially relevant

PUO in late stage HIV:
a system based approach

Clues from history

**Clues from examination**

- Clues from standard tests
- Work-up
- Empirical treatment
The examination

Meticulous and repetitive

Patient 1

• 37y-old White French born ex-IDU for 8y
• Lived in Spain till 2005, travelled Asia/Europe ++
• PMH – pulmonary TB 1998, HCV +ve
• Presented with 6w history of fever, sweats, loss of weight, followed by cough, breathlessness and joint pains
• HIV+ve, CD4 28 cells/mm3, VL 295,000 c/ml
• On methadone
**Chronology of symptoms – patient 1**

- **37y-old White ex-IDU** lived in Spain till 2005, travelled Asia/Europe.
- **HCV +ve.** PMH – pulmonary TB 1998, HCV-RNA +ve. CD4 28 cells/mm³, VL 295,000 c/ml.
- **D THP** Because of weight loss, and history of fever, sweats, joint pains.
- **Started LOP/EFV/TDF CoT prophylaxis (– dapsone because of rash).
- Admitted after 6w with 3-week history of fevers, sweats, and pain on swallowing.
- **PMH of TB**
- **HCV +ve**
- **Lived Spain and travelled Asia/Europe**

**History & associated symptoms**
10/14/2009

History & examination

37y-old White ex-IDU lived in Spain till 2005, travelled Asia/Europe


Weight loss

PMH of TB

Lived Spain and travelled Asia/Europe

HCV +ve

Hepatoma, cirrhosis

Hepatospleno megaly

6w history of fevers, sweats

MAI/TB, lymphoma, CMV, cryptococcus

crypto/microsporidiosis

TB reactivation, MDR/TB

Leishmaniasis, cryptococcus, penicillium, histoplasmosis

1. TB
2. Leishmaniasis
3. Lymphoma
4. MAI

Weight loss

PMH of TB

Lived Spain and travelled Asia/Europe

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crypto/microsporidiosis

TB reactivation, MDR/TB

Leishmaniasis, cryptococcus, penicillium, histoplasmosis

1. TB
2. Leishmaniasis
3. Lymphoma
4. MAI
Patient 2

- 32y-old air-steward UK-born, MSM
- PMH – travelled extensively, recently SE-Asia
- BCG’d, syphilis x 2 treated
- Diagnosed 2002 CD4 187 cells/mm³ but frequently DNA’d
- Poor adherence to drugs
- Presented with 6w history of fever, sweats, weight loss, diarrhoea, dry cough and rash
- HIV+ve, CD4 42 cells/mm³, VL 42,000 c/ml
- Not on ARV or PCP prophylaxis

Chronology of symptoms—patient 2
History & associated symptoms

32y old air-steward MSM. PMH – travelled extensively, BCG’d, syphilis x 2 treated. Diagnosed 2002 but frequently DNA’d, poor adherence to drugs. CD4 42 cells/mm³, VL 42,000,

- 32y old air-steward MSM
- Travelled extensively
- Diagnosed 2002 but frequently missed appointments
- RMS
- Poor adherence to drugs & several combinations
- Present cases with 2w history of fever, sweats, weight loss, and joint pains
- HIV+ve, CD4 42 cells/mm³, VL 42,000 c/ml

6w history of fevers, sweats

- 32y-old air-steward MSM. PMH – travelled extensively, BCG’d, syphilis x 2 treated. Diagnosed 2002 but frequently DNA’d, poor adherence to drugs. CD4 42 cells/mm³, VL 42,000,
- 35y old White-UK MSM
- Presented with weight loss and chronic diarrhoea
- HIV+ve, CD4 24 cells/mm³ and VL >1 million c/ml
- Started LOP/r/TDF/CoT prophylaxis (→ dapsone because of rash)
- Admitted after 6w with 3-week history of fevers, sweats, and pain on swallowing

No prophylaxis

- 37y-old White French born ex-IDU
- Lived in Spain till 2005
- Presented with 6w history of fever, sweats, weight loss, and joint pains
- HIV+ve, CD4 28 cells/mm³, VL 295,000 c/ml
- No prior HIV-related illness

Travelled extensively as airline steward

- 32y-old White MSM from the UK
- Diagnosed 2002 but frequent missed appointments
- Poor adherence to drugs & several combinations
- Present cases with 2w history of fever, sweats, weight loss, and diarrhoea
- HIV+ve, CD4 28 cells/mm³, VL 295,000 c/ml

Dry cough

- Rash
- LN skin/oral abdomen chest/heart
History & examination

- 32y-old air-steward MSM. PMH – travelled extensively, BCG’d, syphilis x 2 treated. Diagnosed 2002 but frequently DNA’d, poor adherence to drugs. CD4 42 cells/mm³, VL 42,000, Mouth/ear ulcers, rash, lung crackles

1. Cryptococcus
2. Histoplasmosis
3. TB
4. Penicillium

PUO in late stage HIV:
a system based approach

Clues from history
Clues from examination

Clues from standard tests
Work-up
Empirical treatment
General rules of investigation

• **Look for the bug:**
  – Culture, microscopy, antigen, PCR, histology
• **Serology much less helpful**
• **Image early:**
  – CT and/or MR initially
• **Biopsy early:**
  – Establishes the diagnosis quicker than any other test invariably
  – Choose the best site to biopsy (groin yields less than other sites for LN) and **repeat** if poor quality

**Beware:**
– Imaging may be atypical so approach an experienced radiologist if necessary
– Histology may be atypical so specific stains must be performed

Investigations – 1\textsuperscript{st} week

• **Bloods**
  – U&E’s, LFTs, FBC & differential, LDH, amylase, glucose
  – CRP/ESR
• **Standard microscopy and bacterial cultures etc**
  – Blood, urine, stool
  – (Induced) sputum: AFB’s, PJP, standard
• **CD4/VL if not available**
• **Antigen/PCR/serology**
  – Toxoplasma
  – Treponema
  – CRAG
  – CMV IgM/PCR
  – Hepatitis B/C
• **Imaging**
  – Chest X-Ray
  – USS abdomen
• **Exercise oximetry (if chesty)**
### Clues from standard tests

#### PATIENT 1
- Hb – 8.6 g/dl
- WCC – 1.5 x 10^9/L
- Platelets – 62 x10^9/L,
- IgG 37 g/l
- CRP 440
- Albumin 23 g/l,
- Liver enzymes – ALT 62 IU/L, GGT 210 IU/L,
- CXR normal

#### PATIENT 2
- 32y-old air-steward MSM. PMH – travelled extensively
- Rash, mouth ulcer, ear excoriation
- Hb – 10.7 g/dl
- WCC – 1.7 (lymph. 0.3) x 10^9/L
- LDH 1567
- Platelets – 161 x10^9/L
- U/E's normal, LFTs normal
- CXR normal

### PUO in late stage HIV:
#### a system based approach

- Clues from history
- Clues from examination
- Clues from standard tests

#### Work-up

- Empirical treatment
Investigations – 2\textsuperscript{nd} week

- **Blood cultures:**
  - Repeat bacterial x 2
  - Mycobacterial x 2
  - Fungal
- **Imaging:**
  - CT scan thorax/abdomen/pelvis with contrast
- **Antigen/PCR/serology:**
  - EBV-PCR/IgM
  - Lyme
  - Q fever
- **Scoping:**
  - Bronchoscopy if CXR possibly abnormal
  - OGD if anaemia or symptoms
- **Other:**
  - Transthoracic ECHO (especially if IDU)
- **Auto-immune screen**
- **SACE**

Investigations 3\textsuperscript{rd} week

- **Antigen/PCR/serology testing:**
  - Bartonella
  - Histoplasma, leishmania, coccidioides (if ever travelled to endemic area)
  - Parvovirus
  - HHV8
- **Imaging:**
  - PET scan
  - Bone scan
  - Indium labelled white cell scan (if WCC raised)
- **Biopsy:**
  - Any odd skin lesion
  - Lymph node if enlarged
  - Laparoscopy with biopsy
  - Percutaneous tissue biopsy
  - Bone marrow (aspiration/trephine) if abnormal FBC or lymphoma/TB/fungal suspected or blind if completely stuck
  - Liver if enlarged +/- deranged LFTs
Patient 1 - Investigations 1st week


- Blood /stool cultures 48 hours - negative
- Stool microscopy – negative
- Cryptococcal antigen - negative
- Treponemal antibody – negative
- HCV +ve, AFP -ve
- Induced sputa – negative for Pneumocystis jirovecii, AFB, standard culture
- Chest X-Ray - normal
- CMV IgM antibody and PCR – negative
- USS abdomen – liver ++/ spleen ++
- Mycobacterial/fungal cultures –ve so far
- OGD – normal
- CT scan chest/abdomen/pelvis – hepatosplenomegaly and multiple lymphadenopathy

Patient 1 - Investigations 2nd week


- Skin biopsy performed
- Bone marrow requested
- Extended serology sent

- Blood/WCC/Platelets as noted above
- Mycobacterial/fungal cultures –ve so far
- OGD – normal
- CT scan chest/abdomen/pelvis – hepatosplenomegaly and multiple lymphadenopathy
Patient 1 - Investigations 3rd week


- Weight loss and chronic diarrhoea
- HIV +ve, CD4 24 cells/mm3 and VL >1 million c/ml
- Started LOP/r/TDF/FTC and CoT prophylaxis (→ dapsone because of rash)
- 37y-old White French born ex-IDU
- Lives in Spain till 2005
- Presented with 6w history of fever, sweats, weight loss, and joint pains
- HIV+ve, CD4 28 cells/mm3, VL 295,000 c/ml
- No prior HIV-related illness

32y-old White MSM from the UK

- Diagnosed 2002 but frequent missed appointments
- Poor adherence to drugs & several combinations
- Present with 2w history of fever, sweats, weight loss, and diarrhoea
- HIV+ve, CD4 42 cells/mm3, VL 42,000 c/ml

Hb – 8.6 g/dl, WCC – 1.5 x 10^9/L Platelets – 62 x10^9/L IgG 37 g/l

USS abdomen – liver ++/ spleen ++

CT scan confirmed USS finding

Mycobacterial/fungal cultures –ve so far

Leishmania/histoplasma serology –ve

Histoplasma/leishmania antigen -ve

Skin biopsy and bone marrow demonstrated numerous Leishmania amastigotes

Diagnosis

Visceral leishmaniasis

Lessons patient 1

- **Travel history** is very important as many infections represent reactivation a long-time after departing the endemic area
- **Biopsy early** especially if there is a lump (skin/LN etc)
- **Bone marrow** aspiration/biopsy if there is cytopenias present
- **Appropriate stains and cultures** must be requested
- Classic features may be absent for any unusual pathogen because of the profound immune depletion
- This patient responded well to liposomal amphotericin B and is doing well
Patient 2 - Investigations 1\textsuperscript{st} week

32y-old air-steward MSM. PMH – travelled extensively, BCG’d, syphilis x 2 treated. Diagnosed 2002 but frequently DNA’d, poor adherence to drugs. CD4 26 cells/mm\(^3\), VL 42,000, Rash, mouth ulcer

\begin{itemize}
  \item 35y old White-UK MSM
  \item Presented with weight loss and chronic diarrhoea
  \item HIV +ve, CD4 24 cells/mm\(^3\) and VL >1 million c/ml
  \item Started LOP/r/TDF/FTC and CoT prophylaxis (→ dapson because of rash)
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\begin{itemize}
  \item Hb – 10.7 g/dl, WCC – 1.7 (lymphocytes 0.3) x 10\(^9\)/L LDH 1567
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Blood /stool cultures 48 hours - negative
Stool microscopy – negative
Cryptococcal antigen - negative
Treponemal antibody - negative
Sputa – negative for Pneumocystis jirovecii, AFB, standard culture
Chest X-Ray - normal
CMV IgG antibody +ve

Patient 2 - Investigations 2\textsuperscript{nd} week

\begin{itemize}
  \item 32y-old air-steward MSM. PMH – travelled extensively, BCG’d, syphilis x 2 treated. Diagnosed 2002 but frequently DNA’d, poor adherence to drugs. CD4 26 cells/mm\(^3\), VL 42,000, Rash, mouth ulcer
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Cryptococcal antigen - negative
Treponemal antibody - negative
Sputa – negative for Pneumocystis jirovecii, AFB, standard culture
Chest X-Ray - normal
CMV IgG antibody +ve

\begin{itemize}
  \item Bronchoscopy and BAL –ve for PCP and AFB
  \item Treated empirically with CoT and steroids
  \item CT/MRI head normal outside cerebral atrophy
  \item LP – normal (standard and PCRs)
\end{itemize}

\begin{itemize}
  \item 2nd week
  \item Increasing SOB and CXR changes consistent with early PCP
\end{itemize}

\begin{itemize}
  \item Skin biopsy performed on ear
  \item Extended serology sent
\end{itemize}
Patient 2 - Investigations 3rd week

32y-old air-steward MSM. PMH – travelled extensively, BCG’d, syphilis x 2 treated. Diagnosed 2002 but frequently DNA’d, poor adherence to drugs. CD4 26 cells/mm³, VL 42,000. Rash, mouth ulcer

Hb – 10.7 g/dl, WCC = 1.7 (lymphocytes 0.3) x 10⁹/L
Platelets = 161 x10⁹/L
LDH 1567, U/E’s normal, LFTs normal
CXR – mild pneumonitis

Penicillum marneffii isolated from blood culture and throat swab
Biopsy of ear demonstrated fungal elements typical for penicillum

Diagnosis: Disseminated penicilliosis

Lessons patient 2

• Again, don’t forget the travel history is essential
• Again, go for early biopsy
• Again, vital that appropriate stains and cultures are requested
• Again classic features may be absent for any unusual pathogen
• This patient initially responded well to liposomal amphotericin B but developed intraocular fungal infection
• After induction, treated with Itraconazole
Meticulous history and examination

- How long have they had a fever
- What other symptoms do they have
- How has the illness evolved
- What past history is there of note
- What do they get up to
- Where were they born
- Where have they been
- Any relevant contacts
- Have antibiotics improved things
- Are they taking their HAART
- Are they taking their prophylactic drugs
- Have they recently started drugs
- What is the CD4 count
- What clues can you gleam

Hands and nails
All lymph nodes
Head and neck
Dilated fundoscopy
Oropharynx
Ears, teeth and sinuses

Heart murmurs
Liver and spleen
Gall bladder
Bone tenderness
Genitourinary
Prostate

1st week investigations

**Bloods**
- U&E’s, LFTs, FBC and differential, LDH, CRP/ESR, amylase, glucose
- Standard microscopy and bacterial cultures etc
  - Blood, urine, stool
  - (Induced) sputum: AFB’s, PJP, standard
- CD4/VL if not available
- Antigen/PCR/serology tests
  - Toxoplasma
  - Treponema
  - CRAG
  - CMV IgM/PCR
  - Hepatitis B/C

**Imaging**
- Chest X-Ray
- USS abdomen
- Exercise oximetry (if chesty)
Meticulous history and examination

1st week investigations

2nd week investigations

Blood cultures:
- Repeat bacterial x 2
- Mycobacterial x 2
- Fungal

Imaging:
- CT scan thorax/abdomen/pelvis with contrast

Antigen/PCR/serology testing
- EBV-PCR/IgM
- Lyme
- Q fever
- Auto-immune screen
- SACE

Scoping:
- Bronchoscopy if CXR possibly abnormal
- OGD if anaemia or symptoms

Other:
- Transthoracic ECHO (especially if IDU)

Meticulous history and examination

1st week investigations

2nd week investigations

3rd week investigations

Diagnosis!

Antigen/PCR/serology testing
- Bartonella
- Histoplasma, leishmania, coccidioides (if ever travelled to endemic area)
- Parvovirus
- HHV8

Imaging:
- PET scan
- Bone scan
- Indium labelled white cell scan (if WCC raised)

Biopsy:
- Any odd skin lesion
- Lymph node if enlarged
- Laparoscopy with biopsy
- Percutaneous tissue biopsy
- Bone marrow (aspiration/trephine)
  if abnormal FBC or lymphoma, TB, fungal suspected or blind if completely stuck
- Liver if enlarged +/- deranged LFTs
Antimicrobials for standard pathogens during work-up

- Stop empirically introduced antibiotics if cultures –ve and no improvement
- Confirm that cultures are cooking before giving any new antibiotics
- Avoid those which have an effect on mycobacteria:
  – Azithromycin and clarithromycin
  – Quinolones (especially ciprofloxacin)
  – Rifampicin
- Avoid azoles (specifically fluconazole) if disseminated fungal infection possible
- Broad spectrum antibiotics usually fine

PUO in late stage HIV:
a system based approach

Clues from history
Clues from examination
Clues from standard tests
Work-up

**Empirical treatment**
Empirical treatment - scenarios

Imaging shows abnormalities but ‘difficult to biopsy’ and going nowhere fast

Mediastinoscopy?
Laparotomy?
Open surgical biopsy?

or

All investigations drawn a blank and significant morbidity from fever

Have you documented fever?
Could this be drug related?
Could this be IRIS?
Have you biopsied BM and Liver?
Have you sought a 2nd opinion, listened to your SPR, searched Medline/Google?
Empirical treatment - scenarios

Imaging shows abnormalities but ‘difficult to biopsy’ and going nowhere fast

or

All investigations drawn a blank and significant morbidity from fever

or

Patient very sick and can’t wait as mortality on the cards

Empirical treatment - information

Need to know:

Likely causes?
- Off or on ARV?
- Travel/origin?
- Age?

What’s been excluded?

Is tissue cooking?
Empirical treatment

• When it is very unlikely that there is an ‘exotic’ cause then the differential is between MAI, lymphoma, and TB
• Drug associated fever and IRIS are possibilities if on ARV and OI-treatment
• Further investigation must continue even if empirical therapy given
• ARVs should continue unless drug-related fever suspected
Recommendation - sickly

**Standard UK**
- Rifampicin
- Clarithro/azithromycin
- Ethambutol
- Ciprofloxacin
- Corticosteroids

**From abroad**
- Amphotericin B (liposomal)
- Itraconazole

**HIV treatment**
- Early

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<tr>
<th>Common:</th>
<th>Standard bacterial disease:</th>
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<tr>
<td>TB MAI</td>
<td>Endocarditis Deep abscess osteomyelitis</td>
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<td>CMV Cryptococcus</td>
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- Clues from standard tests
- Work-up
- Empirical treatment