Challenges in the management of advanced HIV disease from the clinical perspective

Linghua Li, MD, PhD
Guangzhou Eighth People’s Hospital
Center for Infectious Diseases
APACC, June 29, 2018
Prevalence of advanced HIV disease globally

30–40% of PLWH starting ART in low-and middle-income settings have advanced HIV diseases

Number of new HIV infections globally in 2016 and change since 2010

1.8 new HIV infections globally in 2016. Decrease in number of new infections annually since 2010

Proportion of people with advanced HIV disease starting ART by sex and country income group, 2010–2015

1. AVERT.org. source: UNAIDS Data 2017; 2.WHO Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, July 2017

The results are based on 951 855 adults from 55 countries after imputation of missing data. The shaded areas represent 95% confidence intervals.
High prevalence of advanced HIV disease in China

Prevalence of HIV infection in China in 2017

- Number of PLWH alive: 437,377
- Number of death reported: 239,289
- Total number: 676,666

Prevalence of new reported HIV infection in Guangdong province from 2000 to 2016

- Up to the end of 2016:
  - Reported number of HIV-positive/AIDS cases alive: 47,545, including AIDS: 18,671 (39.3%).
  - Death number because of HIV/AIDS: 15,816

Causes: Late HIV test, stigma, late diagnosis of OIs, unavailability of effective medicines, etc.

References:
Leading death causes of HIV/AIDS patients in China

Advanced HIV disease is still the leading death causes of HIV/AIDS patients in China

### Causes of death among HIV-infected inpatients in Shanghai from 2006 to 2015

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Number of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS-related death</td>
<td>233 (76.9)</td>
<td></td>
</tr>
<tr>
<td>Pneumocystis jirovecii pneumonia</td>
<td>80 (26.4)</td>
<td></td>
</tr>
<tr>
<td>NTM/MTB infection*</td>
<td>56 (18.5)</td>
<td></td>
</tr>
<tr>
<td>AIDS-related encephalopathy*</td>
<td>47 (15.5)</td>
<td></td>
</tr>
<tr>
<td>Recurrent bacterial pneumonia</td>
<td>31 (10.2)</td>
<td></td>
</tr>
<tr>
<td>AIDS-related malignancy*</td>
<td>18 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Wasting syndrome</td>
<td>1 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Non-AIDS-related death</td>
<td>70 (23.1)</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>18 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Liver disease</td>
<td>11 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Non-recurrent bacterial pneumonia</td>
<td>9 (3.0)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>8 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Non-AIDS-related malignancy</td>
<td>7 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>6 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Renal disease</td>
<td>5 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>2 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Other*</td>
<td>4 (1.3)</td>
<td></td>
</tr>
</tbody>
</table>

### Causes of death among HIV-infected inpatients in Guangdong from 2001 to 2011

- **Death**: 345 (10.13%)
- **OIs**: 295 (85.5%)
- **Severe pneumonia**: 79
- **NTM/MTB**: 56
- **Talaromycosis**: 52
- **CM**: 17

Mycobacterium tuberculosis (MTB) - leading cause of morbidity and mortality among people living with HIV worldwide.

China mainland: HIV 7.2%; AIDS 22.8%
High undiagnosed rate in HIV/TB patients compared with HIV(-) TB ones

- Atypical clinical, laboratory and radiological features
- Less production of sputum
- False negative result from a TB sputum smear test
- Low detection by TB skin test (TST), interferon-γ release assay (IGRA)
- High prevalence of extrapulmonary and latent TB

High undiagnosed rate in HIV/TB patients

- LTBI activation
- Dissemination
- Transmission
- Developing resistance
- Relapse
Treatment and prevention prophylaxis

Preferred Therapy:

- Initial Phase: 2 Months **INH + [RIF or RFB] + PZA + EMB (AI),**
- Continuation Phase: **INH + (RIF or RFB) daily (5–7 times/week) (AIII)**
- Total Duration of Therapy (For Drug-Susceptible TB): **6-12 months**

Preferred Prevention Prophylaxis:

- **INH x 9 months**

- Poor or prolonged response
- DDI
- Toxicity
- Relapse or IRIS
- Difficulty in excluding TB when providing with pre-emptive therapy

Insufficient Chinese data

WHO Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, July 2017
Talaromycosis (TM)

-The most common fungal infection in AIDS patient in Southern China and Southeast Asia
Diagnosis

✓ Gold standard: direct microscopy finding yeasts with transverse septum

✓ Confirmation with culture demonstrating thermal dimorphism and red pigment in 25°C, ≥5~7 days
  • Bone marrow: 70~100%
  • Skin: 90%
  • Blood: 70%

Challenges:
✓ Delayed diagnosis
✓ Low sensitivity and specificity
✓ Traumatic operation of biopsy
Novel diagnosis-PCR

➢ New diagnostic methods:
✓ Rapid
✓ Highly sensitive and specific
✓ Field-applicable accurate
✓ Cost-effective

➢ Clinical performance of the MP1 real-time PCR assay:
✓ Total sensitivity 62%, 95% CI: 48.2-74.1; total specificity (100%) 95% CI: 83.9-100.
✓ Prior to antifungal therapy sensitivity 70.4%, 95% CI: 51.5-84.1.
✓ Within 48 hours antifungal therapy sensitivity 52.2%, 95% CI: 33.0-70.8

Vanittanakom:
Nested PCR ITS
34 serum samples, sensitivity 68% (24/34)

Pornpraset:
Real-time PCR ITS
20 whole blood samples sensitivity 60% (12/20)

Challenges:
✓ Low sensitivity
✓ Laboring
Novel diagnosis - Serological diagnosis

**MP1p MAb ELISA, Pooled MAb ELISA**

**TABLE 1. Positive rates of MP1p antigen in HIV-infected patients from Guangzhou during 2004-2011**

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of samples</th>
<th>MP1p antigen positive % (No. of samples)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>271</td>
<td>5.17 (14)</td>
</tr>
<tr>
<td>2005</td>
<td>527</td>
<td>6.45 (34)</td>
</tr>
<tr>
<td>2006</td>
<td>884</td>
<td>8.37 (74)</td>
</tr>
<tr>
<td>2007</td>
<td>894</td>
<td>9.62 (86)</td>
</tr>
<tr>
<td>2008</td>
<td>1221</td>
<td>9.42 (115)</td>
</tr>
<tr>
<td>2009</td>
<td>1284</td>
<td>10.28 (132)</td>
</tr>
<tr>
<td>2010</td>
<td>1256</td>
<td>12.58 (158)</td>
</tr>
<tr>
<td>2011</td>
<td>1294</td>
<td>9.72 (118)</td>
</tr>
<tr>
<td>Total</td>
<td>8131</td>
<td>9.36 (761)</td>
</tr>
</tbody>
</table>

**TABLE 2. Prevalence of MP1p antigenemia in HIV-infected patient sera with different levels of CD4 count**

<table>
<thead>
<tr>
<th>CD4 count (cell/µL)</th>
<th>MP1p antigen positive group (% no. of samples)</th>
<th>MP1p antigen negative group (% no. of samples)</th>
<th>Total (no. of samples)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 500</td>
<td>1.65 (6)</td>
<td>98.35 (357)</td>
<td>363</td>
</tr>
<tr>
<td>200 - 500</td>
<td>1.69 (17)</td>
<td>98.31 (991)</td>
<td>1008</td>
</tr>
<tr>
<td>100 - 200</td>
<td>4.53 (14)</td>
<td>95.47 (295)</td>
<td>309</td>
</tr>
<tr>
<td>50 - 100</td>
<td>10.36 (23)</td>
<td>89.63 (199)</td>
<td>222</td>
</tr>
<tr>
<td>&lt; 50</td>
<td>28.06 (220)</td>
<td>71.94 (564)</td>
<td>784</td>
</tr>
<tr>
<td>Total</td>
<td>10.42 (280)</td>
<td>89.58 (2406)</td>
<td>2686</td>
</tr>
</tbody>
</table>

**Study population**

Cases = 184 AIDS culture-confirmed Tm patients without Tm + 26 healthy controls

**Results**

Sensitivity = 82%
Specificity = 93%

**Challenges:**
- Have not evaluated the value for screening of AIDS patients with low CD4+ before ART
- Have not evaluated the value of early diagnosis
Challenge:  
✓ Clinical Trial for pre-emptive therapy

Inhalation of spores

Dissemination of infection

Clinical manifestations

Screen Mp1p if CD4 <100 cells

Jarvis J, et al. CID 2009
Longley N, et al. CID 2016
<table>
<thead>
<tr>
<th>Acute therapy</th>
<th>Maintenance therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin*</td>
<td>Itraconazole 200 mg/d</td>
</tr>
<tr>
<td>Itraconazole 400 mg/d</td>
<td>Itraconazole 400mg/d</td>
</tr>
<tr>
<td>0 wk</td>
<td>2 wk</td>
</tr>
</tbody>
</table>

Based on a Chiang Mai study: 74 patients with HIV-associated talaromycosis treated with amphotericin B x 2 wks, followed by itraconazole for 10 wks. There was one death, and treatment response was 97%.

Treatment strategy requiring update

**Challenges:**
- Fungal drug associated toxicity
- Lack of evidence-based new antifungal strategy
- Cost-effectiveness of combination antifungal therapy
- Few novel antifungal regimens

**AMB vs. ITR**

**IVAPeni Trial**

**Better**

- Microbiologically confirmed penicilliosis

- Consent

- Inclusion/Exclusion criteria

- Randomization

- Amphotericin B 0.7 mg/kg/d x 2 wks

- Itraconazole 400 mg/d x 2 wks (600 mg/night x 3d loading)

- Itraconazole 10 wks

- Survival during first 2 wks

- Monthly follow up for 6 months

- Absolute risk of death over 24 weeks

Le T, et al. NEJM, 2017

Longitudinal quantitative fungal counts in blood

- 0.95 log10 CFU/ml/d

- 0.36 log10 CFU/ml/d
Case

- Male, 38 Y, married, Admitted to hospital May 6, 2017
- Complained having fever and cough over 4 weeks, yellow urine 2 weeks.
- MSM, HBsAg (+) 10 years without anti-HBV treatment
- PE: T 39 °C, several enlarged lymph nodes (2X1cm) around the neck, toufukasu on the tongue and throat, no rash nor other abnormal findings
  - HIV-Ab (+) ; GM (-), Mp1p (+), Culture (bone marrow, blood) (-); CD4+: 5 cells/ul;
  - WBC 4.70 10E9/L, LYM 1.03 10E9/L, RBC 3.42 10E12/L, Hb 52 g/L, PLT 25 10E9/L;
  - TB 186.28 umol/L DB 124.78 umol/l ALT: 50U/L AST: 232U/L ALB 17 g/L
  - ✓ BALF culture: TM (+)
  - ✓ Voriconazole (IV) 2 w, bone marrow TM (+) → AMB 2 w, then bone marrow TM (-), BRE and liver function normal, receiving ART. present CD4+: 186 cells/ul; HIV RNA undetectable.
  - ✓ Make diagnosis without typical rash nor blood culture finding
  - ✓ Anti-fungal treat with patients with MOF and avoid DDI with ARV
Cryptococcal meningitis (CM)

-A common and fatal fungal infection in AIDS patients

Annual incidence of Cryptococcal infection by country

CrAg Screening and pre-emptive treatment

WHO recommends to screen cryptococcal capsular antigen (CrAg) in HIV(+) patients with CD4+ < 100 cells/μl before ART and give pre-emptive fluconazole treatment.

<table>
<thead>
<tr>
<th>Regions</th>
<th>Positive rate for CrAg(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pune, India (n=208)</td>
<td>8</td>
</tr>
<tr>
<td>Vietnam (n=226)</td>
<td>4</td>
</tr>
<tr>
<td>Thailand (n=704)</td>
<td>13.1 (hospitalized with pneumonia)</td>
</tr>
<tr>
<td>Kampala, Uganda (n=609)</td>
<td>8.2</td>
</tr>
</tbody>
</table>

Countries that currently recommend antigen screening in national HIV guideline


Challenges:
✓ No Chinese data
✓ Have not been clinically applied
## Treatment: 2018 WHO vs. Chinese consensus (HIV)

<table>
<thead>
<tr>
<th>WHO</th>
<th>Chinese consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>AmBd(1.0 mg/kg/d)+Flucytosine(100 mg/kg/d)Fluconazole1200mg</td>
<td>AmBd 0.5-1mg/kg/d+ Flucytosine(100 mg/kg/d) ≥4w</td>
</tr>
<tr>
<td>Fluconazole+ Flucytosine</td>
<td>AmBd 0.5-0.7mg/kg/d ≥4w</td>
</tr>
<tr>
<td>AmBd(1.0 mg/kg/d)+Fluconazole1200mg</td>
<td>Fluconazole（600-800mg/d）/Voriconazole/Itraconazole ± Flucytosine ≥4w</td>
</tr>
<tr>
<td></td>
<td>2w</td>
</tr>
</tbody>
</table>

### Challenges:

- Chinese CM patients could not endure the side effects of high dose of AmBd
- Patients increase AMBd gradually to reach the treatment concentration
- Unavailability of some anti-fungal medicines

Treatment: application of Glucocorticoids

Steroid is not recommended in WHO guideline and IDSA

Challenges:
✓ Steroid is still being used in many Chinese CM patients to decrease their intracranial pressure.
✓ Lack of clinical trial and normative strategy for steroid usage in China

✓ Many challenges in the management of advanced HIV diseases.
✓ Proposed future clinical research

1. Evaluate novel diagnostics:
   - Evaluate new TB assay, the Mp1p assay and CrAg screening in prospective clinical studies
   - Build the evidence to support screening for asymptomatic disease and the evidence for pre-emptive therapy

2. Novel treatment strategies:
   - RCTs short-course AMB, Liposomal ampho B, voriconazole for TM
   - RCTs standard anti-CM treatment strategies
   - RCTs new anti-TB treatment strategies
Acknowledgements

Faculty in Infectious Diseases Department of Guangzhou Eighth People’s Hospital

Our research team

Thuy Le