CNS opportunistic infections in developed countries in the HAART era

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Adults and children estimated to be living with HIV as of end 2004

Total: 39.4 (35.9 – 44.3) million
OIs DISTRIBUTION IN THE WORLD HAS TWO DIFFERENT PATTERNS ACCORDING TO HAART ACCESS
Adults and children estimated to be living with HIV as of end 2004

Opportunistic infections (OIs) are the leading cause of death in developing countries.
Pathogenesis of CNS-OIs in AIDS patients

**REACTIVATION OF LATENT INFECTIONS**

- Mycobacterium tuberculosis
- *Pneumocystis jirovecii*, *T. gondii*
- Herpesvirus family (CMV, VZV, HSV, JC virus, EBV); Other

**PROLIFERATION ENDOGENOUS MICROORGANISMS**

- *Candida albicans*
- Coccidia (e.g. *I. belli*)
- Fungi (e.g. *C. neoformans*)
- Other

**EXOGENOUS SOURCE**

- Other
CD4+ T cell counts and CNS-OIs


Incidence of CNS toxoplasmosis in AIDS Patients at the Hosp. Clinic (Barcelona, Spain) between 1984 - 2000

HAART: Highly Active Antiretroviral Therapy (≥2NRTI plus ≥1PI/NNRTI)
CNS opportunistic infections (OI) in developed countries in the HAART era

• Current epidemiology
• Advances in the diagnosis
• Timing of HAART
• Immune reconstitution diseases
• Discontinuation prophylaxis studies
• Conclusions

Total 568 / 9803 patients (5.8%)
Median follow-up 40.9 months (IQR: 12.0-65.0)
Incidence of CNS-Diseases during follow-up

- **Non CNS-D**: (40% decline/year)
- **CNS-D**: (40% decline/year)
Incidence of individual CNS-Diseases during follow-up

Decline of incidence/year

ADC 45%, 95% CI: 40 - 49%
CNS-OIs 37%, 95% CI: 34 - 41%
CNS-D prevalence / CD4 cell counts and plasma VL at diagnosis over calendar year

Number of CNS-D per calendar year

Changes in proportion CNS-OI / ADC  p = 0.095
Changes in CD4 cell counts  p < 0.0001
Changes in HIV-1 RNA copy levels  p = 0.11
Conclusions from the EuroSida study

• Significant decrease of CNS-D incidence.
• Different trends among individual CNS-D (more marked in ADC and PBL, less in PML)
• Increase of CD4 counts at the diagnosis of CNS-D in later years
• Higher risk of CNS-D associated with low CD4 cell count and high plasma VL, but not HAART or calendar year.
2004 AIDS-defining Events in Spain
N = 2,010 cases

- Tuberculosis: 32% = 640 cases
- *P. carinii* pneumonia (PCP): 22%
- Esophageal candidiasis: 16%
- Wasting syndrome: 9%
- CNS toxoplasmosis: 7% = 140 cases
- Bacterial pneumonia: 6%
- Kaposi’s sarcoma: 6%
- PML: 5% = 100 cases
- NHL: 3%
- AIDS-dementia complex: 3%
- Cryptococcosis: 2% = 40 cases
- CMV disease: 2% = 40 cases
Reasons for Failure of Prevention of Toxoplasmic encephalitis (TE)

1. No TE prophylaxis
   - Unaware of HIV-1 infection
   - No access to care
   - Provider omission
   - Early occurrence of OIs
   - Drug intolerance
   - Non-compliance.

2. On TE prophylaxis (breakthrough TE)
   - Drug-drug PK interactions (e.g. Rifampin - TMP/SMX*)
   - Immunologic failure (CD4 <50 cells/µL)

CDC/NIH/HIV Medicine/IDSA Recommendations. MMWR. 2004
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- Conclusions
Advances in diagnosis of CNS OIs in HIV-infected Patients

• Neuroimaging techniques
  - $^{201}T$allium Single-Photon Emission CT (SPECT)
  - Positron Emission Tomography (PET)

• Nucleic acid techniques (CSF)
  - PCR for Herpesvirus family and \textit{M. tuberculosis}

• Immunological techniques (PBMC)
  - Interferon-\textgamma detection methods (TB-ELISPOT)
### Radiological Patterns of CNS Mass Lesions in AIDS Patients: $^{201}$Tl SPECT & PET


<table>
<thead>
<tr>
<th>Imaging technique</th>
<th>Toxoplasmosis</th>
<th>Lymphoma</th>
<th>PML</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enhancement</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Pattern</td>
<td>Ring</td>
<td>Homogenous or ring</td>
<td>—</td>
</tr>
<tr>
<td>Edema</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>SPECT thallium-201</td>
<td>Cold</td>
<td>Hot</td>
<td>Cold</td>
</tr>
<tr>
<td>PET</td>
<td>Hypometabolic</td>
<td>Hypermetabolic</td>
<td>Hypometabolic$^a$</td>
</tr>
</tbody>
</table>

**Note:** PET, positron emission tomography; PML, progressive multifocal leukoencephalopathy; SPECT, single-photon emission CT.

$^a$ Usually hypometabolic, but occasionally hypermetabolic.
Primary CNS Lymphoma in an AIDS Patient
Tallium SPECT studies in patients with Primary CNS Lymphoma

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruiz (1994)</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Lorberboym (1996)</td>
<td>100%</td>
<td>90%</td>
</tr>
<tr>
<td>McArthur (1997)</td>
<td>76%</td>
<td>72%</td>
</tr>
<tr>
<td>Murry (1997)</td>
<td>80%</td>
<td>81%</td>
</tr>
<tr>
<td>Lorberboym (1998)</td>
<td>96%</td>
<td>76%</td>
</tr>
<tr>
<td>Lee VW (1999)</td>
<td>100%</td>
<td>80%</td>
</tr>
<tr>
<td>Antinori (1999)</td>
<td>92%</td>
<td>89%</td>
</tr>
<tr>
<td>Skiest D (2000)</td>
<td>86%</td>
<td>83%</td>
</tr>
<tr>
<td>Giancola ML (2004)</td>
<td>86%</td>
<td>88%</td>
</tr>
</tbody>
</table>
Diagnostic Capability of Positive SPECT Result ($^{201}$Tl uptake $>1.95$) and of EBV-DNA Detection in CSF by PCR for the Diagnosis of AIDS-Related PCNSL


<table>
<thead>
<tr>
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<th>SPECT*</th>
<th>and/or</th>
<th>PCR +</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Sensitivity</td>
<td>92%</td>
<td>100%</td>
<td>85%</td>
</tr>
<tr>
<td>- Specificity</td>
<td>89%</td>
<td>89%</td>
<td>100%</td>
</tr>
<tr>
<td>- PPV</td>
<td>86%</td>
<td>87%</td>
<td>100%</td>
</tr>
<tr>
<td>- NPV</td>
<td>94%</td>
<td>100%</td>
<td>90%</td>
</tr>
</tbody>
</table>

* False negative: 1 case; False positive: 2 cases (cryptococcoma, tuberculoma).
All patients underwent $^{201}$Tl SPECT and LP within 6 days from neuroradiologic finding of FBL. There were 13 PCNSL, 10 TE and 8 cases with other CNS OIs.
Diagnostic Capability of a Positive SPECT Result ($^{201}$TI uptake >1.50) and of the Lesion Size (>2.4 cm) for the Diagnosis of AIDS-Related PCNSL

García F et al. IAC. Geneve. 1998. Abs. 22291

- Sensitivity 75 (51-89)
- Specificity 97 (85-100)
- PPV 95 (71-100)
- NPV 86 (72-94)
Radiological Patterns of CNS Mass Lesions in AIDS Patients: $^{201}$Tl SPECT & PET


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<td>Hypometabolic</td>
<td>Hypermetabolic</td>
<td>Hypometabolic$^a$</td>
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**Sensitivity:** 100%  
**Specificity:** 90%

**NOTE.** PET, positron emission tomography; PML, progressive multifocal leukoencephalopathy; SPECT, single-photon emission CT.

$^a$ Usually hypometabolic, but occasionally hypermetabolic.
Yield of Nucleic Acid Detection in CSF by PCR for the Diagnosis of CNS Infections in HIV-infected Patients


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<thead>
<tr>
<th>Pathogen</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBV</td>
<td>≥ 80%</td>
<td>94-100%</td>
</tr>
<tr>
<td>T. gondii</td>
<td>45-65%</td>
<td>96-100%</td>
</tr>
<tr>
<td>CMV</td>
<td>≥ 80%</td>
<td>≥ 90%</td>
</tr>
<tr>
<td>JC virus</td>
<td>≈ 80%</td>
<td>≈ 95%</td>
</tr>
<tr>
<td>M. tuberculosis</td>
<td>83-100%</td>
<td>88-100%</td>
</tr>
</tbody>
</table>
Diagnostic Approach of Focal Brain Lesions

Contrast-enhancing mass lesion/s (CT/MRI)

**YES**

- **201TI SPECT**
  - **+**
    - PCNSL
  - **-**
    - Toxoplasma serology
      - **+**
        - TE
      - **-**
        - - Tuberculoma
        - - Cryptococcoma
        - - Other

**NO**

- **- PML**
- **- Other**

CSF sampling when feasible !!!
Yield of brain biopsy in patients with AIDS who have focal neurological disease

Skiest DJ. Clin Infect Dis. 2002; 34:103-15

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of subjects</th>
<th>Lymphoma</th>
<th>PML</th>
<th>Toxoplasmosis</th>
<th>Other</th>
<th>Definitive diagnosis</th>
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<td>14</td>
<td>86</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Major morbidity, %&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Mortality, %&lt;sup&gt;b&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>8</td>
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<td>11.5</td>
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</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3.7</td>
<td>3.1</td>
</tr>
</tbody>
</table>

NOTE.  PML, progressive multifocal leukoencephalopathy.

<sup>a</sup> Defined as hemorrhage or permanent neurological deficits; does not include death.

<sup>b</sup> Biopsy-related mortality (death related to biopsy complication within 30 days of biopsy).
Diagnosis of Latent *M. tuberculosis* Infection

**Current method: Tuberculin Skin Test (TST)**
- **Poor specificity:** antigenic cross-reactivity of PPD with BCG and environmental mycobacteria
- **Poor sensitivity:** 75-90% in active disease (lower in disseminated TB and HIV infection; unknown for latent infection)
- Need for return visit
- Operator variability (inoculation & reading)
- Standardisation of reagent
- Painful inflammation & scarring

**Future: Interferon-γ detection methods (TB-ELISPOT).**
- High specificity and sensitivity. Diagnosis Latent & active TB.
- Blood (PBMC), results in 24 h., more expensive than TST.
- Quantiferon-Gold™ (FDA); T-SPOT TB™ (EMEA)
ELISPOT (Enzyme-linked immunospot for interferon-gamma)

- ELISPOT is very specific:
  - Specificity 99.9%
  - It does not give false positive in people with prior BCG vaccination
  - It does not cross-react with common non-tuberculous (atypical) mycobacteria

- ELISPOT is very sensitive:
  - Sensitivity 97.9%
  - Works even in immunosuppressed populations
  - Maintains sensitivity even in active TB, including all types of extrapulmonary TB

HIV-positive: *AIDS, 2002*

HIV-positive pulmonary TB patients (n=39)
- Sensitivity 92%
CNS opportunistic infections (OI) in developed countries in the HAART era

• Current epidemiology
• Advances in the diagnosis
• Timing of HAART
• Immune reconstitution diseases
• Discontinuation prophylaxis studies
• Conclusions
## 2005 Recommended ARV Regimens for Treatment of Antiretroviral Naïve Patients

<table>
<thead>
<tr>
<th>NNRTI-based Regimens</th>
<th>PI-based Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV + 2 NRTIs</td>
<td>LPV/r (Kaletra®)+ 2 NRTIs</td>
</tr>
<tr>
<td>Nevirapine + 2 NRTIs</td>
<td>Atazanavir + 2 NRTIs</td>
</tr>
<tr>
<td></td>
<td>Boosted PI + 2 NRTIs</td>
</tr>
<tr>
<td></td>
<td>Nelfinavir + 2 NRTIs</td>
</tr>
</tbody>
</table>

### Triple NRTI Regimen

- Not recommended as first line Rx.
- Alternative: Trizivir®
- NR: TDF+ABC+3TC or TDF+ddI+EFV

## PI-based regimens

### Non-boosted PIs
- **Atazanavir**
  - With meals
- **Nelfinavir**
  - With meals
- **Indinavir**
- **SGC-SQV**

### Boosted PIs
- **Atazanavir + Ritonavir**
- **Kaletra®**
- **Amprenavir + Ritonavir**
- **Indinavir + Ritonavir**
- **SGC-SQV + Ritonavir**
**NNRTI-based regimens**

<table>
<thead>
<tr>
<th>NNRTIs</th>
<th>NRTIs/NtRTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>AZT</td>
</tr>
<tr>
<td>At night</td>
<td>Lamivudine</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>ddl</td>
</tr>
<tr>
<td></td>
<td>d4T</td>
</tr>
<tr>
<td></td>
<td>Abacavir</td>
</tr>
<tr>
<td></td>
<td>FTC</td>
</tr>
<tr>
<td></td>
<td>Combivir®</td>
</tr>
<tr>
<td></td>
<td>Trizivir®</td>
</tr>
<tr>
<td></td>
<td>Tenofovir</td>
</tr>
</tbody>
</table>

**FUTURE = Combos®**

TDF+FTC+EFV

like Rifater® but in only one pill per day !!!
# Timing of HAART in HIV-infected patients with CNS OIs

<table>
<thead>
<tr>
<th>Acute therapy</th>
<th>Maintenance therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HAART</strong></td>
<td><strong>HAART</strong></td>
</tr>
<tr>
<td>- Overlapping side effects</td>
<td>- Risk of disease progression and death in patients with advances disease (CD4&lt;50 cells/mm3)</td>
</tr>
<tr>
<td>- PK interactions</td>
<td></td>
</tr>
<tr>
<td>- High pill burden</td>
<td></td>
</tr>
<tr>
<td>- Risk of IRD*</td>
<td></td>
</tr>
</tbody>
</table>

IRD = Immune restoration disease / paradoxical reactions.
Prognosis of HIV-1 Infected Drug Naïve Patients Starting HAART according to CD4+ T Cell Count at Baseline

AIDS free survival by CD4 cell count at baseline

Cumulative progression to AIDS or death


Timing of HAART in HIV-infected patients with CNS OIs

- In ART-naïve patients, initiate HAART when there is no effective Rx for OI (e.g. PML). In the remaining cases, HAART should be started after 2 weeks of Rx of OI.

- In ART-experienced patients: A) when an OI occurs within 12 weeks of starting HAART, treatment for the OI should be started and HAART continued; B) when an OI occurs in the setting of virological failure, OI Rx should be started, HIV resistance testing should be performed and a new ART regimen should be started.

- Trials are underway to evaluate the most appropriate timing for initiation of HAART in this context.
Immune Restoration Induced by HAART

Suppression of HIV replication by HAART

Persistent immunodeficiency
- CD4 lymphopaenia (thymus dysfunction)
- Impaired T-cell function despite increased CD4 T-cell counts

Restoration of pathogen-specific immune responses

Regression or prevention of opportunistic infections
Immunopathological response (Immune Restoration Disease)
CNS opportunistic infections (OI) in developed countries in the HAART era

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## Immune Restoration Diseases (IRD/IRIS)


<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Mycobacterium avium</em></td>
<td>Localised / Lymphadenitis</td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Paradoxical reactions</td>
</tr>
<tr>
<td><em>Citomegalovirus</em></td>
<td>Atypical retinitis</td>
</tr>
<tr>
<td><em>Varicela zoster virus</em></td>
<td>Immune recovery retinitis</td>
</tr>
<tr>
<td><em>Herpes simplex virus</em></td>
<td>Dermatomal zoster</td>
</tr>
<tr>
<td><em>HCV/HBV</em></td>
<td>Atypical cutaneous herpes</td>
</tr>
<tr>
<td><em>Cryptococcus neoformans</em></td>
<td>Encephamomyelitis</td>
</tr>
<tr>
<td><em>JC virus</em></td>
<td>Increase liver enzimes (“hepatitis”)</td>
</tr>
<tr>
<td><em>HIV</em></td>
<td>Meningeal symptoms or new locations</td>
</tr>
<tr>
<td></td>
<td>“Inflammatory” PML</td>
</tr>
<tr>
<td></td>
<td>Demyelinating leukoencephalopathy</td>
</tr>
</tbody>
</table>
TB & Immune Reconstitution Inflammatory Reactions (IRIS) with HAART

- **Incidence:** 7-36%. It appears at 6 weeks after starting ART

**CLINICAL SYMPTOMS**
- High fevers
- Lymphadenopathy
- Worsening chest X-ray
- Other (e.g. tuberculoma)

**PREDISPOSING FACTORS**
- Starting ART soon (< 2 mo)
- Extra-pulmonary TB
- Low CD4 cell count
- \( \downarrow \) VL > 2 log\(_{10}\)/mL with ART

**Treatment**
- Mild/Moderate: Nonsteroidal inflammatory drugs
- Severe: Corticosteroids

Paradoxical Reaction of Tuberculoma in a patients with AIDS

Day 0  Anti-TB Rx + AZT  Day +15
Cryptococcosis & Immune Restoration Disease


Treated for initial presentation with *C. neoformans* meningitis

Start HAART

- Asymptomatic immune recovery
- Meningeal symptoms return
- New inflammatory symptoms
  - New opportunistic infection
  - Medication related
  - IRIS

Investigation

- True relapse of *C. neoformans* meningitis
- IRIS-related *C. neoformans* meningitis
- Pneumonitis
- Lymphadenitis
- Abscess
- Cryptococcoma
1. Frequently reported.
2. Prevalence 5% (prospective studies).
3. New onset or worsening meningeal or extra-meningeal symptoms 120 days after starting HAART. Median CD4 cell count of 175 cells/mm³ (nadir 29 cells/mm³).
4. Histology shows yeast but cultures were negative.
5. **Management:** HAART with/without antifungal therapy. Steroids or NSID were added in several cases.
6. Good outcome.
1. Few case reports (≈ 26 cases).
2. Prevalence unknown.
3. New onset or worsening typical PML symptoms 49 days after starting HAART. Median CD4 cell count increase of 149 cells/mm³ (nadir 39 cells/mm³).
4. Presence of inflammation in MRI (4/6) and perivascular inflammatory infiltrates in brain biopsy (7/8).
5. Deaths ≈ 1/3 of cases; Survivors: persistent neurological deficits. It is not known the best management.
PML Immune Reconstitution Disease

Miralles P et al. AIDS. 2001; 15: 1900-02
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OIs PREVENTION IN AIDS PATIENTS

LATENT INFECTION*

DISEASE

RELAPSE

→ Tuberculin skin test & Serologies**

← PRIMARY PROPHYLAXIS (↓ CD4+)

→ TREATMENT OF ACUTE DISEASE

← MAINTENANCE THERAPY / SECONDARY PROPHYLAXIS

* Tissue cysts or proviral DNA.

** IgG serology for *T. gondii* and CMV.
Is it Possible to Discontinue (D/C) OI’s Prophylaxis in Patients with Immunological Reconstitution with HAART? = YES

Stopping prophylaxis can simplify treatment, reduce toxicity and drug interactions, bacterial resistance, lower cost of care and potentially facilitate adherence to HAART.
CNS Toxoplasmosis in AIDS Patients
Guidelines for Preventing OI’s among HIV-Infected Persons - 2004
CDC/NIH/HIV Medicine/IDSA Recommendations

DISCONTINUATION PROPHYLAXIS CRITERIA

**PCP**
- PP/SP D/C if CD4 > 200 cells/µL ≥ 3 mo (AI/BII).
- Restarting if CD4 < 200 cells/µL.

**TE**
- PP D/C if CD4 > 200 cells/µL ≥ 3 mo. (AI).
- SP D/C if CD4 > 200 cells/µL ≥ 6 mo. (CIII).
- Restarting if CD4 < 200 cells/µL.

**MAC**
- D/C PP if CD4 > 100 cells/µL ≥ 3 mo. (AI).
- SP D/C if CD4 > 100 cells/µL ≥ 6 mo. (CIII).
- Restarting if CD4 < 50 cells/µL.

PCP = *P. carinii* pneumonia; TE = Toxoplasmic encephalitis; MAC = Disseminated *M. avium* infection.

## Cohort Studies of D/C of Secondary TE Prophylaxis in AIDS Patients on HAART*

<table>
<thead>
<tr>
<th>Study (yr.)</th>
<th>Entry Criteria</th>
<th>N. of Cases</th>
<th>CD4/µL</th>
<th>F/U Months</th>
<th>TE cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Kirk (99)</td>
<td>CD4 cell count</td>
<td>8</td>
<td>12/393</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>- Guex (00)</td>
<td>&gt;100 or 200/µL</td>
<td>1</td>
<td>29/1100</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>- Jubault (00)</td>
<td>&gt;100 or 200/µL</td>
<td>3</td>
<td>NA</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>- Soriano (00)</td>
<td>&gt;100 or 200/µL</td>
<td>9</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>- Wekselman (01)</td>
<td>&gt;3-6 months</td>
<td>11</td>
<td>109/270</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>- Katlama (01)</td>
<td></td>
<td>19</td>
<td>NA/404</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>- Kirk (02)</td>
<td></td>
<td>75</td>
<td>30/320</td>
<td>18</td>
<td>1¶</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td><strong>126</strong></td>
<td><strong>-/-</strong></td>
<td><strong>-</strong></td>
<td><strong>1 (1%)</strong></td>
</tr>
</tbody>
</table>

*HAART: ≈100% of patients were taking ≥2NRTI+ ≥1PI; F/U: follow-up; NA: Not available; D/C: discontinuation. ¶Incidence (95% CI) was 0.8 (0.02-4.7) episodes per 100 person-years
Randomized Clinical Trials of D/C of Secondary TE Prophylaxis in AIDS Patients on HAART*

**Entry Criteria:** Previous TE episode; CD4 cell count > 200 cells/µL and plasma VL <5,000 c/mL during >3 months with HAART.

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>No. of Cases</th>
<th>CD4/µL</th>
<th>F/U Mo./Yr.</th>
<th>TE relapses Incidence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GESIDA-04/98B¶</td>
<td>- Continuing SP</td>
<td>29</td>
<td>24/364</td>
<td>25/63</td>
</tr>
<tr>
<td></td>
<td>- D/C SP</td>
<td>28</td>
<td>35/416</td>
<td>30/68</td>
</tr>
</tbody>
</table>

*HAART: 98% ≥2NRTI+≥1PI; F/U: follow-up; SP: Secondary prophylaxis; D/C discontinuing.

Toxoplasma gondii-Specific T-Cell Responses Are Restored in AIDS Patients who Discontinued Toxoplasma Encephalitis (TE) Secondary Prophylaxis (PS) after Immunological Reconstitution due to Potent Antiretroviral Therapy (HAART)

Miro JM*, Leujene M, Claramonte X, Martínez E, Ribera E¹, Arrizabalaga J², Arribas JR³, Domingo P⁴, Ferrer E⁵, García F, Plana M, Valls ME, Podzamczer D⁵, Pumarola T, Jacquet A⁶, Mallolas J, Gallart T, Gatell JM.

H. Clínic, ¹H. Vall d’Hebron, ⁴H. Sant Pau & ⁵H. Bellvitge (Barcelona, Spain), ²H. Ntra. Sra. de Aranzazu (Donostia, Spain), ³H. La Paz (Madrid, Spain); ⁶Univ. Libre de Bruxelles (Belgium).

*email: jmmiro@ub.edu
**LONGITUDINAL STUDY**

**Design:** Prospective multicenter longitudinal study.

- 26 AIDS patients with acute TE were included in the study.
- Six patients were not eligible (2 early deaths, 2 cases lost for follow-up and 2 cases did not have TE).
- *In vitro* tests were performed in the 20 AIDS patients with an acute TE since the acute phase until immunological recovery with HAART (PI containing regimen) at the following time points:
  - 20 patients were studied at baseline (T0)
  - 16 patients were sampled at 3 months (T3)
  - 10 patients were sampled at 6 months (T6)
  - 16 patients were sampled between 9-12 months (T12)
  - 8 patients were sampled between 15-18 months (T18)
  - 7 patients were sampled at 24 months (T24)
- All patients were receiving TE maintenance therapy.
Immunological characteristics, plasma HIV viral load and *T. gondii* serology at different time points.

<table>
<thead>
<tr>
<th></th>
<th>Group T0 (n=20)</th>
<th>Group T3 (n=16)</th>
<th>Group T6 (n=10)</th>
<th>Group T12 (n=16)</th>
<th>Group T18 (n=8)</th>
<th>Group T24 (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CD4 absolute cell count</strong></td>
<td>59 (7-171)</td>
<td>143 (43-346)</td>
<td>280 (163-310)</td>
<td>204 (169-365)</td>
<td>301 (169-301)</td>
<td>223 (160-314)</td>
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<td></td>
</tr>
<tr>
<td><strong>CD8 absolute cell count</strong></td>
<td>68 (43-213)</td>
<td>280 (371-693)</td>
<td>441 (376-791)</td>
<td>330 (204-432)</td>
<td>674 (416-769)</td>
<td>688 (359-920)</td>
</tr>
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</tr>
<tr>
<td><strong>CD3+CD4+ % cell count</strong></td>
<td>4.69 (2-11)</td>
<td>15.55 (3-23)</td>
<td>19.26 (13-21)</td>
<td>11.83 (7-19)</td>
<td>16.67 (15-19)</td>
<td>30.78 (25-32)</td>
</tr>
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<td></td>
</tr>
<tr>
<td><strong>CD3+CD8+ % cell count</strong></td>
<td>42.53 (14-59)</td>
<td>45.06 (32-52)</td>
<td>40.81 (35-50)</td>
<td>35.3 (23.44)</td>
<td>30.66 (29-34)</td>
<td>33.38 (21-44)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HIV RNA level</strong></td>
<td>53.700 (10.748-154.000)</td>
<td>449 (195-123.148)</td>
<td>252 (200-2.333)</td>
<td>&lt;200 (&lt;200)</td>
<td>&lt;200 (&lt;200)</td>
<td>&lt;200 (&lt;200)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ig G <em>T. gondii</em> antibodies titer</strong></td>
<td>208 (131-&gt;300)</td>
<td>201 (146-280)</td>
<td>75 (0-225)</td>
<td>32 (0-241)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Data are median; IQR: interquartile range; NA= No available.

* = percentages of CD3+CD4+ or CD3+CD8+ T cells in peripheral blood mononuclear cells.
Lymphoproliferative response (LPR)(SI) to soluble antigen extract of *T. gondii* (SATg) at different time points.
IFN-γ production at 72 hours in response to SATg at different time points

\[ \Delta \text{pg/μL} > 0 \]

28% 33% 38% 71% 83% 100%
Cryptococcal Meningitis in AIDS Patients
CM = Cryptococcal meningitis; CMV = Cytomegalovirus retinitis; ROM: regular ophthalmologic monitoring.

**CM**

SP D/C if CD4 >100-200 cells/µL ≥6 mo (CIII).
- Restarting if CD4 <100-200 cells/µL.

**CMV**

SP D/C of CMV retinitis if CD4 >100-150 cells/µL >6 mo. + location of retinal lesion + vision in the contralateral eye + ROM (BIII).
- Restarting if CD4 <100-150 cells/µL.
# Cohort Studies of D/C of Secondary Prophylaxis of Cryptococcal Meningitis in AIDS Patients on HAART*

<table>
<thead>
<tr>
<th>Studies (yr.)</th>
<th>Entry Criteria</th>
<th>No. of Cases</th>
<th>CD4/µL Nadir/Entry</th>
<th>F/U Months</th>
<th>MAI cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Martinez (00)</td>
<td>CD4 cell count &gt;100 c./µL</td>
<td>6</td>
<td>42/200</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>- Nneka (01)</td>
<td>&gt;100 c./µL or &gt;150 c. /µL &gt;3 months</td>
<td>16</td>
<td>52/249</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>- Rollot (01)</td>
<td>&gt;150 c. /µL for &gt;3 months</td>
<td>6</td>
<td>8/244</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>- Aberg (02)</td>
<td></td>
<td>6</td>
<td>&lt;50/320</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>- Kirk (02)</td>
<td></td>
<td>39</td>
<td>12/297</td>
<td>20</td>
<td>0¶</td>
</tr>
<tr>
<td>- Mussini (04)</td>
<td></td>
<td>100</td>
<td>30/259</td>
<td>28</td>
<td>4¶</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td><strong>173</strong></td>
<td>-</td>
<td>-</td>
<td><strong>5 (3%)</strong></td>
</tr>
</tbody>
</table>

*HAART: Most patients were taking ≥2NRTI+ ≥1PI; F/U: follow-up.
¶Incidence (95% CI) was 0 (0-5.3) and 1.5 (0.4-3.9) episodes per 100 person-years, respectively.
Randomized Clinical Trials of D/C of Secondary Prophylaxis for Cryptococcal Meningitis (CM) in AIDS Patients on HAART

Entry Criteria: Previous CM episode; CD4 cell count > 100 cel./µL & VL <200 c/mL during >3 months with AZT+3TC+Efavirenz.

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>N. of Cases</th>
<th>CD4/µL</th>
<th>F/U Mo.</th>
<th>CM Relapses</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Continuing SP</td>
<td>22</td>
<td>9/&gt;100</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>- Discontinuing SP</td>
<td>20</td>
<td></td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

F/U: follow-up; SP: Secondary prophylaxis.

CNS opportunistic infections (OI) in developed countries in the HAART era

- Current epidemiology
- Advances in the diagnosis
- Timing of HAART
- Immune reconstitution diseases
- Discontinuation prophylaxis studies
- Conclusions
CONCLUSIONS

- CNS OIs have decreased in the HAART era in developed countries. However, they will continue appearing in the future for several reasons: 1) Late HIV diagnosis; 2) Non-compliance with ARV’s or preventive drugs; and, 3) Virological & Immunological HAART failure.

- Diagnosis of CNS OIs has improved in last years with the development on new neuroimaging techniques (SPECT, PET) and new molecular studies (PCR).

- Treatment and prophylaxis regimens for OIs have remained unchanged in recent years. There is no specific effective therapy for PML but HAART.
CONCLUSIONS

• It is not known what is the best timing for starting HAART in patients with acute CNS OIs.

• HAART can induce a clinical worsening of some CNS-OIs with/without atypical neuroimaging manifestations. This paradoxical worsening is known as immune restoration disease and it is usually seen in patients with tuberculosis, cryptococcal meningitis and PML.

• Toxoplasmic encephalitis and cryptococcal meningitis maintenance therapies can be safely discontinued in patients taking effective HAART.
ACKNOWLEDGMENTS

• HIV Unit: Hospital Clínic, Barcelona (Spain).
  – Immunology Laboratory
    M. Plana, M. Lejeune, T. Gallart
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    A. Cruceta, M. Lonca, JL Blanco,
    X. Claramonte, M. Laguno, JA Arnaiz
    F. García, E. Martinez, J. Mallolas,
    JM Miró, JM Gatell.

• GESIDA (Spanish Working Group on AIDS) from the
  SEIMC (Spanish Society of Infectious Diseases and Clinical Microbiology).

• FIPSE (Spanish Foundation on AIDS)

• Spanish AIDS Plan Secretariat from the Spanish Ministry of Health.

• Our patients.