Improving quality of services and retention in HIV care and treatment: Severely immunosuppressed package of care (SIPOC)

Dr. Maureen Syowai Kathuku-Kaati
December 2015
Objectives

1. To understand the mechanism of immunosuppression in HIV-infected clients
2. To understand the conditions associated with severe immunosuppression
3. To understand the approach to management of patients with severe immunosuppression
4. To appreciate the anticipated response to treatment for severely immunosuppressed PLHIV
   - IRIS
   - Clinical progression
5. To introduce the package of care for severely immunosuppressed PLHIV
6. To develop a regional work plan on implementing and monitoring SIPOC regional activities
• HIV impairs or weakens the immune system leading to inability to respond normally to an infection

• Immunosuppression in HIV infected clients takes place in three parts:
  – Establishment of HIV infection at mucosal surfaces
  – Immune response to the virus involving dendritic, B and T cells
  – Subversion of immune response to establish a chronic HIV infection
Establishment of HIV infection

- HIV-1 and HIV-2 uses a cognate recognition of the cell surface CD4 molecule, chemokine receptor (CXCR4 or CCR5) and glycoprotein gp120 to infect CD4+ T cells, macrophages, monocytes, dendritic cells and microglia.
Introduction

Immune response to the virus

1. Cellular response:
   - Lymphocytes: CD4 lymphopenia; decreased naive phenotype and lymphoproliferation
   - Decreased delayed hypersensitivity skin test response to recall antigens
   - Monocytes: decreased phagocytosis, chemotaxis, intracellular killing, and cytokine expression
   - Neutrophils: neutropenia; decreased phagocytosis and intracellular killing
   - NK cells: Decreased natural killer cell-mediated cytotoxicity

2. Humoral response:
   - Decreased B-cell number; polyclonal activation of B cells
   - Increased production of nonspecific immunoglobulins G, A, and M (antibodies)
   - Loss of specific antibody responses

Antibody and cytotoxic lymphocyte activities combat HIV infection, but do not prevent progression.
1. **Primary infection** (1 to 3 months): Peak in HIV RNA copies and steep decline in CD4 cells after infection. HIV replicates without control by the immune system. HIV immune response begins 4 to 8 weeks after infection and VL falls.

2. **Clinical latency** (8-10 years, without ART): CD4 cell concentration increases again and HIV VL declines again. Stabilized plasma concentration = viral set-point.

3. **AIDS** (2-3 yrs, without ART): Rapid increase in VL and decline in CD4 counts usually begins after the CD4 count has dropped to ~ 500 cells/mm³ and AIDS ensues at ~200 cells/mm³
Introduction

Subversion of immune response to establish a chronic HIV infection

Subversion of cellular response
- HIV provirus latency
- Sequestration reservoirs
- Switch of viral strain from R5 to X4
- Downregulation of the surface expression of MHC molecules
- Viral protein epitope mutations
- Reduction of specific CD8+ T cells

Subversion of humoral response
- Antigenic variation - escape from neutralization by anti-bodies due to adaptability of the viral envelope. Lack of correlation between the magnitude of the humoral response and the decrease of viral load.
Introduction

- CD4+ T cells depleting numbers and functional abnormalities lead to profound loss of immune responsiveness
- Impaired CD4+ T cells immune responses of immunomodulatory cytokines production
- The number of circulating CD4+ T cells is a predictor of the immediate risk for opportunistic illnesses
Definition of AIDS:
HIV infection is classified as stage 3 (AIDS) when the immune system of a person infected with HIV becomes severely compromised (measured by CD4 cell count) and/or the person becomes ill with an opportunistic infection.
### CDC staging of HIV infection

**HIV infection stage, based on age-specific CD4 count or CD4 percentage of total lymphocytes**

Surveillance staging system intended primarily for public health surveillance of HIV infection on a population level and clinicians should not use it as a guide to manage patients.

- **Stage 0:** If there was a negative HIV test within 6 months of the first HIV infection diagnosis, the stage is 0, and remains 0 until 6 months after diagnosis.
- **Stage 1:** Determined by the CD4 test immunologic criteria
- **Stage 2:** Determined by the CD4 test immunologic criteria
- **Stage 3:** If a stage-3-defining opportunistic illness has been diagnosed
- **Unknown:** If none of the above apply (e.g., because of missing information on CD4 test results)

<table>
<thead>
<tr>
<th>Stage*</th>
<th>&lt;1 year</th>
<th>1−5 years</th>
<th>6 years through adult</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cells/μL</td>
<td>%</td>
<td>Cells/μL</td>
</tr>
<tr>
<td>1</td>
<td>≥1,500</td>
<td>≥34</td>
<td>≥1,000</td>
</tr>
<tr>
<td>2</td>
<td>750–1,499</td>
<td>26–33</td>
<td>500–999</td>
</tr>
<tr>
<td>3</td>
<td>&lt;750</td>
<td>&lt;26</td>
<td>&lt;500</td>
</tr>
</tbody>
</table>

*Note: The staging system is intended primarily for public health surveillance of HIV infection on a population level and should not be used as a guide to manage patients.*
### Opportunistic infections associated with AIDS

- **Bacterial pneumonia**
- **Candidiasis bronchi, trachea, lungs or oesophagus**
- **Cervical carcinoma**
- **Coccidioidomycosis**
- **Cryptococcosis, extrapulmonary**
- **Cryptosporidiosis**
- **Cytomegalovirus disease**
- **Encephalopathy, HIV-related**
- **Herpes simplex**
- **Histoplasmosis**
- **Isosporiasis, chronic intestinal (>1-month in duration)**
- **Kaposi sarcoma**
- **Lymphoma**

- **Mycobacterium tuberculosis**, pulmonary or extrapulmonary
- **Mycobacterium avium complex (MAC) or Mycobacterium kansasii**
- **Pneumocystis jiroveci** (PCP)
- **Progressive multifocal leukoencephalopathy (PML)**
- **Salmonella septicemia, recurrent (nontyphoid)**
- **Toxoplasmosis of brain**
- **HIV wasting syndrome** (involuntary weight loss >10% of baseline body weight) associated with either chronic diarrhea or chronic weakness and documented fever for ≥1 month
Severe immunosuppression at ICAP-supported facilities

PLHIV initiated on ART in ICAP supported facilities from January to December 2013
Data from 62 facilities censured as at end of March 2015

Severely Immunosuppressed PLHIV

- CD4<100 at ART initiation: 479
- CD4>100 at ART initiation:
  - Female: 333
  - Male: 146

Total PLHIV initiated on ART:
- Total: 8092
- Female: 5077
- Male: 3015

TB status at ART initiation for immunosuppressed PLHIV

- TB Rx: 17%
- Presumptive TB: 7%
- No signs of TB: 74%
- Not Documented: 2%

Data source: C-PAD
Treatment outcomes for severely immunosuppressed PLHIV

<table>
<thead>
<tr>
<th>CD4&lt;100 cells/mm³</th>
<th>ART initiation</th>
<th>6 month outcomes</th>
<th>12 month outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4&lt;100 cells/mm³</td>
<td>479</td>
<td>311</td>
<td>293</td>
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<tr>
<td>Active</td>
<td>9</td>
<td>2%</td>
<td>10%</td>
</tr>
<tr>
<td>Dead</td>
<td>49</td>
<td>10%</td>
<td>2%</td>
</tr>
<tr>
<td>Defaulter</td>
<td>102</td>
<td>21%</td>
<td>8</td>
</tr>
<tr>
<td>LTFU</td>
<td>8</td>
<td>2%</td>
<td>9</td>
</tr>
<tr>
<td>Transfer out</td>
<td>9</td>
<td>2%</td>
<td>2</td>
</tr>
<tr>
<td>CD4&lt;100 cells/mm³</td>
<td>139</td>
<td>29%</td>
<td>9</td>
</tr>
<tr>
<td>Active</td>
<td>10</td>
<td>2%</td>
<td>2</td>
</tr>
<tr>
<td>Dead</td>
<td>28</td>
<td>6%</td>
<td>2</td>
</tr>
<tr>
<td>Defaulter</td>
<td>2</td>
<td>2%</td>
<td>2</td>
</tr>
</tbody>
</table>
Survival analysis of PLHIV stratified by CD4

Mortality is highest for clients enrolled with <100 CD4 counts/ml.

<100 Package of Care being rolled out by program.

Data source: C-PAD
Tuberculosis

- High mortality and severe immunosuppression in hospitalized patients with pulmonary tuberculosis and HIV-2 infection in Guinea-Bissau. (Norrgren et al, 2001)
  - Significantly higher mortality rate in HIV-2-positive compared to HIV-negative individuals
  - CD4 percentage of <10% was an independent predictor of decreased survival in HIV-2-infected subjects
TB treatment outcomes for all forms of TB (Sept 2015)

Eastern

- Treatment Success: 89% HIV-Ve, 81% HIV+Ve
- Transferred out: 3% HIV-Ve, 4% HIV+Ve
- Died: 4% HIV-Ve, 11% HIV+Ve
- LTFU: 3% HIV-Ve, 3% HIV+Ve
- Failed: 1% HIV-Ve, 1% HIV+Ve

Nyanza

- Treatment Success: 94% HIV-Ve, 78% HIV+Ve
- Transferred out: 2% HIV-Ve, 4% HIV+Ve
- Died: 2% HIV-Ve, 12% HIV+Ve
- LTFU: 1% HIV-Ve, 4% HIV+Ve
- Failed: 1% HIV-Ve, 1% HIV+Ve
Cryptococcal Meningitis

• High mortality from CM despite availability of ART and effective anti-fungal treatments
  – Global CM mortality from 9% – 38%
  – SSA CM mortality 37% – 58%
• Kenya mortality:
  • 23% mortality at 12 weeks following diagnosis (Kendi C. et al, 2012);
  • 36% (38/106) in-hospital mortality (Mdodo R. et al, 2010); and
  • 15.4% mortality at 14 days after initiating Amp. B (9.5%) or Fluconazole (20.4%) (Analo A & Olieba C, 2013)
Cryptococcal screening and management

Laboratory diagnosis of cryptococcaemia from 187 HIV clinics in Nyanza

- No. with CD4 done: 21,146
- No. with CD4<100: 1,634 (8%)
- No. with CRAG test: 1,330 (81%)
- No. with Pos CRAG: 127 (10%)

304 immunosuppressed PLHIV not assessed for CM

Management of diagnosed cryptococcaemia from 5 model centers in Nyanza

- No. with pos CRAG: 73
- No. on fluconazole prophylaxis: 43 (59%)
- No. Amp. B Rx: 17 (23%)
- No. fluconazole treatment: 13 (18%)

13 patients lacked an intervention
*100% mortality without intervention
HIV-Associated Cancers: Incidence Pre and Post ART

- Kaposi’s sarcoma
- Non-Hodgkin’s Lymphoma (systemic)
- Immunoblastic lymphoma
- CNS lymphoma
- Burkitt’s lymphoma
- Hodgkin’s disease
- Cervical cancer
- Other cancers

Incidence (per 1000/year)

- Pre-HAART (1992-1996)
- Post HAART (1997-1999)

P<0.05

Approach to patient with severe immunosuppression

• Newly diagnosed PLHIV:
  – All HIV-infected adolescents and adults with CD4 count <500 cells/mm³ irrespective of WHO stage are eligible for ART*
  – Assess symptoms, history, physical examination results, and laboratory results to identify OIs and manage accordingly
  – Monitor response to treatment paying close attention to conditions associated with IRIS

• PLHIV on ART:
  – Assess adherence to ART
  – Assess client for treatment failure and manage treatment failure appropriately
  – Screen for common OIs associated with severe immunosuppression
  – Monitor response to treatment paying close attention to conditions associated with IRIS

*Rapid Advice, NASCOP 2014
Immune Reconstitution Inflammatory Syndrome (IRIS)

- IRIS refers to a paradoxical inflammatory reaction against a foreign antigen (alive or dead) in patients who have started antiretroviral therapy and who have undergone a reconstitution of their immune responses against this antigen
Risk factors for developing IRIS

- Rapid decline in viral load (especially in first three months after ART)
- Low baseline CD4 count (especially <50 cells/μl or <10%) and rapid increase after initiation of ART
- Initiation of ART soon after initiation of treatment for opportunistic infection (OI)
- Disseminated versus localized OI
- ART- naïve patient
General case definitions for IRIS

**General IRIS case definition proposed by French et al (2004)**
Diagnosis requires two major criteria (A+B) or major criterion (A) plus two minor criteria to be fulfilled:

**Major criteria**
A. Atypical presentation of opportunistic infections or tumours in patients responding to ART, manifested by any of the following:
   • Localized disease
   • Exaggerated inflammatory reaction
   • Atypical inflammatory response in affected tissues
   • Progression of organ dysfunction or enlargement of preexisting lesions after definite clinical improvement with pathogen-specific therapy prior to ART and exclusion of treatment toxicity and new diagnoses

B. Decrease in plasma HIV RNA level >1 log10 copies/ml

**Minor criteria**
• Increase in CD4 count after ART
• Increase in an immune response specific to the relevant pathogen
• Spontaneous resolution of disease with continuation of ART
**INSHI* case definition for paradoxical TB-IRIS**

(A) *Antecedent requirements* (both criteria must be met)
- Diagnosis of tuberculosis: the diagnosis of tuberculosis made before starting ART (WHO criteria).
- Initial response to tuberculosis treatment: initial improvement or stabilisation on appropriate anti-TB treatment before ART initiation (however, in patients starting ART within 2wk of starting tuberculosis treatment, insufficient time may have elapsed for a clinical response to be reported).

(B) Clinical criteria (one major criterion or two minor clinical criteria are required)
The onset of TB-IRIS manifestations within 3 months of ART initiation, reinitiation, or regimen change.

**Major criteria**
- New or enlarging lymph nodes, cold abscesses, or other focal tissue involvement
- New or worsening serositis
- New or worsening CNS tuberculosis
- New or worsening radiological features of tuberculosis

**Minor criteria**
- New or worsening constitutional symptoms
- New or worsening respiratory symptoms
- New or worsening abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly, or abdominal adenopathy

(C) Alternative explanations must be excluded if possible
- Tuberculosis drug resistance, poor adherence to treatment, drug toxicity, and another opportunistic infection.

*INSHI, International Network for the Study of HIV-associated IRIS*
Conditions associated with IRIS

1. Mycobacterium tuberculosis
2. Cryptococcal meningitis
3. Toxoplasmosis
4. Kaposi sarcoma
5. Cytomegalovirus retinitis
6. Pneumocystis jirovecii pneumonia
7. Herpes zoster
8. Molluscum contagiosum
9. Folliculitis
10. Genital herpes simplex
11. Human papilloma virus
<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical presentation of IRIS</th>
</tr>
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<tbody>
<tr>
<td>TB</td>
<td>• TB-IRIS often presents in the first 1-6 weeks of starting ART</td>
</tr>
<tr>
<td></td>
<td>• Signs and symptoms: commonly high fever, cough, dyspnoea; new or increased lyphadenopathy (peripheral or mediastinal); lymph node abscesses; worsening of pulmonary disease with new or increased infiltrates or effusion; new or worsening CNS presentation; other new extrapulmonary lesions</td>
</tr>
<tr>
<td>Cryptococcus</td>
<td>• Presents 1 week to 11 months after ART initiation</td>
</tr>
<tr>
<td></td>
<td>• Fever, worsening headache, lymphadenitis, new or worsening signs of meningitis; pulmonary disease and skin lesions</td>
</tr>
<tr>
<td>Malignancies</td>
<td>• New or worsening KS lesions</td>
</tr>
<tr>
<td>PJP</td>
<td>• Fever, cough, dyspnoea in patients on treatment, those recently treated or those undiagnosed. The chest radiograph may show a worsening radiographic picture</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>• Presents within the first 4 months of ART initiation with new or recurrent herpes zoster</td>
</tr>
<tr>
<td>Skin</td>
<td>• New or worsening PPE, eosinophilic folliculitis, new presentation or chronic mucocutaneous herpes lesions</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>• Worsening hepatitis, confirmed by rising ALT or AST</td>
</tr>
</tbody>
</table>
Management of IRIS

• Requires a high index of suspicion and screening for the OIs in severely immunosuppressed patients
• Treat the identified OI as per the national guidelines
• Continue ART
• If patient develops severe symptoms of inflammation: give corticosteroids in cases of TB meningitis, TB pericarditis, toxoplasmosis and cryptococcal meningitis. Prednisolone 1-2mg/kg daily and taper over several weeks as symptoms improve.
• Give NSAIDS (ibuprofen and aspirin) in non-severe cases of inflammation
Expected response to treatment

• Clinical progression of severely immunosuppressed HIV-infected patients depends on virological and immunological improvement irrespective of baseline status (Elena Ferrer et al, June 2015)
  – Analysed factors associated with progression to AIDS/death in severely immunosuppressed (CD4 <200 cells/mm3) HIV-infected patients receiving ART
  – After 5 years follow-up 69.9% had CD4 ≥200 cells/mm3, 64.4% had undetectable viral load and 21% progressed to AIDS/death
  – Achieving a CD4 count ≥200 cells/mm3 was the main predictor of decreased progression to AIDS/death
  – Even in the worse baseline scenario of CD4 ≤100 cells/mm3 and high baseline viral loads, positive virological and immunological responses were associated with dramatic decreases in progression
Why introduce a package of care for clients with severe immunosuppression?

- Structure clinical care to be vigilant in actively identifying clients with severe immunosuppression
- Support screening, diagnosis and management of OIs associated with severe immunosuppression
- Support counselling including adherence and nutritional counselling
- Improve immunity and general well being of the client
- Improve retention in care
- Reduce HIV transmission
- Avert morbidity and mortality associated with severe immunosuppression
ICAP approach to patient with severe immunosuppression

<table>
<thead>
<tr>
<th>ROOM</th>
<th>SERVICES</th>
</tr>
</thead>
</table>
| RECORDS ROOM | - Filing of CD4 results from laboratory  
- Identify and flag files with CD4 less than 100 cells/mm³ or CD4 less than 15% using the checkered SIPOC sticker  
- Insert SIPOC patient assessment form in patient file |
| CLINICAL ROOM | - Clinical assessment including:  
  - TB screening at each clinical visit  
  - Clinical examination including temperature with special attention to detecting Opportunistic Infections (OI) |
| LABORATORY/RADIOLOGY | - Investigations:  
  - Haemoglobin  
  - Xpert MTB/Rif assay testing  
  - Cryptococcal antigen (CrAg) screening  
  - Hepatitis B screening  
  - Stool for parasites and AFB in anyone with diarrhea  
- Other investigations to consider  
  - Chest X-ray in patients with presumptive TB  
  - Liver Function Test (LFT)  
  - Mid-Stream Urine in clients with urinary symptoms  
  - Fine Needle Aspirate (FNA) or biopsy in patients with focal lymphadenopathy |
| CLINICIAN/NUTRITIONIST/COUNSELLOR | - Clinical Management:  
  - Cotrimoxazole Preventive Therapy  
  - Initiation of ART as per national guidelines  
  - IPT after 3 months  
  - Fortnightly clinical visits after ART (Assess for IRIS)  
- Nutritional Assessment:  
  - Nutritional assessment, counseling and supplementation  
  - Grade nutrition and manage accordingly  
- Psychosocial support:  
  - Adherence counseling at each clinic visit  
  - Clinical visits scheduled fortnightly for one month then monthly thereafter  
  - Linkage to peer educator with weekly phone call to assess progress |
ICAP approach to patient with severe immunosuppression

SIPOC checklist

- Detailed clinical assessment
- Haemoglobin
- Xpert MTB/Rif assay test
- Cryptococcal antigen (CrAg) screen
- Hepatitis B screen
- Stool microscopy
- Chest Radiography
- Liver Function Test

- Urinalysis
- FNA or biopsy
- Cotrimoxazole Preventive Therapy
- Anti-retroviral Therapy
- Isoniazid Preventive Therapy
- Psychosocial support
- Nutritional assessment and management
Implementation strategy

1. All ICAP supported facilities
2. Introduction of package of care to CHMT, HMT and HCW:
   • Discuss SIPOC package of care
   • Seek support to access free / subsidized services by the facility for the package of care
   • Participants: CHMT, HMT, HIV clinic health care workers, laboratory staff, pharmacy staff
   • Facilitators: ICAP staff
3. Provide requirements for implementation of package of care
4. Monitor package of care using patient outcomes at 6mo, 12mo, and 24mo
## SIPOC requirements

<table>
<thead>
<tr>
<th>Package of care item</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and examination</td>
<td>Continuation sheet</td>
</tr>
<tr>
<td></td>
<td>Mentorship on documentation of clinical findings and management</td>
</tr>
<tr>
<td>Vitals</td>
<td>Thermometer</td>
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<tr>
<td></td>
<td>Sphygmomanometer</td>
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<tr>
<td>Hb</td>
<td>Laboratory request forms</td>
</tr>
<tr>
<td></td>
<td>Laboratory reagents</td>
</tr>
<tr>
<td></td>
<td>Haematology machine service contract</td>
</tr>
<tr>
<td>CD4 test</td>
<td>Laboratory request forms</td>
</tr>
<tr>
<td></td>
<td>Laboratory reagents</td>
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<tr>
<td></td>
<td>CD4 machine service contract</td>
</tr>
<tr>
<td>Xpert MTB/Rif assay</td>
<td>Xpert MTB/rif request forms, sample transport, falcon tubes, cartridges</td>
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<tr>
<td>CM screening</td>
<td>CrAg strips</td>
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<tr>
<td>Package of care item</td>
<td>Support</td>
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<td>---------------------------------------------------------------</td>
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<tr>
<td>CXR in patients with presumptive TB</td>
<td>Radiological films</td>
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<tr>
<td>Hepatitis B screening</td>
<td>Hepatitis B screening reagents</td>
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<tr>
<td>LFT</td>
<td>Laboratory request forms</td>
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<td></td>
<td>Laboratory reagents</td>
</tr>
<tr>
<td></td>
<td>Biochemistry machine service contract</td>
</tr>
<tr>
<td>Mid-Stream Urinalysis in clients with urinary symptoms</td>
<td>Urinalysis dip sticks</td>
</tr>
<tr>
<td>FNA or biopsy in patients with focal lymphadenopathy</td>
<td>Punch biopsies</td>
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<tr>
<td></td>
<td>Histopathology laboratory support</td>
</tr>
<tr>
<td>Stool for parasites and AFB in anyone with diarrhea</td>
<td>Laboratory request form</td>
</tr>
<tr>
<td></td>
<td>Subsidize stool microscopy costs</td>
</tr>
<tr>
<td>VIA /VILI screening for Ca cervix</td>
<td>Iodine/Acetic acid</td>
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</table>