Management of ART in PLHIV with advanced disease

Dr. Henry Sunpath

AWACC - 27/09/13
OUTLINE

• ADVANCED DISEASE
• EVIDENCE FOR ART ASAP-IMMEDIATE ART
• GUIDELINES IN SA /EXPERT OPINION
• CHALLENGES TO REDUCE MORTALITY
• OPERATIONALISING IN PATIENT ART
• UPREFERRAL & DOWN REFERRAL
• ICU
500,000 need ARV’s EACH year

200,000 well on ARV’s

300,000 dead

High mortality pre ART

200,000 well on ARV’s
Require fast track (ART initiation within 7 days of being eligible)

Patients with low CD4 <200
CNS infections including CCM, Toxoplasmosis, PML
Lung infections – PCP, severe PTB, Bacterial pneumonias
Extrapulmonary and disseminated TB
HIV associated malignancies.
Persistent diarrhoea

Patients with TB/HIV co morbidity with CD4 count < 50
Patients with poor general medical condition and high mortality irrespective of CD4 count
Renal failure
Cardiomyopathy

Dementia

The South African Antiretroviral Treatment Guidelines  March 2013.
In: Department of Health Republic of South Africa and South African National AIDS Council;
### Indications for ARV Therapy

**Symptoms (irrespective of CD4 count)**

<table>
<thead>
<tr>
<th>WHO clinical stage 4*</th>
<th>ART recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other severe HIV-related disorders,†</td>
<td>ART recommended</td>
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<tr>
<td>e.g.: Immune thrombocytopenia</td>
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<tr>
<td>Thrombotic thrombocytopenia</td>
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<td>Polymyositis</td>
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<tr>
<td>Lymphocytic interstitial pneumonitis</td>
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<td>Non HIV-related disorders,‡ e.g.:</td>
<td>ART recommended</td>
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<tr>
<td>Malignancies</td>
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<tr>
<td>Hepatitis B§</td>
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<td>Hepatitis C</td>
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<tr>
<td><strong>CD4+ counts</strong></td>
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<tr>
<td>&lt;200/μl</td>
<td>ART recommended</td>
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<tr>
<td>200 - 350/μl</td>
<td>ART recommended</td>
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<tr>
<td>&gt;350/μl</td>
<td>Defer ART</td>
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</table>
WHO Stage 4 conditions

- HIV wasting syndrome
- Pneumocystis pneumonia
- Recurrent severe bacterial pneumonia
- Chronic herpes simplex infection
- Oesophageal candidiasis
- Extrapulmonary TB
- Kaposi’s sarcoma
- CMV (retinitis or infection of other organs)
- HIV encephalopathy
- Central nervous system toxoplasmosis
- Extrapulmonary cryptococcosis (incl. meningitis)
- Disseminated non-tuberculous mycobacteria infection
- Progressive multifocal leucoencephalopathy
- Chronic cryptosporidiosis
- Chronic isosporiasis
- Disseminated mycosis
- Recurrent septicaemia
- Lymphoma (cerebral or B-cell non-Hodgkin’s)
- Invasive cervical carcinoma
- Atypical disseminated leishmaniasis
- Symptomatic HIV-associated nephropathy
- Symptomatic HIV-associated cardiomyopathy
SA Hospitals-
Prevalence of OIs/Stage 4 conditions

- **Acute OI** — no. (90 %)
  - Pulmonary tuberculosis –39 %
  - Extrapulmonary tuberculosis (including meningitis)-25%
  - Cryptococcal meningitis -10%
  - Chronic diarrhea (>14 days)-9%
  - Bacterial pneumonia -3%
  - *Toxoplasmosis gondii* -2%
  - *Pneumocystis jirovecii* pneumonia-1%

- **Others** (9%)
  - HIV related cardiomyopathy
  - Thrombocytopenia of various causes
  - PML
  - Viral encephalitis ?HSV

- **HIV-associated kidney disease**1%
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- ART as part of inpatient care to pts with OI
- 382 prospectively enrolled
- Median time from admission to ART: 14 d (IQR 11-18)
- Mortality reduction by 50% among those initiated on ART within 3 weeks of admission
<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>N  =382 (%)</th>
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</thead>
<tbody>
<tr>
<td>Median baseline CD4 count (cells/ul) [IQR]</td>
<td>33(12-78)</td>
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<tr>
<td>Baseline CD4 cell count category (%)</td>
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<tr>
<td>0-49 cells/ul</td>
<td>224(62)</td>
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<tr>
<td>50-99 cells/ul</td>
<td>65(18)</td>
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<tr>
<td>100-199 cells/ul</td>
<td>22(15)</td>
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<tr>
<td>200-349 cells/ul</td>
<td>18(5)</td>
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<tr>
<td>Pulmonary tuberculosis</td>
<td>147 (39)</td>
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<tr>
<td>Extrapulmonary tuberculosis (including meningitis)</td>
<td>96 (25)</td>
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<tr>
<td>Cryptococcal meningitis</td>
<td>40 (10)</td>
</tr>
<tr>
<td>Chronic diarrhea (&gt;14 days)</td>
<td>35 (9)</td>
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<tr>
<td>Bacterial pneumonia</td>
<td>11 (3)</td>
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<tr>
<td>Toxoplasmosis gondii</td>
<td>9 (2)</td>
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<tr>
<td>Pneumocystis jirovecii pneumonia</td>
<td>5 (1)</td>
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<tr>
<td>HIV-associated kidney disease</td>
<td>4 (1)</td>
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<tr>
<td>Other cause for admission in ART-eligible patient</td>
<td>20 (5)</td>
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<tr>
<td>Undiagnosed OI</td>
<td>15 (3)</td>
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</table>
During 24 weeks of follow up

Among patients who died, median days to death 33 days (IQR-9 - 95)

Among pts with CrM (ART at median of 14 d), excess mortality not observed

Longer interval between admission and ART initiation independently associated with mortality (>=21 d, OR 2.1 compared with <21 d)

Mortality by 6 months doubled in patients if ART was delayed beyond 3 weeks from OI diagnosis
Outcomes by opportunistic infection among PLHIV commenced on ART at the *Siyaphila* from November 2006 and August 2007

<table>
<thead>
<tr>
<th>Opportunistic Infection</th>
<th>N</th>
<th>Time from admission - ART (median/mean days) *</th>
<th>Time from admission - discharge (median/mean days)</th>
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</thead>
<tbody>
<tr>
<td>All infections a</td>
<td>137</td>
<td>14 / 16</td>
<td>18 / 21</td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>60</td>
<td>13 / 15</td>
<td>17 / 20</td>
</tr>
<tr>
<td>Extra pulmonary TB</td>
<td>28</td>
<td>12 / 15</td>
<td>17 / 19</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>23</td>
<td>18 / 19</td>
<td>22 / 24</td>
</tr>
<tr>
<td>P. jiroveci pneumonia</td>
<td>15</td>
<td>16 / 16</td>
<td>19 / 21</td>
</tr>
<tr>
<td>Chronic diarrhoea</td>
<td>6</td>
<td>16 / 16</td>
<td>19 / 20</td>
</tr>
<tr>
<td>Toxoplasmosis gondii</td>
<td>5</td>
<td>21 / 21</td>
<td>25 / 25</td>
</tr>
<tr>
<td>Other infection b</td>
<td>3</td>
<td>13 / 13</td>
<td>18 / 17</td>
</tr>
</tbody>
</table>

*4-5 DAYS MORE AFTER ART*
IMMEDIATE ART

ACTG A5164 trial-2009
Multicenter: United States and South Africa

Treatable OI or Bacterial infection with CD4 < 200
n = 282
Median CD4 = 29
92% ART naïve

ART within 14 days (Median: 12 days)
Randomised 1:1 (Stratified by infection and CD4 count)
ART deferred until after OI treatment (Median: 45 days)

50 % REDUCTION IN MORTALITY
Followed 48 weeks from study entry

Entry infection
PCP 63%
Cryptococcus 12%
Bacterial 12%
Toxo
TB excluded

Zolopa, PLoS ONE 2009;4:e5575
Grant, PLoS ONE 2010;5:e11416
**TB**

**ART timing and major outcomes in patients with TB and CD4 < 50**

* CAMELIA data represents all patients in trial, majority had CD4 < 50 (median CD4 = 25)

* CAMELIA data represents all patients in trial, majority had CD4 < 50 (median CD4 = 25)


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In individuals with acute opportunistic infections, prompt initiation of ART has been confirmed to reduce mortality. Benefits are assumed to outweigh risks at all stages of HIV infection.

Exceptions -:
1. **Tuberculous meningitis**, for whom the optimal timing of treatment is still unclear what to start. TB meningitis in Vietnam (*CID 2011;52: 1374-1383*)
   RDBPRC 253 HIV associated Tb meningitis (9 months rif-based regimen + steroids +T/S) immediate arm (EFV) or delayed arm (placebo). Survival at 9 months was 35% in immediate arm and 40% in delayed arm (p=NS)

2. **Cryptococcal meningitis**, for whom early HIV treatment has been shown to increase mortality (COAT study)
Starting ART in patients with TB

- CD4 count ≤50 cells/µl: - within 2 weeks of TB treatment when it is clear that the patient’s TB symptoms are improving and that TB therapy is tolerated.

- CD4 count >50 cells/µl: - delayed until after the intensive phase of TB treatment (2 months) unless the patient has other serious HIV-related conditions (e.g. Kaposi’s sarcoma or HIV encephalopathy, persistent diarrhoea etc)

- TB meningitis (TBM) - Recommend starting ART 4 - 8 weeks after TBM diagnosis.
Cryptococcal meningitis (CM) - Recommend starting ART before 3-4 weeks after antifungal treatment (preferably amphotericin B-based) is started.

Pneumocystis pneumonia / bacterial pneumonia / Toxoplasmosis - within 2 weeks of starting treatment for that infection.
<table>
<thead>
<tr>
<th>Contraindication</th>
<th>Regimen</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>All new patients needing treatment, including pregnant women</td>
<td>TDF + FTC (or 3TC) + EFV</td>
<td>Replace EFV with NVP in patients with significant psychiatric co-morbidity or intolerance to EFV and where the neuro-psychiatric toxicity of EFV may impair daily functioning, e.g. shift workers.</td>
</tr>
<tr>
<td>Adolescents</td>
<td>ABC + 3TC + EFV</td>
<td>At age 18 years an adolescent if eligible must be switched to the FDC</td>
</tr>
<tr>
<td>Contraindications to EFV</td>
<td>TDF + (FTC or 3TC) + NVP</td>
<td>Use NVP based regimen: In patients with significant psychiatric co morbidity or intolerance to EFV and where the neuro-psychiatric toxicity of EFV may impair daily functioning, e.g. shift workers.</td>
</tr>
<tr>
<td>Contraindication to TDF</td>
<td>AZT + 3TC + EFV or (NVP)</td>
<td>Renal disease or the use of other nephrotoxic drugs e.g. aminoglycosides</td>
</tr>
<tr>
<td>Contraindication to TDF and AZT</td>
<td>d4T + 3TC+ EFV (or NVP)</td>
<td><strong>Renal disease and anaemia</strong> or the use of other nephrotoxic drugs, aminoglycosides</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>------------------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Contraindication to TDF, AZT and d4T</td>
<td>ABC + 3TC + EFV (or NVP)</td>
<td><strong>Renal disease, anaemia, peripheral neuropathy, the use of other nephrotoxic drugs</strong></td>
</tr>
</tbody>
</table>
WHEN TO START IN THOSE WITH HIGHEST RISK OF MORTALITY?

Within one week

UPON ADMISSION BEFORE OI TREATMENT

AFTER COMPLETION OF OI TREATMENT

Within Two weeks

After two weeks
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Haitian Patient, before and after Receiving Free Treatment for HIV Infection and Tuberculosis.

The photograph on the left was taken in March 2003, and that on the right in September 2003. Many impoverished patients in rural Haiti and Rwanda now receive comprehensive medical care through public-private partnerships.
Why no ART preparation for inpatients?

1. No link between inpatient and outpatient programmes

HIV and AIDS services are delivered by well-funded but separate vertical programmes and people with HIV in the medical wards sometimes fall through the cracks.

“In the medical wards they feel ‘I don’t really deal with it because it’s somebody else’s problem’, ”

Sithole Z. Strategies to meet the demand for palliative care in South Africa due to the HIV epidemic. 2nd APCA Palliative Care Conference, Nairobi, Kenya, Ab0147, 2007
Inpatient care has become a game of “MAKING BEDS”

“Finding beds for patients and then emptying the beds for the next huge influx of patients for care has become a priority at the hospital - the major concerns of the nurse managers – distracting them from other matters. And if you look at the interns that provide most of the medical care, that’s how they are sort of evaluated, “How fast can you get the patient [out], how fast can you empty those beds?”

Sithole Z. Strategies to meet the demand for palliative care in South Africa due to the HIV epidemic. 2nd APCA Palliative Care Conference, Nairobi, Kenya, Ab0147, 2007
What are the barriers to good care?

- **Poverty/Economic**
  - Transportation
  - Food Insecurity
  - Disability Grants
  - Poor social support

- **Institutional**
  - Long wait times
  - Negative staff experiences
  - Linkage to care after testing
  - Poor health literacy
  - No link between inpatient and outpatient care
  - Inadequate upreferral and down referral pathways
  - Limited substance abuse treatment and mental health facilities

- **Political-Migration**
- **Sociocultural**
  -- Perceived stigmatization resulting in delayed presentation
    - Traditional healers
    - Traditional beliefs about HIV/AIDS
    - Influence of charismatic churches

Kagee J Health Psychol, Global Public Health 2010
Western Cape
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When ready, how well are inpatients linked to care?
Linkage into care from hospital
KwaZulu-Natal, South Africa (2006/7)

49 participants-
ART preparation

Median CD4 = 42

TB 76%
PCP 8%
Chronic diarrhoea 8%
CM 6%
Toxoplasmosis 4%

27% died before ART
41% initiated ART
8% loss to follow-up
24% alive and still pre ART.

Murphy,-Sunpath Int J Tuberc Lung Dis 2010;14:903
Low uptake of antiretroviral therapy after admission with human immunodeficiency virus and tuberculosis in KwaZulu-Natal, South Africa


**Result** - The patients with the most advanced disease (CD4 count <50/mm3) were least likely to initiate ART by 6 months.

**Discharge to ART:**
- **median 82 days**

**Discharge to death:**
- **median 95 days**

- 20 (41%) Initiated ART
- 13 (27%) Died Prior to ART
- 12 (24%) Alive, Remain Pre-ART
- 4 (8%) Lost to follow-up

14 Patients Enrolled

* 1 patient died during ART
## Co-treatment of OI and ART

<table>
<thead>
<tr>
<th>Potential challenges</th>
<th>Potential benefits</th>
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<tbody>
<tr>
<td>IRIS</td>
<td>Reduced HIV progression</td>
</tr>
<tr>
<td>Co-toxicities</td>
<td>Reduced mortality</td>
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<tr>
<td>Drug-drug interactions</td>
<td>Clearance of OI</td>
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<tr>
<td>Absorption</td>
<td>Prevent OI recurrence</td>
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<tr>
<td>Pill burden</td>
<td>Prevent re-admission</td>
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<td>Adherence counseling</td>
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</table>
Management of paradoxical IRIS

• **TB-IRIS**
  – Exclude alternative causes for deterioration (especially TB drug resistance)
  – Corticosteroids for life threatening cases
  – In other cases they provide symptomatic benefit
  – Needle aspiration of pus collections

• **Cryptococcal meningitis IRIS**
  – CSF culture to exclude antifungal treatment failure
  – Therapeutic LPs to manage raised intracranial pressure
  – Anecdotal reports of benefit from corticosteroids
• **Pneumocystic pneumonia (PCP) IRIS**
  – Rare, but reports of life-threatening cases requiring ventilation
  – Corticosteroid introduction or dose escalation

  Jagannathan, AIDS 2009;23:1794

• **Progressive Multifocal Leukoencephalopathy (PML) IRIS**
  – Role of corticosteroids controversial
  – Deaths and improvements reported on corticosteroids
  – Most compelling indication is cerebral oedema

  Tan, Neurology 2009;72:1458
  Berger, Neurology 2009;72:1454

• **Cytomegalovirus (CMV) Immune Recovery Vitritis**
  – Peri-ocular corticosteroids

  Henderson, Br J Ophthalmol 1999; 83:540
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- Median time from admission to ART: 14 d (IQR 11-18)
- Mortality reduction by 50% among those initiated on ART within 3 weeks of admission
Patient flow through the system

Acute hospitalization:
- HIV testing
- CD4 cell count measurement
- OI diagnosis and initiation of OI treatment

Early ART criteria:
- Age ≥18 years
- Initial response to OI therapy
- CD4 count of <200 cells/μl or <350 with TB
- Ability to take medications by mouth

Step-down center for early ART
- Evaluation by early ART team members (see Figure 2)
- Rapid HIV education and adherence training

Early ART initiation:
- Patient monitored for early ART toxicity, drug-drug interaction or IRIS
- Ongoing nutritional, psychological and peer support

Outpatient clinic follow-up:
- Weeks 2, 6, 10, 14, 18 and 24 after ART
- Viral load and CD4 cell count measurement at week 24
**Risk vs benefit**
Weigh up the high risk of deferring ART in terms of mortality and morbidity, and the risk for the individual patient of default which cannot easily be predicted.

**During prolonged hospitalisation**
Adherence, toxicity management and psychosocial support can be provided.

Many have not yet been tested for HIV, others might have tested HIV-positive but disengaged from care (some before and some after initiating ART), only to return to care once they have fallen ill.
Trained HIV Counselor
- Rapid HIV education and antiretroviral therapy adherence training
- Assistance with disease disclosure and identification of treatment supporter

Psychologist
- Identify concurrent mental illness including acute stress reactions, anxiety, mood disorders and HIV-associated neurocognitive disorders

Social worker
- Provide patients with help managing the financial costs of illness including hospitalization and loss of employment
- Discharge planning with emphasis on developing support in the home

Nurse
- Patient care and education, medication administration, and chart maintenance

Doctor (Generalist / Family medicine trained in HIV medicine/ID specialist)
- Identify antiretroviral therapy start date
- Manage drug toxicities and immune reconstitution inflammatory syndrome
- Identify need for palliative care

Dietician
- Nutritional assessment with focus on patients with a low body mass index, or chronic diarrhea
Chronic Disease Trajectory
(Saunders Paradigm)

Type of care provided (%)

Diagnosis

Acute care

Palliative care

0

100

Figure 46.1. Inge Corless (2001). Palliative Care – One Does Not Need to be Terminally Ill. Norma L. Chaska, Ed. *The Nursing Professions and Beyond*. Thousand Oaks: Sage Publications
PROGRAMME - Reducing mortality among hospitalised PLHIV in Ethekwini (Sept 2012)
# Programme in Ethekwini

**Dr. Reshma Badal**

<table>
<thead>
<tr>
<th>INST.</th>
<th>MAR</th>
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</table>
Challenges: ART - the hospitalised pts

- **Quality of care varies among hospitals**
  Protocols and guidelines to manage complicated cases in a formal referral unit could be developed using in-house skills and expertise. (ONGOING-TRAINING)

- **ART treatment history**
  Many with extensive ART experience—including some failing current treatment and some who discontinued ART before resistance was known to have developed
Before discharge

• Through the skills of a multidisciplinary team in the inpatient units, ART preparation and initiation was done soon after admission.

• It was ensured that the patient and/or next of kin understood the reasons for urgent initiation before or after discharge.

• A caregiver must act as a directly observed therapy supporter and trained.
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On discharge

• Patients- to attend the ART clinic asap and be informed of reasonable clinic appointment waiting times.

• Provide sufficient medication till the clinic visit.

• Send newly initiated pts on TB treatment with notification and letters for separate clinical visits.

• **Discharging patients directly into the care of adequately counselled family members can be invaluable.**
Keys to successful down referral

• Always be accompanied by a letter detailing the course of treatment and management decisions.
• Was ART interrupted or switched because of drug toxicities

• Date of commencement of TB /OI treatment

• Details of further clinical/drug management required.
Indications for urgent up-referral prior to initiation or when on therapy
(DOH GUIDELINES March 2013)

- eGFR less than 60 ml/min
- Hb less than 8 g/dl
- BMI less than 18.5 kg/m²
- In a patient with TB or other opportunistic infection, poor response to TB or OI treatment
Reasons that patients may require up-referral

• Late presentation to HIV care,

• Complex or challenging opportunistic infections / serious disease,

• Virologic failure with, patterns of erratic adherence to ART,

• Comorbid conditions - kidney or liver disease

• Issues surrounding immune reconstitution inflammatory syndrome

• Serious adverse effects due to ART
Up referral...

Treatment for other conditions that require inpatient care

Severe toxicity from ART such as tenofovir related renal failure

- HIV associated malignancies
- HIV related neurological disorders

Significant lipodystrophy or gynaecomastia from ART requiring plastic surgery

- HIV associated skin conditions requiring dermatology review.

Patient in need of diagnostic procedures such as CT and MRI scanning, endoscopy or biopsy.

Eefje Jong, MD, PhD and Henry Sunpath, MBBS, MFamMed, MPH, Dip HIV Man, Review important considerations and management approaches for treating patients with advanced HIV infection. inPractice Africa –online submitted draft, April 2013. Editors: Theo Smart, Ian Sanne
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Opportunities for care of PLHIV and admitted to an intensive care unit.

ICU admission

HIV infection known
- Review previous history of use of and response to antiretroviral therapy

Receiving combination antiretroviral therapy
- Additional considerations before initiating or continuing antiretroviral therapy
  - Drug-resistance testing
  - Antiretroviral drug delivery, absorption, and dosing
  - Drug–drug interactions
  - Toxic effects of antiretroviral drug
  - Immune reconstitution syndrome
- Continue antiretroviral therapy if HIV RNA is undetectable; consult HIV specialist if HIV RNA is detectable

Not receiving combination antiretroviral therapy
- Condition is not associated with AIDS
- AIDS-associated condition
- Defer antiretroviral therapy if CD4 count >200 cells; consider antiretroviral therapy and consult HIV specialist if CD4 count ≤200 cells and ICU course is prolonged
- Consider antiretroviral therapy and consult HIV specialist

HIV infection suspected
- Test for HIV

HIV positive

HIV negative
- Refer for HIV-prevention counseling and risk reduction
ICU admissions-Complications associated with HIV infection

Pulmonary disease:
• Respiratory failure is the most common reason for ICU admission in HIV +ve patients.
• Conditions- PCP, TB and severe pneumonia(sometimes in combination)
• IRIS
• Acute respiratory distress syndrome

Liver disease:
• Hep B co-infection is common.
• Toxicity associated with some non allopathic medication – liver failure
• Drug induced liver injury due to TB drugs

Renal disease:
• End-stage renal disease may be caused by HIV chronic kidney disease
• Acute renal failure more common – requires fluid resuscitation and may need dialysis
Adverse events due to ART

<table>
<thead>
<tr>
<th>Life-Threatening or Adverse Effect</th>
<th>Principal Antiretroviral Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic hypersensitivity reaction</td>
<td>Abacavir</td>
</tr>
<tr>
<td>Stevens–Johnson syndrome or toxic epidermal necrosis</td>
<td>Nevirapine</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>All antiretroviral agents, especially nevirapine</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Didanosine and stavudine</td>
</tr>
<tr>
<td>Lactic acidosis syndrome, hepatoxity, and hepatic steatosis</td>
<td>NRTIs, especially stavudine, didanosine, and zidovudine</td>
</tr>
<tr>
<td>Nephrotoxicity and acute renal failure</td>
<td>Indinavir and tenofovir</td>
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</tbody>
</table>

* Data are from guidelines listed on the AIDSinfo Web site. This table lists only potential life-threatening and serious adverse effects with an onset starting from the initial dose up to months after the initiation of therapy. However, there are several important adverse effects — including cardiovascular effects, hyperlipidemia, insulin resistance or diabetes mellitus, and osteonecrosis — that may result from antiretroviral therapy.
WORK TOGETHER AS A TEAM!
TAKE UP THE CHALLENGE?
References


