AWACC-2011
ART in the Inpatient Setting
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
Outline of talk

1. High mortality in patients with OIs who are not on early ART after discharge.
2. Advantages and disadvantages of early ART
3. High mortality in smear negative TB when treatment is delayed.
4. ART after TB and other OIs
5. ART IN THE INPATIENT SETTING
# Baseline Characteristics

At the time of admission: $\quad N = 49$

- **Female — no. (%)**: 24 (49%)
- **Time since HIV diagnosis — median**: 2.9 months
- **Subjects with no prior OIs — no. (%)**: 33 (67%)
- **Acute opportunistic infection — no. (%)**
  - **Tuberculosis**
    - **Pulmonary,**: 14 (28%)
    - **Extrapulmonary**: 18 (38%)
  - **PCP**: 4 (8%)
  - **Diarrhea**: 4 (8%)
  - **Cryptococcal meningitis**: 3 (6%)
  - **T. gondii**: 2 (4%)
  - **Other**: 4 (8%)
What happens to patients after acute OI in SA?

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

Patient Trajectory After Discharge

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

* 1 patient died during ART
Outline of talk

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Fast track of patients for ART-2010

Fast track: ART initiation within 2 weeks of being eligible for
1. Pregnant women eligible for lifelong ART
2. Patients with very low CD4 (<100)
3. MDR/XDR TB
4. All adults recently hospitalised with an HIV-linked condition, including TB.

WHO Stage IV Clinical Criteria for Treatment Initiation (in absence of CD4)

- HIV wasting syndrome
- HIV encephalopathy/ADC
- *Progressive multifocal leukoencephalopathy*
- *Toxoplasmosis of the brain >1 month*
- *Cryptosporidiosis with diarrhoea/extrapulmonary*
- Disseminated Mycoses
- Candidiasis-oesophagus, trachea, bronchi, lungs
- Lymphoma
- *Recurrent severe bacterial pneumonias*
- Recurrent septicaemia
- *Symptomatic HIV associated nephropathy*
- *Symptomatic HIV associated cardiomyopathy*
WHO Stage IV Clinical Criteria for Treatment Initiation (in absence of CD4):

- **Kaposis Sarcoma**
- CNS lymphoma
- Invasive Ca cervix
- *Pneumocystis carinii pneumonia*
- *Cryptococcal meningitis*
- CMV disease of an organ other than liver, spleen or lymph nodes
- HSV infection: mucocutaneous >1 month or visceral of any duration
- *Tuberculosis*
ART in Acute OIs-Challenges ....

1. **Poor absorption of ART in very ill pts**- subtherapeutic serum levels = antiretroviral drug resistance.

2. **ART toxicities** - confused with disease manifestations or toxicities of drugs used for OI.

3. **Drug-drug interactions**- among ART and anti-OI drugs may be difficult to manage.

4. **IRIS events**-manifestations that are difficult to distinguish from other clinical conditions.
ART in Acute OIs-Challenges...

5. **Renal or hepatic dysfunction**

Due to HIV and OIs and its treatment or the use of some kinds of non allopathic therapy.

Distorted ART pharmacokinetics (metabolic clearance and volumes of distribution) may reduce ART efficacy and/or increase ART toxicity.

Dosing of ART drugs may be difficult to estimate

Delay in time for ART and anti TB treatment
Outline of talk

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TB/HIV Coinfection...

Study comparing the diagnostic utility of a WHO algorithm (cohort 187/3424) with an observed standard practice (cohort 338/619) in patients admitted to three hospitals in KwaZulu-Natal, South Africa

Recommendation:

TB treatment should be started soon after admission to the wards

Inclusion criteria were

- Age > 15 years
- HIV-infection,
- Signs of being clinically seriously-ill,
- Cough > 2 weeks,
- Radiographic abnormalities consistent with TB,
- At least two negative sputum smears.
Results

1. **Standard practice patients**- Only 47% were given anti-tuberculosis treatment before discharge.

2. **WHO algorithm patients**- had a statistically significant impact on –

   - Lowering the risk of hospitalization at 7 days after admission by 30%.
   - Improving the “risk” of survival at 8 weeks after admission by 23% *(highest in those in whom anti-TB treatment was started within 3 days, with no history of previous TB treatment, and current ART).*
Outline of talk

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5. ART IN THE INPATIENT SETTING
<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion criteria</th>
<th>Time to ART after TB treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The CAMELIA study</strong></td>
<td>Smear positive TB and CD4 ≤ 200 cells</td>
<td>2 weeks vs 8 weeks</td>
</tr>
<tr>
<td><strong>Cambodia-Blanc et al, 18th IAS Conference 2010, Abstract THLBB106</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ACTG 5221 STRIDE study</strong></td>
<td>Confirmed or suspected TB and a CD &lt; 250 cells</td>
<td>2 weeks vs 8-12 weeks.</td>
</tr>
<tr>
<td><strong>Havlir et al, 18th Conference on Retroviruses and Opportunistic Infections, Abstract 38</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SAPiT study</strong></td>
<td>Confirmed or suspected TB and a CD &lt; 500 cells</td>
<td>4 weeks after starting treatment vs 4 weeks of the completion of intensive phase</td>
</tr>
<tr>
<td><strong>Abdool Karim et al, 18th Conference on Retroviruses and Opportunistic Infections, Abstract 39LB</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Results</td>
<td>The CAMELIA study</td>
<td>ACTG 5221 STRIDE study</td>
</tr>
<tr>
<td>-------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Median CD4 = 25 cells and BMI = 17.</td>
<td>No difference in the combined endpoint of AIDS progression and death between the two arms</td>
</tr>
<tr>
<td></td>
<td>A 34% reduction in mortality in those who started at 2 weeks.</td>
<td>In those with CD4 ≤ 50 cells AIDS progression and death was reduced by 42% among those who started at 2 weeks.</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>
Other important results...

Incidence of paradoxical TB-IRIS was approximately 2 to 3 fold higher among those starting ART in the earlier arm.

However in patients with CD4 < 50 these studies demonstrated that the survival benefit of earlier ART outweighs the potential risk that earlier ART may cause excess TB-IRIS related deaths.
No difference in survival among patients starting ART immediately or deferring 2 months. Mortality at 9 months—around 60% in both arms. Patients in this study were treated with adjunctive high dose dexamethasone for the first 6-8 weeks of TB treatment. Grade 4 adverse events were encountered more frequently by patients who started immediately.
Conclusions...ART after TB

- Patients (with CD4 < 50 cells) should be prioritised for rapid medical work-up and counselling to allow them to **start ART within 2 weeks of TB treatment**.
- Patients with a CD4 close to 50 cells or those with other stage 4 defining illnesses it may also be prudent to **start after 2 weeks of TB treatment**.
- Patients with a higher CD4 counts **deferring ART up to 2 months** may reduce the risk of TB-IRIS without compromising outcome.
- In **TB meningitis** mortality is extremely high and unaffected by the exact timing of ART within the first 2 months of TB treatment and deferring ART a few weeks may reduce risk of severe adverse events.
ART after other OIs


ART after other OIs


• OIs – PCP ,Toxoplasmosis ,Cryptococcal meningitis,Bacterial pneumonias
Outline of talk

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5. ART IN THE INPATIENT SETTING
   Why the need for an inpatient service?
6. How to operationalise an inpatient ART programme?
Why an inpatient ART service?
Opportunities for care of PLHIV among those admitted to an inpatient care unit.

A. PROVISION OF ICU CARE AS APPROPRIATE

B. FAST – TRACKING FOR ART INITIATION:
   - Multisystem disorder & variable presentation
   - High mortality group with indistinct boundary between cure and palliation
   - Multidisciplinary team with clinicians trained in care of PLHIV
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, hepatotoxicity, 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>
</tr>
</tbody>
</table>

* Data are from guidelines listed on the AIDSinfo Web site.\(^{24}\) 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.
Opportunities for care of PLHIV among those admitted to an inpatient care unit.

A. PROVISION OF ICU CARE AS APPROPRIATE

B. FAST –TRACKING FOR ART INITIATION:
- Multisystem disorder & variable presentation
- High mortality group with indistinct boundary between cure and palliation
- Multidisciplinary team with clinicians trained in care of PLHIV
HIV palliative care: A paradigm shift

Former Allocation of Resources

- Active disease-specific Rx
- Palliative Rx

Time of diagnosis → End of life

Current Allocation of Resources in Developed Countries

- Active disease-specific Rx
- Palliative Rx

Time of diagnosis → End of life

Proposed Allocation of Resources in Developing Countries

- Active disease-specific Rx
- Palliative Rx

Source: U.S. Department of Health and Human Services - Palliative Care in Resource Poor Settings
Mc Cord- Siyaphila inpatient unit for subacute care of PLHIV 2006-2009
SIYAPHILA HEALTHCARE

Clinical Care: treating the OI and related medical conditions before ART initiation

HIV Counseling Services: ART literacy training before and after ART initiation.

Psychological Care: assesses cognitive disorders and AIDS related dementia

End of Life Care: symptom management and supportive care
Subacute care

Social Care: maintaining linkages to and use of services to ensuring adherence to treatment.

Community Support and Follow up: by linking them to different care providers

Rehabilitation: Physical therapy and nutritional interventions

Spiritual Care: helps to addresses the major life events
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Why the need for an inpatient service?

6. How to operationalise an inpatient ART programme?
Operationalizing Early Inpatient Antiretroviral Therapy (ART) during Hospitalization with Acute Opportunistic Infection (OI) in South Africa

CROI: Boston, March, 2010. Poster 1079
382 Initiated immediate ART

- 247 Assessed at 24 weeks
- 97 Died during 24-week follow-up
- 19 Were lost to follow-up
- 22 Died during inpatient ART initiation
- 80 Died after ART initiation and discharge
- 19 Changed service provider before 24 weeks
- 247 Assessed at 24 weeks

198 Died during inpatient ART initiation and follow-up
198 Died after ART initiation
96 Died during follow-up
19 Changed service provider
19 Were lost to follow-up
<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median baseline CD4 count (cells/ul) [IQR]</td>
<td>33(12-78)</td>
</tr>
<tr>
<td>Baseline CD4 cell count category (%)</td>
<td></td>
</tr>
<tr>
<td>0-49 cells/ul</td>
<td>224(62)</td>
</tr>
<tr>
<td>50-99 cells/ul</td>
<td>65(18)</td>
</tr>
<tr>
<td>100-199 cells/ul</td>
<td>22(15)</td>
</tr>
<tr>
<td>200-349 cells/ul</td>
<td>18(5)</td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>147 (39)</td>
</tr>
<tr>
<td>Extrapulmonary tuberculosis (including meningitis)</td>
<td>96 (25)</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>40 (10)</td>
</tr>
<tr>
<td>Chronic diarrhea (&gt;14 days)</td>
<td>35 (9)</td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
<td>11 (3)</td>
</tr>
<tr>
<td>Toxoplasmosis gondii</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Pneumocystis jirovecii pneumonia</td>
<td>5 (1)</td>
</tr>
<tr>
<td>HIV-associated kidney disease</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Other cause for admission in ART-eligible patient</td>
<td>20 (5)</td>
</tr>
<tr>
<td>Undiagnosed OI</td>
<td>15 (3)</td>
</tr>
</tbody>
</table>
### Timing of ART initiation

Median days from admission with OI to ART initiation - no. [IQR] 1

Days from admission with OI to ART by category, no. (%)

<table>
<thead>
<tr>
<th>Category</th>
<th>No.</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-7 days</td>
<td>181</td>
<td>(47)</td>
</tr>
<tr>
<td>8-14 days</td>
<td>105</td>
<td>(26)</td>
</tr>
<tr>
<td>15-21 days</td>
<td>62</td>
<td>(16)</td>
</tr>
<tr>
<td>&gt;21 days</td>
<td>14</td>
<td>[11-18]</td>
</tr>
</tbody>
</table>

N=382

### 24-week Virologic Outcomes

<table>
<thead>
<tr>
<th>Outcome Description</th>
<th>No.</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent-to-treat (ITT) viral suppression &lt;400 c/mL</td>
<td>206</td>
<td>(57)</td>
</tr>
<tr>
<td>As-treated (AT) viral suppression &lt;400 c/mL</td>
<td>206</td>
<td>(93)</td>
</tr>
</tbody>
</table>

### 24-week Immunologic Outcomes

<table>
<thead>
<tr>
<th>Outcome Description</th>
<th>No.</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median CD4 count improvement (cells/ul)</td>
<td>100</td>
<td>(48-188)</td>
</tr>
</tbody>
</table>
## 24-week Vital Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mortality (%)</td>
<td>97 (25)</td>
</tr>
<tr>
<td>Mortality prior to discharge in the step-down facility</td>
<td>20/102</td>
</tr>
<tr>
<td>Mortality after discharge</td>
<td>77/102</td>
</tr>
<tr>
<td>Among patients who died, median days to death, (IQR)</td>
<td>33 (9-95)</td>
</tr>
</tbody>
</table>

## 24-week Program Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss to follow-up (%)</td>
<td>19 (5)</td>
</tr>
<tr>
<td>Changed service provider (%)</td>
<td>19 (5)</td>
</tr>
</tbody>
</table>

## Serious IRIS Events

<table>
<thead>
<tr>
<th>Event</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRIS events, no. (%)</td>
<td>17 (4)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>14/17</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>2/17</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>1/17</td>
</tr>
<tr>
<td>IRIS-associated deaths</td>
<td>5 (1)</td>
</tr>
</tbody>
</table>
## Multivariate analysis

<table>
<thead>
<tr>
<th>Description</th>
<th>N</th>
<th>24-Week Mortality no. (%)</th>
<th>Univariate Odds Ratio 95% CI</th>
<th>Multivariate Odds Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>382</td>
<td>25%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender-female -male</td>
<td>184</td>
<td>49 (26)</td>
<td>0.9 (0.6-1.5)</td>
<td>1.0 (0.6-1.7)</td>
</tr>
<tr>
<td></td>
<td>198</td>
<td>49(25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age -&lt;40</td>
<td>234</td>
<td>50 (21)</td>
<td>1.7 (1.1-2.7)</td>
<td>1.5 (0.9-2.6)</td>
</tr>
<tr>
<td></td>
<td>148</td>
<td>47 (32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admitting OI</td>
<td>342</td>
<td>89 (26)</td>
<td>0.7 (0.3-1.6)</td>
<td>0.7 (0.3-1.7)</td>
</tr>
<tr>
<td>Other Cryptococcal Meningitis</td>
<td>40</td>
<td>8 (20)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Multivariate analysis

<table>
<thead>
<tr>
<th>Description</th>
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<th>Multivariate Odds Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial CD4 cell count</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0=49 cells/ul</td>
<td>224</td>
<td>51 (23)</td>
<td>0.9 (0.6-1.6)</td>
<td>1.0 (0.6-1.7)</td>
</tr>
<tr>
<td>&gt;50 cells/ul</td>
<td>135</td>
<td>29 (22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRIS in initial 6 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>365</td>
<td>92 (25)</td>
<td>1.2 (0.3-4.6)</td>
<td>1.6 (0.5-4.8)</td>
</tr>
<tr>
<td>Present</td>
<td>17</td>
<td>5 (29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days to ART initiation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;21</td>
<td>301</td>
<td>68 (23)</td>
<td>2.3 (1.3-4.1)</td>
<td>2.1 (1.2-4.0)</td>
</tr>
<tr>
<td>&gt;21</td>
<td>62</td>
<td>25 (40)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**P < 0.016**
Conclusions...

In this clinically advanced population, independently associated with early mortality was time to ART initiation of ≥21 days after OI (OR: 2.1, 95% CI: 1.2-4.0, P=0.016) compared with <21 days.

Mortality at six months doubled with ART initiation >3 weeks
CONCLUSIONS

• Start ART between one to three weeks in most patients after diagnosis of an OI in the inpatient setting.
• Clinicians and a team trained in the integration of care in the inpatient setting (even at specialist care centres) can provide successful acute care.
• In-patient beds (subacute /step down care units) need to be set aside for this programme.
• Integration of services between inpatient programmes and outpatient ART sites will reduce mortality further.
• Good follow up is essential for improvement in term mortality.
Acknowledgements

• The MCH management –for making the care of the most ill patients a priority in the wards.
• Dr.Christina Edwin and the interdisciplinary team at the MCH-Siyaphila programme.
• The patients who have been our precious inspiration
• To all our colleagues in the HIV Medicine fraternity in SA and Internationally who have supported us academically and by their own example.
• To Loving South Africa –for their valuable funds that help us extend the stay of some patients so that we can help them remain alive until discharge.
• The national ARV roll out programme and the 2010 guidelines!
WORK TOGETHER AS A TEAM!
THIS IS THE MAIN CHALLENGE IN THE INPATIENT SETTING?