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.

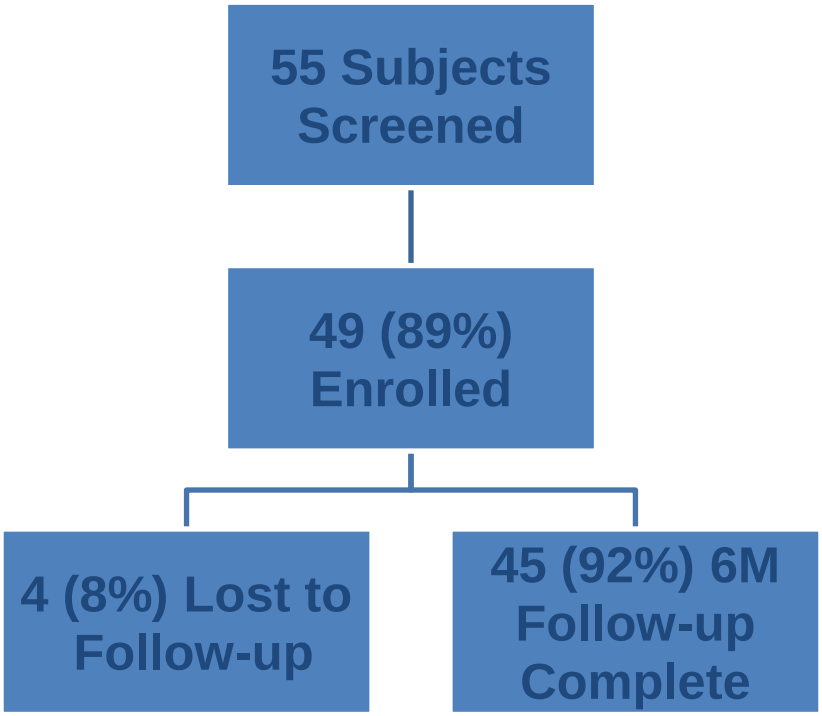
2.Advantages and disadvantages of early ART

3.High mortality in smear negative TB when treatment is delayed.

4.ART after TB and other OIs

5. ART IN THE INPATIENT SETTING

Low uptake of antiretroviral therapy after admission with human immunodeficiency virus and tuberculosis in KwaZulu-Natal, South Africa *Int J Tuberc Lung Dis* 2009;14(7): 903-908. Murphy R.A. ,**Sunpath H**,Taha S.et.al



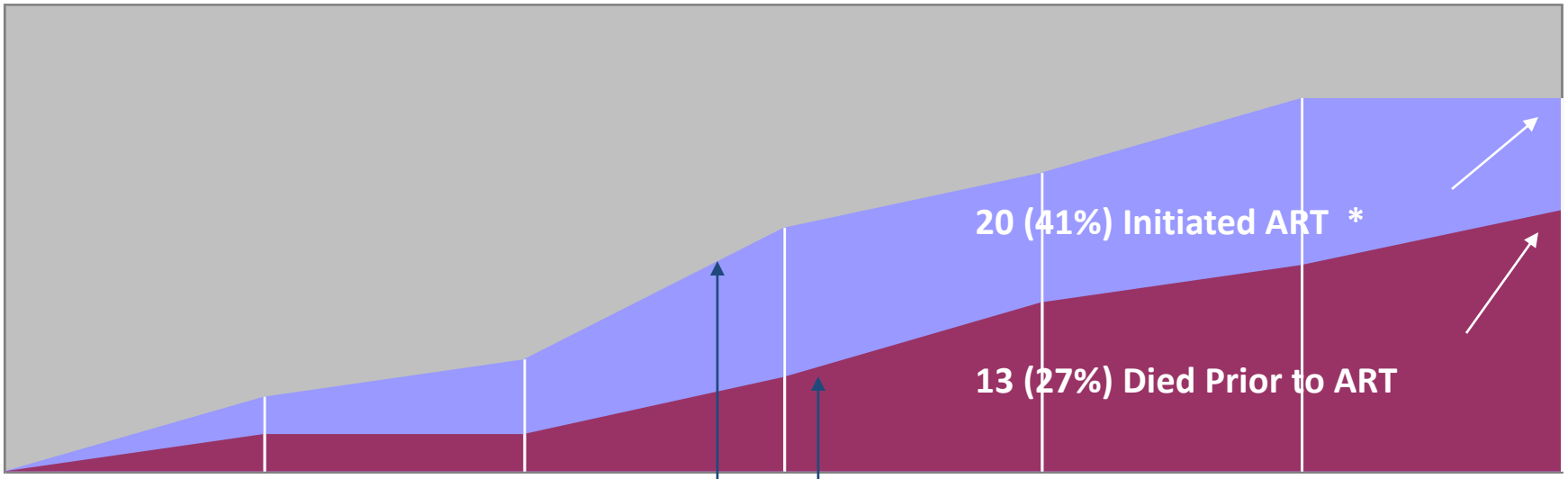
Baseline Characteristics

At the time of admission:	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[2]	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 <u>least</u> likely to initiate ART by 6 months.

Patient Trajectory After Discharge



12 (24%) Alive, Remain Pre-ART
<u>4 (8%) Lost to follow-up</u>
49 Patients Enrolled

*** 1 patient died during ART**

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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**.

Coovadia A, Venter F. Criteria for expedited antiretroviral initiation and emergency triage. *South African Journal of HIV Medicine* 2009; 33:27-28.

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. <u>Poor absorption of ART in very ill pts-</u> subtherapeutic serum levels = antiretroviral drug resistance.

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

3. <u>Drug-drug interactions-</u> among ART and anti-OI drugs may be difficult to manage.

4. **<u>IRIS events -</u>**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

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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

Reducing Mortality in Seriously-ill Patients with HIV and Smear-negative Pulmonary Tuberculosis, KwaZulu-Natal, South Africa…

Holtz TH, Mthitane T, **Sunpath H** et al. Use of a WHO-recommended algorithm to reduce mortality in seriously ill patients with HIV infection and smear-negative pulmonary tuberculosis in South Africa: an observational cohort study. Lancet Infect Dis. 2011 Jul;11(7):533-40.

Inclusion criteria were

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

Results

1. S**tandard 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).**

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	The CAMELIA study Cambodia-Blanc et al, 18th IAS Conference 2010, Abstract THLBB106	ACTG 5221 STRIDE study Havlir et al, 18th Conference on Retroviruses and Opportunistic Infections, Abstract 38	SAPiT study Abdool Karim et al, 18th Conference on Retroviruses and Opportunistic Infections, Abstract 39LB
Inclusion criteria	Smear positive TB and CD4 ≤ 200 cells	Confirmed or suspected TB and a CD < 250 cells	Confirmed or suspected TB and a CD < 500 cells
Time to ART after TB treatment	2 weeks vs 8 weeks	2 weeks vs 8-12 weeks.	4 weeks after starting treatment vs 4 weeks of the completion of intensive phase

	The CAMELIA study	ACTG 5221 STRIDE study	SAPiT study	
Results	Median CD4 = 25 cells and BMI = 17. A 34% reduction in mortality in those who started at 2 weeks.	No difference in the combined endpoint of AIDS progression and death between the two arms In those with CD4 ≤ 50 cells AIDS progression and death was reduced by 42% among those who started at 2 weeks.	No difference in the combined endpoint of AIDS progression or death comparing the two arms In those with CD4 < 50 cells, **earlier ART (at a median of 8 days)** reduced AIDS progression or death by 68% (marginally significant, p=0.06).	

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.

Tuberculosis meningitis study

Torok, 41st Union World Conference on Lung Health 2010

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

- Giseppe M, Antonio C, Setti M et. al. Complete Remission of **AIDS/Kaposi's Sarcoma** after Treatment with a Combination of Two Nucleoside Reverse Transcriptase Inhibitors and One Non-Nucleoside Reverse Transcriptase Inhibitor. *AIDS* 2002; 16: 304-305.
- Carr A, Marriott D, Field AN ET. al. Treatment of HIV-1-associated **Microsporidiosis and Cryptosporidiosis** with Combination Antiretroviral Therapy. *Lance*t 1998; 12: 3-5.
- Clifford DB, Yiannoutsos C, Glicksman DM et. al. HAART improves Prognosis in HIV-Associated **Progressive Multifocal Leukoencephalopathy. *Neurology*** 1999; 52(3): 623-625.

ART after other OIs

- Zolopa A, Andersen J, Komarow L, *et al.* Immediate vs. Deferred ART in Setting of **Acute AIDS-related Opportunistic Infection**: Final Results of a Randomized Strategy trial. Proceedings of the 15th Conference on Retroviruses and Opportunistic Infections; 2008 Feb 3-6; Boston, USA, 2008.
- OIs – PCP ,Toxoplasmosis ,Cryptococcal meningitis,Bacterial pneumonias

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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:

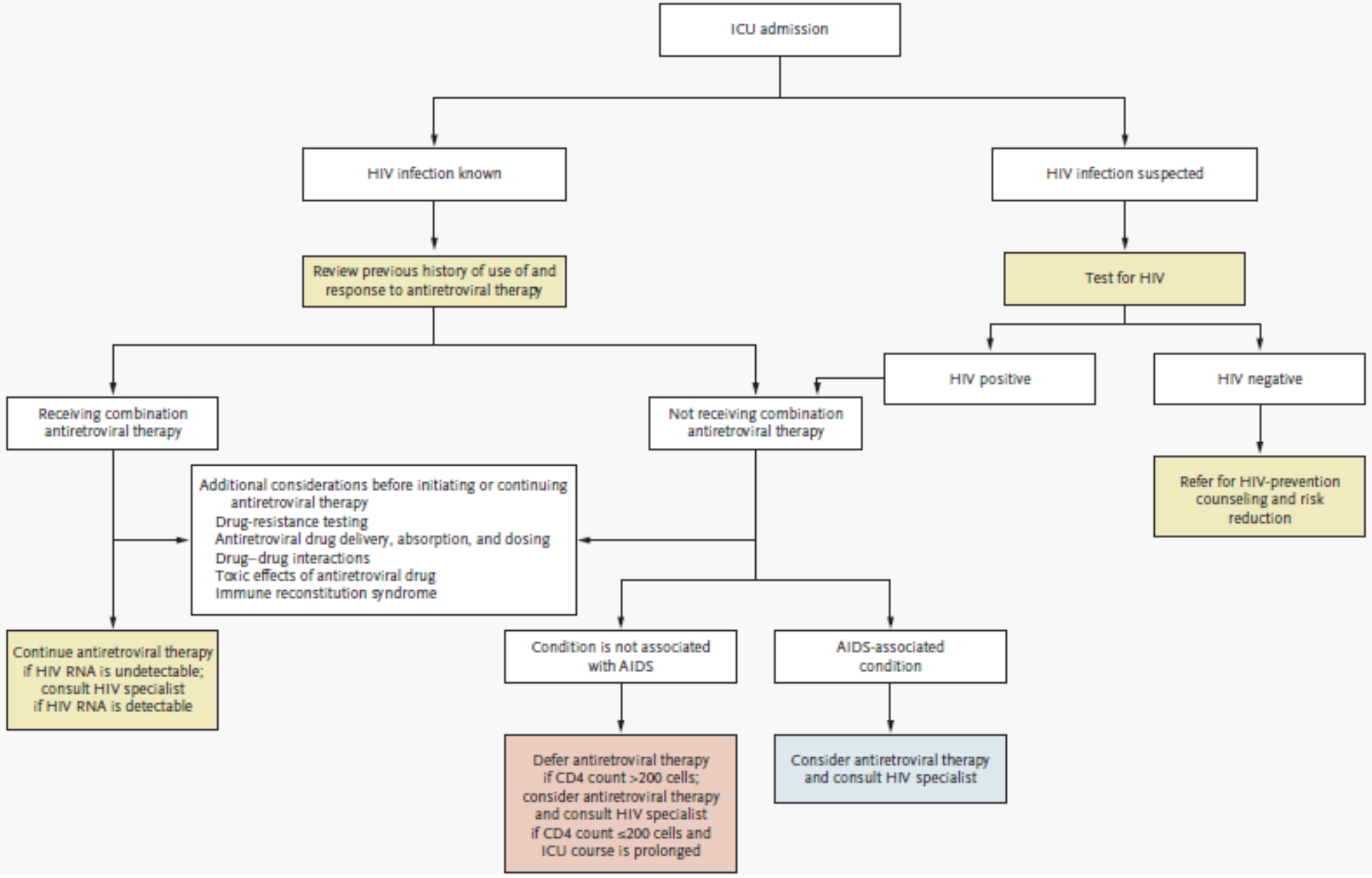
- End-stage renal disease may be caused by HIV chronic kidney disease
- Acute renal failure more common –requires fluid resuscitation and may need dialysis

Adverse events due to ART

Table 2. Potentially Life-Threatening and Serious Adverse Effects of Antiretroviral Agents.*

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

* 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.


ICU admission
HIV infection known
HIV infection suspected
Review previous history of use of and response to antiretroviral therapy
Test for HIV
HIV positive
HIV negative
Receiving combination antiretroviral therapy
Not receiving combination antiretroviral therapy
Refer for HIV-prevention counseling and risk reduction
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
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

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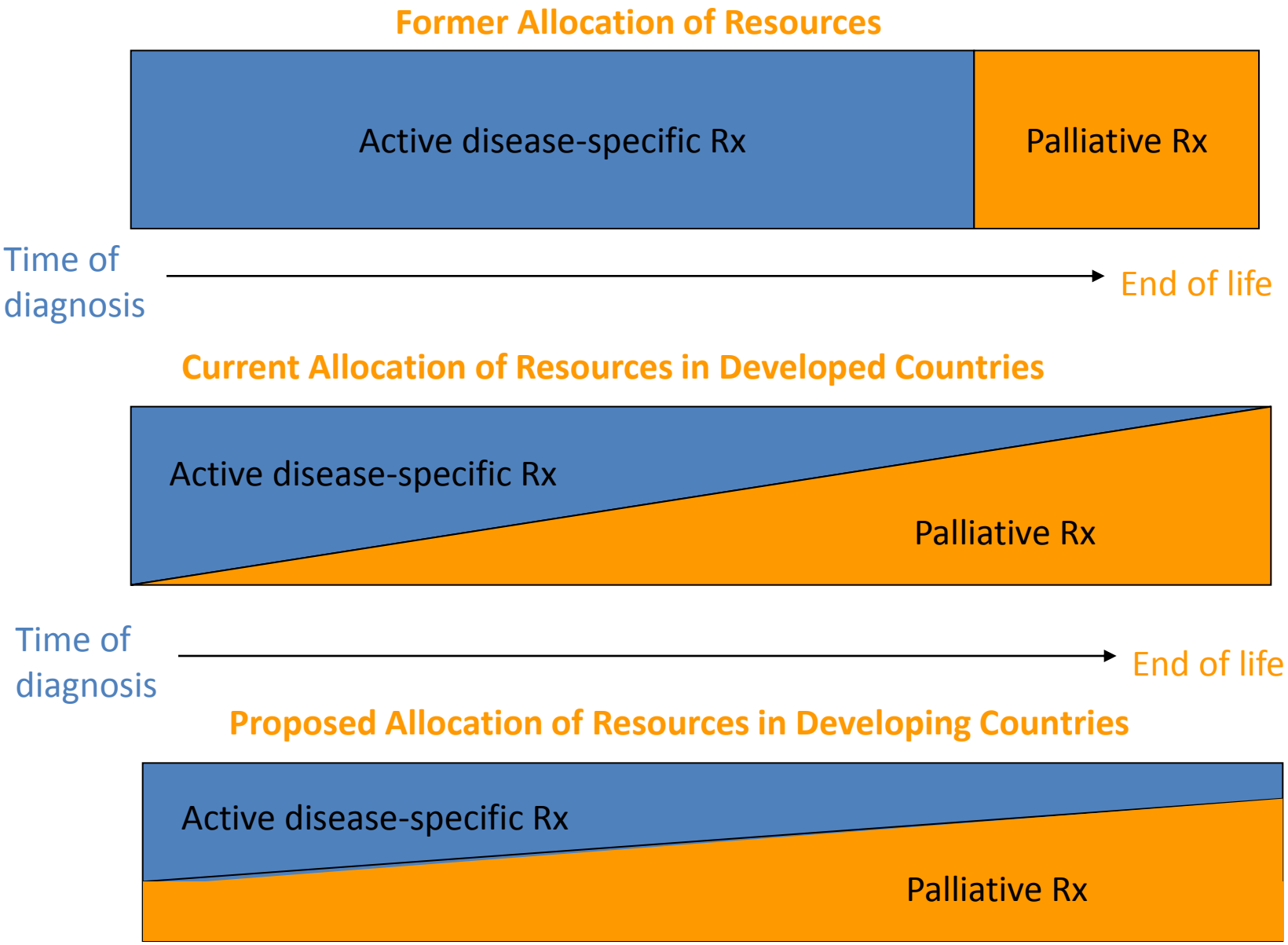
HIV palliative care: A paradigm shift



Source: U.S. Department of Health and Human Services- Palliative Care in Resource Poor Setings

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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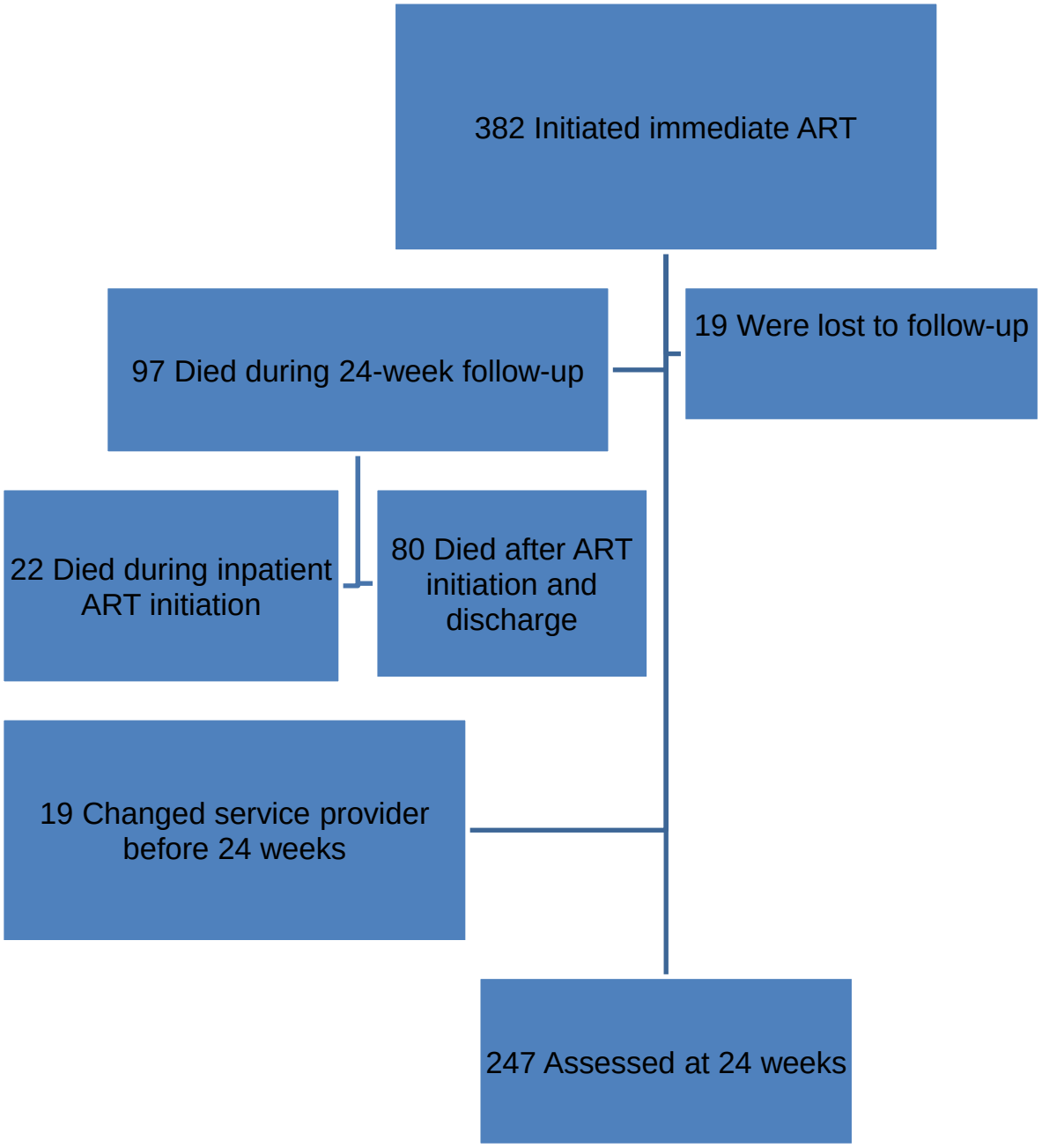
Operationalizing Early Inpatient Antiretroviral Therapy (ART) during Hospitalization with Acute Opportunistic Infection (OI) in South Africa

Sunpath H - Edwin C, Chelin N, et al.

CROI: Boston, March, 2010 .Poster 1079


382 Initiated immediate ART
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

Clinical characteristics	N (%)	
Median baseline CD4 count (cells/ul) [IQR] [1]	33(12-78)	
Baseline CD4 cell count category (%) [1] 0-49 cells/ul 50-99 cells/ul 100-199 cells/ul 200-349 cells/ul	224(62) 65(18) 22(15) 18(5)	
Pulmonary tuberculosis Extrapulmonary tuberculosis (incuding meningitis) Cryptococcal meningitis Chronic diarrhea (>14 days) Bacterial pneumonia *Toxoplasmosis gondii* *Pneumocystis jirovecii* pneumonia HIV-associated kidney disease Other cause for admission in ART-eligible patient [2] Undiagnosed OI [2]	147 (39) 96 (25) 40 (10) 35 (9) 11 (3) 9 (2) 5 (1) 4 (1) 20 (5) 15 (3)	

Timing of ART initiation	**N=382**
Median days from admission with OI to ART initiation – no. [IQR] 1	**14 [11-18]**
Days from admission with OI to ART by category, no. (%)	**15 (4)**
0-7 days	**181 (47)**
8-14 days	**105 (26)**
15-21 days	**62 (16)**
>21 days	
24-week Virologic Outcomes	
Intent-to-treat (ITT) viral suppression <400 c/mL no., (%) [2]	206 (57)
As-treated (AT) viral suppression <400 c/mL no., (%) [3]	206 (93)
24-week Immunologic Outcomes	
Median CD4 count improvement (cells/ul) (IQR) [4]	100 (48-188)

24-week Vital Outcomes	**N (%)**
Overall mortality (%)	**97 (25)**
Mortality prior to discharge in the step-down facility	**20/102**
Mortality after discharge	**77/102**
Among patients who died, median days to death, (IQR)	**33 (9-95)**
24-week Program Outcomes	
Loss to follow-up (%)	19 (5)
Changed service provider (%)	19 (5
Serious IRIS Events	
IRIS events, no. (%)	17 (4)
Tuberculosis	14/17
Cryptococcal meningitis	2/17
Hepatitis B virus	1/17
IRIS-associated deaths [5]	5 (1)

Multivariate analysis

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

Multivariate analysis

Description	N	24-Week Mortality no. (%)	Univariate Odds Ratio 95% CI	Multivariate Odds Ratio 95% CI
Initial CD4 cell count 0=49 cells/ul >50 cells/ul	 224 135	 51 (23) 29 (22)	0.9 (0.6-1.6)	1.0 (0.6-1.7)
IRIS in initial 6 months Absent Present	 365 17	 92 (25) 5 (29)	1.2 (0.3-4.6)	1.6 (0.5-4.8)
Days to ART initiation <21 >21	 301 62	 68 (23) 25 (40)	2.3 (1.3-4.1)	2.1 (1.2-4.0) **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?