REDUCING MORTALITY FROM HIV/TB and other OIs in HOSPITALISED PATIENTS

SAHIV CLINICIANS CONFERENCE
CAPE TOWN 2012.

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Consultant HIV /TB Research Programme

McCord Hospital

A. THE EVIDENCE

B. THE IMPLEMENTATION

ART outcomes - good news

- National programmes reporting good outcomes
- About 1.5 m on treatment

- 1 year survival estimated as 93-95% and 2 year survival 91% in outpatient setting

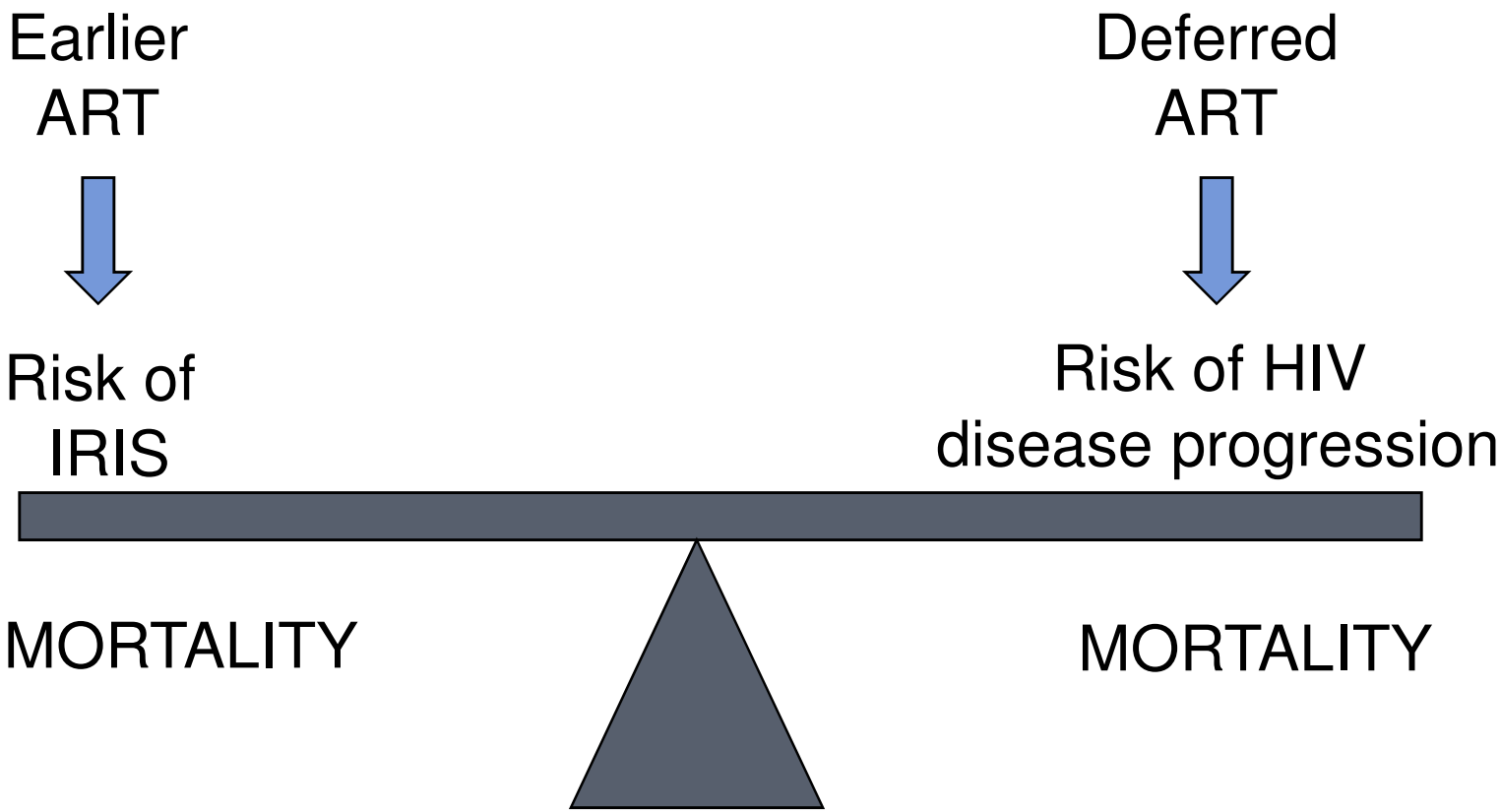
In SA500 000 need ARV's
EACH year

300 000 dead (advanced disease with coinfections) **many in the hospitals!**

200 000 well on ARV's

Who gets opportunistic infections in 2012?

- Those unaware of being HIV infected
- Those aware of HIV, but not taking ART
- Those who have been prescribed ART, but have treatment failure due to factors such as poor adherence, drug toxicity, drug resistance, drug-drug interactions
- (Vast majority: those not on ART at all)



When to start ART after recent diagnosis of OI?

Several recent and ongoing clinical trials

Co-treatment of OI and ART

Potential challenges	Potential benefits
IRIS	Reduced HIV progression
Co-toxicities	Reduced mortality
Drug-drug interactions	Clearance of OI
Absorption	Prevent OI recurrence
Pill burden	Prevent re-admission
Adherence counseling	

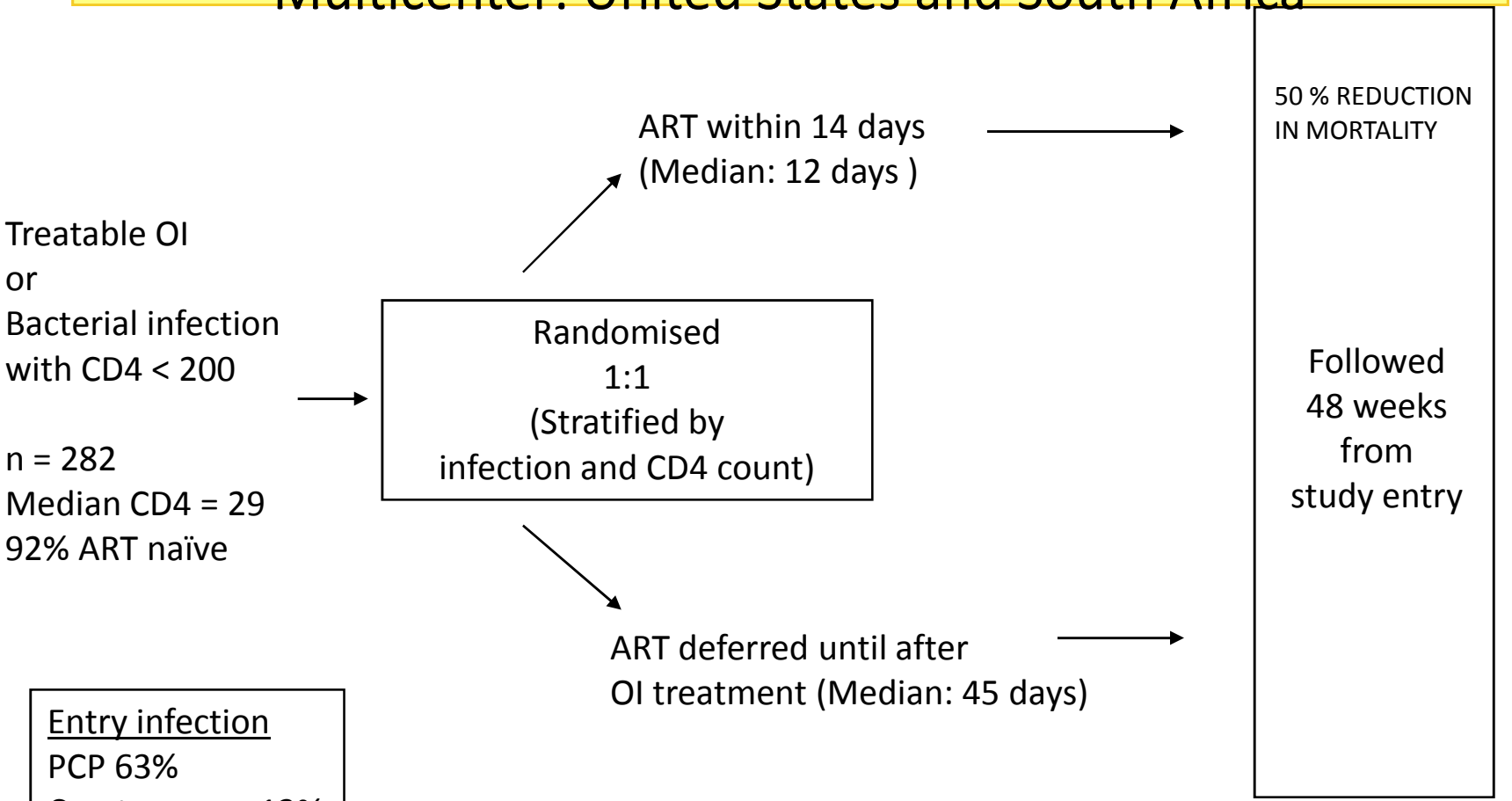
Acute OI: When Should ART be Started?

- Persuasive arguments both for starting early and waiting until OI is treated
- For non-TB OIs, A5164 suggests that treatment should be started within the first 2 weeks of diagnosing the infection
  - Lower risk of AIDS progression or death
- Predominant OIs in that study were PCP and bacterial infections; TB *excluded* . Some data on Toxo and CCM

OTHER OIs

ACTG A5164 trial-2009

Multicenter: United States and South Africa



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

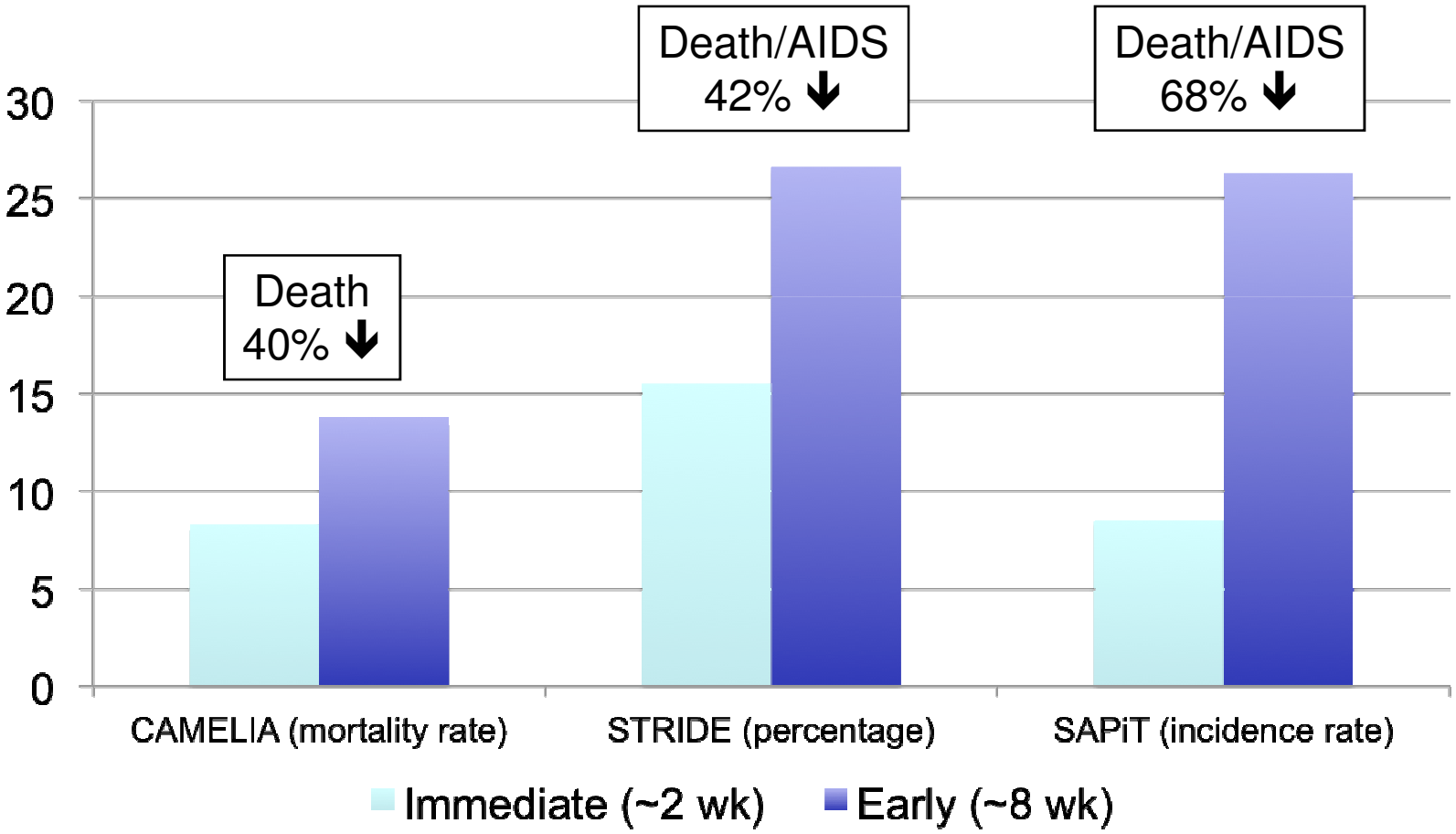
Zolopa, PLoS ONE 2009;4:e5575
Grant, PLoS ONE 2010;5:e11416

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.

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)

	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

CAMELIA, STRIDE and SAPiT trials

Comparing immediate versus early ART:

- ART drug switches were more frequent in immediate arm in SAPiT
- Grade 3 or 4 toxicities were not more frequent in the immediate arm in STRIDE
- TB-IRIS was more frequent in the immediate arm in all 3 studies (2-5 x)
- **SAPiT**

Earlier tx was a/w 5x incidence of IRIS

Pts with CD4 count>50 cells had

-No decrease in mortality,

- 2 fold increase in developing IRIS,
- Nearly 7 fold risk of having to change at least 1 drug in ARV regimen d/t toxicity

Karim SA et al. *Optimal timing of ART during TB therapy: findings of the SAPiT trial.* 18th Conference on Retroviruses and Opportunistic Infections, Boston, abstract 39LB, 2011.

JournalWATCH
MEDICINE THAT MATTERS

Published in AIDS Clinical Care
November 5, 2012

Balancing the Risks and Benefits of Early ART Initiation in HIV-Infected Patients with TB

A secondary analysis from the SAPiT trial reinforces current recommendations

Naidoo K et al. The immune reconstitution inflammatory syndrome after antiretroviral therapy initiation in patients with tuberculosis: Findings from the SAPiT trial. Ann Intern Med 2012 Sep 4; 157:313

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Summary and Comment by Mauro Schechter, MD, PhD

Dr. Schechter is a Professor of Infectious Diseases at Universidade Federal do Rio de Janeiro, Head of the AIDS Research Laboratory at Hospital Universitario Clementino Fraga Filho, and Principal Investigator of Projeto Praça Onze at Hospital Escola São Francisco de Assis in Brazil. He reports no conflicts of interest.

	EARLY INTEGRATED	LATE INTEGRATED	SEQUENTIAL
IRIS per 100 person years	45.5	9.7	19.7
% Severe /life threatening IRIS	35	22	16
% IRIS related hospitalisation	44 2 deaths	22	5

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MEDICINE THAT MATTERS

Comment

- When making decisions about when to start ART in patients with recently diagnosed TB, clinicians must balance the survival benefit against the risk for severe IRIS.
- Although this study included only ambulatory individuals with sputum smear-positive TB, the results support present recommendations to

Start ART within 4 weeks after TB treatment initiation for those with CD4 counts <50 cells/mm3.

Deferring ART initiation until 8 to 12 weeks after TB treatment for most patients with higher CD4-cell counts. Reduces the incidence and severity of IRIS without increasing mortality.

New IAS-USA Guidelines Confirm Commitment to Universal HIV Treatment 23/07/12

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)

SAHIVCS GUIDELINES-SEPT 2012

Starting ART in patients with TB

- CD4 count ≤50 cells/µl: - after 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 2 - 8 weeks after TBM diagnosis.

Starting ART in patients with other OIs

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.

Severe Kaposi's sarcoma and lymphoma, - ART counselling should be expedited and ART should be started as soon as possible.

Summary: Acute OIs and Timing of ART

- Early ART outweighs risk
  - Esophageal candidiasis
  - Crypto/microsporidiosis
  - PML
  - KS
  - PCP
  - Serious bacterial infections
  - TB
- Early ART be beneficial or harmful
  - Toxoplasmosis
  - Tb meningitis
- Early ART is harmful
  - Crypto meningitis

A. THE EVIDENCE

B. THE IMPLEMENTATION

Overview –REDUCING MORTALITY IN THE WARDS.

1.The challenges of early diagnosis and treatment of TB - high mortality in PLHV

2.OPERATIONALISING IMMEDIATE ART TO REDUCE MORTALITY IN TB &other OI.s- THE EVIDENCE

The challenge of numbers…and delayed presentation

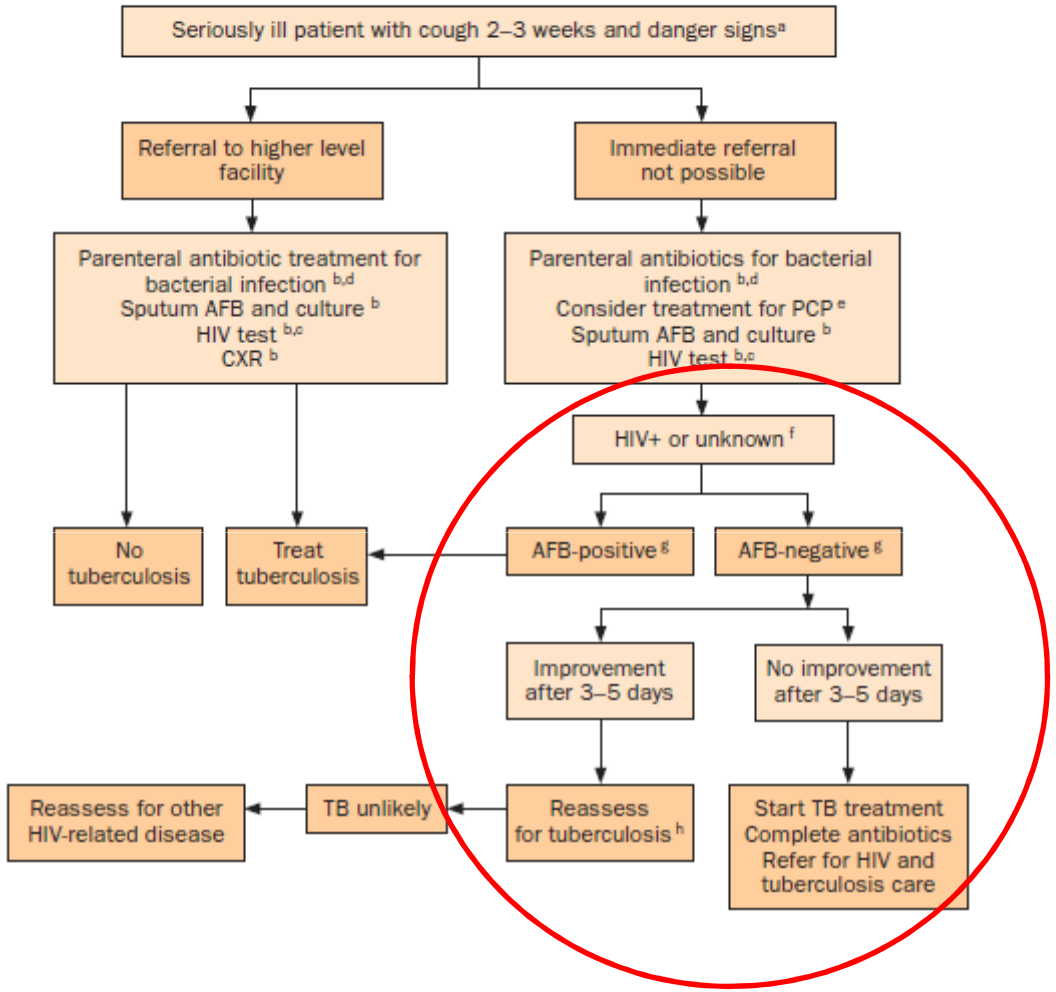
EARLY INPATIENT DIAGNOSIS AND TREATMENT…TB/HIV

THE LARGE NUMBER OF SMEAR NEGATIVE TB PATIENTS & AND LIMITED INFRASTRUCTURE **START TB TREATMENT ASAP** .

LINKING PATIENTS TO CARE FOR **HIV/TB COINFECTION**

START ART ASAP

Algorithm for the diagnosis of tuberculosis in seriously ill HIV-positive patient



The danger signs include any one of: respiratory rate >30/min, fever >39 °C, pulse rate >120/min and unable to walk unaided.

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

Timothy H Holtz, Gaëtan Kabera, Thuli Mthiyane, Tainos Zingoni, Sidhambaram Nadesan, Douglas Ross, Jennifer Allen, Sekai Chideya, Henry Sunpath, Roxana Rustomjee

Lancet Infect Dis 2011; 11: 533–40

	Standard practice N = 338/619	WHO algorithm N= 187/3424
On TB Rx	46%	100%
In hospital after 7 days	38%	27%
Alive after 8 weeks	68%	83%

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.

WHO ALGOTITHIM…

1.Lowering the risk of hospitalization at 7 days after admission by 30%

2. Improving the “risk” of survival at 8 weeks after admission by 23%

Reduced mortality benefit highest in those

= in whom anti-TB treatment was started within 3 days

= with no history of previous TB treatment

= on current ART

START ANTI TB TREATMENT IN SMEAR NEGATIVE PTS ASAP UPON ADMISSION –BY 3-4 DAYS

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..

EARLY INPATIENT DIAGNOSIS AND TREATMENT…TB/HIV

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LINKING PATIENTS TO CARE FOR **HIV/TB COINFECTION**

START ART ASAP

Linkage to care after inpatient stay

Linkage into care from hospital

KwaZulu-Natal, South Africa (2006/7)

49 participants

Median CD4 = 42

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

→

27% died before ART

41% initiated ART

8% loss to follow-up

24% alive and still pre ART.

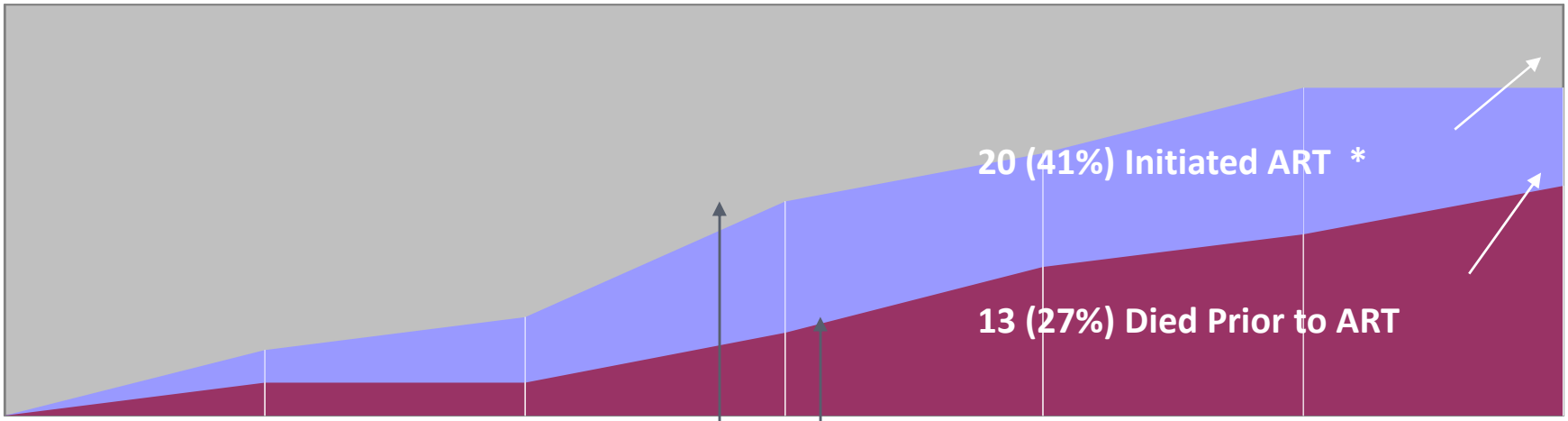
Murphy,-Sunpath Int J Tuberc Lung Dis 2010;14:903

Low uptake of antiretroviral therapy after admission with human immunodeficiency virus and tuberculosis in KwaZulu-Natal, South Africa

Int J Tuberc Lung Dis 2009;14(7): 903-908. Murphy R.A. ,**Sunpath H**, Edwin C.et.al

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

Patient Trajectory After Discharge



GOALS OF THE ART PROGRAMME -2012

HEALTH
KwaZulu-Natal

About treating the sickest patients

- Achieve best health outcomes in most cost-efficient manner
- To prioritise ART for patients with CD4 <200 or with severe disease irrespective of CD4
- To prioritise ART for patients coinfected with TB/HIV
- Avert AIDS-related deaths and expedite ART for hospitalised patients

Why no ART preparation for inpatients?

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

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,' "

2.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?"***

Factors that influenced the type of care…

Care is very depersonalised.

This is mainly due to the time constraints in the setting of increased patient numbers.

"Patient care is simply not how medical staff and nursing staff are evaluated. HIV/AIDS care is not integrated to involve a trained multidisciplinary team" concluded Penn-Kekana**, Medical doctors alone cannot cope!**

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**
  - **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 Pscyhol, Global Public Health 2010
Western Cape

THE BEST TIME TO DO YOUR BEST FOR THE PATIENT IS THE FIRST TIME THE PATIENT PRESENTS TO A HOSPITAL AND NEEDS TO BE ADMITTED.

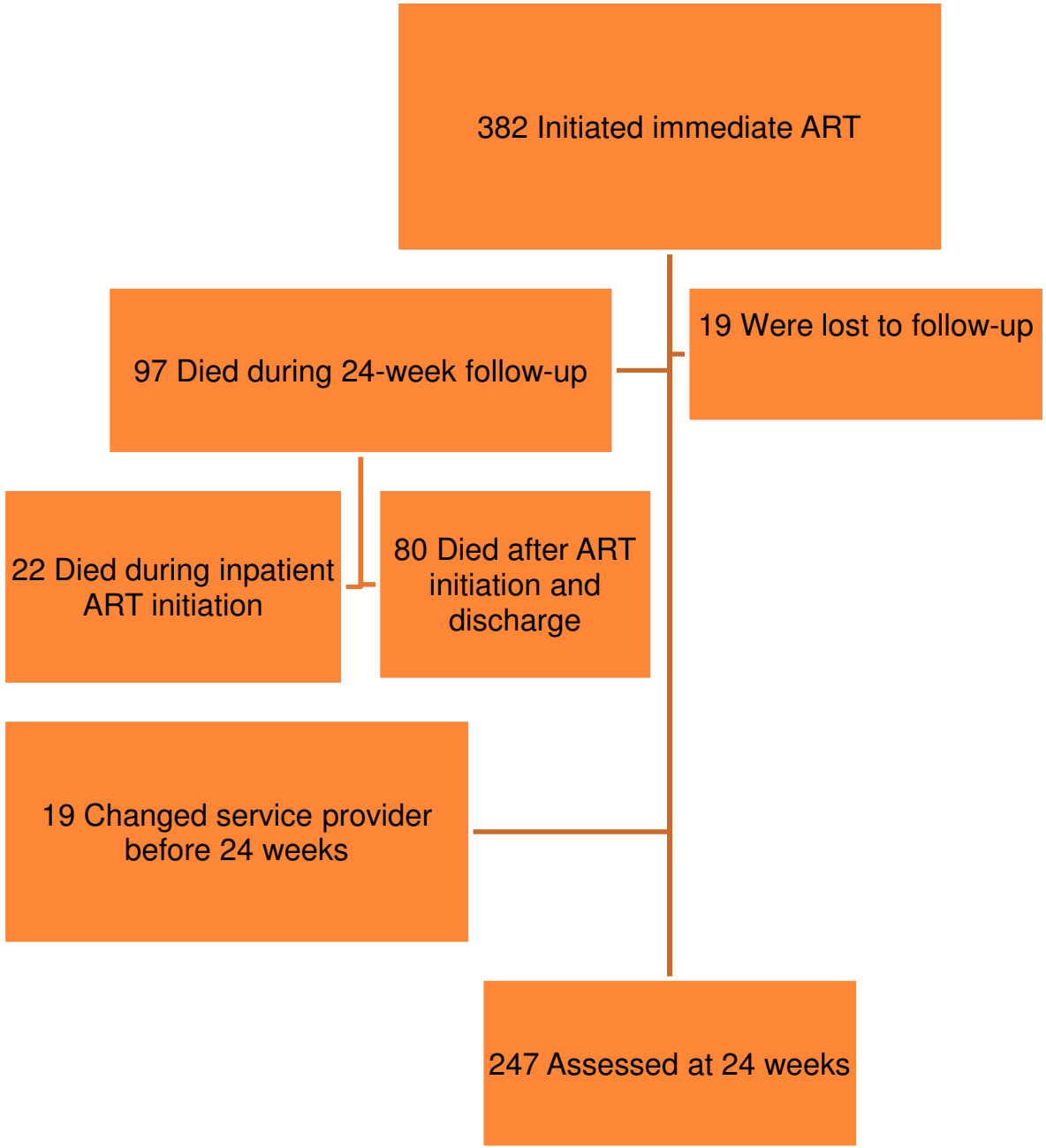
OPERATIONAL RESEARCH-2006-2009
Mc Cord- Siyaphila (SYP)-in patient unit for PLHIV

Operationalizing Early Inpatient ART during Hospitalization with Acute OI

Sunpath H, et al. CROI 2011. #1079

Sunpath H - Edwin C, Chelin N et al.*The International Journal Tuberculosis and Lung Diseases (TB Union Journal). Manuscript number : IJTLD-09-11-0651.R2,July 2012.*

- ART as part of inpatient care to pts with OI
- 11/2006 to 8/2007- of 1126 pts admitted
- 382 prospectively enrolled (Pulm TB 39%; EPTB 25%; CrM 10%, chronic diarrhea 9% others-Toxo)
- Median time from admission to ART: 14 d (IQR 11- 18)
- Median CD4 count at initiation 43 cells/mm3 and median increase by 6 months -100 cells/mm3


382 Initiated immediate ART
19 Were lost to follow-up
97 Died during 24-week 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	224(62)
50-99 cells/ul	65(18)
100-199 cells/ul	22(15)
200-349 cells/ul	18(5)
Pulmonary tuberculosis	147 (39)
Extrapulmonary tuberculosis (incuding meningitis)	96 (25)
Cryptococcal meningitis	40 (10)
Chronic diarrhea (>14 days)	35 (9)
Bacterial pneumonia	11 (3)
Toxoplasmosis gondii	9 (2)
Pneumocystis jirovecii pneumonia	5 (1)
HIV-associated kidney disease	4 (1)
Other cause for admission in ART-eligible patient [2]	20 (5)
Undiagnosed OI [2]	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. (%)	
0-7 days	**15 (4)**
8-14 days	**181 (47)**
15-21 days	**105 (26)**
>21 days	**62 (16)**
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**

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.

THE BEST TIME TO DO YOUR BEST FOR THE PATIENT IS THE FIRST TIME THE PATIENT PRESENTS TO A HOSPITAL AND NEEDS TO BE ADMITTED.

Inpatient ART team –Multidisciplinary team

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

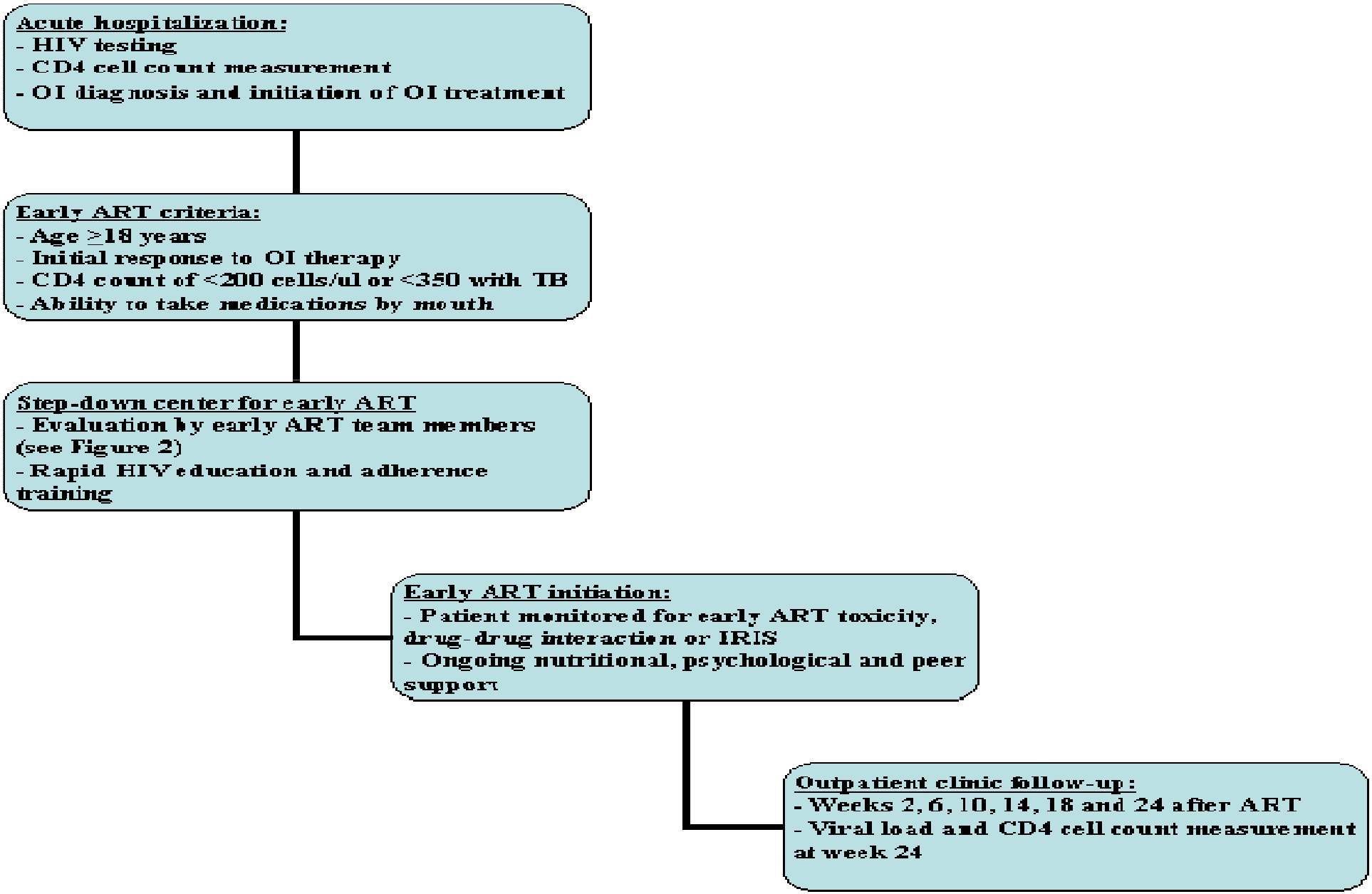
Doctor (Generalist / Family medicine trained in HIV medicine/ID specialist)

- 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

Patient flow through the system



Starting ART in hospital-SAHHIVMED Sept 2012

- Should be strongly considered during prolonged hospitalisation, where adherence, toxicity management and other support can be provided.

- Patients who wait to become severely ill and enter hospital may still have high levels of denial

- **The clinician must carefully 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.**

In Patient ART

"Limited data have shown what many experienced clinicians predicted – that patients who are initiated on ART within the hospital have high default rates. This may be due to several factors" ***ESHUN-WILSON 2010

1. They may be too ill to take in adherence counselling;
2. Discharge may not be managed well.
3. Other patients at high risk

- uncontrolled depression
- • poverty
- • ambivalence about their HIV status
- • those with distrust of the formal health sector
- • lack of home support or high levels of community stigma
- • alcohol or other substance abuse
- • post-partum women.

Before discharge

- The patient and/or next of kin must understand the reasons for initiation.
- If the patient is too ill/not mentally competent, a caregiver and/or family member must act as a directly observed therapy supporter and trained.
- Care should be exercised regarding ART drug interactions with concomitant medication.

On discharge

- Give very clear ART clinic directions, with a referral letter and details of documentation for the clinic.
- Patients should be encouraged to attend the ART clinic asap and should be informed of reasonable clinic appointment waiting times.
- Provide sufficient medication till the ART clinic visit
- Patients discharged on newly initiated TB treatment need separate clinical visits and this should be carefully explained (few programmes as yet offer integrated TB/ART clinical services)
- **Discharging patients directly into the care of adequately counselled family members can be invaluable.**

Follow up

- These patients are initiated on ART as quickly as possible after the underlying opportunistic illnesses have been addressed .
- They are to be counselled about the risk of IRIS, which may be misinterpreted as ART side-effects.
- Follow up closely in the clinic patients at high risk for early mortality ,IRIS and adverse events

1.Patients with a low BMI, anaemia and low albumin levels

2.Patients with newly diagnosed opportunistic illness, especially TB and CM

3. Patients with low CD4 counts.

Ideally, patients should have access to rapid referral systems, in the event of complicated IRIS or side-effects.

OPERATIONALISING Immediate ART TO REDUCE MORTALITY- A feasible HOSPITAL BASED programme

In SA500 000 need ARV's
EACH year

300 000 dead (advanced disease with coinfections) many in the hospitals!

200 000 well on ARV's


GETTY/AFP


aDDS Of OS

Conclusions...

1. Immediate ART saves lives! - International RCTSs and operational research in Durban- mortality reduction by 50% seen at 6 months)

2. Individualised approach to determine the optimal time to initiate ART.

3.Integrate services of a multidisciplinary team -that links the wards and clinic .

4.Interest by the medical practitioner to be trained - good generalist internal medicine experience/training and interest to learn clinical HIV medicine .

5.Innovate care by being able to apply principles of family medicine and palliative care effectively with ART.

Challenges

1. **ALL CLINICIANS TO BE INVOLVED IN THE ART PREPARATION AND INTIATION PROCESS FROM DAY 1 OF ADMISSION**
2. **Need to TRAIN more HCWs in the MDT**

   A complex disease with multiple psychosocial and logistic challenges.

3. **LINKAGE BETWEEN INPT AND OUTPT ART SERVICES**
4. **NEED FOR JUDICIOUS MANAGEMENT OF INPATIENT BEDS**

THE ROAD AHEAD…

eThekwini DOH DIRECTIVE (31/08/12) with CEOs
URGENT meeting of MEDICINE DEPT/ART MANAGERS/NSMs to develop locally appropriate SOPs for immediate ART

- Use medical ward beds or beds allocated under a trained team of medical practitioners (internal medicine /family medicine/ generalists)
- HIV counsellors doing HCT and beginning the ART preparation process.MDT start support work.
- Clinical team (DOCTORS AND NURSES) **starting the ART preparation process on DAY 1 ,** deciding on time to ART initiation AND start immediate ART for all eligible patients.
- SOPs for programme in the ward and follow up of “sick” patients at the hospital clinic by the same team
- Discharge “well” patients after obtaining a clinic appointment and providing a complete summary (prescribed format)

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Get involved

Acknowledgements

- 1. AWACC –Durban annual update
- 2.SA HIV Clinicians Society –guidelines
- 3.DOH –presentations
- 4.HOPE/CENTRA Conference –bimonthly
- 5.HIV/TB Research progrmme at MCH