South to South

PART in Africa

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FROM THE AMERICAN PEOPLE

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Learning Objectives

- Identify the ARV-eligible child
- Prepare the family for ARV initiation
- **Choose an effective 1st line regimen**
- Create an appropriate follow-up schedule for the newly initiated child
- Identify and manage ARV toxicities

South to South

Setting the scene

- What is different in SS Africa?
- Significant numbers of:
  - Deaths
  - New infections
  - Late entry into care
  - Burden of other co-diseases incl. malnutrition

South to South

Setting the scene

- HIV progression rates more rapid in Africa than in industrialised countries?
  - Immune activation aw chronic infections
  - Immunosuppression accompanying malnutrition
  - Immune dysregulation
  - Higher levels of viraemia→more rapid disease course

South to South

Setting the scene

- The ART era
  - ART access has escalated in recent years, but:
  - Fewer than 10% being reached by basic support services.
  - Approx 13% of those in need of ART, receiving it.
  - Comprise 7% of all people receiving ART in SSA

South to South

Reasons for case scenario

- How does this impact on our practice?
- Co-morbid diseases:
  - Polypharmacy (compliance)
  - drug-drug interactions (efficacy, adverse events)
- Late entry into care:
  - Advanced disease and immunosuppression
  - Risks of poor response/IRIS
- Haart in infants and neonates

South to South

Refresher: What's new?

- In young infants, earlier initiation of ART is life-saving
- > 80% of infected infants rapidly become eligible to start ART before 6 months of age.
- All infants < 12 months of age with confirmed HIV infection should be started on ART, irrespective of clinical or immunological stage.
- WHO 2008

South to South

Refresher: planning the regimen

- Considerations:
  - (State/country/site protocol)
  - Potential for drug interactions
  - Incidence and types of drug toxicity with the regimen.
  - Availability/palatability of formulations.
  - Dosing frequency/food and fluid requirements.

South to South

Refresher: planning the regimen

- What's the goal?
  - Maximal and durable viral suppression.
  - Immune restoration.
  - Specific individual requirements (Neuropenetration for example)
- What's recommended?
  - Dual NRTI backbone (key elements)
  - Base with: protease inhibitor/NNRTI/third NRTI
  - Little new information on what's the most effective first line therapy.

South to South

Dual NRTI backbone

- Guideline-specific/patient-specific/(cost)
- Should have
  - a cytidine analogue (3TC, emtricitabine), core component and thymidine or guanosine analogue
- Combinations:
  - ZDV/3TC,
    - Used longest,fdc,
    - No refrigeration, res pat
  - d4T/3TC
    - Comparable ZDV/3TC
    - Less git, haematological SE
    - More metabolic and neurological complications
    - refrigeration
  - ZDV/DdI,

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Dual NRTI backbone cont.

- ‘Alternatives’:
  - ZDV/ABC
  - 3TC/ABC, (favoured>TA)
    - Short t1/2, res risk, can’t use with nnrti (↑toxicity)
  - DdI/3TC

South to South

PI or NNRTI base?

- PI-based:
  - Highly potent
  - High pill-burden, unpalatable
- NNRTI-based:
  - Effective, palatable
  - Low genetic barrier to resistance
- NNRTIs in:
  - Infants (efv, sdNVP)
  - TB co-infection
  - Adolescent girls

South to South

Case scenario

- Are there any medical/ psychosocial contraindications to Haart?
- How can we get around them?
- Any other potential problems?
- (swallowing ,absorption)
- (volume of meds, spacing them)

South to South

The story of YM (HB)

- 1yr 9 mo male toddler
- First visit at 1yr 3 mo for Haart evaluation
- Ex- PMTCT, on Co-trimoxazole prophylaxis
- Clin stage II (eczema,hsm)
- Advanced immunosuppression (CD4 21% absolute 1956 cells
- Baseline screen:
- Alt 368U/L, Ast 225U/L

South to South

YM

- Bili, ALP,GGT?
- Grade 4 hepatotoxicity/hepatitis (PACTG guidelines)
- Hepatitis screen incl. cmv
- Eliminate hepatotoxic drugs
- Cotrimoxazole substituted with Dapsone

YM

- HepBsAg pos, HBsAb neg
- HBcAb pos, HBeAg pos
- Active Hep B infection
- Most likely failed vaccination

HBV and HIV co-infection

- High endemicity of HBV infection in Africa (excl Egypt, Libya, Tunisia, Algeria)
- Risk of progression to chronic infection higher in:
  - Infants infected perinatally
  - HBV infection while immunosuppressed
- Putting them at risk for hepatocellular carcinoma, cirrhosis
- Reactivation of resolved chronic infection is possible with immunosuppression.

South to South

HBV and HIV co-infection

- Lamivudine
- Resistance to Lamivudine develops quickly, but it is still recommended
- May flare up when Lamivudine is removed.
- Tenofovir and Emtricitabine
- Tenofovir not in under 6years, renal toxicity
- Spontaneous resolution (esp if art not an emergency)
- IFN less effective for chronic infections acquired in early childhood.
- Avoid Nevirapine
- ***HBV IRIS***

South to South

The story of TN PCH

- 1 mo old male infant
- Born at home , Term, SGA, BW 2120g, immunized at birth
- PMTCT, formula-fed exclusively
- First presentation at one month of age with a 2/7 history of cough, fever and vomiting
- Clin: wt 2.81kg, in respiratory distress, pneumonia ,cxr ground-glass appearance

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TN

- Clin suspicion of HIV infection and PJP
- (exposed, poor growth, resp findings)
- Treatment initiated with O2, antibiotics, high dose iv Co-trimoxazole and steroids
- HIV infection confirmed with positive HIV DNA pcr
- CD4 320 absolute, 22%, VL >3mil, > log 6.7
- Poor clinical response

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TN

- Urine CMV shell vial (culture positive)
- NPA negative for PJP, CMV, Adeno and RSV
- 10/7 later
- Haart started (Wt 2.6kg, Lt 51cm)
- 1/12 later (still in resp distress, worsening)
- Repeat screen: CMV pp65 pos titre 150, Ganciclovir started 4/7 later.

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CMV co-infection

- ↑ seropositivity and incidence of active cmv infection in women with HIV infection.
- Trend towards more rapidly-progressive disease in perinatally co-infected infants.
- (Diagnostic issues: infection vs disease)
- Pp65, dna pcr
- Not cured by currently available antiviral agents, thus the need for chronic suppressive therapy. (not currently practiced in SA, treat for 2 – 3 weeks)
- Ganciclovir, Cidofovir, Foscarnet

South to South

CMV co-infection

- No data to guide decisions concerning discontinuation of prophylaxis when CD4 ↑ with Haart in children.
- Early initiation of Haart (whilst still on ganciclovir to avoid IRIS)
- AZT best avoided, compound myelosuppression with ganciclovir.

South to South

LS CD

- 6 mo female infant, diagnosed HIV pcr positive at 3 mo
- Clin WHO IV, CD4 49 absolute, 6%
- Wt 3.9kg, Lt 60cm
- Severe GOR, chronic diarrhoea, massive stool water losses
- Screen: Alt 102, Ast 152, GGT 167, ALP 117 Bili

South to South

LS

- Stool: cryptosporidium parvum
- Nitazoxanide trial
- Haart started after measures to control diarrhoea and GOR

South to South

Chronic diarrhoea

- HIV enteropathy/enteritis/cryptosporidiosis/ other microorganisms:
- Advanced disease/epithelial layer/ brush border enzymes damaged
- Absorptive capacity diminished/malnutrition
- Cycle of immunesuppression, infection, malnutrition.
- HAART (Beware PIs)
- Nutritional support:
  - Dietary manipulation (calories, trophic)
  - Nutritional supplement (zinc, vit A)
- Bile salt chelator, antibiotic therapy(protect the gut)
- Antidiarrhoeals

South to South

SM

- 6 mo female infant, diagnosed HIV pcr positive at 3 mo
- Born prematurely at home, Ma's HIV positive status confirmed after delivery, infant received AZT and NVP prophylaxis, exclusively formula-fed.
- Clin WHO IV (marasmic,? RVD encephalopathy, prev adm for ? PJP)
- CD4 690, 20%

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SM

- Seizures, CSF findings suggestive of TB meningitis
- 4 drug anti-TB therapy started (Rif, INH, PZA, Ethionamide) after preliminary TB investigations.
- Wt 3.72kg, Lt 60cm

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ZDV or D4T?

- CNS as a separate compartment/reservoir/potential reseeding into plasma
- Disrupted BBB: friend or foe
- Both have good CNS penetration but more evidence with AZT
- AbC an option, but never tested alone

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TB, HIV co-treatment

- Volume of medication
- Co- toxicity
- Drug interactions
- Rif and NNRTIs/PIs
- Ritonavir boosting
- Double dose Kaletra?
- Risk of IRIS

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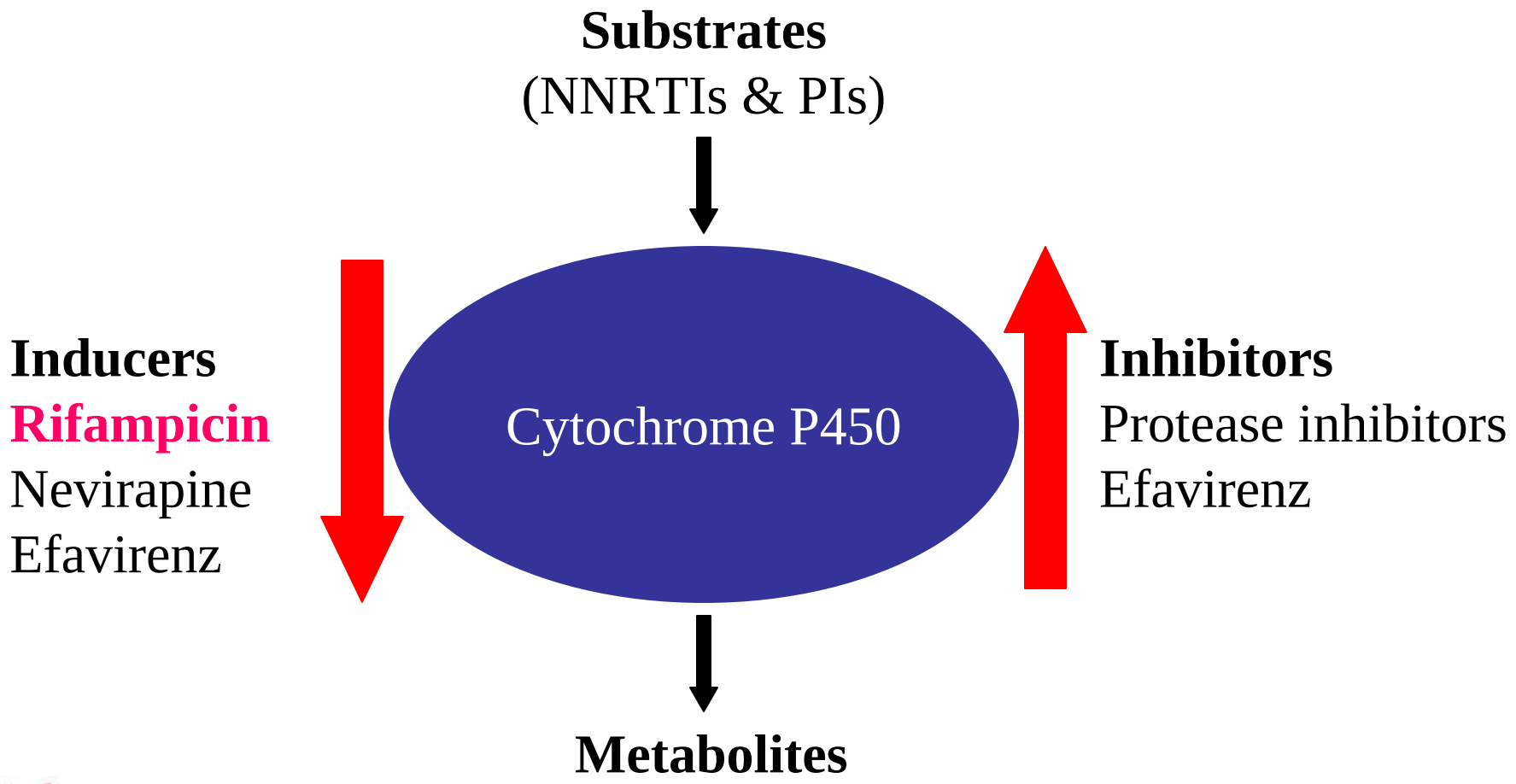
Antiretroviral therapy drug interactions



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Drug interactions

- Shared metabolism
- Isoform CYP3A4
- Rifamycins:
  - potent inducers
  - Inducing effect takes 2 weeks to become maximal, persists for at least 2 weeks after Rifampicin has been stopped.
  - Also increase the activity of efflux multi-drug transporter P-glycoprotein, contributes to elimination of PIs

Goals of ART

- Prevent clinical complications of HIV
- Prolong survival, Improve quality of life
- Ensure optimal immune response through careful assessment and preparation of the patient
- Provide **high quality** care and treatment through application of unique considerations for ARV use in infants, children, and adolescents

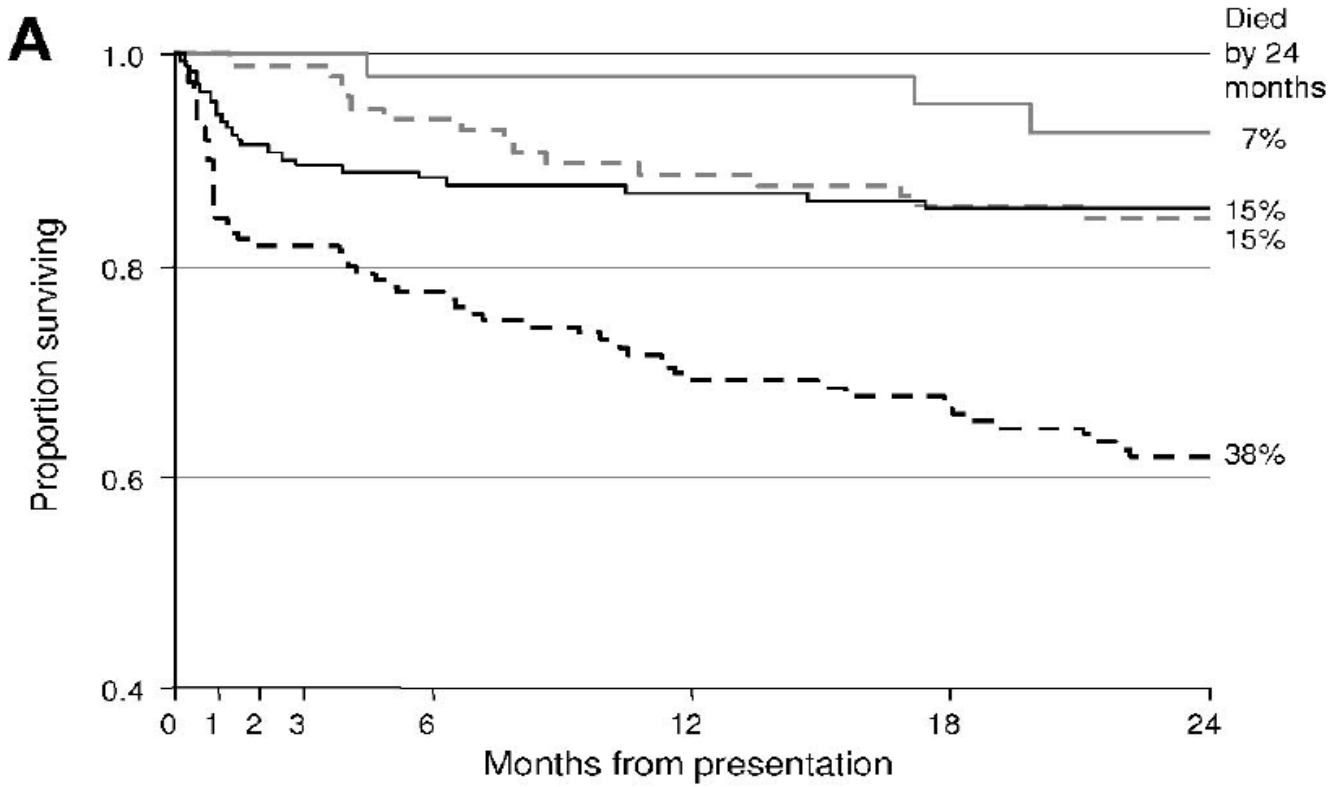
South to South

Reasons for case scenario

- Backlog of intermediate, slow progressors.
- Older age group, learning curve, sound knowledge.
- Young infants:
  - Still a challenge, rapid progressors, high mortality with no Haart.
  - Survivors with significant morbidity.

South to South

Impact of ART



Number of deaths, by months from presentation

	<1	1-3	3-6	6-12	12-18	18- 24	Total at risk
Born to mothers with HIV status known at birth							
-1996	0	1	5	5	3	1	97
1997-	0	0	1	0	1	1	48
Presented after birth and before 1 year							
-1996	25	4	7	13	13	8	161
1997-	10	8	2	2	1	2	175

Doerholt et al PIDJ 2006

Case scenario

- Baby SM
- Let’s read the story
- Let’s stage the child and justify our criteria for staging.
- Let’s decide if the child is eligible for ART or not and on what grounds?
- If we didn’t have definitive infant diagnosis, what else could we do?

South to South

Case scenario

- Let the real work begin.
- Who's involved? (MDT)
- Who needs to do what?

South to South

Case scenario

- Let’s plan the regimen
- Issues with particular drugs

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Case scenario

- Follow-up:
- When? Where?
- Early follow-up:
- Points of concern
- Later follow-up:
- Points of concern

South to South

Points of discussion

- Delay in making diagnosis of HIV infection
- Neurological injury
- Anaemia
- Possible TB
- Mum’s own health
- Status of the older child

South to South

References

- Textbook of Paediatric HIV Care ed Steven Zeichner and Jennifer Read
- HIV Medicine 2007
- www.unaids.org
- www.who.org

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