ART during the first month of life

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Outline

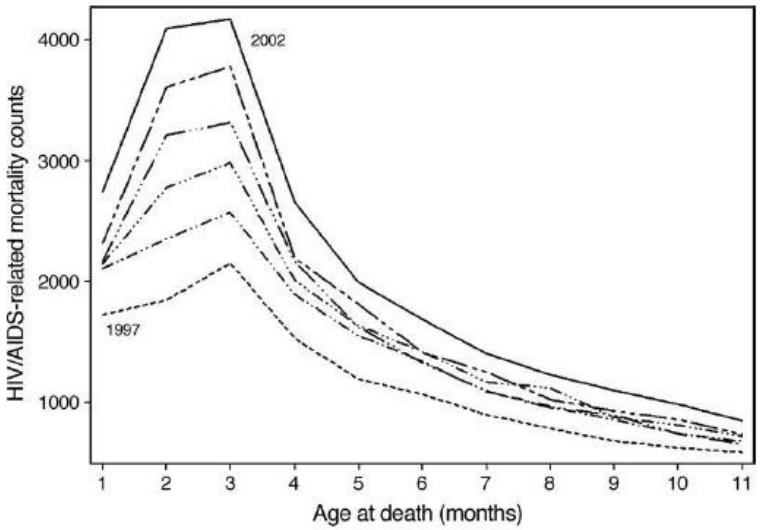
- Why?
  - Pros & cons of starting ART during the neonatal period (<28 days of age)?
- When?
  - Transition from prophylaxis to treatment (cART)
  - When the birth PCR result comes back positive…
- What?
  - ARV choices & dosing issues
- How?
  - Birthing facility / baby clinic / ARV site / hospital
- What's ahead?

Neonatal cART

Why the urgency?

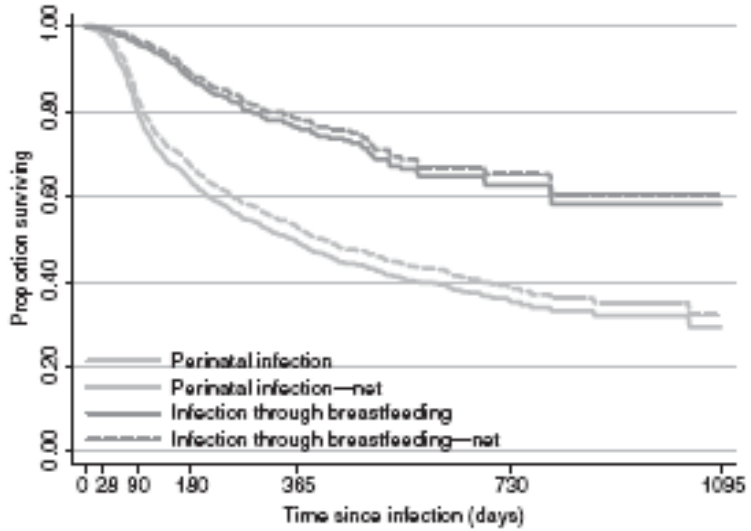
- Mortality
  - In the absence of ART, HIV-related mortality peaks at 2-3 months of age in South Africa (Bourne, AIDS 2009)
  - Intrauterine vs intrapartum postnatal infections:
    Birth HIV PCR testing detects intrauterine infections at highest risk of rapidly progressive disease & provides an opportunity for ART intervention
  - CHER study (Violari, NEJM 2008): Early HIV diagnosis and early cART (6-9 weeks of age) reduced early infant mortality by 76% and HIV progression by 75% compared to ART deferred until clinical or CD4 criteria were met
  - One-third (10/30) of overall mortality occurred in early ART initiation group
- Morbidity
  - 62% of 403 infants who initiated cART at median 8.4 weeks of age had advanced HIV disease (CD4 <25% or <1500 cells/mm^3 or WHO Stage 3 or 4 (Innes, JIAS 2014)

Mortality risk peaks at 2-3 months of age



Bourne et al. AIDS 2009

Survival by perinatal vs breastfeeding transmission



Marston et al. Int. J. Epidemiol. 2011

CHER study: early ART improves survival & slows disease progression

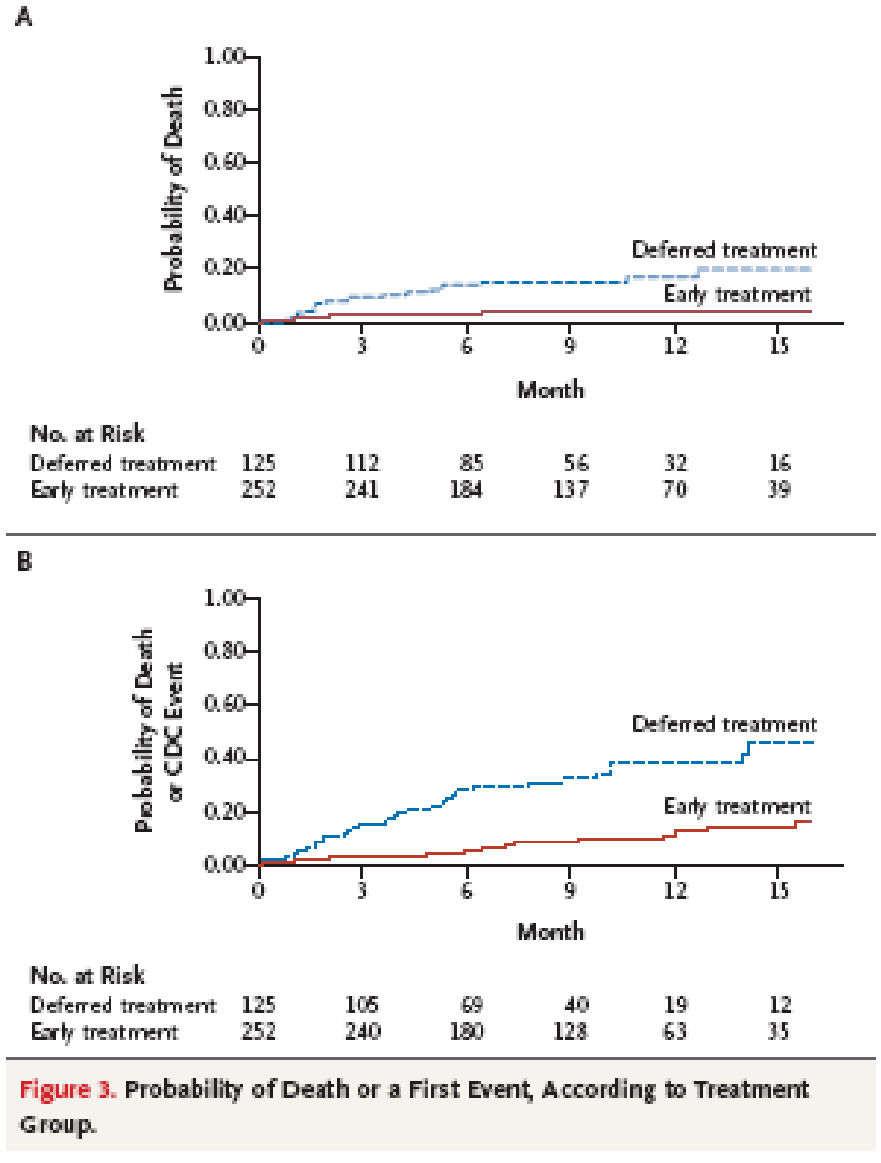


Figure 3. Probability of Death or a First Event, According to Treatment Group.

Violari et al. NEJM 2008

Benefits of early versus delayed cART

Reduced Disease Progression[1]

Progression to CDC stage C or severe stage B: 26% (deferred-therapy group) *vs* 6% (early-therapy group); HZ=0.25, 95% CI: 0.15-0.41, p<0.001

Lower BCG-IRIS incidence[2]

10.9 vs 54.3 per 100 person years in infants with CD4 ≥ 25% at enrolment on early-therapy *vs* deferred-therapy group; HR=0.24, 95% CI 0.11-0.53,p<0.001; Infants with CD4 < 25% at enrolment on early-therapy had intermediate incidence: 41.7/100py

Improved neurodevelopmental outcome[3]

Early ART (n=38) associated with better locomotor quotient s [p=0.010] and general quotients on Griffiths Mental Development Scales [p=0.02] than deferred ART (n=77)

Reduced incidence of otorrhoea[4]

29% on deferred ART and 9% on early ART developed otorrhoea; risk ratio: 3.1, 95% CI 1.31-7.36, p=0.01

[1]Violari A, et al. N Engl J Med 2008;359:2233-2244
[2]Rabie H, et al. Int J Tuberc Lung Dis 2011;15:1194-200
[3]Laugton B, et al. 5th IAS Conference, 2009, Abstract no: MOPEB080
[4]Hainline C, et al. BMC res Notes 2011;4:448

Benefits of early cART

Why the urgency (2)?

- Immune protection
  - Preservation of capacity to respond to routine infant vaccines (Penisieroso, PNAS 2009)

- Size of resting CD4+ T-cell latent HIV reservoir is associated with time to undetectable viral load in infants starting ART at median 8 weeks of age (Persaud, AIDS 2012)
  - Rapid control of HIV viraemia in infants can reduce size of HIV reservoir

- Possibility of later structured ART interruption following very early ART initiation (CHER study)?

- (HIV cure agenda…)

Neonatal cART

Why not? What are the ‘known unknowns’?

- Safety & efficacy of cART in neonatal population
  - PI vs NNRTI-based regimens
  - Uncertain dosing
- Neonatal pharmacokinetics & pharmacodynamics: immature physiological systems (renal, hepatic, GIT)
  - Premature neonates
- Co-morbidities in neonatal period
  - Congenital syphilis, TB, CMV
- Optimal transition from neonatal ARV prophylaxis to neonatal cART?
  - Maternal cART & neonatal ARV prophylaxis also complicates PCR diagnosis in neonate

Neonatal cART

When to start?

- HIV PCR testing before 6 weeks of age, in particular testing at birth or within 1st 48 hours of life, makes cART initiation during neonatal period a possibility
  - Identification of neonates with intrauterine HIV transmission: at highest risk of disease progression & early mortality

- First opportunity is when birth PCR test result is positive
  - Confirmatory testing (repeat PCR / viral load)
  - Impact of point-of-care PCR

- No randomised clinical trial evidence to guide optimal time of cART initiation during 1st 28 days of life
  - Gestational age & clinical condition of neonate are important considerations

- Could a triple ART regimen act as both prophylaxis and initial treatment?

Neonatal cART

Is this a consideration for South Africa?

- National recommendation: Birth PCR testing for all low birth weight infants (<2.5 kg), if positive commence cART [STG 2013]

- Western Cape: Birth PCR testing for all high-risk infants, if postive commence on cART (WC DoH, June 2014)

High risk criteria, WC

Mother	Infant
Check in labour ward	
VL ≥1000 cps/ml from 28 weeks gestation	Born before 37 weeks gestational age
Initiated ART <12 weeks before delivery	Birth weight <2500g, regardless of gestation
Defaulted ART for at least 1 month at any stage during pregnancy	Abandoned newborns / Orphans
Likely NNRTI resistance (failed first or second line regimen at any stage / on second or third line regimen during pregnancy).	
Diagnosed as new HIV-infection from 28 weeks gestation, or in labour / immediately postpartum	
Diagnosed with TB / Syphilis during pregnancy	
Clinical signs of Chorio-amnionitis	
Check in nursery/postnatal ward	
Newly diagnosed TB / Syphilis	Any sick HIV-exposed newborn requiring more than routine neonatal care [for example but not limited to, congenital syphilis, congenital Cytomegalovirus (cCMV) infection etc.]
Untreated TB / Syphilis	

Case study

- 22-year old mother
- Started TB treatment 2 months before delivery
- Started ART 2 weeks before delivery (baseline CD4 count 22)
- PROM, C-section
- Infant 3.1 kg, term
- Birth HIV PCR sent, started on NVP+AZT prophylaxis (high risk transmission)
- PCR result + at D5
- Converted from NVP/AZT to NVP (twice daily)/AZT/3TC on D5
- Managed at district hospital and primary care ARV clinic with telephonic guidance from tertiary hospital ID unit
- Switch from NVP to LPV/r at 2 weeks of age
- AZT & 3TC dose adjustment with age / weight

Neonatal ART
What?

Prophylaxis

- SA
  - NVP (NDOH guidelines)
  - AZT
  - NVP + AZT (W Cape)
  - AZT + 3TC + NVP (Afa)
  - (Promise study: LPV/r or 3TC)
- US
  - Low risk: AZT
  - High risk: AZT + 3 doses of NVP in 1st week
- UK
  - Low risk: AZT
  - High risk: AZT + 3TC + NVP

cART

- NRTI backbone:
  - **AZT + 3TC**
  - ABC + 3TC
  - (d4T + 3TC)
- Third drug
  - NVP
  - LPV/r
- Other options:
  - Raltegravir?
  - Dolutegravir?

Neonatal cART: Unchartered terrain!

Dosing: Special Considerations: Neonates ≤14 Days and Premature Infants

For infants aged ≤14 days and for premature infants (until 42 weeks corrected gestational age), pharmacokinetic (PK) data are currently inadequate to formulate an effective complete cART regimen. Although dosing is available for zidovudine and lamivudine, data are inadequate for other classes of cART. Reports of cardiovascular, renal, and central nervous system toxicity associated with ritonavir-boosted lopinavir in young infants preclude the administration of this agent in the first 2 weeks of life. Currently, a study of early treatment is being developed in the International Maternal Pediatric Adolescent AIDS Clinical Trials network; based on PK modeling, an investigational dose of 6 mg/kg administered twice daily for nevirapine in full-term infants will be tested. Providers considering treatment of infants aged <2 weeks or premature infants should contact a pediatric HIV expert for guidance because the decision about whether to treat and what to use will involve weighing the risks and benefits of using unapproved cART dosing, and incorporate case-specific factors such as exposure to ARV prophylaxis.

Neonatal cART
Zidovudine (AZT)

- 4mg/kg/dose twice daily for first 6 weeks (prophylaxis or treatment)

- At 6 weeks of age:
  - If ≥3kg, use weight band dosing but big increase in dose
    - WHO (2010): 3 - 5.9kg: 60mg (6ml) twice daily (≈10-20mg/kg/dose)
    - US (2014):4 - <9kg: 12mg/kg/dose twice daily
  - If <3kg, use BSA dosing: 180-240mg/m^2/dose twice daily

- Consider d4T if AZT toxicity e.g. bone marrow suppression?
  - d4T solution impractical / not available (can use capsules dispersed in water)
  - Lack of data on dosing of ABC <3 months of age

Neonatal cART

AZT: dose modification required for premature neonates

(US guidelines: 12 Feb 2014)

Dosing Recommendations

Zidovudine Dose For Neonates/Infants (Aged <6 Weeks) For Prevention Of Transmission Or Treatment

Note: Standard neonate dose may be excessive in premature infants

Gestational Age (Weeks)	Zidovudine Oral Dosing	Zidovudine Intravenous Dosing (If Unable to Tolerate Oral Agents)
≥35 weeks	4 mg/kg body weight every 12 hours	3 mg/kg body weight IV every 12 hours
≥30 to <35 weeks	2 mg/kg body weight every 12 hours during first 14 days of life; increased to 3 mg/kg every 12 hours aged ≥15 days	1.5 mg/kg body weight IV every 12 hours during first 14 days of life; increased to 2.3 mg/kg every 12 hours aged ≥15 days
<30 weeks	2 mg/kg body weight every 12 hours during first 4 weeks of life; increased to 3 mg/kg every 12 hours after age 4 weeks	1.5 mg/kg body weight IV every 12 hours until 4 weeks of life; increased to 2.3 mg/kg every 12 hours after age 4 weeks

Pediatric Dose (Aged 6 Weeks to <18 Years)

Body Surface Area Dosing:

- Oral: 240 mg/m^2 body surface area every 12 hours*

Weight-Based Dosing

Body Weight	Twice-Daily Dosing*
4 kg to <9 kg	12 mg/kg
9 kg to <30 kg	9 mg/kg
≥30 kg	300 mg

Capparelli EV, Mirochnick M, Dankner WM, et al. Pharmacokinetics and tolerance of zidovudine in preterm infants. *J Pediatr*. Jan 2003;142(1):47-52

Neonatal cART

Lamivudine (3TC)

- 2mg/kg/dose twice daily for first 4 weeks of life (prophylaxis or treatment)

(US guidelines 2014; Mirochnick 2005 & 2011; Tremoulet 2007 & 2012; Bouazza 2011)

- At 2 weeks of age
  - 4mg/kg/dose twice daily
  - Weight band dosing chart from 3kg body weight

- Relatively low toxicity but studies suggest haematologic toxicity increases when combined AZT/3TC neonatal prophylaxis is used, with increasing numbers of patients requiring treatment discontinuation or blood transfusions (Mandelbrot et al. *JAMA* 2001)

Neonatal cART

Abacavir (ABC): no current role in neonatal cART?

SA guidelines

First Line Regimen	
All infants and children < 3 years of age (or < 10 kg)	ABC + 3TC + LPV/r Note: Do not change regimen on reaching 3 years of age or 10 kg.

US guidelines

Dosing Recommendations

Neonate/Infant Dose:

- Not approved for infants aged <3 months.

Pediatric Dose:

Oral Solution (Aged ≥3 Months):

- 8 mg/kg (maximum 300 mg) twice daily.

Neonatal cART

Nevirapine (NVP)

- Treatment dose of NVP is undetermined <14 days of age
  - Term & premature neonates

- Unresolved issues:
  - Role of lead-in dose in young infants
  - Prophylaxis dose has been once daily, therapeutic dose has been twice daily
  - Sub-optimal potency of NVP-containing regimens in young children (IMPAACT P1060)

- 6mg/kg/dose twice daily is under investigation as a treatment dose (IMPAACT P1115)

- US guidelines (2014) approved dose ≥15 days of age is BSA dose: 200mg/m^2/dose twice daily

Neonatal cART

Lopinavir/ritonavir (Kaletra®)

- Why would we want to use LPV/r as part of a cART regimen in neonates?
  - IMPAACT P1060 study
  - Arm 1: Among children 6-36 months of age with prior exposure to single-dose NVP for perinatal prevention of HIV transmission, cART consisting of AZT + 3TC + LPV/r resulted in better virological outcomes than treatment with AZT + 3TC + NVP (Palumbo et al. *N Engl J Med*. 2010)
  - Arm 2: Virological outcomes were superior with LPV/r compared to NVP-based ART regimens in children 2-36 months of age with no prior exposure to NVP (Violari et al. *N Engl J Med*. 2012)

Neonatal cART

Lopinavir/ritonavir (Kaletra®)

Dosing Recommendations

Neonatal Dose (<14 Days):

- No data on appropriate dose or safety in this age group. Do not administer to neonates before a post-menstrual age of 42 weeks and a postnatal age of at least 14 days because of potential toxicities.

Special populations—neonates: Ritonavir-boosted lopinavir should not be used in the immediate postnatal period in premature infants because an increased risk of toxicity in premature infants has been reported. These toxicities in premature infants include transient symptomatic adrenal insufficiency,[1] life-threatening bradyarrhthymias and cardiac dysfunction,[2-4] and lactic acidosis, acute renal failure, central nervous system depression, and respiratory depression.[4] These toxicities may be from the drug itself and/or from the inactive ingredients in the oral solution, including propylene glycol 15.3%, and ethanol 42.4%.[4] Transient asymptomatic elevation in 17-hydroxyprogesterone levels has been reported in term newborns treated at birth with ritonavir-boosted lopinavir.[1]

Neonatal cART

Lopinavir/ritonavir (Kaletra®)

- Infant dose (14 days – 12 months): 300mg/m^2/dose twice daily (US guidelines 2014)
  - ARV dosing chart from 3kg body weight

- Pharmacokinetic studies (IMPAACT P1030) on infants <6 weeks of age

  - Dose of 300/75 mg/m^2/dose twice daily in term neonates achieved inadequate exposure to LPV compared to older children/adults - suggested studying a higher dose with monitoring of serum drug concentrations and toxicity (Chadwick et al. *Pediatr Infect Dis J*. 2009)

  - 12-hourly doses of 40mg for infants 1–2 kg, 80mg for infants of 2–6kg and 120 mg for infants 6–10kg corresponded with the highest probability of achieving adequate trough values (Urien et al. *Br J Clin Pharmacol*. 2011)

Neonatal cART

Lopinavir/ritonavir (Kaletra®)

- Clinical case series on use of LPV/r in preterm infants (Holgate et al. *Pediatr Infect Dis J* 2012)
  - Eight premature HIV-infected infants
  - Median age at LPV/r-based cART initiation was 27 days
  - Trough values guided dosing: 5 infants required doses above 300 mg/m^2
  - No adverse events were noted, but careful monitoring required

Very Early Infant ART (VEIART)

- Mississippi baby
- ART started at 30 hrs of age
- Regimen:
  - AZT 2 mg/kg/dose 6 hourly
  - 3TC 4 mg/kg/dose twice daily
  - NVP 2 mg/kg twice daily
- NVP switched to LPV/r at day 7 of age

Neonatal cART
How?

- Birth / early HIV PCR testing
  - Risk-based vs universal
  - Lab vs point-of-care testing
- Follow-up of HIV PCR results
  - Birthing facility vs primary care clinic (discharge letter / RTHB)
  - Link to ARV treatment site
  - Tracing defaulters
- Define ARV prophylaxis & cART regimen
  - NVP (low risk)
  - AZT (private sector / formula feeding)
  - AZT + NVP (high risk)
  - AZT + 3TC + NVP?
  - AZT + 3TC + LPVr?
- Standardised monitoring & evaluation
  - Toxicity (FBC/diff, ALT, U&E)
  - Efficacy (VL, CD4)
  - Pre-cART genotyping
- National Helpline / Hotline
  - Premature neonates: hospital guidelines

Neonatal cART

Proposed recommendations based on current knowledge…

- If you obtain a positive HIV PCR result during the neonatal period:
  - Send repeat HIV PCR or viral load to confirm HIV diagnosis but do not wait for result before initiating cART
  - Send baseline FBC/differential, urea & creatinine, ALT
  - Arrange careful & detailed counselling of mother & family
  - Start or switch to:
    - AZT 4mg/kg/dose twice daily (until 6 weeks of age)
    - 3TC 2mg/kg/dose twice daily (until 4 weeks of age)
    - NVP 6mg/kg/dose twice daily (until at least 2 weeks of age)

Neonatal cART

Proposed recommendations based on current knowledge…

- If term infant, switch from NVP to LPV/r at 2 weeks of age (42 weeks post-menstrual age)
- Review on a 2-weekly basis including dose adjustments & FBC/diff/ALT until 2-3 months of age (CD4 & VL according to routine monitoring guidelines)
- If preterm infant and hospitalised, consider switching to LPV/r from 2 weeks of age provided renal & liver function is normal, monitoring for toxicity is available and with careful dose calculation (initial dose: 300mg/m^2/dose twice daily), monitor trough LPV levels if possible
- If preterm & not hospitalised, continue on NVP-based cART regimen until 42 weeks post-menstrual age and at least 2 weeks postnatal age before switching from NVP to LPV/r
- Consider substitution of AZT with ABC after 3 months of age if virologically suppressed

Neonatal cART

What's ahead

- International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) studies:
- P1097: Raltegravir pharmacokinetics & safety in neonates
- P1106: Pharmacokinetic characteristics of antiretrovirals and tuberculosis medicines in low birth weight infants
- P1110: A phase 1 trial to evaluate the safety and pharmacokinetics of raltegravir in HIV-1-exposed neonates at high risk of acquiring HIV-1 infection
- P1115: Very early intensive treatment of HIV-infected infants to achieve HIV remission: A phase I/II proof of concept study

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