Early Infant Diagnosis and Treatment of HIV – a focus on delivery and the neonate

30TH MAY 2019
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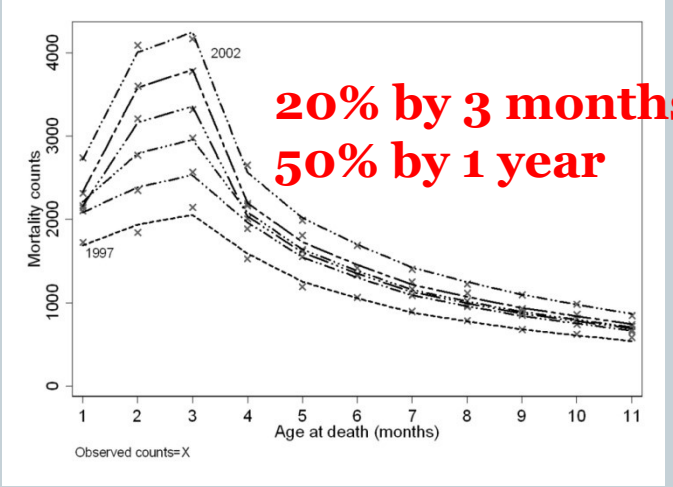
Context

2002-2007: Sd Nevirapine, maternal ART as of 2004/2005 if CD4<200
2008-2010: Mum: CD4<200 → HAART; CD4>=200 → AZT from 28 weeks + sd NVP at labor;
Baby: Sd NVP at birth + 7 day AZT. HIV test at 4-6 weeks
April 2010: HAART (≤350 CD4) or AZT from 14 weeks + Infant NVP for 6 weeks or thro' BF
April 2013: HAART(FDC) to all mothers from time of diagnosis to the end of breastfeeding + Infant 6 weeks NVP
January 2015: HAART (FDC) to all mothers life long, 6-12 weeks NVP to baby, +/- AZT

- Transmission has moved from 20-40% down to 2%
- Early peak of mortality remains
- ART treatment after a diagnosis at birth potentially enables identification of majority of infected newborns



When do we test infants?

TESTING FOR HIV-EXPOSED INFANTS

Birth HIV-PCR for all HIV-exposed infants

10 weeks HIV-PCR for all HIV-exposed infants (who had 6 weeks of NVP or NVP+AZT)

14 weeks HIV-PCR for all HIV-exposed infants (who had 12 weeks NVP)

Age appropriate test (PCR/RT) 6 weeks after complete cessation of breastfeeding

Rapid test at 18 months for all HIV-exposed children

Age appropriate test (PCR/RT) anytime if infant has missed a test or is symptomatic

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Who is exposed?

Testing – Identifying who is exposed

- Maternal testing at delivery facility important

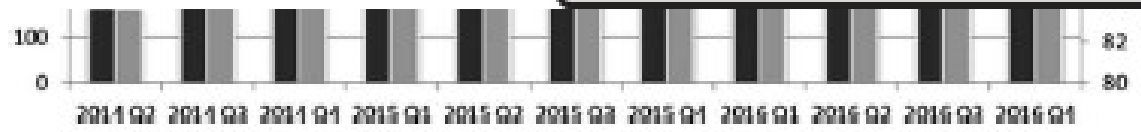
June 2014-
Dec 2016

Women with live births, n=30591

Admission Status:	HIV-negative	HIV-unknown	HIV-positive
n:	23126	601	6864
HIV Test Offered:	16208 (70%)	601 (100%)	
HIV Test Refused/Missed:	1216 (7.5%)	7 (1.2%)	
Tested:	14992	594	
New HIV Positive:	124 (0.8%)	97 (16%)	

221 (3% of Pos) women newly diagnosed at delivery

HIV-positive women, n=7085



Testing dips over holiday periods

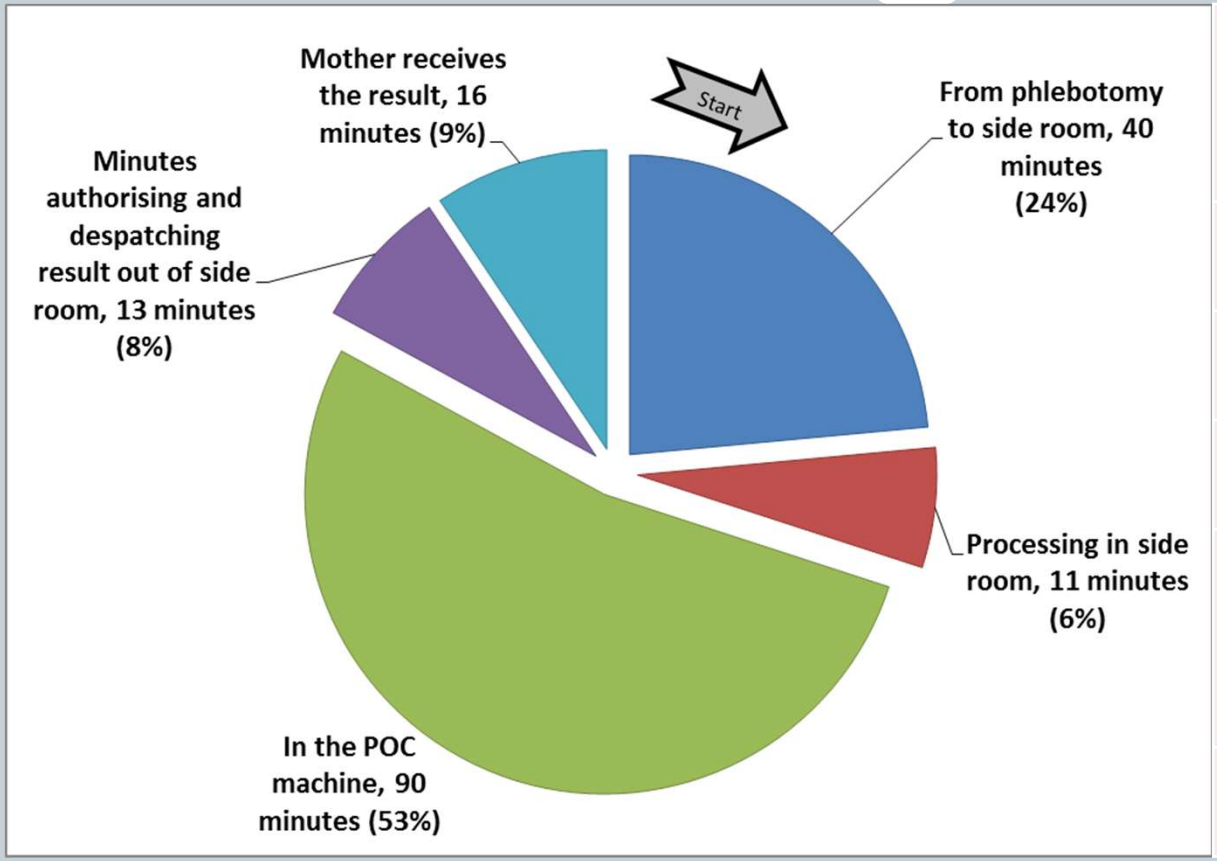
Future Work

- INCREASED ID OF EXPOSED INFANTS
- REDUCING MATERNAL HIV INCIDENCE
- HEU CHILDREN – SPECIFIC NEEDS

How do we test?

EID and POINT of CARE Testing

Results – Phlebotomy to result



	Median minutes	Inter-quartile range
From phlebotomy to side room	40 (24%)	25-58
Processing in side room	11 (6%)	8-14
In the POC machine	90 (53%)	90-90
Authorising and despatching result out of side room	13 (8%)	7-26
Mother receives the result	16 (9%)	10-27

- Result release POC PCR: 2.6 hours (95% CI: 2.3-3.1)
- Result release LAB PCR: 43 hours (95% CI: 31-54)

Results – Receipt of result (Any result)

	Total N=3970	POC and LAB PCR N=2238	LAB PCR only N=1732	p
Mother received neonates results, n (%)	3076 (77.5)	2155 (96.3)	921 (53.2)	<0.0001
Median age in days (IQR)	1 (1-8)	1 (0-1)	10 (9-13)	<0.0001

- Significantly fewer mothers received the result in absence of POC PCR
- Mothers received results significantly later in the absence of the POC PCR
- Time to ART initiation significantly shorter with POC PCR

Results – POC test performance

		LAB PCR Test				
		Positive	Negative	Indeterminate	Error	**Total**
POC	Positive	30	2	0	0	32
PCR	Negative	0	2088	3	7	2098
Test	Error	0	108	0	0	108
	Total	30	2198	3	7	2238

Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
1 (0.88-1)	0.999 (0.99-1)	0.938 (0.79-0.99)	0.995 (0.99-1)
McNemar p	0.157	**Kappa**	0.967

- 30 infected neonates in the POC/LAB PCR group
- Two false positive results – in both cases the POC rerun result was negative as well as concurrent LAB PCR

Results – POC test performance

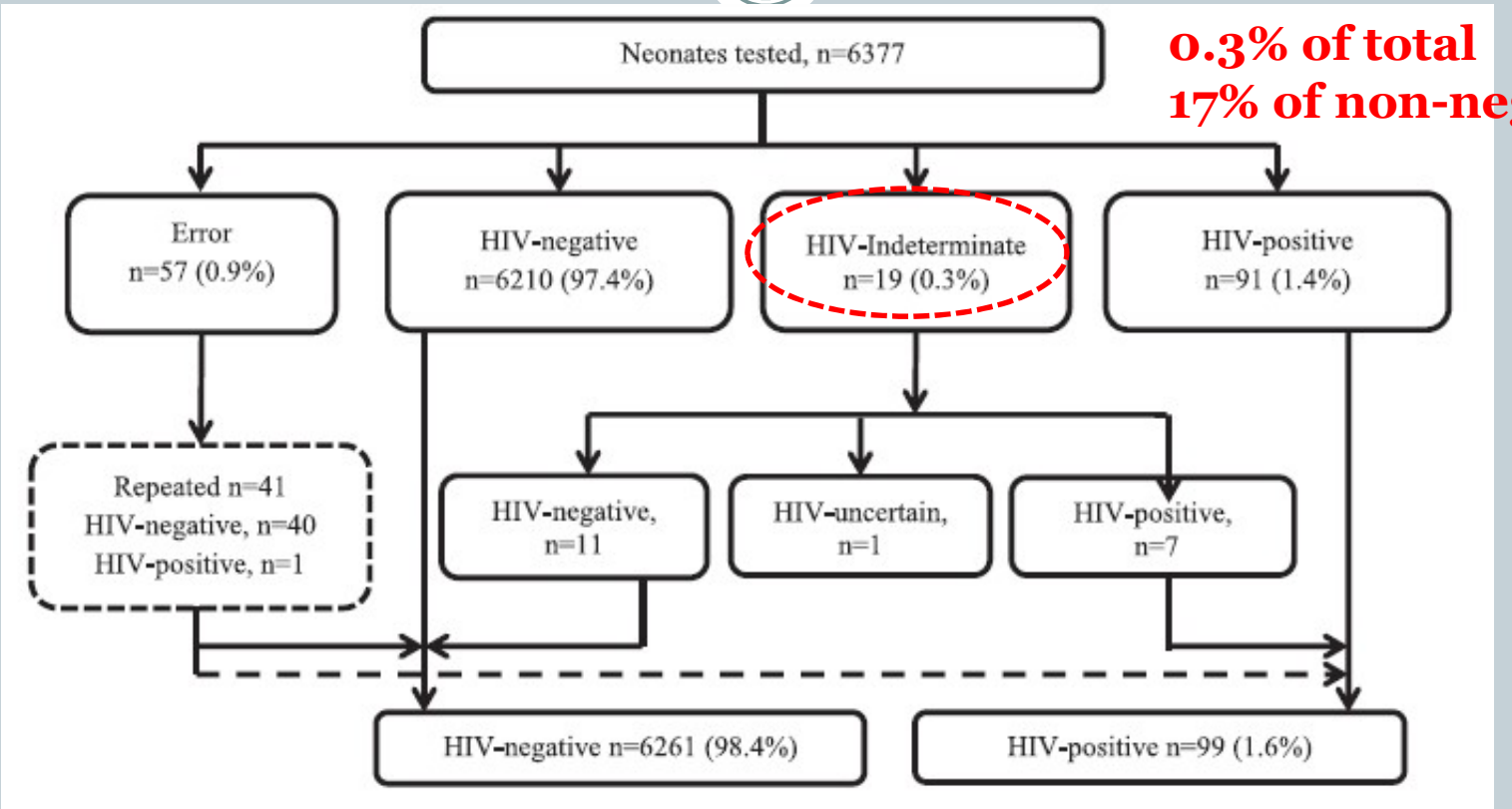
- Error rate: 108/2238 => 4.8% (95%CI: 3.9-5.7)
- Rerun of the same sample:
  - 103 (95.4%) of the samples could be rerun
  - 94/103 (91.3%) yielded a result on the second run
    - 9 cases repeat error – 3 rerun – all negative
    - 94 negative results
- Reduction of error rate: affecting 108=>11 neonates
  - Final error rate 11/2238 (0.5%)
- Specific issues: power failures, pipette supply, dust from renovations, faulty individual modules
- Exclusion of these modifiable factors reduced the error rate to 1.9-3.4%
- Rerunning error samples and identifying repetitive problems early can reduce error rates

Future Work

- IDENTIFYING HOW TO IMPROVE ACCESS TO TESTS AND RESULTS
- ELUCIDATE ROLE OF POC IN CARE

Is the diagnosis clear?

Diagnostic phase of management



- 20-25% of birth non-negative cases (positive and indeterminate) require more than one further confirmatory test.

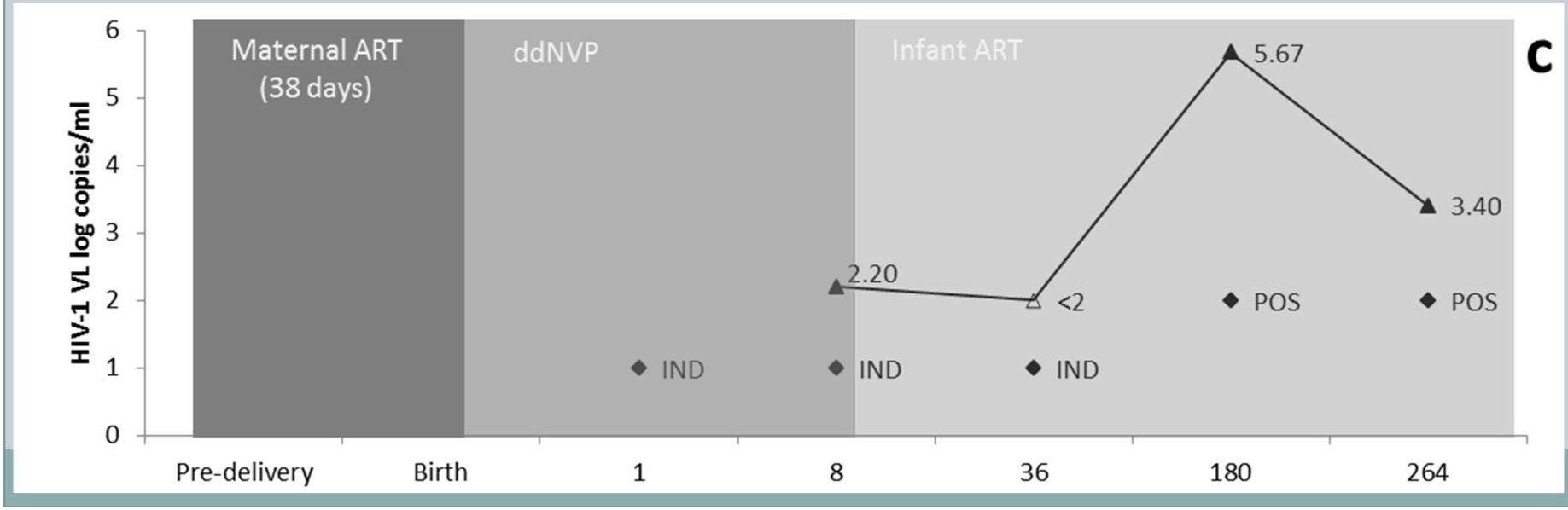
Outcome of INDETERMINATEs

Table 1. Steps in establishing final HIV infection status of 102 infants with non-negative birth PCR results

First PCR result		Second PCR result			Earliest VL result			Final HIV infection status,[†] *N* (%)			
Birth HIV PCR test	*n*	Result	*n*	Age (days)[‡]	*n*	VL (log RNA copies/ml)[‡]	Age (days)[‡]	Positive	Uncertain	Negative	LTFU
Positive	78	Positive	68	2 (1–9)	66	4.48 (3.4–5.4)	2 (1–8)	68			
		Indeterminate	4	4, 4, 8, 40	4	<1.3[e], 2.58, 4.09, 4.56	68, 8, 4, 4	3	1[e]		
		Not tested	6		3	4.30, 5.04, 6.62	1, 4, 94	3			3
		Total birth HIV PCR positive results						74 (95)	1 (1)		3 (4)
Indeterminate	24	Positive	5	6 (6–12)	4	2.29, 2.96, 3.05, 4.45	12, 0, 6, 1	5			
		Indeterminate	7	8 (6–24)	6	TND[j], 3.1 (3.0–3.2)	2 (1–8)	4[a–d]	2[g,i]		1
		Negative	11	7 (3–11)	10	TND (*n* = 9), 2.82[f]	8 (4–10)		2[f,h]	8	1
		Not tested	1		0						1
		Total birth HIV PCR indeterminate results						9 (38)	4 (17)	8 (33)	3 (13)
Total, *n* = 102								83 (81)	5 (5)	8 (8)	6 (6)

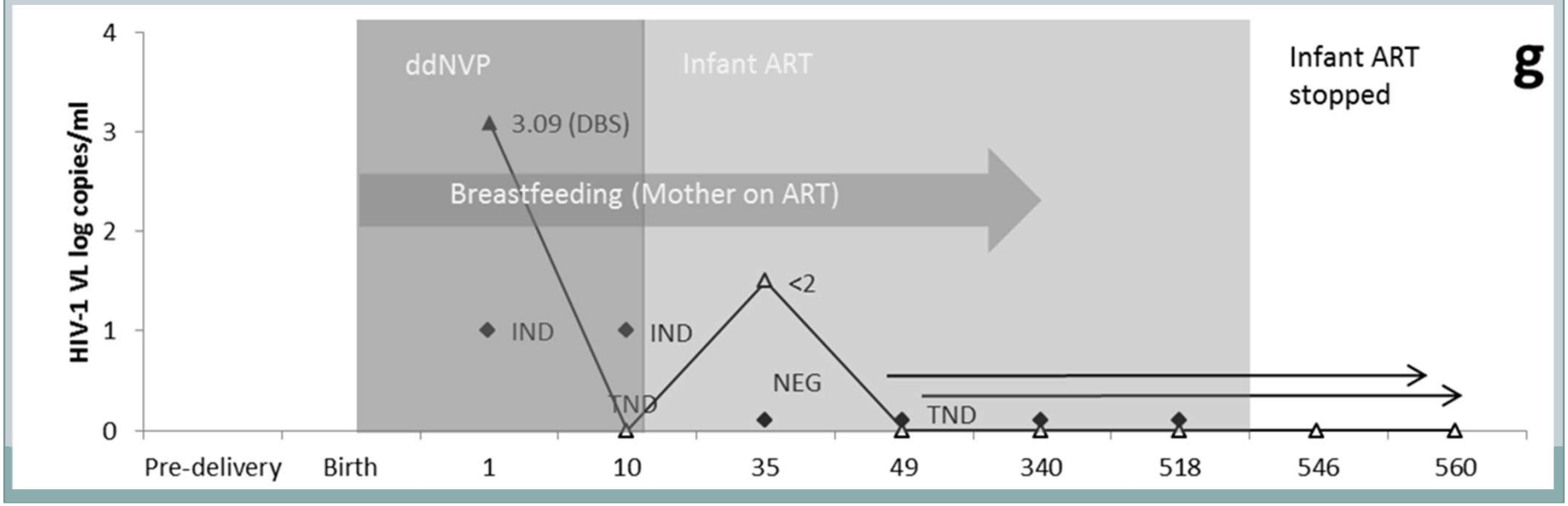
Example Case 1

- Initial indeterminate results
- Low grade VL 158
- Later clear positive results



Example Case 2

- Clear VL on one sample only
- Subsequent negative or indeterminate results
- Case remains uncertain



Future Work

- CRITICAL TO MONITOR DIAGNOSTIC OUTCOMES IN CONTEXT OF DTG INTRODUCTION
- WHILE TRANSMISSION DROPS DIAGNOSIS BECOMES MORE DIFFICULT

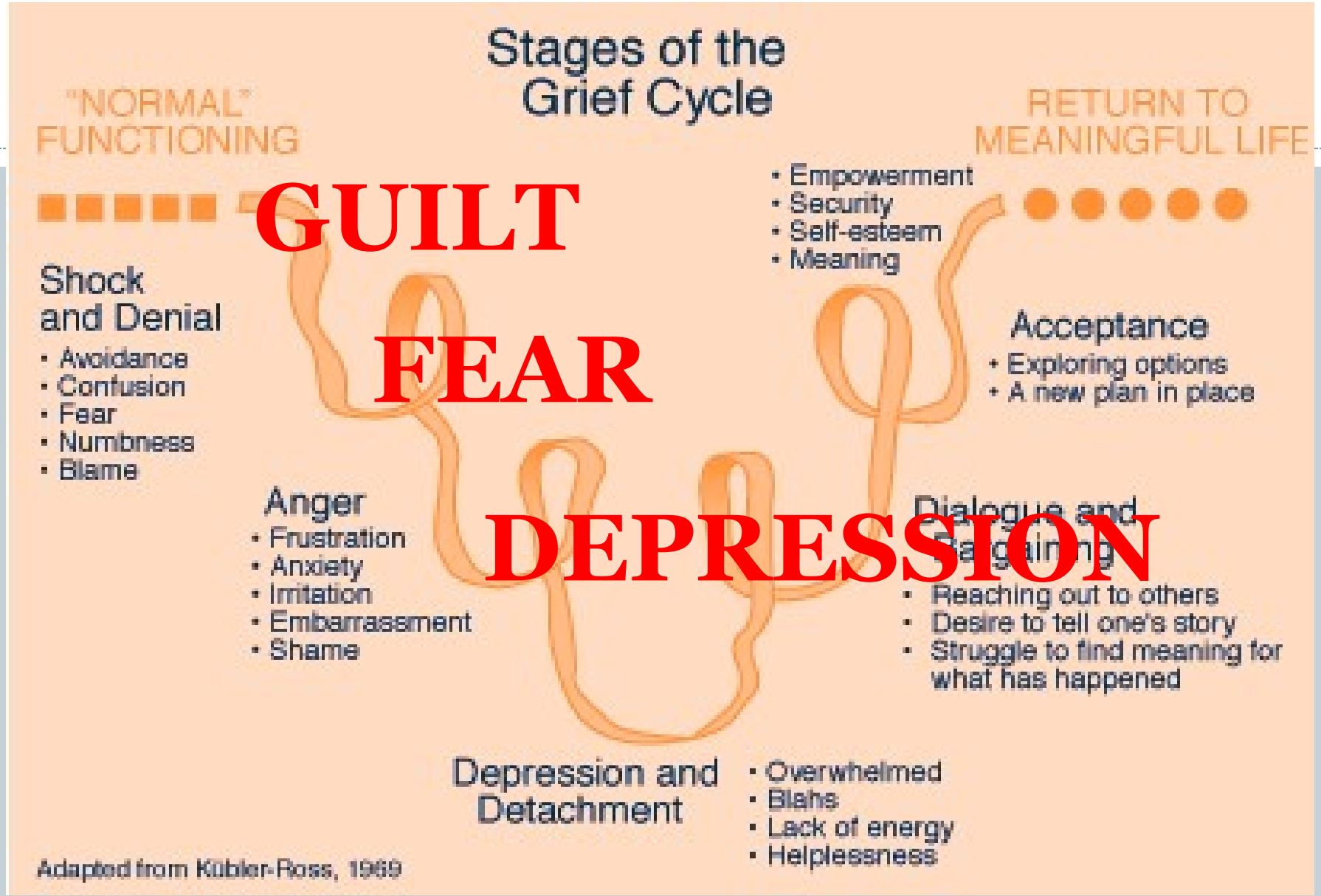
Neonates who have HIV

Results return and ART start

- Different settings must be anticipated:
  - Majority (~80% of cases) generally well out-patient setting
  - 3-5% are born to mothers who are sick/incapacitated
  - 2% of mothers are <20 years old
  - 15-20% neonates are admitted (e.g. prematuri congenital infections, etc) and possibly very ill

ART start

- Three drug regimen according to standard guidelines
  - AZT, 3TC, NVP
- A switch to Lopinavir/rit after 42 weeks PMA
- Simple techniques may assist early adherence, e.g. Careful labelling of syringes


Stages of the Grief Cycle
"NORMAL" FUNCTIONING
RETURN TO MEANINGFUL LIFE
GUILT
FEAR
DEPRESSION
Shock and Denial
• Avoidance
• Confusion
• Fear
• Numbness
• Blame
Anger
• Frustration
• Anxiety
• Irritation
• Embarrassment
• Shame
Depression and Detachment
• Overwhelmed
• Blahs
• Lack of energy
• Helplessness
Dialogue and Bargaining
• Reaching out to others
• Desire to tell one's story
• Struggle to find meaning for what has happened
Acceptance
• Exploring options
• A new plan in place
• Empowerment
• Security
• Self-esteem
• Meaning
Adapted from Kübler-Ross, 1969

Adherence and follow-up

- Both maternal and neonatal adherence critical
- Neonatal adherence
  - Who is available to help? Is the mother alone?
  - Teaching a family member other than mother
  - What are the mother's mobility and work plans?
  - Has a caregiver been identified if the mother plans to return to work?
- Maternal adherence
  - Ideally at same location
  - Emphasis of maternal wellbeing and support critical
  - Support with disclosure
  - Mothers who silence themselves – phenomena assoc. with trauma around caring for a "sick" child

Retention in Care – the journey

- Active early follow-up required with phoning and home visits
- Close links with surrounding facilities
  - Stigma may prevent mothers from accessing local facilities willingly
- Careful documentation important – in case of unanticipated mobility or need to move to another site
- Awareness of common problems affecting mothers:
  - Relationship problems
  - Mental health and substance abuse
  - Physical illness
  - Social disruption and travelling

Key Message

NEWBORN ART REQUIRES EXPERT MEDICAL INPUT IN SOME CASES BUT THE MAJORITY OF INFECTED INFANTS ARE WELL ENOUGH FOR EARLY DISCHARGE AND OUTPATIENT MANAGEMENT

Future Work

- IMPROVED FORMULATIONS FOR INFANTS – KALETRA SYRUP STILL A BARRIER TO ADHERENCE
- COMPREHENSIVE PSYCHO SOCIAL SUPPORT
- REDUCTION IN INFANT MORTALITY STILL A MAJOR CHALLENGE

ART start

- 88 infant diagnosed at birth
- 12 month mortality 14%
- 12 month retention 78%
- 12 month VL <400cps/ml 71%
- VL pre-ART >100,000 predictive of 3-4 times higher mortality

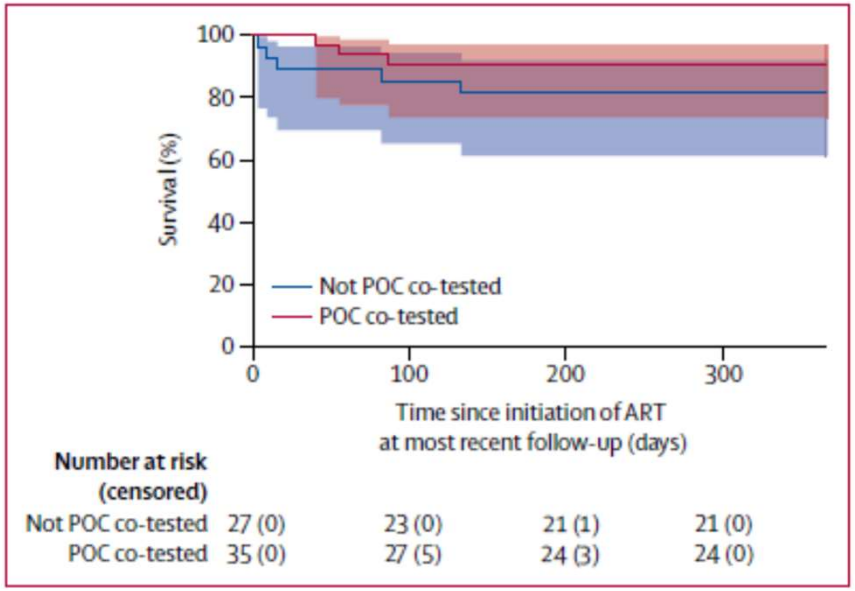
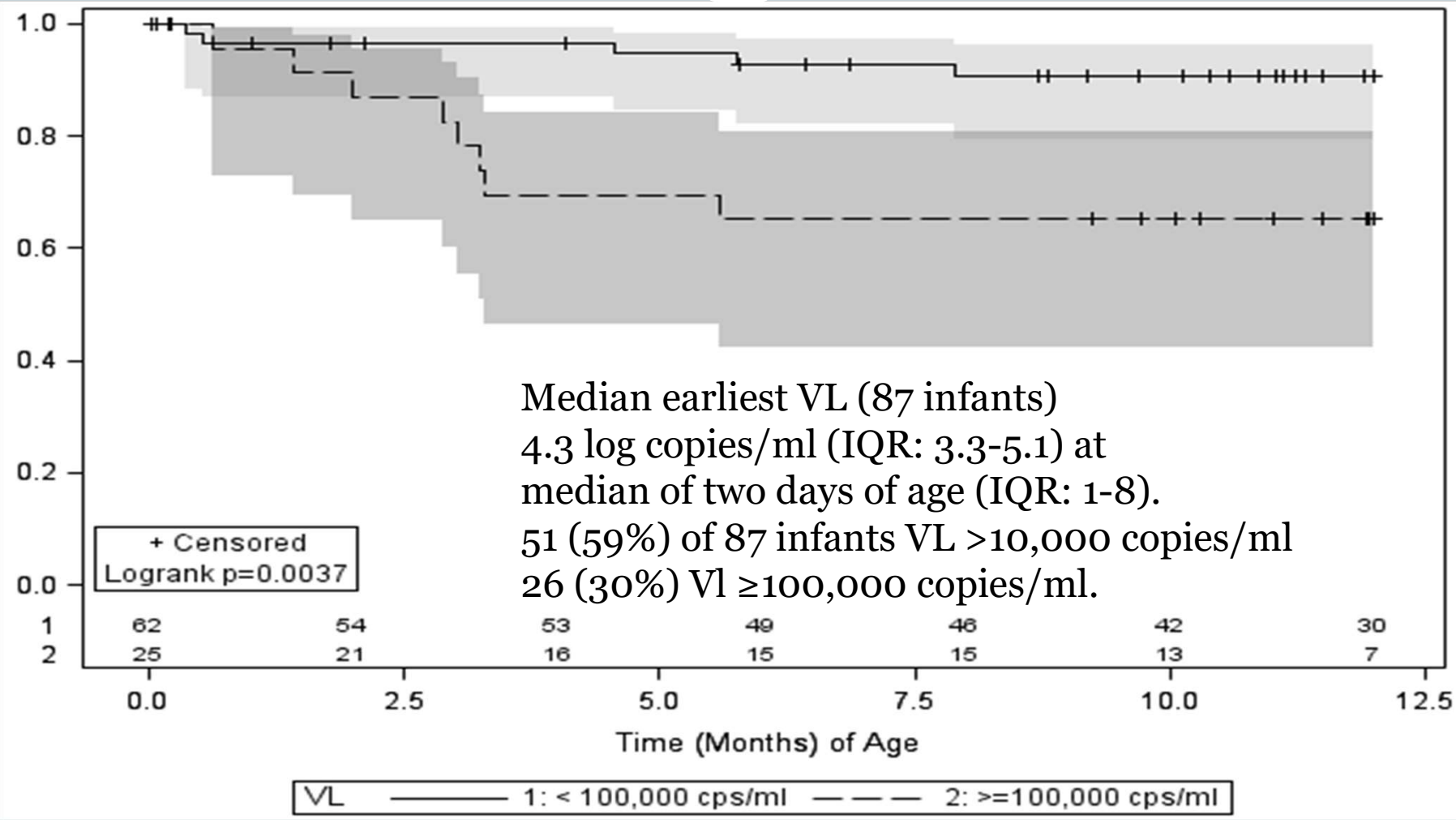


Figure 2: **Mortality in era 3 (universal testing) in the HIV-infected infants who were co-tested (n=35) and those who were not co-tested (n=27) with POC testing**

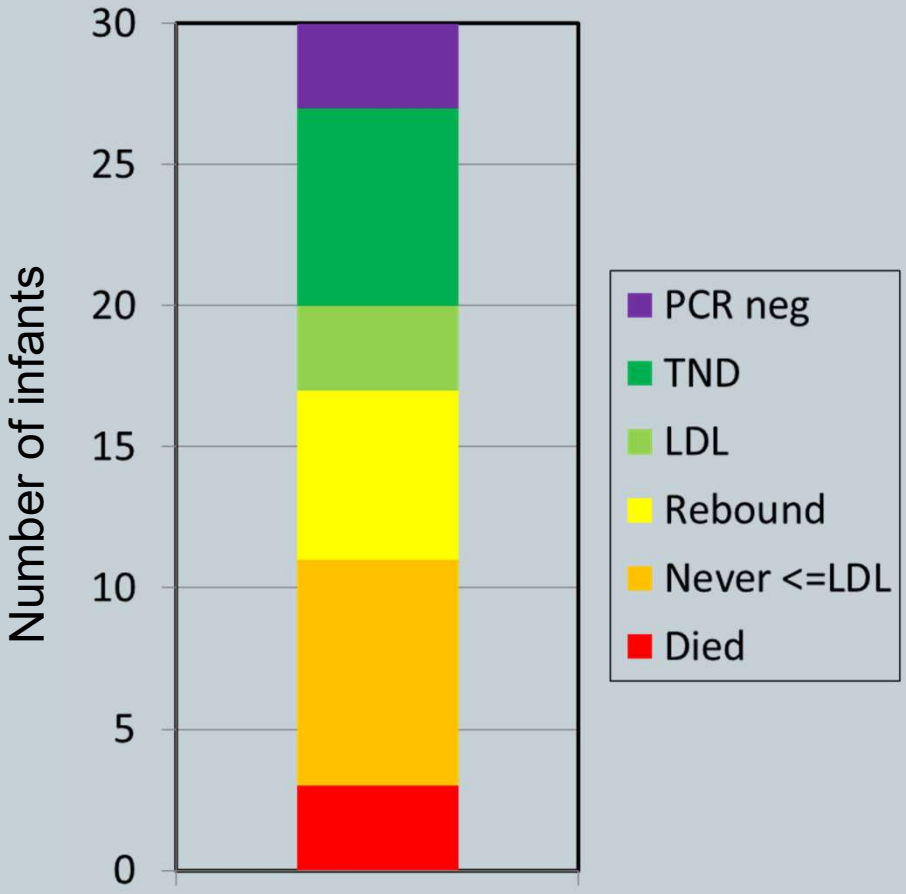
Lines show number at risk and shaded areas show 95% CI. ART–antiretroviral therapy. POC–point of care.

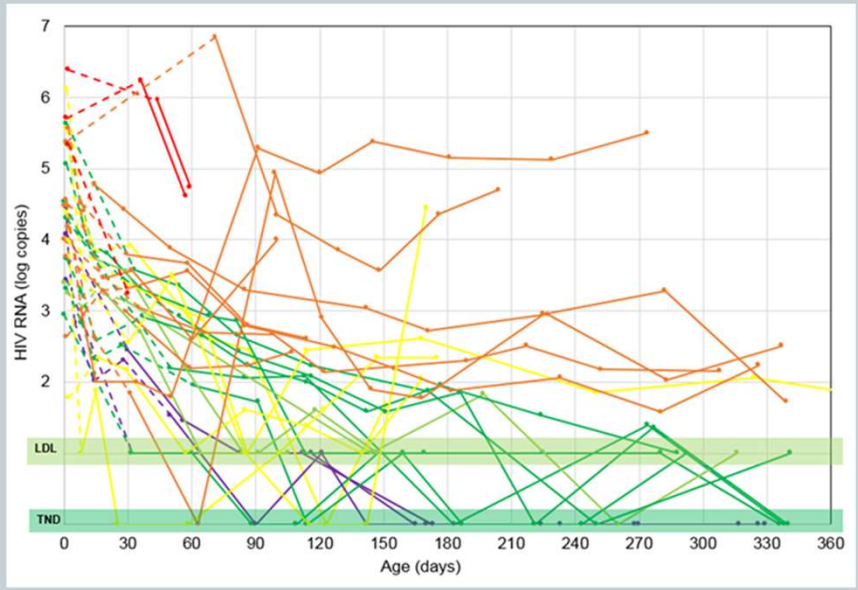
Baseline VL a critical factor for retention/survival



Median earliest VL (87 infants)
4.3 log copies/ml (IQR: 3.3-5.1) at
median of two days of age (IQR: 1-8).
51 (59%) of 87 infants VL >10,000 copies/ml
26 (30%) Vl ≥100,000 copies/ml.

Patterns of virologic response to early treatment over the first year of life





From: Prof L Kuhn et al: Treatment of acute HIV infection in neonates. Presented at CROI 2017.

Future Work

- EFFORTS TO URGENTLY FURTHER REDUCE MORTALITY
- FURTHER CURE RESEARCH
- ANTIBODIES FOR PREVENTION AND TREATMENT

Conclusion

- Great achievements to reduce MTCT
- Diagnostic dilemmas remain and set to increase
  - New drugs, e.g. DTG likely to have a positive effect on MTCT but require monitoring
  - Sentinel sites critical to evaluate implementation
  - POC diagnostics hold promise but implementation needs further cost effectiveness work
- Treatment success in infants modest
  - ART access still a problem
  - Better strategies needed

Important future work

- Sentinel surveillance
  - Introduction of DTG and other drugs
    - EID effect
    - HIV infected infants and treatment
    - Birth defects
    - HEU
  - Cohort
- Targetted research
  - Cure work and improved treatment strategies
  - Better prevention

ESRU Team

- Prof Coovadia, ESRU Research Unit Team
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- Ms Zanele Msomi, Ms Puleng Gabela, Mr Malose Lebelo, Mr Vincent Kgakgadi, Ms Liezel Pienaar
- Ms Rebecca Kgame, Ms Lebogang Phakathi, Mr Mduduzi Linganisa, Mr Peace Khanyile, Ms Jabu Dlamini
- NICD – Prof Gayle Sherman, Prof Caroline Tiemessen and team
- IeDEA – Mary-Ann Davies, Andreas Haas

Thank you!

ANY QUESTIONS

References

- Bourne DE, Thompson M, Brody LL, Cotton M, Draper B, Laubscher R, Abdullah MF, Myers JE: **Emergence of a peak in early infant mortality due to HIV/AIDS in South Africa**. *AIDS* 2009, **23**:101-106.
- Marston M, Becquet R, Zaba B, Moulton LH, Gray G, Coovadia H, Essex M, Ekouevi DK, Jackson D, Coutsoudis A, et al.: **Net survival of perinatally and postnatally HIV-infected children: a pooled analysis of individual data from sub-Saharan Africa**. *Int J Epidemiol* 2011, **40**:385-396.
- Obimbo EM, Mbori-Ngacha DA, Ochieng JO, Richardson BA, Otieno PA, Bosire R, Farquhar C, Overbaugh J, John-Stewart GC: **Predictors of early mortality in a cohort of human immunodeficiency virus type 1-infected african children**. *Pediatr Infect Dis J* 2004, **23**:536-543.
- Lilian RR, Kalk E, Technau KG, Sherman GG: **Birth diagnosis of HIV infection in infants to reduce infant mortality and monitor for elimination of mother-to-child transmission**. *Pediatr Infect Dis J* 2013, **32**:1080-1085
- Technau K, Kuhn L, Coovadia A, Carmona S, Sherman G: **Improving Early Identification of HIV-Infected Neonates with Birth PCR Testing in a Large Urban Hospital in Johannesburg, South Africa: Successes and Challenges** *J Int AIDS Soc* 2017.
- Technau K, Haeri Mazanderani A, Kuhn L, et al. Prevalence and outcomes of HIV-1 diagnostic challenges during universal birth testing – an urban South African observational cohort. *Journal of the International AIDS Society*. 2017;Forthcoming 2017.
- Porter M, Davies MA, Mapani MK, Rabie H, Phiri S, Nuttall J, Fairlie L, Technau KG, Stinson K, Wood R, et al.: **Outcomes of Infants Starting Antiretroviral Therapy in Southern Africa, 2004-2012**. *J Acquir Immune Defic Syndr* 2015, **69**:593-601
- Technau KG, Kuhn L, Coovadia A, Murnane PM, Sherman G: **Xpert HIV-1 point-of-care test for neonatal diagnosis of HIV in the birth testing programme of a maternity hospital: a field evaluation study**. *Lancet HIV* 2017.
- Technau KG, Strehlau R, Patel F, Shiau S, Burke M, Conradie M, et al. Twelve month outcomes of HIV-infected infants identified at birth: An observational cohort study at one maternity site in Johannesburg, South Africa. Lancet HIV. 2018: 5(12):e706-14.