Management of Children with HIV "101"

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Southern African HIV Clinicians Society
2nd Biennial Conference

24th - 27th September 2014
Cape Town International Convention Centre

With excellent prevention strategies:

- Missed opportunities
- Missed exposure
- Late diagnosis

- Poor implementation of good strategies
- Poor adherence and failure
- Seroconversion in pregnancy and breast feeding
- Late diagnosis older children and adolescents

Identification of infants at high risk of transmission

Highest risk of transmission

- Co-morbidities TB
- VL ≥1000 cps/ml from 28 weeks gestation
- Initiated ART <12 weeks before delivery
- Is the 6 weeks PCR still good enough?

“Enhanced Prevention DOH”

- Zidovudine
- Lamivudine
- Nevirapine (dose?)

General comment

- HIV Bad for children
  - Opportunistic infections
  - Organ damage
  - Growth consequences
- Neurological consequences

New challenges

- Diagnosis of very young infants becoming more challenging
- Early therapy to move to **very early** therapy
- Deciding when to do resistance testing prior to therapy

New challenges

- Maintaining therapy
- Preventing failure
- Managing intolerance
- Managing failure
- Managing co morbidity
- Deciding on resistance testing
- Switching

New challenges

- Transition to adult hood
- Sexuality
- Residual morbidity
- Maintaining therapy and suppression
- “navigation” and “simplification”
- “New skills”

Neonatal / very early therapy

- Earlier therapy reduction of the viral reservoir
- Early morbidity and mortality before 6 weeks

- Can we test earlier and can we follow up results to rapidly start ART

Neonatal therapy-Drug and dosing

- Dosing available for zidovudine and lamivudine
- Abacavir – no dose till 3 months of age
- Nevirapine modeled dose -150mg/m^2 OD/BD
- LPV/r – black box warning

What do we know about outcomes

- Mississippi child
- California child
- 12 Canadian infant starting in neonatal period 4 achieved sustain suppression
- 7 preterm infants started on LPV/r based therapy at TBH – 3 suppressed at 6 months, 1 death 3 T/F away

NEJM 2013
CROI 2014
CID 2014
PIDJ 2012

Moving to earlier therapy

- CHER mean age at baseline 7.4 weeks
  - 585 HIV-infected infants screened for the study, **127 (21.7%) were excluded for advanced disease**
- Advantage
  - Neurological – potential differences noted in CHER
  - Tuberculosis

NEJM 2008
AIDS 2012

Other children - PREDICT

- Deferred vs Early ART in children > 12 months of age (median 6,4 years, CD4 20%/619 cells)
- Bottom line – children with deferred therapy where not disadvantaged
  - No difference neurologically (is the needle broken and the damage done)

Lancet 2012

Presentation and course (pre ART)

Presentation	Course	
Static	Developmental arrest	
Progressive	Sub-acute	Relentless / rapid
	Plateau	Indolent

	Age	Clinical	
Motor	Can start at young age	Early	Spastic Diplegia
		Late	Spastic quadriparesis
		Rare	Dystonia Tremor Ataxia Focal signs
Behavior	Older children	ADD/ ADHA / Anxiety Oppositional defiance Conduct disorder	
Cognitive	All	Expressive language deficit Learning disabilities Cognitive scores below childhood norm	

Concerns

- No evidence of programmatic advantage of treating all children < 5 years
- Longer time on drugs
  - Increased risk of failure
  - Adverse effects

Regimens

Regimen	< 3 Years or MTCT	> 3 Years AND 10kg
First Line	Abacavir Lamivudine Kaletra	Abacavir Lamivudine Efavirenz / Nevirapine

The NEW ENGLAND JOURNAL of MEDICINE

2010;363:1510-20.

ORIGINAL ARTICLE

Antiretroviral Treatment for Children with Peripartum Nevirapine Exposure

Paul Palumbo, M.D., Jane C. Lindsey, Sc.D., Michael D. Hughes, Ph.D., Mark F. Cotton, M.Med., Ph.D., Raziya Bobat, M.D., Tammy Meyers, M.D.,

CONCLUSIONS

Among children with prior exposure to single-dose nevirapine for perinatal prevention of HIV transmission, antiretroviral treatment consisting of zidovudine and lamivudine plus ritonavir-boosted lopinavir resulted in better outcomes than did treatment with zidovudine and lamivudine plus nevirapine. Since nevirapine is used for

The NEW ENGLAND JOURNAL of MEDICINE

2012;366:2380-9.

ORIGINAL ARTICLE

Nevirapine versus Ritonavir-Boosted Lopinavir for HIV-Infected Children

Avy Violari, F.C.Paed., Jane C. Lindsey, Sc.D., Michael D. Hughes, Ph.D., Hilda A. Mujuru, M.D., Linda Barlow-Mosha, M.D., Portia Kamthunzi, M.D.,

CONCLUSIONS

Outcomes were superior with ritonavir-boosted lopinavir among young children with no prior exposure to nevirapine. Factors that may have contributed to the suboptimal results with nevirapine include elevated viral load at baseline, selection for nevirapine resistance, background regimen of nucleoside reverse-transcriptase inhibitors, and the standard ramp-up dosing strategy. The results of this trial present policymakers with difficult choices. (Funded by the National Institute of Allergy and Infectious Diseases and others; P1060 ClinicalTrials.gov number, NCT00307151.)

ABC

Table 1. HIV-1 RNA suppression over time. All analyses are intention-to-treat, i.e., ignoring changes to randomized treatment. *P*-values are adjusted for baseline characteristics and test the hypothesis that HIV-1 RNA suppression in at least one treatment group is different from that in the other groups, at each year or over 1–5 years.

	HIV-1 RNA < 400 copies/ml [n/N (%)][a]				HIV-1 RNA < 50 copies/ml [n/N (%)]				HIV-1 RNA < 50 copies/ml; initiated ART with three drugs [n/N (%)]			
Year	ZDV/3TC (n = 36)	ZDV/ABC (n = 44)	3TC/ABC (n = 46)	*P*	ZDV/3TC (n = 36)	ZDV/ABC (n = 44)	3TC/ABC (n = 46)	*P*	ZDV/3TC (n = 29)	ZDV/ABC (n = 33)	ZDV/ABC (n = 38)	*P*
1	17/36 (47)	27/43 (63)	31/45 (69)	0.2	12/36 (33)	19/43 (44)	24/45 (53)	0.2	11/29 (38)	13/33 (39)	22/37 (59)	0.2
2	19/36 (53)	21/41 (51)	32/44 (73)	0.05	9/36 (25)	10/41 (24)	20/44 (45)	0.03	8/29 (28)	9/31 (29)	18/36 (50)	0.06
3	19/36 (53)	20/42 (48)	30/41 (73)	0.02	14/36 (39)	14/42 (33)	19/41 (46)	0.5	12/29 (41)	11/31 (35)	17/33 (52)	0.4
4	18/31 (58)	16/43 (48)	28/36 (78)	0.01	15/31 (48)	8/33 (24)	16/36 (44)	0.06	11/29 (38)	13/33 (39)	22/37 (59)	0.1
5	17/31 (55)	18/36 (50)	30/38 (79)	0.03	10/31 (32)	9/36 (25)	24/38 (63)	0.003	8/24 (33)	7/27 (26)	22/32 (69)	0.002
	Overall difference between randomised groups, years1–5			0.003	Overall difference between randomised groups, years1–5			0.006	Overall difference between randomised groups, years1–5			0.006
	Difference between randomised groups varies over 5 years			0.4	Difference between randomised groups varies over 5 years			0.1	Difference between randomised groups varies over 5 years			0.2

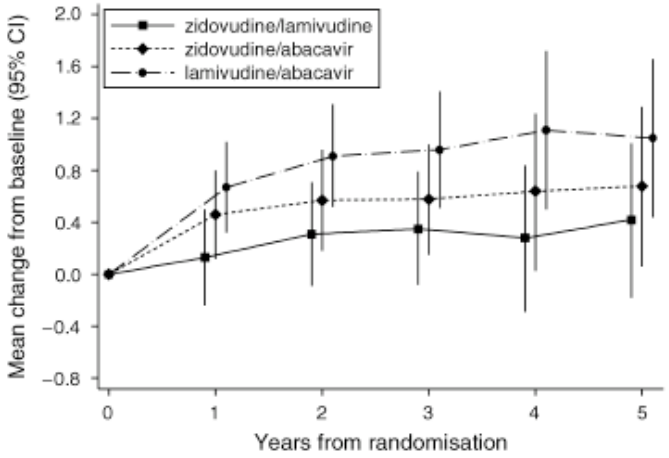
[a]Conservatively assuming that children with HIV-1 RNA recorded as below a limit of detection greater than 50 (e.g., 400) are not below 50 copies/ml (a total of 57 of 569 tests, 10%). ART, Antiretroviral therapy; ZDV, zidovudine; 3TC, lamivudine; ABC, abacavir.

Green AIDS 2007

Clinical responses?

Height-for-age

Mean change (n)	Year 1	Year 3	Year 5
zidovudine/lamivudine	+0.13 (34)	+0.35 (28)	+0.42 (28)
zidovudine/abacavir	+0.46 (43)	+0.58 (42)	+0.68 (36)
lamivudine/abacavir	+0.67 (43)	+0.96 (44)	+1.05 (36)
p (adjusted)	0.005	0.006	0.02



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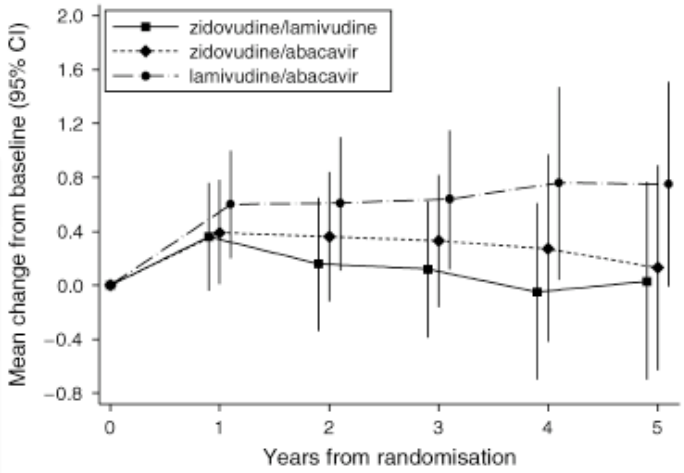
zidovudine/abacavir	+0.39 (43)	+0.33 (43)	+0.13 (36)
lamivudine/abacavir	+0.60 (44)	+0.64 (44)	+0.75 (37)
p (adjusted)	0.4	0.06	0.02



Resistance in PENTA 5

- ZDV/3TC [n=4]
  - 2-M184V alone by 1 year
  - 4 subsequent TAMS -M41L (4);T215Y (2); D67N (1); K70R (1), L210W (1)
- ZDV/ABC [n=6]
  - 4 maintained wild type (3-4.5 yrs)
  - 2/6 wild type followed by TAM: 3–3.5 years (D67N, K70R /K219Q; M41L, D67N, L210W, T215F/Y).
- ABC/3TC [n=6]
  - 2 only the M184V mutation by 3 and 5 years
  - 4 'non-TAM' mutations by year 1-L74V (4), M184V (4), K65R (3), Y115F (1)

- Stavudine selects for K65R, L74V and Q151M

Concern regarding ABC first line

IeDEA – Southern Africa

- Large restrospective cohort
- Increased risk of failure especially in younger children on LPV/r

CHAPAS 3

- Zidovudine vs abacavir
- 57% of naïve children < 3 years of age
- No difference between arms when comparing AZT with ABC

PIDJ 2013
IAS 2014

NEVEREST and NNRTI switching

Nevirapine

- 65.6% of switch children < 50 copies/ml through 24 weeks
- Fewer children in the switch group (84.9%) than in the control group (96.8%) consistently maintained < 1000 copies/ml through 24 weeks post-randomization (p=0.007).

Efavirence

- 4.1 years of age at switch
- On treatment 3.5 years
- Viral rebound low

CROI 2014

We have to be a little cautious

- PMTCT guidelines have changed
- NNRTI resistance does not hamper viral replication
- Watch children who get switched:
  - very early VL

- **South African infants**
  - **56.8 NNRTI, 14.8% NRTI, and 1.3% PI**
- **"PMTCT history is an inadequate means of ruling out pretreatment drug resistance.**
- **Our results support the use of protease inhibitor-based first-line regimens in HIV-infected infants and young children regardless of PMTCT history."**

AIDS 2014

Simplification for Children

- USE PILLS
  - We are going to get more combinations
- ABC Daily ✓
- 3TC Daily ✓
- LPV/r Daily ?
  - LPV/r can be used daily in adult
  - KONCERT study virally suppressed >15 kg
  - Probability of viral rebound in the daily vs twice daily group was 0.141 (90% CI 0.090 ,0.217) vs 0.08 (90% CI 0.044,0.145).

- What will be the role of TDF in the future?

Managing adolescents with vertically acquired HIV

Complex interplay

- Normal changes
- Chronic illness
- Social aspects of HIV
- Health service

SPECIAL RISK FOR FAILURE

The expectation

- Optimized clinical care
- Communication and counseling
- Disclosure
- Psychosocial support
- Mental illness
- Sexual and reproductive health
- Transition into adult care

Consideration

- Psychiatric
- Cardiovascular
- Bone health
- Renal disease

Cardiovascular and Metabolic Toxicity

Lipid profiles

- Hypercholestrolaemia 10-86%
- hypertriglyceridaemia 13–67%

Insulin resistance

- 7–52% (Obesity)

Body habitus changes

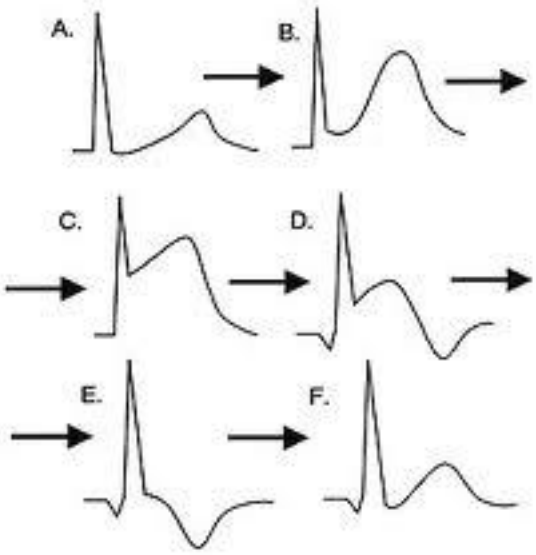
- >50% 12 year olds some aspect

Carotid intima thickness

Reduced pulse wave velocity

Increases in HS-CRP

Increases in P-selectin - ? Role of vascular disease in neurodysfunction



Evolution of Acute MI

Bone health

Role of peak bone mass in osteoperosis

- Before access to ART delayed bone age and reduced BMD
- With ART reduced BMD – bone turn over
- TDF use – decreases in BMD > adults
- Role of Depot contraceptives
- High rates of Vit D Deficiency

Disclosure of status

- Age at disclosure coming down
- Most children learn about the diagnosis 8-10yrs on observational studies
- Dynamic process
- Cares must be consistently encouraged and guided to disclose:
- Mathematics of co-dependency 1+1=1
- Tools

Hi Dr Rabie
I need advice on a 7 year old girl

- Currently talking – AZT,3TC LPV/r second regimen
  - NOV 2012 – VL: log:5,02 -CD4 :59
  - FEB 2013 - VL: log :4,62- CD4:97
  - Clinically unwell with weight loss and OI
- Mother failing second regimen
- Father a “priest” – does not believe in medicine. He refuses testing
- School will help

“Step Up Adherence” What is this actually?

Discuss

- The problem
- Illustrate and explain the perceived/ real discrepancy
- Go through the whole process
  - What
  - Who
  - When
  - How frequently
- Possible solutions

Involve

- Team members
- NGO/community
- Family and support structure

Drug resistance 102

- Transmission resistance
  - NVP/EFV in PMTCT extensive NNRTI resistance
  - Multi drug resistant
- Cumulating TAMS
- The legacy of ritonovir
- The believe that there will never be LPV/r resistance
- The scourge of TB and drug interactions
- The issue of careless management
- The lack of data on dosing and formulation
- Intolerance

Scenario	Rational for testing
Failure of transmission prevention	
Mothers failing first line OR second line therapy during pregnancy	Resistance my include more than “simple NNRTi resistance with possible NRTI and even PI resistance transmitting to the infant
Infants exposed to prologue NVP during breast feeding	Document resistance against second generation NNRTI
Infants fail dual or triple post exposure prevention	Document resistance in the infant to plan therapy
First line failure	
First line failure with NNRTI	Document second generation NNRTI resistance
	Potentially prevents switching NRTI in selected patients
First line Failing boosted protease inhibitor	It is preferable if all these children get tested as there may not be primary mutations conferring PI resistance
Ritonavir full dose therapy and currently on a boosted PI	Probable PI resistance
TB therapy on PI regimen e	Possible PI resistance

Always

- Stay hopeful
- People will continuously surprise you
- Those on third line can do very well

Antiretroviral toxicity

- Drug toxicity much less of a problem than complications of HIV disease
- Drug tolerance HUGE problem
- Children still on stavudine and didanosine are at risk for lipoatrophy and lactic acidosis
  - these drugs should be switched
- Other adverese reactions are similar to adults

Abacavir hypersensitivity

- Rare in African children
  - B*5701, HLA-DR7 and HLA-DQ3.
- It is a syndrome complex
  - Usually with in 6 weeks (median 11 days)
  - Worse just after the dose
- 2 or more of the symptoms should be present
  - Fever :80% of cases
  - Rash: 70% of cases
  - Gastro-intestinal symptoms: may occur without HSR.
  - Constitutional symptoms: include fatigue, myalgias and malaise.
  - Respiratory symptoms: occur in 18%. Distinguish from by influenza

What about tenofovir

- Licensed in the USA for children > 2 years
- There is no formulation
- Care should be taken with regards the potential long term effect especially renal and bone density
- eGFR in adolescents <16 years =height(cm)X40/Creatinine(µmol/l)

- Routine use
  - TDF 300mg daily ≥15 years **and** over 40kg if their eGFR is ≥80
- Switching to TDF in children on 1st line
  - If viral load < 40copies **AND** ≥15 years **AND** over 40kg **AND** eGFR ≥80
- Other
  - Hepatitis B
  - Failing ART with limited other options **AND** eGFR≥80
- Monitoring
  - eGFR Baseline,1 month, 3 months then 6 monthly
  - Serum phosphate Baseline and annually.
  - Urine dipstix

Facts are stubborn, but statistics are more pliable. Mark Twain

- Mark Cotton
- Team at TBH and all peripheral clinics
- ALL the children