



CLINICIAN CONSULTATION CENTER

National rapid response for HIV management and bloodborne pathogen exposures.

The National Perinatal HIV Hotline 2014 CROI Lunch Discussion The High-risk HIV-Exposed Newborn: Obstetric and Infant Care Implications March 5, 2014 CROI Boston, MA

The National Perinatal HIV Hotline (www.nccc.ucsf.edu) hosts roundtable discussions at CROI to promote dialogue around challenging topics and build community among providers. Discussion notes are distributed via the ReproIDHIV listserv. For more information: shannon.weber@ucsf.edu

Calls to the National Perinatal HIV Hotline regarding HIV-exposed infants have doubled since 2008. After CROI 2013 and publication of the "Mississippi baby" case, calls regarding more aggressive infant regimens have increased.

Case #1 - 24 year old G1 presents at 36 weeks, newly diagnosed with HIV, viral load 800,000.

What would you prescribe for the mother? (text to vote answers tallied)

- | | |
|--|----------|
| A. Combivir/kaletra | 2 |
| B. Boosted Reyataz/Truvada | 2 |
| C. A or B + Isentress | 2 |
| D. Initiate DOT with A or B above + Isentress | 7 |
| E. Other | 2 |

Discussion

- Directly observed therapy (DOT):
 - "You have one opportunity to prevent transmission to the baby and not much time to get it done."
 - Social issues/comorbidities often accompany these cases and can be addressed through DOT.
 - Patients are generally receptive to admission for DOT
 - One county hospital provider noted no administrative challenges in admitting patients for DOT.
 - Outpatient DOT can also be a successful option
- Use of Isentress
 - Impressive results with Isentress and rapid viral decay: approximately 1 log/week
 - One provider felt she could get "practically any patient undetectable with 2-3 weeks of Isentress"
 - Consider frequent viral load monitoring and request rapid turn-around to affect mode of delivery
- Other regimens
 - One provider recommended ATV/r/TRV because it is a once daily regimen
 - One provider recommended enrollment in P1081 study (Combivir + LPV/r vs RAL vs EFV)
- Mode of Delivery
 - ACOG & perinatal guidelines recommend against cesarean for plasma viral load <1000; many providers follow this recommendation
 - Some providers raised concern over potential discrepancy between genital tract and plasma viral load; one provider not comfortable using plasma viral load as proxy for vaginal viral load unless patient on ARVs x 12 weeks
 - One provider pondered using cesarean delivery as a means of reducing perinatal transmission and avoiding more aggressive treatment for the baby
 - Pat Garcia data from 1999 NEJM showed no transmissions when plasma viral load <1,000
 - no transmission data to date suggests changing mode of delivery based on concern for vaginal compartment viremia
 - National organizations recommend avoiding the first cesarean section. Placenta accretas can result in massive blood loss and require life threatening hysterectomies for delivery. Surgical data shows HIV-infected women have worse wound healing/higher morbidity.

- Timing of delivery
 - Rapid turn-around of viral loads facilitates changing mode of delivery after shorter periods of ARVs
 - Without rapid turn-around of viral loads, many would schedule a cesarean at 38 wks
 - With rapid turn-around of viral loads, some would consider continuing the pregnancy past 38 weeks to reduce the viral load further/allow longer exposure to ARVs and allow for a trial of labor
 - One provider emphasized importance of coordination with pediatrics team re: timing and mode of delivery

Data

Viral decay in pregnancy

- Median time to VL<1000: 14 days
- Median time to VL<400: 26 days
- Factors that *may* be associated with slower decay
 - Higher viral load
 - Poor adherence
 - Lower CD4 count
 - ARV experienced
 - ARV regimen

Aziz et al. Time to viral load suppression in antiretroviral-naïve and -experienced HIV-infected pregnant women on highly active antiretroviral therapy: implications for pregnant women presenting late in gestation. BJOG Nov 2013: vol 120 (12) 1534-47.

RAL in pregnancy

- 4 patient case series (ARV naïve): mean viral decay 1.1 log/week
- 14 patient case series (ARV naïve and experienced): initiate RAL at 36 wks; mean 2.4 log decay over 17 days
- Case report (acute HIV): 5 log drop within 10 weeks

Hegazi & Hay. HIV seroconversion in the third trimester of pregnancy: using raltegravir to prevent mother-to-child transmission. Int J of STD & AIDS 2013.

Westing et al. Rapid decline in HIV viral load when introducing raltegravir-containing antiretroviral treatment late in pregnancy. AIDS Patient Care STDS. 2012 Dec;26(12):714-7.

Nobrega et al. Use of Raltegravir in Late-Presenting HIV-Infected Pregnant Women. AIDS Research and Human Retroviruses. November 2013, 29(11): 1451-1454.

Take Aways

- **Consider Isentress, use of DOT, and frequent viral load monitoring in cases of patients with viremia near term.**
- **Balance risks of perinatal transmission against risks of cesarean section in determining mode of delivery.**
- **More data is needed to change mode of delivery based on concern for increased viral burden in the genital tract.**

Case #1 - continued

- **24 yo G1 presents at 36 wks, newly diagnosed with HIV, viral load 800,000.**
- **Admitted for DOT with Reyataz/Truvada/Isentress**
- **Delivered by c-section at 38 weeks s/p 3 hrs IV AZT**
- **Viral load 2 days prior to delivery: 80,000**

What would you prescribe the infant? (text to vote tallied)

- **Zidovudine alone** **0**
- **Zidovudine /Nevirapine prophylactic dose** **6**
- **Zidovudine /Nevirapine/Lamivudine prophylactic dose** **4**
- **Zidovudine /Nevirapine/Lamivudine treatment dose** **5**
- **“The Mississippi Protocol”** **2**
- **Other** **0**

Discussion

- This has to be a discussion with the mom and whomever else she wants to be involved. I would start with the AZT/NVP prophylactic doses and within 12 hours I would be saying, here are all our options with the known and unknown risks and benefits.
- The argument for AZT/NVP would be it is the closest to the guidelines. Actually, strictly speaking this falls out of the current guidelines as it is a woman who initiated therapy but has suboptimal plasma viral load at delivery. There is no real data about that specific circumstance. There is extrapolation from HPTN 040 on which the recommendation is based. In that study is based on women who had only received AZT through delivery so even that you can't be sure.
- In HPTN 040, the 3-drug showed no benefit in transmission, but demonstrated more toxicity, with elevated incidence of neutropenia.
- One reason to use 3TC is to avoid resistance in an in utero-infected infant.
- The only ARV medications with currently treatment doses in this age are zidovudine and lamivudine per the federal guidelines. Zidovudine and lamivudine are adjusted for age based on the range of renal clearance that happens in the baby.
- The only discussion on dosing is for nevirapine. It is not as simple as extrapolating the dosing because of changes in metabolism in newborns, it differs dramatically over the first few weeks of life - an order of magnitude higher for treatment dose. Blackbox warning in US for LPV/r. The other difference in the MS child is the daily dosing, where in the prophylaxis regimen you have 48 and 96 hours after birth dosing, based on the slow hepatic clearance and assuming the 2 mg per kg will give us the target troughs.
- The target troughs for nevirapine differ for prophylaxis vs treatment ... but you don't need a higher dose of zidovudine and lamivudine, that is important because of the higher mitochondrial toxicities of zidovudine and lamivudine not just in 040 but in Mandelbrot late 90's data.
- Most people are considering AZT plus one or two drugs. 040 is suggested to show 2 drugs is the same as 3 but there is a complaint the third drug is nelfinavir which is no longer available and may not have been a perfect drug. But then yes or no for lamivudine sounds like an open question for some.
- In very high-risk cases, mom presents without prior treatment or with a very high viral load or with their CD4 being very low, all the risks for transmission. We have to consider not just prophylaxing the infant but treatment. I think the previous point of 3 drugs to prevent resistance. There are two reasons for using the 3 drugs at therapeutic doses. It would undoubtedly provide prophylaxis. The second is it would provide therapy should this child have in utero infection.
- A lot of focus in 040 is the intra-partum infected kids but we have to remember that more of the kids were in-utero infected kids. For those kids you would certainly not want to be using the prophylactic regimen. You get to the question of whether it might not be better to be using empiric treatment dosing until you rule out infection, this is an important question to study.
- Post exposure prophylaxis in adults is full therapy treatment. But with fewer drugs. But if we were bathed in drugs like these kids are would you take 2 drugs or 3 drugs? At prophylaxis or treatment dosing?
- How many of the people who now use NVP treatment dosing are seeing liver toxicity? I have used it and have had bad experiences with a lot of toxicities in infants using it at treatment dosing. That would be my biggest concern. We have zero data in the less than 2 week age group.
- We have no evidence that this is the right dose. We have nothing but model PK for the first 2 weeks of life. We need to collect this PK dosing with toxicity data to understand what is happening when they are treated at a higher dose. We feel okay about what we know about toxicity at prophylaxis dosing. We have only anecdotal data at higher dosing.
- We use the treatment dosing, same being used in p1115. We have had more than 10 infants and no liver toxicity.
- This best judgment for MS baby was based on it being very high risk. The benefit of discussing and working as a community is to round up cases and document all these cases so that we get a sense of the cases.
- Consider enlisting the pediatric pharmacologist, who may be amenable to running the levels. Discussing how to dose and how to draw levels for us. Perhaps it is time for protocols.

Data

HPTN 040: infants of mothers with no ARV during pregnancy (other than ZDV in labor), arms were:

- ❑ ZDV x 6 wks
- ❑ ZDV x 6 wks + NVP birth, 48 hrs later, 96 hrs later
- ❑ ZDV x 6 wks + 3TC x 2 wks + NFV x 2 wks

Nielsen-Saines, *NEJM*. 2012. 366; 2368-79

Table 2. Infant HIV-1 Infections According to Treatment Group.*

Infection Status	Overall (N=1684)	Zidovudine (N=566)	Zidovudine plus Nevirapine (N=562)	Zidovudine plus Nelfinavir and Lamivudine (N=556)	P Value†
Infected in utero					
Infants — no.	93	37	28	28	
Kaplan–Meier rate — % (95% CI)	5.7 (4.7–6.9)	6.8 (5.0–9.3)	5.1 (3.5–7.3)	5.2 (3.6–7.4)	0.24
Infected during intrapartum period					
4–6 wk					
Infants — no.	32	17	8	7	
Kaplan–Meier rate — % (95% CI)	2.1 (1.5–3.0)	3.4 (2.1–5.4)	1.6 (0.8–3.1)	1.4 (0.7–2.9)	0.07
3 mo					
Infants — no.	47	24	11	12	
Kaplan–Meier rate — % (95% CI)	3.2 (2.4–4.2)	4.8 (3.2–7.1)	2.2 (1.2–3.9)	2.4 (1.4–4.3)	0.046
Infected in utero or during intrapartum period					
Infants — no.	140	61	39	40	
Kaplan–Meier rate — % (95% CI)	8.5 (7.3–10.0)	11.0 (8.7–14.0)	7.1 (5.2–9.6)	7.4 (5.4–9.9)	0.03
Uninfected — no.	1447	474	490	483	
Unknown — no.	97	31	33	33	

Empiric treatment vs prophylaxis dosing

	Prophylaxis	Treatment	“Mississippi Case”
ZDV	4 mg/kg PO Q12h	4 mg/kg PO Q12h	2 mg/kg Q6h
3TC	2 mg/kg PO Q12h	2 mg/kg PO Q12h	4 mg/kg Q12h
NVP	8-12 mg (total) PO x 3	?	2 mg/kg Q12h

- Mississippi Case: NVP replaced with LPV/r at 1 week, Prior to FDA warning of no LPV/r <14 d of life

Target serum levels of NVP differ for prophylaxis vs treatment

Prophylaxis

- ❑ Trough ~ 100 ng/mL
- ❑ Peak ~ 1,000 to 1,500 ng/mL

Treatment

- ❑ Trough > 3,000 ng/mL
- ❑ Peak <10,000 ng/mL

What is the risk of hepatotoxicity from NVP?

- ❑ HPTN 040:
 - ❑ 3 dose ppx, 2.5% had elevated AST/ALT. but similar for all arms (p=0.43)
- ❑ BAN trial :
 - ❑ 10 mg daily for 2 weeks then increasing, until 28 wks
 - ❑ 16 cases (1.9%) with hypersensitivity rxn, resolved with change to 3TC
- ❑ HPTN 046:
 - ❑ Daily NVP for 6 months, 0.5% had GIII ALT elevation, but comparable to placebo.

Discussion

Clinical Trials:

IMPAACT P1110 (*enrolling!*)

- A PHASE I TRIAL TO EVALUATE THE SAFETY AND PHARMACOKINETICS OF RALTEGRAVIR IN HIV-1-EXPOSED NEONATES AT HIGH RISK OF ACQUIRING HIV-1 INFECTION
- DESIGN:
 - Phase I, open label, non-comparative dose-finding study
- POPULATION:
 - HIV-1 exposed full-term neonates (aged ≤48 hours) assessed as high risk of acquiring HIV-1 infection and their mothers.
- Cohort 1: Raltegravir oral granules for suspension
 - single dose within 48 hrs
 - second dose at 7-10 days of life
- Cohort 2: Raltegravir oral granules for suspension
 - starting within 48 hrs
 - continued for 6 weeks in addition to standard of care ARV for PMTCT prophylaxis
- *In BOTH cohorts, RAL is in addition to standard of care PMTCT prophylaxis*

IMPAACT P1115 (in development)

- Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV REMISSION: A Phase i/ii Proof of Concept Study
- Subjects:
 - Infants aged ≤ 48 hours of birth born to women with HIV infection who did not receive ARVs during pregnancy
 - Infants ≤ 10 days of age with documented *in utero* HIV infection who initiated ART outside of the study within 48 hours of birth
 - Mothers of infants in both cohorts
- INITIAL INFANT ART REGIMEN:
 - 2 NRTIs + NVP (6 mg/kg bid)
 - Modelled NVP dose, PK and safety to be studied, dose may be revised
 - FOLLOW UP:
 - LPV/r added at ≥ 14 days of age and ≥ 42 weeks postmenstrual age
 - 4 drugs until definitively suppressed, then 3
 - ART cessation for long term suppressed at > 2 years of age
- Find out the IMPAACT trial site closest to your institution (ahead of time, ideally)
 - Email to IMPAACT.OperationsCenter@fstrf.org

Take Aways

- **Data are currently insufficient to compose 3 drug regimen with treatment dosing for infants < 2 weeks of age**
- **However, in light of a perceived potential for cure, and recognition of the imperfect outcomes in HPTN 040, providers around the US are handling the management of high risk of infected infants in the first weeks of life in a diversity of ways.**
- **P1115 and P1110 should add important data to this context**
- **Decisions about management in decision should be made in discussion with families**
- **Discussions with parents or providers about management of high risk or infected young infants should clearly articulate differences between treatment vs. prophylaxis dosing and rationale for management of in-utero vs intrapartum infection.**

This material is intended for educational purposes for healthcare providers only. It is not intended as a substitute for professional medical care or advice, nor to replace a healthcare professionals' clinical judgment regarding their individual patient care.

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