

Pediatric Pharmacy Advocacy Group

Current Controversies in Perinatal HIV Management


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Overview

- Updates in potential teratogenicity of antiretrovirals
- Preferred regimens for the perinatal population
- Post-exposure prophylaxis for neonates




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Objectives

At the end of the presentation, the learner should be able to

1. Select 1st line regimens for the prevention of mother to child transmission of HIV.
2. Identify potentially teratogenic antiretrovirals and describe their possible negative effects.
3. Recommend post-exposure prophylaxis for an infant born to a woman with HIV.



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Scenario

- Ashley is a 17yo female presenting for routine HIV follow up appointment
- HIVRNA suppressed with fixed-dose abacavir/lamivudine/dolutegravir once daily
- She describes N/V and notes her LMP was 2 months ago
- Qualitative HCG comes back positive
- What are the implications?



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Dolutegravir

- Approved in 2013 as stand-alone tablet and 2014 as FDC with abacavir/lamivudine
- Integrase Strand Transfer Inhibitor (INSTI)
 - Class known for rapid virologic decay
 - Minimal adverse effects
 - Comprise all recommended first-line regimens
- Minimal drug interactions
- High genetic barrier to resistance

FDC = fixed dose combination



Tuesday [package insert], ViiV Healthcare, 2013.

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Dolutegravir in Pregnancy

- Twenty-nine pregnant women studied
 - Paired postpartum comparisons:

	2 nd trimester	3 rd trimester
AUC ₀₋₂₄	↓ 37%	↓ 29%
C _{max}	↓ 25%	↓ 26%

- 27 of 29 (93%) virologically suppressed at delivery
- No HIV transmission to infants
- Standard dose adequate
- Readily crosses the placenta
- No abnormalities in rat and rabbit studies



Mulligan N, et al. AIDS 2018;32(6):729-37. Tuesday [package insert], ViiV Healthcare, 2013.


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Safety of Dolutegravir

Authors	Location	N	Congenital abnormalities	Timing of DTG initiation in those with abnormalities
Thorne, et al.	Europe	84	4; no NTD	1 st trimester
Mulligan, et al.	US	29	2; no NTD	Not reported
Bornhede, et al.	Sweden	36	0	---
Grayhack, et al.	US	66	2; no NTD	Not reported
Money, et al.	Canada	80	4; no NTD	1 st trimester
Zash, et al.	Botswana	280	0	---

DTG = dolutegravir
NTD = neural tube defect

Thorne, et al. IAS 2017. www.netap.org/2017/IAS/045_08.htm
Mulligan, et al. AIDS 2018;32(6):729-37.
Bornhede, et al. Eur J Clin Microbiol Infect Dis 2018;37:495-500.
Grayhack, et al. AIDS 2018;32:207-21.
Money, et al. HIV Drug Therapy 2018. <http://www.hivdrugsow.org/2018-posters>
Zash, et al. Lancet Glob Health 2018;6(7):e0054-10.




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Updated Botswana Data

- Ongoing birth outcome surveillance
 - Eight centers in Botswana
 - Dolutegravir-based regimen 1st line for all adults since 5/2016
- Unplanned interim analysis for NTD
 - 426 infants born to women on DTG from conception
 - 4 (0.94%) had NTD: encephalocele, myelomeningocele, iniencephaly, anencephaly
 - NTD in non-DTG exposed infants: 14 of 11,300 (0.12%)
 - NTD in non-HIV-exposed infants: 61 of 66,057 (0.09%)

Zash, et al. N Engl J Med 2018;379(10):979-81.
Antiretroviral Pregnancy Interim Report 2018. www.aprregistry.com




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Perinatal Guidelines – New ART

- For women not on antiretroviral therapy
- 2 NRTI backbone
 - Tenofovir disoproxil fumarate/emtricitabine
 - Abacavir/lamivudine
- Add 3rd agent
 - BID raltegravir (INSTI)
 - Daily atazanavir boosted with ritonavir (PI)
 - BID darunavir boosted with ritonavir (PI)

NRTI = nucleoside reverse transcriptase inhibitor
PI = protease inhibitor



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Perinatal Guidelines – Switch ART?

- Continue regimen if tolerated and suppressed
- Consider switch in certain situations
 - Known pharmacokinetic changes affecting suppression
 - Potential teratogenicity
 - Gestational age of fetus
- Women on dolutegravir-based regimens
 - Switch if in 1st trimester
 - Preferred antiretroviral for 2nd and 3rd trimester

ART = antiretroviral therapy

DHHS Perinatal Guidelines 2019. <https://aidsinfo.nih.gov/guidelines>



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Efavirenz Teratogenicity?

- Historically avoided in women of childbearing age through 1st trimester
 - Cranial defects seen in cynomolgus monkeys
- 2.3% with 1st trimester exposures have birth defects (2.7% seen in general population)
- FDA labeling recommends avoiding
- DHHS Perinatal Guidelines recommend as alternative
- WHO recommends 1st line

Antiretroviral Pregnancy Interim Report 2018. www.apregistry.com
Switch (package insert). Bristol Myers Squibb, 2013.
DHHS Perinatal Guidelines 2019. <https://aidsinfo.nih.gov/guidelines>



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Fast-Forward to Ashley’s Delivery

- ART switched to FDC tenofovir disoproxil fumarate/emtricitabine + BID raltegravir 400mg
- Virologically suppressed throughout pregnancy
- Out of ART for final 2 weeks of pregnancy
- HIVRNA the week before delivery = 2,400 copies/mL



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Post-Exposure Prophylaxis: Neonates

- All neonates receive zidovudine x 4 weeks
 - High placental transfer
 - Excellent penetration to BBB
 - Risk of transmission < 1% in those with mothers with virologic suppression
- Additional antiretrovirals for those born to mothers without virologic suppression
 - How many more ARVs?
 - Which ones?
 - What duration?



PHHS Perinatal Guidelines 2019. <https://aidsinfo.nih.gov/guidelines>

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Disproven Cure

- 30 month old child diagnosed with HIV at birth
- Initiated on 3 drug regimen at 30 hours of age
- Achieved virologic suppression by 29 days of age
- ART discontinued between 15 and 18 months of age
- Virologic suppression continued x 2 years

ART = antiretroviral therapy



Persaud D, et al. N Engl J Med 2013;369(15):1420-35.

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Current Guidelines

- Neonates born to mothers with detectable viral loads at delivery at higher risk
- Three recommended regimens
 - Zidovudine x 6 weeks + nevirapine x 3 doses
 - Zidovudine x 6 weeks + lamivudine and nevirapine x 2-6 weeks
 - Zidovudine x 6 weeks + lamivudine and raltegravir x 2-6 weeks




PHHS Perinatal Guidelines 2019. <https://aidsinfo.nih.gov/guidelines>

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Two vs Three Antiretrovirals

- Randomized controlled trial studying 1,684 infants in N. America, S. America, and S. Africa
- All born to HIV-infected mothers and started ART within 48h of birth
- Three possible regimens
 - Zidovudine x 6 weeks
 - Zidovudine x 6 weeks + 3 doses of nevirapine
 - Zidovudine x 6 weeks + lamivudine and nelfinavir x 2 weeks
- Primary outcome = HIV infection




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Results

- Transmission rates at 3 months of age

Zidovudine	Zidovudine + nevirapine	Zidovudine + lamivudine + nelfinavir	P value
24/566 (4.8%)	11/562 (2.2%)	12/556 (2.4%)	0.046


- Indicates 2-3 drugs needed for high-risk situations
- Increased adverse effects with 3 drug regimen



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Rationale for Raltegravir Regimen

- Recently approved for pediatric patients at least 2kg
 - Studied in 26 infants in Brazil, South Africa, U.S.
 - No HIV transmission, even in high-risk group
 - No drug-related adverse events (hyperbilirubinemia of greatest concern)
- INSTIs stop integration of HIV into human DNA
 - Seen as the “point of no return”



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Future Directions

- Early intensive antiretroviral therapy to achieve remission
 - Infants randomized to one of three 4-5 antiretroviral regimens
 - Anticipated completion 2021
- PrEP for pregnant women and their infants
 - Phase 2
 - Tenofovir disoproxil fumarate/emtricitabine
 - Anticipated completion 2022

PrEP = pre-exposure prophylaxis

<https://clinicaltrials.gov/ct2/show/NCT02140255>

<https://clinicaltrials.gov/ct2/show/NCT02067276>



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Summary

- Growing body of information regarding the use of ARVs during and after pregnancy
- Possible neural tube defects with dolutegravir
 - Avoid in women of childbearing age
 - Consider switch through 1st trimester
- Efavirenz not as concerning?
- Post-exposure prophylaxis
 - 4 weeks zidovudine
 - Consider raltegravir as part of 3 drug regimen if needed



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