ALL HIV-EXPOSED INFANTS SHOULD RECEIVE TRIPLE DRUG ANTIRETROVIRAL PROPHYLAXIS – YES!

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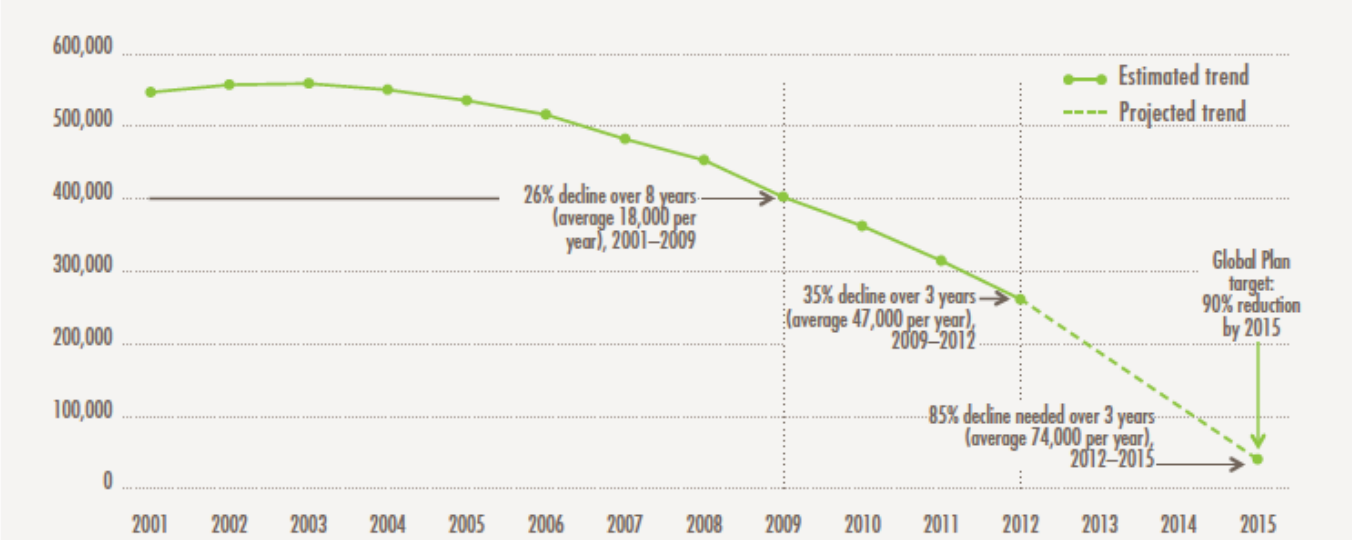
Perinatal HIV Transmission

- Despite massive scale-up of ARV availability and programs to reduce perinatal transmission, an estimated 260,000 infants were infected in 2012
- Even if "virtual elimination" achieved by 2015+, 40,000 infants will be infected with HIV annually

FIGURE 1.2

Estimated number of new HIV infections in children (aged 0–14): Global trend and projections, 2001–2015

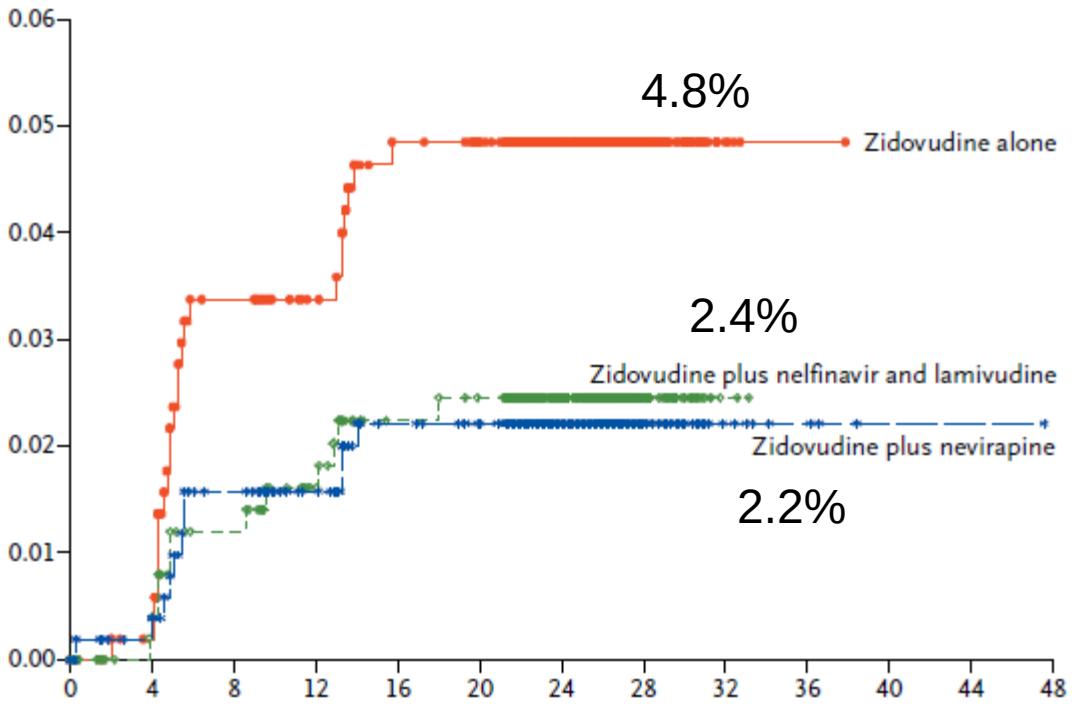


Source: UNICEF analysis of UNAIDS 2012 HIV and AIDS estimates.

Towards an AIDS-free generation: Children and AIDS 6th Stocktaking report, 2013 UNAIDS.

Triple Drug ARV Prophylaxis

- Only 1 randomized clinical trial has assessed the efficacy of triple drug ARV prophylaxis - NICHD 040/PACTG 1043



- 1,684 formula-fed infants whose mothers were diagnosed with HIV infection within 48 hours of birth randomized to
  - ZDV (6 wks)
  - ZDV (6 wks) + 3 doses of NVP (7 days)
  - ZDV (6 wks) + 3TC/NFV (2 wks)
- Both combination regimens more effective than ZDV alone (p=0.046) at 3 months of age

Nielsen-Saines K et al. NEJM 366:2368, 2012.

Special Considerations from NICHD 040/PACTG 1043 Findings

- Wrong third drug?
  - Nelfinavir pharmacokinetics performed in 26 infants
  - AUC0-12 failed to reach the 10% for adult level in 46% of the infants
  - Not recommended in children less than 2 years of age due to low levels and minimal PK data to support a dosing regimen
- Resistance?
  - Would nevirapine based regimens fare as well in resource-limited regions where NNRTI usage for prophylaxis and treatment is greater and baseline resistance rates higher?

Mirochnick M et al. Pediatr Infect Dis J 30:769, 2011; Nielsen-Saines K et al. NEJM 366:2368, 2012.

Triple Drug ARV Prophylaxis

Survey Data – US

- 134 perinatal HIV providers
- 62% had used combination prophylaxis in past year
  - AZT, 3TC, nevirapine most common
    - 77% for 2 or more of these
  - 12% used lopinavir/r in their combination regimen
  - Response to scenarios indicated increasing use with more risk factors for transmission

McKeegan AIDS Pat Care STD 25:1, 2011.

Pregnancy Registry – Europe

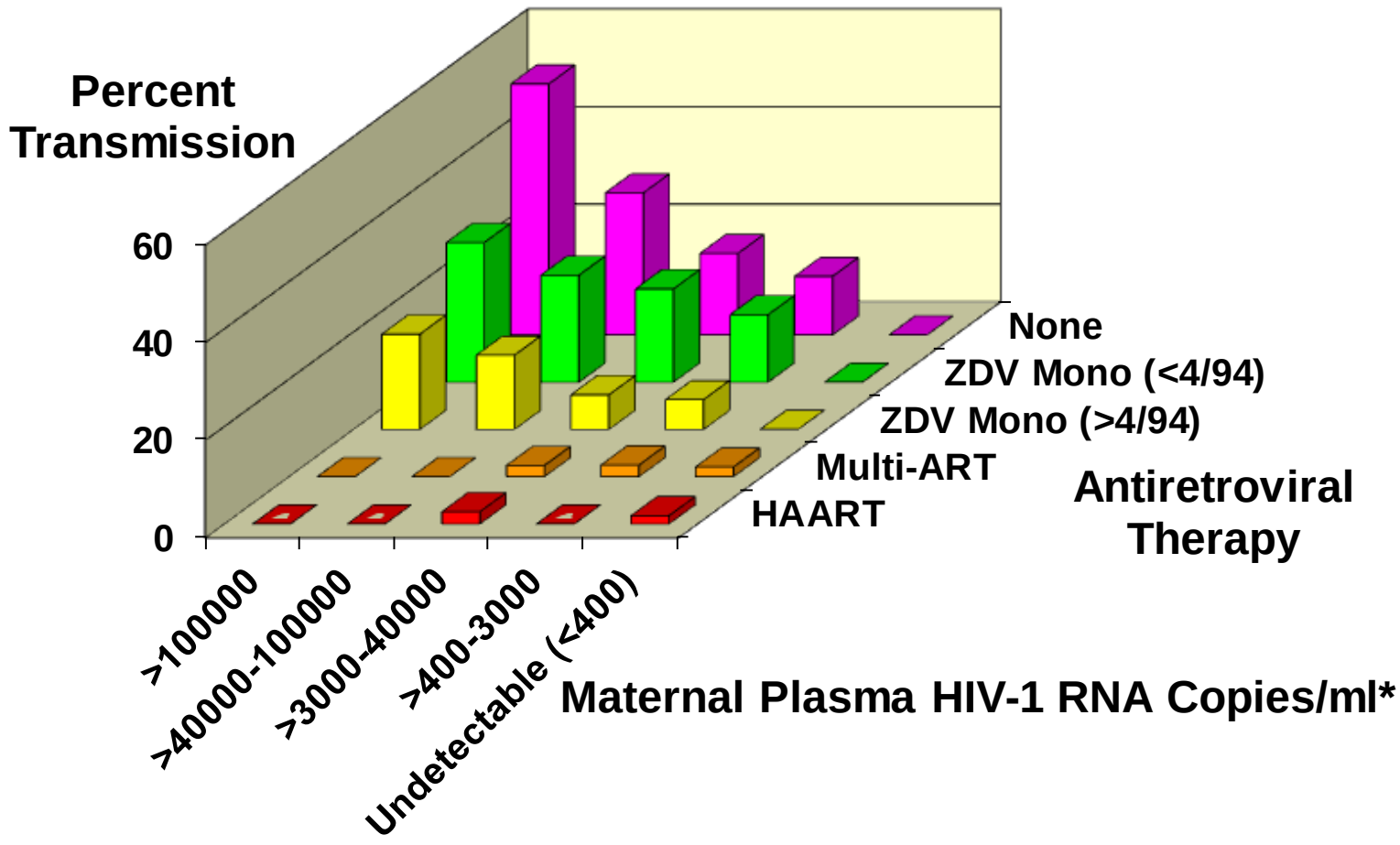
- 5,285 mother-infant pairs from 8 countries
- 1,105 (23%) infants had combination ARV prophylaxis; 677 (61.3%) received 3 drugs
  - 615 (55.8%) received AZT, 3TC, single dose nevirapine
  - 48 (4.4%) received PIs
  - Unable to demonstrate differences in HIV transmission based on infant prophylaxis regimens

Chiappini AIDS 27:991, 2013.

Top Reasons to Support Triple Drug Prophylaxis in Infants

- Viral load, a strong indicator of risk for HIV transmission, is not routinely measured in women in resource-limited setting
- In settings of treatment in adults and children and some prophylaxis studies, three drugs are more effective than one- or two-drug regimens
- Early aggressive prophylaxis may reduce viral reservoirs and optimize chance for a “functional cure” or prolonged remission if infant is infected, as well as improve neurologic outcomes
- Toxicities of triple-drug regimens are usually mild and reversible

Maternal Delivery HIV RNA Levels and Antiretroviral Use are Independently Associated With Perinatal Transmission



Cooper E et al, JAIDS 2002; 29:484-94.

Viral Load at Delivery

- In resource-rich countries, viral load measured during pregnancy with adherence reinforcement, assessment of viral resistance and changes in drug regimen when undetectable viral loads are not achieved
- In resource-limited countries, a standard antenatal regimen is prescribed without assessment of resistance nor efficacy of the regimen in suppressing viral load
- Thus, in resource-limited countries, unable to identify those infants at highest risk of transmission to offer combination ARV prophylaxis
- Public health approach – provide triple ARV prophylaxis for all

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More is better

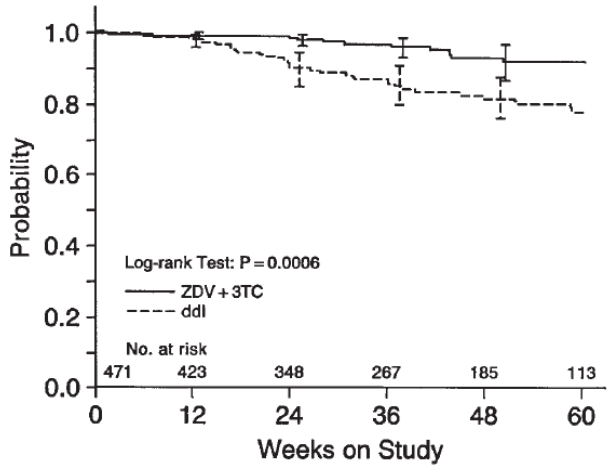


Fig 1. Kaplan-Meier plot of proportion of patients without a primary endpoint versus time in weeks in patients in the ZDV/3TC *(solid line)* and ddI monotherapy *(dashed line)* treatment groups.

PACTG 300 demonstrated that ZDV and 3TC resulted in less clinical disease progression than ddI alone

PACTG 338 demonstrated that addition of the PI ritonavir resulted in greater rates of virologic suppression

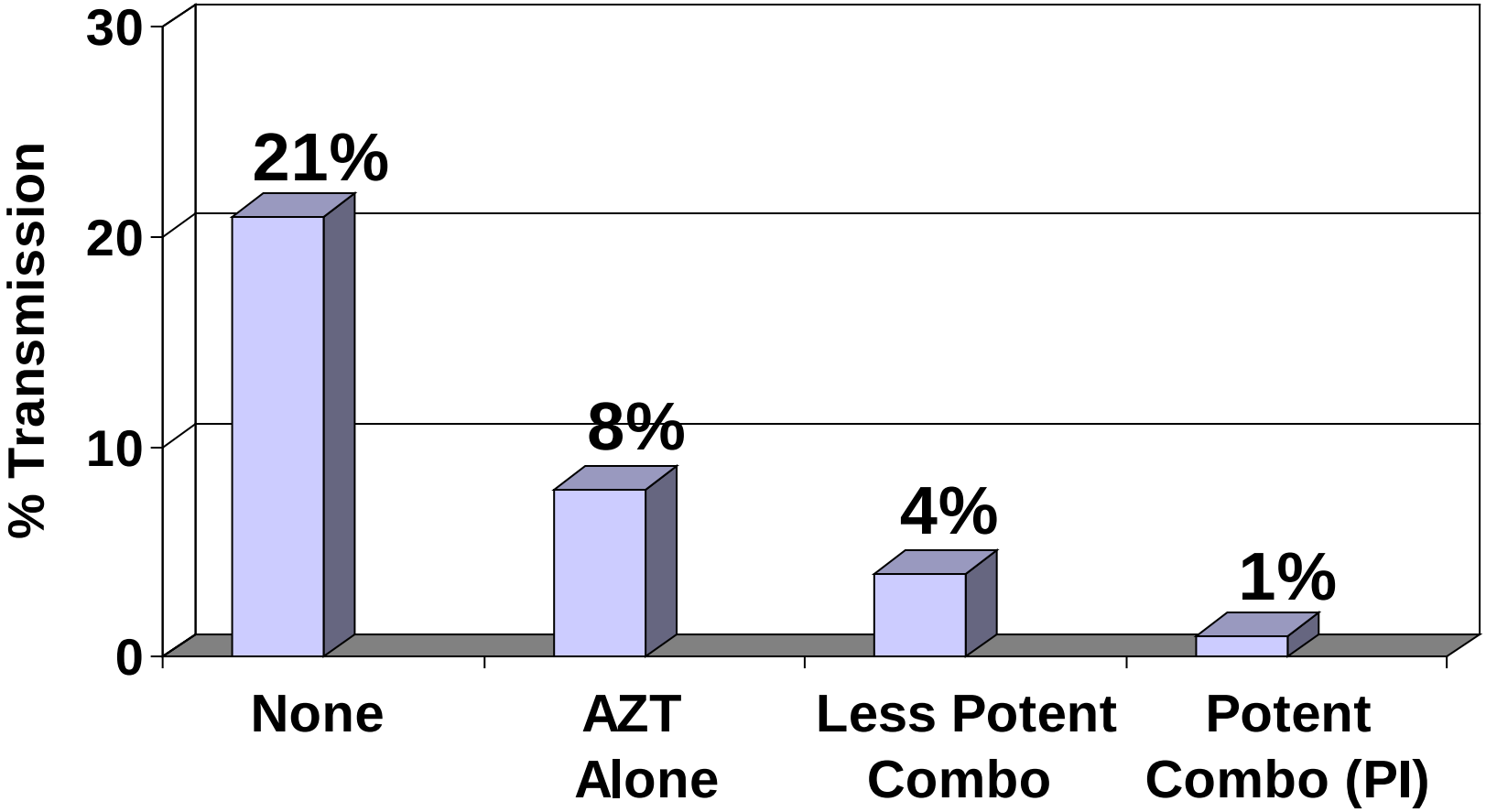
Table 2. Proportion of Children With Undetectable HIV RNA Levels at Baseline Receiving Original Randomized Treatment, by Group*

	No. (%) of Children					
	HIV RNA <400 Copies/mL			HIV RNA <10 000 Copies/mL		
Week	Zidovudine/ Lamivudine (n = 95)	Zidovudine/ Lamivudine/Ritonavir (n = 93)	Stavudine/ Ritonavir (n = 92)	Zidovudine/ Lamivudine (n = 95)	Zidovudine/ Lamivudine/Ritonavir (n = 93)	Stavudine/ Ritonavir (n = 92)
0				31 (33)	24 (26)	34 (37)
4	24 (25)	48 (52)†	46 (50)†	52 (55)	71 (76)†	68 (74)†
12	11 (12)	50 (54)†	48 (52)†	40 (42)	56 (60)†	62 (67)†
24	8 (8)	44 (47)†	31 (34)†	32 (34)	56 (60)†	49 (53)†
36		36 (39)	34 (37)		49 (53)	46 (50)
48		39 (42)‡	25 (27)‡		54 (58)	44 (48)

*HIV indicates human immunodeficiency virus. Blank spaces indicate end of treatment.
†P<.01 in comparison with zidovudine-lamivudine group.
‡P = .04 for triple therapy vs stavudine/ritonavir.

McKinney J Pediatr 133:500, 1998. Nachman JAMA 283:492, 2000.

More Potent Antiretroviral Regimens – Less Perinatal Transmission



Women & Infants Transmission Study, 1990-1999, Cooper E et al. JAIDS 2002;29:484-94.

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- Toxicities of triple-drug regimens are usually mild and reversible

Early Aggressive Prophylaxis/Therapy Can Limit Chronic Infection

- The “Mississippi Baby”
  - Therapeutic doses of ARVs administered to a high-risk infant at 30 hours of age
  - Treatment continued through 18 months of age
  - Absence of viral rebound for two years off ARVs, recent rebound
  - Very early ART may interfere with either the quantities or qualities of persistent reservoirs of replication competent virus
- Thai studies
  - Fiebig I (NAT +, P24 -, 3rd gen EIA -) adult patients had extremely low reservoir size with no detected HIV integrated in PBMC and memory CD4 T cell subsets before and after ART
  - Studies in children treated before 6 months of age, some beginning at birth, demonstrate very low levels of markers of HIV persistence and undetectable HIV-specific immune responses

Persaud N Engl J Med 369:1828, 2013; Ananworanich J CROI 2013 *and* AIDS 28:1015, 2014

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NICHD 040/PACTG 1043

- Grade 2 neutropenia is any value less than 1,000
- Six weeks of AZT was accepted with significantly more grade 3 (< 7gm) hemoglobin compared to placebo

Appendix 3: All Grade 2 or higher laboratory abnormalities overall and by study arm

	Overall N= 1684	ZDV N= 566	ZDV + NVP N= 562	ZDV + 3TC/NFV N= 556	*p-value*[2]
	No. Events (No. Subjects)	No. Events (No. Subjects)	No. Events (No. Subjects)	No. Events (No. Subjects)	
Neutropenia	407 (330)	116 (93)	109 (84)	182 (153)	< 0.0001
Alanine Aminotransferase (ALT) increase	40 (34)	15 (13)	16 (13)	9 (8)	0.49
Aspartate Aminotransferase (AST) increase	46 (43)	20 (18)	11 (11)	15 (14)	0.43
Anemia	822 (432)	294 (153)	237 (132)	291 (147)	0.35
Thrombocytopenia[1]	33 (26)	11 (9)	9 (7)	13 (10)	0.75
Total	1348 (865)	456 (286)	382 (247)	510 (332)	

[1] Thrombocytopenia values of 75,000 or less are included in the table.
[2] Chi square tests were used to calculate p-values.

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Are We There Yet?

- More information about drug safety and pharmacokinetics in infants and preterm infants, as well as acceptable formulations are needed to effectively implement triple-drug prophylaxis
- In light of our inability to conduct a RCT of 3-drug vs. 1-2-drug infant prophylaxis regimens, our focus should be here