Novedades en la transmisión vertical del VIH

18ª Jornada de Tratamiento Anrirretroviral en Pediatría
Barcelona, 24 de Octubre de 2014

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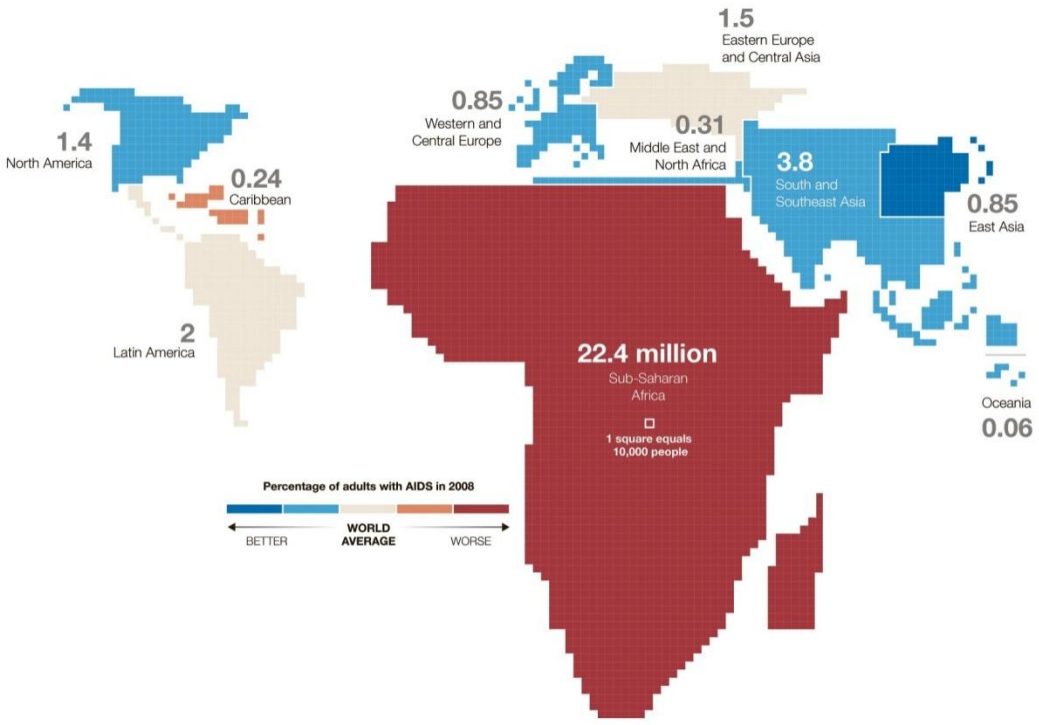
Resumen

- Epidemiología
- Prevención de la TV en países de baja renta: lo opción B+
- Prevención de la TV en países de alta renta
- *The Mississipi baby…*

Epidemiología



En 2012: 33.5 millones HIV+
(50% mujeres)

1.5 millones gestantes

Sólo 62% recibieron ARV

37 mil gestantes fallecidas

260 mil casos de TV
(**700 infecciones al día**)

Berti et al, PIDJ. In press

Report	Years	Country	Mother To Child Transmission rate
Canadian Pediatric AIDS	1997-2010	Canada	1%
ECS	2005-2007	Western European Countries	1%
Swedish Cohort	1999-2007	Sweden	
AmRo Study		Neth	No cases
Denmark Cohort	2008		0.5%
ECS and the Swiss Mother & Child HIV Cohort Study	200	ern European Countries	0.6-1.6%
United Kin Ireland	2000-2006	UK and Ireland	0.8%
French Perinatal Cohort	1997-2004	France	1.3%
Italian Register		Italy	1.3%
Madrid Cohort	2000-20		1.6%

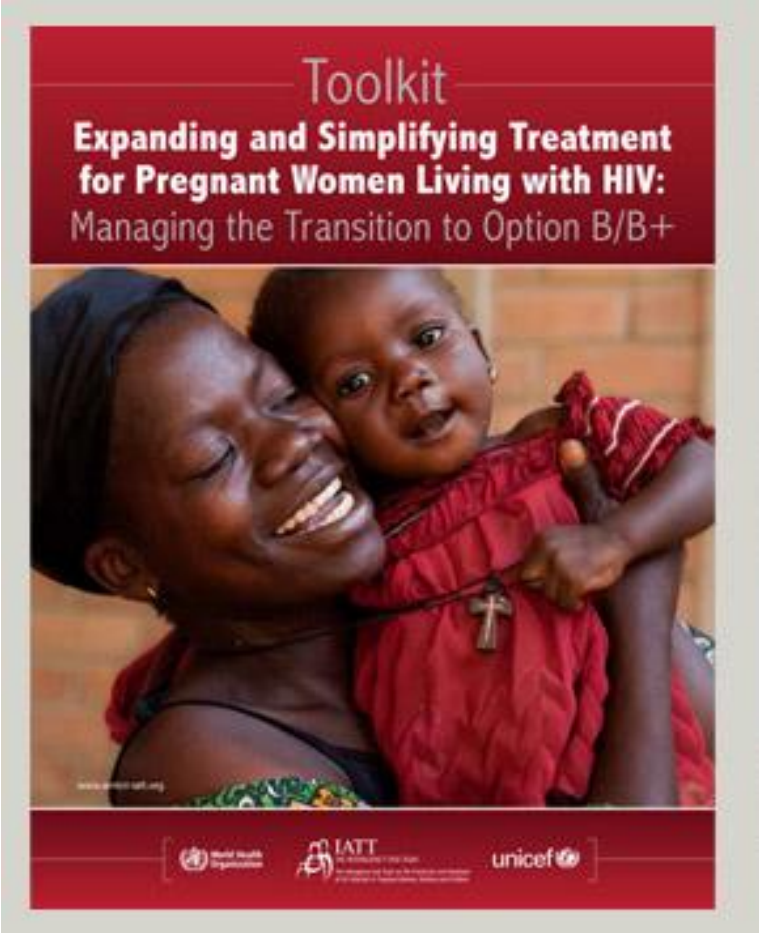
INMIGRACIÓN

Oportunidades perdidas en >75% de casos

UDVPs, trabajadoras del sexo y tráfico de mujeres

Re		Country	Mother To Child mission rate
St. Petersburg, Russia Cohor			
Moscow AIDS Centre	200		
Ukraine national data	2007	Ukra	
Ukraine European Collaborative Study Group in EuroCoord	2008-2010	Ukraine	4.1%
Moldova Cohort	2007	Moldova	1.7%
Belarus Cohort	2007	Belarus	4.7%

Prevención de la TV del VIH en países de baja renta: option B/B+

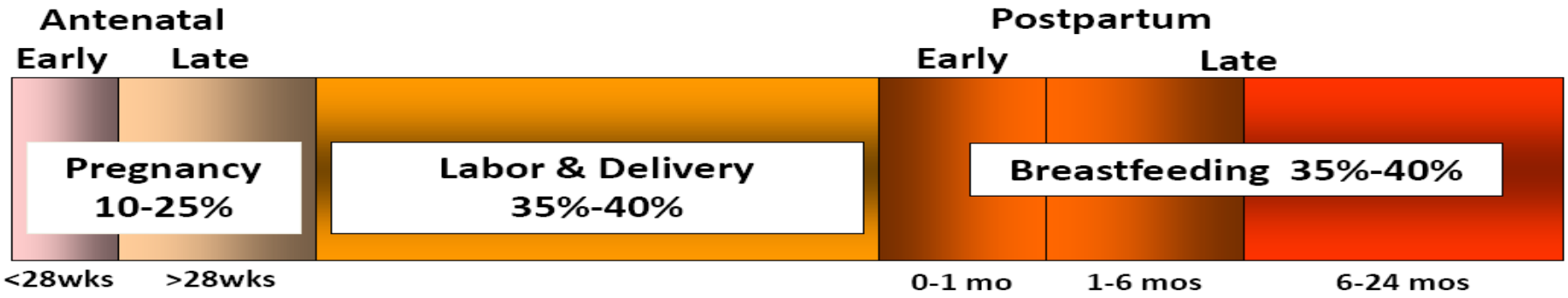


OBJETIVOS

… en 2015:
disminución del 90% en TV y del 50% en mortalidad materna…

Desde Abril de 2012, opción B+

Prevención de la TV en países de baja renta



Mother needs **HAART for herself**: Neonate:

Lifelong HAART — 4-6wk ZDV or NVP

Mother does **NOT need HAART** for herself: Neonate:

Option A: ZDV + sdNVP at delivery + ZDV/3TC 7d — NVP until 7d BF c.

Option B: HAART until 7d after BF cessation — 4-6wk ZDV or NVP

Option B+: lifelong HAART

Prevención de la TV en países de baja renta

Ventajas de la opción B+:

- No es necesario monitorizar CD4 (pre ni post)
- Se protege también a futuros embarazos
- Menor riesgo de transmisión sexual
- Mejor salud materna

Pero… representa un ENORME RETO programático y económico

Prevención de la TV en países de baja renta

- For programmatic and operational reasons, particularly in generalized epidemics, all pregnant and breastfeeding women living with HIV should initiate ART and maintain it as lifelong treatment (option B+) *(conditional recommendation, low quality of evidence) (4)*.

WHO, Junio de 2013

(TARGA recomendado: TDF + FTC o 3TC + EFV, *QD single pill*)

Riesgo fetal asociado a la exposición a fármacos antirretrovirales

… in resource-constrained settings, where rapid expansion in ARV drugs use in pregnancy (and conception) is expected… there is an ethical imperative to sistematically and critically evaluate the safety of these recommendations for the fetus/infant…

- WHO Pregnancy Registry Protocol
- PEPFAR Project in Malawi and Uganda
- ARV Pregnancy Registry (http://www.apregistry.com/)

Mofenson LM. PLoS One 2014

Prevención de la TV en países de alta renta

Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health *and* Interventions to Reduce Perinatal HIV Transmission in the United States

Developed by the HHS Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission—A Working Group of the Office of AIDS Research Advisory Council (OARAC)

(actualizada en Marzo de 2014)

Prevención de la TV en países de alta renta

Preferred Two-NRTI Backbone	
ABC/3TC	Available as FDC, can be administered once daily, but potential HSR. ABC **should not be used** in patients who test positive for HLA-B*5701.
TDF/FTC or 3TC	TDF/FTC available as FDC. Either TDF/FTC or TDF and 3TC can be administered once daily. TDF has potential renal toxicity, thus TDF-based dual NRTI combinations should be used with caution in patients with renal insufficiency.
ZDV/3TC	Available as FDC. NRTI combination with most experience for use in pregnancy but has disadvantages of requirement for twice-daily administration and increased potential for hematologic toxicity.
PI Regimens	
ATV/r + a Preferred Two-NRTI Backbone	Once-daily administration.
LPV/r + a Preferred Two-NRTI Backbone	Twice-daily administration. Once-daily LPV/r is not recommended for use in pregnant women.
NNRTI Regimen	
EFV + a Preferred Two-NRTI Backbone **Note:** May be initiated after the first 8 weeks of pregnancy	Concern because of birth defects seen in primate study; risk in humans is unclear (see Teratogenicity and Table 7). Postpartum contraception must be ensured. Preferred regimen in women requiring co-administration of drugs with significant interactions with PIs.

Prevención de la TV en países de alta renta

HIV/Hepatitis C Coinfection

- The Panel discusses availability of new anti-hepatitis C drugs and the lack of data on these new agents in pregnancy. Interferon alfa and pegylated interferon are not recommended in pregnancy and ribavirin should not be used in pregnancy **(AII)**. Because management of HIV/hepatitis C coinfection in pregnancy is complex, consultation with an expert in management of these conditions is recommended.

Monitoring of the Woman and Fetus during Pregnancy

- While monitoring of CD4 T lymphocyte (CD4) cell count during pregnancy is generally recommended every 3 months, this can be reduced to 6-month intervals in patients on cART with consistently suppressed viral load who have immune reconstitution (CD4 cell count increase well above the threshold for risk of opportunistic infection) **(CIII)**.

Prevención de la TV en países de alta renta

Intrapartum Antiretroviral Therapy/Prophylaxis

- The HIV RNA threshold for requiring administration of intravenous (IV) zidovudine during labor (in addition to continuing antepartum cART) has been modified to be consistent with the threshold for scheduled cesarean delivery and based on additional data summarized in the section.
- IV zidovudine should be administered to HIV-infected women with HIV RNA >1,000 copies/mL (or unknown HIV RNA) near delivery **(AI)**, but it is not required for HIV-infected women receiving combination ARV regimens who have HIV RNA ≤1,000 copies/mL consistently during late pregnancy and near delivery and no concerns regarding adherence to the regimen.

Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

Postpartum Care

Infant Antiretroviral Prophylaxis

(Last updated:1/29/2013; last reviewed:7/31/2012)

Printer-Friendly Files

Section Only PDF (172 KB)

Full Guideline PDF (4.7 MB)

Panel's Recommendations

- The 6-week neonatal component of the zidovudine chemoprophylaxis regimen is recommended for all HIV-exposed neonates to reduce perinatal transmission of HIV **(AI)**.
- Zidovudine, at gestational age-appropriate doses, should be initiated as close to the time of birth as possible, preferably within 6 to 12 hours of delivery **(AII)**.

Infant Antiretroviral Prophylaxis

- A 4-week neonatal zidovudine chemoprophylaxis regimen can be considered when the mother has received standard cART during pregnancy with consistent viral suppression and there are no concerns related to maternal adherence **(BII)**.

be made in consultation with a pediatric HIV specialist, preferably before delivery, and should be accompanied by counseling of the mother on the potential risks and benefits of this approach **(BIII)**.

- In the United States, the use of ARV drugs other than zidovudine and nevirapine cannot be recommended in premature infants because of lack of dosing and safety data **(BIII)**.

ORIGINAL ARTICLE

Three Postpartum Antiretroviral Regimens to Prevent Intrapartum HIV Infection

N ENGL J MED 366;25 NEJM.ORG JUNE 21, 2012

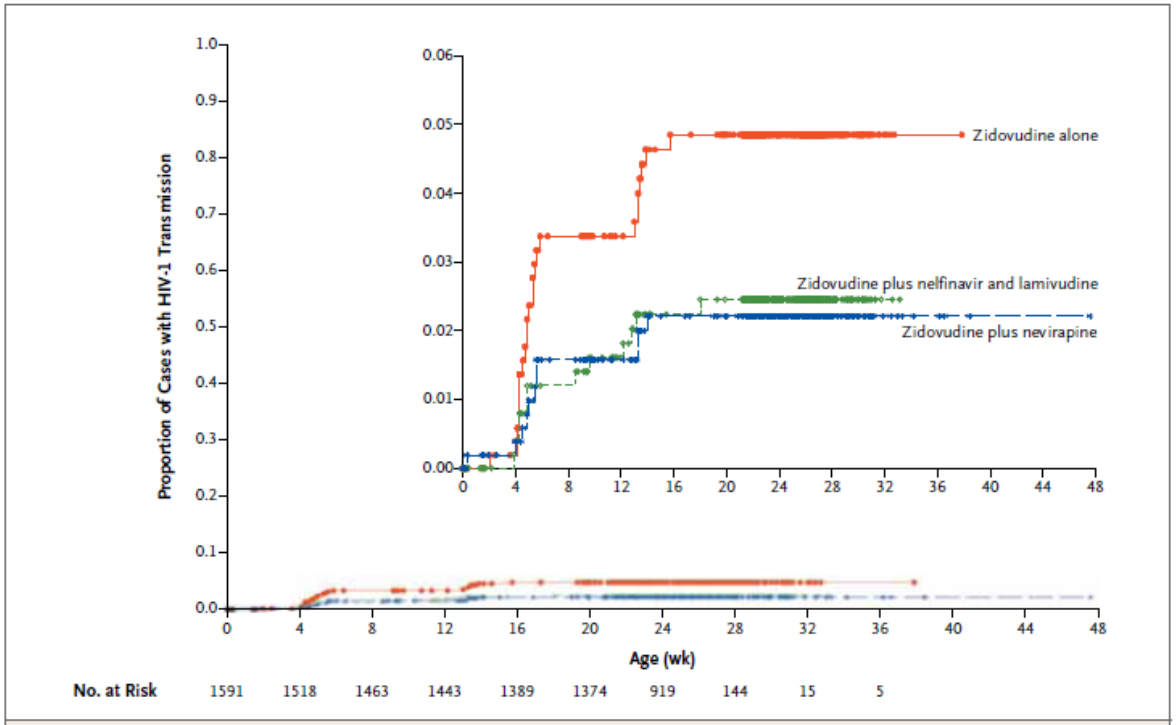


Figure 1. Intrapartum HIV-1 Transmission According to Treatment Group.

Kaplan–Meier curves for intrapartum transmission differed significantly (P=0.03 for the overall comparison). Transmission rates were highest in the zidovudine-alone group (3.4% at 4 to 6 weeks vs. 1.6% in the two-drug group and 1.4% in the three-drug group; 4.8% at 3 months vs. 2.2% in the two-drug group and 2.4% in the three-drug group).

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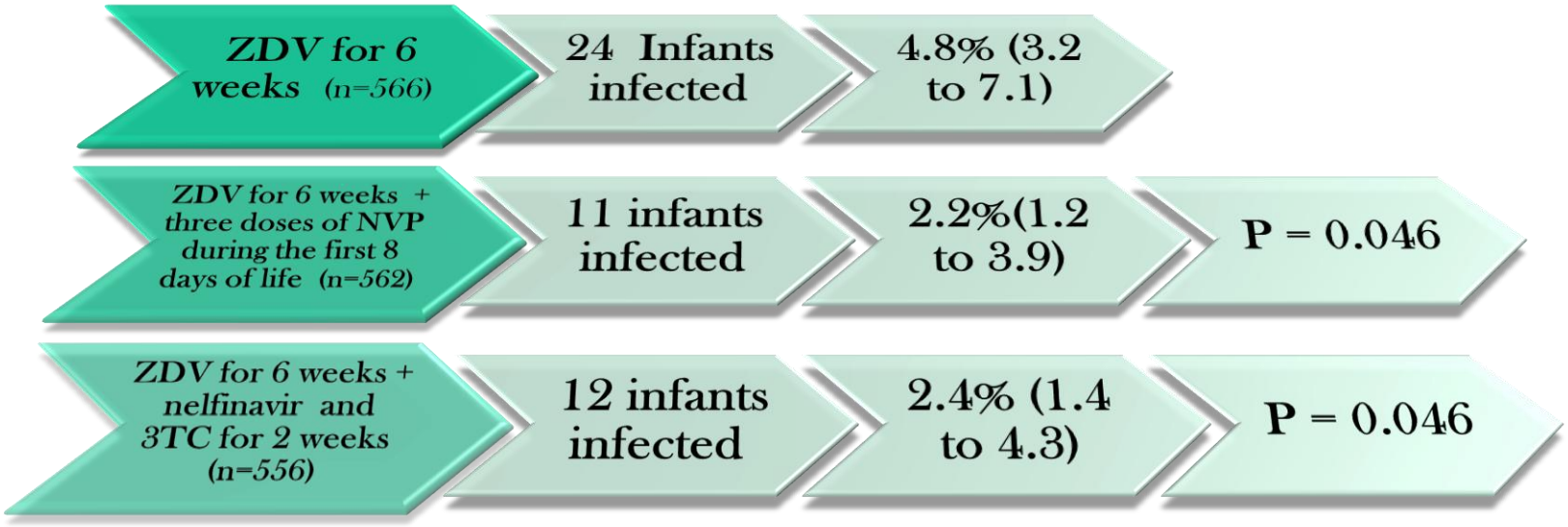

DX materno al parto + LA exclusiva

***Outcome* principal: infección VIH a los 3 meses**

Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

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Infant Antiretroviral Prophylaxis

(Last updated:1/29/2013; last reviewed:7/31/2012)

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Panel's Recommendations

- The 6-week neonatal component of the zidovudine chemoprophylaxis regimen is recommended for all HIV-exposed neonates to reduce perinatal transmission of HIV **(AI)**.
- Zidovudine, at gestational age-appropriate doses, should be initiated as close to the time of birth as possible, preferably within 6 to 12 hours of delivery **(AII)**.
- Infants born to HIV-infected women who have not received antepartum antiretroviral (ARV) drugs should receive prophylaxis with zidovudine given for 6 weeks combined with three doses of nevirapine in the first week of life (at birth, 48 hours later, and 96 hours after the second dose), begun as soon after birth as possible **(AI)**.
- In other scenarios, the decision to combine other drugs with the 6-week zidovudine regimen should be made in consultation with a pediatric HIV specialist, preferably before delivery, and should be accompanied by counseling of the mother on the potential risks and benefits of this approach **(BIII)**.
- In the United States, the use of ARV drugs other than zidovudine and nevirapine cannot be recommended in premature infants because of lack of dosing and safety data **(BIII)**.

Recomendaciones de la Sociedad Española de Infectología Pediátrica para el seguimiento del niño expuesto al virus de la inmunodeficiencia humana y a fármacos antirretrovirales durante el embarazo y el periodo neonatal

An Pediatr (Barc). 2012;76(6):360.e1–360.e9

Tabla 3 Pautas recomendadas de profilaxis neonatal con ARV

Zidovudina en monoterapia: gestante con buen control del embarazo, que recibe TARGA, llega al parto con viremia plasmática indetectable (< 50 copias/ml) y sin otros factores de riesgo
ZDV por vía oral (10 mg/ml), en el recién nacido de > 34 semanas: 4 mg/kg cada 12 horas, durante 4 semanas. Por vía EV: 1,5 mg/kg cada 6 horas; pasar a vía oral (a la dosis antes indicada) cuando tolere, y completar 4 semanas En prematuros ≤ 34 semanas: 2 mg/kg cada 12 horas por vía oral durante 2 semanas; después 2 mg/kg cada 8 horas 2 semanas más (vía EV: 75% de la vía oral). En prematuros ≤ 30 semanas: 2 mg/kg cada 12 horas por vía oral durante las 4 semanas (vía EV: 75% de la vía oral) Triple terapia: cualquier recién nacido cuya madre llegue al parto con viremia detectable (> 50 copias/ml)
ZDV por vía oral (10 mg/ml, misma pauta), **más**... 3TC por vía oral (10 mg/ml): en las primeras 12 horas de vida; 2 mg/kg cada 12 h durante 4 semanas, más... NVP por vía oral (10 mg/ml), se escogerá entre una de las dos pautas siguientes: – 3 dosis de NVP (4 mg/kg): la 1.ª en las primeras 48 horas de vida; la 2.ª y la 3.ª a las 48 y 96 horas de la 1.ª, respectivamente – 2 mg/kg al día durante 7 días, y 4 mg/kg al día durante la segunda semana, y suspender. Si la madre ha recibido ≥ 3 dosis de NVP pre-parto: NVP a 4 mg/kg al día durante 14 días, iniciándola a las 48-72 horas de vida (Nota: con estas pautas, no se han notificado rash o hepatotoxicidad graves por NVP) **Prematuro de riesgo**: prematuridad en que la madre no llegue al parto con carga viral indetectable (< 50 copias/ml) o en los que coincidan otros factores de riesgo
ZDV por vía oral (10 mg/ml, según pauta). Puede valorarse añadir en algunos casos: Dosis única de NVP por vía oral a la madre si no la recibía ya (200 mg, al menos 2 horas antes del parto) o al recién nacido (2 mg/kg, vía oral)

ASOCIACIÓN ESPAÑOLA DE PEDIATRÍA

Recomendaciones de la Sociedad Española de Infectología Pediátrica para el seguimiento del niño expuesto al virus de la inmunodeficiencia humana y a fármacos antirretrovirales durante el embarazo y el periodo neonatal

An Pediatr (Barc). 2012;76(6):360.e1-360.e9

Dudas pendientes…

- Demasiados fármacos?
- Toxicidad?
- Sensibilidad de los tests diagnósticos?
- Y el prematuro?
- Virus materno con mutaciones de resistencia?

Riesgo asociado a la exposición del feto a fármacos antiretrovirales

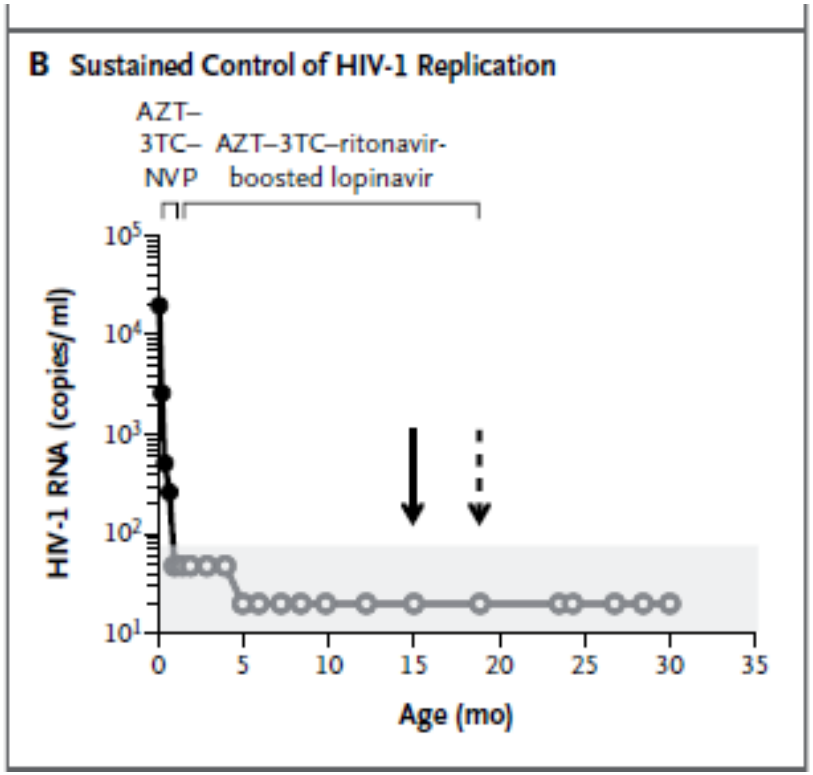
Decreased HIV MTCT

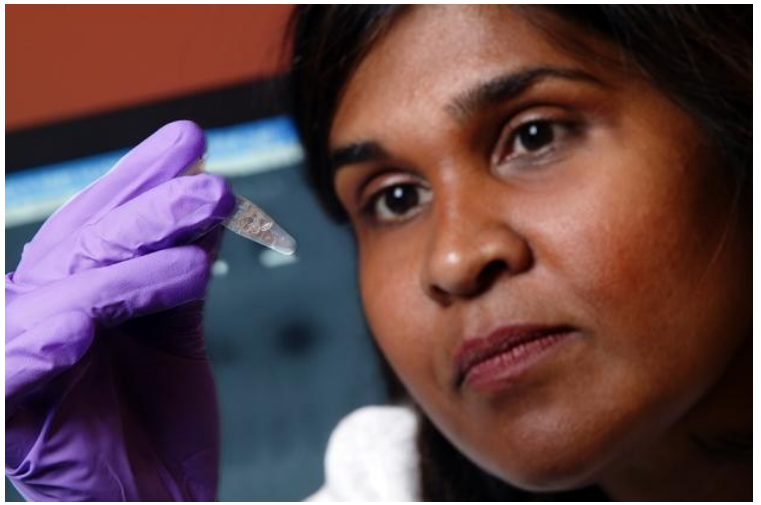
- Teratogenicity?
- Mitochondrial toxicity
- Carcinogenesis
- Bone toxicity
- Anemia
- Growth problems?
- Neurological LT development?
- Prematurity
- Low birth weight

BRIEF REPORT

Absence of Detectable HIV-1 Viremia after Treatment Cessation in an Infant

Deborah Persaud, M.D., Hannah Gay, M.D., Carrie Ziemniak, M.S., Ya Hui Chen, B.A., Michael Piatak, Jr., Ph.D., Tae-Wook Chun, Ph.D., Matthew Strain, M.D., Ph.D., Douglas Richman, M.D., and Katherine Luzuriaga, M.D.





(*Marzo 2013*)

… the Llobregat babies !!

Absence of detectable HIV-1 prov... [J Acquir Immune Defic Syndr. 2002] - PubMed - NCBI - Windows Internet Explorer proporciona

http://www.ncbi.nlm.nih.gov/pubmed/12447018

Archivo Edición Ver Favoritos Herramientas Ayuda

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http://aidsinfo.nih.gov/co... | Absence of detectable ...

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J Acquir Immune Defic Syndr. 2002 Dec 1;31(4):450-2.

Absence of detectable HIV-1 provirus DNA after early highly active antiretroviral therapy in children infected by vertical transmission.

Muñoz-Almagro C, Fortuny C, Juncosa T, Garcia-Fructuoso MT, Gonzalez-Cuevas A, Latorre C.

PMID: 12447018 [PubMed - indexed for MEDLINE]

CROI 2014
Conference on Retroviruses and Opportunistic Infections

75LB **Very Early Combination Antiretroviral Therapy in Perinatal HIV Infection: Two Case Studies**

Deborah Persaud[1], Audra Deveikis[2], Hannah Gay[3], Jagmohan Batra[2], Tempe Chen[2], David E. Michalik[2], Kaitlin Rainwater-Lovett[1], Carrie Ziemniak[1], Katherine Luzuriaga[4], Yvonne Bryson[5]

[1]Pediatrics, The Johns Hopkins University School of Medicine, Baltimore, MD, United States, [2]Pediatrics, Miller Children's Hospital, Long Beach, CA, United States, [3]Pediatrics, University of Mississippi Medical Center, Jackson, MS, United States, [4]Pediatrics, University of Massachusetts Medical School, Worcester, MA, United States, [5]Pediatrics, UCLA School of Medicine, Los Angeles, CA, United States

Mississipi baby, aún sin TARGA; *California baby*, recibe TARGA

Cura funcional? (***Hit hard, hit early***), ensayos clínicos en curso

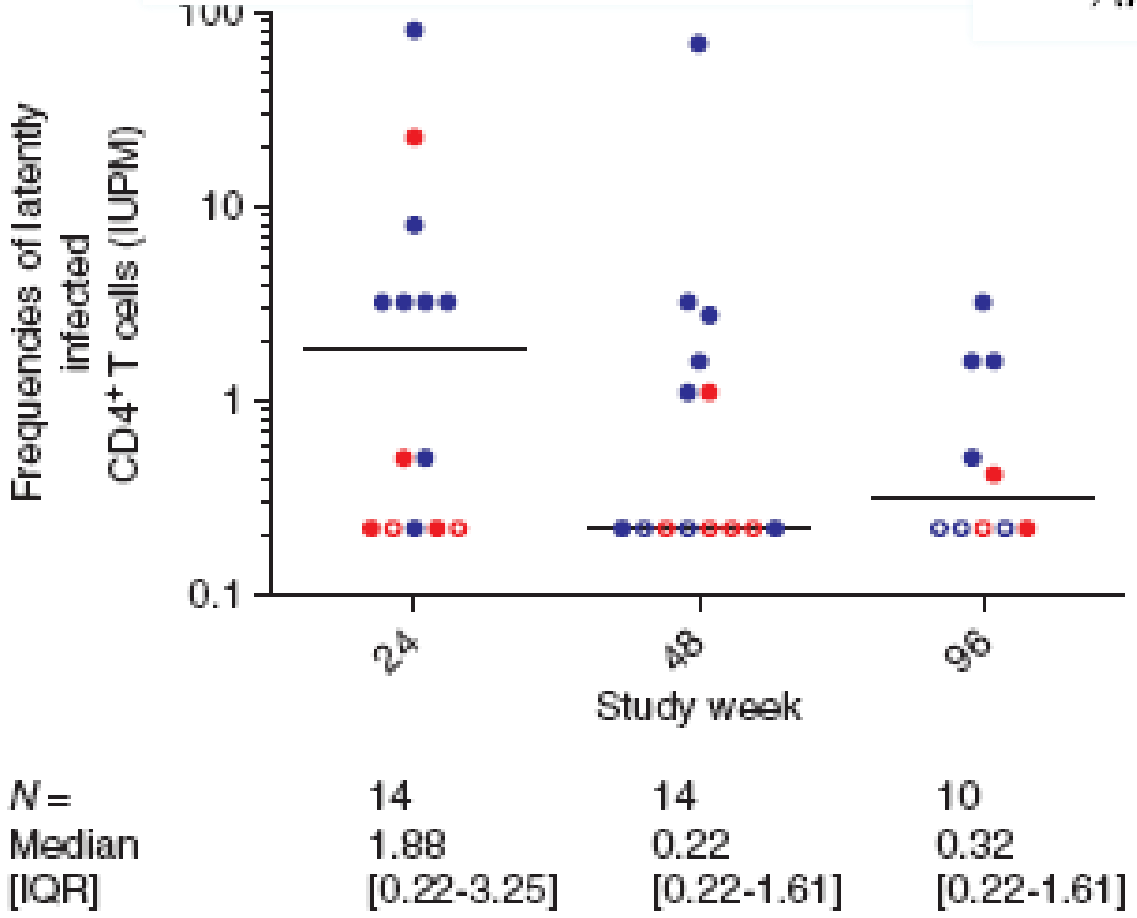
Elite controller? (excepcional en TV)

… el TARGA muy precoz puede incidir en la calidad y cantidad de reservorios de virus viable

Dynamics of the resting CD4$^+$ T-cell latent HIV reservoir in infants initiating HAART less than 6 months of age

Deborah Persaud[a], Paul E. Palumbo[b], Carrie Ziemniak[a], Michael D. Hughes[c], Carmelita G. Alvero[c], Katherine Luzuriaga[d], Ram Yogev[e], Edmund V. Capparelli[f] and Ellen G. Chadwick[e]

AIDS 2012, 26:1483–1490



Los reservorios de linfocitos CD4 infectados se asocian a:

- Inicio tardío de TARGA
- - Mayor viremia basal
- Tiempo hasta la supresión de la replicación viral

Early time-limited antiretroviral therapy versus deferred therapy in South African infants infected with HIV: results from the children with HIV early antiretroviral (CHER) randomised trial

Mark F Cotton, Avy Violari*, Kennedy Otwombe, Ravindre Panchia, Els Dobbels, Helena Rabie, Deirdre Josipovic, Afaaf Liberty, Erica Lazarus, Steve Innes, Anita Janse van Rensburg, Wilma Pelser, Handre Truter, Shabir A Madhi, Edward Handelsman, Patrick Jean-Philippe, James A McIntyre†, Diana M Gibb†, Abdel G Babiker†, on behalf of the CHER Study Team*

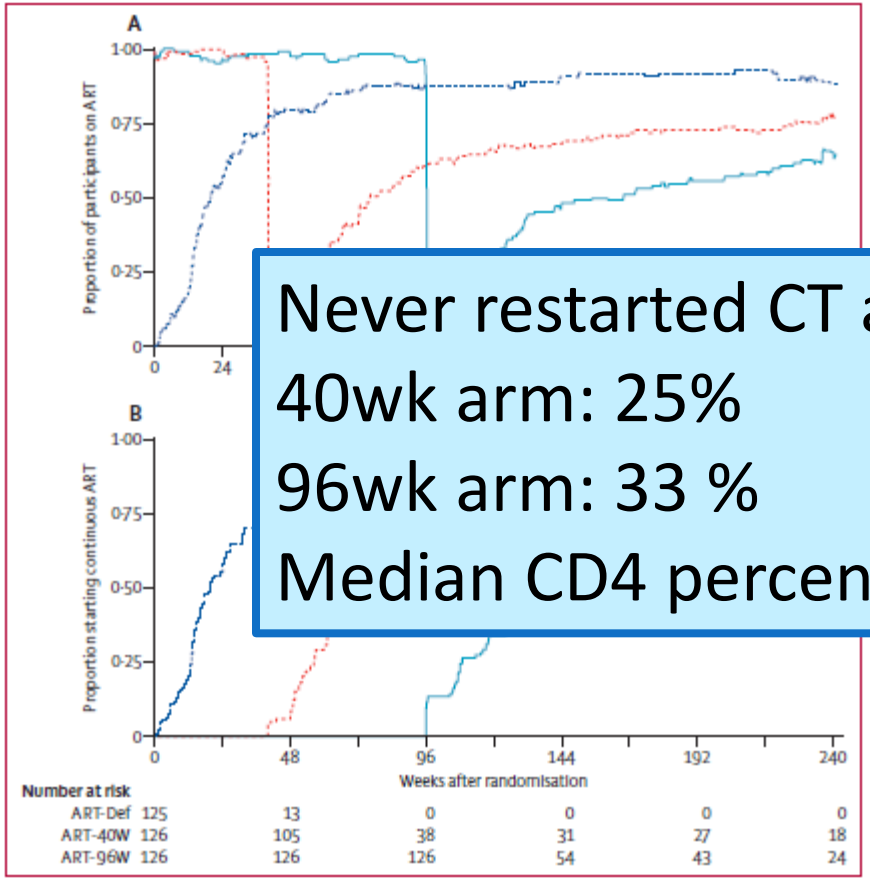


Figure 2: Use of ART in the trial

Never restarted CT at the end of the trial

40wk arm: 25%

96wk arm: 33 %

Median CD4 percentage: 31%

	ART-Def (n=125)	ART-40W (n=126)	ART-96W (n=126)
Number of participants enrolled	125	126	126
Total number of endpoints	48 (38·4%)	32 (25·4%)	26 (20·6%)
		11 (8·7%)	9 (7·1%)
		14 (11·1%)	11 (8·7%)
		7 (5·6%)	5 (4·0%)
		7 (5·6%)	6 (4·8%)
		6 (4·8%)	5 (4·0%)
		1 (0·8%)	2 (1·6%)
		5 (4·0%)	3 (2·4%)
		1 (0·8%)	1 (0·8%)
		0	0

early ART regimen restricted to 40 weeks. ART-96W=early ART regimen restricted to 96 weeks. CD4%=percentage of CD4-positive T lymphocytes. CDC=Centers for Disease Control and Prevention.

Table 2: Primary endpoints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International weekly journal of science
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HIV rebound dashes hope of 'Mississippi baby' cure
Virus resurfaces in infected child 27 months after antiretroviral therapy stopped.
Heidi Ledford
10 July 2014
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LIBERIA
Monrovia
Ebola by the numbers: The size, spread and cost

(*Julio 2014*)

Moltes gràcies

ton@hsjdbcn.org