

Early antiretroviral therapy of HIV-infected infants in resource-limited countries: possible, feasible, effective and challenging.

Renaud Becquet, Lynne Mofenson

► **To cite this version:**

Renaud Becquet, Lynne Mofenson. Early antiretroviral therapy of HIV-infected infants in resource-limited countries: possible, feasible, effective and challenging.. AIDS, Lippincott, Williams & Wilkins, 2008, 22 (11), pp.1365-8. 10.1097/QAD.0b013e32830437f5 . inserm-00271778

HAL Id: inserm-00271778

<https://www.hal.inserm.fr/inserm-00271778>

Submitted on 6 Jul 2009

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Early antiretroviral therapy of HIV-infected infants in resource-limited countries: possible, feasible, effective and challenging

Becquet Renaud ^{1 2 *}, Mofenson Lynne M. ³

¹ *ISPED, Institut de Santé Publique, d'Epidémiologie et de Développement Université Victor Segalen - Bordeaux II, 146 rue Léo Signat 33076 Bordeaux Cedex,FR*

² *Centre épidémiologie et biostatistique INSERM : U897, Université Victor Segalen - Bordeaux II, FR*

³ *Pediatric, Adolescent, and Maternal AIDS Branch NIH, Center for Research on Mothers and Children, Eunice Kennedy Shriver,US*

* Correspondence should be addressed to: Renaud Becquet <Renaud.Becquet@isped.u-bordeaux2.fr>

MESH Keywords Anti-HIV Agents ; administration & dosage ; therapeutic use ; Antiretroviral Therapy, Highly Active ; methods ; Developing Countries ; Drug Administration Schedule ; HIV Infections ; drug therapy ; transmission ; virology ; HIV-1 ; Humans ; Infant ; Infant, Newborn ; Infectious Disease Transmission, Vertical ; Medically Underserved Area ; Treatment Outcome ; Viral Load

Combination antiretroviral therapy (cART) has transformed pediatric HIV infection in resource-rich countries from a fatal infection to a treatable chronic disease. Children treated with cART have significantly decreased risk of progression to AIDS or death, improved growth and body composition parameters, reduced risk and severity of infectious complications, decreased hospitalizations, improvement in neurocognitive parameters, and reversal or prevention of HIV-related organ damage [1–7].

However, more than 90% of pediatric HIV infection occurs in resource-limited countries. In such countries, over 60% of HIV-infected children die prior to their third birthday [8]. At the end of 2007, 2.5 million children were estimated to be living with HIV infection, and about 420,000 continue to be newly infected yearly, primarily in low-resource countries through mother to child transmission of HIV (MTCT) [9]. While funding from the World Health Organization 3×5 initiative, the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), and the Global Fund have dramatically increased access of individuals in resource-limited countries to cART, targeting and inclusion of children in these programs has been disappointingly slow. Of the estimated 600,000 children who require HAART in sub-Saharan Africa, less than 5% are receiving therapy [10]. Barriers to pediatric treatment include lack of appropriate testing technology for early identification of HIV infection in infants, lack of availability of appropriate and affordable pediatric antiretroviral drug formulations, lack of personnel with health care expertise in treatment of children, infrastructure needs, and an apparent lack of prioritization and advocacy for treatment of children [11].

Despite slow progress in implementing pediatric treatment programs, there have been numerous publications that demonstrate that HIV-infected children in resource-limited countries respond to cART as well as children in resource-rich countries, and that implementation of treatment programs for large numbers of children can be accomplished in such settings despite multiple challenges [12–19]. However, in these settings treatment is often initiated at older ages and later stages of immune suppression than in resource-rich countries; in 7 recent studies on pediatric treatment published between 2007–2008 from resource-limited countries, the median ages at initiation of cART were 6 to 8 years old, and the median baseline CD4+ percentage at start of cART was 6% to 12% [12–17, 19].

Recovery of immune status with cART in children has been shown to be dependent on the baseline CD4+ count at initiation of treatment, and is also more robust in younger than older HIV-infected children [20–22]. Thus, initiation of therapy prior to severe immune suppression is desirable. Additionally, initiation of cART in children with severe immune suppression is more likely to result in the development of immune inflammatory reconstitution syndrome (IRIS), which can be associated with significant morbidity and potential mortality in the early months after initiation of cART [23]. Since the median survival of untreated perinatally-infected children in resource-limited countries is only 1.6 years [8], initiation of treatment in infancy, prior to immune deficiency, would seem to be desirable for optimal survival of infected children. Recent data from a South African clinical trial (Children with HIV Early Antiretroviral Therapy [CHER] study) of initiation of HAART in asymptomatic perinatally-infected children with normal CD4 percentage (CD4 >25%) prior to age 12 weeks, compared to waiting to start HAART until the child meets clinical or immune criteria, demonstrated a 75% reduction in early mortality [24]. Based in part on these data, treatment guidelines in the United States now recommend that all HIV-infected children under age 1 year diagnosed with HIV infection are started on cART regardless of clinical, immune or virologic status [25].

However, the issue of which cART regimen to start in HIV-infected infants is problematic in low resource settings, as there is a limited pediatric drug formulary. The current WHO- recommended first-line cART regimen in such countries is a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen (which would be nevirapine in young children). However, nevirapine, given as a single intrapartum/newborn dose, is a key drug in the prevention of MTCT in Africa: it is less costly than any other regimen, easy to implement, safe and effective in a single-dose intervention, and also used to optimize the efficacy of more complex peri-partum ARV regimens [26, 27]. However, the safety and efficacy of this regimen has been tempered by the rapid and frequent emergence of resistance mutations to

NNRTIs in both women and infants exposed to single dose nevirapine [28]. These resistance mutations could compromise the subsequent therapeutic response to infant NNRTIs-based ARV treatment (ART), as suggested by the recent findings of a study conducted on a small group of HIV-infected children treated from 8.5 months of age in Botswana [29].

The paper from Prendergast and colleagues published in this issue of AIDS adds to the evidence that excellent adherence and virologic response can be achieved in HIV-infected children receiving cART in sub-Saharan Africa [30]. Prendergast et al. assessed adherence to antiretroviral therapy and virological and clinical outcome one year after cART initiation among 63 South African infants. All these children had been previously exposed to single-dose nevirapine, and about 40% of them had developed NNRTI resistance mutations. The children were randomized to receive immediate (median age, 1 month) initiation of cART when HIV was diagnosed (N=40, 36 of whom completed 1 year cART) or deferred until CD4+ count decreased to $\leq 20\%$ (N=20). Of note, 16 of the 20 (80%) infants in the deferred group had CD4+ drop to $\leq 20\%$ within the first year of life, demonstrating the rapid progression to immune suppression in HIV-infected infants; 13 of these children were started on cART at a median age of 5 months (1 child died before therapy could be started, and 2 started cART after age 1 year). The cART regimen administered to 94% of infants was a 4-drug, 3-class regimen (zidovudine, lamivudine, nelfinavir, nevirapine). For the first year of cART, mean measured adherence to treatment was 95%. Overall median pre-cART viral load was 952,000 copies/mL. Ten infants required a switch to second line therapy during the first year; 5 due to viral failure (9.4%), the others due to need for concurrent tuberculosis treatment. Only one of the 5 infants with viral failure had a baseline NNRTI resistance mutation.

After 1 year of cART, viral load was <400 and <50 copies/mL in 100% and 94%, respectively, of infants in the immediate ART group, and 100% and 92% of infants in the deferred ART group. Time to undetectable viral load was not significantly different between groups (median approximately 4 months after initiation of cART). Most importantly, there was no difference in time to undetectability between infants with and without NNRTI resistance mutations. Another interesting finding is that infants starting immediate ART had significantly fewer illness episodes and were less likely to be admitted to hospital than those in the deferred group.

Using an intent to treat approach to evaluate success of first-line cART, 39/49 children (80%) achieved a viral load decrease to <400 copies/mL, a success rate similar to that seen in studies in resource-rich countries. In a study of early treatment of 52 infants aged 2 to 11 months in the U.S., 83% of infants receiving a 4-drug, 3-class regimen (stavudine, lamivudine, nevirapine and nelfinavir) similar to that in the current study achieved viral suppression to <400 copies/mL at 48 weeks; interestingly, response to a 4-drug regimen in these infants was superior to response to a 3-drug regimen (72% suppression at 48 weeks) [31]. Additionally, initiation of cART at <3 months of age was associated with better virologic response after 200 weeks of therapy (60% with HIV RNA <400 copies/mL in those <3 months when cART started vs 30% in those starting at >3 months).

Although promising, the Prendergast study results should be read carefully to avoid misinterpretations. First, this study was not designed to investigate the impact of perinatally acquired nevirapine-based resistance mutations on the therapeutic response to cART including an NNRTI. In this study, children were treated with a 3-class drug combination, including NNRTIs but also a protease inhibitor. Although a 4-drug regimen is potentially complex to roll-out in Africa, such a regimen conferred a good virological response, despite high baseline viral loads and high prevalence of resistance mutations to NNRTIs. The public health implication of these findings are therefore potentially important, but there remains an urgent need for the development of simplified paediatric ARV regimens, optimized for children previously exposed to single-dose nevirapine. A number of other clinical trials are ongoing to evaluate response to treatment in infected children exposed to single-dose nevirapine.

Second, the controversial question of when to start ART in infants is of crucial interest [32]. However, the low number of infants included in the study resulted in lack of statistical power to explore differences in morbidity and mortality between the immediate and deferred cART groups. Additionally, the majority of the children in the deferred arm required initiation of therapy before age 1 year based on immunologic decline. Although only limited conclusions related to these outcomes can be drawn from Prendergast et al. study, they add to the recent CHER study's findings that provide good evidence for a benefit to starting ART early in infants, e.g. as soon as diagnosis of HIV-infection has been made available [24]. However, the benefits of early initiation need to be balanced against the costs and drawbacks of such a strategy: impact of cART on the quality of life, management of adverse effects, the repercussions of the development resistance mutations in a context where therapeutic options are limited, the likeliness of a lifelong therapy and its relationship with long-term adherence [33].

Thus, the Prendergast paper adds to a growing body of evidence suggesting that good clinical outcomes can be obtained in African HIV-infected children treated with cART, even in decentralized primary health care facilities. The study also demonstrates that an excellent virological response to ART is achievable in African children aged less than one year, despite perinatally acquired nevirapine-based resistance mutations. All of these encouraging findings can lead to enhanced survival of HIV-infected children in resource-constrained settings, but important challenges still need to be faced. Early paediatric HIV diagnosis, development of paediatric drug formulations and simplified ARV regimens optimized for infants previously exposed to antiretroviral drugs to prevent MTCT are critical to allow the timely start of appropriate treatment and to improve the quality of life of HIV-infected children. Moreover, considerable progress towards the prevention of new paediatric HIV infections are needed, it is therefore now crucial to speed up the

transition from research on prevention of MTCT to wide-scale practice with innovative, easy to implement and effective interventions addressing the overall risk of MTCT.

References:

1. Chiriboga CA, Fleishman S, Champion S, Gaye-Robinson L, Abrams EJ Incidence and prevalence of HIV encephalopathy in children with HIV infection receiving highly active anti-retroviral therapy (HAART). *J Pediatr.* 2005; 146: 402- 407
2. Gibb DM, Duong T, Tookey PA, Sharland M, Tudor-Williams G, Novelli V Decline in mortality, AIDS, and hospital admissions in perinatally HIV-1 infected children in the United Kingdom and Ireland. *Bmj.* 2003; 327: 1019-
3. Gona P, Van Dyke RB, Williams PL, Dankner WM, Chernoff MC, Nachman SA, Seage GR 3rd Incidence of opportunistic and other infections in HIV-infected children in the HAART era. *Jama.* 2006; 296: 292- 300
4. Judd A, Doerholt K, Tookey PA, Sharland M, Riordan A, Menson E Morbidity, mortality, and response to treatment by children in the United Kingdom and Ireland with perinatally acquired HIV infection during 1996–2006: planning for teenage and adult care. *Clin Infect Dis.* 2007; 45: 918- 924
5. McConnell MS, Byers RH, Frederick T, Peters VB, Dominguez KL, Sukalac T Trends in antiretroviral therapy use and survival rates for a large cohort of HIV-infected children and adolescents in the United States, 1989–2001. *J Acquir Immune Defic Syndr.* 2005; 38: 488- 494
6. Nachman SA, Lindsey JC, Moye J, Stanley KE, Johnson GM, Krogstad PA, Wiznia AA Growth of human immunodeficiency virus-infected children receiving highly active antiretroviral therapy. *Pediatr Infect Dis J.* 2005; 24: 352- 357
7. Patel K, Hernan MA, Williams PL, Seeger JD, McIntosh K, Van Dyke RB, Seage GR 3rd Long-term effectiveness of highly active antiretroviral therapy on the survival of children and adolescents with HIV infection: a 10-year follow-up study. *Clin Infect Dis.* 2008; 46: 507- 515
8. Newell ML, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. *Lancet.* 2004; 364: 1236- 1243
9. WHO 2007 AIDS epidemic update. 2007;
10. Boerma JT, Stanecki KA, Newell ML, Luo C, Beusenbergh M, Garnett GP Monitoring the scale-up of antiretroviral therapy programmes: methods to estimate coverage. *Bull World Health Organ.* 2006; 84: 145- 150
11. Adams LV, Palumbo P The time to treat the children is now. *J Infect Dis.* 2007; 195: 1396- 1398
12. Bolton-Moore C, Mubiana-Mbewe M, Cantrell RA, Chintu N, Stringer EM, Chi BH Clinical outcomes and CD4 cell response in children receiving antiretroviral therapy at primary health care facilities in Zambia. *Jama.* 2007; 298: 1888- 1899
13. George E, Noel F, Bois G, Cassagnol R, Estavien L, Rouzier Pde M Antiretroviral therapy for HIV-1-infected children in Haiti. *J Infect Dis.* 2007; 195: 1411- 1418
14. Janssens B, Raleigh B, Soeung S, Akao K, Te V, Gupta J Effectiveness of highly active antiretroviral therapy in HIV-positive children: evaluation at 12 months in a routine program in Cambodia. *Pediatrics.* 2007; 120: e1134- 1140
15. Kabue MM, Kekitiinwa A, Maganda A, Risser JM, Chan W, Kline MW Growth in HIV-infected children receiving antiretroviral therapy at a pediatric infectious diseases clinic in Uganda. *AIDS Patient Care STDS.* 2008; 22: 245- 251
16. Puthanakit T, Aupibul L, Oberdorfer P, Akarathum N, Kanjanavanit S, Wannarit P Sustained immunologic and virologic efficacy after four years of highly active antiretroviral therapy in human immunodeficiency virus infected children in Thailand. *Pediatr Infect Dis J.* 2007; 26: 953- 956
17. Reddi A, Leeper SC, Grobler AC, Geddes R, France KH, Dorse GL Preliminary outcomes of a paediatric highly active antiretroviral therapy cohort from KwaZulu-Natal, South Africa. *BMC Pediatr.* 2007; 7: 13-
18. Rouet F, Fassinou P, Inwoley A, Anaky MF, Kouakoussui A, Rouzioux C Long-term survival and immuno-virological response of African HIV-1-infected children to highly active antiretroviral therapy regimens. *AIDS.* 2006; 20: 2315- 2319
19. Wamalwa DC, Farquhar C, Obimbo EM, Selig S, Mbori-Ngacha DA, Richardson BA Early response to highly active antiretroviral therapy in HIV-1-infected Kenyan children. *J Acquir Immune Defic Syndr.* 2007; 45: 311- 317
20. Newell ML, Patel D, Goetghebuer T, Thorne C CD4 cell response to antiretroviral therapy in children with vertically acquired HIV infection: is it associated with age at initiation?. *J Infect Dis.* 2006; 193: 954- 962
21. Patel K, Hernán MA, Williams PL Long-term effects of highly active antiretroviral therapy on CD4 evolution among children and adolescents infected with HIV-1: five years and counting. *Clin Infect Dis.* 2008;
22. Resino S, Alvaro-Meca A, de Jose MI, Martin-Fontelos P, Gutierrez MD, Leon JA Low immunologic response to highly active antiretroviral therapy in naive vertically human immunodeficiency virus type 1-infected children with severe immunodeficiency. *Pediatr Infect Dis J.* 2006; 25: 365- 368
23. Puthanakit T, Aupibul L, Oberdorfer P, Akarathum N, Kanjananit S, Wannarit P Hospitalization and mortality among HIV-infected children after receiving highly active antiretroviral therapy. *Clin Infect Dis.* 2007; 44: 599- 604
24. Violari A, Cotton M, Gibb D Antiretroviral therapy initiated before 12 weeks of age reduces early mortality in young HIV-infected infants: Evidence from the Children with HIV Early Antiretroviral Therapy (CHER) Study [Abstract WESS103]. The 4th IAS Conference on HIV Pathogenesis, Treatment, and Prevention Sydney, Australia 2007;
25. Working Group for Antiretroviral Therapy and Medical Management of HIV-Infected Children Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. February 28 2008 2008;
26. Jackson JB, Musoke P, Fleming T, Guay LA, Bagenda D, Allen M Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet.* 2003; 362: 859- 868
27. Lallemand M, Jourdain G, Le Coeur S, Mary JY, Ngo-Giang-Huong N, Koetsawang S Single-Dose Perinatal Nevirapine plus Standard Zidovudine to Prevent Mother-to-Child Transmission of HIV-1 in Thailand. *N Engl J Med.* 2004; 351: 217- 228
28. Arrive E, Newell ML, Ekouevi DK, Chaix ML, Thiebaut R, Masquelier B Prevalence of resistance to nevirapine in mothers and children after single-dose exposure to prevent vertical transmission of HIV-1: a meta-analysis. *International Journal of Epidemiology.* 2007; 36: 1009- 1021
29. Lockman S, Shapiro RL, Smeaton LM, Wester C, Thior I, Stevens AJ Response to antiretroviral therapy after a single, peripartum dose of nevirapine. *N Engl J Med.* 2007; 356: 135- 147
30. Prendergast A, Mphatswe W, Tudor-Williams G, Rakgotho M, Pillay V, Thobakgale C Early virological suppression with three-class antiretroviral therapy in HIV-infected African infants. *AIDS.* 2008;
31. Luzuriaga K, McManus M, Mofenson L, Britto P, Graham B, Sullivan JL the PACTG 356 Investigators A Trial of Three Antiretroviral Regimens in HIV-1-Infected Children. *N Engl J Med.* 2004; 350: 2471- 2480
32. Welch SB, Gibb D When Should Children with HIV Infection Be Started on Antiretroviral Therapy?. *PLoS Med.* 2008; 5: e73-
33. Orne-Gliemann J, Becquet R, Ekouevi DK, Leroy V, Perez F, Dabis F Children and HIV/AIDS. From research to policy and action in resource-limited settings. *AIDS.* 2008;