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ULB

- Acquired by mother to child transmission (MTCT): 20 to 35% risk
- Natural history of infected children
 - 30%: severe immune deficiency by the age of 1 year, poor short term clinical outcome
 - 70%: progressive immune deficiency over years, poor long term clinical outcome

Vaccination of children with HIV infection

Concerns about

- risk/benefits balance
- impaired response or loss of protection

as immunisation programmes are started

- at an age where diagnosis of MTCT is still pending
- at a time marked immune attrition can occur
- at an age where the risk of vaccine preventable illnesses is highest

Concerns regarding vaccines safety in HIV-infected children

- Increased HIV replication due to activation and proliferation of T cells, cytokine release with consequent immunologic deterioration.
 - plasma VL, if increased after vaccination, generally returns to baseline within 6-8 weeks.
 - long term consequences of these repeated bursts of transient viremia unknown
 - illness due to the same pathogen would probably induce a more substantial effect on viral replication and CD4 cell depletion
- Increased risk of adverse events with live attenuated vaccines

Concerns regarding defective vaccine responses in HIV-1 infected hosts

- Defective primary immune response
 - destruction and functional alteration of antigen-presenting cells
 - direct effect of HIV on B cells
 - high level of antigen non-specific hypergammaglobulinemia
 - failure of B cell to proliferate on stimulation
- Defects in generation of immunologic memory
 - Indirect effect of HIV-impaired T-cell help on B cells
 - Defective capacity of B cells to differentiate in response to CD40 and B cell receptor trigger
- Clonal deletion/depletion of memory T and B cells

HIV infection in children in the era of highly active antiretroviral therapy (HAART)

- Reduction to <2% of MTCT
- Early treatment (<3 months old, asymptomatic) associated with marked reduction in the risk of disease progression
- Late treatment (older children with immune depression) results in immune reconstitution

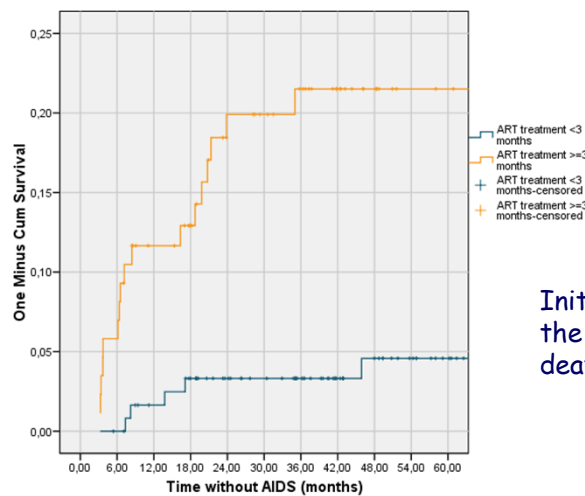
HIV infection in children in the era of HAART

- Clinical situations in industrialized countries
 - Children born in the HAART era, having received early treatment
 - Untreated immune depressed children:
 - late diagnosis in childhood,
 - originating from countries without access to ARV,
 - treatment failures
 - Children with immune reconstitution after HAART

HIV-infected children treated early in life (age <3 months) with HAART

- No or minor clinical progression

Risk of developing AIDS according to age at initiation of ART (<3 months et >= 3 months)



Initiation of therapy after the age of 3 months: AIDS or death risk X 5 (IC: 2.0-12.6)

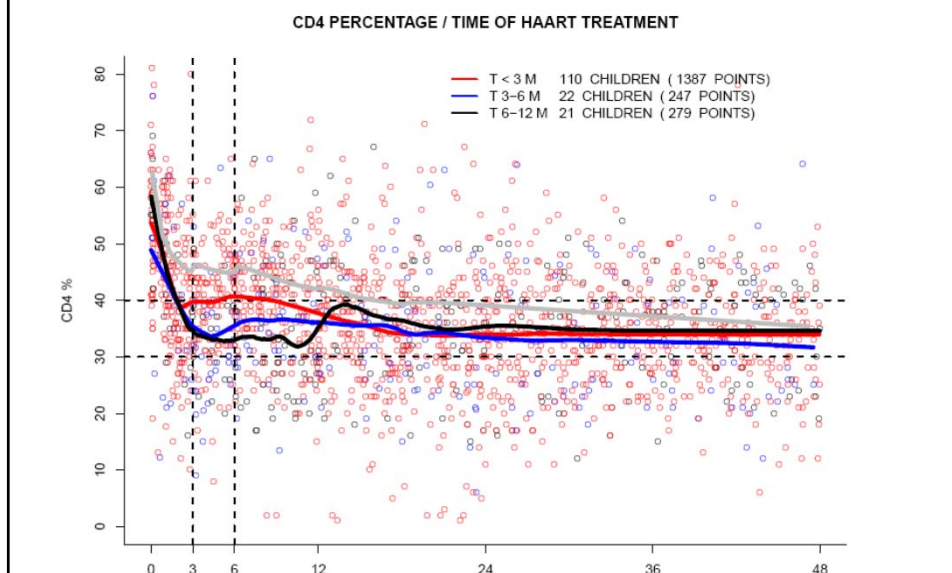
T Goetghebuer, E Haelterman for EIC, 2007

HIV-infected children treated early in life (age <3 months) with HAART

- No or minor clinical progression
- Prevention of CD4 T cell attrition

Immunological and virological outcome in HIV-infected infants according to the age ARV treatment initiation

Goetghebuer et al. CID 2011



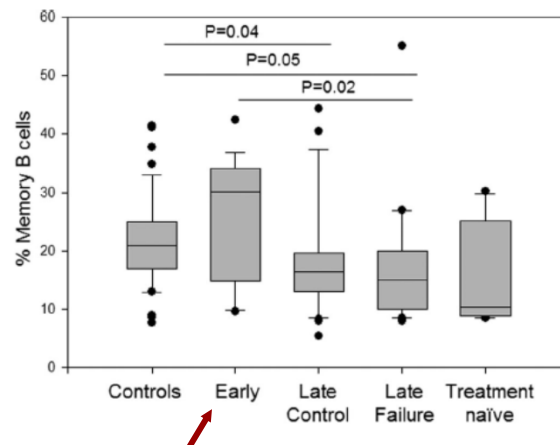
HIV-infected children treated early in life (age <3 months) with HAART

- No or minor clinical progression
- Prevention of CD4 T cell attrition
- Limited information suggests preservation of the normal development of the memory B cell compartment and vaccine responses

Timing of HAART defines the integrity of memory B cells and the longevity of humoral responses in HIV-1 vertically-infected children

Simone Pensieroso^{a,b,1}, Alberto Cagigi^{a,1}, Paolo Palma^{b,c,1,2}, Anna Nilsson^{a,d}, Claudia Capponi^c, Elio Freda^b, Stefania Bernardi^c, Rigmor Thorstensson^e, Francesca Chiodi^a, and Paolo Rossi^{b,c}

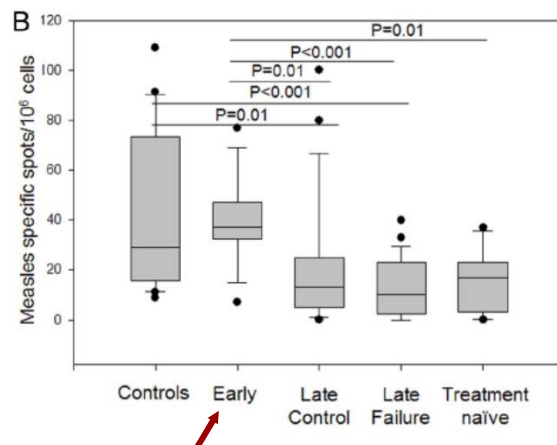
PNAS 2009



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Vaccination of HIV-infected children having received early (age <3 months) antiretroviral therapy

- Vaccination according to standard schedule (including rotavirus vaccine)
- In addition, immunise against
 - Influenza yearly
 - Varicella if seronegative
 - Hepatitis A
- When feasible evaluate serologic response to vaccine - no clear guidelines on this

Untreated immunodepressed HIV-infected children

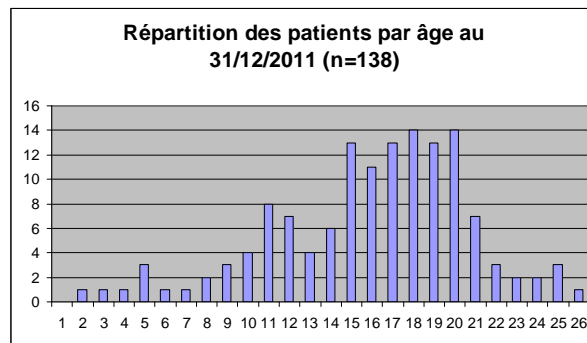
- Poor immune protection against vaccine preventable disease, resulting from
 - A poor primary response
 - A defective generation of memory responses
 - The loss of memory cells
- If severely immune deficient (<15% CD4), at increased risk of adverse events with live attenuated vaccines
- Post-exposure passive immunisation should be proposed if feasible

HIV-infected children with late initiation of HAART

- Immunoreconstitution if suppression of viral multiplication
- Improvement in clinical status

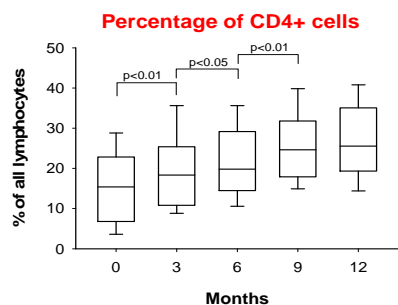
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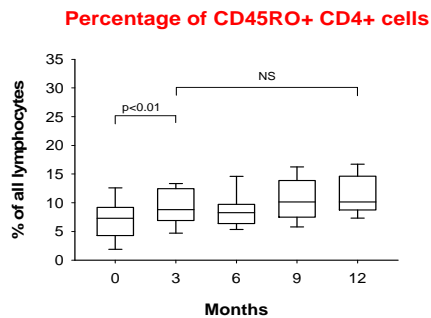
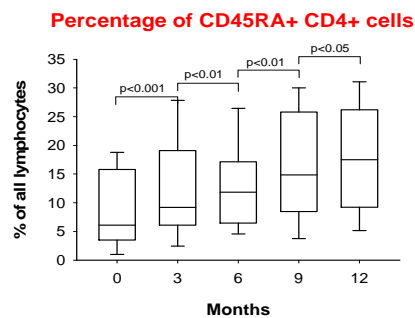
Characteristics of immune reconstitution after HAART in children

- Primarily through the generation of naive T-cells rather than expansion of memory T-cells



Age-related immune reconstitution in HIV-infected children

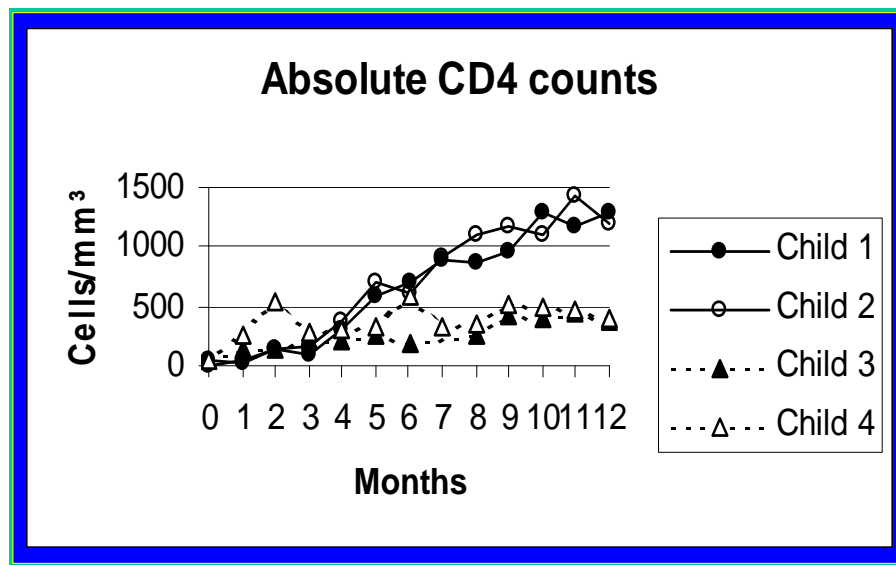
M. Hainaut et al, Ped Infect Dis 2003



Characteristics of immune reconstitution after HAART in children

- Primarily through the generation of naive T-cells rather than expansion of memory T-cells
- The recovery of naive CD4 cells occurs more rapidly at a younger age

Immune restoration on HAART according to age at initiation of therapy



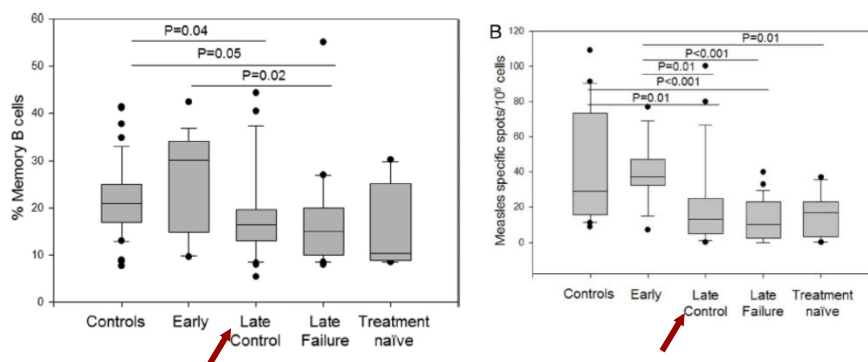
Characteristics of immune reconstitution after HAART in children

- Primarily through the generation of naive T-cells rather than expansion of memory T-cells
- The recovery of naive CD4 cells occurs more rapidly at a younger age
- Memory B cells of HIV-infected children treated later in life are reduced in number and their function is compromised

Timing of HAART defines the integrity of memory B cells and the longevity of humoral responses in HIV-1 vertically-infected children

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Revaccination of HIV-infected children with an history of immune deficiency on HAART

- HAART is unlikely to restore memory T cells for vaccine antigens to which children were exposed before treatment
- HAART should restore the ability of the immune system to respond to vaccine antigens
- As a consequence children on HAART generally have low immunity to vaccines received before starting HAART and would benefit from revaccination against childhood diseases

Revaccination of HIV-infected children with an history of immune deficiency on HAART

- Children vaccinated while on HAART may lose protective immunity faster than children not infected by HIV, probably because of persistent B-cell abnormalities
- As a consequence they should be monitored, if feasible, for the persistence of adequate protective immunity

Gaps in knowledge regarding revaccination of HIV-infected children with an history of immune deficiency on HAART

- The best timing of revaccination after starting HAART
- The effect of age at the start of HAART on response to revaccination
- Responses to primary vaccination after starting HAART
- Necessity for and timing of repeat doses after revaccination while on HAART

Remaining concerns regarding vaccines safety in HIV-infected children in the ARV era

- Live vaccines not to be used if $CD4 < 15\%$ or $200/mm^3$:
 - MMR
 - Varicella
 - Yellow fever
- Live vaccines not to be used if safer inactivated alternative exists :
 - Live intranasal influenza
 - Oral poliomyelitis
 - These vaccines should also not be used in close contacts
- BCG should not be used in low endemicity countries, although risk of adenitis substantially reduced by early ART

Conclusions 1

- HIV-infected children treated early (<3 months of age) and with adequate and persistent response to treatment should
 - be vaccinated according to standard schedule
 - receive, in addition, influenza, varicella and hepatitis A vaccine
- HIV-infected children with immune depression should not be considered to be protected against vaccine-preventable diseases if previously vaccinated. If exposed, other approaches of protection should be used.

Conclusions 2

- In children on HAART with immune reconstitution
 - consider complete revaccination if CD4 cell count nadir was low
 - in addition immunise against influenza (yearly), varicella (if CD4 >15% and seronegative) and hepatitis A
 - responses will be better if CD4 cell counts are restored (>500/ μ L or >25%)
 - expect good antibody and lymphoproliferative responses to revaccination but waning of protective immunity over time
 - adequate levels of protective immunity should be monitored regularly

References

- Menson et al. Guidance on vaccination of HIV-infected children in Europe. *HIV Medicine*, 2012; 13:333-336
- Obaro et al. Immunogenicity and efficacy of childhood vaccines in HIV-1-infected children. *Lancet Infect Dis*, 2004;4:510-18
- Sutcliffe et al. Do children infected with HIV receiving HAART need to be revaccinated? *Lancet Infect Dis*, 2010;10:630-42

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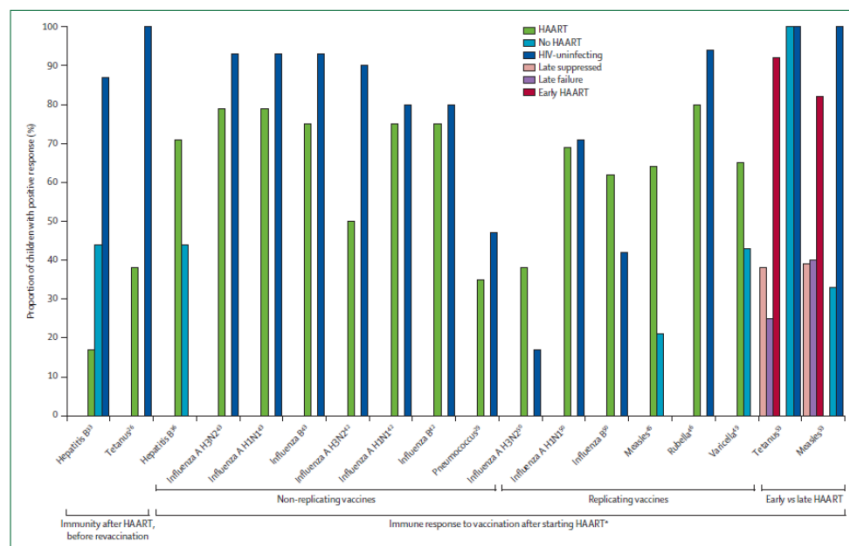


Figure: Comparison of immune responses to vaccination between children infected with HIV on HAART and control groups. Late suppressed=children who were started on HAART after age 1 year in whom viral suppression was achieved. Late failure=children who were started on HAART after age 1 year in whom viral suppression was not achieved. Early HAART=children who were started on HAART within the first year of life. HAART=all children on HAART. No HAART=children infected with HIV who either had no history of HAART or were not in receipt of HAART. HIV-uninfected=children in the HIV-uninfected control group. *Children may have received new vaccines or may have been revaccinated with prior vaccines.

Tetanus and diphtheria

- Antibody responses are reduced in magnitude and durability even on-HAART
- Reimmunization rather than a single booster may be necessary to achieve durable protective anti-TT titres
- Diphtheria is a weaker antigen than TT
- AB titres should be measured 5-yearly to guide boosting

Pertussis

- Lack of clinically relevant correlates of protection
- Those started on HAART after infancy are unlikely to have immunological memory to primary pertussis immunization
- Reimmunization with 3 doses of age-appropriate vaccine preparations is advised up to 6 and perhaps 10 years