
Summary of Evidence

When to start ART in infants

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Search Strategy

- Medline
- Embase
- BMJ Clinical Evidence
- The Cochrane Library
- Trip Database
- SUM search
- Bandolier
- Institute for Clinical Systems Improvement
- CROI 2005-2008 Abstract book
- IAS conferences 2005-2007 Abstract book

Pediatric or Children or Infants

HIV infection

Antiretroviral treatment

**Highly active antiretroviral
therapy**

Drug name

Found: 453 clinical trials, 9 meta-analysis, 152 RCT,
328 review, 257 multicenter studies

Of interest: 70

Studies- Inclusion Criteria

- ✓ Infant subjects
 - ✓ Infants well represented
 - ✓ Outcomes stratified according to age
 - ✓ Early antiretroviral treatment
 - ✓ Early vs deferred
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References selected

- **Chadwick EG**, Capparelli, EV, Yogev K, Pinto J, et al. Pharmacokinetics, safety and efficacy of lopinavir/ritonavir in infants less than 6 months of age: 24 week results. *AIDS* 2008, 22:249-55
 - **Chadwick EG**, Rodman JH, Britto P, Powell C, et al. Ritonavir-based highly active antiretroviral therapy in human immunodeficiency virus type 1-infected infants younger than 24 months of age. *Pediatr Infect Dis Journal* 2005; 24: 793-800
 - **Luzuriaga K**, McManus M, Mofenson L, Britto P, Graham B, Sullivan J. A trial of three antiretroviral regimens in HIV-1-infected children. *N Engl J Med* 2004; 350: 2471-80
 - **Vander Linden D**, Hainaut M, Goetghebuer T, Haelterman E, Schmitz V, Maes P, Peltier A, Levy J. Effectiveness of early initiation of protease inhibitor-sparing antiretroviral regimen in human immunodeficiency virus-1 vertically infected infants. *Pediatric Inf Dis J* 2007; 26:359-361
 - **Chiappini E**, Galli L, Tovo PA, Gabiano C, et al. Virologic, immunologic, and clinical benefits from early combined antiretroviral therapy in infants with perinatal HIV-1 infection. *AIDS* 2006; 20: 207-215.
 - **Faye A**, Le Chenadec J, Dollfus C, Thuret I, et al. Early versus deferred antiretroviral multidrug therapy in infants infected with HIV Type 1. *Clin Infect Dis* 2004; 39: 1692-1698
 - **Pediatric European Network for Treatment of AIDS (PENTA)**. Highly active antiretroviral therapy started in infants under 3 months of age: 72-week follow-up for CD4 cell count, viral load and drug resistance outcome. *AIDS*. 2004; 18:237-245. Updated 5 years outcomes, CROI 2008
 - **European Infant Collaboration group**. Effect of early antiretroviral therapy on the risk of AIDS/death in HIV infected infants: the European Infant Collaborative Study. (Submitted)
 - **Berk D**, Falkovitz-Halpern MS, Hill DW, Albin C, et al. temporal trends in early clinical manifestations of perinatal HIV infection in a population-based cohort. *JAMA*. 2005; 293:2221-2231.
 - **Abrams EJ**, Wiener J, Carter R, Kuhn L, Palumbo P, Nesheim S, Lee F, Vink P, Bulterys M; Perinatal AIDS Collaborative Transmission Study (PACTS) Group. Maternal health factors and early pediatric antiretroviral therapy influence the rate of perinatal HIV-1 disease progression in children. *AIDS*. 2003 Apr 11;17(6):867-77
 - **The Malawi Paediatric Antiretroviral Treatment Group**. Antiretroviral therapy for children in the routine setting in Malawi. *Trans Roy Soc Trop Med Hyg* 2007;101:511-6.
 - **Prendergast A**, Mphatswe W, Tudor-Williams G et al. Early immunological suppression with three-class antiretroviral therapy in HIV-infected African infants. (Submitted)
 - **Violari A**, Cotton M, Gibb D. et al. on behalf of the CHER Study Team. 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. Special session: 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention: Abstract no. WESS103. Updated data still unpublished.
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Outcomes selected

When to start treatment in Infants		
Outcomes	Relative importance (rank 1→9 most critical)	Comments
→ Mortality (1 st year)	9	critical
→ Mortality (5 years)	9	critical
→ Disease progression (clinical definition)	8	critical
→ Severe/LT events	7	critical
→ Major Adverse Events	7	critical
→ Detectable viral load	6	
→ CD4	6	
→ WAZ/HAZ	6	
→ Drug resistance	5	
→ Switch rate	5	
→ Default rate	5	

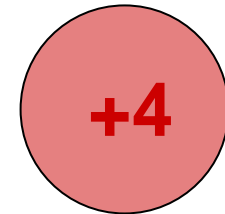
Ranking the evidence...

Comparison: EARLY vs DEFERRED ANTIRETROVIRAL TREATMENT IN INFANTS (\leq 11 MONTHS)							
Outcome: EARLY MORTALITY (<1ST) YEAR							
Population group: HIV INFECTED INFANTS (\leq 11 MONTHS)							
No of studies	Design	Limitations	Consistency	Directness or generalisability	Imprecise or sparse data	Other factors	QUALITY RANK
Outcome:							
Outcome:							
Outcome:							
Outcome:							

Design

- **2 RCT**

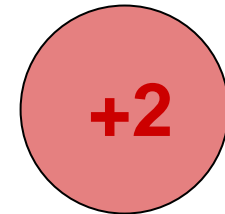
CHER study
Prendergast et al.



HIGH

- **11 “Observational”**

4 trials
6 cohort studies
1 case control study



LOW



Only 3 studies in RLS

Limitations

- Was concealment of allocation to treatment group adequate?
- Were the participants and investigators blinded?
- Was an ITT analysis reported?
- Were all the withdrawals and patients lost to follow up accounted for?
- Was the trial stopped early for benefit?

Prendergast study not blinded:

MINOR LIMITATION

NO DOWNGRADE!

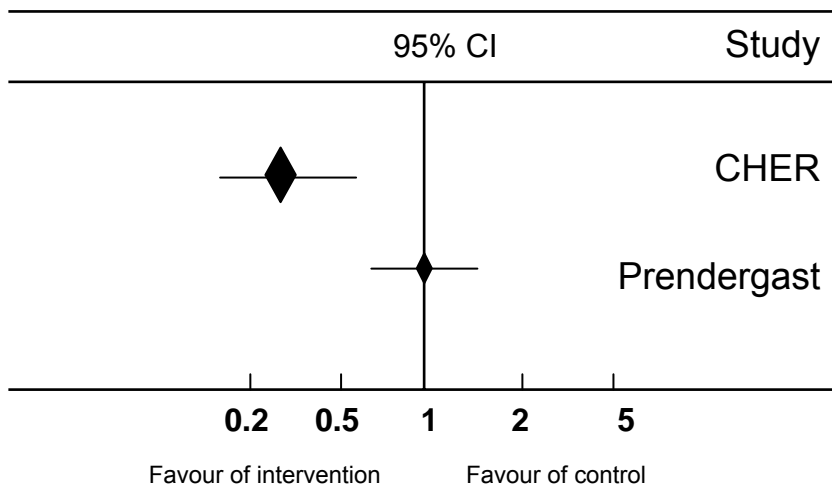


+4



Consistency

- ➔ Consistency refers to the similarity of estimates of effect across studies.
- ➔ To evaluate the degree of consistency of the results of the available studies you should evaluate the **direction** and **size** of the effect.



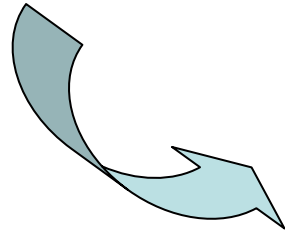
IMPORTANT INCONSISTENCY

DOWN GRADE -1 ! ➔

+3

Indirectness

- ✓ Indirect comparison?
- ✓ Indirect population?



1. Different inclusion criteria between the two studies.
2. 80% were not breastfed in CHER and 60% in P. study. How is it going to be in breastfeeding population?

INDIRECT POPULATION

SOME UNCERTAINTY

DOWNGRADE! -1



+2

Imprecision

- ✓ Sample size → Prendergast study small sample size apparently enough powered
- ✓ Number of events → <300
- ✓ Confidence interval → 95% CI

IMPRECISE DATA

DOWNGRADE ! -1



+1

Other Factors

➤ Publication/reporting bias

➤ Large effects



CHER study was discontinued
because of benefits
HR 0.24 (95%CI)

➤ Dose response curve

➤ Direction of confounding factors



Prendergast study inclusion
criteria are likely to reduce the
effect (reduction in mortality)

UPGRADE!!

+1 plus +1



+3

Observational

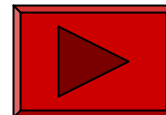
No of studies	Design	Limitations	Consistency	Directness or generalisability	Imprecise or sparse data	Other factors	QUALITY RANK
<p>The majority of the observational studies available were not designed to compare "early initiation" vs "clinical-immunological guided initiation" therefore what follows is mainly an inference from observational studies that assess early treatment outcomes OR clinical-immunological guided initiation outcomes.</p>							
9	Observational 2	All but one were not designed to assess "Early-vs-Deferred" Some limitations -1	Direction and size of the effect appear consistent (all but Malawi) No important inconsistency	Early immunological or clinical guided is not as early in asymptomatic children: Indirect comparison RLS vs RuLS (very different mortality background as well as different breastfeeding approach): Indirect population Major uncertainty -1	Good sample sizes	The confounder is likely to increase the outcome +1	1 VERY LOW QUALITY

Ranking

GRADE

Software

GRADEprofiler 3.2 beta

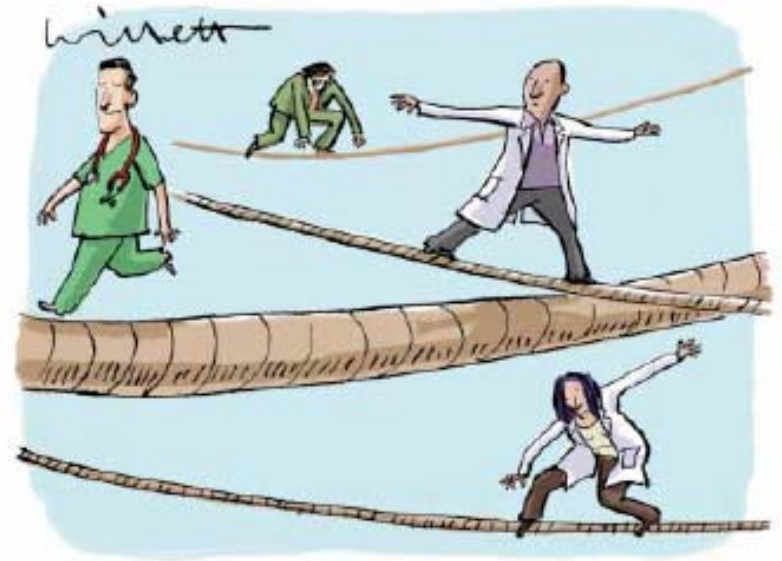


Final Ranking

Starting ART treatment in all infants
≤ 11 months compared with
waiting for clinical or immunological
eligibility
is supported by a

**LOW TO VERY LOW
QUALITY OF EVIDENCE**

Thank you!



“Whenever a theory appears to you as the only possible one, take this as a sign that you have neither understood the theory nor the problem which it was intended to solve”- - Karl Popper
