

Survival of HIV-1 vertically infected children

Authors: Mary-Ann Davies¹, Diana Gibb², Anna Turkova^{2,3}

Authors affiliations:

¹Centre for Infectious Disease Epidemiology and Research, School of Public Health and Family Medicine, Faculty of Health Sciences, University of Cape Town, South Africa.

²MRC Clinical Trials Unit at University College London, Institute of Clinical Trials & Methodology, London, UK.

³St Mary's Hospital, Imperial College Healthcare Trust, London, UK.

Corresponding author

Mary-Ann Davies

Centre for Infectious Disease Epidemiology and Research

Falmouth Building Level 5

University of Cape Town Faculty of Health Sciences

Anzio Rd, Observatory, 7925

Cape Town, South Africa

Telephone: +27 21 4066808

email: mary-ann.davies@uct.ac.za

ABSTRACT

Purpose of review: It is 20 years since the start of the combination antiretroviral therapy (cART) era and >10 years since cART scale-up began in resource-limited settings. We examined survival of vertically HIV-infected infants and children in the cART era.

Recent findings: Good survival has been achieved on cART in all settings with up to ten-fold mortality reductions compared to before cART availability. Although mortality risk remains high in the first few months after cART initiation in young children with severe disease, it drops rapidly thereafter even for those who started with advanced disease, and longer term mortality risk is low. However, suboptimal retention on cART in routine programs threatens good survival outcomes and even on treatment children continue to experience high comorbidity risk; infections remain the major cause of death. Interventions to address infection risk include co-trimoxazole prophylaxis, isoniazid preventive therapy, routine childhood and influenza immunization and improving maternal survival.

Summary:

Pediatric survival has improved substantially with cART and HIV-infected children are aging into adulthood. It is important to ensure access to diagnosis and early cART, good program retention as well as optimal co-morbidity prophylaxis and treatment to achieve the best possible long-term survival and health outcomes for vertically infected children.

Keywords:

combination antiretroviral therapy, survival, children, tuberculosis, malignancy,

Abbreviations

ADC	AIDS-defining cancer
ARROW	Antiretroviral Research for Watoto
cART	combination antiretroviral therapy
CHER	Children with HIV Early antiRetroviral study
CY	child years
DR-TB	Drug resistant tuberculosis
EID	early infant diagnosis
EPPICC	European Pregnancy and Paediatric HIV Cohort Collaboration
LTFU	loss to follow-up
PCV	pneumococcal conjugate vaccine
PMTCT	prevention of mother to child transmission
RCT	randomized controlled trial
RLS	resource-limited settings

Introduction

HIV-related paediatric deaths in 2014 were impressively nearly 50% fewer than in 2004, largely due to reductions in new paediatric infections (58% decrease since 2000) through prevention of mother to child transmission (PMTCT) programs [1,2,3]. Nevertheless, HIV remains a leading cause of child deaths, especially among those >5 years old where the burden of children infected before good coverage of effective PMTCT is substantial [4]. Globally, HIV is the twelfth leading cause of child deaths and among the top five leading causes in high prevalence countries [4]. Optimizing survival of the 2.6 million children living with HIV therefore remains important [3].

Survival of children in the absence of combination antiretroviral therapy

In sub-Saharan Africa approximately half of perinatally infected and a quarter of infants infected through breastfeeding will die before their second birthday, compared to <5% infant mortality in HIV-exposed uninfected infants [5,6,7]. Mortality in untreated perinatally infected infants was so high that in South Africa it caused an increase in all-cause mortality at 2-3 months of age from 1997-2002 [8]. In the United States/Europe mortality in the absence of combination antiretroviral therapy (cART) was lower; 1-year mortality was 6.5-30% in 6-month-old infants [9,10].

Due to survivor bias, mortality without cART decreases markedly in children surviving to two years. The Joint United Nations Programme on HIV/AIDS (UNAIDS) Spectrum model estimates that survival probability to age 20 years without cART increases with timing of infection from 9% (infected at birth) to 24% (infected through breastfeeding), although data to inform assumptions for children aged >2.5 years is limited [11,12,13]. Annual mortality estimates without treatment in USA/Europe ranged from 1.2-12.0% in 2 year olds to 0.2–2.1% in children aged 10 years; CD4 was a poorer predictor of mortality in younger children [10]. In resource-limited settings (RLS), mortality is higher for equivalent age and CD4 values, and CD4 is less discriminatory for predicting mortality than in

well-resourced countries; annual risk varied by CD4% from 2.6-32.5% in 1-2 year olds to 0.6-23.0% in children ≥ 7 years (Figure 1) [10,14]. Viral load was a much weaker predictor of mortality than CD4 count/percent [10].

Impact of cART on survival

Developed country cohorts of mainly older children, initially demonstrated the survival benefit of cART [15]. Subsequently, studies have examined whether there is a survival benefit of immediate versus deferred therapy. The Children with HIV Early antiRetroviral (CHER) randomized controlled trial (RCT) showed 75% mortality reduction by 40 weeks in infants aged < 3 months who started immediate early limited cART (until first or second birthday) compared to deferring until immunologic or clinical progression (defined as WHO 2006 cART initiation thresholds) [16]. However, a smaller RCT showed no mortality benefit of immediate cART at CD4 15-24% versus deferring until a CDC Stage C event or CD4 $< 15\%$ in older Thai children (median age 6.4 years) [17]. Notably, the overall event rate was low and few children were in the younger age groups where the benefit of immediate cART is likely to be highest [17]. Causal modelling analyses that adjust for time-dependent confounding affected by prior treatment showed no mortality benefit of immediate cART in 1-5 year old children, possibly because few children in routine care presented with CD4 count > 750 cells/ μl or CD4% $> 25\%$ (WHO 2010 cART initiation threshold) and a high proportion was lost to follow-up (LTFU) with likely mortality under-ascertainment [18,19]. For children 5-10 years old, causal modelling showed a small but significant mortality benefit of 0.4% (95% Confidence Interval [CI]: 0.02-0.6%) by 5 years of follow-up when starting cART immediately versus deferring until CD4 < 500 cells/ μl (Figure 2) [20].

Survival on cART in routine care

Middle and high income countries: Long-term cohorts from USA and Europe report a ten-fold mortality rate decline over calendar years (7.2-8.2/100 child years (CY) in the late 1990s vs 0.6-0.8/100 CY in 2000-2006), with plateauing thereafter [21,22]. In these cohorts, 72-83% of children received cART [21,22] and 6-10 year survival probabilities during the cART era were >94-98% [22,23,24]. The European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) reported nearly ten-fold higher mortality in the first 6 months on cART (2.5/100 CY vs 0.27/100 CY) compared to later. After the first 6 months on cART, children <2 years old and adolescents ≥14 years had higher mortality versus 5-<14 year olds (aHR [95%CI] <2 years: 3.7 [1.2-10.8]; >14 years: 1.8 [0.9-3.7]). Mortality was 50% lower in high versus middle income (Thailand and Eastern Europe) countries [25]. Mortality was only 5% by nearly 6 years median follow-up in an EPPICC study of infants starting cART (median age <4 months) [26]. Despite overwhelming cART success, mortality remains nearly 30 times higher than in the general population [22].

Resource limited settings: There are >80 publications of survival on cART from a range of RLS [27,28,29,30,31,32], including trials, cohorts and national programs, with increasing follow-up durations. Clinical trials with high retention and adherence demonstrate good survival on cART, especially after the first 6 months, even in peripheral clinics [16,33,34,35,36]. In the Antiretroviral Research for Watoto (ARROW) RCT of different monitoring strategies, one-year mortality on cART ranged from 1.3%-10.1% in children aged 4-15 years with CD4 ≥100 and <50 cells/μl respectively [36]. Corresponding values for children 4 months to 3 years were 9.1% (CD4% <5%) and 2.8% (CD4% >10%) (Figure 3) [36]. Although mortality was high in the first 3 month of cART, it declined rapidly to <5% by one year for all age and CD4 strata [36]. The third Children with HIV in Africa – Pharmacokinetics and Adherence of Simple ARV Regimens trial (CHAPAS 3) of different nonnucleoside reverse transcriptase inhibitor-based first-line cART regimens reported similar low

mortality of 4.0% by 2.3 years median follow-up [35]. In CHER, mortality was 9% by median follow-up of 4.8 years in infants initiating immediate cART at <3 months old [33].

Routine cART programmes in RLS suggest poorer and more variable survival than trials, partly due to lower retention and programmatic or adherence-related challenges, including drug stockouts.

Indeed, better survival in children with greater adherence to placebo in a co-trimoxazole prophylaxis trial suggests that good adherence may be a surrogate for overall better child care [37]. Mortality by 2 years or more on cART from routine programs in RLS ranges from 3.7 to 29% [38,39] and rates vary from 1.3-6.0/100 CY [40,41]. Children still initiate treatment with severe disease with mortality remaining higher in the first year (Figure 3)[42]. Young age and severe disease are consistently associated with higher mortality [28,31,43,44,45,46]. Prognostic models for RLS predict one-year mortality on cART ranging from <2% (children 5-10 years, no severe disease, CD4%>10%) to >45% (infants, severe disease, CD4<5%)[47,48]. Nevertheless, nearly 60% of children in the prognostic model study cohort had characteristics predicting low (<5%) 1-year mortality [47].

Importantly, there are concerns about survival on cART and interpreting outcomes of routine programs in RLS. First, routine cohorts frequently report high LTFU (>10%) with likely unascertained mortality [38,49,50,51]. In Malawi, mortality was 11% among children traced from three weeks after a missed visit [52]; using longer durations to define LTFU, mortality was nearly 40% among LTFU [38]. Second, many programs have high transfer rates, particularly in recent years with decentralisation of cART programmes [23,28,31,53,54,55,56,57,58]. While decentralization may contribute to better retention [54,59], limited ability to track outcomes after transfer hampers long-term survival assessment. Additionally, unrecorded transfers to another facility add to high LTFU rates with underestimation of survival at the program level [52]. Third, some programs report worsening outcomes [39,45,54]; from 2005-2008 in Cote d'Ivoire, one-year mortality and LTFU increased from 3% to 11% and 2% to 23% respectively [45]. In rural Mozambique mortality and LTFU were 16-24% and 25-70% respectively with substantial heterogeneity between districts [39]. Finally, infants

remain vulnerable with poor outcomes in routine care in RLS despite WHO recommendations for universal cART since 2010 [60]. Although more infants have initiated cART with less severe disease [61,62,63], a substantial proportion still start treatment late [64,65]. In Southern Africa, despite significant improvements after 2010, one-year mortality (13%) and LTFU (19%) remained high overall [61]. While annual mortality on cART was lower in Botswana (4.6/100CY), only 60% of infants initiated treatment [56]; 39% of all HIV-infected infants died [56].

Infant survival requires early infant diagnosis (EID) with rapid cART initiation. In 2014, only 50% of HIV-exposed infants were tested by age 2 months; only a third of those diagnosed started cART promptly [66,67,68]. At best, most infants initiate treatment between 12-14 weeks, after the infant mortality peak [8,69]. Innovative approaches (point-of-care assays; adding birth EID) may accelerate diagnosis and cART initiation; but further implementation research is needed [69,70,71,72,73].

With increasing coverage of PMTCT, most new pediatric infections are in infants whose mothers did *not* access PMTCT; hence not identified through post-PMTCT EID programs. Identifying children missed by EID is critical, and remains challenging [74]. The proportion of children newly diagnosed through provider-initiated testing in hospitals or malnutrition centres is high (6%-22%). Testing strategies outside PMTCT programmes need to be strongly emphasized [72,75,76,77,78,79,80,81,82].

Models of care to optimize real world survival on cART

Given WHO 2015 recommendations to start everyone on cART [83] and UNAIDS targets (90% of HIV-infected people are diagnosed, 90% retained on cART, with 90% virologic suppression [84]), focus is shifting from “when to start” to achieving optimal treatment access and outcomes. Encouragingly, decentralization of pediatric HIV care has increased with good outcomes [85]. Survival and retention may be better for children treated nearer their homes, especially with community support

[38,41,50,86]. Facilities with better quality of care [29] and high health worker morale report better outcomes, particularly lower LTFU [45]. Good outcomes in Rwanda ($\leq 5\%$ one-year LTFU or mortality) were ascribed to staff mentoring and decentralization [59].

Comorbidities that reduce survival in HIV-infected children

Even with cART, comorbidity incidence (including tuberculosis, childhood infections and malignancies) is higher in HIV-infected than uninfected children [87,88,89,90,91]; infections still predominate as causes of death [21,22,92,93]. AIDS-defining infections have declined, but non-AIDS defining conditions (sepsis; pneumonia) remain relatively stable [21,22,92,93,94]. The contribution of non-infectious conditions (metabolic syndrome, renal, liver and cardiovascular disease) in children is not clear.

Tuberculosis: In 2015, global estimates showed that up to 30% of HIV-infected child deaths may be tuberculosis-related [95]. HIV-infected children are more than twice as likely to die from tuberculosis compared to HIV-uninfected children [96,97,98]; within pediatric HIV cohorts tuberculosis increases mortality risk 2-4 times [99,100]. Infants are at the highest risk with nearly 30% mortality with bacteriologically confirmed tuberculosis [101]. While cART reduces tuberculosis-related mortality substantially [99,102], delays in cART initiation remain challenging [100,103]. Unlike in adults [104,105], there are no RCTs on the optimal timing of cART initiation in tuberculosis co-infected children. Observational studies showed better survival with starting cART within 2 months (or less) of tuberculosis therapy compared to later [106,107,108], but it is unclear whether early cART improves survival in co-infected children without severe immunocompromise.

Treatment outcomes for children with drug resistant tuberculosis (DR-TB) vary widely. A South African study of DR-TB (55% of children HIV-infected) found 20% overall mortality [109], while a systematic review found mortality was twice as high in HIV-infected compared to uninfected children (11.5% vs. 6%) [110].

Malignancy: Cancer is ≥ 5 -10 times more common in HIV-infected compared to uninfected children [87,91,111,112,113]. In the cART era, AIDS-defining cancers (ADCs) have reduced dramatically, but non-ADC rates remain unchanged or increased [87,91,114]. Treatment outcomes are worse in HIV-infected vs HIV-uninfected children [111]. In South Africa >80% of HIV-infected children with cancer presented with advanced disease; only a third survived. Survival was higher (57.8%) if treated with cART and chemotherapy [115]. In Uganda, half of HIV-infected children with cancer died or were LTFU; mortality was at least three-fold higher than the clinic crude mortality rate (33% vs 5-10%) [116]. The increasing rates of some non-ADCs in the cART era is likely due to increased life expectancy allowing development of these cancers, however the impact of long-term cART has been debated. With vertically infected children surviving into adulthood there is growing concern about malignancy risk and associated mortality.

Interventions other than ART to improve survival in HIV-infected children

Co-trimoxazole

Use of cotrimoxazole nearly halved all-cause mortality in cART-naïve Zambian children despite high levels of bacterial resistance [117,118]. The ARROW trial found fewer hospitalizations when continuing co-trimoxazole in Ugandan/Zimbabwean children after 2 years of cART, hence WHO recommends continuing prophylaxis until adulthood if prevalence of bacterial infections and malaria is high [119,120]. Co-trimoxazole appears protective against incident tuberculosis in HIV-infected adults and possibly children [89,121] and reduces mortality and morbidity in people with HIV/tuberculosis [122,123]. Adding co-trimoxazole to anti-tuberculosis treatment has been successfully implemented in high tuberculosis burden countries with 87% coverage in co-infected patients [95].

Evidence of survival benefit of **isoniazid preventive treatment** (IPT) in HIV-infected children is conflicting. IPT halved all-cause mortality in an RCT including mostly cART-naïve children [124]; a subsequent cohort study demonstrated additional benefit of IPT on tuberculosis incidence in children on cART [125]. Contrastingly, an RCT in infants showed no mortality or tuberculosis prevention benefit of pre-exposure IPT [126], however infants were screened for tuberculosis exposure at every visit, with prompt post-exposure IPT. While this approach is unlikely to be feasible in routine care where uptake of post-exposure IPT has been shown to be very low [127,128], pre-exposure IPT for children in HIV clinics can have high uptake and treatment completion [129]. Although WHO has recommended pre-exposure IPT since 2004, coverage remains disappointingly low [95]. Barriers to IPT implementation include exaggerated fear of resistance development [130], unavailability of single entity isoniazid formulations in RLS and concerns about increased pill burden affecting cART adherence [131]. A scored fixed dose combination of isoniazid, vitamin B6 and co-trimoxazole was highly acceptable to adults and children >5 years in the Reduction of EARly mortalITy in HIV-infected Adults and Children Starting Antiretroviral Therapy trial [132] and could help overcome universal IPT implementation barriers; a half-strength scored dispersible tablet is needed for younger children.

Routine immunization

Since common childhood infections remain the leading causes of death in HIV-infected children, routine childhood immunisations may improve survival [94]. *Haemophilus influenzae*, pneumococcal conjugate vaccines (PCV) and seasonal influenza vaccinations prevent severe infections in HIV-infected children [88,133]. Influenza and PCV may reduce tuberculosis-related mortality as influenza epidemics lead to increased hospitalizations for invasive pneumococcal disease and pulmonary tuberculosis [88]. Further, PCV appeared protective against tuberculosis[134]. The high prevalence of rotavirus gastroenteritis in HIV-infected infants in RLS indicates a potential survival benefit of vaccination [135,136]. Rotavirus vaccine efficacy is lower in high-mortality countries but disease

burden is higher, hence the absolute benefit is large [137]. A package of preventive strategies addressing common co-morbidities should be considered to optimize survival.

Maternal health, socio-economic status and treatment of OI in adults

Several studies show links between maternal and infant survival - maternal HIV/AIDS or tuberculosis-related death reduce child survival [138,139,140]. Maternal cART protected against under-five mortality; death rates in children of HIV-infected mothers were reduced to levels of children of HIV-uninfected mothers [141]. Maternal health is therefore important and “Option B+” (lifelong cART for pregnant/breastfeeding women) offers key child survival benefit.

Conclusion

Pediatric survival has improved substantially with cART; with the additional success of PMTCT programs in preventing new infant infections, focus can start to shift from averting deaths to optimizing health for adolescence and adulthood. Nevertheless, there remain substantial survival gains to be made especially in RLS by strengthening health systems and improving models of decentralised HIV care to ensure access to diagnosis and early cART at all levels of the health system, continuous drug supplies, better adherence and retention, prophylaxis and treatment for co-morbidities, as well as promoting maternal survival including maternal cART.

Key points

- Good survival has been achieved during the cART era in all settings with up to ten-fold mortality reductions compared to before cART availability.
- Immediate cART has been shown to improve survival compared to deferring until clinical or immunological progression in infants in the CHER RCT, and in children aged 5-10 years in causal modelling analyses of cohort data.
- Since mortality risk remains high in the first few months after cART initiation in young children with severe disease, it is important to improve access to early diagnosis and cART before disease progression; nevertheless mortality drops rapidly after the first 6 months on cART even for those who started with advanced disease, and longer term mortality risk is low in all settings
- Routine programs providing pediatric cART in resource-limited settings frequently report high loss to follow-up which may include unascertained mortality and suboptimal retention on cART threatens potential good survival outcomes.
- HIV-infected children continue to experience high comorbidity risk even when treated with cART with infections remaining the major cause of death; interventions shown to reduce infection risk and related mortality include co-trimoxazole prophylaxis, isoniazid preventive therapy, routine childhood and influenza immunization and improving maternal survival.

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Conflicts of interest

None

Figures:

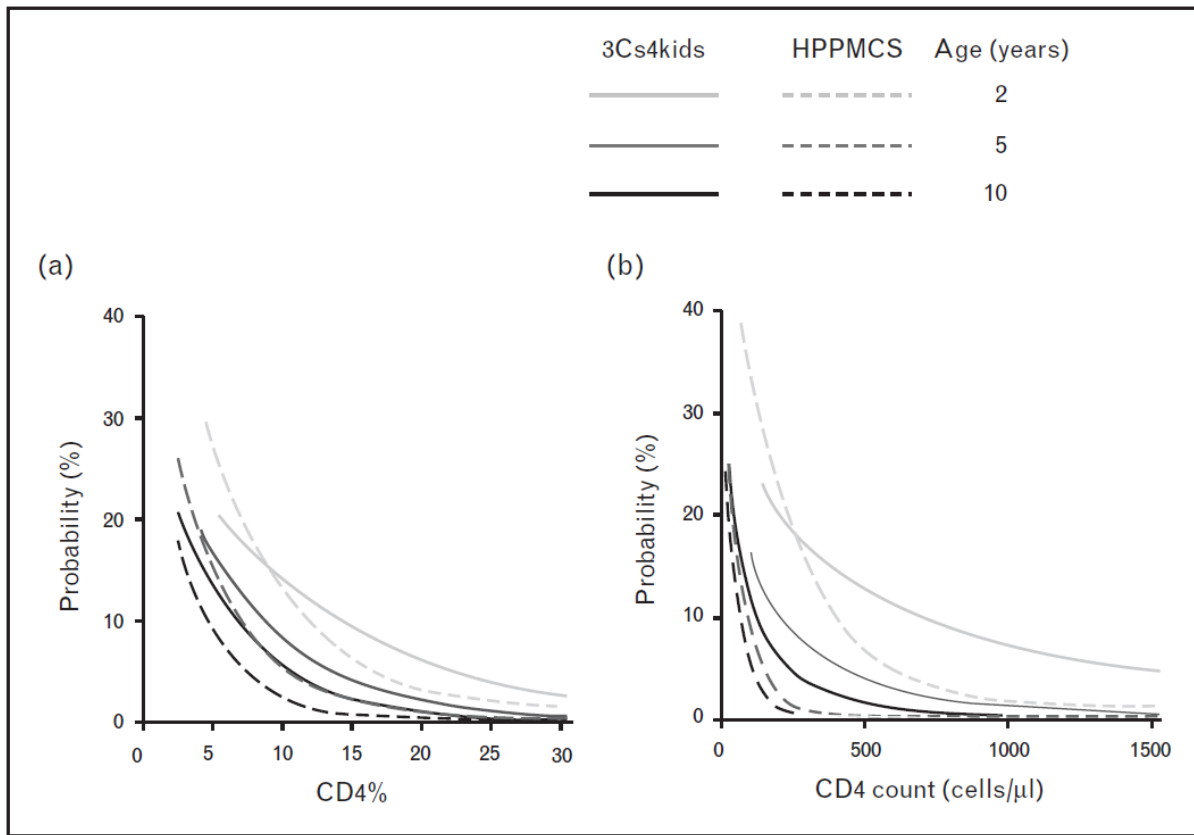


Figure 1. Estimated risk of death within 12-months in Cross Continents Collaboration for Kids

(3Cs4kids) (low and middle-income countries) compared with HIV Paediatric Prognostic

Collaborative Study (HPPMCS)(USA and Europe) according to age and: (a) CD4% (b) CD4 cell count.

Estimates in 3Cs4kids apply to a child receiving co-trimoxazole prophylaxis. Curves are truncated at

the 5th and 95th centiles for each age. Source: Cross Continents Collaboration for Kids (3Cs4kids)

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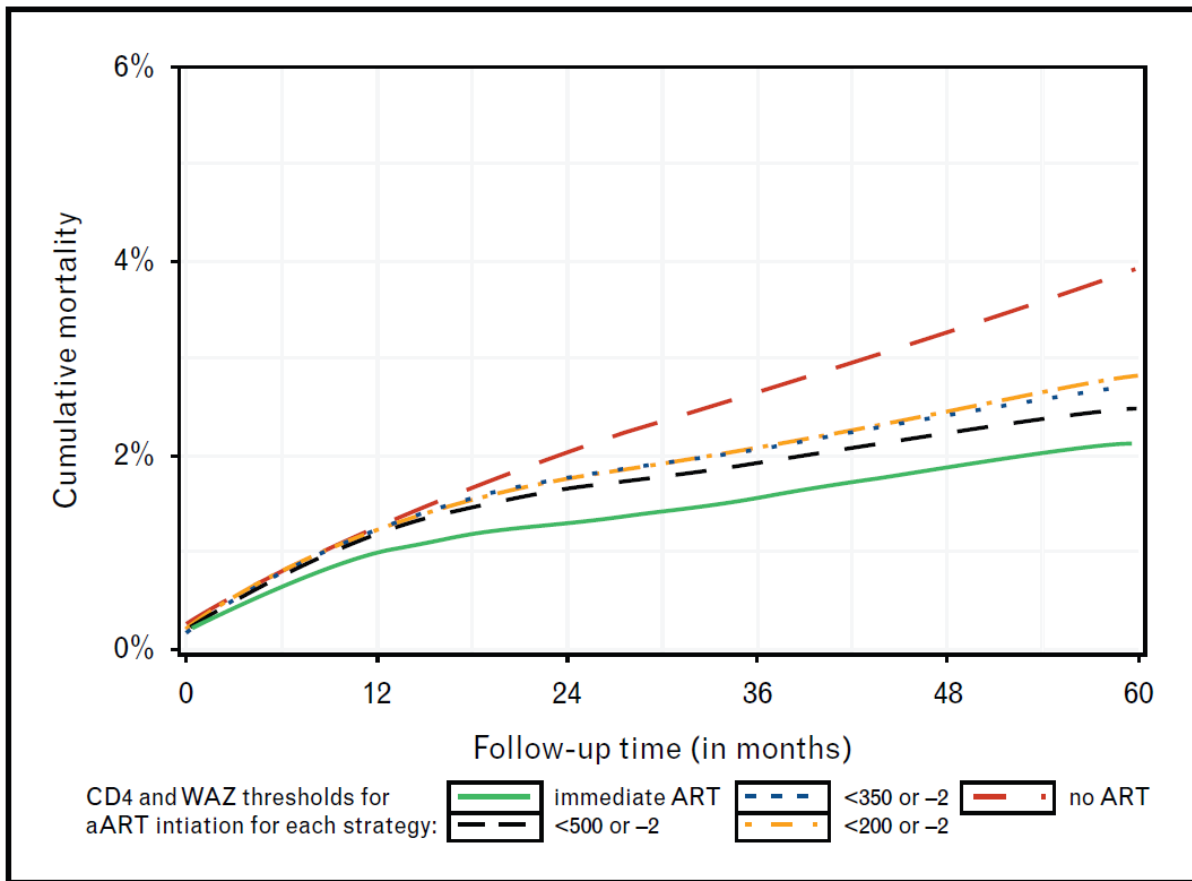


Figure 2. Estimated mortality from enrolment into HIV care in children aged 5-10 years at enrolment with initial CD4 >500 cells/ μ l from Southern Africa, West Africa and Europe comparing different cART initiation strategies as follows: immediate cART; cART at CD4 < 500 or weight-for-age z-score (WAZ)<-2; CD4 <350/WAZ <-2; CD4 <200/WAZ <-2; no cART. The mortality difference between immediate cART (solid green line) and deferring cART to CD4 >500 cells/ μ l or WAZ<-2 is 0.4% (95%CI: 0.02-0.6%). Mortality is estimated from g-computation to adjust for time-dependent confounding affected by prior treatment of CD4 count, CD4 percent and weight-for-age z-score.

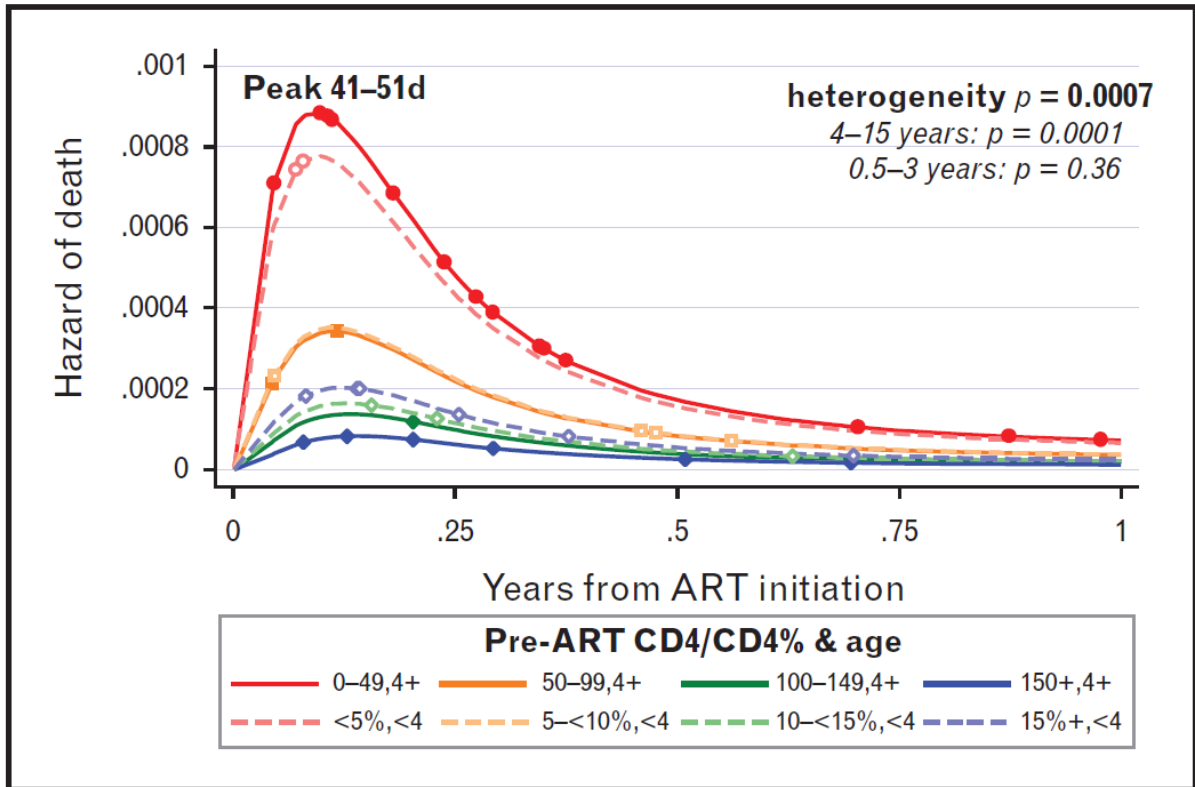


Figure 3. Daily risk of death through 1 year on cART in children aged 4 months to 15 years in the ARROW RCT according to age and pre-cART CD4 count or percent using flexible parametric models on log-normal scale with 1 interior knot. Points show times when deaths occurred. Source: Walker AS, et al. Mortality in the year following antiretroviral therapy initiation in HIV-infected adults and children in Uganda and Zimbabwe. *Clinical Infectious Diseases*. 2012; 55:1707-18.

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