Early antiretroviral therapy in HIV-infected infants: can it lead to HIV remission?

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Interventions to prevent mother-to-child HIV transmission have been extremely successful, but new HIV infections continue to occur in infants. Strong evidence indicates that combination antiretroviral therapy (ART) for treatment should be started in HIV-infected infants to prevent early morbidity and mortality. In 2013, the report of the Mississippi baby, who was started on ART within 30 h of life and maintained off-treatment remission for 27 months before HIV was once again detectable, generated renewed interest in very early ART initiation. The case stimulated interest in the possibility of HIV remission, which we define as maintenance of plasma viraemia below the threshold of detection in the absence of ART, after early treatment initiation. The possibility of HIV remission elicits much hope, given that children with HIV infection currently face a lifetime of treatment. The potential for early ART to lead to HIV remission in infants can be thought of in terms of six factors: rapidity of viral suppression with very early ART; initial viral suppression rate with early ART; later virological control after early treatment; the effect of early treatment on the viral reservoir size; outcomes of randomised trials of structured treatment interruption; and the likelihood of viral rebound in neonates after ART cessation. Review of existing data suggests that achieving long-term remission off treatment remains elusive, and concentrated attention and commitment of the scientific community is needed to investigate the factors that might help to reach this goal.

Introduction

Despite tremendous success in prevention of mother-to-child HIV transmission, new HIV infections continue to occur in infants as a result of several factors, including the high prevalence and incidence of HIV in women of childbearing age, incomplete implementation of interventions for prevention of mother-to-child HIV transmission, and suboptimal timing of and adherence to antiretroviral therapy (ART). In 2016, more than 150 000 children became infected with HIV.[1]

Strong evidence indicates that combination ART should be initiated in HIV-infected infants early in the first year of life to reduce morbidity and mortality. In 2008, there was a shift away from initiating ART in children on the basis of clinical and immunological status (as in adults at the time) to starting ART in all children younger than 1 year of age as soon as they were diagnosed, regardless of clinical and immunological status.[2] Support for this shift was largely due to results from the South African Children with HIV Early Antiretroviral Therapy (CHER) randomised trial,[3,4] which showed a reduction in mortality by 76% among infants randomised to immediate ART compared with those who were given deferred ART. Data from observational studies also supported this approach.[5–7] In subsequent treatment guidelines, the advice to initiate ART irrespective of clinical and immunological status was extended to all children younger than 5 years in 2013, and to all children in 2016.[8–10] Despite the recommendation to treat all early, the optimal timing of when to initiate treatment in infants remains unclear.

A pragmatic consideration necessary for early ART initiation is early diagnosis. Diagnosis in infants is reliant on virological testing, specifically HIV-1 DNA PCR tests.[10–12] Enrolment into the CHER trial was largely reliant on routine diagnostic testing, which was scheduled at that time around 4–6 weeks of age. Infants enrolled into the CHER trial were a median of 7·4 weeks (IQR 6·6–8·9) of age at enrolment. Thus, the findings from this trial cannot directly address the question of very early ART initiation. For the purpose of this Review, we define very early as within the neonatal period (ie, first 28 days of life).

In 2013, the report of the Mississippi baby generated renewed interest in the timing of ART initiation for infants. This child was started on ART within 30 h of life and maintained off-treatment remission for 27 months (from 18 months to 45 months of age) before HIV was once again detectable.[13,14] The case resulted in a critical shift in thinking, stimulating interest in the possibility of HIV remission (figure 1). We use this term to refer to maintaining plasma viraemia below the threshold of detection in the absence of ART.[15–17] In this Review, we assess the current published data in support of the possibility for early ART to lead to HIV remission in infants.

Viral suppression with very early ART

Evidence from studies in the era before use of effective antiretroviral regimens for prevention of mother-to-child HIV transmission and treatment indicates that, without treatment, plasma HIV RNA counts can be high in the postnatal period and peak at a median of 100 000–1 000 000 copies per mL in the first 2–3 months.[18–20] After this peak, without treatment, viraemia decreases in some infants quickly to reach a viral set point, but in others it continues to decrease gradually for months or years.[21,22] Theoretically, initiation of ART before this viral peak might favourably influence the viral reservoir. In addition, earlier initiation reduces the period of viraemia for the infant.

The extent of viral suppression 6 months after starting ART was examined in 13 neonates who were initiated on

ART within 28 days of life (appendix p 1).[13,14,23–30] ART was started in ten of these neonates within 48 h of life.[13,23–25,29,30] All but one infant were initiated on nevirapine plus a nucleoside reverse transcriptase inhibitor backbone of zidovudine and lamivudine. The other was initiated on ritonavir-boosted lopinavir.[26] The overall pattern of viral load decline was biphasic: an initial rapid phase-one decline followed by a slower second-phase decline (figure 2).[31,32] Viral suppression to below the detectable limit was achieved in 12 of 13 neonates by 6·2 months of age (mean 2·7 months). One neonate had low level of viraemia in the first year despite reports of excellent adherence, and eventually viral load was suppressed to less than 20 copies per mL at 18 months and target not detected at 20 months.[25]

Overall, these data seem to support the notion that initiation of ART in the neonatal period can successfully achieve viral suppression by 6 months of age. However, the generalisability of this pattern is questionable. The true denominator of HIV-infected neonates treated is unclear. We suspect the published viral load data are from a highly selective group of neonates. For example, one study[23] only published data on the four infants who achieved virological suppression. Studies of the effects of early ART initiation on viral load in larger and more representative cohorts of HIV-infected neonates, with clear descriptions of denominators, are urgently needed.

Initial viral suppression with early or late ART

More data exist on early initiation of ART if the focus is expanded beyond the neonatal period to throughout infancy. Two trials[3,4,33] done in South Africa randomised the timing of ART, allowing for a comparison of early versus deferred initiation of ART. The first trial (CHER)[3,4] did not routinely monitor viral loads or report on rates of initial viral suppression in their randomisation groups. Reported rates of later viral suppression of the cohort are further complicated by planned treatment interruptions in the early ART group.[34] In the second trial,[33] which randomised 63 infants to immediate (median 1·0 month) or deferred (median 4·7 months) initiation of a four-drug regimen, the viral load was suppressed to less than 400 copies per mL in 78% of the immediate group and 85% of the deferred group on their first-line regimen by 12 months after starting ART. The study noted that the time for the viral load to reach less than 50 copies per mL was not significantly different between the groups.

Of 23 studies that assessed initial virological responses when ART was initiated in infancy (appendix pp 2–3),[5,6,28,35–53] most reported initial viral suppression at 6 months after starting ART, with a few exceptions.[28,33,38,41,49] Stratified data were extracted if the study specifically presented stratified results among infants starting ART at younger than 12 months of age (eg, by age group or treatment group). The reported percentage of children who achieved initial viral suppression varied greatly, ranging from 19% to 81%.[37,52] An ecological plot of median age at ART initiation by the percentage of infants with initial viral suppression at 4, 6, or 12 months after starting ART by study shows that, on a group level, no clear association exists between median age at ART initiation and viral suppression rates (figure 3).

A few studies provided a direct comparison of initial viral suppression between infants who started ART early and those who started late, with no consistent findings.[6,37–39,50] A European observational study[37] reported a better response in children started early (<3 months) than in children started 3–12 months of age. Similarly,

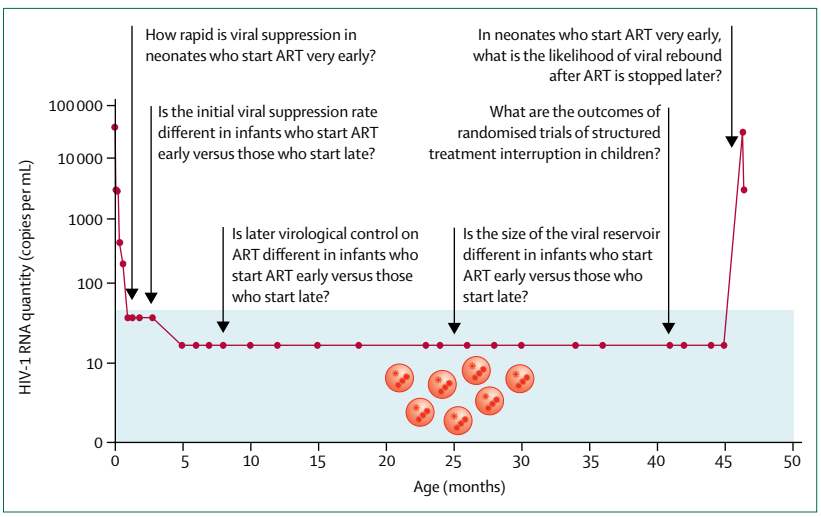

Figure 1: **Six questions developed to help inform whether early antiretroviral therapy (ART) might be able to lead to HIV remission in some infants, as in the case of the Mississippi baby[13,14]**

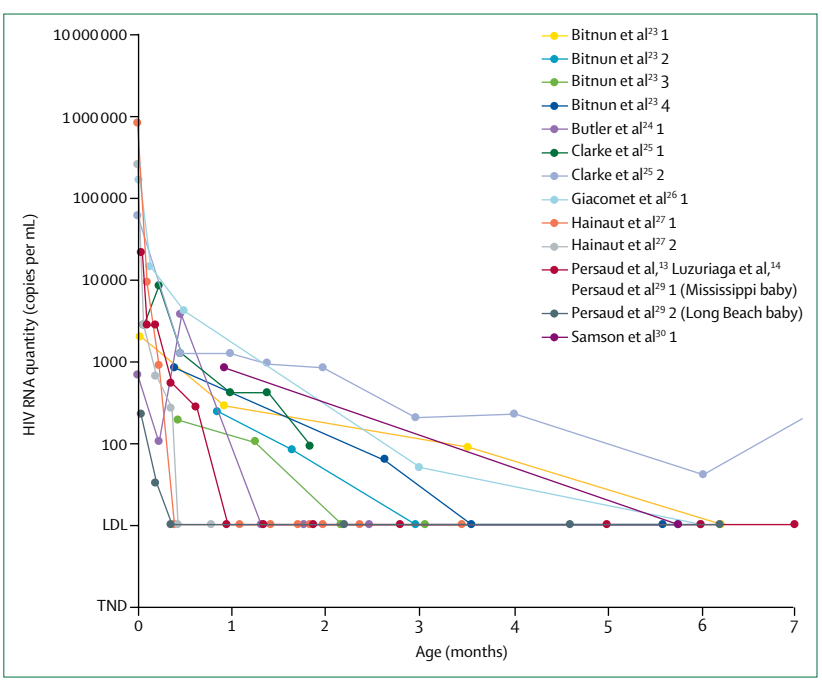

Figure 2: **Viral loads in neonates from initiation of combination antiretroviral therapy to over 6 months (n=13)**
LDL=lower detection limit. TND=target not detected.

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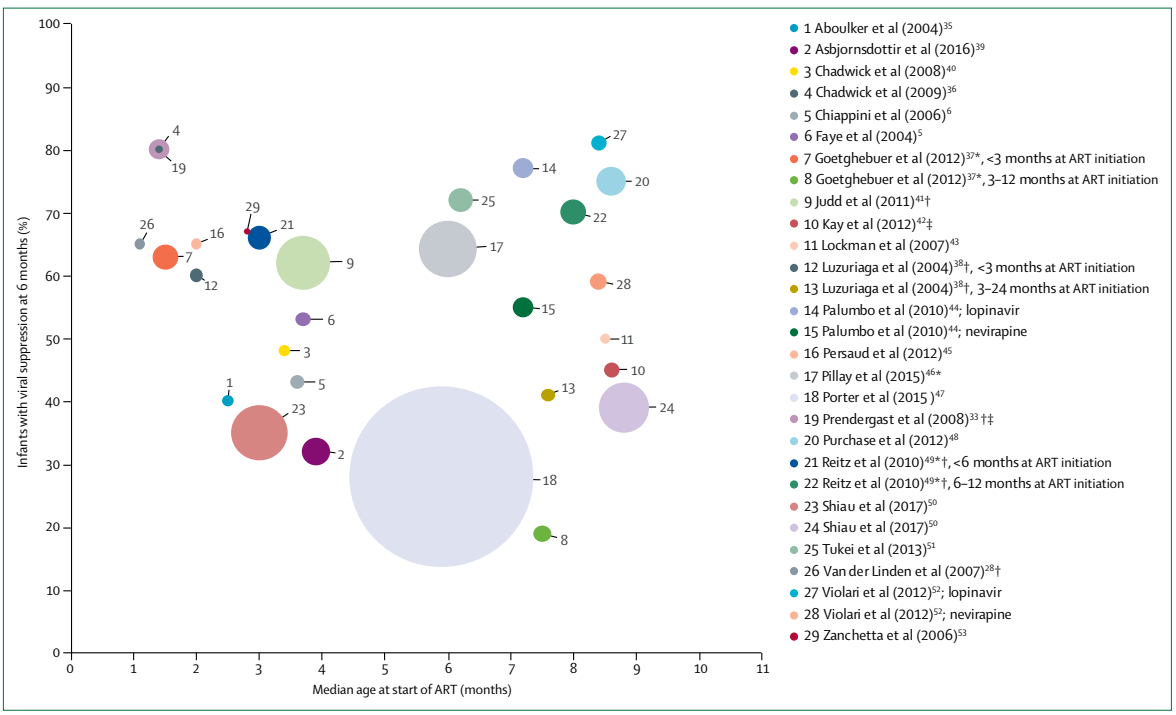

Figure 3: **Ecological study plot of median age at antiretroviral therapy (ART) initiation and percentage of infants with viral suppression at 6 months after starting treatment**

The size of the circle reflects the size of the study. *Median age at ART initiation was estimated as the midpoint of the range. †Did not have 6-month suppression rate. ‡Has children older than 12 months.

a multicentre Italian case-control study[6] found better suppression among infants starting ART early (<6 months); however, their comparison group had a wider age range, including those who started ART at 6–52 months. A randomised trial of ART initiation in infants done in the USA (PACTG 356)[38] that stratified according to age (<3 months or 3–24 months) did not find different short-term viral suppression at 16 weeks or 48 weeks between groups, but suppression to less than 400 copies per mL at week 200 did differ. Data from our group in South Africa indicated no difference in initial suppression to less than 50 copies per mL by 6 months for children in whom ART was initiated before 6 months (early) versus 6–24 months (late).[50] One study[39] with an older comparison group found that infants (median age 3·9 months) were less likely than children (median age 4·8 years) to suppress viral load to less than 250 copies after 6 months of ART.

Taken together, data on viral suppression and rate of initial viral suppression indicate that infants in whom ART is initiated very early (in the neonatal period) can achieve viral suppression, but there is not strong evidence to show that initial viral suppression is higher in infants who start ART early (<6 months) than among those who start later.

Virological control after early ART

Understanding of long-term virological control is important to determine how long an infant should be suppressed on ART before treatment could be interrupted to achieve HIV remission. Studies[54–57] that compared later virological control between infants in whom ART was initiated early versus later show reasonably consistent results of better long-term viral suppression on ART in infants who start early. A study[57] of 20 infants who participated in the CHER study compared later virological control between 12 infants in whom ART was initiated early (<2 months) and eight in whom it was initiated late (2–9 months of age). At 7–8 years of age, 75% of the early group had an undetectable viral load compared with 38% of the late group (p=0·17). In an updated report,[6] 40 infants who started ART at a median age of 3·48 months had significantly lower median viral load until 6 years of age than did 91 children who started ART at a median of 2·21 years of age.[54] Our group reported better virological control after achievement of initial viral suppression in South African children starting ART early at younger than 6 months of age than in children starting ART at 6–24 months of age in two cohorts.[50]

Viral reservoir size

HIV establishes diverse and dynamic viral reservoirs, where replication-competent forms of the virus persist and can replenish the pool of actively replicating virus in the human body. HIV remission is a greater possibility if early treatment can reduce the viral reservoir. The ability to characterise the viral reservoir is important as both an

alternative approach to study virological outcomes and a method to assess whether HIV remission has been achieved. However, the size of the viral reservoir is difficult to measure since latently infected cells are located throughout the body and at different concentrations; thus, the most appropriate assay for measuring the viral reservoir is not clearly established.[58] Most studies in children measure the reservoir by either the quantitative viral outgrowth assay to measure the frequency of latently infected CD4 cells that release replication-competent virus after cellular stimulation (ie, induced replication-competent provirus) or real-time PCR to measure total and integrated cell-associated HIV DNA in peripheral blood mononuclear cells or CD4 cells.[59,60]

Five studies[45,56,57,61,62] compared reservoir size after treatment initiation in children who started treatment earlier versus those who started later. Of these studies, three measured HIV DNA by PCR, one measured the frequency of latently infected CD4 cells by viral outgrowth assay, and one used both methods. Three studies measured total HIV DNA in peripheral blood mononuclear cells, whereas one measured HIV DNA in CD4 cells (figure 4); in these four studies, the number of participants was between eight and 30. The reservoir was measured at different median lengths of time on ART, ranging from 12 months to 200 months. In these four studies, reservoir size was smaller among children who started treatment early than among children who started treatment late. The median age at ART initiation was between 1·8 months and 2·4 months in the early group and between 6 months and 155 months in the older group. Evidence of a smaller reservoir size in children starting ART early has also been observed when using viral outgrowth assays.[45,57]

Additional data from children who started ART very early, with no comparison of early versus late initiation, indicate that the viral reservoir is low and sometimes not detectable. In four neonates who started ART within 72 h of life and achieved sustained virological suppression, HIV DNA was not detected in CD4 cells at 2·5–7·5 years of age.[23] HIV DNA was detectable at low concentrations at a median of 6·3 years in a group of 15 children who started ART at a median of 17 weeks in Thailand.[63]

Overall, these data provide support for the concept that treatment at earlier ages results in a smaller viral reservoir than does treatment at later ages. However, measurement issues make it difficult to interpret the actual size of the latent reservoir. PCR methods measure the total number of infected cells, but many of these cells are not clinically relevant (eg, defective and non-replicating cells), leading to an overestimate in the number of latently infected cells. By contrast, the viral outgrowth assay has poor sensitivity and underestimates the number of cells with replication-competent virus. In addition, studies that compare the viral reservoir in infants who start ART early versus late have a wide range of older ages, making it difficult to make more precise comparisons (eg, 2 months *vs* 3 months).

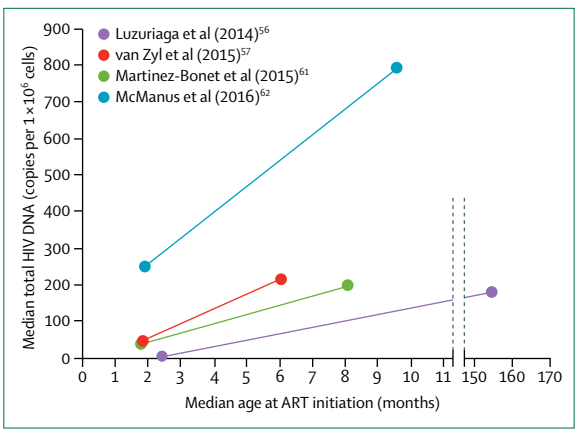

Figure 4: **Data from studies of infants and children comparing markers of the size of the viral reservoir comparing early and late ART initiation**
All cells are peripheral blood mononuclear cells except in Martinez-Bonet and colleagues,[61] in which CD4 cells were used.

More data from across the range of ages at which early ART is initiated are needed, as well as consideration of other factors that could determine the size and composition of the viral reservoir, such as maternal characteristics and host genetic factors. Furthermore, these studies only assessed reservoirs in peripheral blood, but there are probably relevant reservoirs in other tissues (eg, brain and lymph nodes) that should be taken into account.

Randomised trials of structured treatment interruption

Because HIV remission requires the ability to maintain viral control in the absence of ART, it is important to review studies of the likelihood of viral control off ART. In children, treatment interruption studies were originally done as a potential strategy to reduce toxic effects of drugs and the adherence burden of taking daily medication, and were not designed to investigate remission. Despite this caveat, these studies still inform the question of whether children can maintain viral control off treatment.[64–66]

The PENTA 11 trial[64,65] studied supervised treatment interruption versus continuous ART in 109 HIV-infected children and found no greater risk of adverse clinical outcomes with treatment interruption, but 98% of children in the interruption group had viral loads of more than 400 copies per mL at 12 weeks compared with 2% in the continuous group. Most children randomised to the interruption group (86%) restarted ART by the end of the trial.[65] Another randomised trial of supervised treatment interruption versus continued ART in Kenya (OPH03)[66] also found no short-term differences in morbidity or growth between groups, but was stopped early because 66% of children in the interruption arm had to restart ART by 3 months and 86% by 18 months. A trend was observed towards higher incidence of lymphadenopathy in the supervised treatment interruption arm than in the continued ART arm, but no differences were found in

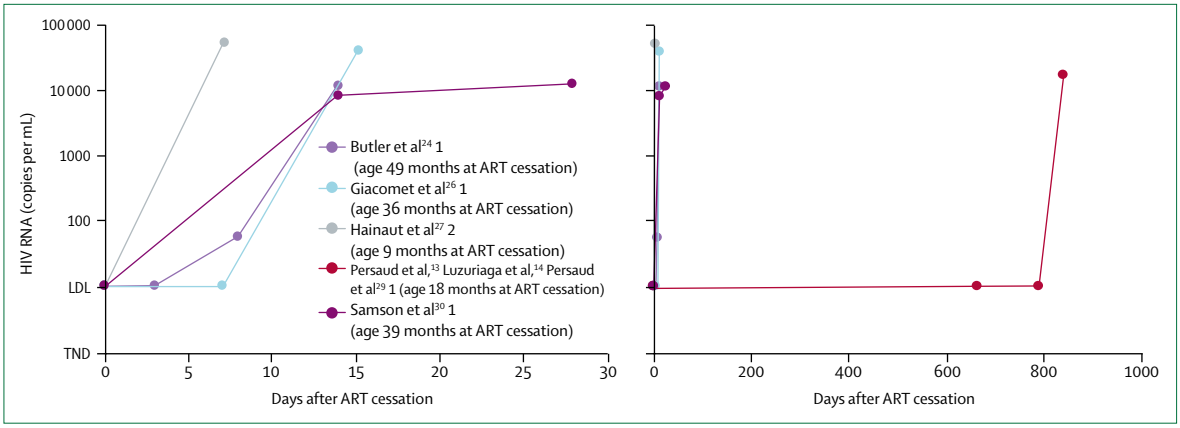

Figure 5: **Time to HIV RNA viral rebound in days after treatment cessation in HIV-infected infants who started antiretroviral therapy (ART) in the neonatal period and later stopped ART (n=5)**
LDL=lower detection limit. TND=target not detected.

serious adverse clinical events. In both trials, initiation of ART was at a median age of 2 years[64,65] and 3 years,[66] well outside the time that would be considered early in the current context.

More informative for the possibility of supervised treatment interruption after very early initiation of ART is the CHER trial,[3,4] which compared early limited ART for 40 weeks or 96 weeks to deferred ART in infants initiated on ART at 6–12 weeks of life, closer to the time of infection. Early limited ART was associated with better clinical and mortality outcomes after 5 years than was deferred ART. However, this study did not include an early continuous arm as a comparison group and viral outcomes are yet to be published. Of note, up to 80% of children in the interruption arms had to restart therapy by the end of follow-up. Although evidence supports the safety of supervised treatment interruption, it is not a recommended HIV management approach.

Viral rebound after treatment cessation

The only direct way to test whether viral control will be maintained off ART is to stop treatment. ART was stopped in five of the 13 neonates mentioned previously, who were initiated on ART within the neonatal period,[13,14,24,26,27,30] and all five of these infants had viral rebound (figure 5). In the Mississippi baby, viral rebound did not happen until 27 months after stopping ART, but in the other four children virus rebounded within 15 days of ART cessation (appendix p 4). With one exception (4 days), no noticeable difference was seen in the age at which ART was initiated in the Mississippi baby (30 h) compared with the other infants (30 min, 12 h, and 24 h). Time to viral suppression was faster in the Mississippi baby (0·95 months) than in three of the other infants (1·3, 5·8, and 6·0 months), but not the fourth (0·4 months). Maternal viral load close to birth was known for four infants. Two were low (156 and 2736 copies) and comparable to that of the Mississippi baby's mother (2434 copies); the fourth mother had a high viral load, but the exact value is not known. To better understand differences in time to viral rebound between these neonates and others, various factors related to achieving HIV remission (eg, timing of in-utero infection, genetic differences, co-infections, and immunological parameters) urgently need to be investigated. Of note, post-discontinuation of ART, clinical symptoms and potential indicators of disease progression or syndrome consistent with acute infection were reported in one infant.[24] No symptoms were reported in the other infants.

Also relevant to this Review are three recent cases of HIV remission in infants and young children who were initiated on ART early, although they did not start ART in the neonatal period. The first case, a French teenager who started ART at 3 months of age has maintained undetectable and low levels of plasma RNA for more than 12 years off treatment.[67] The second case is a child who was initiated on early treatment at 8·7 weeks, interrupted ART 40 weeks later, and has now maintained an undetectable viral load after 8·5 years off ART.[68] Last, post-ART viral control has also been reported in a perinatally infected child started on ART at 4·9 years during chronic infection.[69] Given that clinical guidance discourages treatment interruption, other than the CHER trial and these anecdotal reports, there has been little opportunity to investigate viral dynamics when ART is withdrawn children treated early.

Discussion

This Review assessed six questions relevant to advancing the study of early ART and HIV remission and yielded the following findings. First, data describing viral response in neonates who initiated ART are scarce, and existing case reports probably represent a highly selective group of infants. Hence, the generalisability of published viral load patterns is questionable. Second, very few studies have been done to compare virological outcomes in infants who were initiated on ART early versus those were started late. Most

studies were not designed to answer the question of treatment timing, and thus there is little consideration of the conditions that select infants to be in one group or the other, limiting the inferences that can be made from these data. Third, although early ART does seem to be associated with smaller reservoir size, the predictive value of this small viral reservoir for other outcomes is unknown, and the measures that are available have their drawbacks. Last, only a few children have been initiated on treatment early, subsequently taken off treatment, and followed up closely, hindering the assessment of the possibility of HIV remission.

Taken together, the evidence to support a link between early ART and HIV remission is not clear. Although the Mississippi baby generated a great deal of enthusiasm and a reasonably long period of remission was achieved in this case, it might be attributable to other factors and not solely to very early treatment. In the other, albeit small number of, reported cases of very early treatment (ie, in the neonatal period) and subsequent interruption, viral rebound was reported to occur less than 2 weeks after interruption. However, recent new cases of perinatally infected children who were treated early and are in apparent remission continue to generate enthusiasm.[67–69] Evidence suggests that early ART is associated with better sustained virological control and smaller reservoir sizes, and this, too, provides enthusiasm for the possibility of HIV remission.

In the future, to understand whether early ART can result in HIV remission, studies need to be designed with this endpoint in mind. These studies will require prospective data in larger cohorts with clearly defined and representative populations of HIV-infected neonates and infants starting ART early, as well as a careful consideration of what information should be collected to measure HIV remission. At the very least, future studies will need to include systematic measures of virological outcomes, including detailed markers of the viral reservoir. In addition, to determine the feasibility of HIV remission, studies will need to build in supervised treatment interruptions to test whether virological control off ART is possible, which brings in complex ethical and practical considerations.

Clinically, the public health field continues to move towards HIV diagnosis at birth and very early initiation of ART, and therefore the goal of very early ART should be kept in mind. Is it to reduce morbidity and mortality? Is it to improve long-term virological outcomes? Or is it to achieve HIV remission? Viral endpoints might not be consistent with morbidity and mortality endpoints. This Review has demonstrated that different goals have different levels of evidence, and evidence for some of these outcomes is insufficient.

In addition, there is a crucial need to understand whether the potential benefits of very early ART outweigh the potential risks. Very early treatment of newborn babies is reliant on drug options that are potent, not toxic, and supported by dosing, formulations, and safety data. Currently, few options exist for combination treatment of neonates. Neonates are unique from older infants and children because they have differences in physiology and metabolism that change rapidly in the first few weeks of life. Premature neonates and those with comorbidities are even more complicated. Only a handful of antiretroviral drugs have formulations, dosing, and safety data that allow for their use in neonates (appendix p 5). Several of these drugs are considered suboptimal and no longer used in adults. Neither formulations nor dosing are ideal; some drugs are given at investigational doses (eg, nevirapine) and others are not approved for neonates younger than 1 month (eg, ritonavir-boosted lopinavir and abacavir). Special issues affect the ability of these drugs to be used broadly in neonates. For example, in sub-Saharan Africa, many HIV-infected infants harbour resistance mutations to non-nucleoside and nucleoside reverse transcriptase inhibitors.[70] Ritonavir-boosted lopinavir is available as a liquid formulation in the neonatal period, but because of toxic effects associated with lopinavir or other components of the oral formulation, which contains alcohol and propylene glycol, it is not recommended for use in infants younger than 2 weeks of age or for preterm infants until they reach a postmenstrual age of 42 weeks. In addition, the new pellet formulation is not recommended for newborn babies. Newer potent drugs such as the integrase inhibitors raltegravir and dolutegravir are under investigation. At high concentrations, raltegravir might displace bilirubin from albumin and can increase the risk of bilirubin neurotoxicity in neonates.[71] Dolutegravir, in addition to bilirubin displacement concerns, interacts with other medications including nevirapine, which is given to infants as part of perinatal prophylaxis regimens. An urgent need exists for better drugs and formulations for use among HIV-infected neonates. Ongoing clinical trials of combination ART in neonates, including IMPAACT P1115 (ClinicalTrials.gov identifier NCT02140255), BHP-074 in Botswana (NCT02369406), and the Leopard Study in South Africa, (NCT02431975), will generate additional dosing and safety data.

Search strategy and selection criteria

PubMed was searched for relevant peer-reviewed publications from Jan 1, 1993, to Nov 1, 2017, using the search terms ("HIV") AND ("antiretroviral therapy" OR "ART") AND ("infant" OR "neonate"). Recent HIV conference proceedings from 2013 to 2017 (Conference on Retroviruses and Opportunistic Infections, International AIDS Conference, and International AIDS Society Conference) were reviewed for additional relevant abstracts. Studies were selected if they were relevant to at least one of the six questions developed to guide the Review.

Finally, implementing very early treatment raises several programmatic and logistical challenges. Early ART cannot occur without early diagnosis, which remains a weak point in the prevention of mother-to-child HIV transmission cascade in many settings. Birth PCR testing, even if blood samples can be collected in the first hours of life, relies on central laboratories with turnaround times in days or even weeks leading to inevitable attrition, as mothers need to be recalled for results.[72] The introduction of point-of-care tests for early infant diagnosis, particularly at birth, holds promise for reducing this attrition but still requires coordinated linkage to care.[73] Furthermore, to initiate infants on ART early and continue treatment (with undetectable virus) long enough to attain HIV remission, infants and their mothers need to be engaged and retained in ongoing care. This engagement is challenging giving the nature of the affected population and existing health services. With broadening rollout of programmes for prevention of mother-to-child HIV transmission, new paediatric infections increasingly occur in women who are diagnosed late in pregnancy or at delivery, have had less previous engagement with the health-care system to access antenatal care and prevention of mother-to-child HIV transmission services, or are non-adherent to treatment or disengaged from care.[74] There are also many structural challenges that affect long-term engagement in care, including inadequate transportation systems, health-care services with limited hours of operation, and persistent HIV stigma within family communities and among health workers.

HIV-infected children currently face a lifetime of treatment with ART, which has led to remarkable increases in survival, but sustaining adherence to ART life-long is a formidable challenge. The potential for long-term remission off ART after very early neonatal ART initiation is provocative and elicits hope. Review of existing data suggests that this goal might remain elusive and still requires the concentrated attention and commitment of the scientific community.

Contributors

SS and LK conceived the idea for this Review. SS wrote the first and successive drafts of the manuscript. SS, LK, SMA, and EJA contributed to intellectual content. All authors reviewed the final version submitted to the journal.

Declaration of interests

We declare no competing interests.

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References

1 UNAIDS. UNAIDS data 2017. http://www.unaids.org/sites/default/files/media_asset/20170720_Data_book_2017_en.pdf (accessed Nov 1, 2017).
2 WHO. Antiretroviral therapy for HIV infection in infants and children: towards universal access: recommendations for a public health approach. Geneva: World Health Organization, 2010.
3 Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med* 2008; **359:** 2233–44.
4 Cotton MF, Violari A, Otwombe K, et al. 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. *Lancet* 2013; **382:** 1555–63.
5 Faye A, Le Chenadec J, Dollfus C, et al. Early versus deferred antiretroviral multidrug therapy in infants infected with HIV type 1. *Clin Infect Dis* 2004; **39:** 1692–98.
6 Chiappini E, Galli L, Tovo PA, et al. Virologic, immunologic, and clinical benefits from early combined antiretroviral therapy in infants with perinatal HIV-1 infection. *AIDS* 2006; **20:** 207–15.
7 Goetghebuer T, Haelterman E, Le Chenadec J, et al. Effect of early antiretroviral therapy on the risk of AIDS/death in HIV-infected infants. *AIDS* 2009; **23:** 597–604.
8 WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization, 2013.
9 WHO. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: World Health Organization, 2015.
10 WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach, 2nd edn. Geneva: World Health Organization, 2016.
11 Rakusan TA, Parrott RH, Sever JL. Limitations in the laboratory diagnosis of vertically acquired HIV infection. *J Acquir Immune Defic Syndr* 1991; **4:** 116–21.
12 De Rossi A, Ades AE, Mammano F, et al. Antigen detection, virus culture, polymerase chain reaction, and in vitro antibody production in the diagnosis of vertically transmitted HIV-1 infection. *AIDS* 1991; **5:** 15–20.
13 Persaud D, Gay H, Ziemniak C, et al. Absence of detectable HIV-1 viremia after treatment cessation in an infant. *N Engl J Med* 2013; **369:** 1828–35.
14 Luzuriaga K, Gay H, Ziemniak C, et al. Viremic relapse after HIV-1 remission in a perinatally infected child. *N Engl J Med* 2015; **372:** 786–88.
15 Deeks SG, Lewin SR, Ross AL, et al. International AIDS Society global scientific strategy: towards an HIV cure 2016. *Nat Med* 2016; **22:** 839–50.
16 Mellors J, Persaud D, Tucker JD, et al. Towards an HIV cure: a global scientific strategy. *Nat Med* 2012; **12:** 607–14.
17 Ananworanich J. The emerging potential for HIV cure for infants, children, and adults. 23rd Conference on Retroviruses and Opportunistic Infections; Seattle, WA; Feb 13–16, 2017. 12 (abstr).
18 Shearer WT, Quinn TC, LaRussa P, et al. Viral load and disease progression in infants infected with human immunodeficiency virus type 1. Women and Infants Transmission Study Group. *N Engl J Med* 1997; **336:** 1337–42.
19 Palumbo PE, Kwok S, Waters S, et al. Viral measurement by polymerase chain reaction-based assays in human immunodeficiency virus-infected infants. *J Pediatr* 1995; **126:** 592–95.
20 De Rossi A, Masiero S, Giaquinto C, et al. Dynamics of viral replication in infants with vertically acquired human immunodeficiency virus type 1 infection. *J Clin Invest* 1996; **97:** 323–30.
21 McIntosh K, Shevitz A, Zaknun D, et al. Age- and time-related changes in extracellular viral load in children vertically infected by human immunodeficiency virus. *Pediatr Infect Dis J* 1996; **15:** 1087–91.
22 European Collaborative Study. Level and pattern of HIV-1-RNA viral load over age: differences between girls and boys? *AIDS* 2002; **16:** 97–104.
23 Bitnun A, Samson L, Chun TW, et al. Early initiation of combination antiretroviral therapy in HIV-1-infected newborns can achieve sustained virologic suppression with low frequency of CD4+ T cells carrying HIV in peripheral blood. *Clin Infect Dis* 2014; **59:** 1012–19.
24 Butler KM, Gavin P, Coughlan S, et al. Rapid viral rebound after 4 years of suppressive therapy in a seronegative HIV-1 infected infant treated from birth. *Pediatr Infect Dis J* 2015; **34:** e48–51.
25 Clarke DF, Yildirim I, Cooper ER. Rapid initiation of antiretrovirals in two newly diagnosed HIV infected infants. *Pediatr Infect Dis J* 2017; **36:** 61–62.

26 Giacomet V, Trabattoni D, Zanchetta N, et al. No cure of HIV infection in a child despite early treatment and apparent viral clearance. *Lancet* 2014; **384:** 1320.

27 Hainaut M, Peltier CA, Gerard M, Marissens D, Zissis G, Levy J. Effectiveness of antiretroviral therapy initiated before the age of 2 months in infants vertically infected with human immunodeficiency virus type 1. *Eur J Pediatr* 2000; **159:** 778–82.

28 Van der Linden D, Hainaut M, Goetghebuer T, et al. Effectiveness of early initiation of protease inhibitor-sparing antiretroviral regimen in human immunodeficiency virus-1 vertically infected infants. *Pediatr Infect Dis J* 2007; **26:** 359–61.

29 Persaud D, Deveikis A, Gay H, et al. Very early combination antiretroviral therapy in perinatal HIV infection: two case studies. 21st Conference on Retroviruses and Opportunistic Infections; Boston, MA; March 3–6, 2014. 75LB (abstr).

30 Samson L, Brophy J, Bitnun A, et al. Is functional HIV cure possible following perinatal infection? A cautionary tale. 23rd Annual Canadian Conference on HIV/AIDS Research; St. John's, NL; May 1–4, 2014. O067 (abstr).

31 Luzuriaga K, Wu H, McManus M, et al. Dynamics of human immunodeficiency virus type 1 replication in vertically infected infants. *J Virol* 1999; **73:** 362–67.

32 Palumbo P, Wu H, Chadwick E, et al. Virologic response to potent antiretroviral therapy and modeling of HIV dynamics in early pediatric infection. *J Infect Dis* 2007; **196:** 23–29.

33 Prendergast A, Mphatswe W, Tudor-Williams G, et al. Early virological suppression with three-class antiretroviral therapy in HIV-infected African infants. *AIDS* 2008; **22:** 1333–43.

34 Violari A, Cotton M, Otwombe K, et al. Does early initiation of ART in infants affect virological and resistance outcomes? Data from the CHER trial after 6 years of follow-up. *J Int AIDS Soc* 2012; **15** (suppl 4)**:** 18085.

35 Aboulker JP, Babiker A, Chaix ML, et al. 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:** 237–45.

36 Chadwick EG, Pinto J, Yogev R, et al. Early initiation of lopinavir/ritonavir in infants less than 6 weeks of age: pharmacokinetics and 24-week safety and efficacy. *Pediatr Infect Dis J* 2009; **28:** 215–19.

37 Goetghebuer T, Le Chenadec J, Haelterman E, et al. Short- and long-term immunological and virological outcome in HIV-infected infants according to the age at antiretroviral treatment initiation. *Clin Infect Dis* 2012; **54:** 878–81.

38 Luzuriaga K, McManus M, Mofenson L, et al. A trial of three antiretroviral regimens in HIV-1-infected children. *N Engl J Med* 2004; **350:** 2471–80.

39 Asbjornsdottir KH, Hughes JP, Wamalwa D, et al. Differences in virologic and immunologic response to antiretroviral therapy among HIV-1-infected infants and children. *AIDS* 2016; **30:** 2835–43.

40 Chadwick EG, Capparelli EV, Yogev R, 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.

41 Judd A. Early antiretroviral therapy in HIV-1-infected infants, 1996–2008: treatment response and duration of first-line regimens. *AIDS* 2011; **25:** 2279–87.

42 Kay J, Wanzira H, Sandison T, et al. Virologic suppression in nevirapine-exposed HIV-infected infants initiating antiretroviral therapy in rural Uganda. *J Trop Pediatr* 2012; **58:** 194–99.

43 Lockman S, Shapiro RL, Smeaton LM, et al. Response to antiretroviral therapy after a single, peripartum dose of nevirapine. *N Engl J Med* 2007; **356:** 135–47.

44 Palumbo P, Lindsey JC, Hughes MD, et al. Antiretroviral treatment for children with peripartum nevirapine exposure. *N Engl J Med* 2010; **363:** 1510–20.

45 Persaud D, Palumbo PE, Ziemniak C, et al. Dynamics of the resting CD4$^+$ T-cell latent HIV reservoir in infants initiating HAART less than 6 months of age. *AIDS* 2012; **26:** 1483–90.

46 Pillay V, Davies MA, King S, Eley B. Short-term treatment outcomes of children starting antiretroviral therapy in the intensive care unit, general medical wards and outpatient HIV clinics at Red Cross War Memorial Children's Hospital, Cape Town, South Africa: a retrospective cohort study. *S Afr Med J* 2015; **105:** 220–27.

47 Porter M, Davies MA, Mapani MK, et al. Outcomes of infants starting antiretroviral therapy in Southern Africa, 2004–2012. *J Acquir Immune Defic Syndr* 2015; **69:** 593–601.

48 Purchase SE, Van der Linden DJ, McKerrow NH. Feasibility and effectiveness of early initiation of combination antiretroviral therapy in HIV-infected infants in a government clinic of Kwazulu-Natal, South Africa. *J Trop Pediatr* 2012; **58:** 114–19.

49 Reitz C, Coovadia A, Ko S, et al. Initial response to protease-inhibitor-based antiretroviral therapy among children less than 2 years of age in South Africa: effect of cotreatment for tuberculosis. *J Infect Dis* 2010; **201:** 1121–31.

50 Shiau S, Strehlau R, Technau KG, et al. Early age at start of antiretroviral therapy associated with better virologic control after initial suppression in HIV-infected infants. *AIDS* 2017; **31:** 355–64.

51 Tukei VJ, Murungi M, Asiimwe AR, et al. Virologic, immunologic and clinical response of infants to antiretroviral therapy in Kampala, Uganda. *BMC Pediatr* 2013; **13:** 42.

52 Violari A, Lindsey JC, Hughes MD, et al. Nevirapine versus ritonavir-boosted lopinavir for HIV-infected children. *N Engl J Med* 2012; **366:** 2380–89.

53 Zanchetta M, Walker S, Burighel N, et al. Long-term decay of the HIV-1 reservoir in HIV-1-infected children treated with highly active antiretroviral therapy. *J Infect Dis* 2006; **193:** 1718–27.

54 Chiappini E, Galli L, Tovo PA, et al. Five-year follow-up of children with perinatal HIV-1 infection receiving early highly active antiretroviral therapy. *BMC Infect Dis* 2009; **9:** 140.

55 Estripeaut D, Mosser J, Doherty M, et al. Mortality and long-term virologic outcomes in children and infants treated with lopinavir/ritonavir. *Pediatr Infect Dis J* 2013; **32:** e466–72.

56 Luzuriaga K, Tabak B, Garber M, et al. HIV type 1 (HIV-1) proviral reservoirs decay continuously under sustained virologic control in HIV-1-infected children who received early treatment. *J Infect Dis* 2014; **210:** 1529–38.

57 van Zyl GU, Bedison MA, van Rensburg AJ, Laughton B, Cotton MF, Mellors JW. Early antiretroviral therapy in South African children reduces HIV-1-infected cells and cell-associated HIV-1 RNA in blood mononuclear cells. *J Infect Dis* 2015; **212:** 39–43.

58 Chun TW, Moir S, Fauci AS. HIV reservoirs as obstacles and opportunities for an HIV cure. *Nat Immunol* 2015; **16:** 584–89.

59 Eriksson S, Graf EH, Dahl V, et al. Comparative analysis of measures of viral reservoirs in HIV-1 eradication studies. *PLoS Pathog* 2013; **9:** e1003174.

60 Bruner KM, Hosmane NN, Siliciano RF. Towards an HIV-1 cure: measuring the latent reservoir. *Trends Microbiol* 2015; **23:** 192–203.

61 Martinez-Bonet M, Puertas MC, Fortuny C, et al. Establishment and replenishment of the viral reservoir in perinatally HIV-1-infected children initiating very early antiretroviral therapy. *Clin Infect Dis* 2015; **61:** 1169–78.

62 McManus M, Mick E, Hudson R, et al. Early combination antiretroviral therapy limits exposure to HIV-1 replication and cell-associated HIV-1 DNA levels in infants. *PLoS One* 2016; **11:** e0154391.

63 Ananworanich J, Puthanakit T, Suntarattiwong P, et al. Reduced markers of HIV persistence and restricted HIV-specific immune responses after early antiretroviral therapy in children. *AIDS* 2014; **28:** 1015–20.

64 Paediatric European Network for the Treatment of AIDS. Response to planned treatment interruptions in HIV infection varies across childhood. *AIDS* 2010; **24:** 231–41.

65 Bunupuradah T, Duong T, Compagnucci A, et al. Outcomes after reinitiating antiretroviral therapy in children randomized to planned treatment interruptions. *AIDS* 2013; **27:** 579–89.

66 Wamalwa D, Benki-Nugent S, Langat A, et al. Treatment interruption after 2-year antiretroviral treatment initiated during acute/early HIV in infancy. *AIDS* 2016; **30:** 2303–13.

67 Frange P, Faye A, Avettand-Fenoel V, et al. HIV-1 virological remission lasting more than 12 years after interruption of early antiretroviral therapy in a perinatally infected teenager enrolled in the French ANRS EPF-CO10 paediatric cohort: a case report. *Lancet HIV* 2016; **3:** e49–54.

68 Violari A, Cotton MF, Kuhn L, et al. Viral and host characteristics of a child with perinatal HIV-1 following a prolonged period after ART cessation in the CHER trial. 9th IAS Conference on HIV Science; Paris, France; July 23–26, 2017. 5836 (abstr).

69 McMahon JH, Chang J, Tennakoon S, et al. Post-treatment control in an adult with perinatally acquired HIV following cessation of antiretroviral therapy. *AIDS* 2017; **31:** 1344–46.

70 Kuhn L, Hunt G, Technau KG, et al. Drug resistance among newly diagnosed HIV-infected children in the era of more efficacious antiretroviral prophylaxis. *AIDS* 2014; **28:** 1673–78.

71 Clarke DF, Acosta EP, Rizk ML, et al. Raltegravir pharmacokinetics in neonates following maternal dosing. *J Acquir Immune Defic Syndr* 2014; **67:** 310–15.

72 Lilian RR, Kalk E, Technau KG, Sherman GG. Birth diagnosis of HIV infection in infants to reduce infant mortality and monitor for elimination of mother-to-child transmission. *Pediatr Infect Dis J* 2013; **32:** 1080–85.

73 Hsiao NY, Dunning L, Kroon M, Myer L. Laboratory evaluation of the Alere q point-of-care system for early infant HIV diagnosis. *PLoS One* 2016; **11:** e0152672.

74 Technau KG, Kalk E, Coovadia A, et al. Timing of maternal HIV testing and uptake of prevention of mother-to-child transmission interventions among women and their infected infants in Johannesburg, South Africa. *J Acquir Immune Defic Syndr* 2014; **65:** e170–78.