

Novel therapies / hopes for HIV cure in perinatally acquired HIV positive adolescents

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Abstract: Successful roll-out of paediatric antiretroviral therapy (ART) has led to a significant increase in survival of adolescents and young people growing up with HIV. Those on suppressive ART since childhood represent a unique group particularly well-positioned to interrupt ART and achieve post-treatment control (PTC), or HIV remission. This may be a consequence of early and sustained treatment since infancy, the small size of the HIV reservoir, the presence of a functioning thymus and a more “flexible” immune system better able to respond to novel immune therapeutic interventions when compared to adults who acquired HIV at a time of immunological maturity and thymic involution.

Recent findings: In the past year there have been additional case reports of post-treatment viral control amongst perinatally acquired HIV adolescents and young adults (PaHIV-AYA). In this article we review and compare the characteristics of post-treatment control in PaHIV-AYA and discuss the potential implications of these observations for the growing population of adolescents living with HIV. The correlation between low levels of HIV DNA and seroreversion may provide a feasible screening tool to select candidates most suitable for future intervention studies and viral remission.

Conclusion: Whilst it is premature to anticipate an HIV cure, there is much anticipation that with early ART and additional interventions to perturb the residual viral reservoir, future viral remission off ART might be feasible for PaHIV-AYA. However, given the safety and effectiveness of current ART, a critical debate must evaluate the risks against benefits of any novel intervention, especially amongst adolescents as they become sexually active.

Keywords: Perinatal HIV infection, HIV remission, post-treatment control

Introduction: Progression to AIDS and ultimately death is strikingly different in PaHIV+ infants when compared to horizontally infected adults. Without ART, 50% of HIV-infected infants in Africa will die by age 2 years (1). This compares to a median survival time of 11 years from time of infection in adults without treatment (2). One explanation for this observation may be the impact of immune ontogeny (3) and preserved thymic function (4). Data from the CHER trial identified a survival benefit of initiation of immediate ART compared with deferral for HIV-positive infants (5, 6). The 2015 World Health Organisation recommendations (7), support ART initiation irrespective of CD4 count and disease staging for all HIV-positive infants and children; significantly reducing HIV related mortality and morbidity (8) and leading to an increasing population of PaHIV-AYA. The current population of PaHIV-AYA were born in the era of CD4 count driven ART initiation. Therefore, the majority of the current cohort of PaHIV-AYA survived infancy in the absence of ART and represent a particularly unique cohort with preserved immune function, low levels of immune activation, possibly enriched for

“protective” HLA alleles and in some rare cases possession of a chemokine receptor (d32-CCR5) deletion (9). Previous detailed review articles in the field have described the HIV-specific immune responses amongst children growing up with HIV (3) as well as the potential for cure amongst this group of young people (10).

We summarise future planned research amongst this cohort and describe rare but informative case reports of PTC amongst PaHIV-AYA.

Adolescence is a transitional phase of growth and development between childhood and adulthood; the World Health Organisation (WHO) definition of adolescence being any person aged between 10 and 19 years and ‘young people’ as between 19-24 years of age (11). By the end of 2016 there were an estimated 2.1 million adolescents living with HIV worldwide. Additionally, 150 adolescents die from AIDS-related causes every day. Between 2000 and 2015, AIDS-related mortality declined for all age groups except adolescents, where deaths more than doubled (12). Adolescence is a period of dramatic change in physical and emotional development and adherence is particularly challenging for this age group. Hence there is a strong incentive to explore alternative options that can maintain health and limit the risk of viral transmission during this period.

Defining HIV Cure: A sterilising cure for HIV; defined as the absence of all traces of virus including detection of viral proteins, or cells with integrated viral DNA without ART has been achieved in one man (13). However, a functional cure or remission; accepted as the absence of detectable HIV viraemia following cessation of ART (14) despite detectable latently infected cells in blood or tissue maybe more feasible and scalable. In both situations there must be no risk of disease progression or onward viral transmission, both issues cited as very important from patient surveys addressing issues around HIV remission (15).

HIV reservoirs: Whilst ART controls HIV replication to ‘undetectable’ (<20 copies/ml) levels of viral RNA in the plasma, there remains a pool of latently infected cells, termed the viral reservoir, that are inaccessible to ART and invisible to immune clearance; a function of latently HIV-infected cells being largely transcriptionally silent (16). The HIV reservoir cells are thought to be focused in CD4 bearing central memory cells enriched within lymphoid tissue, the central nervous system and in gut associated lymphoid tissue (GALT) (17-20). The size of the HIV reservoir as measured by either the number of CD4+ expressing cells or total peripheral blood mononuclear cells (PBMCs), harbouring total or integrated HIV DNA, is highly variable between people living with HIV (PLWH) but has been shown to relate to the time from HIV acquisition to starting ART, the length of time on suppressive ART (21) and genetic factors, such as CCR5 d32 gene deletion (22), the latter associated with better viral control (23).

Non-human primate models have demonstrated that an HIV reservoir is rapidly established within three days from infection and that early ART initiation can reduce the size of this reservoir. The reservoir size correlates with time to viral rebound after ART interruption (24). Similarly in adults, ART initiated in acute infection results in approximately 10-100 fold lower frequency of latently infected resting CD4+ lymphocytes when compared with ART started in chronic infection (25-27) and is associated with enhanced immune recovery (28), potentially conferring a better chance of PTC (29). This has been demonstrated in several interesting case

reports (30) and cohorts (29, 31). Similarly amongst HIV-positive children, initiation of ART in infancy results in a smaller viral reservoir when compared to suppressive therapy initiated in later childhood (32). In a study of 144 adolescents with PaHIV established on ART, 46% of the adolescents suppressed from the first year of life had HIV proviral DNA concentration below the level of detectability (<4 copies/10⁶ PBMC) compared to 11% of those who achieved viral suppression after their first birthday (33). In addition to timing of ART initiation, the length of therapy also correlates with the size of the viral reservoir (27). The reservoir in children on ART continues to decay for up to 10 years, but in adults the total HIV DNA appears to plateau after approximately 4 years on treatment (34).

Whilst total HIV DNA per million PBMC or CD4+ T-cells may over-estimate the size of the functional HIV reservoir (35), using this assay, the number of cells harbouring both total and integrated HIV DNA predicts both the rate of CD4 T cell decline and time to viral rebound following treatment interruption amongst adults treated in primary HIV infection (29, 31, 36). Similarly amongst PaHIV-AYA, those with the smallest HIV reservoir may have the best potential to control virus after treatment interruption.

Recent case reports of PTC amongst PaHIV-AYA: For the majority of people living with HIV on suppressive ART, treatment interruption is followed by plasma viral recrudescence within 4 weeks (37). Time to viral rebound after treatment interruption may be extended to 20 weeks following interventions, such as the passive infusion of broadly neutralising antibodies, VCR01, 3BNC117, (38, 39) perturbing the HIV reservoir, prior to treatment interruption, however, the clinical significance of such a delay is limited.

The ‘Mississippi baby’ was the first paediatric case of sustained virological control following unplanned treatment interruption. The child commenced ART at 30 hours of age, stopped treatment aged 18 months, and remained aviraemic until rebound occurred more than 2 years later (40, 41). The first paediatric report of PTC from a randomised trial of ART interruption following early treatment was in a South African child diagnosed at 32 days of age and enrolled in the ‘CHER’ study (table 1). This child commenced treatment at 8.5 weeks of age and continued until one year of age when treatment was interrupted as per protocol but at the age of 9 years remains aviraemic off therapy (42). Within the French ANRS EPF-CO10 paediatric cohort is a PaHIV-positive adolescent who has maintained PTC off ART for over 12 years. ART was started at 3 months of age (HIV RNA 2,170,000 copies/ml) then discontinued by the family between 5.8 and 6.8 years of age. She has remained aviraemic (<50 copies/ml) through to age 18.6 years. These 3 cases suggest that very occasionally long term HIV-1 remission off ART can be achieved in PaHIV children who initiated treatment shortly after birth, however the length of remission remains uncertain (43).

A single case report of post-treatment control has been described in a 25 year old Australian woman with PaHIV who had established viraemia as a child and then a prolonged period of ART. This is a very unusual case as this individual had a protracted period of viraemia on and off ART as a child. This case may represent the impact of immune recovery as well as low level viral reservoir (44).

Table 1. Details of remission and biomarkers during PTC in recent cases of PTC in PaHIV AYP

	South-African Child (42)	French adolescent (43)	Australian youth (44)
Details of remission			
Age starting ART	8.7 weeks	3 months	3.5 years

Duration of ART	40 weeks	5.8 - 6.8 years	18.1 years
Duration of remission	8.75 years (ongoing)	11.5 years (ongoing)	2 years
Viral factors			
HIV subtype	C	H	B
Plasma HIV RNA	<20 c/ml	<4 c/ml	<105 c/ml
Replication-competent HIV	No replication-competent virus detected. (p24 ELISA and ultrasensitive nested RT-PCR)	P24 detected in culture supernatant at all time points (Generic HIV-1 RNA Charge Virale test and by p24 ELISA)	NA
Reservoir size			
PBMCs	5.0 c/10 ⁶ cells	316 c/10 ⁶ cells	NA
Total CD4+ T cells	NA	NA	8 c/10 ⁶ cells
Immunological factors			
HIV-specific T cell responses	Weak gag-specific CD4+ cell response	Barely detectable CD8 T cell responses to gag/nef/pol. CD4 T cell responses to gag/nef/pol within the same range as a viraemic PaHIV patient and an elite controller	NA
HIV-specific antibodies	Negative by ELISA but weakly reactive to Gag p40 and p24. High IgA2 response (mucosal) to gp41	strong reactivity to p68, p55, p40, p34, and p24, weaker reactivity to gp160 and gp41, and no reactivity to gp110 or p18	NA
Mutation in CCR5 delta 32	NA	NA	No
HLA alleles associated with variation in HIV disease progression	HLA DQB1*06; KIRAA1 potentially disadvantageous for spontaneous virological control	homozygosity at several HLA loci (A*2301-, B*1503/4101, C*0210/0802, DRB1*1101-, and DQB1*0602-) which has been linked to rapid disease progression	HLA-B1402/C0802 which has been associated with an elite controller

Values represent most recent published/presented data

c/ml, copies per millilitre; c/10⁶, copies HIV DNA per million; IU/10⁶, infectious units per million; NA, result not available

In summary, over the past 18 months there have been three new case reports of PTC in PaHIV-AYA. However, as treatment interruption is not a strategy currently recommended outside of a closely monitored clinical trial, the frequency of such cases remains unknown. However the vast majority of PaHIV children and AYA who interrupt therapy rebound within weeks, with only one of 377 children enrolled in the CHER study exhibiting PTC (5).

Cure strategies and potential intervention approaches in PaHIV-AYP: In the vast majority of PaHIV-AYA, ART alone, even if commenced within hours of birth will not be sufficient to confer a significant period of PTC. Case reports of early treated infants where ART is interrupted have demonstrated rapid viral rebound, despite low levels of HIV DNA and the child being HIV-seronegative (45). It is likely that for adults as well as PaHIV-AYA additional interventions that perturb the viral reservoir will be necessary (46, 47). Future HIV cure strategies will probably require a combination approach which will include attempts to reduce or activate the latent reservoir (48) with an accompanying technique to remove the activated latently infected cells; described as a “Kick and Kill” strategy. Additional HIV cure strategies include modification of host cells to resist HIV-1, engineered T cells to eliminate HIV-infected cells, broadly HIV-1 neutralizing monoclonal antibodies (49), immune checkpoint inhibitors (50) and therapeutic vaccination (17, 51).

Immune modification: Uniquely amongst PaHIV-AYA, manipulation of the immune system with therapeutic T-cell vaccine strategies (52, 53) may be more effective due to the enhanced capacity to respond to new antigens. Therapeutic vaccination in treated PaHIV-AYA with T-cell prime boost epitopes maybe more efficient at generating potent HIV-specific immune responses, better able to eliminate residual latently infected cells than in adults with mature immune systems. Alternatively, passive infusion of monoclonal broadly neutralising

antibodies have the potential to significantly enhance HIV-specific immunity and consequently impact the size of the HIV reservoir (49). Several studies focused to PaHIV-AYA are planned to explore this further. VRC01, a broadly neutralising antibody (BNAbs) targeting the HIV CD4 binding site, has been shown to be safe as a passive infusion amongst HIV+ adults (38, 54). In two studies, A5340 and NIH 15-I-0140, adults on suppressive ART received a dose of VCR01 then discontinued ART and received several subsequent doses of VRC01. In both trials, VRC01 did not produce durable suppression of viraemia. A phase I/II, multi-site, randomized controlled trial of VRC01 in HIV infected infants is planned with an estimated completion date in early 2020 (55).

In the PEDVAC trial, an HIV DNA vaccine representing HIV subtypes A,B and C, and encoding Env, Rev, Gag and RT was administered to 10 PaHIV children aged 6-16 years on suppressive ART. The vaccine was well tolerated with no episodes of virological failure or decline in total CD4 lymphocyte count. Lymphoproliferative responses to a virion antigen HIV-1 MN were higher in those vaccinated than in the control group. Transient higher cellular responses were noted to Gag but not to the other vaccine components. Interestingly, increased anti-RT cellular reactivities were seen in some of the children (only seen in a minority of adults inoculated with the same vaccine). Therefore, potentially some children may have a better ability to react with viral rRT proteins than adults (56). Please see table 2. for details of upcoming, ongoing and recently completed HIV cure research recruiting adolescent participants.

Table 2. Upcoming, ongoing and recently completed HIV cure research recruiting adolescent participants

Trial	Intervention	Country	Study type	Phase	Estimated enrolment	Estimated completion date	Ages eligible
Stem cell transplantation							
IMPAACT P1107: Cord blood transplantation using CCR5-Δ32 donor cells for the treatment of HIV and underlying disease	N/A	U.S.A.	Observational: Cohort	N/A	25	March 2023	Over 12 months
NCT02140944 Open to enrolment							
BMT CTN 0903: Allogeneic transplant in individuals with chemotherapy-sensitive hematologic malignancies and coincident HIV infection	N/A	U.S.A.	Interventional: Single group assignment	Phase II	18	December 2018	Over 15 years
NCT01410344 Closed to enrolment							
Immune response after stem cell transplant in HIV-positive patients with hematologic cancer	N/A	U.S.A.	Interventional: Single group assignment	Phase II	9	Completed	All ages
NCT00968630 Open to enrolment							
Vaccines							
REMUNE HIV/AIDS Vaccine Phase II Pediatric Safety & Efficacy Clinical Study	Full dose vs low dose Killed HIV-1 whole virus vaccine	U.S.A.	Interventional: Randomized controlled trial	Phase II	26	November 2019	3 months to 16 years
NCT02291809 Not yet open to enrolment							

REMUNE + AMPLIVAX IR103 HIV/AIDS Phase III Safety & Efficacy Study (RAISE)	Killed HIV-1 whole virus vaccine + immunomodulatory oligonucleotide (IMO) adjuvant vs IMO adjuvant alone	U.S.A.	Interventional: Randomized controlled trial	Phase III	500	June 2019	16 years and older
NCT02366026 Not yet open to enrolment							

Challenges to HIV cure approaches amongst AYA living and with HIV: Adolescence is a period of transition from childhood through to adulthood and for many can be a difficult time. In the context of developing decisional capacity, life choices are often influenced by a desire to conform with peers, increased risk-taking behaviour and a focus on self-image. HIV-infected adolescents have disproportionately higher rates of disengagement in care, poor ART adherence and virological failure when compared with both younger children and adults (57, 58). These factors could contribute to unfavourable outcomes when considering an HIV intervention approach which is likely to require frequent clinic visits, very close monitoring and the addition of new drugs and interventions. Yet for the same reasons, establishing ART free remission prior to the turbulent period of adolescence remains a tantalising goal.

As with all cure approaches, there is a critical balance to explore between safety and potential gains of any novel intervention. Currently the safest intervention amongst PaHIV-AYA is to encourage excellent adherence maintaining viral suppression throughout this period of maturation. However globally we are failing to achieve this with some studies citing only one in ten adolescents retained on suppressive therapy. (57, 59).

Treatment interruption studies are not without risk; small studies of PaHIV-AYA interrupting therapy, like adults, have shown rapid viral rebound in the majority of cases, even amongst adolescents starting ART early and with very low levels of viral reservoir (60). Amongst 23 young people who chose to interrupt treatment, viral rebound was observed in all, with an increase in the size of the viral reservoir (60). Viral rebound may be detrimental to an individual's own health but also confers an increased risk of onward transmission to partners and offspring. Adolescence is a period of sexual debut (61), often accompanied by high rates of partner change, unprotected sex and sexually transmitted infections (62, 63). For these reasons, some argue that adolescence may be an inappropriate time to interrupt therapy.

The majority of women in this age group are of childbearing age and any intervention that disrupts gene transcription, such as latency reversing agents including histone deacetylase inhibitors (64) may be teratogenic (65). The changes in host gene expression would pose a significant safety concern in children and it remains uncertain how long these changes may persist (66, 67). Hence, it may not be the best approach for PaHIV-AYA.

Predictive biomarkers for intervention trials and PTC: In the absence of clear biomarkers that can accurately determine HIV remission, many HIV cure strategies in a clinical trial setting involve treatment interruption with close monitoring for viral rebound (68). As discussed above lower levels of HIV reservoir predicted PTC (29) as do biomarkers of inflammation and exhaustion (69). Interestingly, relevant data has demonstrated a correlation between measures of HIV reservoir and the qualitative and quantitative HIV-specific antibody response (70-72), which may be an accessible biomarker predicting individuals with the best chance of achieving PTC with future remission strategies.

Conclusions: Perinatally infected children and AYA living with HIV are a unique cohort who may be specially placed for future cure initiatives. Of particular interest are those AYA who have had suppressed HIV viraemia for many years, evidence of a robust immune recovery and consequent low level of viral reservoirs. Biomarkers that might assist the selection of those most likely to respond to future cure initiatives can enhance safety and help PaHIV-AYA and their clinicians make realistic choices.

Key points:

- With early ART and additional interventions to perturb the residual viral reservoir, PTC off ART might be feasible for PaHIV-AYA in the future.
- Any novel cure intervention strategy must evaluate risk against benefit, especially amongst adolescents as they become sexually active.
- HIV antibody response may be an accessible biomarker to identify those individuals most likely to have low viral reservoirs and hence suited for future interventions towards PTC.

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