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REVIEW

Antiretroviral therapy interruptions: impact on HIV treatment and transmission

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Introduction: Successful management of pediatric and adult human immunodeficiency virus (HIV) disease includes lifelong administration of antiretroviral therapy (ART). The need for the continuous use of antiretroviral drugs throughout the life course poses a challenge to children, adolescents, and adults living with HIV and their caregivers. Historically, treatment interruptions have been viewed as a negative therapeutic strategy. Recently, however, treatment interruptions or treatment reduction strategies have become a focus of investigations as innovative approaches to the long-term management of HIV disease. Current challenges with treatment interruptions include identifying an appropriate timeframe for length of interruptions and identifying HIV patient populations in whom the treatment interruption can be successful.

Objective: In this review, we aimed at summarizing recent studies of planned and unplanned treatment interruptions in children and adults living with HIV.

Materials and methods: We searched two databases (PubMed and Cochrane Controlled Trials Register) using keywords (HIV OR AIDS OR acquired immunodeficiency syndrome OR HIV-1 OR antiretroviral) AND (treatment interruption OR planned interruption OR therapeutic interruption OR unplanned interruption), for published randomized and nonrandomized clinical trials and observational cohort studies in children and adults (from birth to 99 years of age) in global settings covering a period from 2012 to 2018. In this review, only the studies that contained pediatric and adolescent populations with baseline immunological, virological, and clinical characteristics and outcomes after treatment interruption were included.

Results: A total of 174 eligible citations from the two databases were identified. We identified 10 prospective treatment interruption studies on children (five studies) and adults (five studies) during 2012–2018 with a total of 863 pediatric and 273 adult subjects. Collectively, recent studies on children and adults with HIV infection suggest that treatment interruptions with proper monitoring can be successful by instituting well-defined immunological and virological parameters or thresholds such as CD4 count, CD4%, and HIV RNA viral load that identify low-risk populations with treatment failure. In addition to standard virological and immunological outcome measurements, selected biomarkers that help detect early immune activation may also be useful in the monitoring of treatment interruption.

Conclusion: Treatment interruptions in adult and especially pediatric patients with well-controlled HIV disease may provide an alternative opportunity to optimize long-term HIV management by minimizing drug-associated toxicity and improving long-term adherence and quality of life.

Keywords: HIV, antiretroviral therapy, treatment interruptions

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Introduction

More than 34 million adults and 1.8 million children are estimated to be living with human immunodeficiency virus (HIV) globally with the majority living in sub-Saharan Africa.[1] The number of newly infected adults has declined worldwide by 30% between 2000 and 2015, and in children aged <15 years, it has declined even further by 69%.[1] There were still an estimated 2.1 million new HIV infections in 2015, and the global coverage with antiretroviral therapy (ART) remained low at 49% despite significant global investment in the AIDS response that has increased from 5 to 19 billion during the first 15 years of our current century.[1] Although the global scale-up of antiretroviral drug access, health system strengthening, and community initiatives has proven successful in improving HIV treatment through increased access to medication, counseling, support groups, and behavioral interventions, unplanned treatment interruptions continue to occur among populations living with HIV.[2] Multiple challenges contribute to unplanned treatment interruptions in infants and adults. Adherence challenges in infants and children include issues with palatability, swallowability, and dispensability of antiretroviral drugs.[3] In adolescents and adults, adherence challenges more frequently include adverse events, discrimination, lack of confidentiality, treatment costs, and provider-associated factors such as distance to point of care, limited face-to-face counseling, and lack of trust.[4] As optimal treatment of HIV is aimed at preventing viral replication and suppressing the viral load, avoiding unplanned treatment interruptions can decrease the likelihood of sustained detectable viral load, generating drug resistance and causing a decline in CD4 cells.

Historically, treatment interruptions have been viewed as a negative therapeutic strategy following the findings of the Strategies for Management of ART (SMART) study, where episodic ART guided by CD4 cell count in adults resulted in the rise of opportunistic infections, death, and a decrease in the quality of life compared to continuous ART.[5] Other adult studies have shown that prolonged interruption of ART increases the risk of adherence failure once ART is reintroduced, thus potentially increasing the risk of HIV transmission.[6] These findings have led to a decreased interest to conducting such studies in adults. Recently, treatment interruptions or treatment reduction strategies continue to be investigated as a novel approach to the long-term management of HIV disease. Moreover, several structured ART interruption studies in children displayed favorable results as they demonstrated quick recovery of the CD4 count and viral suppression in comparison to groups of children on continuous ART.[7] Our review of the recent literature on ART interruptions in children and adults evaluated virological and immunological outcomes in populations with suppressed and unsuppressed HIV infection and the impact of treatment interruption on HIV transmission.

Materials and methods

We searched two databases (PubMed and Cochrane Controlled Trials Register) covering a period from 2012 to 2018 for all the available randomized and nonrandomized clinical trials and observational cohort studies globally. Only data from completed or published studies were used in this review. No abstracts were included in the review.

Using search keywords (HIV OR AIDS OR acquired immunodeficiency syndrome OR HIV-1 OR antiretroviral) AND (treatment interruption OR planned interruption OR therapeutic interruption OR unplanned interruption), a total of 174 eligible citations from the two databases were identified. Exclusions included the following: abstracts, animal studies, editorials, opinions, nonclinical studies, and studies without data. The selected studies were classified into child (birth to <18 years of age) and adult (18 years and older) categories. A total of 10 prospective trials and studies were selected for our review. Outcome measures in our review and analysis included the following: immunological outcomes such as the change in CD4 cell count and CD4%; virological outcomes such as the change in plasma HIV RNA viral load and $\log_{10}$, changes in HIV drug resistance; and clinical outcomes such as death and progression of HIV disease.

The search included the quality studies that collected data in pediatric subjects starting at birth and adults to 99 years of age who had undergone treatment interruption in which immunological parameters were collected to evaluate treatment interruption. Both authors independently evaluated each of the studies from the search. Only the studies that included target populations, baseline characteristics, and immunological, virological, and clinical outcomes of treatment interruption were included.

Results

Treatment interruptions in infants and children living with HIV

We have identified five treatment interruption studies in children during 2012–2018 with a total of 863 participants

(Table 1). The Children with HIV Early anti-Retroviral (CHER) trial evaluated the strategies for deferred ART initiation in infants and young children compared to the early start and further interruption of ART at 40 and 96 weeks of treatment.[8] In the CHER trial, 377 infants from South Africa were randomly allocated to one of the three groups: deferred ART, immediate ART for 40 weeks, or immediate ART for 96 weeks with subsequent treatment interruption. The results showed that virological failure, defined as HIV RNA viral load of >10,000 copies/mL after 24 weeks on ART, was more frequent in the ART deferred group, occurring in 10 children (8%) in comparison to one child each (<1%) in the groups that underwent treatment interruptions at 40 and 96 weeks on ART.[8] Primary outcome of death was considerably higher in the ART deferred group compared to the groups that were started on ART and underwent treatment interruption, occurring in 21 children (16%) in the ART deferred group, and in 11 (8%) and 9 (7%) children in the 40 and 96 weeks treatment interruption groups.[8] Failure due to ART toxicity did not occur in any child in the study.[8] Time to restarting ART after treatment interruption ranged from 33 weeks (26–45) in the group that stopped ART after 40 weeks to 70 weeks (35–109) in those who were on ART for a longer period of 96 weeks. After 4.8 years at the end of the trial, 19% of children who stopped after 40 weeks and 32% of children who stopped ART after 96 weeks remained off ART.[8] While the primary aim of the CHER trial was to evaluate the strategies for the initiation of ART in pediatric participants, its treatment interruption data suggested no evidence of excess disease progression during subsequent treatment interruption and with less overall ART exposure in those children who started early on treatment. CHER trial data also support the hypothesis that longer time on primary ART may permit longer subsequent interruption without compromising immunological, clinical, and virological outcomes.[8]

In the Optimizing Pediatric HIV-1 Therapy 03 (OPH-03) study, 121 infants from Kenya younger than 13 months of age were initiated on ART and 75 (62%) of infants completed at least 24 months of ART therapy.[9] Of those who completed 24 months of ART, 42 children were randomized to either the planned treatment interruption or continuous ART arms.[9] Of the 21 children in the treatment interruption group at 3 months post randomization, the median CD4% decreased from 34% to 23%, and 14 (66%) children met the ART restart criteria. The median CD4 cell count in those children restarting ART was not statistically significant as it decreased from 1390 to 1365 cells/μL.[9] Interestingly, in the continuous ART arm, one-third (35%) of children contained an elevated HIV RNA viral load of >1000 copies/mL at 3 months of treatment. After 18 months following the randomization and 15 months following the restart of ART, of the 14 children who met the restarting criteria, there were no significant differences in CD4% between both arms.[9] Growth, measured as *z*-scores for weight for age, weight for height, and height for age, also showed no significant differences at 18 months post randomization.[9] Only seven children in the treatment interruption group remained off ART longer than 5 months, and the data safety and monitoring board (DSMB) had recommended that randomization should be stopped due to the short durability of treatment interruption.[9] Short treatment interruption in this pediatric study did not appear to compromise the 18-month outcomes including CD4%, viral suppression, child's growth, or morbidity compared to continued ART among infants who started early ART.

In the Pediatric European Network for Treatment of AIDS (PENTA 11), a multi-country and multiregional trial, children with undetectable HIV RNA viral load of <50 copies/mL and CD4% of at least 30% (2–6 years), or CD4 count of at least 500 cells/μL (7–15 years) were randomized to continuous ART or planned treatment interruption and were recommended to resume ART at the end of the trial.[7] A total of 101 children (51 on continuous ART and 50 who experienced treatment interruption; with a median baseline age of 9.2 years) participated in the long term with a median duration of 4.6 years of follow-up. At baseline, prior to randomization, the median CD4% was 37%, and the median CD4 cell count was 970 cells/μL.[7] After 2 years, the difference in CD4% between the treatment interruption and continuous ART arms was small with overlapping 95% CIs for both study groups. The median CD4% was 32%, and the CD4 cell count was 792 cells/μL in children who experienced treatment interruptions compared to the median CD4% of 36% with a CD4 cell count of 927 cells/μL in children on continuous ART.[7] The percentage of children with an HIV RNA viral load of <50 copies/mL decreased in both groups by the end of the study period: from 94% to 76% in the continuous treatment arm and from 86% to 60% in the treatment interruption arm.[7] A total of 15 out of 50 children in the treatment interruption arm experienced a second treatment interruption, but none had a third interruption of ART.[7]

In our published study, we have retrospectively collected data from a perinatal cohort of 136 children and adolescents

Table 1 Studies evaluating TI in children and adults

Study identifier	Study	Eligibility criteria	TI duration/number of subjects	End point
Pediatric studies				
NCT00102960 (CHER)[8]	Open trial in HIV-infected infants <12 weeks randomized (1:1:1) to deferred ART, immediate ART for 40 or 96 weeks followed by TI to assess time to failure of first-line ART via immunological, clinical, and virological parameters or death	Infants 6–12 weeks CD4%: >25%	TI duration: 16–109 weeks until CD4% <25% Subjects: n=377	HIV RNA viral load, CD4%, death
NCT00428116 (OPH-03)[9]	Randomized trial in children with chronic HIV infection on ART that was started at <13 months of age and completed at least 24 months of treatment before randomization to the TI group versus continuous ART	Infants <13 months of age CD4%: >25% Normal growth	TI duration: 18 months Subjects: n=140	HIV RNA viral load, CD4 count, CD4%, growth
ISRCTN 36694210 (PENTA 11)[7]	A Phase II, multicenter, open randomized trial in children aged 2–15 years with chronic HIV infection on any antiretroviral regimen containing three or more drugs undergoing planned TI	Children 2–15 years Viral load (HIV RNA viral load): <50 copies/mL CD4%: >30% (2–6 years) CD4 cell count: >500 cells/μL (7–15 years)	TI duration: 24 months Subjects: n=109	HIV RNA viral load, CD4 count, CD4%, lipids
UO1 AI69503-03S2[10]	Retrospective study of a larger longitudinal cohort study of children and adolescents with HIV to assess immunological and virological parameters in subjects who experienced TI	Children and adolescents: 0–24 years	TI duration: >4 weeks Subjects: n=38	HIV RNA viral load, CD4 count, CD4%
ISRCTN 97755073 (PENTA 16 BREATHER)[11]	Open, randomized, international, non-inferiority trial evaluating the efficacy of efavirenz-based ART on short cycles of 5 days on and 2 days off in maintaining virological suppression	Children and adolescents 8–24 years HIV RNA viral load: <50 copies/mL for >12 months CD4 cell count: >350 cells/μL	Duration: 48 weeks Subjects: n=199	HIV RNA viral load, CD4 count, CD4%, disease progression, HIV drug resistance, and drug toxicity
Adult studies				
ISRCTN 75856952 (STOPAR)[13,14]	Randomized, open-label, multicenter study in adults with chronically suppressed HIV >18 years of age assessed genotypic resistance, short- and long-term clinical and immunological consequences following staggered TI where NNRTIs were discontinued 7 days before the nucleoside reverse-transcriptase inhibitors	Adults >18 years HIV RNA viral load: <50 copies/mL CD4 count: >500 cells/μL	TI duration: median of 183 days with nadir CD4 cell count of <200 cells/μL and 463 days with nadir CD4 cell count of 200–350 cells/μL Subjects: n=106	Genotypic resistance, disease progression, virological failure, immunological failure
ISS-PART[15]	Randomized study in chronically HIV-suppressed adults comparing the outcomes of 2 years of PTIs versus continued ART at five periods in time (1, 1, 2, 2, and 3 months) separated by 3 months of therapy between each period	Adults 32–57 years old HIV RNA viral load: <50 copies/mL before first PTI Detectable viral load during PTI	TI duration: 1, 2, and 3 months Subjects: n=12	CCR5 tropism, HIV RNA viral load, CD4 count
Substudy of ACTG 5170 trial[16]	Observational prospective study in chronically suppressed and unsuppressed adults with HIV investigated the impact of NAbs on CD4 T-cell count and viral load in a cohort of ART recipients who underwent extended structured TI	Adults >18 years HIV RNA viral load: <55,000 copies/mL CD4 count >350 cells/μL	TI duration: 96 weeks Subjects: n=50	NAbs, CD4 count, HIV RNA viral load

(*Continued*)

Table 1 (*Continued*)

Study identifier	Study	Eligibility criteria	TI duration/number of subjects	End point
ANRS 116 SALTO[17]	Secondary analysis of multicenter study with participants on stable cART regimen, with HIV RNA viral load of 5000 copies/mL for at least 6 months and a CD4 cell count above 450 cells/μL at TI. For the secondary analysis, participants on triple-drug ART with HIV RNA viral load below 400 copies/mL were selected for PTI and monitored (week 2, months 1, 2, 4, and 6, and every 3 months thereafter, until month 36 to determine whether HIV replication can be controlled following PTI started early in the course of infection	Adults >18 years HIV RNA viral load: <400 copies/mL CD4 count >450 cells/μL	TI duration: 36 months Subjects: n=95	HIV RNA viral load
Cohort of A5340 and NIH15-I-0140[18]	Analysis of 10 participants with chronically suppressed HIV who participated in a passive antibody transfer study, where human monoclonal antibody (VRC01) was administered intravenously 3 days before and 14 and 28 days after discontinuation of ART	Adults >18 years HIV RNA viral load: <40 copies/mL	TI duration: median of 57 days (range of 22–115 days) Subjects: n=10	HIV RNA viral load, CD4 count

Abbreviations: ACTG, AIDS Clinical Trials Group; ANRS, Agence Nationale de Recherche sur le Sida; ART, antiretroviral therapy; CHER, Children with HIV Early anti-Retroviral; HIV, human immunodeficiency virus; ISS-PART, Istituto Superiore di Sanità-Pulsed ART; NAbs, neutralizing antibodies; NNRTI, non-nucleoside reverse-transcriptase inhibitor; OPH-03, Optimizing Pediatric HIV-1 Therapy 03; PENTA, Pediatric European Network for Treatment of AIDS; PTI, planned treatment interruption; TI, treatment interruption.

in the US and identified 38 children who experienced planned and unplanned treatment of at least 4 weeks of duration within the settings of routine clinical care.[10] Median treatment interruption lasted 0.98 years with a range between 0.4 and 2.4 years. The median CD4 count and CD4% were lower in children and adolescents who experienced treatment interruptions in comparison to those on continuous ART. The median CD4 count, CD4%, and HIV RNA viral load prior to treatment interruption were 789 cells/μL, 27%, and 2362 copies/mL, respectively.[10] In the same cohort of children prior to restarting ART, the median CD4 count, CD4%, and HIV RNA viral load were 493 cells/μL, 22%, and 52,002 copies/mL. After a median time of 1.8 months following the restart of ART in children who experienced treatment interruption, the CD4 count and CD4% increased to 613 cells/μL and 26%, respectively, while HIV RNA viral load decreased to 2510 copies/mL.[10] Of the 38 children who experienced treatment interruption, six (15%) children experienced at least one additional episode of treatment interruption.[10]

The PENTA 16 BREATHER trial was an open, randomized, international, non-inferiority trial evaluating the efficacy of efavirenz-based ART on short cycles of 5 days on and 2 days off in maintaining virological suppression in 199 children and adolescents aged 8–24 years who were followed for 48 weeks.[11] Prior to initiating the trial, participants must have been on a stable continuous ART with an HIV RNA viral load of <50 copies/mL for the previous 12 months. Of the 99 participants randomized to short-cycle ART and 100 on continuous ART, 157 (79%) participants were 8–17 years of age, 42 (21%) were 18–24 years of age, and 185 (93%) of participants completed all scheduled visits up to week 48.[11] The primary endpoint evaluating virological failure, defined as HIV RNA viral load of >50 copies/mL by 48 weeks, showed no differences as it occurred in six participants in the short-cycle ART group and seven in the continuous ART group. Of the eight participants in the short-cycle group in whom the ART regimen was changed, six were due to virological failure, one due to an adverse event, and one due to compliance issues. Major non-nucleoside reverse-transcriptase

inhibitor (NNRTI) mutations occurred in seven participants experiencing virological failure (two in the short-cycle group and five in the continuous ART group).[11] No significant CD4 count or CD4% differences occurred between both groups.[11] No differences occurred between groups in the evaluation of grade 3/4 adverse events or serious adverse events.[11] Overall, the trial showed non-inferiority of short-cycle therapy and continuous ART with similar safety results.

Overall, despite expected declines in the CD4 cell counts and rise in HIV viral load accompanying treatment interruption, reviewed pediatric studies on the treatment interruption of ART did not appear to cause significant compromise of immunological or virological outcomes 1–2 years following treatment interruption. No increase in deaths was reported in the treatment interruption cohorts of any study compared to the continuous ART cohorts. Further, children in the PENTA 11 planned treatment interruption and continuous treatment arms performed similarly on neurocognitive assessments evaluating information processing speed, sustained attention, short-term memory, and quality-of-life scores, suggesting the lack of the long-term effect on the pediatric neurodevelopmental milestones.[12]

Treatment interruptions in adults living with HIV

We have identified five treatment interruption studies in adults during 2012–2018 with a total of 273 subjects (Table 1). The STOPAR study, a randomized, open-label, multicenter study in adults with chronically suppressed HIV assessed genotypic resistance and short- and long-term clinical and immunological consequences following staggered treatment interruption.[13,14] STOPAR study participants had a median CD4 cell count of 845 cells/μL, CD4 cell nadir count of 344 cells/μL, and HIV RNA viral load of <50 copies/mL prior to being randomized to either continuous ART or the planned staggered treatment interruption arm.[13,14] Staggered treatment interruption was defined as restarting ART once the CD4 cell count dropped below 350 cells/μL or the occurrence of any significant clinical event (B or C disease in Center for Disease Control classification), and then re-interrupting ART again once the CD4 cell count reached 500 cells/μL and the HIV RNA viral load was undetectable at <50 copies/mL.[14] In this study, the CD4 cell count progressively declined in the treatment interruption cohort (56 participants) compared to the continuous ART cohort (50 participants) over the course of the study; median CD4 cell counts at three different time intervals (48, 96, and 144 weeks) were 546, 493, and 480 cells/μL in the treatment interruption cohort and 796, 783, and 772 cells/μL in the continuous ART cohort.[14] Therapeutic failure, defined as CD4 cell count of <200 cells/μL (immunological failure), or maintaining a viral load of >1000 copies/mL for 6 months after restarting treatment (virological failure), or a viral load of >50 copies/mL performed on two separate occasions (virological rebound), occurred in seven (14%) participants in the continuous ART cohort and 15 (27%) participants in the treatment interruption cohort.[14] Of note, 10 participants (20%) in the continuous ART cohort required modification in ART due to ART drug toxicity, while there were no ART modifications in the treatment interruption cohort.[14] There were no deaths in the treatment interruption cohort, and 27 participants (48%) did not receive ART throughout the entire study.[14] Seven participants exhibited emerging HIV resistance mutations following treatment interruption with M184V mutation being the most common as it occurred in three participants.[13] Among participants with repeated treatment interruptions, no new HIV resistance mutations appeared compared to the first genotypic resistance testing.[13]

The Istituto Superiore di Sanità-Pulsed ART (ISS-PART) was a randomized study in chronically HIV-suppressed adults comparing immunological and virological outcomes in adults undergoing multiple treatment interruptions versus continuous ART over 2 years. Throughout the study, repetitive treatment interruptions consisting of 1, 1, 2, 2, and 3 months were separated by 3 months of consecutive ART between each interruption period.[15] All participants in the ISS-PART study had HIV RNA viral load of <200 copies/mL and a median CD4 cell count of 664 cells/μL prior to treatment interruption.[15] All participants experienced reactivation of the viral replication (HIV RNA viral load) during treatment interruptions and the CD4 counts ranged from 363 to 836 cells/μL.[15] Evaluation of HIV RNA viral load following treatment interruptions at 1 and 2 months showed a return to baseline virological suppression at 1 month after restarting ART in most participants.[15] Planned treatment interruptions lasting 3 months did not show a consistent return to suppressed viral load in most participants compared to shorter treatment interruptions of 1 and 2 months of duration.[15] Changes in CCR5 tropism were not associated with increased viral load or development of other HIV resistance mutations following treatment interruptions.[15]

The AIDS Clinical Trials Group (ACTG) 5170 trial was a multicenter observational prospective study in adults with HIV which investigated the impact of neutralizing antibodies (NAbs) on CD4 cell count and viral load in a cohort of adults receiving ART who underwent treatment interruption.[16] For the sub-study, 50 of 167 participants who exhibited a CD4 cell count decline 24 weeks following treatment interruption

were selected, and 38 (76%) were present throughout the entire 96 weeks of the sub-study.[16] The median CD4 cell count at study initiation was 855 cells/μL and HIV RNA viral load ranged from <50 to 12,441 copies/mL. At the end of the study period, the median CD4 cell count was 454 cells/μL with a mean HIV RNA viral load of 4.27 $\log_{10}$ copies/mL.[16] The ACTG 5170 sub-study also divided the participants into progressors (>40% reduction in CD4 cell count through week 24) and non-progressors (no more than a 20% decline), and the mean $\log_{10}$ viral loads in both groups were comparable at the conclusion of the study period.[16] In the progressor cohort, nine of 25 participants restarted ART therapy before study conclusion as their CD4 cell count fell below 250 cells/mL, while none of the participants in the non-progressor cohort restarted ART throughout the study period.[16]

The French National Agency of Research on AIDS (ANRS) 116 SALTO trial was a prospective, open-label, multicenter trial in adults with stable continuous ART who underwent treatment interruptions.[17] A secondary analysis of participants on triple-drug ART with HIV RNA viral load below 400 copies/mL was selected for treatment interruption and monitored (week 2, months 1, 2, 4, and 6, and every 3 months thereafter, until month 36) to determine whether HIV replication can be controlled following treatment interruption that was started early in the course of infection.[17] The study included 95 participants with a median CD4 cell count of 813 cells/μL, CD4 nadir cell count of 382 cells/μL, and HIV RNA viral load of <400 copies/mL prior to planned treatment interruption. Viral load of participants at 12 months on treatment interruption was still <400 copies/mL in seven participants and viral suppression <400 copies/mL lasted up to 36 months in four participants.[17]

From the A5340 and NIH15-I-0140 studies, which evaluated the safety, pharmacokinetics, and antiviral activity of the human monoclonal antibody (VRC01), 10 subjects with chronically suppressed HIV were selected where VRC01 was administered intravenously 3 days before and 14 and 28 days after discontinuation of ART.[18,19] The median CD4 cell count was 724 cells/μL, CD4 nadir cell count was 345 cells/μL, and HIV RNA viral load was <40 copies/mL prior to planned treatment interruption with three doses of VRC01.[18] The median duration before restarting ART, which was defined as a decrease of >30% in baseline CD4 count, CD4 count of <350 cells/μL, or HIV RNA viral load of >1000 copies/mL for >2 weeks was 57 days with a range of 22–115 days.[18]

Discussion

Although significant advances in pediatric HIV drug development have been made, current antiretrovirals medications do not ensure efficient coverage for HIV-infected children due to a limited number of pediatric formulations, palatability and pill size challenges for many ARVs, and few incentives for drug manufacturers to develop new formulations as the number of children with HIV continues to decline worldwide.[3] Treatment interruptions in children with HIV are currently not recommended due to the concern for morbidity and mortality as disease progression in infancy is rapid and young children under 3 years of age are at an increased risk of dying from HIV.[20] The CHER trial results have brought a new prospective to the management of pediatric ART after demonstrating that infants started on ART early in life tolerated planned treatment interruption of their ART well, and displayed better immunological and clinical outcomes compared to the infants with deferred start of ART.[21] Although the other pediatric treatment interruption OPH-03 study was stopped after 14 of 21 infants had to restart ART within 3 months based on the restart criteria, it provided reassuring data on the 18-month outcomes of children who experienced treatment interruptions. The study also showed a lack of significant consequences from short-term discontinuation of ART and provided important insight into the design of future treatment interruption trials for children.

With the current scale-up of the point-of-care viral load monitoring, treatment interruption in children with early successful ART may prove a practical alternative, particularly in perinatally infected children who were started on ART early after the diagnosis and demonstrated sustained virological suppression. The PENTA 11 study has demonstrated that with proper follow-up, treatment interruptions can be safe and produce fast immunological recovery especially in younger children (2–6 years of age).[7] The study also noted differences of CD4 naive and memory cell populations in comparison to adults. Although in adults upon ART initiation changes first occur in CD4 memory cells followed later by an increase in naive cells, the reconstitution in children follows a different pattern where an increase in CD4 memory cells is derived from the naive pool.[22] This implies that although CD4 cell count decline occurs during treatment interruption, a balance is achieved and maintained in both CD4 memory and naive compartments, thus ensuring that treatment interruptions can be successful in children.[22]

Currently, we anticipate that the high effectiveness and tolerability of integrase inhibitor-based ART will significantly facilitate the daily management of HIV by the children and their caregivers and may potentially eliminate the need for treatment interruption consideration. However, we may also argue that other efficient and better tolerated ARVs

introduced over the past few years have not removed the need for daily drug intake and will therefore continue to pose the consideration for treatment interruptions in the future. Our observational longitudinal cohort study of children and adolescents with HIV has confirmed long-term negative effect of unplanned treatment interruptions on immunological and virological outcomes among perinatally infected children and adolescents.[10] Our study further emphasized that non-adherence and ARV drug toxicity remain major challenges to the uninterrupted ART in pediatric populations.[10] Finally, high rates of non-adherence to ART among adolescent populations in our and other published studies lead to the high rates of unplanned treatment interruptions lasting from weeks to months among these high-risk populations.[23] The results of the BREATHER study highlight the need to address planned treatment interruption of ART among adolescents as a potential alternative strategy to decrease non-adherence rates, treatment fatigue, and avoiding the undisclosed and unplanned discontinuation of ART.

For adults living with HIV, earlier treatment interruptions studies such as the SMART trial have closed the door on treatment interruption consideration for several years. The SMART trial offered treatment interruption to adults with CD4 cell counts of >350 cells/mL and reintroduction of ART when the CD4 cell count was <250 cells/μL. Due to a higher risk of opportunistic infections and death, the SMART trial was discontinued prior to completion.[5] Other large adult studies such as the Long-Term Treatment Interruption (LOTTI) trial had more favorable results on treatment interruptions with regard to AIDS defining events when applying a higher threshold of CD4 cell count of >700 cells/mL to start planned treatment interruption and restarting ART when the CD4 cell count was <350 cells/mL.[24] Despite significant advancements in the development of effective and tolerable fixed-dose formulations of ARVs for adults in the past decade, however, the issue of treatment interruption has not become irrelevant to adult HIV care and treatments. Recently published PSITAR cohort study results reemphasizes why treatment interruption is a viable alternative in the right population as it reported ART modification in 68 of 277 participants with recently diagnosed HIV during the first year of therapy with the main reason for discontinuation of therapy being intolerance or toxic effects of medication (64%), followed by provider's decision (16%) and treatment failure (10%).[25]

The results of the STOPAR study also provided new evidence for the feasibility of treatment interruptions in adults living with HIV as almost half of the adults did not have to restart ART for >3 years, no patients experienced a clinical failure or serious adverse event, and all participants maintained a CD4 count of >350 cells/μL.[14] Despite overall positive results, although investigators of this successful trial discouraged the use of treatment interruption due to severe immunological decline in several participants with a baseline high CD4 cell count, it should be noted that several of those participants had a low CD4 cell nadir count.[14] It is plausible to consider whether adults with a high CD4 count and a high CD4 nadir count could be good candidates for treatment interruption, while those with low CD4 cell nadir might not be eligible candidates for planned and controlled discontinuation of ART. The results of the adult studies also generated the question on whether the adults who tolerated treatment interruptions well the first time and achieved a high CD4 cell count with undetectable viral load after reintroduction of ART with no change in their genotypic resistance testing are eligible candidates for subsequent treatment interruptions.

Other adult studies, such as the ISS-PART, which evaluated pulsatile interruption of ART with 3-month periods of treatment in between and the sub-cohort of the A5340/NIH15-I-0140, which evaluated length of treatment interruptions following the administration of VRC01, have shown prolonged time required to return to baseline viral suppression once ART was restarted.[15,18] This is an important aspect to consider in adults with high rebound in viral load during treatment interruptions as these populations would differ from the non-progressor cohorts in the 5170 trial and the SALTO study (Table 1), where the participants with low or undetectable viral load during treatment interruption were capable to tolerate interruptions for an extended time period.[15–17] The ISS-PART study also did not show the relationship between the development of negative CCR5 tropism and increase in viral load during planned treatment interruption as there was no association between CCR5 tropism change and accumulation of the HIV resistance-associated mutations.[15]

Another important aspect in considering treatment interruption includes its potential to improve the person's quality of life. The PENTA 16 BREATHER study of structured weekend-based treatment interruption in adolescents showed a preference for structured treatment interruptions and satisfaction with the clinical trial experience and planned treatment interruptions among young people as well as non-inferiority in comparison to continuous ART and similar safety results.[11] Other studies in adults such as the Options in Management with Antiretrovirals (OPTIMA), which was a randomized trial that included 368 adult participants also showed reassuring results as there was no difference in

health-related quality of life between the planned treatment interruption and continued ART cohorts after a median of 3 years of follow-up.[26]

An important aspect to consider in the management of HIV is transmission of the virus from mother to child and horizontally. Treatment interruptions during pregnancy and breastfeeding have not been considered to be a good option due to the high risk of mother-to-child transmission along with high infant and young child mortality associated with HIV. For the horizontal transmission of HIV, planned treatment interruptions may improve adherence, increase the use of condoms, decrease unplanned ART interruptions, and therefore provide the benefit of decreasing transmission of the virus. A study by Cohen et al,[27] where 1763 participants with HIV were randomized to receive early versus delayed ART and followed for 5 years along with their partners showed a 93% lower risk of linked partner infection than delayed ART (three in early ART, 43 in delayed ART).[27] Another study that involved 3381 discordant couples in which one partner was seropositive for both HIV-1 and herpes simplex virus type 2, and their HIV-1 seronegative partners, showed that 66 (70%) of 94 transmissions occurred when the viral load was >50,000 copies/mL, even if the CD4 count was >200 cells/μL.[28] HIV preexposure prophylaxis that was studied in 4747 HIV-1 sero-discordant heterosexual couples in Uganda and Kenya (Partners PrEP trial) showed high efficacy of 67% and 75% for ART (tenofovir or tenofovir–emtricitabine) when compared to placebo alone.[29] Reduction in HIV-1 viral load combined with increased condom use may also help with decreased horizontal HIV transmission.[30] Early ART initiation with baseline CD4 count of >350 cells/μL has also been shown to decrease the risk of HIV transmission by 90% in a study in Cote d'Ivoire.[31] Overall, the rate of horizontal HIV transmission is lower when the CD4 count is high and the viral load is low. As HIV viral load increases during treatment interruptions, an increase in barrier protection such as condoms is needed to decrease the potential increase in the rate of HIV transmission.

Based on our review of recent studies, we conclude that treatment interruptions can be successful in both children and adults by identifying participants with reassuring stable or excellent immunological and virological parameters. Clearly, populations with high viral load, low CD4 cell count, and multiple chronic conditions cannot be considered for treatment interruptions due to their increased risk of not tolerating treatment interruptions. For the adult population, participants with a high CD4 cell count (>500 cells/μL), high CD4 nadir count, and undetectable viral load who have been chronically suppressed are at a lower risk of treatment interruption not being successful. Subjects with early treatment following diagnosis are also good candidates for treatment interruptions as generally they can maintain a low viral load for longer periods of time. Subjects with a high CD4 count but low nadir count who are chronically suppressed can still be considered for treatment interruption if there is close follow-up as they are at a higher risk of viral rebound. However, if the subject does not appear to be a good candidate for treatment interruption or if they have not tolerated previous planned or unplanned treatment interruptions, then management should focus on maintaining adherence to ART as it will decrease the risk of opportunistic infections, death, progression to AIDS, and non-AIDS complications such as HIV-associated kidney disease, neurologic, and cardiovascular disease among many others.

Children appear to be better candidates for treatment interruption than adults as they are generally started on ART early in the course of the disease due to early diagnosis of perinatally acquired HIV. Children also have a lower prevalence of other chronic comorbidities associated with adults such as cardiovascular, renal, and hepatic diseases.[7] More prospective pediatric treatment interruption studies are needed, and they not only can help identify best strategies for long-term management of HIV in children, but can also help advance our understanding of the best approaches to treatment interruption and simplification of ART among adults living with HIV.

Finally, the importance of treatment interruptions as a strategy in HIV management has become significant in recent years as we redefine our definitions of HIV cure in the absence of complete eradication to include sustained virological remission following the discontinuation of ART.[32] Following a critical step of early initiation of ART, other different therapeutic strategies such as latency-reversing therapy, use of broadly NAbs, and therapeutic HIV vaccines are being considered along with planned treatment interruptions and discontinuations. Treatment interruptions can help determine whether an individual is in HIV remission and requires close monitoring and prompt resumption of ART with the rebound of HIV viral load to prevent development of unfavorable immunological and clinical consequences. Due to the uncertainty of an HIV cure as we are in the discovery phases of research,[32] treatment interruptions provide a feasible alternate option in the management of HIV.

Conclusion

Although earlier ART studies led to the recommendations against planned treatment interruptions in participants

on ART, the quest for this consideration in the long-term management of this lifelong health condition remains. The growing body of literature on treatment interruption studies from clinical trials to clinical observations of children and adults living with HIV has provided new insights into the management of HIV including consideration for treatment interruptions. Well-planned and monitored treatment interruptions can provide medical providers with the opportunity to reduce long-term ARV drug toxicity, increased adherence, and quality of life. Specifically for pediatric HIV management, studies in children have shown that high proportion of children (30%) undergo treatment interruptions in routine clinical care. With proper parameters and close follow-up, treatment interruption studies in children have demonstrated that the long-term immunological and virological outcomes are similar among those who underwent treatment interruptions compared to children on continuous ART. Some recent literature in adults has also demonstrated success for planned and well-managed treatment interruptions in adults with a baseline high CD4 cell count, high nadir CD4 cell count, and a low HIV RNA viral load. Collectively, recent studies in children and adults suggest that treatment interruptions with proper monitoring can be considered as an alternative treatment strategy by instituting parameters to identify low-risk populations of treatment failure.

Key points

- Treatment interruptions can be favorable in pediatric and adult populations with well-controlled human immunodeficiency virus (HIV) disease and intact immune systems.
- Planned treatment interruptions may increase adherence while minimizing drug toxicity and improving quality of life.
- In the pediatric populations, specifically, treatment interruptions have produced better outcomes compared to adult populations and may represent an alternative HIV management strategy during certain developmental stages.

Disclosure

The authors report no conflicts of interest in this work. The authors have no relevant affiliations or financial involvement with any organizations or entity with a financial interest in or financial conflict with the subject matter or material discussed in the manuscript.

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