

Antiretroviral adherence for adolescents growing up with HIV: understanding real life, drug delivery and forgiveness

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Ther Adv Infectious Dis

2020, Vol. 7: 1–12

DOI: 10.1177/
2049936120920177

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Abstract: Poorer adherence to medication is normal in adolescence and is one of a range of risk-taking behaviours common during a developmental stage that encompasses enormous cognitive, physical, sexual, social and emotional change. For adolescents living with human immunodeficiency virus (HIV) infection, poor adherence to antiretroviral therapy (ART) confers two significant challenges: poor health, but also the specific additional burden of onward transmission to partners. Late adolescence (15–19 years) is the only age group where HIV-associated mortality is rising, driven by poor adherence to ART and lack of access to second-line therapy, particularly amongst surviving perinatally infected young people. A previous lack of well-powered randomised multimodal behavioural ART adherence interventions specifically targeting adolescents is now being addressed and ongoing studies registered to ClinicalTrials.gov are described in the context of previous data. Accepting that despite enhanced support, some adolescents will continue to struggle with adherence, we must address how best to use existing ART agents to reduce mortality and allow adolescents the time to mature into adult life. Single-tablet regimens with a high genetic barrier to resistance based on integrase inhibitors and boosted protease inhibitors exist, but global access, in resource limited settings of young people living with HIV reside, is limited. Pragmatically, such regimens tolerate the intermittent adherence so characteristic of adolescence, preserving immune function, without the rapid evolution of resistance. The potential role of long-acting injectable ART, specifically cabotegravir and rilpivirine, is discussed and future strategies including ultra-long-acting drug-delivery systems and broadly neutralising monoclonal antibodies explored.

Keywords: adherence, adolescents, antiretroviral therapy, HIV, viral suppression

Received: 30 June 2019; revised manuscript accepted: 22 March 2020.

Introduction

Globally, an estimated 1.8 million children aged up to 14 years and 5 million young persons aged 15–25 years live with human immunodeficiency virus (HIV), the majority in low- and middle-income settings.¹ Improved access to antiretroviral therapy (ART) has resulted in increasing numbers of perinatally infected children (PaHIV) entering adolescence and transitioning into adult care where they join their behaviourally infected (BHIV) peers.² However, whilst ART has dramatically improved survival for all people living with HIV, late adolescence (15–19 years) is the only age group where HIV-associated mortality

continues to rise, driven by the survivors of the perinatal epidemic and in stark contrast to all other age groups where mortality continues to fall.³ In both resourced and resource-limited settings, retention in care and rates of viral suppression are lower in adolescents when compared with adults or younger children.^{4–7}

Whilst the period of transition from paediatric to adult HIV services provides a particular risk for disengagement from care, in settings where transition occurs in late adolescence, rates of viral suppression begin to decline whilst still in paediatric services and cannot solely be attributable to

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transition of care.⁸ Poorer adherence to therapy during adolescence is by no means limited to HIV and is almost universal for those growing up with chronic diseases of childhood.² For example, glycaemic control in type 1 diabetics starts to decline from 10 years of age, continues to decline through to 18 years of age with evidence of subsequent improvement in early adult life and has been linked to cognitive and psychosocial maturity, with poorer control associated with problems of executive functioning, particularly impulse control.^{9–11} Executive functioning, the complex cognitive processing that allows for reasoned decision making, develops through frontal lobe maturation from early adolescence and continues into the third decade. Poorer executive functioning, reported in adolescents living with PaHIV, particularly those with a prior CDC C diagnosis, has been associated with increased rates of risk-taking behaviours including suboptimal adherence to medication.^{12–14} Although the challenges of negotiating many of the normal developmental tasks of adolescence are similar for those living with chronic diseases of childhood, few disease states share the added burdens of stigma and the impact of the perinatal epidemic within families including parental and sibling loss, poverty and migration. Negotiating one's sexuality with a sexually transmissible disease before having ever had sex and the subsequent considerations around disclosure to each sexual partner potentially adds a further layer of complexity.^{15,16} The knowledge that undetectable equals untransmittable may act as a motivator for improving adherence for adolescents who previously had to negotiate HIV status disclosure to HIV-negative partners, and information to access pre and post exposure prophylaxis in the event of condom failure, irrespective of plasma viral load.^{17,18} In this context, multimodal adherence interventions, behavioural, antiretroviral and the potential for long-acting (LA) agents are explored.

Behavioural interventions

Barriers to ART adherence can be patient related (suboptimal self-management skills, lack of family/social support, HIV stigma, lack of knowledge, mental health issues, drug use, poverty), regimen related (pill number, size, frequency, tolerability, drug–drug interactions), healthcare related (lack of youth friendly services and staff, drug stock outs, transportation, insurance, clinic location and opening hours) and societal (poverty, lack of

collaboration between organisations, stigma).^{19–21} Recent reviews of interventions to improve ART adherence in adolescents highlight the potential benefits of community group and individual adherence support, youth friendly services and eHealth, but emphasise the small number of studies that include adolescents, inadequate sample sizes without appropriate comparison groups, use of surrogate measures of adherence rather than plasma HIV viral load and frequently inadequate length of follow-up post intervention required to assess sustainability.^{22–25} The impact of cash transfers, both conditional and unconditional, and of multimodal economic strengthening interventions to improve child and adolescent health have been explored from pre-conception through to adolescence.^{26–29} Aims at improving maternal–infant outcomes, relieving poverty, retention in education, improving mental health and psychosocial well-being and reducing sexual risk including HIV acquisition effects have been mixed. In ART adherence, small early pilot studies of cash incentives showed promise, and a cluster randomised study in over 700 Ugandan 10–16 year olds showed a significant improvement in viral suppression in those receiving a multimodal savings led economic empowerment intervention, although modest.^{30,31} The need for rigorously evaluated multimodal ART adherence intervention studies that encompass the adolescent within the family and the wider community is being addressed; studies registered on ClinicalTrials.gov and recruiting adolescents in June 2019 are summarised in Table 1. The breadth of ongoing studies, both in terms of intervention and geographical location highlight a global research response aiming for equality, where viral suppression rates for adolescents approach those of adult populations.

Antiretroviral therapy

Accepting that adolescence is a particularly challenging time for adherence, how best can we employ existing ART regimens to support young people living with HIV into adulthood? Ideally a regimen would be well tolerated with a high genetic barrier to resistance, treat hepatitis B co-infection and have minimal drug–drug interactions, particularly with hormonal contraception and *Mycobacterium tuberculosis* therapy. Regimens with medium- and long-term toxicities including mood/neuropsychiatric, metabolic/lipodystrophy/weight gain, bone and renal would be avoided.

Table 1. Currently recruiting ART adherence intervention studies including adolescents living with HIV; June 2019.

Study title	Country	Study type and intervention	<i>n</i>	Age of participants	Primary outcome*	ClinicalTrials.gov identifier
Youth Engagement Study (YES): Intervention to increase HIV treatment engagement and adherence for young people living with HIV	US	Randomised mHealth Stigma-motivational-decision intervention Interactive <i>versus</i> passive texting	400	16–35	VL suppression	NCT03665532
Technology Based Community Health Nursing to Improve cART adherence and Virologic Suppression in Youth living with HIV (Tech2check)	US	Randomised <i>versus</i> SOC Technology-enhanced community health nursing intervention	120	12–25	VL suppression	NCT03600103
Adherence Interventions for HIV Youth via Text & Cell Phone - Sequential Multiple Assignment Randomized Trial (SMART)	US	Randomised – sequential Cell phone <i>versus</i> SMS support With <i>versus</i> without incentives	190	15–24	VL suppression	NCT03535337
Triggered Escalating Real-time Adherence (TERA) Intervention	US	Randomised <i>versus</i> SOC Electronic dose monitor	120	13–24	VL suppression	NCT03292432
FANMI: Community Cohort Care for HIV-Infected Adolescent Girls in Haiti	Haiti	Randomised <i>versus</i> SOC Community peer group	160	16–23	Retention VL suppression*	NCT03286504
Providing unique support for health (PUSH) Study for young black men who have sex with men (YBMSM)	US	Randomised <i>versus</i> SOC Mobile-enhanced engagement intervention	465	15–24	VL suppression	NCT03194477
Connecting Youth and Young adults to optimise ART Adherence: YouTHrive efficacy trial	US	Randomised YouTHrive intervention <i>versus</i> weekly information only emails	300	15–24	VL suppression	NCT03149757
Stepped care for youth living with HIV	US	Randomised eHealth enhanced SOC <i>versus</i> Stepped care: eSOC ± online peer support ± coaching	220	12–24	VL suppression	NCT03109431
Positive Steps to enhanced problem solving skills (STEPS)	US	Randomised <i>versus</i> SOC STEPS; daily 2-way SMS ± CBT	192	16–29	VL suppression Self-report	NCT03092531
Motivational Enhancement system for Adherence (MESA) for youth starting ART	US	Randomised <i>versus</i> SOC 2 session computer delivered motivational intervention MESA	200	16–24	VL suppression Hair ART level Self-report	NCT02761746
Comparing the effectiveness of 2 alcohol + adherence interventions for HIV+ Youth	US	Randomised home <i>versus</i> clinic 4-session motivational enhancement therapy	400	16–24	VL suppression Alcohol use	NCT01969461
Virological treatment failure and drug resistance in HIV-infected Kenyan children (RESPECT)	Kenya	Single group assignment <i>versus</i> SOC MEMS cap monitoring	685	4–19	Viral Resistance Adherence MEMS* VL Suppression*	NCT03120065

(Continued)

Table 1. (Continued)

Study title	Country	Study type and intervention	n	Age of participants	Primary outcome*	ClinicalTrials.gov identifier
Suubi4her: A combination intervention addressing HIV risk behaviours among older adolescent girls transitioning into adulthood in Uganda	Uganda	Randomised <i>versus</i> SOC Youth development account (YDA) YDA + multiple family Groups	1260	14–17	STI acquisition VL suppression*	NCT03307226
VITAL Start: Brief facility-based video intervention	Malawi	Randomised <i>versus</i> SOC Video-based pre-ART counselling in pregnant women	892	16+	VL suppression and retention	NCT03654898
Impact of HIV Drug Resistance Testing, and Subsequent Change to an Individualized therapy in Tanzania	Tanzania	Randomised Resistance testing individualised ART <i>versus</i> standard second line	1250	0.1–99	VL suppression	NCT03557021
A Prospective Cohort Study Evaluating a Psychosocial Programme for Adolescents Living with HIV and their caregivers in Botswana	Botswana	Observational Community support clubs ± Residential camps	506	10–19	VL suppression	NCT03571555
Measuring and Monitoring adherence to ART With Pill Ingestible Sensor System	US	Randomised <i>versus</i> SOC Proteus digital health feedback (PDHF) system	165	17+	Adherence measured by sensor	NCT02797262
Using Social Media to Improve ART Retention and Treatment (SMART) Outcomes Among Youth Living with HIV (YLHIV) in Nigeria - The Youth SMART Study	Nigeria	Randomised <i>versus</i> SOC Facilitated online support group	500	15–22	Retention Self-report*	NCT03516318
HIV Awal (Early) Testing and Treatment Indonesia Project in key populations: Intervention phase	Indonesia	Non-randomised multi-component includes SMS text reminders Motivational interviewing	1000	16–50	VL suppression	NCT03659253
Village based <i>versus</i> Clinic-based ART Care – a cluster randomized controlled trial in Lesotho (VIBRA)	Lesotho	Randomised <i>versus</i> SOC Village based ART refill <i>versus</i> clinic based	262	10+	VL suppression	NCT03630549
Reaching 90% HIV Suppression: The Role of Point-of-Care (POC) Viral Load Monitoring in Nigeria	Nigeria	Randomised <i>versus</i> SOC POC VL testing	794	0–99	VL suppression	NCT03533868
PROvideMinor-friendly Services for Integrated TB/HIV Care in Lesotho Study (PROMISE Study)	Lesotho	Randomised <i>versus</i> SOC Minor-friendly TB/HIV services	641	15+	ART initiation VL suppression* Self-report*	NCT03537872
Dolutegravir, Darunavir/Ritonavir and Optimized NRTI Recycling as a Third-line Antiretroviral Regimen in Cambodia	Cambodia	Single group assignment	54	15+	VL suppression	NCT03602690
Strategy for maintenance of HIV suppression with once daily integrase inhibitor + darunavir/ritonavir (DRV/r) in children (SMILE)	Multisite Global	Randomised <i>versus</i> SOC Suppressed switch to DRV/r + integrase	300	6–17	VL failure	NCT02383108

ART, antiretroviral therapy; cART, combination antiretroviral therapy; CBT, cognitive behavioural therapy; HIV, human immunodeficiency virus; MEMS, medication electronic monitoring system; NRTI, nucleoside reverse transcriptase inhibitor; SMS, short messaging service; SOC, standard of care; VL, viral load.
Search criteria in ClinicalTrials.gov accessed June 2019: HIV; Adherence; Youth; Children.
Selected currently recruiting studies that included participants aged 10–17 years.
*Outcomes measures are primary: viral load suppression (HIC) or adherence assessment and/or viral suppression included in secondary outcomes (LMIC).

Historic paediatric first line regimens based on the non-nucleoside reverse transcriptase inhibitors (NNRTI) efavirenz (EFV) and nevirapine and the older protease inhibitors (PI) such as nelfinavir resulted in high rates of triple class HIV-1 associated resistance mutations as PaHIV adolescents entered adult care.^{32,33} The subsequent arrival of newer agents, both within class, once-daily boosted PIs darunavir (DRV) and atazanavir and newer class integrase strand inhibitors (INSTI) dolutegravir (DTG) and bictegravir (BIC), offer convenient once-daily dosing, and increasingly when combined with a dual nucleoside backbone, as single-tablet regimens (STRs) with a high genetic barrier to resistance. A recent meta-analysis suggests that STRs are associated with improved adherence when compared with multi-tablet regimens.³⁴

DTG, with a dual nucleoside backbone, is recommended as a first-line ART in guidelines globally and is currently licensed from 6 years old.³⁵ In treatment-naïve adults, DTG is superior to EFV, LPV and raltegravir (RAL) in terms of viral suppression, CD4 recovery, treatment discontinuation and a lower potential for drug–drug interactions.³⁵ DTG has a high genetic barrier to resistance; in treatment naïve studies, while rates of virological failure were low, integrase resistance was remarkably absent.³⁶

BIC, as yet unlicensed for those under 18, demonstrates non-inferiority to DTG independent of nucleoside backbone in adults with early data suggesting a comparably high genetic barrier to resistance.^{37–40} Adolescent studies are ongoing with adult fixed dose combination (FDC) dosing of BIC, emtricitabine and tenofovir alafenamide (B/F/TAF) from 12 years and 35 kg with a favourable interim analysis in a stable adolescent switch study.⁴¹

Second-generation INSTIs offer robust STRs with favourable safety and tolerability profiles and a very low risk of emergent resistance in the presence of virological failure, ideal for adolescents where intermittent adherence is predictable and maintaining immune function; reducing HIV-associated morbidity and mortality is sometimes a more realistic goal. World Health Organization (WHO) recommendations for DTG based ART as first-line therapy for all age groups reflect the advantages of DTG *versus* EFV-based ART in terms of tolerability and accumulation of resistance.³⁵ However concerns emerged in May 2018 of a potential increased risk of neural tube defects in infants born

to women who conceived on DTG in an observational cohort from Botswana.⁴² This association has not yet been reported in other cohorts and a public health approach suggests a substantial benefit switching to DTG-based regimens, including for adolescents and women of child bearing age in sub-Saharan Africa,^{43,44} particularly in the context of rising levels of NNRTI resistant virus.⁴⁵ Certainly, the individual cost for a young woman switching from a well-tolerated single-tablet DTG containing regimen to a boosted PI (bPI) in the first trimester of pregnancy and subsequent viral rebound is documented.⁴⁶ Adolescence is the peak age of first pregnancy globally and, hence, for young women living with HIV, the DTG concerns in pregnancy presented impediment to global switch however more recent data supports the use of DTG in women of child bearing potential.

Transmitted drug resistance (TDR) is of concern, potentially for recently infected young adults living with BHIV but more significantly for perinatally infected infants, although reassuringly to date, TDR impacting on integrase remains extremely infrequent.^{47–49} Global rates of perinatal transmission have declined by 35% since 2010, however worrying rates of pre-treatment drug resistance are reported in infants: 30% in an Argentinian cohort with and without exposure to ART for prevention of mother to child transmission; 5% to PIs, 9% to NRTIs and 18% to NNRTIs.^{50,51} Such infants have treatment options limited to regimens based around boosted lopinavir and RAL.⁵² Whether the global role out of DTG based ART for women of child-bearing age will result in a rise in TDR to INSTIs in infants requires surveillance as such mutations will impact on RAL and on DTG when infant formulations of the latter become available.

In treatment-experienced patients, more representative of the current cohort of perinatally infected adolescents, DTG was superior to RAL in terms of viral suppression and fewer treatment-emergent INSTI resistance mutations when added to an optimised background.⁵³ In highly treatment experienced adults with INSTI resistance due to prior RAL/elvitegravir exposure, twice-daily DTG with an optimised regimen achieved viral suppression in almost two thirds.⁵⁴ In treatment-experienced adolescents, DTG appears safe, well tolerated and with an optimised background, achieved viral suppression rates of 44–66% whilst acknowledging the challenges of

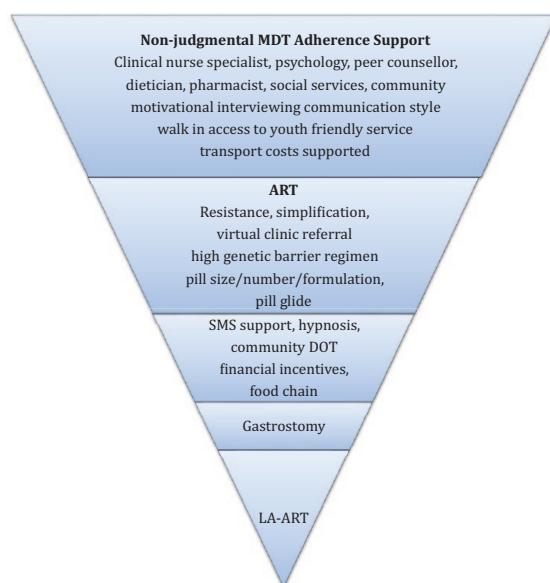


Figure 1. 900 Clinic schematic approach to individualised patient support with established poor adherence to ART.

ART, antiretroviral therapy; DOT, directly observed therapy; LA-ART, long acting antiretroviral therapy; MDT, multidisciplinary team; SMS, short message service.

established adherence issues.^{55,56} One adolescent acquired treatment-emergent INSTI resistance.⁵⁶ For adolescents with dual class resistance living in resourced settings, the introduction of the first bPI STR – DRV/cobisistat/F/TAF in combination with DTG – offers the potential of a potent triple class regimen with a high genetic barrier to resistance in only two pills once daily.⁵⁷ An analysis of seven adult studies of once-daily DRV reported treatment-emergent DRV resistance of <0.1%.⁵⁸

For adolescents struggling with adherence, even with the potential risk of further DR developing, the risks associated with stopping ART completely far outweigh the benefits of retention on some ART due to poorer immunological outcomes and should be avoided.⁵⁹ The pill size – and for those with access only to lopinavir, pill number and frequency – and gastrointestinal toxicity associated with bPIs has been a challenge for many adolescents who have failed first-line NNRTI-based therapy. In the Dawning study, adults failing first-line NNRTI-based therapy ($n=627$) were randomised to either DTG or ritonavir boosted lopinavir (LPV/r) with an investigator led choice of dual nucleoside backbone, one of which was fully active on resistance testing.⁶⁰ At week 48, 84% in the DTG group achieved viral suppression compared with 70% on LPV/r [adjusted difference

13.8%; 95% confidence interval (CI) 7.3–20.3; $p<0.0001$]. More grade 2–4 drug-related adverse events (14% LPV/r *versus* 4% DTG) were reported with LPV/r, driven by gastrointestinal disorders. Whilst LPV/r is virologically inferior to DRV/r and a higher pill burden, the option of DTG as second line therapy in combination with F/TAF is attractive, currently in resourced settings, as two small pills, generally well tolerated and increasingly used in our adolescent practice as part of a multimodal approach to supporting adherence^{61,62} (Figure 1). The recent interim analysis of the Gilead 4030 switch study suggests that even with high levels of archived NRTI resistance, adults suppressed on DTG and emtricitabine and tenofovir alafenamide (F/TAF) or emtricitabine and tenofovir disoproxil fumarate (F/TDF) randomised 1:1 switch to B/F/TAF maintained very high rates of viral suppression, a second-generation option for a small single pill with a high genetic barrier to resistance, although further data of this strategy in second line is required.⁶³

WHO guidance recommends DTG in combination with an optimised NRTI backbone as the preferred second line regimen for adolescents and children with approved DTG dosing.¹⁷ Previous ‘holding’ regimens such as lamivudine monotherapy following first-line failure are associated with immunological decline and highlight the urgent need for global access to second-line therapy.^{64,65} Yet despite two decades of marked improvement in both access to ART and in pill burden, frequency, toxicity and tolerability, some continue to struggle with daily oral medication and perhaps LA formulations offer a welcome alternative, being used with some success in therapeutic areas such as contraception and mental health.

LA injectable formulations for the treatment of HIV-1

At least 15 LA ART agents are being investigated in preclinical or advanced clinical trials, both in prevention of HIV acquisition and in treatment of established infection.⁶⁶ For HIV treatment, the NNRTI rilpivirine (RPV), already licensed as a once-daily oral agent (FDC with F/TDF, F/TAF or as dual maintenance therapy with DTG) is currently in phase III clinical trials as an injectable nanosuspension. LATTE2, a phase IIb study of safety, efficacy and tolerability of RPV-LA combined with the long acting INSTI cabotegravir (CAB) as maintenance therapy in adults achieving viral suppression on oral CAB/lamivudine (3TC)

and abacavir (ABC).⁶⁷ LA-RPV/CAB given either four or eight weekly intervals was as effective as oral CAB/3TC/ABC, was safe and generally well tolerated, with injection site reactions, moderate in 15%, rarely leading to discontinuation (<1%). Recent data presented from the subsequent ongoing phase III studies, ATLAS and FLAIR, injectable LA-RPV/CAB administered every 4 weeks demonstrated non-inferiority to oral triple therapy and whilst rates of virological failure were low, treatment emergent INSTI resistance was reported.^{68,69} Participants aged 18 and older were on suppressive ART without history of virological failure (ATLAS) and treatment naïve (FLAIR). A dose-finding study of oral and LA-CAB and for LA-RPV is currently recruiting in virally suppressed adolescents age 12–17 years weighing at least 35 kg.⁷⁰ Whilst awaiting licensing, LA-RPV/CAB is available on compassionate basis and individual case reports of viral suppression in adolescents/young adults with a history of poor adherence are encouraging and includes those with limited prior resistance in reverse transcriptase.⁷¹ The long-acting therapy to improve treatment success in early life (LATITUDE) study aims to examine this strategy in more detail, randomising adults age 18 and over with a prior history of poor adherence and/or loss to follow up, but without NNRTI or INSTI resistance, to either LA-RPV/CAB or oral standard of care, which may exclude many young people with previous failure on first line therapy.⁷² All require a 20-week oral lead in period and to have achieved a viral load <400 copies/ml prior to randomisation. It remains to be seen how adolescents struggling with oral medication will achieve viral suppression prior to maintenance therapy with LA injectables and subsequently adhere to visits every 4 weeks and injection tolerability. Extending the injection interval to 8 weeks is being explored in an extension of the LATTE study and would be favourable to both patients and providers.⁷³ Injection-site reactions are common and whilst tolerated within clinical trials, a selected population willing to both participate in a clinical trial and opt for one encompassing injections within a real-world setting in an adolescent population is untried. An additional challenge for the implementation of injectable ART amongst this hard to reach group is the requirement to attend injection visits. For those not attending repeat dosing visits, discontinuation of LA-ART results in subtherapeutic plasma levels of CAB and RPV that decline over time with the risk of treatment emergent resistance.⁷⁴ Virological failure in the setting of LA-CAB/RPV has resulted

in treatment emergent INSTI and NNRTI resistance, albeit infrequently in clinical trials, but leading to future treatment option challenges.^{67–69} Owing to their long half-lives, measurable levels of LA-CAB and LA-RPV have been reported in some individuals a year after cessation and current guidance is for a transition to oral ART for those deciding to stop LA-ART. This may be a challenge in an adolescent population who chose LA-ART because of challenges raised by adherence to daily oral ART.⁴ Perhaps lessons can be learnt from other LA agents. Discontinuations of the contraceptive injectable depot medroxyprogesterone acetate (Depot Provera) are greater than 40% at 12 months.⁷⁵ Evidence suggest rates of continuation can be improved through self *versus* provider administration (73% *versus* 45%; incidence rate ratio of 0.40 (95% CI 0.31–0.51; $p < 0.0001$), improving local community access, adherence counselling and text reminders.^{76–78} The recently published ECHO study of the impact of long-acting contraceptives and HIV acquisitions, highlights the very real need for closer integration of reproductive health and HIV services, both for prevention and treatment.⁷⁹ Implementation studies focusing on reducing subsequent discontinuation of LA-ART as treatment for HIV-1 should run in parallel with their introduction outside of clinical trials. Whilst lessons learnt from, and linkage to, LA contraceptive services may improve outcomes for young women, whether this is translatable to young men is unknown, however early data on the use of LA-ART antipsychotics in adolescents (80% male) suggests improvement in adherence and clinical outcome measures.⁸⁰ Even with injection intervals extended to 8 weeks delivery and managing cessation, this will remain a challenge for both adherence and healthcare provision in many settings and longer-acting agents are required, perhaps comparable with the contraceptive implant or intrauterine system.⁸¹ Ultra-LA drug-delivery systems that deliver ART but are removable have considerable potential advantages, particularly in reducing the risk of acquiring resistance mutations on cessation and are currently being developed in animal models.^{82,83}

Future strategies

Alternative non-ART approaches to controlling viral replication have a potentially important role for optimal management of adolescents living with HIV. HIV-specific broadly neutralising monoclonal antibodies (bNAbs) have been

shown in animal models to have the potential to both prevent viral acquisition, to suppress viral replication and to delay viral rebound following treatment interruption.^{84,85} Phase I clinical trials suggest that potent bNAbs to HIV-positive participants with bNAb sensitive viral reservoirs given in combination can both maintain viral suppression post ART interruption and in untreated patients reduce viraemia in selected patients with an antibody-sensitive virus.^{86,87} Whilst bNAbs are under investigation in adult adherent cohorts as a potential HIV ‘cure’ approach, they may have a key alternative value as a mode of viral control off daily oral ART amongst vulnerable youth who struggle to adhere to current therapies. The latter raises the important question as to the potential future role of combination bNAbs infusions for adolescents unable to adhere to ART, or with multi-class ART drug-resistant virus, potentially in conjunction with LA-ART where appropriate.

Conclusion

PaHIV entering adolescence and transitioning to adult care continue to face significant challenges, including sustained adherence to ART in all settings. Encouragingly the data gap of well-powered controlled studies of multimodal interventions to support retention and adherence is being addressed. However once-daily STRs with a high genetic barrier to resistance are already available; the challenge is rapid global access for a vulnerable hard to reach population. Encouragingly if (ultra-)LA-ART prove safe and effective, the potential for combining with implantable contraceptives would offer a truly youth-friendly future for those living with HIV and as pre-exposure prophylaxis for their uninfected peers.

Author contributions

CF conceived the article and wrote the initial draft. SA and SF commented on, edited and contributed to the final draft.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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