Towards an ideal antiretroviral regimen for the global HIV epidemic

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Abstract

Currently, immediate initiation of antiretroviral therapy (ART) is recommended for all individuals with HIV infection. However, among the 37 million people estimated to be living with HIV/AIDS, only 17 million are actively on treatment. Optimal use of ART among HIV-infected and at-risk individuals reduces morbidity, mortality, transmission and acquisition of HIV infection. ART regimen choices are affected by factors such as economic differences between resource-rich and low- and middle-income countries (LIMC), drug availability, and considerations for use in special populations. Ideal ART regimens combine high efficacy, high tolerability, low toxicity, low pill burden, affordability and global availability. Here, we highlight five aspects to be considered when thinking of an ideal global ART regimen: (1) the co-administration with other medications especially tuberculosis treatment; (2) treatment for specific populations such as women, children, adolescents, older people and acutely infected individuals; (3) efficacy; (4) safety, tolerability and convenience; and (5) affordability and global access for all PLWH.

Introduction

By the end of 2015, 37 million people were living with HIV (PLWH) globally and 1.9 million new HIV cases were diagnosed in that year. Declines in the rates of new HIV infections among adults have slowed and different regions in the world continue to experience increases in new infections [1]. Meanwhile, by making access to treatment the central focus of action, we have seen a rapid scale-up of treatment over the last 6 years and millions of people with HIV are living long and healthy lives. However, there are still millions of people in need of antiretroviral therapy (ART) [2].

Globally, the preventive effect of ART has been limited because 40% (35–44%) of PLWH do not know their HIV status and 62% (59–65%) are not virally suppressed [1]. Over the last few years, the clinical and public health benefits of early ART initiation have been demonstrated [3–5] and guidelines around the world now recommend that we 'treat all' [6–11]. Yet, the average CD4 cell count at treatment initiation has increased only modestly. Data from the global IeDEA Network show that between 2010 and 2014, the median CD4 cell count at enrolment into care remained lower than 300 cells/mm^3 [12].

In addition to suboptimal immune status, in 2014, roughly 40% of new HIV infections were among people from key populations. Key populations are still not being reached at scale or with effective HIV prevention, testing and treatment services. Data from the care cascade among different key populations around the world show a common denominator of low viral suppression rates [13–16]. By improving antiretroviral regimens, we may contribute towards overcoming this challenging scenario. More acceptable and easy-to-tolerate ART is essential to increase retention in care and viral suppression, to achieve the 90-90-90 target. In high-income countries, current treatment guidelines include integrase-based three-drug regimens as the preferred option for treatment initiation [6,8,11]. While an efavirenz (EFV)-based regimen remains the preferred option in the World Health Organization (WHO) guidelines, integrase inhibitors are now positioned as alternative options [10].

In aiming for an ideal regimen for the global epidemic, several aspects need to be taken into consideration. In this review, we address five aspects of this ideal regimen including: (1) the co-administration with other medications especially tuberculosis treatment; (2) treatment for specific populations: women, children, adolescent, older people and acutely infected individuals; (3) efficacy; (4) safety, tolerability and convenience; and (5) affordability and global access for all PLWH.

Concomitant treatment of HIV and tuberculosis

An ideal regimen would have to be safe and effective when administrated concomitantly with anti-tuberculosis drugs. Tuberculosis is the leading cause of HIV/AIDS-related morbidity and mortality [17] but concurrent ART dramatically reduces tuberculosis mortality risk [18]. Pill burden, drug–drug interactions, toxicity and immune reconstitution inflammatory syndrome (IRIS) are challenges to preventing and treating HIV–tuberculosis co-infection. Nevertheless, drug–drug interaction studies are usually included late in the process of drug development and data on the use of new antiretroviral drugs such as dolutegravir (DTG), tenofovir alafenamide fumarate (TAF) and EFV 400 mg in association with anti-tuberculosis drugs are still pending (Table 1). Drug–drug interaction studies are also needed for tuberculosis chemoprophylaxis drugs. Recently, unfortunate results were reported in a drug–drug interaction study to evaluate the steady-state pharmacokinetics of DTG with weekly isoniazid plus rifapentine in HIV-negative healthy volunteers with the study being terminated early due to the development of a flu-like syndrome and grade 2–4 elevation of transaminases [19].

Treatment for specific populations: women, children, adolescent, older people and acutely infected individuals

Women now represent 52% of the almost 37 million people worldwide living with HIV [21]. Nevertheless, women overall and pregnant women in particular, have been repeatedly under-represented in drug-development studies and treatment recommendations are extrapolated from studies in predominantly male populations. However, sex differences in antiretroviral pharmacokinetics may influence drug efficacy and predisposition to certain adverse events [22]. Furthermore, the pharmacological management of HIV requires consideration of key sexual and reproductive health concerns, including drug–drug interactions with hormonal contraception, use of ARVs to prevent mother-to-child transmission, and management of HIV-infected women in the

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Table 1. Ongoing studies addressing efficacy, safety and pharmacokinetics of new antiretrovirals in association with anti-tuberculosis drugs

Study	Drug	Intervention	Major outcomes	*n*	Study countries	Expected completion
SSAT 062 (NCT02832778)	EFV 400mg	EFV 400 mg in PLWH in presence of RIF and INH, with and without TB	pK data, AEs, treatment discontinuation, influence of genetic polymorphism and EFV exposure	35	Uganda and UK	Q2 2017
INSPIRING (ING117175) (NCT02178592)	DTG	DTG *vs.* EFV in PLWH with TB confection using RIF (50 mg DTG twice, daily vs 600 mg EFV once, daily during TB treatment)	Safety/efficacy: VL at 24 and 48 weeks, CD4 changes, treatment discontinuation, AEs; HIV drug resistance	125	Argentina, Brazil, Mexico, Peru, Russian Federation, South Africa, Thailand	Q4 2017
SSAT 075 (planning stage)	TAF	TAF and TDF pK in presence of RIF (HIV negative patients)	TDF-DP levels	20	South Africa	Q4 2017

ABC: abacavir; AE: adverse events; ATV/r: atazanavir/ritonavir; COBI, cobicistat; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; INH: isoniazid; PLWH: people living with HIV; pK: pharmacokinetics; RIF: rifampin; TAF: tenofovir alafenamide fumarate; TB: tuberculosis; TDF: tenofovir disoproxil fumarate; TFV-DP: tenofovir diphosphate; VL: HIV viral load; XTC: lamivudine or emtricitabine; 3TC: lamivudine
Sources: Clayden *et al.* [20]; Clinicaltrials.gov (accessed: March 2017)

Table 2. Ongoing studies on new antiretroviral drugs during pregnancy

Study	Drug	Intervention	Major outcomes	*n*	Study countries	Expected completion
SSAT 063 (NCT02499874)	EFV 400 mg	EFV 400 mg pK and safety in pregnant women with HIV using ARV regimens containing EFV at standard dose	pK data in third trimester and post-partum; maternal and infant AEs, adverse pregnancy outcomes; genetic polymorphism's influence on EFV pK	25	Uganda, UK	Q2 2017
DOLPHIN 1 (NCT02245022)	DTG	DTG pK in pregnant women with HIV	pK data in third trimester and 2 weeks postpartum; maternal VL at delivery	60	South Africa, Uganda	Q4 2017
DOLPHIN 2 (planning stage)	DTG	DTG safety/efficacy and tolerability in pregnant women with HIV	pK data in third trimester and 18 weeks postpartum, maternal VL at delivery, breast milk sterilisation	250	South Africa, Uganda	Q1 2021
ING200336 (NCT02075593)	DTG	DTG pK and safety in unintended pregnancies in ARIA study (DTG/ABC/3TC vs ATV/r+TDF/FTC)	pK data in second and third trimester; pK in neonates, maternal and infant adverse events; adverse pregnancy outcomes, maternal disease progression and fetal transmission	25	Spain, Russia, UK, USA	Q1 2019
WAVES OLE (NCT01705574)	TAF	TAF safety/efficacy/tolerability in pregnant women with HIV (TAF/FTC/EVG/COBI *vs* ATV/r+TDF/FTC)	Maternal VL at 48 weeks	583	Belgium, Dominican Republic, France, Italy, Mexico, Portugal, Puerto Rico, Russia, Thailand, Uganda, USA, UK	Q2 2017
IMPAACT P1026s (NCT00042289)	DTG and TAF	DTG and TAF pK in women with HIV on ART >20 weeks of pregnancy and postpartum	pK data during pregnancy and postpartum, pK data in neonates, maternal cord-blood ration, maternal and infant AEs, adverse pregnancy outcomes	100	Argentina, Botswana, Brazil, Puerto Rico, South Africa, Thailand, Uganda, USA	Q3 2017
IMPAACT P2010 (planning stage)	DTG and TAF	DTG and TAF safety/efficacy in women with HIV starting ART at 14–28 weeks of pregnancy (DTG+TAF/FTC *vs* DTG/TDF/FTC *vs* EFV/TDF/XTC)	Maternal VL at delivery, adverse pregnancy outcomes, maternal toxicity, fetal deaths, infant AEs, mother–infant ARV transfer at birth and from breast milk	549	Argentina, Botswana, Brazil, Puerto Rico, South Africa, Tanzania, Thailand, USA, Zimbabwe	Q3 2018
PANNA (NCT00825929)	DTG and TAF	DTG and TAF safety/efficacy in women with HIV receiving ART and <33 weeks of pregnancy	pK data in week 33 of pregnancy and 4–6 weeks after delivery, pK data in neonates; maternal VL and fetal transmission; maternal and infant AEs; adverse pregnancy outcomes	32	Belgium, Germany, Ireland, Italy, the Netherlands, Spain, UK	Q4 2020

ABC: abacavir: AE: adverse events; ATV/r: atazanavir/ritonavir; COBI, cobicistat; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; pK: pharmacokinetics; TAF: tenofovir alafenamide fumarate; TDF: tenofovir disoproxil fumarate; VL: HIV viral load; XTC: lamivudine or emtricitabine; 3TC: lamivudine
Sources: Clayden *et al.* [20]; Clinicaltrials.gov (accessed: March 2017); www.impaactnetwork.org/studies/(accessed: March 2017)

context of age-associated comorbidities and menopause [23]. Although most historical ART regimens are safe in pregnancy and for the fetus, there is scant data on newer drugs, and studies for these populations are still under way or yet to be initiated (Table 2).

Children, adolescents and older people are additional populations that have specific ART needs. A major challenge in treatment optimisation in children and adolescents is related to the long timeline for the development of new drugs. In addition, lack of appropriate formulations and dosing guidance remain key barriers for optimal use of drugs among children. Limited drug options, limited age indications, unfavourable formulations and poor adherence are a few of the other challenges [24–26]. Adolescents experience obstacles to accessing health services on their own and frequently struggle with the linked domains of adherence, retention and stigma. Data from a meta-analysis of the adolescent HIV continuum of care in South Africa showed that only 14% accessed

Table 3. Antiretroviral pipeline for children and adolescents living with HIV

Study	Phase	Regimen	Age (years)	Expected completion
GS-US-183-0160 (NCT01923311)	II/III	EVG/r	Up to 17	Q1 2017
CR108265 (NCT02993237)	I	DRV/COBI swallowing tablets; DRV/COBI/FTC/TAF swallowing tablets	12–17	Q2 2017
GS-US-292-1515 (NCT02276612)	II/III	EVG/COBI/FTC/TAF	12–17	Q3 2017
GS-US-236-0112 (NCT01721109)	II/III	EVG/COBI/FTC/TDF	12–17	Q3 2017
IMPAACT P1093 (NCT01302847)	I/II	DTG film-coated tablets DTG granules for suspension	Up to 17	Q2 2018
ING114916 (NCT01536873)	III	DTG 50 mg (expanded access)	>12	Q3 2018
SMILE (PENTA 17) (NCT02383108)	II/III	EVG+DRV/r	6–17	Q3 2018
GS-US-380-1474 (NCT02881320)	II/III	Bictegravir/FTC/TAF	6–17	Q4 2018
ODYSSEY (PENTA 20) (NCT02259127)	II/III	DTG	6–18	Q2 2019
GS-US-311-1269 (NCT02285114)	II/III	TAF	6–17	Q1 2020
GS-US-216-0128 (NCT02016924)	II/III	ATV/COBI; DRV/COBI	3 months–17 years	Q4 2020
GS-US-292-0106 (NCT01854775)	II/III	EVG/COBI/TAF/FTC	6–17	Q4 2021
IMPAACT 2006	II	DTG	1 month–3 years	In development

ABC: abacavir; ATV/r: atazanavir/ritonavir; COBI, cobicistat; DRV: darunavir DTG: dolutegravir; EFV: efavirenz; r: ritonavir; EVG: elvitegravir; FTC: emtricitabine; TAF: tenofovir alafenamide fumarate
Sources: Clayden *et al.* [20]; Clinicaltrials.gov (accessed: March 2017); www.impaactnetwork.org/studies (accessed March 2017)

ART, 12% were retained in care and only 10% were virally suppressed [24]. Meanwhile, data from the global IeDEA Network, including children who initiated ART between 2010 and 2014, mostly from South Africa, showed some promising results: 80% of those who were retained in care remained virologically suppressed 3 years after ART initiation [12]. Friendlier and more effective ART regimens could increase virological suppression and reduce the high loss to follow-up rates in these populations. Several clinical trials are ongoing for children and adolescents, mostly evaluating newer drugs (Table 3).

Finally, as the prevalence of HIV infection among those who are over 50 years of age has been increasing over time, specific strategies to treat this ageing population are needed. Most randomised trials of ART exclude older patients or people with comorbidities. Moreover, ageing of the HIV-infected population will be followed by an increase in the burden of comorbidities and the need for additional medications [27]. Having antiretroviral drugs that can be given safely and efficaciously alongside other medications is crucial.

As the cure and prevention agenda advances, the management of individuals with acute infection will become more common. Data from the RV 254 study show that there is a rapid decrease in the frequency of cells harbouring total HIV DNA in all Fiebig stages after ART initiation in acutely infected individuals, whereas, it remains stable in chronically infected individuals [28]. Until we have evidence to support ART interruption, these individuals will be treated with ART for decades making friendlier regimens ever more important.

Efficacy

A meta-analysis of 114 studies published up to 2012 shows the progress of ART measured by the increasing proportion of people with an undetectable viral load over time [29]. Single-pill formulations, made available a decade ago, have certainly contributed to the progressively higher levels of viral suppression. This translates into effectiveness. Data from the global IeDEA network including 26,000 adults who initiated ART between 2010 and 2014 show that 90% of individuals who remained in care were virologically suppressed after 3 years of ART [12]. More tolerable regimens could reduce the negative consequences of loss to follow-up on viral load suppression. Data on viral suppression from a network meta-analysis conducted to inform WHO guidelines that compared ART regimens, and included studies published up to 2015, suggested that DTG and raltegravir (RAL) are superior to standard-dose EFV, both at 48 and 96 weeks. Also, the results suggest a clear hierarchy within the INSTI class, with DTG being the most efficacious, followed by RAL, and then elvitegravir. Of note, EFV 400 mg was non-inferior to standard-dose EFV [30].

Safety, tolerability and convenience

Safety, tolerability and convenience are three important challenges to be addressed in current drug development to tackle poor adherence, transmitted drug resistance and WHO's last target of 90% of those on ART with viral suppression. On safety, over time, the number of people discontinuing ART due to adverse events has decreased from 14% to 4%, between 1995 and 2010 [29]. Additionally, recent studies have shown that DTG, RAL and EFV 400 mg were protective of discontinuation due to adverse events compared with standard dose EFV [30]. EFV 400 mg was shown in the ENCORE study to be non-inferior to the standard dose of 600-mg daily, with fewer adverse events [31]. This strategy could lead to savings in costs resulting from a 33% reduction in the active pharmaceutical ingredient. The first fixed-drug combination product with EFV 400 mg is currently under FDA review [32,33]. Similarly, TAF has comparable viral activity to tenofovir and switching to this newer formulation was shown to improve renal and bone markers [34,35].

To address transmitted drug resistance (TDR) new drugs may be needed, especially in low- and middle-income countries (LMIC) where it is a growing concern. In a recent global meta-analysis, it was shown that high-income countries are facing high but stable TDR prevalence across men who have sex with men (MSM), persons who inject drugs and heterosexuals. Conversely, TDR levels are relatively low but rapidly increasing in LMIC, with a disproportionately higher drug resistance burden in MSM [36]. Antiretroviral regimens with a high genetic barrier to resistance

and higher tolerability may mitigate TDR increases by diminishing the generation of new antiretroviral-resistant strains. Results from the TasP-ANRS study, conducted in South Africa, showed a prevalence of almost 9% of pre-ART resistance. Moreover, when using next-generation sequencing, twice as many low-level variants were detected. Non-nucleoside reverse transcriptase inhibitors (NNRTI), predominantly K103N, were the most frequent mutations [37]. Beyond primary resistance, ACTG 5288, a large multinational third-line study in LMIC, showed that the resistance profile of individuals with confirmed PI-based second-line failure included 23% that were resistant to lopinavir and atazanavir and 4% that were also resistant to darunavir/ritonavir (DRV/r) [38].

In light of these findings, the development of new drugs for treatment of cross-class resistance HIV should remain a priority. Although not a comprehensive review, we highlight some of the drugs in development that target drug-resistant HIV. The first is fostemsavir (GSK3684934 – formerly BMS-663068), a first-in-class attachment inhibitor that binds to HIV-1 gp120, preventing initial viral attachment and entry into the host CD4 T cell. It is active against CCR5-, CXCR4- and dual-tropic (R5X4) strains of HIV and has a unique resistance profile with no *in vitro* cross-resistance to other classes of antiretrovirals [39]. Results from the Phase 3 study in heavily ART-experienced adults are expected in mid-2017. In the integrase inhibitor class, bictegravir (BIC), which is active *in vitro* against viral strains with integrase resistance, is currently in clinical development in combination with TAF and emtricitabine in a single-tablet fixed-dose combination. In the Phase 2 study, which was not powered to show non-inferiority, both BIC and DTG showed equivalence with regard to the primary endpoint at week 24: 63 of 65 (97%) participants receiving BIC and 31 of 33 (94%) receiving DTG had undetectable viral loads (<50 copies/mL). Forty-eight-week results showed that 97% of the BIC arm *versus* 91% of the DTG arm had a viral load <50 copies/mL in a snapshot analysis [40]; Phase 3 studies are ongoing.

New agents are also being developed with convenience in mind. MK-8591, formerly known as EFdA is a once-weekly dosing nucleoside reverse transcriptase translocation inhibitor with potent antiviral activity. Preclinical data have established that the properties of MK-8591 are ideal for long-acting administration, both as treatment and pre-exposure prophylaxis (PrEP). Early data on a slow release parenteral formulation with an option for it to be removed showed sustained release for more than 180 days in rat studies [41].

Ibalizumab, a long-acting monoclonal antibody active against HIV strains resistant to all approved antiretroviral agents, is under development as an intravenous infusion for administration every 2 weeks. Results from a Phase 3 study in patients with very limited treatment options showed that 43% of patients achieved viral suppression at week 24 [42]. And finally, GS-CA1, a first-in-class inhibitor of HIV capsid function was shown to have high potency to act in multiple steps in the HIV replication cycle and to allow for low-dose long-acting administration [43]. It is important to highlight that many of these studies were performed solely in the United States, participants were overwhelmingly male and at least one of the studies used TAF, which remains unavailable or unaffordable for many of those living with HIV globally.

Convenience is also being sought in reduced-drug regimens for drug-naive and suppressed patients. Successful results from the PADDLE study [44] paved the way to the ongoing Phase 3 trials evaluating dual-drug combination of DTG plus lamivudine (3TC). Similarly, the Lamidol study (ANRS 167) showed efficacy and safety of switching to dual therapy with DTG plus 3TC in virologically suppressed patients [32]. The Phase 3 Sword 1 and 2 studies evaluated the efficacy of switching current triple ART to DTG plus rilpivirine in virologically suppressed patients with week-48 results demonstrating that this strategy had high efficacy and was non-inferior to the continuation of triple ART [45]. Similarly, a two-drug combination strategy with long-acting cabotegravir and rilpivirine was evaluated in the LATTE 2 study and week-48 data showed that this combination was successful in maintaining viral suppression [46]. Furthermore, this was the first study to show that an all parenteral regimen dosed every other month can maintain virological suppression. Phase 3 ATLAS (NCT01599364) and FLAIR (NCT02938520) studies are ongoing and partially enrolled. In the future, we will see more and more compounds with reduced dosing frequency while maintaining virological suppression.

Affordability and global access for all PLWH

Where are we heading and how do we achieve affordability and global access? The current WHO-recommended regimen is an EFV-based fixed-dose combination, with easy once-daily dosing that allows for treatment harmonisation in all populations. As for alternative combinations, the demonstrated improved efficacy, safety and tolerability of DTG and EFV 400 mg could be part of a larger solution to improve retention, which is a challenge, particularly in LMIC settings. A cost-effectiveness analysis by Phillips *et al.* considered multiple ways of incorporating DTG in sub-Saharan Africa as well as scenarios where NNRTI resistance varied from 0 to 20%. Compared to EFV, DTG was assumed to lead to lower rates of resistance, and greater efficacy and tolerability. The authors projected that over the next 20 years, a change from EFV to DTG would be cost-effective, particularly if all individuals who were on first-line ART were switched to DTG, and more so in places where NNRTI resistance is higher [47]. However, some challenges remain. Results for individuals co-infected with tuberculosis and women who are pregnant or breastfeeding are not yet available with clinical trials still ongoing and initial results expected in late 2017 (Tables 1 and 2).

Currently DTG is available in a fixed-dose combination that includes 3TC and abacavir; however, this requires HLA screening and does not allow therapy to be initiated immediately. Fixed-dose combinations with tenofovir and 3TC are expected in 2018 [33]. Large studies are ongoing mostly in LMIC to gather more data on the safety and efficacy of these regimens among adults and children (Table 4). As the number of individuals using DTG expands, data emerging from different cohorts show higher adverse event-driven discontinuation rates than those reported in clinical trial data. In an observational study (ATHENA cohort, Netherlands), Hoffman and colleagues showed that discontinuation rates due to neuropsychiatric adverse events were higher for DTG compared to other integrase inhibitors, and the discontinuation rates were especially high among women and older patients, both populations under-represented in randomised clinical trials [48]. On the other hand, in recent reports, Hsu and colleagues did not find an increased risk of psychiatric disorders in HIV patients using DTG [49], and Llibre *et al.* found no increased risk of adverse events when comparing DTG versus RAL or elvitegravir [50]. None the less, results from the ATHENA cohort showed that the use of integrase inhibitors in late presenters was an independent risk factor for IRIS [51], similarly in the French Dat'AIDS cohort study, an integrase-based regimen was associated with a higher risk of IRIS [52]. These results point to the need for additional studies addressing safety and tolerability of DTG. In the interim and as we move forwards with DTG scale-up in LMIC countries, a surveillance platform to capture targeted adverse events would be very useful to more rapidly assess these toxicities and complications.

Table 4. Ongoing studies with new antiretroviral drugs in low- and middle-income settings

Study	Drug	Intervention	Major outcomes	*n*	Countries	Expected completion
NAMSAL (ANRS 12313) (NCT02777229)	DTG	Safety/efficacy of DTG *vs* EFV in initial ART of PLWH in RLS (TDF/3TC+DTG *vs* TDF/3TC+EFV)	VL at 24 and 48 weeks, CD4 changes, disease progression, treatment discontinuation, AEs; HIVDR, time to viral suppression	606	Cameroon	**Q3 2018**
ADVANCE (WRHI 060)	DTG TAF	Safety/efficacy of DTG and TAF in initial ART (TDF+FTC+DTG *vs* TAF+FTC+DTG *vs* TDF+FTC+EFV)	VL at 24 and 48 weeks, CD4 changes, disease progression, treatment discontinuation, AEs; HIVDR,	1050	South Africa	**Q4 2019**
DAWNING (NCT02227238)	DTG	Safety/efficacy of DTG *vs* LPV/r in PLHIV failing first-line ART (2NRTI+DTG vs 2NRTI+LPV/r)	VL at 96 weeks, CD4 changes, disease progression, treatment discontinuation,	612	Argentina, Brazil, Chile, China, Colombia, Kenya, Mexico, Peru, Romania, Russia, South Africa, Thailand, Ukraine	**Q4 2018**
ODYSSEY (PENTA 20) (NCT02259127)	DTG	2NRTI+DTG *vs* SoC in children/young adults (6–18 years) with HIV starting first-line or switching to second-line ART	VL at 24 and 48 weeks, CD4 changes, disease progression, treatment discontinuation, AEs	700	Argentina, Austria, Belgium, Brazil, Denmark, France, Ireland, Germany, Italy, the Netherlands, Poland, Portugal, Romania, Spain, Sweden, Switzerland, Thailand, Uganda, UK, Ukraine, USA	**Q3 2019**
ARIA (NCT01910402)	DTG	Safety/efficacy of DTG *vs* ATV/r in initial ART of women with HIV (ABC/3TC/DTG *vs* TDF/3TC+ATV/r)	VL at 24 and 48 weeks, CD4 changes, disease progression, treatment discontinuation, AEs HIVDR	495	Belgium, Dominican Republic, France, Italy, Mexico, Portugal, Puerto Rico, Russia, Thailand, Uganda, UK, USA	**Q4 2020**

ABC: abacavir ; AE: adverse events; ATV/r: atazanavir/ritonavir; ART: antiretroviral therapy; COBI: cobicistat; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; HIVDR: HIV drug resistance; LPV/r: lopinavir/ritonavir; NRTI: Nucleoside reverse transcriptase inhibitors; PLWH: people living with HIV; pK: pharmacokinetics; RLS: resource limited settings; SoC: standard of care; TAF: tenofovir alafenamide fumarate; TB: tuberculosis; TDF: tenofovir disoproxil fumarate; TFV-DP, tenofovir diphosphate; VL: HIV viral load; XTC: lamivudine or emtricitabine; 3TC: lamivudine
Sources: Clayden *et al.* [20]; Clinicaltrials.gov (accessed: March 2017)

Table 5. Dolutegravir use as first-line ART regimen in low- and middle-income countries

Country	Number of PLWH on ART (ART coverage)	Expected number of PLWH on DTG in 12 months	Programmatic approach	Main budget support	Estimated DTG price per patient per year (USD)
Botswana	170,000 (78% coverage)	50,000	Nationwide phased roll-out	PEPFAR	200 (MoH/ViiV agreement)
Brazil	455,000 (64% coverage)	100,000	Nationwide phased roll-out	Brazilian MoH	500 (MoH/ViiV agreement)
Kenya	820,000 (59% coverage)	20,000	Pilot study in 20 high volume ART sites (CHAI UNITAID optimal ARV project)	UNITAID	44 (Aurobindo/CHAI agreement)
Nigeria	850,000 (30% coverage)	6500	Pilot study in three selected ART facilities (UNITAID- CHAI optimal ARV project)	UNITAID	44 (Aurobindo/CHAI agreement)
Uganda	750,000 (57% coverage)	6500	Pilot study in two high volume districts (UNITAID-CHAI optimal ARV project)	UNITAID	44 (Aurobindo/CHAI agreement)

ART: antiretroviral therapy; CHAI: Clinton Health Access Initiative; DTG: dolutegravir; MoH: Ministry of Health; PLWH: people living with HIV

However, to deliver the potential highlighted thus far, ART's affordability and global access are critical aspects. Botswana and Brazil have already adopted DTG as the recommended first-line regimen showing just how fast new options can be introduced in LMIC. Cambodia, Kenya, Nigeria, Tanzania, Zimbabwe and South Africa have included or plan to soon include DTG in their national treatment guidelines (Table 5). There were several notable milestones towards increasing access to these clinically superior and/or cost-effective regimens in LMICs. The Clinton Health Access Initiative has been critical in facilitating the regulatory process for getting EFV 400 mg and its first fixed-dose combination as well as with the first generic DTG formulation by Aurobindo [33]. Cheaper DTG, TAF and DTG fixed-dose combination generics can be sold to certain LMIC through voluntary licences negotiated with pharmaceutical companies by the Medicines Patent Pool. However, for these negotiations to hold, manufacturers must commit to treatment access needs in middle-income countries, which will be home to 70% of PLWH before the end of this decade [53]. For example, China, South America, Russia and Eastern European countries are not included in most of these agreements. As a result, the prices in these countries can make these drugs unaffordable. Other countries may have voluntary licences but if the company does not register the drug for regulatory approval, the drug cannot be accessed.

For all the optimism and hope behind the efforts to dramatically reduce new HIV infections and minimise HIV-related mortality, HIV remains a significant health challenge in all countries. Effective ART is a cornerstone of every plan to reduce and contain the epidemic – for treatment and for prevention. However, the ideal combination therapy must be a combination of factors that includes, but is not limited to, drugs. Conflict and post-conflict settings pose specific challenges to HIV prevention and care efforts. The correlation between ART coverage and the Global Peace Index (GPI) – a measure of stability and military conflict in a country – shows that countries with the worst GPI (Somalia, Sudan, Yemen, Nigeria, Afghanistan) have the worst ART coverage (A Pozniak and A Hill, personal communication). This correlation was found

to be more important than region, HIV prevalence or gross income and illustrates other factors to be considered when aiming to achieve high-ART coverage in all countries.

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