Review of Long-Acting Injectable Candidates for HIV Treatment and Prevention

September 2018

Executive Summary

Despite the wide range of available fixed-dose regimens, adherence to daily lifelong ART is still a challenge for many patients. Long-acting (LA) injectable antiretroviral candidates as an alternative to oral daily therapy are currently being evaluated for the treatment and prevention of HIV infection. Other non-injectables such as implants, patches, vaginal rings are also currently under development. While LA formulations could help overcome adherence issues, multiple barriers and concerns must be addressed overcome before they can be widely accepted for use (Table 1). Many drug candidates for HIV treatment and prevention are still in the early stages of development (Table 2 and 3). Considering the process of drug development, from preclinical testing to final regulatory approval, we can only expect more injectable LA drugs to enter to market around mid-2020s.

Table 1: Advantages and Disadvantages of injectable LA antiretrovirals

Advantages	Disadvantages
• May address adherence issues due to less frequent dosing schedule • May be preferred for patients who wish to avoid burden or stigma of daily oral antiretrovirals • Fewer (or different) side effects • Potential to reduce the need for costly laboratory tests to monitor treatment efficacy • Lower overall drug dose • High acceptability and patient satisfaction	• Frequent clinic visits may be resource-intensive and pose barrier to adherence • Oral lead-in periods will require careful management • Potential long-lasting side effects • High dosing volumes may result in painful injection site reactions • Some people may not like injections • Potentially very high cost • Potential for resistance in non-adherent patients • Lack of safety data in pregnancy • Contraindication for patients with co-infections (e.g. Hepatitis B, tuberculosis)

Table 2: List of long-acting injectable candidates for treatment

Drug	Manufacturer	Type	Status
Cabotegravir Long-acting plus Rilpivirine Long-acting (CAB LA plus RPV LA)	ViiV/Janssen	Integrase inhibitor + Non-nucleoside reverse transcriptase inhibitor (NNRTI)	Phase 3
MK-8591 (EFdA)	Merck	Nucleoside reverse transcriptase translocation inhibitor (NRTTI)	Phase 2
Elsufavirine	Viriom	NNRTI	Preclinical
Albuvirtide	Frontier	Fusion Inhibitor	Phase 3
Ibalizumab	TaiMed Biologics	Monoclonal antibody	Phase 3
PRO 140	CytoDyn	Monoclonal antibody	Phase 3
VRC01	NIAID VRC	Monoclonal antibody	Phase 1/2
VRC01LS	NIAID VRC	Monoclonal antibody	Phase 1/2
GS-9131	Gilead	Capsid inhibitor	Phase 1
GS-CA1	Gilead	Capsid Inhibitor	Phase 1

Table 3: List of long-acting injectable candidates for prevention

Drug	Manufacturer	Type	Status
Cabotegravir	ViiV	Integrase inhibitor	Phase 3
VRC01	NIAID VRC	Monoclonal antibody	Phase 1/2
VRC01LS	NIAID VRC	Monoclonal antibody	Phase 1/2

Efficacy and safety data for HIV treatment and prevention

1. Cabotegravir LA plus Rilpivirine LA

The most advanced clinical trials for injectable LA antiretrovirals at present involve cabotegravir and rilpivirine. Cabotegravir is an experimental INI and structural analogue of dolutegravir first evaluated as an oral tablet and later as an injectable nanosuspension (1,2). It has a potent anti-HIV-1 activity, a half-life of about 40 hours when dosed orally, and a low propensity for drug-drug interactions(1,2). Rilpivirine, an NNRTI with in-vitro activity against HIV-1 and resistance to some NNRTIs (3), is also evaluated as a nanosuspension formulation (4). Cabotegravir LA plus rilpivirine LA injections have significant potential to improve HIV treatment and prevention due to their infrequent dosing schedule.

Table 4: LATTE-2 Results at 96 weeks (2)

Study Arm	% with plasma HIV-1 RNA <50 copies/mL	Serious adverse events	Withdrawals due to adverse-events
IM CAB LA 400mg plus RPV LA 600mg every 4 weeks	87%	11%	7%
IM CAB LA 600mg plus RPV LA 900mg every 8 weeks	94%	11%	2%
Oral CAB + Abacavir/Lamivudine	84%	16%	2%

HIV Treatment:

The **LATTE-2** trial investigated intramuscular (IM) cabotegravir LA plus rilpivirine LA given in 4 or 8-week intervals (following a 20-week oral induction period) against an oral cabotegravir regimen combined with ABC/3TC in HIV-1 positive adults to maintain viral suppression (2). Pre-specified efficacy criteria were met as 87% and 94% of the 4-week and 8-week group achieved viral suppression through 96 weeks, compared to 84% in the oral treatment group (Table 4) (2). Injection site pain of mild to moderate intensity was also the most commonly reported adverse event, which lasted a median duration of 3 days (2). With no treatment-related serious adverse events, the authors concluded that cabotegravir LA plus rilpivirine LA was highly effective, safe and well tolerated for maintenance therapy (2). Treatment with IM cabotegravir LA plus rilpivirine LA was also highly acceptable, with 99% of patients who received the LA injections reported that they would be highly satisfied to continue doing so, compared to 78% reported in the oral treatment arm (2).

More recently, 48-week results from the **ATLAS** trial showed that switching to a cabotegravir LA plus rilpivirine LA regimen injected every 4 weeks in virologically suppressed patients met the primary endpoint for non-inferiority (the proportion of participants with plasma HIV-1 RNA ≥50 copies per milliliter [c/mL] using the FDA Snapshot algorithm at Week 48), and hence demonstrated similar

efficacy as the standard of care of a daily oral regimen comprised of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a third agent (5). Overall safety, virologic response and drug resistance results for the injectable LA regimen were also consistent with results from the phase II LATTE-2 study (5).

Table 5: ECLAIR Results (6)

Study Arm	Treatment-related adverse events	Withdrawal due to adverse events (injection phase)
Injectable CAB LA 800 mg every 12 weeks	80%	0%
Placebo	48%	5%

HIV Prevention:

The **ECLAIR** study ran from 2014 to 2016 and tested cabotegravir LA against a placebo for HIV prevention in 127 participants of which a majority were men who have sex with men (MSM) (6). Results indicated that the injectable cabotegravir LA was well tolerated and safe (Table 5), even though the frequency of grade 2 or higher adverse events was higher in the cabotegravir group (80%) compared to placebo (48%) (6). The most commonly reported adverse event was injection-site pain, of a mean duration of 5.4 days. However, there were no withdrawals due to adverse events during the injection phase in the cabotegravir group (6). Most (75%) of patients said they were generally more satisfied with the injection-based treatment than with an oral regimen one week after the third injection (6). Furthermore, the absorption rate of the cabotegravir LA 800mg was faster than predicted, indicating that dosing may have to be reduced from every 3 months to every 2 months in future studies (6).

Ongoing trials for injectable Cabotegravir LA plus Rilpivirine LA

HIV Treatment

Besides the **ALTAS** trial, there are two other phase 3 trials currently underway by ViiV to study the safety and efficacy of IM cabotegravir LA plus rilpivirine LA (Table 6). The **FLAIR** trial is designed to evaluate the switch to the same regimen of IM cabotegravir LA plus rilpivirine LA in ART-naïve patients who are virologically suppressed on the INI-containing single tablet regimen of abacavir/lamivudine/dolutegravir (ABC/3TC/DTG) (7). The switch study have enrolled 570 participants and is intended to complete by 2022 (7,8). Alongside, **ATLAS-2M** trial is comparing cabotegravir LA plus rilpivirine LA administered every 4 or 8 weeks (9).

HIV Prevention

Although rilpivirine LA has been shown to be safe in healthy female volunteers in the **HPTN 076** prevention trial (4)**,** its clinical development has since been discontinued (10). This makes cabotegravir LA the lead product for HIV prevention. At present, the safety and acceptability data of cabotegravir LA is pending the completion of phase 1 and 2 studies (Table 6) (9,11). The HIV Prevention Trials Network (HPTN) has also begun the twin placebo-controlled studies of **HPTN-083** and **HPTN-084** in December of 2016 which expected to continue through 2022 (12,13). Both are Phase 2b/3 non-inferiority trials evaluating injectable cabotegravir LA 600mg compared to daily oral TDF/3TC for PrEP in HIV-uninfected trans-gender women, MSM and women (12,13). All studies mentioned thus far have excluded pregnant women and patients with active tuberculosis (TB), thus leaving unanswered critical questions about applicability to these special populations.

Table 6: Ongoing Cabotegravir/Rilpivirine Studies

Treatment Trials (7–9)	**Product**	**Number of participants**	**End Date**	**Prevention Trials** (9,11–13)	**Product**	**Number of participants**	**End Date**
FLAIR	CAB LA plus RPV LA	570	2022	**Phase I PK**	CAB	16	2019
ATLAS-2M	CAB LA plus RPV LA	1020	2022	**HPTN 077**	CAB	199	2018
				HPTN 083/ HPTN 084	CAB	4500, 3200	2021 2022

2. Other Long-acting Injectable Candidates

Broadly neutralizing HIV antibodies (bNabs)

Ibalizumab

Since March 2018, ibalizumab has been approved by the U.S. Food and Drug Administration (FDA) in treatment-experienced patients with multi-drug resistant HIV, based on combined results from only 292 patients over a long development phase (14). In the most recently completed **TMB-301** study, viral load was reduced by a median of 2.5 log copies/mL and 59% of participants achieved virologic suppression (viral load <50 copies/mL) after 24 weeks of ibalizumab use with an optimized background regimen (15). After 24 weeks, participants were allowed to continue ibalizumab up to 48 weeks in the extended **TMB-311** study, and all 15 participants with suppressed viral load at 24 weeks maintained through week 48 (15). Potential barriers to its uptake could include its high drug cost and programmatic challenges as it is not self-administered (16).

PRO 140

In the Phase 2b **CD01** study (n=41), once-weekly PRO 140 monotherapy demonstrated moderate efficacy in virologically suppressed patients (17). This was followed by the positive results from the completed 25-week phase 2b/3 **CD02** trial in which approximately 81% of heavily ART-experienced patients on PRO 140 in combination with their existing ART achieved viral suppression with plasma HIV-1 RNA viral load <50 copies/mL (18). Trial data also showed a statistically significant reduction in HIV-1 RNA viral load by 0.5log or more with PRO 140 from baseline compared to placebo (18,19). In the ongoing Phase 3 monotherapy **CD03** trial, virologically suppressed patients enrolled were prescreened for CCR5-tropic HIV-1 infection and approximately 40% of patients were able to maintain viral suppression with a 350mg weekly subcutaneous injection of PRO 140 (20). Subsequently, the trial protocol was revised to increase the weekly dose to 525 mg and the response rate increased to approximately 70% (20). In July 2018, CytoDyn Inc. announced that it had received clearance to increase the weekly PRO 140 dose further to 700mg for newly enrolled patients and patients who failed to maintain viral suppression on lower doses (20). CytoDyn Inc. would be submitting a Biologics License Application to the U.S. FDA at the end of 2018 (18).

VRC01 and second-generation antibodies

With laboratory studies showing the ability to stop up to 90% of HIV strains worldwide from infecting human cells, VRC01 is a bNab currently being studied as a form of passive immunization (21). At present, there are two large tandem NIAID-supported prevention trials evaluating VRC01 in Sub-Saharan Africa, which slated to end by 2022 (22,23). Second-generation VRC01-like antibodies have also been developed using different optimization approaches (24). VRC01LS, an altered form of the VRC01 monoclonal antibody with a half-life more than four times longer, has been demonstrated to be safe in healthy subjects in a new report recently published (25).

Pharmacokinetic studies on VRC07-523-LS, a clonal relative of VRC0, have also showed longer half-lives of 7 to 10 days in rhesus macaques, compared to VRC01 (5 to 6 days) (26). This paves the way for antibody-based products which potentially could be given on a 6-monthly basis by subcutaneous injection for prevention. Early-phase clinical trials of VRC01LS, VRC07-523LS and other bNabs for HIV treatment and prevention are also currently underway (24,27,28).

Nucleoside Reverse Transcriptase Translocation Inhibitor: MK-8591

LA formulations of Merck's MK-8591 (formerly known as EFdA) showed long-term suppression of viremia in HIV+ animal studies (29,30). Additional Phase I dosing data in healthy adults, presented at CROI 2018, showed that multiple daily dosing of MK-8591 as low as 0.25mg was well tolerated and expected to suppress HIV (31). Merck is now recruited 120 treatment-naïve patients for a Phase 2B trial, **DRIVE2SIMPLIFY**, intended to evaluate the safety, tolerability, PK and efficacy of once daily oral MK-8591 administered with doravirine and lamivudine, ending by 2020 (32).

Non-nucleoside reverse transcriptase inhibitor: Elsufavirine

Based on 48-week data demonstrating better tolerability and non-inferiority to efavirenz, elsufavirine is an oral NNRTI that is recently approved in Russia in July 2017 for treatment of HIV in combination with other antiretrovirals (33). At IAS 2017, pre-clinical pharmacokinetic data supporting the development of an injectable LA formulation was reported (34). LA subcutaneous and IM formulations are currently being studied outside the US (35).

Fusion Inhibitor: Albuvirtide

Albuvirtide is an injectable LA antiretroviral approved for use in treatment-experienced patients who have failed first and second-line therapy in China since June 2018 (36). Based on interim 48-week data from Phase 3 **TALENT** study, albuvirtide plus lopinavir/ritonavir (LPV/r) showed superiority over LPV/r plus two NRTIs as second-line therapy (37). While there was better renal safety over tenofovir disoproxil fumarate (TDF), high cholesterol and triglycerides were reported more commonly in the albuvirtide arm (37). In July 2017, the drug company, Frontier, announced a licensing agreement with Rockerfeller University in the U.S.to develop a co-formulation of albuvirtide with the broadly neutralizing HIV antibody 3BNC117.(38)

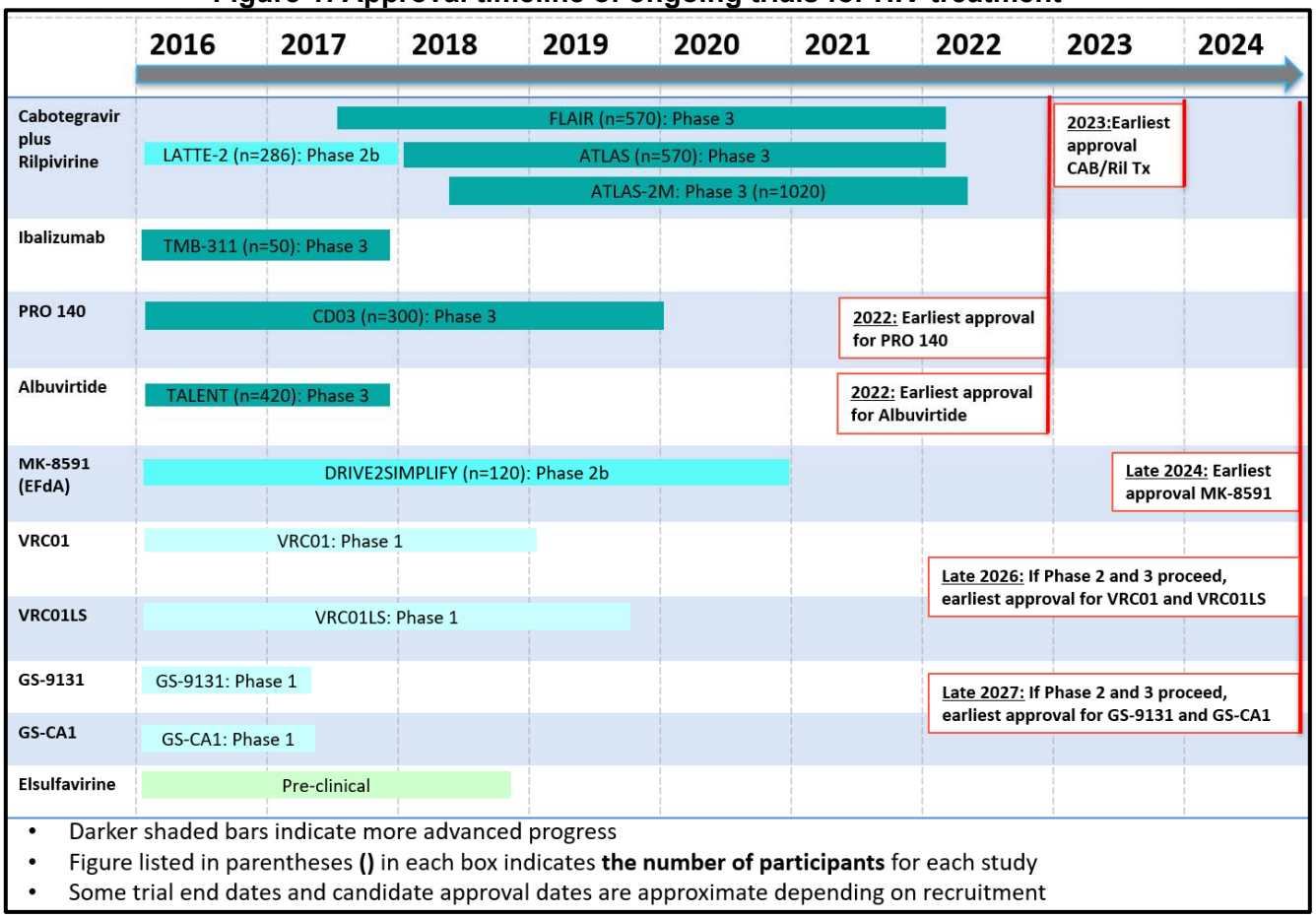
GS-9131 and GS-CA1

Gilead's GS-9131 is a prodrug of the adenosine nucleotide analog GS-9148.(39) Data presented at CROI 2017 highlighted its potent in vitro activity against HIV-1 and HIV-2, with a favorable resistance profile and additive to synergistic antiviral activity in combination with other antiretrovirals (40). Similarly, Gilead's investigational capsid inhibitor GS-CA1 demonstrated high potency in studies presented at CROI 2017 and is currently being developed as a subcutaneous injection for animal studies (41). These two candidates must overcome manufacturing hurdles in order to bring cost down before they can be tested further (42). However, there has been no new or ongoing data on both drug candidates since 2017.

3. Approval timeline

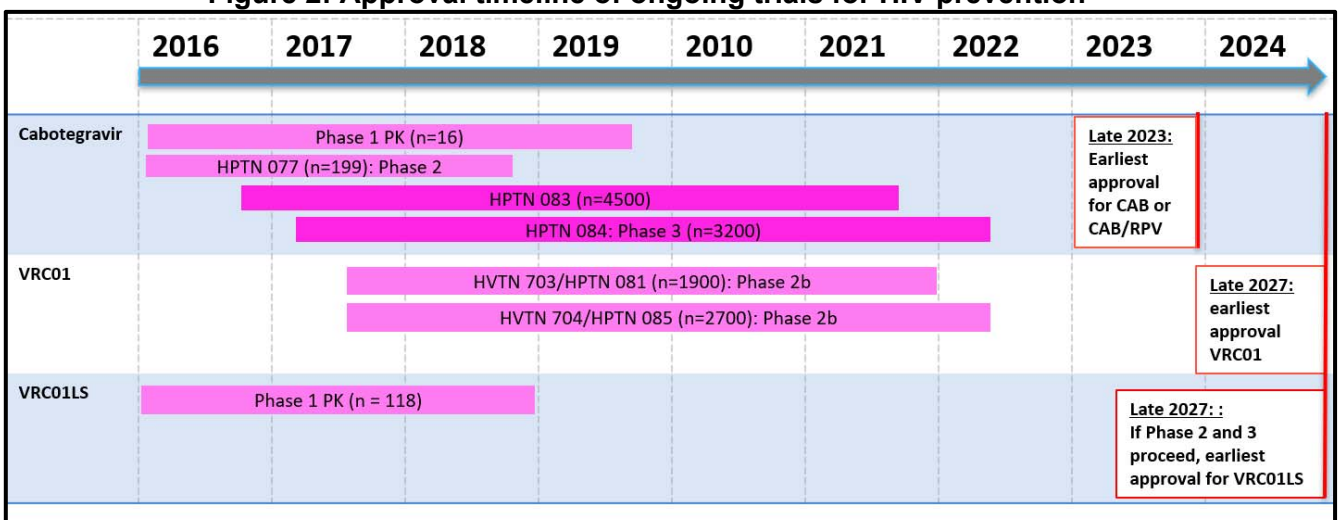
Figure 1 and 2 shows the approval timeline of ongoing trials for long-acting injectable candidates for HIV treatment and prevention discussed earlier in Section 2.

Figure 1: Approval timeline of ongoing trials for HIV treatment



- Darker shaded bars indicate more advanced progress
- Figure listed in parentheses **()** in each box indicates **the number of participants** for each study
- Some trial end dates and candidate approval dates are approximate depending on recruitment

Figure 2: Approval timeline of ongoing trials for HIV prevention



- Darker shaded bars indicate more advanced progress
- Figure listed in parentheses **()** in each box indicates **the number of participants** for each study
- Some trial end dates and candidate approval dates are approximate depending on recruitment

4. Barriers to uptake in the current development landscape

Current injectable formulations focused on LA cabotegravir/rilpivirine face multiple barriers to uptake if proven to be efficacious enough for large-scale development.

Considerations for Resource-Limited Settings

Infrastructure required to administer rilpivirine could be prohibitive in low- and middle-income settings because it requires a cold chain for storage. All candidates for wide-scale use in ARV programs should be formulated without such constraints. Administration of injections is resource-intensive, requiring considerable staff time compared to oral therapy (42). The oral lead-in period of current injectable LA drug candidates to rule out rare hypersensitivity reactions may also add complexity to their implementation. According to current estimates, 22% of patients who begin treatment do not complete it (43). Painful site injections and frequent visits to the clinic for time-intensive appointments may also potentially affect adherence. More information is needed to ascertain whether long-term adherence will improve, for some population, with less dependency to oral daily intake.

Furthermore, LA injection-based therapies for HIV treatment are unlikely to become standard of care in resource-limited settings if its treatment-associated costs remain high. For instance, the current list price for ibalizumab in 2018 is US$ 118,000 (wholesale acquisition cost) (16). LA injection-based therapies might be even less cost-effective if we include the programmatic costs for providing the infusions at healthcare settings. Although prices are not yet known for other candidates from other therapeutic classes and other formulations excluding infusions, they are expected to lower than that of ibalizumab. Similarly, the current WHO-recommended first-line regimen of tenofovir/lamivudine/dolutegravir (TDF/3TC/DTG) will be available as a fixed-dose combination at a cost of US$75 in most low and middle-income countries (44). If broadly neutralizing monoclonal antibodies show success in the randomised controlled trials, manufacturers would also need to demonstrate the feasibility of producing them at a reasonable cost and in setting with weak cold-chain infrastructure before they can be considered for broader use(45).

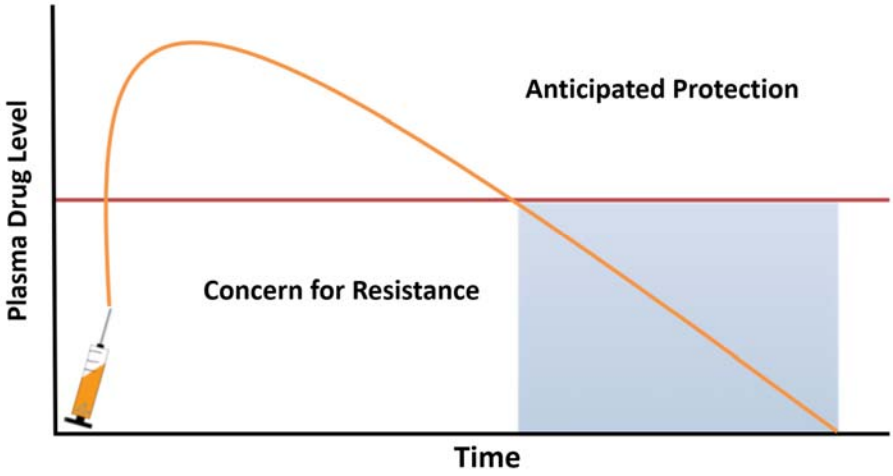
Adverse Events

To support their greater use, injectable LA antiretroviral candidates would need to show similar tolerability profile as tenofovir/emtricitabine (TDF/FTC) which is widely accepted as the standard choice for pre-exposure prophylaxis. A meta-analysis of 13 randomised clinical trials of TDF/FTC as PrEP showed no significant difference in risk of Grade 3/4 clinical adverse events or serious adverse events, including renal or bone adverse outcomes, when compared to control regimens (46). In comparison, the proportion of participants in the 4-week and 8-week cabotegravir LA plus rilpivirine LA injection group in the **LATTE-2** trial who reported Grade 3-4 adverse events was higher compared to oral treatment group (4-week group: 18% vs 8-week group: 21% vs oral treatment: 13%) (2). Injection-site reactions such as pain and swelling were most commonly reported, and results in 2 patients from the 8-week group (1%) withdrawing within 8 weeks of initiating dosing (2). Although this is a small proportion of withdrawals, this could mean a significant number of patients when applied to the large absolute numbers of the HIV epidemic.

Concern for antiretroviral resistance

Follow-up data from the **ECLAIR** prevention study revealed that a significant proportion of participants experienced an extended PK tail of residual drug levels after administration of the final dose for up to 52 weeks (47). At 24, 36 and 48 weeks after the last LA cabotegravir injection, a respective 41%, 22% and 16% of participants had subtherapeutic drug levels between the lower limit of quantification but below the IC_{90} (47), the level of drug that slows HIV replication by 90% during treatment (illustrated by Figure 3). Similarly, quantifiable rilpivirine levels was found in plasma and female genital tract fluids after 18 months after a single dose administration of LA rilpivirine injection as PrEP (4). These extended subtherapeutic PK tails mean that there is a long period even after discontinuing LA PrEP in which patients could develop antiretroviral resistance if they get infected with HIV, limiting future treatment or prevention options. Particularly for patients with a history of non-adherence or are lost to follow-up, this could potentially jeopardize the use of integrase inhibitors with high generic barrier to resistance such as dolutegravir.

Figure 3: Graph showing extended PK tail (48)



In addition, such an extended PK tail means that those who stop LA PrEP with continued risk behaviour may have to take oral PrEP for a year or more after completing their final dose of cabotegravir LA. Such an arrangement is counter-productive for patients who have specifically chosen an injectable LA formulation for improved adherence (49). On top of the oral lead-in period which may be required to rule out any hypersensitivity reactions, the need to use different antiretroviral formulations (oral and injectable) within a single treatment or prevention regimen also does not seem to offer any additional benefit compared to a once daily oral regimen (49). Patients who only adhere to a partial regimen also run the risk of being developing resistance or getting infected with HIV (49). Moving ahead, more information is required to evaluate long-term adherence rates in specific population groups with higher risk of non-adherence. Further characterization of injectable LA formulations' extended PK profile will also be necessary to inform clinical management during the PK tail.

Women of child-bearing potential / Pregnancy

As cabotegravir is an analogue of dolutegravir, the recent safety signal regarding the potentially increased risk of neural tube defects in babies born to women who become pregnant after taking dolutegravir at conception or the immediate period after should be a cause of concern (50). With this safety signal, WHO and regulatory authorities in Europe and USA have since recommended that women of child-bearing potential to avoid using DTG without effective contraception for the time being (51,52). Adolescent girls and women of childbearing potential who do not currently want to become pregnant can continue to receive DTG together with consistent and reliable contraception. This puts a slight delay towards the large-scale transition to dolutegravir-based first-line ART regimens in many countries. To avoid a similar situation at such a late stage of product development, studies on pregnant women should also be planned ahead.

Patients with Tuberculosis

Cabotegravir and rilpivirine are contraindicated for patients taking rifampin for TB co-infection.(53,54) In some countries, HIV/TB co-infection makes up one third of the patient volume, therefore eliminating a key group of potential treatment recipients. In 2016, 11% of all HIV positive patients were coinfected with TB globally, the majority of whom were on rifampin treatment (55).

Patients with Hepatitis B

Current tenofovir-based therapy for HIV patients has proven effective in helping treat patients with HIV/HBV co-infection, and discontinuation of these drugs can cause serious complications associated with reactivation of HBV (56). Initiation onto tenofovir-based antiretroviral treatment has a strong prophylactic benefit among co-morbid populations, and a switch to a standard of care that did not involve tenofovir could risk losing this protective effect.(57) Hepatitis B (HBV) virus is present in an estimated 10% of all cases of HIV-1 infection globally, so the percentage of patients at risk of reactivated HBV, and therefore ineligible for treatment that does not include TDF, is significant (58,59).

Target product profile for injectable long-acting antiretroviral

Ideally, a target product for an injectable LA treatment and prevention of HIV intended to improve adherence should possess the following characteristics. It must be safe and inexpensive in order to reach all groups.

- Exhibit similar or improved efficacy data to existing optimal oral therapies
- Be composed of a fixed-dose combination of injectable products
- High genetic barrier to resistance
- Incur minimal injection-associated adverse events
- Low in cost
- Safe in patients with TB, Hepatitis B co-infection and pregnancy (including periconception period)
- Low dosage volume of less than 2mL per injection
- No cold-chain requirement

Table 7 outlines the ideal and minimum acceptable profile for a long-acting injectable antiretroviral should some of the barriers be difficult to overcome.

Table 7: Ideal and minimum acceptable profile for a long-acting injectable antiretroviral candidate

Product Properties	Ideal profile	Minimum acceptable profile
Primary Indication	Viral suppression <50 copies/mL	Maintenance therapy
Patient Population	All HIV+ patients who are eligible for antiretroviral treatment	Patients excluded pregnant women and those with comorbidities
Resistance Profile	Improved resistance profile compared to oral regimens	Favorable resistance profile compared to oral regimens
Dosage Form	<2mL per injection	2mL per injection
Efficacy	Increased viral suppression when compared to oral therapy	As effective as oral therapy
Risk/Tolerability	No to mild risk of adverse events, no side effects, even at injection site	Mild to moderate side risk of adverse events, few side effects
Potency	Much higher potency compared to oral regimens, allowing for infrequent dosing	High potency compared to oral regimens

References

1. Margolis DA, Brinson CC, Smith GHR, de Vente J, Hagins DP, Eron JJ, et al. Cabotegravir plus rilpivirine, once a day, after induction with cabotegravir plus nucleoside reverse transcriptase inhibitors in antiretroviral-naive adults with HIV-1 infection (LATTE): a randomised, phase 2b, dose-ranging trial. Lancet Infect Dis [Internet]. 2015 Oct 1;15(10):1145–55. Available from: https://doi.org/10.1016/S1473-3099(15)00152-8
2. Margolis DA, Gonzalez-Garcia J, Stellbrink H-J, Eron JJ, Yazdanpanah Y, Podzamczer D, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. Lancet [Internet]. 2017 Sep 23;390(10101):1499–510. Available from: https://doi.org/10.1016/S0140-6736(17)31917-7
3. Nelson MR, Elion RA, Cohen CJ, Mills A, Hodder SL, Segal-Maurer S, et al. Rilpivirine versus efavirenz in HIV-1-infected subjects receiving emtricitabine/tenofovir DF: pooled 96-week data from ECHO and THRIVE Studies. HIV Clin Trials. 2013;14(3):81–91.
4. Bekker L-G, Li SS, Tolley B, Marzinke MA, Mgodi N, Justman JE, et al. HPTN 076: TMC278 LA safe, tolerable and acceptable for HIV pre-exposure prophylaxis. Conference on Retroviruses and Opportunistic Infections, February 13-16 2017, Seattle, Washington; 2017. Report No.: Abstract 421LB.
5. Healthcare V. ViiV Healthcare reports positive 48-week results for first pivotal, phase III study for novel, long-acting, injectable HIV-treatment regimen [Internet]. 2018. Available from: https://www.viivhealthcare.com/media/press-releases/2018/viiv-healthcare-reports-positive-48-week-results-for-first-pivotal-phase-iii-study-for-novel-long-acting-injectable-hiv-treatment-regimen.aspx [Date accessed: 6 September 2018]
6. Markowitz M, Frank I, Grant RM, Mayer KH, Elion R, Goldstein D, et al. Safety and tolerability of long-acting cabotegravir injections in HIV-uninfected men (ECLAIR): a multicentre, double-blind, randomised, placebo-controlled, phase 2a trial. lancet HIV. 2017 Aug;4(8):e331–40.
7. ClinicalTrials.gov. Study to Evaluate the Efficacy, Safety, and Tolerability of Long-acting Intramuscular Cabotegravir and Rilpivirine for Maintenance of Virologic Suppression Following Switch From an Integrase Inhibitor in HIV-1 Infected Therapy Naive Participants [Internet]. 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT02938520 [Date accessed: 1st August 2018]
8. ClinicalTrials.gov. Study Evaluating the Efficacy, Safety, and Tolerability of Switching to Long-acting Cabotegravir Plus Long-acting Rilpivirine From Current Antiretroviral Regimen in Virologically Suppressed HIV-1-infected Adults [Internet]. 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT02951052 [Date accessed: 1st August 2018]
9. ClinicalTrials.gov. Efficacy, Safety and Tolerability Study of Long-acting Cabotegravir Plus Long-acting Rilpivirine (CAB LA + RPV LA) in Human-immunodeficiency Virus-1 (HIV-1) Infected Adults [Internet]. 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT03299049 [Date accessed: 1st August 2018]
10. AIDSinfo. Rilpivirine LA (HIV prevention) [Internet]. 2018. Available from: https://aidsinfo.nih.gov/drugs/581/rilpivirine-la--hiv-prevention/0/patient [Date accessed: 1st August 2018]
11. ClinicalTrials.gov. Pharmacokinetic Study of Cabotegravir Long-acting in Healthy Adult Volunteers [Internet]. 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT02478463?term=cabotegravir&rank=4 [Date accessed: 1st August 2018]
12. ClinicalTrials.gov. Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), For Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women Who Have Sex With Men [Internet]. 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT02720094 [Date accessed: 1st August 2018]
13. ClinicalTrials.gov. Evaluating the Safety and Efficacy of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women [Internet]. 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT03164564 [Date accessed: 1st August 2018]
14. U.S. Food and Drug Administration. FDA approves new HIV treatment for patients who have limited treatment options [Internet]. 2018. Available from: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm599657.htm [Date accessed: 1st August 2018]
15. Emu B, Fessel WJ, Schrader S, Kumar PN, Richmond G, Win S, et al. Forty-eight-Week Safety and Efficacy On-Treatment Analysis of Ibalizumab in Patients with Multi-Drug Resistant HIV-1. Open Forum Infect Dis [Internet]. 2017 Oct 4;4(Suppl 1):S38–9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5632088/
16. i-BASE. FDA approves ibalizumab in the US to treat multidrug HIV resistance [Internet]. 2018. Available from: http://i-base.info/htb/33659 [Date accessed: 1st August 2018]
17. Dhody K, Pourhassan N, Kazempour K, Green D, Badri S, Mekonnen H, et al. PRO 140, a monoclonal antibody targeting CCR5, as a long-acting, single-agent maintenance therapy for HIV-1 infection. HIV Clin Trials [Internet]. 2018 May 4;19(3):85–93. Available from: https://doi.org/10.1080/15284336.2018.1452842
18. CytoDyn Inc. CytoDyn Announces Positive Results from Completed Pivotal PRO 140 HIV Combination Trial [Internet]. 2018. Available from: https://ir.cytodyn.com/press-releases/detail/284 [Date accessed: 4th August 2018]
19. Dhody K, Kazempour K, Pourhassan N, Maddon PJ. Primary efficacy results of PRO 140 SC in a pivotal Phase 2b/3 study in heavily treatment-experienced HIV-1 patients [Internet]. American Society for Microbiology (ASM) Microbe; June 7-11, 2018; Atlanta, GA; 2018. Available from: http://www.natap.org/2018/HIV/061118_02.htm

[Date accessed: 1st August 2018]
20. CytoDyn Inc. CytoDyn Announces Significantly Improved Response Rate at Higher Dose of PRO 140 in HIV Phase 3 Monotherapy Trial [Internet]. 2018. Available from: https://content.equisolve.net/cytodyn/news/2018-07-30_CytoDyn_Announces_Significantly_Improved_Response__286.pdf [Date accessed: 27th August 2018]
21. AIDSinfo. NIH Launches Large Clinical Trials of Antibody-Based HIV Prevention [Internet]. 2016. Available from: https://aidsinfo.nih.gov/news/1669/nih-launches-large-clinical-trials-of-antibody-based-hiv-prevention [Date accessed: 1st August 2018]
22. ClinicalTrials.gov. Evaluating the Safety and Efficacy of the VRC01 Antibody in Reducing Acquisition of HIV-1 Infection in Women [Internet]. 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT02568215 [Date accessed: 1st August 2018]
23. ClinicalTrials.gov. Evaluating the Safety and Efficacy of the VRC01 Antibody in Reducing Acquisition of HIV-1 Infection Among Men and Transgender Persons Who Have Sex With Men [Internet]. 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT02716675 [Date accessed: 1st August 2018]
24. The Collaboration for AIDS Vaccine Discovery. Mascola: BNAbs for Passive Immunization [Internet]. Available from: https://www.cavd.org/grantees/Pages/Grantee-mascola.aspx [Date accessed: 4th August 2018]
25. Gaudinski MR, Coates EE, Houser K V, Chen GL, Yamshchikov G, Saunders JG, et al. Safety and pharmacokinetics of the Fc-modified HIV-1 human monoclonal antibody VRC01LS: A Phase 1 open-label clinical trial in healthy adults. PLOS Med [Internet]. 2018 Jan 24;15(1):e1002493. Available from: https://doi.org/10.1371/journal.pmed.1002493
26. Rudicell RS, Kwon Y Do, Ko S-Y, Pegu A, Louder MK, Georgiev IS, et al. Enhanced potency of a broadly neutralizing HIV-1 antibody in vitro improves protection against lentiviral infection in vivo. J Virol. 2014 Nov;88(21):12669–82.
27. ClinicalTrials.gov. Evaluating the Safety and Pharmacokinetics of VRC01 and VRC01LS, Potent Anti-HIV Neutralizing Monoclonal Antibodies, in HIV-1-Exposed Infants [Internet]. 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT02256631 [Date Accessed: 1st August 2018]
28. ClinicalTrials.gov. Safety and Virologic Effect of a Human Monoclonal Antibody, VRC-HIVMAB080-00-AB (VRC01LS), With Broad HIV-1 Neutralizing Activity, Administered Intravenously to HIV-Infected Adults [Internet]. 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT02840474?term=vrc01ls&rank=1 [Date accessed: 1st August 2018]
29. Markowitz M, Gettie A, Bernard L St., Mohri H, Grasperge B, Blanchard J, et al. Low Dose MK-8591 protects Rhesus Macaques against rectal SHIV infection [Internet]. Conference on Retroviruses and Opportunistic Infections, March 4-7 2018, Boston, Massachusetts; 2018. Report No.: Abstract 89LB. Available from: http://www.croiconference.org/sessions/low-dose-mk-8591-protects-rhesus-macaques-against-rectal-shiv-infection [Date accessed: 1st August 2018]
30. Markowitz M, Gettie A, Bernard L St., Mohri H, Grasperge B, Blanchard J, et al. Weekly oral MK-8591 protects male rhesus macaques against repeated low dose intrarectal challenge with SHIVC109P3 [Internet]. 9th IAS Conference on HIV Science, July 23-26 2017, Paris, France; 2017. Report No.: Abstract MOAX0203LB. Available from: http://programme.ias2017.org/Abstract/Abstract/5533 [Date accessed: 1st August 2018]
31. Matthews RP, Rudd DJ, Levine V, Zhang S, Sterling L, Grobler J, et al. Multiple Daily Doses of MK-8591 as Low as 0.25 mg Are Expected to Suppress HIV [Internet]. Conference on Retroviruses and Opportunistic Infections, March 4-7 2018, Boston, Massachusetts; 2018. Report No.: Abstract 26. Available from: http://www.croiconference.org/sessions/multiple-daily-doses-mk-8591-low-025-mg-are-expected-suppress-hiv [Date accessed: 1st August 2018]
32. ClinicalTrials.gov. MK-8591 With Doravirine and Lamivudine in Participants Infected With Human Immunodeficiency Virus Type 1 (MK-8591-011) (DRIVE2Simplify) [Internet]. 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT03272347 [Date accessed: 1st August 2018]
33. Viriom. Viriom Obtains First Market Approval of Elsulfavirine (Elpida®) for Treatment of HIV-1 Infection in Russia [Internet]. 2017. Available from: https://www.viriom.com/news/2017/11/30/viriom-obtains-first-market-approval-of-elsulfavirine-elpida-for-treatment-of-hiv-1-infection-in-russia [Date accessed: 1st August 2018]
34. Bichko V, Rogovoy B, Koryakova A, Karapetian R, Sankar S, Nikoulin I, et al. Pre-clinical pharmacokinetics of elsulfavirine/VM1500A long acting injectable formulations [Internet]. 9th International AIDS Society Conference on HIV Science, 23-26 July 2017, Paris, France; 2017. Available from: http://programme.ias2017.org/Abstract/Abstract/1515
35. Viriom. Pipeline [Internet]. 2018. Available from: www.viriom.com/pipeline [Date accessed: 1st August 2018]
36. Barber J. Frontier Biotechnologies' Aikening gains approval in China as first domestically developed HIV therapy [Internet]. FirstWord Pharma. 2018. Available from: https://www.firstwordpharma.com/node/1570731 [Date accessed: 1st August 2018]
37. Xie D. Efficacy and safety of long acting HIV fusion inhibitor albuvirtide in antiretroviral-experienced adults with HIV-1: interim 48 week results from the randomized, controlled, phase 3, non-inferiority TALENT study [Internet]. Glasgow Congress on HIV Therapy, 23-26 October 2016, Glasgow, Scotland; 2016. Report No.: O336. Available from: http://www.natap.org/2016/GLASGOW/GLASGOW_38.htm [Date accessed: 1st August 2018]
38. Frontier Biotechnologies Inc. Frontier Biotech Sponsored The "HIV Broad Spectrum Neutralizing Antibodies and Functional Cure" Forum at Tsinghua University [Internet]. 2017. Available from: http://www.frontierbiotech.com/en/news/details_11_40.html [Date accessed: 1st August 2018]

39. Cihlar T, Ray AS, Boojamra CG, Zhang L, Hui H, Laflamme G, et al. Design and profiling of GS-9148, a novel nucleotide analog active against nucleoside-resistant variants of human immunodeficiency virus type 1, and its orally bioavailable phosphonoamidate prodrug, GS-9131. Antimicrob Agents Chemother. 2008 Feb;52(2):655–65.
40. White KL, Margot N, Stray K, Yu H, Stepan G, Boojamra C, et al. GS-9131 is a Novel NRTI with Activity Against NRTI-Resistant HIV-1 [Internet]. Conference on Retroviruses and Opportunistic Infections, February 13-16 2017, Seattle, Washington; 2017. Report No.: 436. Available from: http://www.croiconference.org/sessions/gs-9131-novel-nrti-activity-against-nrti-resistant-hiv-1 [Date accessed: 1st August 2018]
41. Tse WC, Link JO, Mulato A, Niedziela-Majka A, Rowe W, Somoza JR, et al. Discovery of Novel Potent HIV Capsid Inhibitors with Long-Acting Potential [Internet]. Conference on Retroviruses and Opportunistic Infections, February 13-16 2017, Seattle, Washington; 2017. Report No.: 38. Available from: http://www.croiconference.org/sessions/discovery-novel-potent-hiv-capsid-inhibitors-long-acting-potential [Date accessed: 1st August 2018]
42. HIV i-BASE. HIV Pipeline 2017: New Drugs in Development. [Internet]. 2017. Vol 18:(1) pp 7-10. Available from: http://i-base.info/htb/wp-content/uploads/2017/07/HIV-Pipeline-2017-full-version.pdf [Date accessed: 1st August 2018]
43. Bain LE, Nkoke C, Noubiap JJN. UNAIDS 90–90–90 targets to end the AIDS epidemic by 2020 are not realistic: comment on “Can the UNAIDS 90–90–90 target be achieved? A systematic analysis of national HIV treatment cascades”. BMJ Glob Heal [Internet]. 2017 Mar 1;2(2). Available from: http://gh.bmj.com/content/2/2/e000227.abstract
44. UNITAID. New high-quality antiretroviral therapy to be launched in South Africa, Kenya and over 90 low- and middle- income countries at reduced price. [Internet]. 2017. Available from: https://unitaid.eu/news-blog/new-high-quality-antiretroviral-therapy-launched-south-africa-kenya-90-low-middle-income-countries-reduced-price/#en [Accessed 22nd May 2018]
45. Barnhart M. Long-Acting HIV Treatment and Prevention: Closer to the Threshold. Glob Heal Sci Pract [Internet]. 2017 Jun 27;5(2):182–7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5487081/
46. Pilkington V, Hill A, Hughes S, Nkwolo N, Pozniak A. Meta-analysis of the risk of Grade 3 / 4 or Serious Clinical Adverse Events in 12 randomised trials of PrEP (n=15,678) [Internet]. 2018. Available from: Unpublished
47. Ford SL, Stancil BS, Markowitz M, Frank I, Grant RM, Mayer KH, et al. ECLAIR Study of Cabotegravir (CAB) LA Injections: Characterization of Safety and PK During the ‘PK Tail’ Phase. HIV Research for Prevention (HIVR4P) conference, October 17 - 21 2016, Chicago; 2016. Report No.: Abstract OA12.06LB.
48. HIV Prevention Trials Network. HPTN 083: Give PrEP a Shot! [Internet]. 2017. Available from: https://www.hptn.org/sites/default/files/inline-files/HPTN083Webinar_0.pdf [Date accessed: 1st August 2018]
49. Arya V, Au S, Belew Y, Miele P, Struble K. Regulatory challenges in developing long-acting antiretrovirals for treatment and prevention of HIV infection. Curr Opin HIV AIDS. 2015 Jul;10(4):278–81.
50. World Health Organisation. Dolutegravir and the risk of neural tube defects [Internet]. 2018. Available from: http://www.who.int/medicines/publications/drugalerts/Statement_on_DTG_18May_2018final.pdf [Accessed 11th July 2018]
51. European Medicines Agency. New study suggests risk of birth defects in babies born to women on HIV medicine dolutegravir [Internet]. 2018 [cited 2018 Jul 11]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/05/news_detail_002956.jsp&mid=WC0b01ac058004d5c1
52. Department of Health and Human Services. Recommendations Regarding the Use of Dolutegravir in Adults and Adolescents with HIV who are Pregnant or of Child-Bearing Potential [Internet]. 2018. Available from: https://aidsinfo.nih.gov/news/2109/recommendations-regarding-the-use-of-dolutegravir-in-adults-and-adolescents-with-hiv-who-are-pregnant-or-of-child-bearing-potential [Accessed 11th July 2018]
53. Crauwels H, van Heeswijk RPG, Stevens M, Buelens A, Vanveggel S, Boven K, et al. Clinical perspective on drug-drug interactions with the non-nucleoside reverse transcriptase inhibitor rilpivirine. AIDS Rev [Internet]. 2013;15(2):87–101. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med7&NEWS=N&AN=23681436
54. Ford SL, Sutton K, Lou Y, Zhang Z, Tenorio A, Trezza C, et al. Effect of Rifampin on the Single-Dose Pharmacokinetics of Oral Cabotegravir in Healthy Subjects. Antimicrob Agents Chemother. 2017 Oct;61(10).
55. UNAIDS. Fact sheet - Latest statistics on the status of the AIDS epidemic [Internet]. Available from: http://www.unaids.org/en/resources/fact-sheet [Accessed 20th May 2018]
56. Dore GJ, Soriano V, Rockstroh J, Kupfer B, Tedaldi E, Peters L, et al. Frequent hepatitis B virus (HBV) rebound among HIV – HBV coinfected patients following antiretroviral therapy interruption in the SMART study. AIDS [Internet]. 2010 Mar 27;24(6):857–65. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2881334/
57. Shilaih M, Marzel A, Scherrer AU, Braun DL, Kovari H, Rougemont M, et al. Dually Active HIV/HBV Antiretrovirals as Protection Against Incident Hepatitis B Infections: Potential for Prophylaxis. J Infect Dis. 2016 Aug;214(4):599–606.
58. Puoti M, Airoldi M, Bruno R, Zanini B, Spinetti A, Pezzoli C, et al. Hepatitis B virus co-infection in human immunodeficiency virus-infected subjects. AIDS Rev [Internet]. 2002;4(1):27–35. Available from: http://europepmc.org/abstract/MED/11998781
59. Kourtis AP, Bulterys M, Hu DJ, Jamieson DJ. HIV-HBV coinfection--a global challenge. N Engl J Med. 2012

May;366(19):1749–52.