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Use of long-acting injectable antiretroviral agents for Human Immunodeficiency Virus: A review

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Abstracy

The development of potent antiretroviral drugs has significantly reduced morbidity and mortality associated with human immunodeficiency virus infection, however, the effectiveness of these medications depends upon consistent daily oral intake. Non-adherence can lead to the emergence of resistance, treatment failure and disease progression. This has necessitated the development of long-acting antiretroviral formulations administrable via an infrequent dosing regimen. Long-acting injectable forms of cabotegravir and rilpivirine have reached advanced stages in clinical trials both for the treatment and prevention of HIV. Other long-acting agents are at various stages of development. This review evaluates the current research on the development of long-acting injectable antiretroviral agents for the treatment and prevention of HIV.

Keywords: Cabotegravir, Rilpivirine, Antiretrovirals, Intramuscular, Non-adherence

Highlights

- Long-acting injectable antiretroviral agents are being developed as potential alternatives to pill-based treatment regimens for HIV.
- Two of these agents, cabotegravir and rilpivirine, have been demonstrated as tolerable and efficacious at managing infection when administered in combination.
- Other long-acting injectable antiviral agents are at various stages of development.

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Background

In recent decades human immunodeficiency virus (HIV) infection has become a chronic manageable condition [1,2]. Its treatment is centred on the use of highly active antiretroviral therapy (HAART), which consists of three antiretroviral drugs that are taken daily, typically in pill forms [2]. There is also approval for the use of two antiretroviral drugs, tenofovir and emtricitabine, for pre-exposure prophylaxis in prevention among high-risk individuals [3,4]. HAART is effective in achieving viral suppression in more than 90% of patients but this suppression requires consistent daily use [5–7]. Oral daily intake of antiretroviral drugs has been shown to be a burden causing distress for patients and leading to non-adherence in a significant number [7]. Non-adherence can predispose to the emergence of drug-resistant HIV strains, treatment failure and disease progression [8–10]. There has therefore been an effort to simplify HIV treatment and prevention with the use of long-acting injectable antiretroviral agents that allow monthly administration [11–16].

These agents include forms of traditional antiretroviral drugs, as well as forms of newer antiviral agents such as humanised antibodies and broadly neutralizing antibodies [17–19]. Most developing long-acting injectable antiretroviral agents can be administered intramuscularly or subcutaneously, however other methods of delivery are also being researched. These alternative delivery methods include implants, patches, vaginal rings and intravenous administration [20–22].

The aim of this review is to evaluate the available evidence on the development and use of long-acting injectable antiretroviral agents in HIV treatment and prevention.

Integrase strand transfer inhibitors (INSTI)

The integrase strand transfer inhibitors are a class of antiretroviral drugs that block the HIV integrase enzyme thereby preventing viral integration into the host genome. There are currently four approved oral formulations: raltegravir, elvitegravir, dolutegravir and bictegravir. They generally have a high barrier to resistance[23]. Members of this class, including the investigational drug cabotegravir, are being developed for use as long-acting injectables [24] see Table 1.

Cabotegravir

Cabotegravir (GSK 1265744) is an investigational drug that belongs to the second generation of INSTIs [25,26]. It is produced in an oral form as well as in an injectable form (subcutaneous and intramuscular) [26,27]. The half-life of the drug is 20-40 days as an injectable formulation which makes up to bimonthly use potentially possible [26,28].

Reports from phase II prevention trials demonstrated that injectable cabotegravir was safe and well-tolerated among the participants [29,30]. A separate phase III non-inferiority trial investigated the prophylactically administeradministration ed of intramuscular cabotegravir to prevent HIV infection among men who have sex with men (MSM) and transgender (TGW) women. A preliminary report of this trial supports the effectiveness of cabotegravir at preventing HIV infection, compared with oral administered tenofovir/emtricitabine combination [31,32].

Clinical trials continue to assess the use of injectable cabotegravir for pre-exposure prophylaxis (PrEP) [29,31]. Findings from a study among over 3,000 women in 7 African countries unequivocally conclude that long-acting injectables cCabotegravir effectively protected women from HIV acquisition when used as PrEP [33].

Raltegravir

Raltegravir is another INSTI that is being developed as a long-acting injectable [34]. It is approved in its oral form for treatment and prevention (post-exposure prophylaxis (PEP)) of HIV [1], but its development as a long-acting agent is still in the preclinical stage. A study on humanised bone marrow-liver-thymus (BLT) mice had subcutaneous long-acting raltegravir administered at 7.5mg., il

In this study the pharmacokinetic properties were similar to ~~400mg~~ those of 400mg oral raltegravir and the treatment showed potency at protecting the BLT mice from HIV vaginal challenge up to four weeks following single-dose administration, whilst the control mice were not protected from HIV infection. The plasma level of the drug was also noted to be comparable to that of the oral form [35]. This report also revealed the presence of the active drug in the female genital tract of the mice, a finding that if reproduced in humans may indicate usefulness as preventive intervention as sexual intercourse is one of the common routes of HIV transmission.

Dolutegravir

Oral forms of dolutegravir have proven efficacious, with oral dolutegravir being one of the first drugs approved as part of dual therapy in the management of HIV infection due to its very high potency [36]. However the development of a long-acting injectable form is still at a very early stage [37].

Bictegravir

Bictegravir oral formulation is the most recent INSTI to secure US Food and Drug Administration (FDA)approval. It is also at an early stage of development into a long-acting injectable [38]. It has the highest barrier to resistance among the INSTI group [34], and a long-acting injectable could also potentially possess this quality.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

~~This group of antiretroviral drugs~~NNRTIs alter the reverse transcriptase enzyme of HIV and inhibit its replication [23,39]. Oral formulations of NNRTIs have been in clinical use for decades and their use as long-acting agents is being evaluated [40].

Rilpivirine

Rilpivirine (TMC278) is a second-generation NNRTI with an approved oral form. This form is combined with other antiretroviral drugs for treatment-naïve HIV-1 infected individuals with a viral load (HIV-1 RNA) of 100,000 copies/ml or below [41,42]. A long-acting injectable form of rilpivirine with a half-life of 30-90 days has been developed. This form allows administration as an intramuscular injection once every four

to eight weeks [11,43–45]. This is in contrast to the oral form which has a half-life of 24–45 hours and must therefore be taken daily to be effective [46]. A comparable drug concentration to that of the oral form was detected in the plasma up to 84 days following administration of the long-acting injectable in early clinical studies [11,43]. The injectable form is at an advanced stage of development in combination with cabotegravir as a long-acting agent for HIV treatment. A study reported its safety in a phase I trial and *ex vivo* evaluation revealed that it suppressed infection up to four months after administration [47]. Further clinical development of rilpivirine for pre-exposure prophylaxis is expected, however, a major concern with the suitability of rilpivirine for prevention is its low barrier to resistance [48].

Cabotegravir and rilpivirine combination

The combination of cabotegravir and rilpivirine is the most widely studied long-acting injectable regimen developed for the management of HIV. Several studies have reported the safety and tolerability of the long-acting formulations in separate use [11,29,43], and numerous recent studies report their use in combination. In the Long-Acting antireTroviral Treatment Enabling (LATTE) study involving 243 subjects, combined oral cabotegravir and rilpivirine demonstrated superior efficacy to an efavirenz plus dual NRTIs based-regimen for up to 96 weeks: virologic suppression was seen among 86% of the former treatment group, compared to up to 68% of the latter. The combination was determined to be efficacious and safe lending support for their further study [49].

In a separate study conducted among 40 healthy adults a 14-day lead-in of oral cabotegravir was given, followed by monthly intramuscular and subcutaneous injections of cabotegravir and rilpivirine at a dose range of 200-800 mg and 600-1200 mg respectively for a duration of 3 months. Targeted plasma concentrations (0.66 µg/mL) of the drugs were attained within three days of administration, and there were no significant adverse reactions or laboratory abnormalities reported [24]. This corroborates the earlier studies on the tolerance and safety of the drugs [29,43].

A separate study, LATTE-2, involved 309 ART-naïve HIV-1 positive adult patients. The study utilised an induction phase of cabotegravir followed by a 96-week maintenance phase, composed of either

long-acting cabotegravir and rilpivirine at four- or eight-weeks intervals or the control treatment (daily, oral cabotegravir) (figure 1). At week 96, HIV-1 RNA was below 50 copies/ml in 87% of the four-weekly group, 94% of the eight-weekly group and 84% of the control group. Adverse reactions were comparable among the three groups with injection site reaction (ISR) being the most common followed by nasopharyngitis, diarrhoea and headaches [12]. The efficacy of the dual long-acting cabotegravir and rilpivirine was shown to be comparable to the oral triple regimen, consistent with the findings of the LATTE study.

In the phase III Antiviral Therapy as Long-Acting Suppression Study (ATLAS) study, the combination of long-acting cabotegravir and rilpivirine was compared to a triple oral regimen (figure 2). The long-acting injectable combination had similar virologic suppression rates to the triple oral regimen (285/308 (92.5%) compared to 294/308 (95.5%) at week 48 of therapy). Confirmed virologic failure was infrequent and similar in both arms. There was a low rate of serious adverse effects 13/308 (4.2%) and withdrawal-related to the injection (1.3%). The ISR throughout the 48 weeks period in the injection group was 1460 out of 6978 injections administered. The reaction was most often mild and resolved within three days [50].

A separate phase III study, First Long-Acting Injectable Regimen (FLAIR) (figure 3), supports the findings of the ATLAS study. FLAIR demonstrated the non-inferiority of injectable cabotegravir plus rilpivirine to oral abacavir/dolutegravir/lamivudine. HIV 1 RNA was below 50 copies/ml in 265/283 (93.6%) of the long-acting treatment group participants and 264/283 (93.3%) in the control group participants. The virologic failure and rate of adverse reactions were similar in the two groups and to that of the participants in the ATLAS study [51]. The ATLAS and FLAIR studies assessed the use of the long-acting agents at four-week intervals. An extension of the ATLAS study, ATLAS-2M (figure 2,) investigated the administration of the drugs at 8 eight-weekly intervals. An eight-weekly regimen of long-acting cabotegravir and rilpivirine was compared with a four-weekly regimen, and it was determined that, at 48 weeks of administration, the 8 eight-weekly regimen of cabotegravir and rilpivirine long-acting injectables was non-inferior to the 4 eight-weekly regimen [52].

The results of these phase III trials revealed the efficacy and tolerability of combined cabotegravir and rilpivirine long-acting injectables. The combination received approval for use in Canada in early 2020 while European Medicine Agency and United States Food and Drug Administration gave approval for the use in October 2020 and January 2021 respectively [53–55]. It should be noted that children and adolescents were excluded in phase III studies and LATTE studies. A new study tagged More Options for Children and Adolescents (MOCHA) is underway and aims to define the pharmacokinetics and safety of cabotegravir and rilpivirine injections in children age 12 to 17 [56]. It should be noted that the current studies excluded patients with advanced HIV (CD4 < 200 cells/mm^3) and those having used ART long-term [12,57]. Determining the efficacy of these drugs amongst these groups are desirable. Similarly, the studies excluded patients with major comorbidities such as renal and liver diseases. The longest duration of follow-up reported with the use of the long-acting injectables so far is 96 weeks [12], therefore longer-term follow-up may be warranted.

Drug Resistance

The development of resistance is an area of great concern in any drug-centred treatment strategy [58]. One way in which long-acting agents seek to address this issue is through improved adherence to reduce the rate or possibility of resistance development [8]. However, the possibility of the emergence of resistance during therapy remains. In studies the emergence of resistance has been demonstrated to be similar among those using long-acting injectables and the control groups [51,52].

Further, there are potential limitations associated with the use of long-acting injectable antiretroviral agents in patients with resistance to an oral regimen. In clinical trials, those with detectable drug resistance or virologic failure were excluded. This may influence the generalization of the study's findings in these group of patients. Therefore, studies to address this will be warranted.

Drug-drug interactions

The interactions of antiretroviral drugs with other medications is an important aspect of HIV management [59]. For example rilpivirine interacts with proton-pump inhibitors, anti-convulsants (carbamazepine and phenytoin) and rifampicin, all reducing the plasma level of the drug [60].

Rifampicin also interacts with cabotegravir. The former is a potent liver enzyme inducer that increases the metabolism of cabotegravir and may lead to its early clearance from the circulation, leading to a subtherapeutic level which may predispose to the emergence of resistance and virologic failure [61]. Rifampicin is a key component in the management of tuberculosis (TB)and TB has a high incidence among PLWHIV [62].

Future studies should assess the potential interactions of cabotegravir with other medications used to treat common comorbidities amongst HIV patients, such as hepatitis B and C. A study on the interactions of orally administered dolutegravir and daclatasvir, a hepatitis C antiviral agent, showed that the latter alters the pharmacokinetic properties of dolutegravir, with the maximum observed concentration and the end of dosing interval concentration increased by 29% and 45% respectively. However, this alteration was not clinically significant [63]. Carbamazepine interactions with dolutegravir required the doubling of its dose [64]. These interactions should be considered when designing and implementing long-acting formulations. However, it should also be considered that it is not necessarily possible to fully extrapolate studies on oral formulations to the injectables [65].

Patient experience and satisfaction

Patient satisfaction is important to treatment adherence. The HIV Treatment Satisfaction Questionnaire (HIVTSQ) is used to assess the treatment convenience, continuation of therapy and how flexible a treatment option is among other components. Studies have measured patient satisfaction regarding long-acting injectables using the HIVTSQ.

There was a high level of treatment satisfaction among the two long-acting treatment groups and the oral control group in the LATTE-2 study with 246/254 (97%) picking a score of 5 or 6 out of a total of 6 (the higher the score the higher the level of satisfaction), and with more participants satisfied to continue intramuscular therapy than oral (99% in both intramuscular group and 78% in the oral group) at week 96. However, the non-inclusion of those that dropped out before the 96-week should be noted [12].

In a qualitative study of 27 participants in Spain and the United States in the same LATTE-2 trials convenience, privacy, reduction in stigmatisation and discrimination were all important benefits believed to be associated with the use of injectable ARVs, but respondents still desired a less frequent regimen that would further reduce the number of healthcare visits [66]. It should be considered that the increase in satisfaction among the injectable group may have been influenced by the selection of individuals who consented to the use of intramuscular treatment at the start of the randomisation.

Similarly, a high level of satisfaction was reported in the ATLAS and FLAIR studies (99% and 97 % respectively) among the injection arm [57], whilst in the study on the use of cabotegravir injection for the prevention of HIV infection (ÉCLAIR trial), a significant number of the participants were satisfied with cabotegravir injection 75% (n=64), expressed a desire to continue usage 79% (n=68) and were willing to recommend it for others 87% (n=75) [67].

Challenges

The results of the ongoing clinical trials on injectable antiretrovirals for HIV treatment and prevention have been encouraging, but some challenges still need to be resolved. There will be a need for patients to adhere to the injection schedule as non-adherence will expose the virus to a sub-therapeutic level of drugs over an extended period and may contribute to the selection of resistant strains especially among individuals that are lost to follow-up [29]. For patients that missed injections, there may be a need to return them to oral medications. Studies among patients with poor adherence will likely be desirable to understand the acceptability of the regimen and how to manage their circumstances.

The development of easy-to-use subcutaneous injections may address the need for patients to present at health facilities for drug administration. It was documented that in a ~~rural Uganda~~ population of HIV positive women in rural Uganda, subcutaneous long-acting depot medroxyprogesterone acetate was successfully used, indicating the possibilities of adopting a comparable scheme for injectable antiretrovirals in similar communities [68]. However, health care workers will still need to follow-up patients, as the management of HIV involves more than maintaining drug administration. Drug-related adverse events may be an issue in some patients, for example. The use of short oral lead-in was to address this problem, but idiosyncratic reactions may still occur even among those that tolerated the oral formulations [69].

Furthermore, injections of current formulations have been associated with ISR and pain leading to discomfort, a factor that may affect acceptability [12]. It is possible the development of low volume injections may help to reduce problems associated with administration. There is also a need to develop injectables used in combination, but delivered separately, into a single combined injection to reduce the number of injections administered per healthcare visit, simplifying administration further and reducing the number of injections.

Another concern is the requirement for the rilpivirine injectable formulation to be stored between 2 to 8^0C [70]. This may be a particular concern in resource-poor environments, potentially limiting distribution and accessibility. A possible solution would be to use the existing cold-chain channels that are being used to distribute vaccines in these areas. This may pose an organisational challenge, requiring the collaboration of stakeholders to be successful.

There remains a need for long-term data and real-world experience on the use of long-acting injectables, in addition to studies on specific groups of patients excluded from the studies here reviewed, such as those with advanced progression to AIDS, as well as children and adolescents. These challenges present opportunities for more research.

Conclusion

Current oral antiretroviral drugs have been successful at reducing HIV morbidity and mortality and have contributed to prevention efforts. However, adherence is crucial to sustaining progress in the long-term. The development of long-acting injectable formulations has the potential to simplify antiretroviral therapy and promote adherence by allowing for up to bimonthly administration. There are many long-acting injectable antiretroviral formulations at various stages of preclinical and clinical development for use in the prevention and treatment of HIV. Whilst this review has focused on the most developed injectable antiretrovirals, the development of additional groups (including capsid inhibitors and entry inhibitors) is underway (see Table 1).

This review includes agents already approved as oral formulations as well as investigational drugs. Of these cabotegravir and rilpivirine are the most studied, and both have demonstrated non-inferiority to a triple oral ARV regimen.

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Table 1 Long-acting injectable antiretroviral agents

Class	Agents	Developmental Stage	References
Nucleoside reverse transcriptase inhibitors (NRTIs)	Tenofovir Alafenamide Fumarate*	Preclinical	[71]
	Emtricitabine*	Preclinical	[26]
Non-nucleoside reverse transcriptase inhibitors (NRTIs)	Rilpivirine	Phase III	[24,57,72]
	Elsulfavirine+	Preclinical	[73,74]
	Cmpd1+	Preclinical	[75]
Protease inhibitors (PIs)	Atazanavir	Preclinical	[76]
	Ritonavir	Preclinical	[33]
Integrase strand transfer inhibitors (INSTI)	Cabotegravir+	Phase III	[27-29]
	Raltegravir	Preclinical	[35]
	Dolutegravir	Preclinical	[37]
	Bictegravir	Preclinical	[38]
Entry inhibitors	Maraviroc	Preclinical	[77]
Capsid inhibitors	GS-CA1+	Phase I	[78,79]

*The agents being developed as co-formulated long-acting agents +No FDA approved oral formulation. INSTI and NRTIs group are further discussed in this review being the most developed.

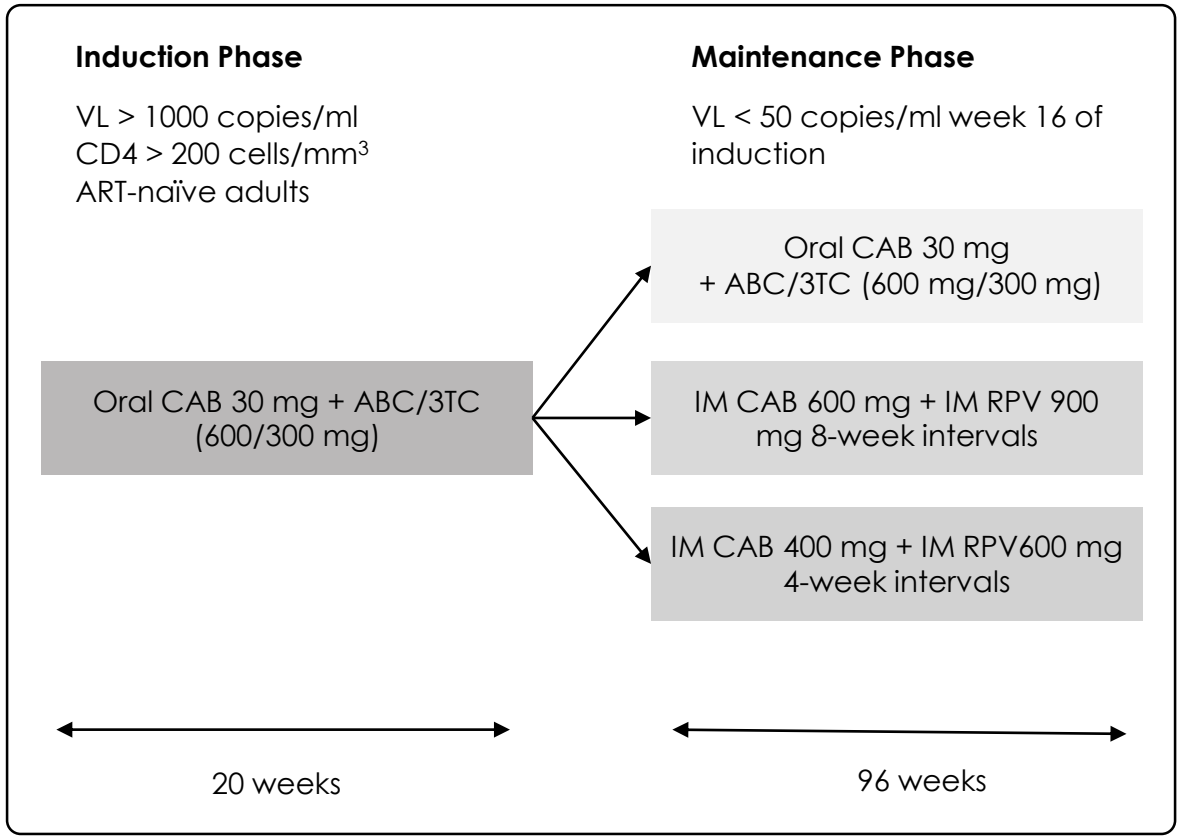

Figure 1 LATTE-2 study. Comparison of oral daily cabotegravir/abacavir/lamivudine with long-acting cabotegravir and rilpivirine use at 4-week and 8-week intervals. VL- viral load, ART- antiretroviral therapy, CAB- cabotegravir, ABC/3TC- abacavir/lamivudine, RPV- rilpivirine, IM- intramuscular, adapted from [61, 62]

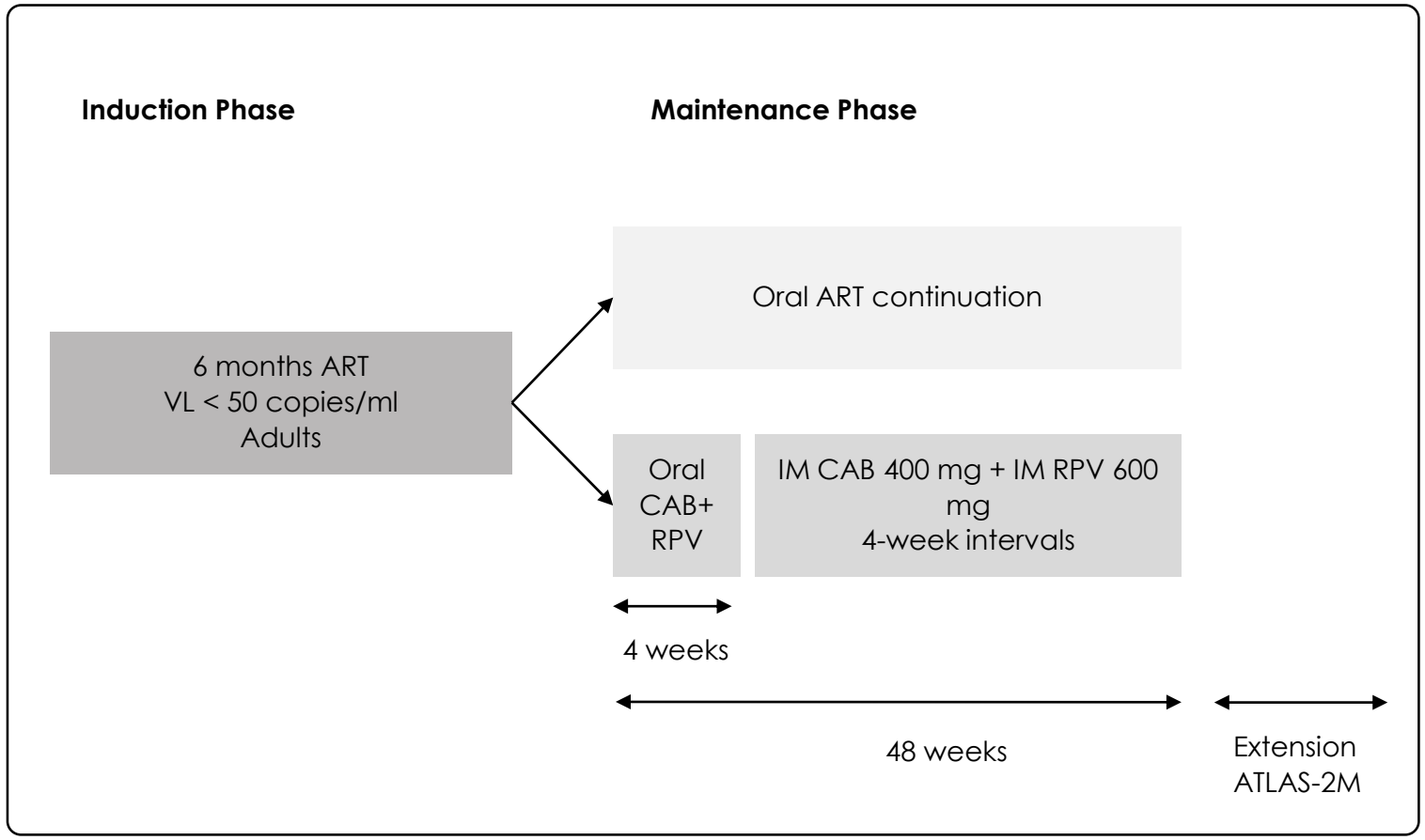

Figure 2 ATLAS study. Monthly intramuscular cabotegravir and rilpivirine combination compared with oral antiretrovirals. VL- viral load, ART- antiretroviral therapy, CAB- cabotegravir, RPV- rilpivirine, IM- intramuscular [61]

Figure 3 Source File

Click here to access/download;Figure;Figure 3_Source File.pptx

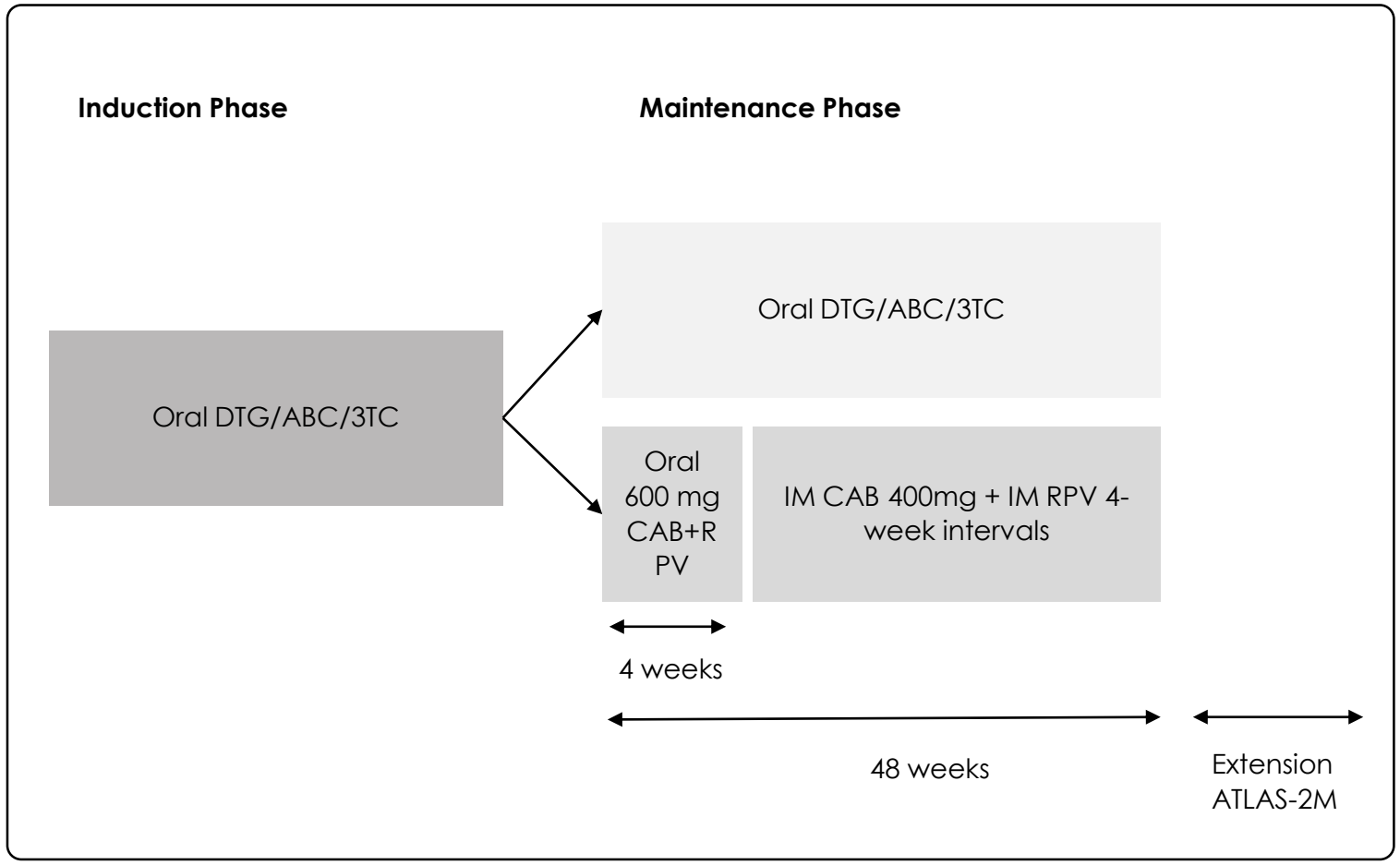

Figure 3 FLAIR study. Comparison of oral dolutegravir/abacavir/lamivudine with injectable cabotegravir and rilpivirine combination used monthly. DTG- dolutegravir, ABC- abacavir, 3TC- lamivudine, CAB- cabotegravir, RPV- rilpivirine, IM- intramuscular, adapted from [61]

Use of long-acting injectable antiretroviral agents for Human Immunodeficiency Virus: A review

Background

In recent decades human immunodeficiency virus (HIV) infection has become a chronic manageable condition [1,2]. Its treatment is centred on the use of highly active antiretroviral therapy (HAART), which consists of three antiretroviral drugs that are taken daily, typically in pill forms [2]. There is also approval for the use of two antiretroviral drugs, tenofovir and emtricitabine, for pre-exposure prophylaxis in prevention among high-risk individuals [3,4]. HAART is effective in achieving viral suppression in more than 90% of patients but this suppression requires consistent daily use [5–7]. Oral daily intake of antiretroviral drugs has been shown to be a burden causing distress for patients and leading to non-adherence in a significant number [7]. Non-adherence can predispose to the emergence of drug-resistant HIV strains, treatment failure and disease progression [8–10]. There has therefore been an effort to simplify HIV treatment and prevention with the use of long-acting injectable antiretroviral agents that allow monthly administration [11–16].

These agents include forms of traditional antiretroviral drugs, as well as forms of newer antiviral agents such as humanised antibodies and broadly neutralizing antibodies [17–19]. Most developing long-acting injectable antiretroviral agents can be administered intramuscularly or subcutaneously, however other methods of delivery are also being researched. These alternative delivery methods include implants, patches, vaginal rings and intravenous administration [20–22].

The aim of this review is to evaluate the available evidence on the development and use of long-acting injectable antiretroviral agents in HIV treatment and prevention.

Integrase strand transfer inhibitors (INSTI)

The integrase strand transfer inhibitors are a class of antiretroviral drugs that block the HIV integrase thereby preventing viral integration into the host genome. There are currently four approved oral formulations: raltegravir, elvitegravir, dolutegravir and bictegravir. They generally have a high barrier to resistance[23]. Members of this class, including the investigational drug cabotegravir, are being developed for use as long-acting injectables [24] see Table 1.

Cabotegravir

Cabotegravir is an investigational drug that belongs to the second generation of INSTIs [25,26]. It is produced in an oral form as well as in an injectable form (subcutaneous and intramuscular) [26,27]. The half-life of the drug is 20-40 days as an injectable formulation which makes up to bimonthly use potentially possible [26,28].

Reports from phase II prevention trials demonstrated that injectable cabotegravir was safe and well-tolerated among the participants [29,30]. A separate phase III non-inferiority trial investigated the prophylactic administration of intramuscular cabotegravir to prevent HIV infection among men who have sex with men (MSM) and transgender (TGW) women. A preliminary report of this trial supports the effectiveness of cabotegravir at preventing HIV infection, compared with oral administered tenofovir/emtricitabine combination [31,32].

Clinical trials continue to assess the use of injectable cabotegravir for pre-exposure prophylaxis (PrEP) [29,31]. Findings from a study among over 3,000 women in 7 African countries unequivocally conclude that long-acting injectable cabotegravir effectively protected women from HIV acquisition when used as PrEP [33].

Raltegravir

Raltegravir is another INSTI that is being developed as a long-acting injectable [34]. It is approved in its oral form for treatment and prevention (post-exposure prophylaxis (PEP)) of HIV [1], but its development as a long-acting agent is still in the preclinical stage. A study on humanised bone marrow-liver-thymus (BLT) mice had subcutaneous long-acting raltegravir administered at 7.5mg.I In

this study the pharmacokinetic properties were similar to those of 400mg oral raltegravir and the treatment showed potency at protecting the BLT mice from HIV vaginal challenge up to four weeks following single-dose administration, whilst the control mice were not protected from HIV infection. The plasma level of the drug was also noted to be comparable to that of the oral form [35]. This report also revealed the presence of the active drug in the female genital tract of the mice, a finding that if reproduced in humans may indicate usefulness as preventive intervention as sexual intercourse is one of the common routes of HIV transmission.

Dolutegravir

Oral forms of dolutegravir have proven efficacious, with oral dolutegravir being one of the first drugs approved as part of dual therapy in the management of HIV infection due to its very high potency [36]. However the development of a long-acting injectable form is still at a very early stage [37].

Bictegravir

Bictegravir oral formulation is the most recent INSTI to secure US Food and Drug Administration (FDA) approval. It is also at an early stage of development into a long-acting injectable [38]. It has the highest barrier to resistance among the INSTI group [34], and a long-acting injectable could also potentially possess this quality.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

NNRTIs alter the reverse transcriptase enzyme of HIV and inhibit its replication [23,39]. Oral formulations of NNRTIs have been in clinical use for decades and their use as long-acting agents is being evaluated [40].

Rilpivirine

Rilpivirine (TMC278) is a second-generation NNRTI with an approved oral form. This form is combined with other antiretroviral drugs for treatment-naïve HIV-1 infected individuals with a viral load (HIV-1 RNA) of 100,000 copies/ml or below [41,42]. A long-acting injectable form of rilpivirine with a half-life of 30-90 days has been developed. This form allows administration as an intramuscular injection once every four

to eight weeks [11,43–45]. This is in contrast to the oral form which has a half-life of 24-45 hours and must therefore be taken daily to be effective [46]. A comparable drug concentration to that of the oral form was detected in the plasma up to 84 days following administration of the long-acting injectable in early clinical studies [11,43]. The injectable form is at an advanced stage of development in combination with cabotegravir as a long-acting agent for HIV treatment. A study reported its safety in a phase I trial and *ex vivo* evaluation revealed that it suppressed infection up to four months after administration [47]. Further clinical development of rilpivirine for pre-exposure prophylaxis is expected, however a major concern with the suitability of rilpivirine for prevention is its low barrier to resistance [48].

Cabotegravir and rilpivirine combination

The combination of cabotegravir and rilpivirine is the most widely studied long-acting injectable regimen developed for the management of HIV. Several studies have reported the safety and tolerability of the long-acting formulations in separate use [11,29,43], and numerous recent studies report their use in combination. In the Long-Acting antireTroviral Treatment Enabling (LATTE) study involving 243 subjects, combined oral cabotegravir and rilpivirine demonstrated superior efficacy to an efavirenz plus dual NRTIs based-regimen for up to 96 weeks: virologic suppression was seen among 86% of the former treatment group, compared to up to 68% of the latter. The combination was determined to be efficacious and safe lending support for their further study [49].

In a separate study conducted among 40 healthy adults a 14-day lead-in of oral cabotegravir was given, followed by monthly intramuscular and subcutaneous injections of cabotegravir and rilpivirine at a dose range of 200-800 mg and 600-1200 mg respectively for a duration of 3 months. Targeted plasma concentrations (0.66 µg/mL) of the drugs were attained within three days of administration, and there were no significant adverse reactions or laboratory abnormalities reported [24]. This corroborates the earlier studies on the tolerance and safety of the drugs [29,43].

A separate study, LATTE-2, involved 309 ART-naïve HIV-1 positive adult patients. The study utilised an induction phase of cabotegravir followed by a 96-week maintenance phase, composed of either

long-acting cabotegravir and rilpivirine at four- or eight-week intervals or the control treatment (daily oral cabotegravir) (figure 1). At week 96, HIV-1 RNA was below 50 copies/ml in 87% of the four-weekly group, 94% of the eight-weekly group and 84% of the control group. Adverse reactions were comparable among the three groups with injection site reaction (ISR) being the most common followed by nasopharyngitis, diarrhoea and headaches [12]. The efficacy of the dual long-acting cabotegravir and rilpivirine was shown to be comparable to the oral triple regimen, consistent with the findings of the LATTE study.

In the phase III Antiviral Therapy as Long-Acting Suppression (ATLAS) study, the combination of long-acting cabotegravir and rilpivirine was compared to a triple oral regimen (figure 2). The long-acting injectable combination had similar virologic suppression rates to the triple oral regimen (285/308 (92.5%) compared to 294/308 (95.5%) at week 48 of therapy. Confirmed virologic failure was infrequent and similar in both arms. There was a low rate of serious adverse effects 13/308 (4.2%) and withdrawal-related to the injection (1.3%). The ISR throughout the 48 weeks period in the injection group was 1460 out of 6978 injections administered. The reaction was most often mild and resolved within three days [50].

A separate phase III study, First Long-Acting Injectable Regimen (FLAIR) (figure 3), supports the findings of the ATLAS study. FLAIR demonstrated the non-inferiority of injectable cabotegravir plus rilpivirine to oral abacavir/dolutegravir/lamivudine. HIV 1 RNA was below 50 copies/ml in 265/283 (93.6%) of the long-acting treatment group participants and 264/283 (93.3%) in the control group participants. The virologic failure and rate of adverse reactions were similar in the two groups and to that of the participants in the ATLAS study [51]. The ATLAS and FLAIR studies assessed the use of the long-acting agents at four-week intervals. An extension of the ATLAS study, ATLAS-2M (figure 2,) investigated the administration of the drugs at eight-weekly intervals. An eight-weekly regimen of long-acting cabotegravir and rilpivirine was compared with a four-weekly regimen, and it was determined that, at 48 weeks of administration, the eight-weekly regimen of cabotegravir and rilpivirine long-acting injectables was non-inferior to the eight-weekly regimen [52].

The results of these phase III trials revealed the efficacy and tolerability of combined cabotegravir and rilpivirine long-acting injectables. The combination received approval for use in Canada in early 2020 while European Medicine Agency and United States Food and Drug Administration gave approval for the use in October 2020 and January 2021 respectively [53–55]. It should be noted that children and adolescents were excluded in phase III studies and LATTE studies. A new study tagged More Options for Children and Adolescents (MOCHA) is underway and aims to define the pharmacokinetics and safety of cabotegravir and rilpivirine injections in children age 12 to 17 [56]. It should be noted that the current studies excluded patients with advanced HIV (CD4 < 200 cells/mm^3) and those having used ART long-term [12,57]. Determining the efficacy of these drugs amongst these groups are desirable. Similarly, the studies excluded patients with major comorbidities such as renal and liver diseases. The longest duration of follow-up reported with the use of the long-acting injectables so far is 96 weeks [12], therefore longer-term follow-up may be warranted.

Drug Resistance

The development of resistance is an area of great concern in any drug-centred treatment strategy [58]. One way in which long-acting agents seek to address this issue is through improved adherence to reduce the rate or possibility of resistance development [8]. However, the possibility of the emergence of resistance during therapy remains. In studies the emergence of resistance has been demonstrated to be similar among those using long-acting injectables and the control groups [51,52].

Further, there are potential limitations associated with the use of long-acting injectable antiretroviral agents in patients with resistance to an oral regimen. In clinical trials, those with detectable drug resistance or virologic failure were excluded. This may influence the generalization of the study's findings in these group of patients. Therefore, studies to address this will be warranted.

Drug-drug interactions

The interactions of antiretroviral drugs with other medications is an important aspect of HIV management [59]. For example rilpivirine interacts with proton-pump inhibitors, anti-convulsants (carbamazepine and phenytoin) and rifampicin, all reducing the plasma level of the drug [60].

Rifampicin also interacts with cabotegravir. The former is a potent liver enzyme inducer that increases the metabolism of cabotegravir and may lead to its early clearance from the circulation, leading to a subtherapeutic level which may predispose to the emergence of resistance and virologic failure [61]. Rifampicin is a key component in the management of tuberculosis (TB)and TB has a high incidence among PLWHIV [62].

Future studies should assess the potential interactions of cabotegravir with other medications used to treat common comorbidities amongst HIV patients, such as hepatitis B and C. A study on the interactions of orally administered dolutegravir and daclatasvir, a hepatitis C antiviral agent, showed that the latter alters the pharmacokinetic properties of dolutegravir, with the maximum observed concentration and the end of dosing interval concentration increased by 29% and 45% respectively. However, this alteration was not clinically significant [63]. Carbamazepine interactions with dolutegravir required the doubling of its dose [64]. These interactions should be considered when designing and implementing long-acting formulations. However, it should also be considered that it is not necessarily possible to fully extrapolate studies on oral formulations to the injectables [65].

Patient experience and satisfaction

Patient satisfaction is important to treatment adherence. The HIV Treatment Satisfaction Questionnaire (HIVTSQ) is used to assess the treatment convenience, continuation of therapy and how flexible a treatment option is among other components. Studies have measured patient satisfaction regarding long-acting injectables using the HIVTSQ.

There was a high level of treatment satisfaction among the two long-acting treatment groups and the oral control group in the LATTE-2 study with 246/254 (97%) picking a score of 5 or 6 out of a total of 6 (the higher the score the higher the level of satisfaction), and with more participants satisfied to continue intramuscular therapy than oral (99% in both intramuscular group and 78% in the oral group) at week 96. However, the non-inclusion of those that dropped out before the 96-week should be noted [12].

In a qualitative study of 27 participants in Spain and the United States in the same LATTE-2 trials convenience, privacy, reduction in stigmatisation and discrimination were all important benefits believed to be associated with the use of injectable ARVs, but respondents still desired a less frequent regimen that would further reduce the number of healthcare visits [66]. It should be considered that the increase in satisfaction among the injectable group may have been influenced by the selection of individuals who consented to the use of intramuscular treatment at the start of the randomisation.

Similarly, a high level of satisfaction was reported in the ATLAS and FLAIR studies (99% and 97 % respectively) among the injection arm [57], whilst in the study on the use of cabotegravir injection for the prevention of HIV infection (ÉCLAIR trial) a significant number of the participants were satisfied with cabotegravir injection 75% (n=64), expressed a desire to continue usage 79% (n=68) and were willing to recommend it for others 87% (n=75) [67].

Challenges

The results of the ongoing clinical trials on injectable antiretrovirals for HIV treatment and prevention have been encouraging, but some challenges still need to be resolved. There will be a need for patients to adhere to the injection schedule as non-adherence will expose the virus to a sub-therapeutic level of drugs over an extended period and may contribute to the selection of resistant strains especially among individuals that are lost to follow-up [29]. For patients that missed injections, there may be a need to return them to oral medications. Studies among patients with poor adherence will likely be desirable to understand the acceptability of the regimen and how to manage their circumstances.

The development of easy-to-use subcutaneous injections may address the need for patients to present at health facilities for drug administration. It was documented that in a population of HIV positive women in rural Uganda, subcutaneous long-acting depot medroxyprogesterone acetate was successfully used, indicating the possibilities of adopting a comparable scheme for injectable antiretrovirals in similar communities [68]. However, health care workers will still need to follow-up patients, as the management of HIV involves more than maintaining drug administration. Drug-related adverse events may be an issue in some patients, for example. The use of short oral lead-in was to address this problem, but idiosyncratic reactions may still occur even among those that tolerated the oral formulations [69].

Furthermore, injections of current formulations have been associated with ISR and pain leading to discomfort, a factor that may affect acceptability [12]. It is possible the development of low volume injections may help to reduce problems associated with administration. There is also a need to develop injectables used in combination, but delivered separately, into a single combined injection to reduce the number of injections administered per healthcare visit, simplifying administration further and reducing the number of injections.

Another concern is the requirement for the rilpivirine injectable formulation to be stored between 2 to 8^0C [70]. This may be a particular concern in resource-poor environments, potentially limiting distribution and accessibility. A possible solution would be to use the existing cold-chain channels that are being used to distribute vaccines in these areas. This may pose an organisational challenge, requiring the collaboration of stakeholders to be successful.

There remains a need for long-term data and real-world experience on the use of long-acting injectables, in addition to studies on specific groups of patients excluded from the studies here reviewed, such as those with advanced progression to AIDS, as well as children and adolescents. These challenges present opportunities for more research.

Conclusion

Current oral antiretroviral drugs have been successful at reducing HIV morbidity and mortality and have contributed to prevention efforts. However, adherence is crucial to sustaining progress in the long-term. The development of long-acting injectable formulations has the potential to simplify antiretroviral therapy and promote adherence by allowing for up to bimonthly administration. There are many long-acting injectable antiretroviral formulations at various stages of preclinical and clinical development for use in the prevention and treatment of HIV. Whilst this review has focused on the most developed injectable antiretrovirals, the development of additional groups (including capsid inhibitors and entry inhibitors) is underway (see Table 1).

This review includes agents already approved as oral formulations as well as investigational drugs. Of these cabotegravir and rilpivirine are the most studied, and both have demonstrated non-inferiority to a triple oral ARV regimen.

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