Investigational drugs in HIV: Pros and cons of entry and fusion inhibitors (Review)

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Received September 2, 2018; Accepted November 29, 2018

DOI: 10.3892/mmr.2019.9840

Abstract. Despite the profound changes and improvements reached in the field of HIV treatment, tolerability and adherence to highly active antiretroviral therapy remains a challenge. Furthermore, multi-experienced patients could take advantage of drugs with different mechanisms of action to combat the spread of resistance to actual therapy. For these reasons identification of new HIV drugs is crucial. Among all the molecules that at present are under investigation, entry and fusion inhibitors pose an interesting class owing to their peculiar characteristics, including prevention of entry of the virus into the human cells. In this study, we reviewed articles, clinical trials, and conference communications about all the drugs under investigation belonging to the class of entry and fusion inhibitors that are at least in phase I clinical trials.

Contents

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Key words: HIV fusion inhibitors, anti-HIV agents, HAART, safety, antiviral drug resistance

1. Introduction

HIV continues to be an important challenge and a major global public health issue. According to the last WHO report, there were approximately 36.7 million individuals living with HIV, with 1.0 million individuals succumbing to HIV-related causes and 1.8 million newly infected ones at the end of 2016, globally (1). Despite global policies and the general advice to treat every HIV patient, only 54% of adults and 43% of children living with HIV are currently receiving antiretroviral therapy (1).

The HIV treatment regimen is termed highly active antiretroviral therapy (HAART) and its main goal is to suppress HIV replication and reduce viral loads (VLs) below the detectable level. In fact, it has been proven that suppression of HIV replication improves life expectancy and quality of life (2,3). The second aim of HAART is immune recovery. Both effects are essential for any HIV drug: Failing an acceptable immune recovery is one of the leading causes for comorbidities in HIV-infected patients, because of a constant pro-inflammatory status (4,5) that leads to several chronic diseases including diabetes mellitus, chronic kidney dysfunction, cardiovascular diseases and cancer (4-30).

Over 25 drugs and their combinations have been approved for clinical use, however, the optimal drug regimen has yet to be identified. HAART is a long-life effective treatment. Available drugs can achieve undetectable VL and immune restoration but co-morbidities, adverse effects (AEs), drug interactions

and insurgence of resistance are unsolved problems. Several drugs have been studied to resolve these problems. Among them there are new possible components of the 'entry and fusion inhibitors' class. All the drugs of the 'entry and fusion inhibitors' class share some peculiar characteristic that could represent an advance in HIV control. They are the only drugs that prevent entry of the virus into the human cells. This mechanism of action may prevent the infection of new cells during the rounds of ongoing replication that are present also in patients on HAART and which is thought to be the cause of refueling of the HIV reservoir (31). These drugs potentially play a role in the prevention of new infections through the Pre-exposure prophylaxis (PrEP) and in multidrug-resistant patients.

The very first steps of the infectious cycle of HIV are attachment, fusion and entry of viral particles in the human cells. During this phase, HIV glycoproteins such as gp120, and gp41, play a crucial role (32). The envelope protein gp120 binds the CD4 receptor on the host cell surface, starting a cascade of conformational changes in gp120 that exposes the chemokine receptor binding domains and allows them to interact with the target receptor. The main co-receptors used by HIV-1 for entry into the cell are the chemokine receptors CCR5 and CXCR4. Tropism, or binding with the co-receptors, is so important that HIV-1 is classified either exclusively using CCR5 (R5) or CXCR4 (X4), or using both co-receptors (R5X4 or dual-tropic). Once gp120 is bound with the CD4 protein and the co-receptor, the N-terminal fusion peptide gp41 penetrates the cell membrane and the loop structure, formed by gp120, CD4 and co-receptor, allowing the fusion of the viral and host membranes. Subsequently, entry of the viral capsid occurs (33).

All the chemical compounds that act against these events have been grouped in the 'entry and fusion inhibitors' class. They are further sub-classified depending on their target in: CD4-receptor inhibitors, co-receptor antagonists (CCR5 and CXCR4), and fusion inhibitors (34).

At present, only two drugs of this class have been approved: Maraviroc, a CCR5 antagonist, and enfuvirtide, a gp41 antagonist. Fig. 1 presents the drugs currently studied and their targets, while Table I focuses on the study phase the drugs are currently in.

In this paper we reviewed the articles, clinical trials and conference communications with regard to all the drugs belonging to the class of entry and fusion inhibitors that are at least in phase I clinical trials.

2. CCR5 antagonist

PRO-140. PRO-140 is a humanized IgG4 monoclonal antibody (mAb), that binds to hydrophilic extracellular domains on CCR5 and competitively inhibits viral entry of HIV-1 (35,36). It is used only in patients with an R5-type HIV virus (36,37). At antiviral concentrations, PRO-140 does not prevent CC-chemokine signaling (35,36).

Notably, *in vitro* PRO-140 has exhibited activity against viruses resistant to maraviLaroc, the only CCR5 antagonist approved for HIV treatment [Jacobson *et al* (37): CCR5 monoclonal antibody PRO 140 inhibited HIV-1 resistant to maraviroc, a small molecule CCR5 antagonist. International AIDS Conference, Mexico City 2008, abs TUAA0305].

When a virogical failure (VF) occurs, no change in co-receptor tropism and no significant change in virus susceptibility to PRO-140 and maraviroc have been reported (38) [Lalezari *et al*: PRO 140 single-agent maintenance therapy for HIV-1 infection: A 2-year update. Conference on retroviruses and opportunistic infections (CROI), February 13-16, 2017, Seattle, abs 437].

Currently, PRO-140 appears to be a well-tolerated drug. No drug-related serious adverse effects (SAEs), discontinuations because of AEs, or any notable patterns of toxicity have been previously reported. The most common AE was a mild, transient, and self-resolving injection site reaction that has occurred in less than 10% of participants (38,39).

In a randomized, double-blind, placebo-controlled dose-ranging phase 2a study, Jacobson *et al* reported that subcutaneous PRO-140 demonstrated potent and prolonged antiretroviral activity (35). Authors of that study recruited adults affected by only CCR5-tropic virus at screening, with a mean age of 42.4 standard deviation (SD) ± 7.09 years. Inclusion criteria were: Plasma HIV-1 RNA ≥5,000 copies/ml, CD4 + T cell ≥300 cells/mm^3 (with a nadir >200 cells/mm^3) and no history of AIDS-defining illnesses. The 44 participants did not receive antiretroviral therapy for ≥12 weeks and were randomized into one of four treatment groups: Placebo, 162 mg subcutaneously once a week, 324 mg subcutaneously once a week, and 324 mg subcutaneously twice a week.

The reduction for the PRO-140 groups was statistically significant relative to the placebo group. The best performances were reached in the 324 mg weekly group in which 73% of subjects had a VL of <400 copies/ml while no placebo subject had such a VL (P=0.001). The mean maximum reduction in HIV-1 RNA observed for the 324 mg weekly dose was 1,65 log. Individual viral nadirs were typically observed on day 22 (range, day 15-29).

Low-titred anti-PRO-140 antibodies (1:32 or less) were detected in three subjects treated with the 324 mg weekly dose.

After these proof-of-concept studies, two different strategies of treatment with PRO-140 were evaluated in phase IIb/III clinical trials.

The study 'A randomized, double-blind, placebo-controlled trial, followed by single-arm treatment of PRO 140 in combination with optimized background therapy (OBT) in treatment-experienced HIV subjects' (NCT02483078; https://clinicaltrials.gov/ct2/show/NCT02483078?term = NCT02483078&rank =1), evaluated the possibility of adding this new drug to an OBT, chosen on the basis of a subject's resistance test results and treatment history, in treatment-experienced patients with a virologic failure. After one week of overlap with existing ART and PRO-140 (350 mg SC weekly) all the patients received PRO-140 and an OBT, while in the second arm, PRO-140 is due to be substituted with a placebo.

The study 'PRO 140 SC as single agent maintenance therapy in virally suppressed subjects with CCR5-tropic HIV-1 infection' (NCT02859961; https://clinicaltrials.gov/ct2/show/NCT02859961? term = NCT02859961 & rank =1) is also ongoing. It is a multi-center study designed to evaluate the efficacy, safety, and tolerability of the strategy of shifting clinically stable patients receiving suppressive combination antiretroviral therapy to PRO-140 monotherapy (350 mg sc weekly) and maintaining viral suppression for 48 weeks

Table I. Entry and fusion inhibitors

Drug	Target	Study phase	Clinical studies
Fostemsavir	gp120	III	BRIGHTE study (ongoing)
Ibalizumab	CD4 (dominio 2)	III	NCT00784147 (complete)
Albuvirtide	gp41	III	TALENT study (complete, unpublished results)
UB-421	CD4 (dominio 1)	III	NCT03149211 (ongoing)
NCT01668043 (complete)			
PRO-140	CCR5	III	NCT02483078 (ongoing)
NCT02355184 (ongoing)			
NCT02990858 (ongoing)			
NCT02859961 (ongoing)			
Cenicriviroc	CCR5 e CCR2	IIb	NCT02128828 (complete)
Monomeric DAPTA	CCR5	II	NCT00000392 (complete)
Combinectin	gp120 e gp41	Pre-clinical	---
Vedolizumab	α4β7 integrin	Pre-clinical	---

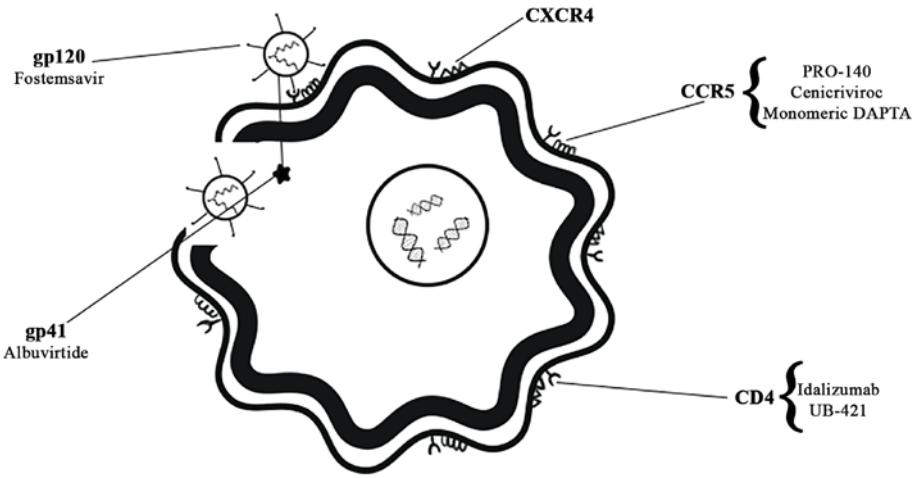

Figure 1. Entry and fusion inhibitors and their targets on a CD4+ T-lymphocyte.

following study entry. Consenting patients are to be shifted from a combination antiretroviral regimen to weekly PRO-140 monotherapy for 48 weeks during the treatment phase with the one week overlap of existing retroviral regimen and PRO-140 at the beginning of the study treatment and also one week overlap at the end of the treatment in subjects that do not experience virologic failure.

This strategy should be innovative and noteworthy for stable patients, improving their quality of life and their adherence to treatment. PRO-140 drug interactions are currently unknown.

Cenicriviroc. Cenicriviroc (CVC) is a small molecule that binds to a domain of CCR5 and subsequently blocks HIV-1 entry inhibiting interaction between HIV-1 gp120 and CCR5 (40). CVC may have an anti-inflammatory effect as it is also a CCR2 antagonist (41).

Cenicriviroc has a plasma half-life of approximately 35 h and may be used once daily (42).

CVC, administered orally and once daily, demonstrated potent antiviral activity and good tolerance between HIV-1-infected subjects, that were antiretroviral-experienced, and naive to CCR5 antagonists (43).

CVC exhibits high levels of resistance *in vitro*. Complete resistance to CVC developed after 67 weeks, with several amino acid changes in both the V3 and other Env regions (44).

A phase 2b, multicenter, randomized, double-blind, double-dummy study evaluated, at 24 and 48 weeks, the proportion of virologic success. It also compared the safety and tolerability of two different doses of CVC (100 and 200 mg orally) with those of EFV (42). Those authors used TDF/FTC as a backbone for all the participants. The three arms were: CVC 100 mg, 58 patients; CVC 200 mg, 57 patients; and EFV 28 patients.

The proportion of virologic success was similar in all the treatment arms at week 24 (76, 73 and 71%) and week 48 (68, 64 and 50%). In addition, the rates of virologic non-response were not significantly different in the treatment groups at week 48 (15, 20 and 11%).

None of the efavirenz-treated patients with VF had emergent NRTI mutations. However, NRTI mutations (M184I

and/or V) accounted for 75% of the VFs with CVC 100 mg and for 33% of the VFs with CVC 200 mg. One participant with VF who was in the 200 mg CVC group had a tropism switch from R5 to X5R5 tropic virus.

The following percentages of AE, related to treatment, were found (42): 50% in the 100 mg CVC group, 44% in the 200 mg CVC group, and 71% in the EFV group. The most frequent were: Nausea (12%), headache (10%), diarrhea (7%), and abnormal dreams (7%). SAEs occurred in 1 participant in each group, accounting for 2, 2 and 4 of patients.

CVC does not inhibit CYP-mediated activity and does not induce CYP3A4 in human hepatocytes.

The interaction between CVC and ritonavir, darunavir, atazanavir, efavirenz and dolutegravi [Lefebvre *et al*, 'Pharmacokinetics of cenicriviroc when administered with and without ritonavir, darunavir/ritonavir or atazanavir/ritonavir', International Workshop on Clinical Pharmacology of HIV Therapy, Amsterdam 2013, abs O_09A and O_09B] has been previously described.

CVC may play a role in treatment-experienced patients with a multiresistant R5 virus.

Monomeric DAPTA. Monomeric DAPTA (mDAPTA) is a synthetic compound derived from the gp120 V-2 region of HIV. It is a selective CCR5 co-receptor antagonist that binds this co-receptor and subsequently inhibits the interaction between HIV-1 gp120 and CCR5 (46-48).

In vitro, Agrawal *et al* demonstrated that mDAPTA is 1,000-fold more potent than maraviroc in inhibiting virus entry (49). In fact, it completely inhibited the release of virus (X4 and R5) from PBMCs from all the samples of HIV-uninfected and HIV-infected patients with VL <50 copies/ml. The authors' disclosure was that mDAPTA prevents HIV recovery and the production of replication-competent HIV from CD8-depleted patient PBMCs.

An interesting phase I trial tested an intra-nasal administration of mDAPTA 3 times a day for up to 32 weeks, given either alone or in combination with current HAART. The mean VL did not change in the study period, being 3.71 log copies/ml at baseline and 3.85 log copies/ml at week 24. By contrast, a complete suppression of active HIV replication in the circulating monocyte (CD14) population was observed. Furthermore, the investigators of that study were unable to isolate infectious virus from any plasma sample (50). This fact indicates a disconnection between PCR detection of HIV RNA and extremely infectious plasma virus in these long-term non-progressor subjects. Authors of that study observed an immune restoration with a mean CD4+ cell count increase from 540 to 652 cell/μl.

A phase 2 study is still ongoing (NCT00951743; https://clinicaltrials.gov/ct2/show/ NCT00951743?term = NCT00951743 & rank =1). This is a 24-week, double-blind, two-arm study in which mDAPTA is compared to placebo. In total, 40 HIV-infected individuals in HAART and with VL <200 copies ml were randomized to receive 0.01 mg of mDAPTA intranasally twice a day or placebo.

In the phase 1 study (50) conducted neither AEs nor nasal pathologies were reported.

No resistance or changes in tropism during treatment was registered. No drug interactions are known.

3. gp120 antagonist

Fostemsavir. Fostemsavir is a pro-drug of temsavir (TMR) a molecule that prevents viral entry by binding to the viral envelope gp120 and interfering with virus attachment to the host CD4 receptor (51). TMR binds directly to the virus and not human cells, and is active against R5, X4 and R5X4 HIV-1 (51-55).

In a multiple-ascending dose study, the average plasma half-life of TMR was 3.2-4.5 h (immediate-release formulation) and 7-14 h (extended-release formulation) (Mascolini, 'Levels of novel HIV attachment inhibitor with or without Ritonavir', 12 th International Workshop on Clinical Pharmacology of HIV Therapy, Miami 2011).

After 8 days of monotherapy, fostemsavir achieved a maximum median decrease in HIV-1 RNA from baseline of 1.21 to 1.73 log copies/ml (56).

Suboptimal efficacy of TMR was associated with the presence of the M426L, S375, M434 and M475 substitutions (54,55).

No *in vitro* cross-resistance was observed with other classes of antiretrovirals (52,53), with any other entry inhibitors (ibalizumab and enfuvirtide).

In phase 2b studies TMR showed similar efficacy to a ritonavir-boosted atazanavir (ATV/r) using tenofovir disoproxil fumarate (TDF) and raltegravir (RAL) as companions (42,57). Specifically, Thompson *et al* showed that, through week 48, the proportion of fostemsavir subjects with a VL <50 copies/ml was 77-95% versus 88% for ATV/r subjects (42). A difference occurred in virologic response rates according to the baseline VL. The virologic response was 74-100% with a baseline VL <100,000 copies/ml VL versus 60-91% in subjects with ≥100,000 copies/ml. Across fostemsavir arms, median CD4 T cell count increases from baseline were 145-186 cells/μl and similar to the ATV/r arm (142 cells/μl).

The Brighte study (NCT02362503; https://clinicaltrials.gov/ct2/show/NCT02362503?term = NCT02362503 & rank =1), a phase 3 study, is ongoing and aims to evaluate whether fostemsavir is an optimal option in heavily treated experienced adults with limited therapeutic options (≤2 classes of active antiretrovirals remaining). After several phase 2 studies the dosage selected for this clinical trial was 600 mg tablets orally twice daily. All the patients also received an OBT.

Grade 2 to 4 treatment-related AEs occurred in 8.5-18% of patients, the most common of which were nausea, diarrhea, headache, vomiting, fatigue, and asthenia (42,58). SAEs occurred in 0-2% of patients (42,58).

4. gp41 antagonists

Albuvirtide. Albuvirtide (ABT) is a peptide derived from gp41 that inhibits the formation of a six-helix bundle structure in gp41, which is necessary for fusion of the viral and cellular membranes (59).

The first attempt of combination therapy using ABT and available drugs led to an open-label, randomized, parallel phase 2 trial (60). Naïve patients with a VL >5,000 copies/ml and a CD4+ cell count >350 cells/μl, were randomized to receive an intravenous infusion of 160 or 320 mg weekly and lopinavir/ritonavir (LPV/r) 400/100 mg twice daily. At the 47 th day the

mean VL decrease was 1.91 log and 2.20 log, while the CD4+ cell count change was -5 cells/μl and 52 cells μl for the 160 and 320 mg groups, respectively.

The TALENT study, a phase 3 trial, is ongoing (NCT02369965; https://clinicaltrials.gov/ct2/show/NCT02369965). Participants are children and adults (aged 16-60 years) with HIV who have had treatment failure with a standard first-line ART regimen containing NRTIs or NNRTIs. VL of ≥1,000 copies/ml at baseline was observed. All the patients received LPV/r and were randomized to receive ABT (320 mg i.v. weekly) or tenofovir and lamivudine. An interim analysis (61), showed that, at week 48, 80.4% of the patients in ABT arm had VL <50 copies/ml versus 66% of the patients in the other arm. The CD4+ cell count was similar for both arms.

The most common AEs reported were: Diarrhea (7.5%), headache (2.2%), and dizziness (2.2%) (61). SAEs occurred in 5.6% of participants in a phase 3 trial. No injection site reaction has been reported. ABT does not affect serum cretinine or eGFR levels but high cholesterol (12.9%) and high triglycerides (32.3%) were reported as laboratory abnormalities [Xie (61) International congress of drug therapy in HIV infection, Glasgow 2016].

In Glasgow, Xie (61) presented an interim analysis of the TALENT study showing that mutations at amino acid positions 36, 40, 126 and 144 could represent mechanism of resistance for ABT.

In patients treated with LPV/r and ABT, a decrease of LPV/r exposure was identified. However, this decrease did not lead to a change in the usual doses of these drugs (62). No other drug interactions are known at present.

An NDA was accepted by China FDA in July 2016 for this drug that could become the first long-acting anti-HIV new drug.

5. CD4 antagonists

Ibalizumab. Ibalizumab is a humanized monoclonal antibody (mAb) that acts by binding to the interface between domains 1 and 2 of the CD4 receptor (63). The post-binding conformational effects caused by this interaction prevent viral entry and fusion (64). Unlike other monoclonal antibodies that, targeting domain 1 of CD4, have been found to be immunosuppressive (65,66), ibalizumab has no immunosuppressive effects (67,68), because its binding site to CD4 receptors is distant from the binding site of MHC II molecules (63).

Ibalizumab has an average half-life of 3-3.5 days when administered subcutaneously (69), and can be administered once a week. Additionally, an intramuscular administration is being evaluated (Lin *et al*: 'Intramuscular ibalizumab: Pharmacokinetics, safety, and efficacy vs iv administration' CROI, Seattle 2017, abs 438). Owing to the limited data, optimal dosage and route of administration remain to be verified even if the best results have been obtained with an intravenous administration of 25 mg/kg every two weeks (70). The first evidence of a good antiviral effect of ibalizumab in humans was reported among 30 HIV-positive patients in ART with virologic failure and a VL of >5,000 copies/ml (70). Those subjects that received 25 mg/kg of ibalizumab had a peak mean reduction of 1.11 log on day 21 after a single dose. The increased peak of CD4+ cells was on day 1 suggesting that an increase may have been due to the redistribution of CD4 cells from lymphoid tissue rather than an immune restoration. Khanlou *et al* confronted ibalizumab and an optimized background regimen (OBR) versus an OBR alone in multi-resistant HIV patients (Khanlou *et al*: 'Safety, efficacy and pharmacokinetics of ibalizumab in treatment-experienced HIV-1 infected patients: A phase 2b study.' 51 st ICAAC Chicago 2011, abs H2-794b). In this phase 2b trial ibalizumab was administered intravenously in two doses: 800 mg every 2 weeks or 2,000 mg every 4 weeks. In the ibalizumab arms, the VLs showed a significant decrease (1.5-1.6 log copies/ml) while the mean increase in the CD4 T cell count after 24 weeks was of 37-40 cells/μl. Norris *et al*, demonstrated that, in treatment-experienced patients with a multiresistant virus, ibalizumab added to OBR had a better performance than the OBR alone. In ibalizumab plus OBR arm the subjects obtained a peak mean reduction of 0.95-1.16 log versus 0.2 log of the placebo plus OBR group [Norris, 'TNX-355 in combination with optimized background regimen (OBR) exhibits greater antiviral activity than OBR alone in HIV treatment experienced patients' Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington 2005, abs LB-26]. In another phase I trial (69), ibalizumab was tested as a monotherapy for 9 weeks in subjects with a VL >5,000 copies/ml and a CD4+ cell count between 100-500/μl. Jacobson *et al,* chose three different schedules: 10 mg/kg once a week, 10 mg/kg loading dose followed by 6 mg/kg every 2 weeks, and 25 mg/kg every 2 weeks (69). Almost all the subjects exhibited a decrease of VL between 0.5 and 1.7 log copies/ml with a peak within the first week. The VLs returned to baseline values by the end of treatment. In all the study arms, after an initial increase in CD4+ cell counts, all the subjects returned to the baseline CD4+ cell count, reinforcing the idea that a redistribution of CD4 cells from lymphoid tissue is the real cause of this rapid peak, as suggested by Kuritzkes *et al* (70).

Moreover, reduced susceptibility to ibalizumab relative to baseline appeared in 93% of the subjects after the treatment. This finding discouraged the use of ibalizumab in monotherapy.

The preliminary results of a phase III trial (NCT02475629) were presented (Lewis, 'Long-acting ibalizumab in patients with multi-drug resistant hiv-1: A 24-week study,' CROI, Seattle 2017, abs 449LB). Those authors tested ibalizumab in treatment-experienced patients infected with multi-drug resistant HIV-1. Patients must have been treated with HAART for at least 6 months and be failing with a VL >1,000 copies/ml and a mean CD4+ cell counts of 150 cells/μl. After two weeks of monotherapy the patients received ibalizumab and an OBR. At week 24, 43% of participants had a VL <50 copies/ml and 50% <200 copies/ml. The authors disclosed that this schedule had a good tolerability and high efficacy, even in patients that have failed with >10 ARV agents. Only 1 drug-related AE (IRIS) led to treatment discontinuation.

Ibalizumab is being evaluated also for PreP in healthy volunteers at risk for HIV according to clinical history and sexual behaviors (NCT01292174).

Secondary resistance has been described after one single omission in a patient that has accidentally received placebo instead of ibalizumab (71) and when this drug was used in monotherapy (69). However, this resistance has no cross-

reaction to other entry and fusion inhibitors such as maraviroc and enfuvirtide (69,72).

Mild AEs have been reported in <15% of the cases, the most frequent were: rash, headache, nausea and diarrhea (Khanlou *et al*, 'Safety, efficacy and pharmacokinetics of ibalizumab in treatment-experienced HIV-1 infected patients: A phase 2b study'. 51 st ICAAC 2011, abs H2-794b). Norris, 'TNX-355 in combination with optimized background regimen (OBR) exhibits greater antiviral activity than OBR alone in HIV treatment experienced patients.' Interscience conference on antimicrobial agents and chemotherapy, Washington 2005, abs LB 2-26). Grade 3-4 AEs have been described in 2-4% of subjects in ibalizumab arm versus 5% in placebo arm [Norris, 'TNX-355 in combination with optimized background regimen (OBR) exhibits greater antiviral activity than OBR alone in HIV treatment experienced patients' Interscience conference on antimicrobial agents and chemotherapy, Washington 2005, abs LB 2-26]. No drug-related deaths or discontinuation occurred during clinical trials.

UB-421. UB-421 is a humanized IgG1 monoclonal antibody (mAb) that competitively binds to domain 1 of CD4 receptors and inhibits HIV-1 entry into cells. *In vitro*, UB-421 has demonstrated activity ability against both X4 and R5-tropic virus (Wang, 'A phase 2 open-label trial of antibody UB-421 monotherapy as a substitute for HAARTI'. CROI, Seattle 2017, abs 450 LB).

In a phase IIa trial (NCT01668043), with naïve HIV-infected adults in Taiwan the investigators obtained an average VL reduction of 2.27 and 2.45 log copies/ml after 8-week monotherapy on 10 mg/kg/weekly or 25 mg/kg/biweekly, respectively.

In another phase II open label study (Wang, 'A phase 2 open-label trial of antibody UB-421 monotherapy as a substitute for HAARTI'. CROI, Seattle 2017, abs 450 LB) was administered UB-421 as a monotherapy as a replacement of HAART in 29 HIV-1-infected adults with virologic suppression. All the subjects were assigned to Cohort 1 (10 mg/kg weekly of UB-421 for 8 weeks) or to Cohort 2 (25 mg/kg bi-weekly for 16 weeks). The authors reported that 27 out of the 29 patients completed the monotherapy period (8 and 16 weeks) with no virologic rebound (VR) defined as a VL >400 copies/ml in two consecutive visits. At the end of treatment 22 patients resumed the previous HAART successfully but 5 refused the HAART treatment. Among them the VR was detected as 35-62 days after the last UB-421 dose. At the end of the study CD4+ cell count remained stable and CD8+ increased. Interestingly, they observed a mean 2.24-fold reduction in 10 out of 11 patients that had a proviral DNA >100 copies/10^6 PBMC at baseline. The most common drug-related AE was mild to moderate skin rash (48.3% of subjects), and no death or drug-related SAE occurred.

UB-421 is being evaluated in a phase III trial (NCT03149211) as substitution therapy for HAART in adults who are virologically suppressed on a stable ART regimen.

No drug resistance was reported after 8 weeks of monotherapy with UB-421 (73).

6. Discussion

Despite the revolution achieved in the field of HIV treatment in the last three decades, there are still some important issues that require attention.

First, with HAART HIV changed from a lethal disease to a chronic one but a cure remains elusive. Furthermore, many patients are diagnosed at late stage with a low immune recovery (23). Second, since it is a chronic disease that needs life-long treatment, HIV is burdened with a lot of co-morbidities due to the virus and treatment thereof (17). The safe profile showed by entry inhibitors could represent advancement in terms of drug-related toxicities in comparison with actual HAART.

Third, it has been proven that even if we could obtain a stable virologic suppression, most of the co-morbidities that come from immune activation cannot be defeated if we are unable to combat the HIV reservoir (20,21). Some of these new drugs have shown partial efficacy against the HIV reservoir, as described above.

Finally, it is imperative to confront the issue of prevention. Even if condoms and sexual education remain the milestones of prevention, in recent years the idea of PrEP has gained ground. Furthermore, in this field the entry inhibitors could be additional weapons against the spread of HIV infection.

Entry and fusion inhibitors are a new class of antiretroviral drugs that could play a role in particular settings. Being a relatively new class with no or less cross-reactions and few mechanisms of resistance demonstrated thus far, they could be used as a rescue therapy in experienced patients with MDR viruses. Fostemsavir, Ibalizumab, Albuvirtide and Cenicriviroc are being tested in clinical trials as 'third drugs' in patients with problem of drug resistance.

Another possible use is a monotherapy with an entry inhibitor (UB-421, PRO-140 and monomeric DAPTA), in stable undetectable patients. This substitution therapy for stable patients could be safer especially for older patients with co-morbidities. In fact, the entry inhibitors showed a very good safety profile in their first clinical trials, probably also because they act outside the human cells and target the HIV proteins having a low toxicity. Furthermore, it has been suggested by the VISCONTI study that in selected patients, after a period with an effective therapy that could also reduce the HIV reservoir, we could stop therapy obtaining a good control of the HIV infection (74). All those patients have extremely low HIV DNA levels, and some entry inhibitor showed an effect in reducing HIV DNA in the first clinical trials.

The most important limitation in clinical practice is likely to be viral tropism. All those entry inhibitors that bind one of the two main co-receptors would not be used in every clinical setting. This is the case of CCR5 antagonists.

In conclusion, entry and fusion inhibitors are very promising drugs that could reach some features required in new HIV treatments. They showed good safety and efficacy and seem to be optimal in long-term treated patients for the lack of significant drug-drug interactions and drug resistances.

Obviously, all of them have to demonstrate this good quality in future clinical trials. Currently the possible uses are: PrEP, rescue therapy for MDR HIV, de-escalation for stable patients and being the 'third drug' in conventional HAART.

Acknowledgements

Not applicable.

Funding

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

EVR and GN conceived and designed the subject. EVR, MC and MRP retrieved concerned literatures and wrote the article. FC, AF, GV, FdA and IP reviewed and edited the article. MdR, BC, GP and GN revised the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. World Health Organization: HIV/AIDS fact sheet. 2018. Accessed 12 February 2018. http://www.who.int/en/news-room/fact-sheets/detail/hiv-aids.
2. McMahon JH, Elliott JH, Bertagnolio S, Kubiak R and Jordan MR: Viral suppression after 12 months of antiretroviral therapy in low- and middle-income countries: A systematic review. Bull World Health Organ 91: 377-385, 2013.
3. Thompson MA, Aberg JA, Hoy JF, Telenti A, Benson C, Cahn P, Eron JJ, Günthard HF, Hammer SM, Reiss P, *et al*: Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA panel. JAMA 308: 387-402, 2012.
4. Castronuovo D, Cacopardo B, Pinzone MR, Di Rosa M, Martellotta F, Schioppa O, Moreno S and Nunnari G: Bone disease in the setting of HIV infection: Update and review of the literature. Eur Rev Med Pharmacol Sci 17: 2413-2419, 2013.
5. Scarpino M, Pinzone MR, Di Rosa M, Madeddu G, Focà E, Martellotta F, Schioppa O, Ceccarelli G, Celesia BM, d'Ettorre G, *et al*: Kidney disease in HIV-infected patients. Eur Rev Med Pharmacol Sci 17: 2660-2667, 2013.
6. Pomerantz RJ and Nunnari G: HIV and GB virus C-can two viruses be better than one? N Engl J Med 350: 963-965, 2004.
7. Nunnari G, Coco C, Pinzone MR, Pavone P, Beretta M, Di Rosa M, Schnell M, Giorgio C and Cacopando B: The role of micronutrients in the diet of HIV-1-infected individuals. Front Biosci (Elite Ed) 4: 2442-2456, 2012.
8. Pinzone MR, Berretta M, Cacopardo B and Nunnari G: Epstein-barr virus- and Kaposi sarcoma-associated herpesvirus-related malignancies in the setting of human immunodeficiency virus infection. Semin Oncol 42: 258-271, 2015.
9. Pinzone MR, Di Rosa M, Celesia BM, Condorelli F, Malaguarnera M, Madeddu G, Martellotta F, Castronuovo D, Gussio M, Coco C, *et al*: LPS and HIV gp120 modulate monocyte/macrophage $CYP_{27}B1$ and $CYP_{24}A1$ expression leading to vitamin D consumption and hypovitaminosis D in HIV-infected individuals. Eur Rev Med Pharmacol Sci 17: 1938-1950, 2013.
10. Pinzone MR, Cacopardo B, Condorelli F, Di Rosa M and Nunnari G: Sirtuin-1 and HIV-1: An overview. Curr Drug Targets 14: 648-652, 2013.
11. Capetti A, Landonio S, Meraviglia P, Di Biagio A, Lo Caputo S, Sterrantino G, Ammassari A, Menzaghi B, Franzetti M, De Socio GV, *et al*: 96 Week follow-up of HIV-infected patients in rescue with raltegravir plus optimized backbone regimens: A multicentre Italian experience. PLoS One 7: e39222, 2012.
12. Visalli G, Paiardini M, Chirico C, Cervasi B, Currò M, Ferlazzo N, Bertuccio MP, Favaloro A, Pellicanò G, Sturniolo G, *et al*: Intracellular accumulation of cell cycle regulatory proteins and nucleolin re-localization are associated with pre-lethal ultra-structural lesions in circulating T lymphocytes: The HIV-induced cell cycle dysregulation revisited. Cell Cycle 9: 2130-2140, 2010.
13. Celesia BM, Nigro L, Pinzone MR, Coco C, La Rosa R, Bisicchia F, Mavilla S, Gussio M, Pellicanò G, Milioni V, *et al*: High prevalence of undiagnosed anxiety symptoms among HIV-positive individuals on cART: A cross-sectional study. Eur Rev Med Pharmacol Sci 17: 2040-2046, 2013.
14. Visalli G, Bertuccio MP, Currò M, Pellicanò G, Sturniolo G, Carnevali A, Spataro P, Ientile R, Picerno I, Cavallari V, *et al*: Bioenergetics of T cell activation and death in HIV type 1 infection. AIDS Res Hum Retroviruses 28: 1110-1118, 2012.
15. Trovato M, Ruggeri RM, Sciacchitano S, Vicchio TM, Picerno I, Pellicanò G, Valenti A and Visalli G: Serum interleukin-6 levels are increased in HIV-infected patients that develop autoimmune disease during long-term follow-up. Immunobiology 223: 264-268, 2018.
16. D'Aleo F, Ceccarelli M, Venanzi Rullo E, Facciolà A, Di Rosa M, Pinzone MR, Condorelli F, Visalli G, Picerno I, Berretta M, *et al*: Hepatitis C-related hepatocellular carcinoma: Diagnostic and therapeutic management in HIV-patients. Eur Rev Med Pharmacol Sci 21: 5859-5867, 2017.
17. Squillace N, Ricci E, Quirino T, Gori A, Bandera A, Carenzi L, De Socio GV, Orofino G, Martinelli C, Madeddu G, *et al*; CISAI Study Group: Safety and tolerability of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil fumarate in a real life setting: Data from surveillance cohort long-term toxicity antiretrovirals/antivirals (SCOLTA) project. PLoS One 12: e0179254, 2017.
18. Facciolà A, Venanzi Rullo E, Ceccarelli M, D'Aleo F, Di Rosa M, Pinzone MR, Condorelli F, Visalli G, Picerno I, Fisichella R, *et al*: Kaposi's sarcoma in HIV-infected patients in the era of new antiretrovirals. Eur Rev Med Pharmacol Sci 21: 5868-5869, 2017.
19. Zanet E, Berretta M, Benedetto FD, Talamini R, Ballarin R, Nunnari G, Berretta S, Ridolfo A, Lleshi A, Zanghì A, *et al*: Pancreatic cancer in HIV-positive patients: A clinical case-control study. Pancreas 41: 1331-1335, 2012.
20. Nunnari G, Sullivan J, Xu Y, Nyirjesy P, Kulkosky J, Cavert W, Frank I and Pomerantz RJ: HIV type 1 cervicovaginal reservoirs in the era of HAART. AIDS Res Hum Retroviruses 21: 714-718, 2005.
21. Nunnari G, Leto D, Sullivan J, Xu Y, Mehlman KE, Kulkosky J and Pomerantz RJ: Seminal reservoirs during an HIV type 1 eradication trial. AIDS Res Hum Retroviruses 21: 768-775, 2005.
22. Martellotta F, Berretta M, Cacopardo B, Fisichella R, Schioppa O, Zanghì A, Spartà D, Cappellani A, Talamini R, Izzi I, *et al*: Clinical presentation and outcome of squamous cell carcinoma of the anus in HIV-infected patients in the HAART-era: A GICAT experience. Eur Rev Med Pharmacol Sci 16: 1283-1291, 2012.
23. Celesia BM, Castronuovo D, Pinzone MR, Bellissimo F, Mughini MT, Lupo G, Scarpino MR, Gussio M, Palermo F, Cosentino S, *et al*: Late presentation of HIV infection: Predictors of delayed diagnosis and survival in Eastern Sicily. Eur Rev Med Pharmacol Sci 17: 2218-2224, 2013.
24. Bearz A, Vaccher E, Martellotta F, Spina M, Talamini R, Lleshi A, Cacopardo B, Nunnari G, Berretta M, Tirelli U, *et al*: Lung cancer in HIV positive patients: The GICAT experience. Eur Rev Med Pharmacol Sci 18: 500-508, 2014.
25. Capetti A, Meraviglia P, Landonio S, Sterrantino G, Di Biagio A, Lo Caputo S, Ammassari A, Menzaghi B, De Socio GV, Franzetti M, *et al*: Four years data of raltegravir-based salvage therapy in HIV-1-infected, treatment-experienced patients: The SALIR-E study. Int J Antimicrob Agents 43: 189-194, 2014.
26. Nuvoli S, Caruana G, Babudieri S, Solinas P, Pellicanò G, Piras B, Fiore V, Bagella P, Calia GM, Yue M, *et al*: Body fat changes in HIV patients on highly active antiretroviral therapy (HAART): A longitudinal DEXA study. Eur Rev Med Pharmacol Sci 22: 1852-1859, 2018.
27. Ceccarelli M, Condorelli F, Venanzi Rullo E and Pellicanò GF: Editorial - Improving access and adherence to screening tests for cancers: A new, though old, challenge in the HIV epidemics. World Cancer Res J 5: e1030, 2018.

28. Ceccarelli M, Rullo EV, Facciolà A, Madeddu G, Cacopardo B, Taibi R, D'Aleo F, Pinzone MR, Picerno I, di Rosa M, *et al*: Head and neck squamous cell carcinoma and its correlation with human papillomavirus in people living with HIV: A systematic review. Oncotarget 9: 17171-17180, 2018.
29. D'Aleo F, Cama BAV, Paolucci IA, *et al*: New and old assumptions on lung cancer in People Living with HIV. World Cancer Res J 5: e1036, 2018.
30. Visalli G, Facciolà A, D'Aleo F, Pinzone MR, Condorelli F, Nunnari G, Pellicano GF, Ceccarelli M and Venanzi Rullo E: HPV and urinary bladder carcinoma: A review of the literature. World Cancer Res J 5: e1038, 2018.
31. Pace MJ, Agosto L, Graf EH and O'Doherty U: HIV reservoirs and latency models. Virology 411: 344-354, 2011.
32. Wyatt R and Sodroski J: The HIV-1 envelope glycoproteins: Fusogens, antigens, and immunogens. Science 280: 1884-1888, 1998.
33. Briz V, Poveda E and Soriano V: HIV entry inhibitors: Mechanisms of action and resistance pathways. J Antimicrob Chemother 57: 619-627, 2006.
34. Ray S, Fatima Z and Saxena A: Drugs for AIDS. Mini Rev Med Chem 10: 147-161, 2010.
35. Jacobson JM, Saag MS, Thompson MA, Fischl MA, Liporace R, Reichman RC, Redfield RR, Fichtenbaum CJ, Zingman BS, Patel MC, *et al*: Antiviral activity of single-dose PRO 140, a CCR5 monoclonal antibody, in HIV-infected adults. J Infect Dis 198: 1345-1352, 2008.
36. Trkola A, Ketas TJ, Nagashima KA, Zhao L, Cilliers T, Morris L, Moore JP, Maddon PJ and Olson WC: Potent, broad-spectrum inhibition of human immunodeficiency virus type 1 by the CCR5 monoclonal antibody PRO 140. J Virol 75: 579-588, 2001.
37. Jacobson JM, Thompson MA, Lalezari JP, Saag MS, Zingman BS, D'Ambrosio P, Stambler N, Rotshteyn Y, Marozsan AJ, Maddon PJ, *et al*: Anti-HIV-1 activity of weekly or biweekly treatment with subcutaneous PRO 140, a CCR5 monoclonal antibody. J Infect Dis 201: 1481-1487, 2010.
38. CytoDyn Inc: An extension of protocol PRO 140_CD01 TS Study. ClinicalTrials.gov. Identifier: NCT02355184. First posted: February 4, 2015. https://clinicaltrials.gov/ct2/show/NCT02355184.
39. CytoDyn Inc: A randomized, double-blind, placebo-controlled trial, followed by single-arm treatment of PRO 140 in combination w/ optimized background therapy in treatment-experienced HIV subjects (PRO 140). ClinicalTrials.gov Identifier: NCT02483078. First posted: June 26, 2015. https://clinicaltrials.gov/ct2/show/NCT02483078.
40. Baba M, Takashima K, Miyake H, Kanzaki N, Teshima K, Wang X, Shiraishi M and Iizawa Y: TAK-652 inhibits CCR5-mediated human immunodeficiency virus type 1 infection in vitro and has favorable pharmacokinetics in humans. Antimicrob Agents Chemother 49: 4584-4591, 2005.
41. Marier J-F, Trinh M, Pheng LH, Palleja SM and Martin DE: Pharmacokinetics and pharmacodynamics of TBR-652, a novel CCR5 antagonist, in HIV-1-infected, antiretroviral treatment-experienced, CCR5 antagonist-naïve patients. Antimicrob Agents Chemother 55: 2768-2774, 2011.
42. Thompson M, Saag M, DeJesus E, Gathe J, Lalezari J, Landay AL, Cade J, Enejosa J, Lefebvre E and Feinberg J: A 48-week randomized phase 2b study evaluating cenicriviroc versus efavirenz in treatment-naive HIV-infected adults with C-C chemokine receptor type 5-tropic virus. AIDS 30: 869-878, 2016.
43. Lalezari J, Gathe J, Brinson C, Thompson M, Cohen C, Dejesus E, Galindez J, Ernst JA, Martin DE and Palleja SM: Safety, efficacy, and pharmacokinetics of TBR-652, a CCR5/CCR2 antagonist, in HIV-1-infected, treatment-experienced, CCR5 antagonist-naive subjects. J Acquir Immune Defic Syndr 57: 118-125, 2011.
44. Baba M, Miyake H, Wang X, Okamoto M and Takashima K: Isolation and characterization of human immunodeficiency virus type 1 resistant to the small-molecule CCR5 antagonist TAK-652. Antimicrob Agents Chemother 51: 707-715, 2007.
45. Visseaux B, Charpentier C, Collin G, Bertine M, Peytavin G, Damond F, Matheron S, Lefebvre E, Brun-Vézinet F and Descamps D; ANRS CO5 HIV-2 Cohort: Cenicriviroc, a novel CCR5 (R5) and CCR2 antagonist, shows in vitro activity against R5 Tropic HIV-2 Clinical Isolates. PLoS One 10: e0134904, 2015.
46. Polianova MT, Ruscetti FW, Pert CB and Ruff MR: Chemokine receptor-5 (CCR5) is a receptor for the HIV entry inhibitor peptide T (DAPTA). Antiviral Res 67: 83-92, 2005.
47. Pollicita M, Ruff MR, Pert CB, Polianova MT, Schols D, Ranazzi A, Perno CF and Aquaro S: Profound anti-HIV-1 activity of DAPTA in monocytes/macrophages and inhibition of CCR5-mediated apoptosis in neuronal cells. Antivir Chem Chemother 18: 285-295, 2007.
48. Goodkin K, Vitiello B, Lyman WD, Asthana D, Atkinson JH, Heseltine PN, Molina R, Zheng W, Khamis I, Wilkie FL, *et al*: Cerebrospinal and peripheral human immunodeficiency virus type 1 load in a multisite, randomized, double-blind, placebo-controlled trial of D-Ala1-peptide T-amide for HIV-1-associated cognitive-motor impairment. J Neurovirol 12: 178-189, 2006.
49. Agrawal L, Ducoudret O, Baichoo N, Laznicka M, Ruff M and Pert C: mDAPTA, a potent CCR5 receptor blocker, prevents viral recovery from CD8-depleted patient PBMCs with VL< 50 background. International AIDS Society. http://www.abstract-archive.org/Abstract/Share/4495
50. Polianova MT, Ruscetti FW, Pert CB, Tractenberg RE, Leoung G, Strang S and Ruff MR: Antiviral and immunological benefits in HIV patients receiving intranasal peptide T (DAPTA). Peptides 24: 1093-1098, 2003.
51. Langley DR, Kimura SR, Sivaprakasam P, Zhou N, Dicker I, McAuliffe B, Wang T, Kadow JF, Meanwell NA and Krystal M: Homology models of the HIV-1 attachment inhibitor BMS-626529 bound to gp120 suggest a unique mechanism of action. Proteins 83: 331-350, 2015.
52. Nowicka-Sans B, Gong Y-F, McAuliffe B, Dicker I, Ho HT, Zhou N, Eggers B, Lin PF, Ray N, Wind-Rotolo M, *et al*: In vitro antiviral characteristics of HIV-1 attachment inhibitor BMS-626529, the active component of the prodrug BMS-663068. Antimicrob Agents Chemother 56: 3498-3507, 2012.
53. Li Z, Zhou N, Sun Y, Ray N, Lataillade M, Hanna GJ and Krystal M: Activity of the HIV-1 attachment inhibitor BMS-626529, the active component of the prodrug BMS-663068, against CD4-independent viruses and HIV-1 envelopes resistant to other entry inhibitors. Antimicrob Agents Chemother 57: 4172-4180, 2013.
54. Ray N, Hwang C, Healy MD, Whitcomb J, Lataillade M, Wind-Rotolo M, Krystal M and Hanna GJ: Prediction of virological response and assessment of resistance emergence to the HIV-1 attachment inhibitor BMS-626529 during 8-day monotherapy with its prodrug BMS-663068. J Acquir Immune Defic Syndr 64: 7-15, 2013.
55. Zhou N, Nowicka-Sans B, McAuliffe B, Ray N, Eggers B, Fang H, Fan L, Healy M, Langley DR, Hwang C, *et al*: Genotypic correlates of susceptibility to HIV-1 attachment inhibitor BMS-626529, the active agent of the prodrug BMS-663068. J Antimicrob Chemother 69: 573-581, 2014.
56. Nettles RE, Schürmann D, Zhu L, Stonier M, Huang SP, Chang I, Chien C, Krystal M, Wind-Rotolo M, Ray N, *et al*: Pharmacodynamics, safety, and pharmacokinetics of BMS-663068, an oral HIV-1 attachment inhibitor in HIV-1-infected subjects. J Infect Dis 206: 1002-1011, 2012.
57. Lalezari JP, Latiff GH, Brinson C, Echevarría J, Treviño-Pérez S, Bogner JR, Thompson M, Fourie J, Sussmann Pena OA, Mendo Urbina FC, *et al*: Safety and efficacy of the HIV-1 attachment inhibitor prodrug BMS-663068 in treatment-experienced individuals: 24 week results of AI438011, a phase 2b, randomised controlled trial. Lancet HIV: 427-37, 2015.
58. Vii V Healthcare: Attachment inhibitor comparison in heavily treatment experienced patients. ClinicalTrials.gov Identifier: NCT02362503. First posted: February 13, 2015. https://clinicaltrials.gov/ct2/show/NCT02362503.
59. Xie D, Yao C, Wang L, Min W, Xu J, Xiao J, Huang M, Chen B, Liu B, Li X, *et al*: An albumin-conjugated peptide exhibits potent anti-HIV activity and long in vivo half-life. Antimicrob Agents Chemother 54: 191-196, 2010.
60. Zhang H, Jin R, Yao C, Zhang T, Wang M, Xia W, Peng H, Wang X, Lu R, Wang C, *et al*: Combination of long-acting HIV fusion inhibitor albuvirtide and LPV/r showed potent efficacy in HIV-1 patients. AIDS Res Ther 13: 8, 2016.
61. Xie D: International congress of drug therapy in HIV infection 23-26 October 2016, Glasgow, UK. J Int AIDS Soc 19: 21487, 2016.
62. Yang W, Xiao Q, Wang D, Yao C and Yang J: Evaluation of pharmacokinetic interactions between long-acting HIV-1 fusion inhibitor albuvirtide and lopinavir/ritonavir, in HIV-infected subjects, combined with clinical study and simulation results. Xenobiotica 47: 133-143, 2017.
63. Song R, Franco D, Kao C-Y, Yu F, Huang Y and Ho DD: Epitope mapping of ibalizumab, a humanized anti-CD4 monoclonal antibody with anti-HIV-1 activity in infected patients. J Virol 84: 6935-6942, 2010.

64. Bruno CJ and Jacobson JM: Ibalizumab: An anti-CD4 monoclonal antibody for the treatment of HIV-1 infection. J Antimicrob Chemother 65: 1839-1841, 2010.
65. Merkenschlager M, Buck D, Beverley PC and Sattentau QJ: Functional epitope analysis of the human CD4 molecule. The MHC class II-dependent activation of resting T cells is inhibited by monoclonal antibodies to CD4 regardless whether or not they recognize epitopes involved in the binding of MHC class II or HIV gp120. J Immunol 145: 2839-2845, 1990.
66. Delmonico FL, Knowles RW, Colvin RB, Cavender DE, Kawai T, Bedle M, Stroka D, Preffer FI, Haug C and Cosimi AB: Immunosuppression of cynomolgus renal allograft recipients with humanized OKT4A monoclonal antibodies. Transplant Proc 25: 784-785, 1993.
67. Reimann KA, Burkly LC, Burrus B, Waite BC, Lord CI and Letvin NL: In vivo administration to rhesus monkeys of a CD4-specific monoclonal antibody capable of blocking AIDS virus replication. AIDS Res Hum Retroviruses 9: 199-207, 1993.
68. Moore JP, Sattentau QJ, Klasse PJ and Burkly LC: A monoclonal antibody to CD4 domain 2 blocks soluble CD4-induced conformational changes in the envelope glycoproteins of human immunodeficiency virus type 1 (HIV-1) and HIV-1 infection of CD4+ cells. J Virol 66: 4784-4793, 1992.
69. Jacobson JM, Kuritzkes DR, Godofsky E, DeJesus E, Larson JA, Weinheimer SP and Lewis ST: Safety, pharmacokinetics, and antiretroviral activity of multiple doses of ibalizumab (formerly TNX-355), an anti-CD4 monoclonal antibody, in human immunodeficiency virus type 1-infected adults. Antimicrob Agents Chemother 53: 450-457, 2009.
70. Kuritzkes DR, Jacobson J, Powderly WG, Godofsky E, DeJesus E, Haas F, Reimann KA, Larson JL, Yarbough PO, Curt V, *et al*: Antiretroviral activity of the anti-CD4 monoclonal antibody TNX-355 in patients infected with HIV type 1. J Infect Dis 189: 286-291, 2004.
71. Fessel WJ, Anderson B, Follansbee SE, Winters MA, Lewis ST, Weinheimer SP, Petropoulos CJ and Shafer RW: The efficacy of an anti-CD4 monoclonal antibody for HIV-1 treatment. Antiviral Res 92: 484-487, 2011.
72. Zhang X-Q, Sorensen M, Fung M and Schooley RT: Synergistic in vitro antiretroviral activity of a humanized monoclonal anti-CD4 antibody (TNX-355) and enfuvirtide (T-20). Antimicrob Agents Chemother 50: 2231-2233, 2006.
73. United Biomedicals: Study to evaluate safety and efficacy of UB421 antibody in HIV1 infected adults. ClinicalTrials.gov Identifier: NCT01668043. First posted: August 17, 2012. https://clinicaltrials.gov/ct2/show/NCT01668043.
74. Sáez-Cirión A, Bacchus C, Hocqueloux L, Avettand-Fenoel V, Girault I, Lecuroux C, Potard V, Versmisse P, Melard A, Prazuck T, *et al*; ANRS VISCONTI study group: Post-treatment HIV-1 controllers with a long-term virological remission after the interruption of early initiated antiretroviral therapy ANRS VISCONTI Study. PLoS Pathog 9: e1003211, 2013.