Recent advances in antiretroviral treatment and prevention in HIV-infected patients

Fernando Maltez[a], Manuela Doroana[b], Teresa Branco[c] and Cristina Valente[d]

[a]Infectious Diseases Service – H. Curry Cabral, [b]Infectious Diseases Service – H. Santa Maria, Centro Hospitalar Lisboa Norte, [c]Medical Service – H. Fernando da Fonseca, Lisbon and [d]Infectious Diseases Service – Centro Hospitalar de Coimbra, Coimbra, Portugal

Correspondence to Fernando Maltez, Infectious Diseases Service, Hospital de Curry Cabral, Rua da Beneficiência n° 8, 106-166 Lisboa, Portugal
Tel: +00351 217924280; fax: +00351 217924281; e-mail: fmaltez@hccabral.min-saude.pt

Current Opinion in HIV and AIDS 2011, 6 (suppl 1):S21–S30

Purpose of review

To discuss new antiretroviral agents (ARVs) and alternative ARV treatment strategies that are currently being evaluated, and to provide an overview of the most recent advances in HIV vaccine development.

Recent findings

There is a continuous need for improvements in ARV therapy (ART) and several new ARVs are currently undergoing clinical investigation, including the non-nucleoside reverse transcriptase inhibitor rilpivirine, the integrase inhibitor elvitegravir, the chemokine receptor 5 co-receptor antagonist vicriviroc and the maturation inhibitor bevirimat. Strategies to optimize ART, such as treatment interruption, induction-maintenance and class-sparing regimens, are also being evaluated and have had varying success to date. However, vaccination still remains the optimal solution, and one second-generation preventative HIV vaccine has produced encouraging results in a recent phase III trial.

Summary

Global prevention and treatment with ARVs that are effective, well tolerated and have high barriers to the development of HIV resistance are the main strategies to fight HIV/AIDS while we await the development of an effective vaccine.

Keywords

antiretrovirals, HIV, strategies, vaccination

Curr Opin HIV AIDS 6 (suppl 1):S21–S30

1746-630X

Introduction

More than 25 years after the identification of HIV as the causative agent of AIDS, the disease continues to spread in some countries [1]. Current antiretrovirals (ARVs) have significantly prolonged the time to both AIDS development and death in those infected with HIV [2], although ARV success has ultimately been limited by toxicity, drug-drug interactions and other factors that determine patient compliance and, consequently, the emergence of resistance. Thus, there is a continuous need for existing agents to be improved and for the development of new drugs and drug classes that are effective, safe, have a higher genetic barrier to resistance, penetrate viral reservoirs more effectively and have activity against resistant viruses. Another challenge is to develop strategies that maximize the efficacy of currently available drugs for as long as possible; how to start, when to start, how to change and when to change ARV therapy (ART) are all crucial elements of this strategy. However, it should be noted that access to new drugs and strategies serves no purpose if the chain of new infections is not broken and if the low levels of prevention and education that are currently in place persist. Unfortunately, relative to the advances made in treatment, prevention strategies have lagged behind considerably. The creation of an HIV vaccine represents the greatest hope for globally controlling the pandemic and preventing further socio-economic damage, and this will be the most important concern of the scientific community during this century. Owing to numerous factors, including the current lack of an effective HIV vaccine, there has been recent enthusiasm regarding the potential use of effective ART to prevent transmission of HIV, although well-designed trials are needed to determine the efficacy and feasibility of this strategy [3]. In this review, we summarize recent advances in ARV agents, in ARV therapeutic strategies and in HIV vaccine development.

Overview of new ARVs under investigation

Several new ARVs are currently undergoing clinical evaluation, most of which are new members of existing drug classes, such as non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase inhibitors or chemokine receptor 5 (CCR5) inhibitors [4]. The aim of such 'next-generation' agents is to improve upon the limitations of currently used drugs, including sensitivity, resistance and

tolerability. Moreover, as many of these agents are being evaluated for once-daily administration, they may potentially confer some benefits in terms of compliance. However, there are few new agents under investigation that are derived from natural products, leaving this an area deserving of further research effort [4].

Rilpivirine

Rilpivirine (TMC278), a diarylpyrimidine derivative, is a second-generation NNRTI, which is active against wild-type HIV-1 and strains that are already resistant to other NNRTIs. Rilpivirine is a potent reverse transcriptase inhibitor and its antiviral activity is additive to that of other ARVs.

Rilpivirine demonstrated antiviral efficacy in patients naïve to therapy in phase II clinical studies [5•,6] and, as a result, is currently being evaluated in treatment-naïve patients in two ongoing 96-week, randomized, double-blind, phase III trials, known as ECHO and THRIVE. Preliminary pooled 48-week data from the phase III trials (n = 1368) suggest that once-daily rilpivirine 25 mg provides virological suppression noninferior to that of efavirenz, when used in combination with nucleoside reverse transcriptase inhibitors (NRTIs), with most patients in both treatment groups achieving HIV-1 RNA levels of < 50 copies/mL (84.3% vs 82.3%; between-group difference 2.0% [95% CI −2.0, 6.0]) [7•]. Moreover, rilpivirine appears to have a good tolerability profile. The most common adverse reactions to occur with rilpivirine in various trials included nausea, vomiting, headache and dizziness. Although rilpivirine was associated with a 10% incidence of rash and a 30% incidence of neuropsychiatric disorders, the incidence of these events was lower than with the comparator.

Rilpivirine offers the convenience of once-daily oral dosing (25 mg), and long-acting parenteral formulations are also under investigation [8]. Oral rilpivirine should always be taken with food, as it increases exposure to the drug by 45% [9]. However, drugs, such as rifampicin, that induce the cytochrome P450 (CYP) enzyme, CYP3A4, can reduce rilpivirine exposure and should therefore not be co-administered with rilpivirine [10]. Use of drugs that increase gastrointestinal pH, such as proton pump inhibitors (e.g. omeprazole) and H_2-receptor antagonists (e.g. famotidine), may also reduce rilpivirine exposure [11,12]. Consequently, proton pump inhibitors should not be coadministered with rilpivirine [11]; H_2-receptor antagonists can be used, provided they are administered several hours before or after rilpivirine [12].

Three mutations have been identified as being associated with decreased susceptibility to rilpivirine *in vitro* (K101P, Y181I and Y181V) and the resistance profile of rilpivirine appears to be more robust than those of first-generation NNRTIs [13]. Thus, rilpivirine may represent a viable future NNRTI treatment option for ART-naïve patients and, like the second-generation NNRTI etravirine, may potentially have use in the treatment of HIV-infected patients with resistance to other NNRTIs, although its use in this setting has yet to be evaluated.

Elvitegravir

Elvitegravir (GS-9137) is an HIV integrase inhibitor that inhibits the integration of viral DNA into the host's chromosomal DNA. The drug has demonstrated potent antiviral activity against viruses with resistance to NNRTIs, NRTIs and protease inhibitors (PIs).

The antiviral efficacy of elvitegravir has been assessed predominantly in treatment-experienced patients. One randomized, dose-ranging, phase II study (n = 278) compared the efficacy of once-daily elvitegravir 20, 50 or 125 mg boosted with ritonavir with that of a comparator ritonavir-boosted PI (PI/r), in combination with an active background regimen, in treatment-experienced patients [14•]. The elvitegravir arms were found to be noninferior (50 mg/day) or statistically superior (125 mg/day; p = 0.021) to the PI/r arm with regard to the time-weighted average change from baseline in HIV RNA levels through week 24 of therapy (−1.44 and −1.66 vs −1.19 $\log^{10}$ copies/mL; intent-to-treat [ITT] analysis). However, the elvitegravir 20 mg/day treatment arm was prematurely terminated following a review of the data at 8 weeks which found high rates of virological failure. Use of a PI/r (darunavir/r or tipranavir/r) was permitted after week 8 in the remaining elvitegravir arms. As a result, the 16-week timepoint was considered to be the latest timepoint least likely to be affected by any potentially confounding effects of PI/r addition; however, the findings at 16 weeks corroborated those of the 24-week analysis.

In addition, two ongoing, randomized, double-blind, phase III trials are currently comparing once-daily elvitegravir/r with twice-daily raltegravir, in combination with a background regimen (a PI/r plus a second agent), in treatment-experienced patients [15,16].

Elvitegravir is metabolized by CYP3A4 and pharmacological studies have shown that it can be boosted with 100 mg of ritonavir administered once daily. In combination with ritonavir, the oral bioavailability of elvitegravir is increased and its systemic exposure is increased ≈20-fold. As an alternative to ritonavir, the non-ritonavir boosting agent cobicistat is being evaluated. Elvitegravir has been coformulated with emtricitabine, tenofovir disoproxil fumarate (DF) and cobicistat in a single tablet for once-daily administration. This fixed-dose combination (the Quad pill) was recently compared with once-daily fixed-dose efavirenz/tenofovir DF/emtricitabine

(Atripla®) in a randomized, double-blind, phase II trial in treatment-naïve patients (n = 71) [17•]. Most patients in each treatment group achieved an HIV RNA level of <50 copies/mL after 24 weeks of therapy (90% vs 83%; ITT analysis), with the Quad pill meeting criteria for noninferiority relative to Atripla®.

Elvitegravir/r does not appear to require dosage adjustment when co-administered with NRTIs or NNRTIs [10,18]. Similarly, the elvitegravir dosage (150 mg/day) does not require adjustment upon co-administration with darunavir/r, tipranavir/r or fosamprenavir/r [10,18,19], although should be reduced to 85 mg/day in combination with atazanavir/r or lopinavir/r [20,21]. The pharmacokinetics of elvitegravir/r are unaltered when coadministered with the CCR5 inhibitor maraviroc, although as exposure to maraviroc is increased, a reduced maraviroc dosage may be required [22].

With regard to other drugs, the dosage of rifabutin should be reduced to 150 mg once daily or three times weekly when coadministered with elvitegravir/r [23]. Dosage adjustments are not required when elvitegravir/r is taken with omeprazole, although elvitegravir/r and antacids should be administered at least 2 hours apart owing to a reduction in elvitegravir exposure upon coadministration [24].

Elvitegravir demonstrated a good tolerability profile in the phase II trial, with the most commonly reported adverse events being upper respiratory tract infection, diarrhoea, nausea and fatigue [14•]. The integrase mutations that developed most commonly with elvitegravir in this trial included Q148R/H/K, N155H, E92Q and E138K [25]. Notably, raltegravir has been shown to select for mutations at these integrase amino acid positions *in vivo* and evidence for cross-resistance between elvitegravir and raltegravir has been observed [25].

Owing to its activity against HIV strains with resistance to other ARVs and its efficacy in treatment-experienced patients to date, elvitegravir should be a welcome addition to current salvage therapy options, particularly as it can be administered once daily. However, given the potentially low threshold for resistance associated with integrase inhibitors, monotherapy should be avoided [26].

Vicriviroc

Vicriviroc maleate (SCH 417690; hereafter referred to as vicriviroc) is a new CCR5 co-receptor antagonist, a class of drugs that bind specifically to the CCR5 co-receptor of the host cell, preventing entry of the virus. The antiviral activity of vicriviroc is generally similar to that of maraviroc (the first approved drug in this class), which is indicated for use in treatment-experienced patients.

Vicriviroc, as a component of combination ART, was shown to provide virological suppression for up to 48 weeks in treatment-experienced patients infected with CCR5-tropic HIV in randomized, double-blind, phase II trials, known as VICTOR-E1 (n = 114) and ACTG 5211 (n = 118) [27–29], with an open-label extension of VICTOR-E1 indicating sustained antiviral efficacy with vicriviroc for up to 96 weeks [30]. Consequently, the efficacy of the drug in CCR5-tropic HIV-infected treatment-experienced patients is currently being evaluated in two identically designed, randomized, double-blind, phase III trials (n = 857 randomized), known as VICTOR-E3 and VICTOR-E4, in which patients are treated with vicriviroc 30 mg or placebo once daily, in combination with an optimized background regimen (OBR) consisting of at least two ARVs. Pooled data from these studies showed no difference between the vicriviroc and placebo groups for the proportion of patients with an HIV RNA level of <50 copies/mL after 48 weeks of therapy (64% vs 61%) [31•]. However, vicriviroc appeared to be effective in those who had two or fewer ARVs in their OBR (70% vs 55% of placebo recipients; p = 0.02) in further analyses [31•].

In addition, the efficacy of vicriviroc 30 mg once daily is currently being compared with that of tenofovir DF/emtricitabine, each in combination with atazanavir/r, in treatment-naïve patients with CCR5-tropic HIV infection in a phase III study [32]. If effective, such a nucleoside-sparing first-line treatment regimen would enable other classes of agents to be withheld for subsequent lines of therapy. Of note, an earlier phase II trial in treatment-naïve patients was terminated prematurely owing to an increased rate of virological failure in those who received vicriviroc 25 or 50 mg once daily relative to those who received efavirenz, each in combination with a dual NRTI regimen [33].

Adverse events, such as headache (15%) and diarrhoea (10%) have been reported with vicriviroc. However, there is no record of serious side effects in humans, in particular those involving the central nervous system (CNS), such as seizures, which have occurred in animal species at very high plasma concentrations of vicriviroc. Furthermore, vicriviroc does not appear to be associated with serious laboratory or electrocardiographic abnormalities. Although certain malignancies developed in some treatment-experienced patients who participated in the phase II ACTG trial involving vicriviroc, a causal relationship with the drug was not considered to be determinable [28] and no new malignancies occurred during the extended follow-up of the trial [29].

Vicriviroc is metabolized primarily by CYP3A4, has a half-life of 28–33 hours (enabling once-daily administration) and can be administered with or without food

[10,34]. Moreover, no dosage adjustment seems to be necessary when ritonavir is used in combination with vicriviroc [10]. However, as vicriviroc is a CCR5 co-receptor antagonist, it is vital that a viral tropism test is performed before initiating treatment; if the viral strain uses the chemokine (CXC motif) receptor 4 (CXCR4) co-receptor or both CXCR4 and CCR5 (i.e. is dual-tropic), vicriviroc should not be used [35,36].

Bevirimat

Bevirimat (PA-457) belongs to a novel class of ARVs known as maturation inhibitors and has been studied in phase I and II trials [37–39]. The drug works by specifically inhibiting the final stage in Gag processing, namely the conversion of the capsid precursor (CA-SP1/p25) to the capsid protein (CA/p24). After treatment with bevirimat, the viral particles released by the infected cells have abnormal structures and are therefore non-infectious.

Bevirimat has demonstrated antiviral activity even in patients infected with resistant viruses. Its administration in combination with other ARVs appears to be safe, and *in vitro* it demonstrates synergy with approved ARVs. Bevirimat has good oral bioavailability and a long half-life of about 2 days, enabling once-daily administration; however, it is still unknown which dosage will prove to be the most effective. The drug is metabolized by glucuronidation and seems to have no drug interactions. *In vitro*, for reasons yet unknown, strains of HIV already resistant to PIs show hypersusceptibility to bevirimat [40]. Further development of bevirimat has currently been suspended.

Overview of new ARV therapeutic strategies

Although eradication of HIV remains an elusive prospect, ART is now able to maintain viral suppression in infected individuals, preserving their immune systems for prolonged periods of time. The current standard of care for the treatment of HIV in the developed world is highly active ART (HAART), usually a combination of two NRTIs and an NNRTI or PI [41,42]. However, concerns still exist regarding the long-term toxicity associated with chronic drug exposure, the need for daily medication adherence, the development of HIV resistance, drug-drug interactions and the costs associated with treatment. Several drug-sparing strategies are being explored to minimize ARV requirements. These include intermittent therapy, induction-maintenance regimens and class-sparing combinations [43].

Intermittent therapy was first thought to be a strategy that could reduce drug exposure and toxicity, and usually consists of predefined periods on and off therapy, or scheduled treatment interruptions guided by $CD4^+$ cell count. Although exploratory studies seemed promising, the more recently completed trials that used a $CD4^+$ cell count guided approach, including TRIVACAN (n = 386) [44], STACCATO (n = 430) [45] and the large SMART study (n = 5472) [46], showed a higher incidence of morbidity, not only opportunistic diseases and death, but also renal, hepatic and cardiovascular events, in the treatment interruption arms than in the continuous therapy arms. These data do not support the general use of treatment interruption as a simplification strategy in HIV-infected individuals [43], except perhaps in selected populations.

Single-drug-class therapy was initially studied with NRTIs, including both once-daily and fixed-dose triple combinations [47–50]. However, these trials generally showed a greater risk of virological failure with NRTIs than with NNRTI-based regimens when used in the initial treatment of HIV infection.

Like NRTIs, PIs (which combine potency with a high genetic barrier to resistance) have also been studied as monotherapy. Lopinavir/r has been the PI most extensively studied in this setting, with data available from six randomized controlled studies. One such study is the MONARK trial (n = 138), which compared lopinavir/r with the triple combination of lopinavir/r, zidovudine and lamivudine in ART-naïve patients with $CD4^+$ cell counts of >100 cells/μL and HIV RNA levels of <100,000 copies/mL [51]. There were no significant differences between the treatment groups in terms of virological suppression after 24 or 48 weeks of therapy in the ITT analysis. However, major PI mutations were detected in 3 of 21 patients with virological failure in the lopinavir/r alone arm and in none of those with virological failure in the triple-therapy arm.

In a recent systematic review of all PI-monotherapy studies published in peer-reviewed journals or presented at conferences up to 2008 [52], the overall efficacy of PI/r monotherapy was found to be inferior to that of HAART, although the efficacy was improved if patients were started on monotherapy after having virological suppression for at least 6 months. This strategy is called induction-maintenance and is based on the assumption that after a phase of maximal suppressive HAART (induction), the same level of viral suppression could be maintained by fewer drugs (maintenance). Trials using NRTIs and/or a first-generation PI as maintenance therapy have produced variable findings [53–58], but PI/r monotherapy maintenance has also been studied in the past few years. Advantages of this approach would be reduction of side effects (including avoidance of long-term NRTI toxicity) and fewer drug interactions and costs. One further benefit could be reduction of ARV resistance, as failure of PI/r regimens seldom selects for major PI resistance mutations.

Atazanavir/r, a once daily PI/r with a good metabolic profile, was studied as maintenance monotherapy in small, non-comparative trials [59–61]. Virologic suppression was generally maintained, although one study was prematurely stopped because of an excess of virologic failures [59]. Reassuringly, no major PI mutations could be detected in the virologic failures, either by standard genotyping or by single genome sequencing that detects low frequency mutations. This finding reaffirms the results of previous trials showing that PI resistance mutations are uncommon when PI monotherapy fails.

The more recently approved PI, darunavir/r, has also been studied as maintenance monotherapy. Two large trials (MONET [62] and MONOI-ANRS 136 [63]) comparing darunavir/r monotherapy with darunavir/r plus a double nucleoside backbone in virologically suppressed patients were presented at the 2009 International AIDS Society Conference. At 48 weeks in both trials, the efficacy of the monotherapy arm was noninferior to that of the standard triple regimen. Moreover, in the three patients who experienced viral failure in the MONOI-ANRS 136 trial no new mutations related to darunavir resistance were detected [63].

However, PI monotherapy simplification strategies remain associated with concerns regarding limited penetration of the drug into viral resevoirs and the possibility of viral replication in the CNS or genital tract [64]. With the introduction of new classes of agents, such as integrase inhibitors and CCR5 co-receptor antagonists, other maintenance combinations are possible, and studies are already underway to explore these very well tolerated drugs as components of alternative regimens [65]. In addition, combining raltegravir, the first approved integrase inhibitor, with a PI (either lopinavir/r, atazanavir or darunavir/r) is currently being explored as a potential class-sparing approach in treatment-naïve patients in several ongoing studies [66–68]. Indeed, ART will continue to be developed, with the aim of reducing toxicity, improving convenience and enhancing the potency and durability of response, while preserving patient quality of life.

Update on HIV vaccination research

As currently available treatments are not effective in eradicating HIV, vaccination represents the optimal solution to the global impact of this infection. The primary goal of an HIV vaccine is to prevent the establishment of a persistent infection, with the ideal vaccine being able to block infection completely and provide sterilizing immunity [69]. However, an alternative, perhaps more realistic, vaccination goal is to lower the steady-state viral load achieved after primary HIV-1 infection (i.e. the viral set point). A safe and effective therapeutic vaccine that could reduce viral load could potentially reduce transmission, improve public health outcomes and reduce costs associated with long-term ART exposure. Moreover, a vaccine capable of reducing the need for ART may help to reduce the burden of disease [70]. However, there are numerous obstacles to generating effective vaccines against HIV-1, including the remarkable diversity of the virus and its capacity to evade selective pressures through genetic variation and to establish latent viral reservoirs, and the fact that there is no method to elicit broadly reactive antibody responses, no clear immune correlates of protection and no small-animal models [69].

Humoral and cell-mediated immunity in HIV infection

Vaccines induce memory immune responses that expand upon pathogen exposure to prevent or control an infection. Memory can be induced for both B and T cells. B cells produce antibodies, whereas $CD8^+$ T cells (cytotoxic T lymphocytes [CTLs]) recognize and destroy cells that are virus infected. $CD4^+$ T cells are often referred to as "helper T cells" as they produce factors that are required for the growth and differentiation of $CD8^+$ T cells and B cells [71].

The general aim of a vaccine is to stimulate the production of neutralizing antibodies. However, unlike other infections, infection with HIV typically fails to provide protective immunity that lasts. Within weeks of being infected with HIV, circulating antibodies appear which are the basis for the diagnostic HIV ELISA test, yet the virus continues to destroy immune system cells, primarily $CD4^+$ T cells [72].

How extensively HIV pathogenesis is controlled by humoral and innate immunity is still unclear, although one HIV antigen potentially relevant to protective humoral immunity is the envelope (Env) glycoprotein, which exists as a trimer on the surface of the virus particle [69,70]. Many of the conserved epitopes of the Env glycoprotein of HIV-1 are shielded from antibody recognition by extensive N-linked glycosylation [69,73], and some conserved regions (e.g. the chemokine co-receptor binding site) form only after Env has bound to $CD4^+$ and undergone a subsequent change in conformation [69,74]. Moreover, any N-linked glycan mutations that develop may also facilitate the evasion of neutralizing antibody responses [69,73]. In spite of the progress that has been made in understanding the structure and function of Env, no candidate vaccines to elicit Env-specific, broadly neutralizing antibodies are currently being studied in clinical trials.

Virus-specific T-lymphocyte responses appear to play a pivotal role in the control of HIV-1 replication and are

consequently being investigated in vaccination strategies. Data indicate that during an acute HIV infection, virus-specific $CD8^+$ T-lymphocyte responses are coincident with primary viremia control [75,76]. However, despite vigorous $CD8^+$ CTL responses directed at the virus, the majority of individuals fail to clear the infection, perhaps because the selective pressure exerted by the CTLs may drive viral mutational escape. This strongly suggests that vaccines against persistent viruses should elicit early and strong humoral responses in addition to cellular responses.

Approaches for the development of an HIV vaccine

Several types of vaccine are currently licensed for human use: live-attenuated viruses, whole inactivated viruses and viral protein subunits [69,71]. Although these traditional technologies have been very successful in generating vaccines against various viruses, they have not yet yielded a successful HIV vaccine. In spite of the fact that good short-term protection against the development of infection has been seen with live-attenuated virus vaccines in non-human primates, the risks associated with using such HIV vaccines in humans have been too high, owing to the potential for vaccines to generate virulent variants or cause disease in those who are immunocompromised. Although animal models initially gave some hope for whole inactivated virus vaccines, the protective immunity was later found to be mediated by antibodies against human cellular proteins present in the outer membrane of the immunizing virus that had been incorporated during its production in human cell lines. Both whole inactivated virus and viral protein subunit vaccines provide immune protection mainly via the elicitation of antibodies, but such vaccines have so far been unsuccessful in eliciting protective antibodies against HIV [71]. However, data from nonhuman primates suggest that incorporating Toll-like receptor adjuvants into HIV protein subunit vaccination strategies may increase their utility [77]. In addition to using adjuvanted proteins and peptides in vaccination, other new vaccine concepts and strategies include gene-delivery technologies (e.g. live recombinant viral vectors, or DNA vaccines) and the combined use of at least two antigen delivery modalities in heterologous prime/boost regimens [69,71].

The use of viral vectors to deliver HIV antigens to specific target cells is the main strategy currently being explored. A great variety of viruses, including adenoviruses, poxviruses, parvoviruses, alphaviruses, paramyxoviruses, rhabdoviruses and herpesviruses, have been used to construct live and infectious recombinant vectors (e.g. ALVAC), and bacterial vaccine vectors, such as Bacillus Calmette-Guérin, *Salmonella* or *Listeria monocytogenes*, are also being investigated [69,78–80]. The construction of recombinant viral vectors usually involves the removal of important viral genes (thus rendering the vector replication defective, potentially allowing for greater safety) and then filling the resulting empty space with genes for the desired vaccine antigens [78,81].

Plasmid DNA vaccines proved to be disappointing in preclinical studies conducted in non-human primates [79], although in untreated HIV-infected patients the first HIV DNA vaccines were safe and induced varying immune responses [82]. The immunogenicity of the vaccines could be improved by approaches such as promoter modification or use of cytokine adjuvants or synthetic genes [79,82]. However, DNA vaccines appear to be most useful when used as the priming component of prime-boost vaccination strategies that use live recombinant vaccines for boosting [79].

Several candidate HIV protein subunit vaccines have been developed, the first of which employed the HIV-1 envelope subunit proteins gp120 and gp160 (purified or recombinant) with the hope of eliciting neutralizing antibodies against HIV-1 to treat infection [70]. Lipopeptides represent another type of therapeutic HIV vaccine, the first of which was composed of a lipid group covalently coupled to a synthetic Gag peptide containing several CTL epitopes restricted by varying HLA alleles. Lipopeptide vaccines are capable of inducing $CD4^+$ and $CD8^+$ T-cell responses to a variety of known and novel T-cell epitopes [82]. Lipopeptides have shown promise in trials, both alone and as adjuvants to facilitate the delivery of protein subunit vaccines and to boost other therapeutic or prophylactic vaccines [70].

Antigen-presenting cells, such as dendritic cells (DC), are instrumental in inducing an immune response against HIV, although their functional capacity declines during the infection [70]. DCs have been investigated as a potential therapeutic vaccine approach, with around 50% of patients who received DCs loaded with inactivated autologous HIV-1 achieving viral load suppression without ART in one study [82]. However, in another trial, administration of HIV peptide-loaded DCs followed by HAART interruption did not reduce viral set points beyond those observed before the initiation of HAART [82].

Clinical trials using first-generation HIV-1 vaccines

There are currently more than 30 trials evaluating preventive HIV vaccine candidates. However, despite a number of promising phase I and II studies, the most advanced candidates have so far been unsuccessful. In initial studies, HIV vaccine candidates with the hope of

eliciting humoral antibody responses were evaluated, including synthetic peptides and recombinant proteins [83]. In spite of being safe and well tolerated, the subunit vaccine based on monomeric recombinant gp120 failed to protect against HIV-1 infection because the elicited antibodies could not neutralize primary HIV-1 isolates, despite showing some neutralizing activity against laboratory strains *in vitro*. Although early vaccine studies were unsuccessful, many lessons were learned from them as well as from fundamental research on the HIV Env protein.

Clinical trials using second-generation HIV-1 vaccines

Once the potential role of cell-mediated immune responses in controlling HIV infection was recognized, researchers broadened their scope to evaluate vaccines that incorporated the more conserved internal proteins of HIV as well as the envelope, and gave more attention to evaluating vaccines that induced both humoral and cell-mediated responses.

A randomized, double-blind, placebo-controlled, phase-III trial, known as RV144, was designed to evaluate the efficacy of the ALVAC-HIV vaccine (a non-replicating recombinant canarypox virus vector containing genes from HIV) boosted with the protein vaccine AIDSVAX B/E (gp120) in preventing HIV-1 infection. The trial was conducted in Thailand in 16,402 HIV-negative individuals and the results were recently published [84••]. In the modified ITT analysis, the vaccine had an efficacy of 31.2% ($p = 0.04$ vs placebo). Further analysis of the immune responses generated in vaccinees is needed, with an attempt to identify a correlate of protection. Follow-up clinical trials would also be beneficial in order to fully understand the vaccine effect and the potential for further vaccine development.

In addition, phase I clinical trials have evaluated a trivalent mixture of recombinant adenovirus serotype 5 vectors (rAd5) expressing the Gag, Pol and Nef of clade B HIV-1. Data from these studies suggested that, in general, the vaccine was well tolerated and immunogenic, although pre-existing neutralizing antibodies against the vaccine vector were seen to partially suppress the response to the vaccine [69]. Subsequently, two "proof-of-concept" phase IIb efficacy studies, known as Step [80] and Phambili [85], were initiated to determine if this vaccine could prevent HIV-1 infection or reduce viral loads post-infection in adults at high risk of HIV-1 infection. However, the studies were discontinued in 2007 because of a failure of the STEP trial to meet its efficacy endpoints [80]. Furthermore, the vaccine was associated with a greater number of HIV-1 infections than placebo in volunteers who had pre-existing Ad5-specific neutralizing antibody titers, seemingly suggesting that rAd5 vector vaccines may be associated with a higher, rather than lower, risk of contracting HIV in these individuals. Further analysis of the acquisition data showed a statistically significant increased risk of infection in vaccinated men who were uncircumcised [80].

Future vaccine approaches

Further research into the structure, function and immunogenicity of the Env glycoprotein is needed to facilitate efforts in generating improved Env immunogens that are capable of eliciting broad neutralizing antibody responses against HIV. However, as the optimal vaccine is likely to be a combination vaccine capable of eliciting both T-lymphocyte and neutralizing-antibody responses, these two vaccine strategies should ideally be pursued and developed simultaneously [69]. Some current vaccine approaches, such as heterologous recombinant adenovirus prime-boost regimens [69] or vaccine cocktail strategies [86], may offer new hope.

Conclusion

The prognosis of patients infected with HIV has improved dramatically over the last 26 years owing to the introduction of numerous effective anti-HIV drugs. However, limitations, such as toxicity and the development of resistance, have continuously driven the search for alternative agents, and several 'next-generation' agents are currently in development. Given the considerable progress that has been made in the treatment of HIV to date, there is hope that future research will yield effective novel therapies to further extend the current drug arsenal. In contrast, generating an effective preventative or therapeutic vaccine against HIV has proven to be much more difficult. HIV vaccines that incorporate HIV proteins/epitopes representing a broad range of strains and that induce a strong cross-reactive immune response are needed, and although this has not yet been achieved, the field of HIV vaccine research is progressing. However, as HIV vaccine development will continue to be a challenge, efficacy trials will certainly require the collaboration of product developers, governments, funders and researchers in multiple countries.

Acknowledgements

The authors would like to thank Emma Deeks, PhD, of *in*Science Communications, a Wolters Kluwer business, for incorporating peer review comments with funding by Janssen-Cilag.

Conflicts of interest

Fernando Maltez is on the board and has received honoraria for lectures from Janssen-Cilag, Merck Sharp & Dohme and Gilead Sciences; Teresa Branco has received honoraria for consultancies and lectures from Merck, Bristol-Myers Squibb and ViiV; Cristina Valente was on the board of Janssen-Cilag, Merck Sharp & Dohme, Roche, Gilead Sciences, Bristol-Myers Squibb, ViiV and Abbott Laboratories, has received honoraria for consultancies, expert testimony and lectures from

Janssen-Cilag, Merck Sharp & Dohme, Roche, Gilead Sciences and Bristol-Myers Squibb and for manuscript preparation and development of educational presentations from Janssen-Cilag, Gilead Sciences and Bristol-Myers Squibb.

Funding for the preparation of this publication was provided by Janssen-Cilag, Portugal.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1 WHO/UNAIDS/UNICEF. 2009 [cited 2010 Aug 4]; Available from: http://data.unaids.org/pub/report/2009.

2 Detels R, Munoz A, McFarlane G, *et al.* Effectiveness of potent antiretroviral therapy on time to AIDS and death in men with known HIV infection duration. Multicenter AIDS Cohort Study Investigators. JAMA 1998; 280:1497–1503.

3 Cohen MS, Gay CL. Treatment to prevent transmission of HIV-1. Clin Infect Dis 2010; 50 (Suppl 3):S85–S95.

4 Mehellou Y, De Clercq E. Twenty-six years of anti-HIV drug discovery: where do we stand and where do we go? J Med Chem 2010; 53:521–538.

5 • Pozniak AL, Morales-Ramirez J, Katabira E, *et al.* Efficacy and safety of TMC278 in antiretroviral-naive patients: week 96 results of a phase IIb randomized trial. AIDS 2010; 24:55–65.

The present paper demonstrates potent and sustained anti-viral efficacy with rilpivirine for up to 96 weeks in HIV-infected treatment-naïve patients.

6 Goebel F, Yakovlev A, Pozniak AL, *et al.* Short-term antiviral activity of TMC278–a novel NNRTI–in treatment-naive HIV-1-infected subjects. AIDS 2006; 20:1721–1726.

7 • Cohen C, Molina J-M, Cahn P, *et al.* Pooled week 48 safety and efficacy results from the ECHO and THRIVE phase III trials comparing TMC278 vs EFV in treatment-naïve, HIV-1-infected patients. Journal of the International AIDS Society 2010, 13(Suppl 4):O48. Published: 8 November 2010.

The present pooled analysis from the first phase III studies of rilpivirine demonstrates that rilpivirine provides virological suppression noninferior to that of efavirenz, when used in combination with NRTIs, in treatment-naïve patients with HIV-1 infection.

8 Baert L, van't Klooster G, Dries W, *et al.* Development of a long-acting injectable formulation with nanoparticles of rilpivirine (TMC278) for HIV treatment. Eur J Pharm Biopharm 2009; 72:502–508.

9 Hoetelmans R, Kestens D, Marien K, *et al.* Effect of food and multiple dose pharmacokinetics of TMC278 as an oral tablet formulation [abstract no. TuPe3.1B10]. 3rd International AIDS Society Conference on HIV Pathogenesis and Treatment; 2005; Rio de Janeiro.

10 Brown KC, Paul S, Kashuba AD. Drug interactions with new and investigational antiretrovirals. Clin Pharmacokinet 2009; 48:211–241.

11 Crauwels HM, van Heeswijk RPG, Kestens D, *et al.* The pharmacokinetic (PK) interaction between omeprazole and TMC278, an investigational non-nucleoside reverse transcriptase inhibitor (NNRTI). J Int AIDS Soc 2008; 11 Suppl.1: 239.

12 Van Heeswijk R, Hoetelmans R, Kestens D, *et al.* The pharmacokinetic (PK) interaction between famotidine and TMC278, a next generation non-nucleoside reverse transcriptase inhibitor (NNRTI), in HIV-negative volunteers [abstract no. TUPDB01]. 4th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention; 2007; Sydney.

13 Rimsky LT, Azijn H, Tirry I, *et al. In vitro* resistance profile of TMC278, a next-generation NNRTI; evidence of a higher genetic barrier and a more robust resistance profile than first generation NNRTIs. 18th International HIV Drug Resistance Workshop; 2009; Florida.

14 • Zolopa AR, Berger DS, Lampiris H, *et al.* Activity of elvitegravir, a once-daily integrase inhibitor, against resistant HIV Type 1: results of a phase 2, randomized, controlled, dose-ranging clinical trial. J Infect Dis 2010; 201:814–822.

The present study indicates that once-daily elvitegravir/ritonavir, in combination with active background therapy, can provide effective virological suppression in treatment-experienced patients with HIV-1 infection.

15 Gilead Sciences. Mulitcenter, randomized, double-blind, double-dummy, phase 3 study of the safety and efficacy of ritonavir-boosted elvitegravir (EVG/r) versus raltegravir (RAL) [ClinicalTrials.gov identifier NCT00708162]. US National Institutes of Health, ClinicalTrials.gov. [cited 2011 May 2]; Available from: http://www.clinicaltrials.gov

16 Gilead Sciences. Phase 3 study of the safety and efficacy of ritonavir-boosted elvitegravir (EVG/r) versus raltegravir (RAL) [ClinicalTrials.gov identifier NCT00707733]. US National Institutes of Health, ClinicalTrials.gov. [cited 2011 May 2]; Available from: http://www.clinicaltrials.gov

17 • Cohen C, Shamblaw D, Ruane P, *et al.* Single-tablet, fixed-dose regimen of elvitegravir/emtricitabine/tenofovir disoproxil fumarate/GS-9350 achieves a high rate of virologic suppression and GS-9350 is an effective booster. 17th Conference on Retroviruses and Opportunistic Infections; 2010; San Francisco.

The present study demonstrates that a once-daily fixed-dose tablet containing three antiretroviral agents (elvitegravir, emtricitabine and tenofovir disoproxil fumarate) in combination with a non-ritonavir boosting agent can provide virological suppression noninferior to that seen with once-daily fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naïve patients.

18 Schafer JJ, Squires KE. Integrase inhibitors: a novel class of antiretroviral agents. Ann Pharmacother 2010; 44:145–156.

19 Ramanathan S, Mathias AA, Shen G, *et al.* Lack of clinically relevant drug-drug interaction between ritonavir-boosted GS-9137 (elvitegravir) and fosamprenavir/r [abstract]. 4th International AIDS Society Conference; 2007; Sydney.

20 Mathias A, Ramanathan S, Hinkle J, *et al.* Effect of atazanavir/r on the steady-state pharmacokinetics of elvitegravir [abstract no. A-1417]. 47th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2007; Chicago.

21 Mathias A, West S, Enejosa J, Kearney B. A pharmacokinetic interaction between lopinavir/r and elvitegravir [abstract no. A-1418]. 47th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2007; Chicago.

22 Ramanathan S, Abel S, Tweedy S, *et al.* Pharmacokinetic interaction of ritonavir-boosted elvitegravir and maraviroc. J Acquir Immune Defic Syndr 2010; 53:209–214.

23 German PI, West S, Hui J, Kearney BP. Pharmacokinetic interaction between elvitegravir/ritonavir and dose-adjusted rifabutin [abstract no. P19]. 9th International Workshop on Clinical Pharmacology of HIV Therapy; 2008; New Orleans, LA.

24 Ramanathan S, Hinkle J, Enejosa J, Kearney B. Pharmacokinetic evaluation of drug interactions with ritonavir-boosted HIV integrase inhibitor GS-9137 (elvitegravir) and acid-reducing agents [abstract no. 69]. 8th International Workshop on Clinical Pharmacology of HIV Therapy; 2007; Budapest.

25 McColl DJ, Fransen S, Gupta S, *et al.* Resistance and cross-resistance to first generation integrase inhibitors: insights from a phase II study of elvitegravir (GS-9137) [abstract no. 9]. Antiviral Therapy 2007; 12 (Suppl. 1):S11.

26 Koelsch KK, Cooper DA. Integrase inhibitors in salvage therapy regimens for HIV-1 infection. Curr Opin HIV AIDS 2009; 4:518–523.

27 Suleiman J, Zingman BS, Diaz RS, *et al.* Vicriviroc in combination therapy with an optimized regimen for treatment-experienced subjects: 48-week results of the VICTOR-E1 phase 2 trial. J Infect Dis 2010; 201:590–599.

28 Gulick RM, Su Z, Flexner C, *et al.* Phase 2 study of the safety and efficacy of vicriviroc, a CCR5 inhibitor, in HIV-1-Infected, treatment-experienced patients: AIDS clinical trials group 5211. J Infect Dis 2007; 196:304–312.

29 Gulick R, Su Z, Flexner C, *et al.* ACTG 5211: phase II study of the safety and efficacy of vicriviroc (VCV) in HIV-infected treatment-experienced subjects: 48 week results [abstract]. 4th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention; 2007; Sydney.

30 McCarthy MC, Suleiman J, Diaz R, *et al.* Vicriviroc long-term safety and efficacy: 96-week results from the VICTOR-E1 study [poster no. H-923]. 49th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy; 2009; San Francisco.

31 • Gathe J, Diaz R, Fatkenheuer G, *et al.* Phase 3 trials of vicirviroc in treatment-experienced subjects demonstrate safety but not significantly superior efficacy over potent background regimens alone. 17th Conference on Retroviruses and Opportunistic Infections; 2010; San Francisco.

The present paper discusses pooled data from two ongoing phase III trials and indicates that the addition of vicriviroc to an optimized background regimen provides no additional benefit over the background regimen alone over a period of 48 weeks in treatment-experienced patients.

32 Schering-Plough. Efficacy and safety of vicriviroc in HIV-infected treatment-naive subjects (study P04875AM5) [ClinicalTrials.gov identifier NCT00551018]. US National Institutes of Health, ClinicalTrials.gov. [cited 2011 May 2]; Available from: http://www.clinicaltrials.gov

33 Landovitz RJ, Angel JB, Hoffmann C, *et al.* Phase II study of vicriviroc versus efavirenz (both with zidovudine/lamivudine) in treatment-naive subjects with HIV-1 infection. J Infect Dis 2008; 198:1113–1122.

34 Schurmann D, Fatkenheuer G, Reynes J, *et al.* Antiviral activity, pharmacokinetics and safety of vicriviroc, an oral CCR5 antagonist, during 14-day monotherapy in HIV-infected adults. AIDS 2007; 21:1293–1299.

35 Dau B, Holodniy M. Novel targets for antiretroviral therapy: clinical progress to date. Drugs 2009; 69:31–50.

36 Schering Plough Research Institute. Investigator's brochure update (SCH417690): summary of important changes 04 Aug 2009. Schering Plough Research Institute, New Jersey, USA.

37 Smith PF, Ogundele A, Forrest A, *et al.* Phase I and II study of the safety, virologic effect, and pharmacokinetics/pharmacodynamics of single-dose 3-o-(3',3'-dimethylsuccinyl)betulinic acid (bevirimat) against human immunodeficiency virus infection. Antimicrob Agents Chemother 2007; 51:3574–3581.

38 Lalezari J, McCallister S, Gigliotti M, *et al.* A phase 2 safety and efficacy study of bevirimat (BVM) in heavily treatment experienced HIV+ patients identifies the target phase 3 study profile [abstract no. H-891]. 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy and 46th Annual Meeting of the Infectious Diseases Society of America - a joint meeting; 2008; Washington, DC.

39 Bloch M, Bodsworth N, Mather G, *et al.* Efficacy, safety and pharmacokinetics of MPC-4326 (bevirimat dimeglumine) 200 mg BID and 300 mg BID monotherapy administered for 14 days in subjects with HIV-1 infection [slide presentation]. 2009 [cited 2011 May 2]; Available from: http://www.myriad pharma.com/about-us/scientific-presentations

40 Stoddart CA, Joshi P, Sloan B, *et al.* Potent activity of the HIV-1 maturation inhibitor bevirimat in SCID-hu Thy/Liv mice. PLoS One 2007; 2:e1251.

41 Gazzard BG. British HIV Association Guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy 2008. HIV Med 2008; 9:563–608.

42 Thompson MA, Aberg JA, Cahn P, *et al.* Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society-USA panel. JAMA 2010; 304:321–333.

43 McKinnon JE, Mellors JW, Swindells S. Simplification strategies to reduce antiretroviral drug exposure: progress and prospects. Antivir Ther 2009; 14:1–12.

44 Danel C, Moh R, Minga A, *et al.* CD4-guided structured antiretroviral treatment interruption strategy in HIV-infected adults in west Africa (Trivacan ANRS 1269 trial): a randomised trial. Lancet 2006; 367:1981–1989.

45 Ananworanich J, Gayet-Ageron A, Le Braz M, *et al.* CD4-guided scheduled treatment interruptions compared with continuous therapy for patients infected with HIV-1: results of the Staccato randomised trial. Lancet 2006; 368:459–465.

46 El-Sadr WM, Lundgren JD, Neaton JD, *et al.* CD4+ count-guided interruption of antiretroviral treatment. N Engl J Med 2006; 355:2283–2296.

47 Gulick RM, Ribaudo HJ, Shikuma CM, *et al.* Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. N Engl J Med 2004; 350:1850–1861.

48 Khanlou H, Yeh V, Guyer B, Farthing C. Early virologic failure in a pilot study evaluating the efficacy of therapy containing once-daily abacavir, lamivudine, and tenofovir DF in treatment-naive HIV-infected patients. AIDS Patient Care STDS 2005; 19:135–140.

49 Gallant JE, Rodriguez AE, Weinberg WG, *et al.* Early virologic nonresponse to tenofovir, abacavir, and lamivudine in HIV-infected antiretroviral-naive subjects. J Infect Dis 2005; 192:1921–1930.

50 Perez-Elias MJ, Moreno A, Moreno S, *et al.* Higher virological effectiveness of NNRTI-based antiretroviral regimens containing nevirapine or efavirenz compared to a triple NRTI regimen as initial therapy in HIV-1-infected adults. HIV Clin Trials 2005; 6:312–319.

51 Delfraissy JF, Flandre P, Delaugerre C, *et al.* Lopinavir/ritonavir monotherapy or plus zidovudine and lamivudine in antiretroviral-naive HIV-infected patients. AIDS 2008; 22:385–393.

52 Bierman WF, van Agtmael MA, Nijhuis M, *et al.* HIV monotherapy with ritonavir-boosted protease inhibitors: a systematic review. AIDS 2009; 23:279–291.

53 Pialoux G, Raffi F, Brun-Vezinet F, *et al.* A randomized trial of three maintenance regimens given after three months of induction therapy with zidovudine, lamivudine, and indinavir in previously untreated HIV-1-infected patients. Trilege (Agence Nationale de Recherches sur le SIDA 072) Study Team. N Engl J Med 1998; 339:1269–1276.

54 Mallolas J, Pich J, Penaranda M, *et al.* Induction therapy with trizivir plus efavirenz or lopinavir/ritonavir followed by trizivir alone in naive HIV-1-infected adults. AIDS 2008; 22:377–384.

55 Markowitz M, Hill-Zabala C, Lang J, *et al.* Induction with abacavir/lamivudine/zidovudine plus efavirenz for 48 weeks followed by 48-week maintenance with abacavir/lamivudine/zidovudine alone in antiretroviral-naive HIV-1-infected patients. J Acquir Immune Defic Syndr 2005; 39:257–264.

56 Katlama C, Fenske S, Gazzard B, *et al.* TRIZAL study: switching from successful HAART to Trizivir (abacavir-lamivudine-zidovudine combination tablet): 48 weeks efficacy, safety and adherence results. HIV Med 2003; 4:79–86.

57 Opravil M, Hirschel B, Lazzarin A, *et al.* A randomized trial of simplified maintenance therapy with abacavir, lamivudine, and zidovudine in human immunodeficiency virus infection. J Infect Dis 2002; 185:1251–1260.

58 Havlir DV, Marschner IC, Hirsch MS, *et al.* Maintenance antiretroviral therapies in HIV infected patients with undetectable plasma HIV RNA after triple-drug therapy. AIDS Clinical Trials Group Study 343 Team. N Engl J Med 1998; 339:1261–1268.

59 Karlstrom O, Josephson F, Sonnerborg A. Early virologic rebound in a pilot trial of ritonavir-boosted atazanavir as maintenance monotherapy. J Acquir Immune Defic Syndr 2007; 44:417–422.

60 Wilkin TJ, McKinnon JE, DiRienzo AG, *et al.* Regimen simplification to atazanavir-ritonavir alone as maintenance antiretroviral therapy: final 48-week clinical and virologic outcomes. J Infect Dis 2009; 199:866–871.

61 Swindells S, DiRienzo AG, Wilkin T, *et al.* Regimen simplification to atazanavir-ritonavir alone as maintenance antiretroviral therapy after sustained virologic suppression. JAMA 2006; 296:806–814.

62 Arribas J, Horban A, Gerstoft J, *et al.* The MONET trial: darunavir/ritonavir monotherapy shows non-inferior efficacy to standard HAART, for patients with HIV RNA < 50 copies/mL at baseline [abstract]. 5th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention; 2009; Cape Town, South Africa.

63 Katlama C, Valentin MA, Algarte-Genin M, *et al.* Efficacy of darunavir/ritonavir maintenance monotherapy in patients with HIV-1 viral suppression: a randomized open-label, noninferiority trial, MONOI-ANRS 136. AIDS 2010; 24:2365–2374.

64 Sahali S, Chaix ML, Delfraissy JF, Ghosn J. Ritonavir-boosted protease inhibitor monotherapy for the treatment of HIV-1 infection. AIDS Rev 2008; 10:4–14.

65 Ripamonti D, Maggiolo F, Bombana E, *et al.* Efficacy, safety and tolerability of dual therapy with raltegravir and atazanavir in antiretroviral experienced patients [abstract no. MOPEB067]. 5th International AIDS Society Conference on HIV Pathogenesis and Treatment; 2009; Cape Town, South Africa.

66 Reynes J, Lawal A, Pulido F, *et al.* Lopinavir/ritonavir (LPV/r) combined with raltegravir (RAL) demonstrated similar antiviral efficacy and safety as LPV/r combined with tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) in treatment-naive HIV-1-infected subjects: PROGRESS 48 week results. 18th International AIDS Conference; 2010; Vienna.

67 National Institute of Allergy and Infectious Diseases. Safety and effectiveness of raltegravir and darunavir/ritonavir in treatment-naive HIV-infected adults [ClinicalTrials.gov identifier NCT00830804]. US National Institutes of Health, ClinicalTrials.gov. [cited 2011 May 2]; Available from: http://www.clinicaltrials.gov

68 Kozal MJ, Lupo S, DeJesus E, *et al.* The SPARTAN study: a pilot study to assess the safety and efficacy of an investigational NRTI- and RTV-sparing regimen of atazanavir (ATV) experimental dose of 300 mg BID plus raltegravir (RAL) 400 mg BID (ATV+RAL) in treatment-naive HIV-infected subjects. 18th International AIDS Conference; 2010; Vienna.

69 Barouch DH. Challenges in the development of an HIV-1 vaccine. Nature 2008; 455:613–619.

70 Puls RL, Emery S. Therapeutic vaccination against HIV: current progress and future possibilities. Clin Sci (Lond) 2006; 110:59–71.

71 Robinson HL. HIV/AIDS vaccines: 2007. Clin Pharmacol Ther 2007; 82:686–693.

72 Kallings LO. The first postmodern pandemic: 25 years of HIV/AIDS. J Intern Med 2008; 263:218–243.

73 Wei X, Decker JM, Wang S, *et al.* Antibody neutralization and escape by HIV-1. Nature 2003; 422:307–312.

74 Kwong PD, Wyatt R, Robinson J, *et al.* Structure of an HIV gp120 envelope glycoprotein in complex with the CD4 receptor and a neutralizing human antibody. Nature 1998; 393:648–659.

75 Koup RA, Safrit JT, Cao Y, *et al.* Temporal association of cellular immune responses with the initial control of viremia in primary human immunodeficiency virus type 1 syndrome. J Virol 1994; 68:4650–4655.

76 Borrow P, Lewicki H, Hahn BH, *et al.* Virus-specific CD8+ cytotoxic T-lymphocyte activity associated with control of viremia in primary human immunodeficiency virus type 1 infection. J Virol 1994; 68:6103–6110.

77 Wille-Reece U, Flynn BJ, Lore K, *et al.* Toll-like receptor agonists influence the magnitude and quality of memory T cell responses after prime-boost immunization in nonhuman primates. J Exp Med 2006; 203:1249–1258.

78 Schoenly KA, Weiner DB. Human immunodeficiency virus type 1 vaccine development: recent advances in the cytotoxic T-lymphocyte platform "spotty business". J Virol 2008; 82:3166–3180.

79 Girard MP, Osmanov SK, Kieny MP. A review of vaccine research and development: the human immunodeficiency virus (HIV). Vaccine 2006; 24:4062–4081.

80 Buchbinder SP, Mehrotra DV, Duerr A, *et al.* Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial. Lancet 2008; 372:1881–1893.

81 Girard MP, Bansal GP. HIV/AIDS vaccines: a need for new concepts? Int Rev Immunol 2008; 27:447–471.

82 Boberg A, Isaguliants M. Vaccination against drug resistance in HIV infection. Expert Rev Vaccines 2008; 7:131–145.

83 Pitisuttithum P. HIV vaccine research in Thailand: lessons learned. Expert Rev Vaccines 2008; 7:311–317.

84 •• Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, *et al.* Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. N Engl J Med 2009; 361:2209–2220.
The present paper provides preliminary evidence for the effectiveness of a vaccine in preventing HIV-1 infection in a community-based population.

85 Gray G on behalf of HVTN 503 (Phambili). Why we unblinded Phambili. HVTN full group meeting, Seattle. 2007 [cited 2011 May 2]; Available from: http://www.hvtn.org/fgm/1107slides/Gray.pdf.

86 Hurwitz JL, Zhan X, Brown SA, *et al.* HIV-1 vaccine development: tackling virus diversity with a multi-envelope cocktail. Front Biosci 2008; 13:609–620.