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Universal Antiretroviral Regimens: Thinking Beyond One-Pill-Once-a-Day

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Abstract

Purpose of Review—Poor adherence to oral antiretroviral treatment in a subpopulation of persons with HIV-1 infection interferes with the potential success of the drug regimens in treating the infection. Here we review long acting antiretroviral strategies currently in clinical development that could prove useful for the treatment of HIV-1 infection in individuals not succeeding with short acting oral regimens.

Recent Findings—Pharmaceutical nanotechnology has succeeded in creating two novel long-acting injectable antiretroviral compounds, carbotegravir and rilpivirine, that have completed early clinical trials demonstrating safety, tolerability, and prolonged antiretroviral activity. 4′-ethynyl-2-fluoro-2′-deoxyadenosine (EFdA; MK8591) is a novel nucleoside reverse transcriptase inhibitor in early clinical development as a long acting orally administered drug and in a long-acting polymer implant. Broadly neutralizing and cell-entry inhibitor monoclonal antibodies have demonstrated potent antiviral activity in early human trials; however, there is substantial baseline resistance. In addition, monotherapy leads to rapid resistance in those with baseline susceptibility.

Summary—Long acting antiretroviral chemical compounds and monoclonal antibodies have demonstrated potent anti-HIV activity in early stage clinical investigations, and are actively being studied in advanced clinical trials for treatment and prevention. Strategies to manage toxicities and waning drug levels of chemical compounds, as well as primary and secondary resistance to current monoclonal antibodies are important considerations.

Keywords

HIV; long-acting antiretroviral drugs; polymer implants; broadly-neutralizing anti-HIV monoclonal antibodies; HIV cell entry inhibitors

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Introduction

Orally-administered combination antiretroviral drug therapy has had impressive success in suppressing viral replication in HIV-infected individuals and largely protecting them from the complications of HIV-1 infection. Incomplete recovery of the CD4 T cell population and residual immune impairment, mild neurocognitive dysfunction, and a continued risk of cardiovascular and other “non-AIDS” events, all associated with persistent immune activation, remain as problems. But, by and large, the morbidities and mortality from HIV disease have greatly diminished. Furthermore, oral regimens have become simpler and less toxic over time, so that several well tolerated one-pill-a-day coformulated single tablet regimens (STRs) are now available.

Nevertheless, there is a substantial subpopulation of HIV-infected persons, estimated at up to 28%, who are not succeeding with oral ART to attain full suppression of HIV-1 viremia, putting themselves at continued risk of disease complications and death, and placing others in the community at risk of continued spread of the infection[1]. The major factor interfering with the success of oral treatment is poor adherence to the regimen. The availability of parenteral long-acting alternatives, which can also be given in a supervised manner, could improve the rates of treatment success overall and help lower rates of HIV-1 transmission. In addition, there are situations when the self-administration of oral medication is difficult, often because of gastrointestinal, neurologic, or psychiatric disease. In such cases, parenteral therapy would be a valuable option for those wishing to start or continue ART[2].

Low rates of adherence have also impaired the effectiveness of orally administered pre-exposure prophylaxis (PreP) regimens for those at high risk of acquiring HIV-1 infection[3]. Long-acting parenterally-administered agents are being evaluated for this purpose in ongoing clinical trials. Long-acting agents have proven useful in other arenas, such as preventing pregnancy and treating schizophrenia[4,5].

Although in most cases daily oral STRs seem best suited for widespread ARV treatment and prevention, alternative methods of drug delivery, particularly injectable or implantable ARVs, could meet the needs of the global epidemic better than available oral drugs. Here we review long-acting agents actively in clinical development, with an emphasis on recent studies, and explore future directions of investigation in this field (Table 1).

Long-Acting Antiretroviral Strategies

Less Frequent Administration of Oral Drugs

Although once-daily administration of oral ARVs is the current standard of care, less frequent administration of existing and investigational oral ARV's may be a possibility. Tenofovir, whose intracellular active metabolite tenofovir-diphosphate has a half-life of 60-100 hours, could easily be given less often than once per day while maintaining antiviral effects[6]. Efavirenz, with a plasma half-life of 45-60 hours, is also a good candidate for less frequent dosing. Since regimens involving administration every other or every 3rd day would be difficult to remember, and since an every Monday, Wednesday, Friday regimen may be just as difficult, if not more difficult, to adhere to than an every-day regimen, one possibility

might be to aim for a once-weekly dosing, which could have convenience and even economic advantages over daily therapy.

4′-ethynyl-2-fluoro-2′-deoxyadenosine (EFdA)—4′-ethynyl-2-fluoro-2′-deoxyadenosine (EFdA; MK8591) is a member of a novel class of 4′-substituted NRTIs that retain the 3′-hydroxyl group, unlike currently approved NRTIs. This chemical modification renders these molecules more potent as antivirals because of higher affinity for the active site of the HIV reverse transciptase[7]. The mechanism of action of EFdA is different from that of other NRTI's, in that incorporation of EFda-monophosphate blocks primer translocation once incorporated into the nascent RNA-DNA duplex. EFdA also has a halogen substitution at the 2-position of the adenine ring that impairs degradation by adenosine deaminase, resulting in an extended intracellular half-life[7]. EFdA has substantial efficacy in treatment and prevention of HIV in animal models using doses as low as 0.1 mg/kg.day. in addition, the drug appears to be safe and well tolerated. Early clinical development of this drug is now underway.

The half-life of EFdA-triphosphate, the active metabolite, in human PBMC's is greater than 72 hours, suggesting the potential for once-weekly dosing[7]. One of the challenges with weekly EFdA as treatment for HIV infection would be finding suitable partners with similar pharmacokinetic properties. Possibilities would include efavirenz and oral tenofovir prodrugs, but further work will be required to demonstrate the feasibility of such an approach.

Long-acting Injectables

Pharmaceutical nanotechnology allows the creation of injectable drugs which are very slowly eliminated from the body, resulting in formulations that can be administered once every few months. Intramuscular injection of nanoformulated versions of the approved neuroleptic drug paloperidone has been approved and is available for chronic administration every 4-6 weeks. Similar formulation technology has now been applied to several approved and investigational antiretroviral drugs, as explained below[8]. Potential advantages of these approaches for HIV treatment and prevention include less frequent dosing because of the longer apparent half-life, a lower drug dose per day because of nanoformulation properties, protection from poor adherence to daily oral drugs, and the possibility of directly observed therapy, especially if the dosing interval is long. These approaches are attractive for patients suffering from pill fatigue, and in settings where HIV stigma is an issue, affording better protection of health privacy than daily oral regimens. Disadvantages include managing or avoiding adverse effects that might occur after injection, especially for irreversible and/or serious AE's, what to do about recipients who become pregnant after such an injection, how to manage the prolonged low-level pharmacokinetic “tail” at the end of a dosing interval, and what to do about missed appointments for drug injection[8]. In order to prevent the occurrence of serious side effects following an intramuscular injection, there may be a regulatory requirement for an oral version of the same drug that can be taken for some period of months initially to assure tolerance; this obviously offsets the adherence advantages of the injection, and for investigational drugs means the development of two formulations rather than one. There is also the need in HIV treatment strategies to pair drugs

with similar pharmacokinetic properties so that they can be given on the same schedule or, preferably, coformulated.

Cabotegravir—Cabotegravir is a potent investigational HIV-1 integrase strand transfer inhibitor (InSTI) with a chemical structure very close to that of dolutegravir[9]. Cabotegravir was developed largely because of its suitability for long-acting/extended-release (LA/ER) formulation. A long-acting parenteral formulation has been developed by creating nanocrystals that are milled to a fairly uniform size. To date, the drug has been well tolerated, both as an oral version given as 30 mg daily, or as the intramuscular injection, given every 8-12 weeks. The most significant adverse effects from the intramuscular version have been injection site reactions. A single intramuscular injection of 400 mg of this formulation given to HIV-seronegative volunteers produced detectable concentrations of cabotegravir in plasma for more than 48 weeks[9]. Because cabotegravir is an investigational agent, it has always been given to HIV-infected volunteers in combination with other active ARV's, but with an oral lead-in period that is generally 6 months in duration in order to ensure that the recipient will be able to tolerate the drug long-term.

Rilpivirine—Rilpivirine is a nonnucleoside reverse transcriptase inhibitor (NNRTI) commonly used as an oral agent for the treatment of HIV infection at a daily dose of 25mg. Because rilpivirine also has chemical properties suitable for nanoformulation, a parenteral long-acting formulation consisting of a suspension of nanocrystals has also been developed and tested. A single 1200 mg intramuscular dose of rilpivirine (RPV-LA) produced detectable plasma concentrations in HIV-seronegative volunteers for up to 84 days[10]. Because the oral formulation of rilpivirine was already approved and was known to be generally safe and well tolerated, this extra step in product development was not required to begin testing the injectable LA/ER counterpart.

One disadvantage of rilpivirine as compared to cabotegravir is its know ability to prolong the corrected QT interval (QTc) in a concentration-dependent manner in humans. This is a known risk factor for cardiac arrhythmia. Fortunately, single i.m. doses of RPV-LA as high as 1200 mg have produced plasma concentrations below those associated with QTc prolongation with the oral version of the drug[10].

Combination studies—Since the treatment of chronic HIV infection requires a combination of active agents, and since LA-rilpivirine and LA-cabotegravir were the first two such formulations developed for human use, combination studies involving these two agents have been carried out. LATTE (Long Acting

Antiretroviral Treatment Enabling) was a Phase 2b study in which 243 HIV-1-infected participants were randomized to oral cabotegravir 10, 30, or 60 mg/day, or to a control arm of efavirenz, in combination with an investigator-selected NRTI regimen of abacavir/lamivudine or tenofovir/emtricitabine. After 24 weeks of triple-drug oral therapy, participants were randomized to the combination of oral cabotegravir and oral rilpivirine 25 mg/day for an additional 72 weeks to assess the feasibility of this 2-drug regimen. To date, this combination regimen has been well tolerated and highly effective at suppressing HIV,

although a single participant developed resistance to both cabotegravir and rilpivirine while on study, presumably as a consequence of poor adherence[11].

The LATTE-2 study is a Phase 3 evaluation of the combination of injectable cabotegravir with rilpivirine in HIV-infected participants. This study enrolled 310 ARV naive patients, who received 20 weeks of daily oral cabotegravir 30mg plus NRTIs, followed by an injectable regimen of cabotegravir-LA plus rilpivirine-LA every 4 or 8 weeks[8]. The primary endpoint, a comparison of the week 32 antiviral activity, tolerability, and safety of the intramuscular dosing regimens to oral cabotegravir 30mg plus ABC/3TC orally once daily found that the i.m. regimens were statistically non-inferior to the oral regimen[12]. These promising results have prompted further investigation of LA-RPV and LA-cabotegravir in HIV prevention. Additional treatment trials are being planned.

Other Drug Delivery Technologies

Beyond intramuscular injection of LA/ER formulations like LA-RPV and LA-cabotegravir, other technologies are being explored for long-term delivery of ARV's. For example, biologically inert non-degradable polymers have been used clinically for several decades to deliver hormonal contraception to women. These products are generally implanted subcutaneously in the interior upper arm, and can deliver effective contraception for 3 years or more after a single implant. A silicone implant impregnated with tenofovir alafenamide (TAF) can produce measurable concentrations of tenofovir in the plasma of beagle dogs for more than 6 weeks[13]. A polymer implant containing EFdA produces concentrations of this NRTI that remain higher than the in vitro IC_{50} for inhibition of HIV for more than 6 months in rats[14]. This suggests the feasibility of developing an EFdA implant that could provide antiretroviral coverage for a year or longer.

Potential advantages of implants over intramuscular injections include the fact that implants are removable in case of toxicity, produce more consistent and predictable drug release, and their pharmacokinetic properties may not be dependent on the injection site. In addition, implants can remain in place for years given as their inert, non-degradable subcutaneous versions. However, implants require specialized devices and training for insertion, a minor surgical procedure if they need to be removed, and are more expensive and complex to manufacture, making transition to a generic marketplace more difficult as compared to i.m. injectable formulations.

Despite their many challenges, newer technologies like implants may make ARV delivery more convenient, accessible and reliable as compared to oral and injection formulations. At some point in the near future, these technologies could also become candidates for inclusion in a universal antiretroviral regimen.

Monoclonal Antibodies

Broadly neutralizing anti-HIV-1 monoclonal antibodies

Several monoclonal antibodies have been identified in recent years that neutralize 80% or more of clinical HIV isolates in vitro by binding extracellular portions of the HIV envelope protein[15]. These so-called broadly-neutralizing monoclonal antibodies hold potential for

HIV treatment and prevention. Advantages of such an approach include the fact that these antibodies can be easily “humanized,” giving them qualities of high tolerability and long plasma half-life. Although the half-lives of these antibodies are slightly shorter in HIV-infected individuals compared to uninfected volunteers[16,17,18,19], further chemical modification to the Fc domain may result in much longer plasma half-lives, allowing dosing intervals of up to several months[20]. Unlike small molecule oral ARVs, these agents may induce beneficial host cell-mediated immunity by eliciting antibody-dependent cellular cytoxic (ADCC) and other Fc-mediated responses. Of course, this approach also presents a number of challenges, including the fact that these agents are likely to be expensive, require intravenous administration, are subject to pre-existing resistance, and may also select for antibody-resistant viruses during use. Nonetheless, the great promise of these agents has led to their preclinical and clinical development, as described below.

VRC01—High-throughput neutralization assay screening of large numbers of HIV-infected patient samples, combined with newer technologies to allow antigen-specific single B cell sorting, have enabled the identification of several potent broadly active neutralizing anti-HIV monoclonal antibodies, from which clinical grade material have been produced[15]. VRC01 is one of a class of monoclonal antibodies targeting the CD4 binding site of the HIV-1 gp120 envelope protein[21]. VRC01 neutralizes 80-90% of HIV-1 viral isolates tested *in vitro*[21,22], but the rate of primary resistance seen in clinical trials seems to be higher[23].

Potent antiviral activity was demonstrated in viremic individuals with sensitive virus, but plasma HIV-1 RNA levels returned to baseline, associated with the emergence of relative resistance to VRC01[17]. In two clinical trials in HIV-infected persons interrupting ART, all study participants experienced viral rebound, with only a slight delay compared to historical controls[23]. Baseline VRC01 resistance in subpopulations of virus was common, and these viral subpopulations emerged under the pressure of VRC01 exposure. VRC01 exposure also induced new resistance mutations[23]. Notably, no anti-VRC01 antibodies were detected in any of these clinical trials[17,23]. Additional trials are underway studying the potential for preventing the acquisition of HIV-1 infection in high-risk pediatric, adolescent, and adult populations.

3BNC117—The CD4-binding site antibody, 3BNC117, which has more *in vitro* potency and breadth than VRC01[23,24], has also been studied in clinical trials[18,25]. As with VRC01, dose-related antiviral activity was seen, the magnitude of which was influenced by baseline viral resistance, and resistance developing on therapy led to earlier viral rebound[18]. In this study, 3BNC117 was also found to improve neutralizing IgG responses in patients against a panel of heterologous HIV isolates, perhaps either through inducing the evolution of immunogenic viral variants or forming immunogenic immune complexes with virus[26]. In another trial, when ART was interrupted, the average time to viral rebound was prolonged in the 3BNC117-treated compared to matched historical controls, but as with VRC01, viral rebound was associated with the emergence of resistant viral variants[25].

10-1074—10-1074 is a monoclonal antibody directed against a glycan-dependent neutralization epitope in the V3 loop of gp120, neutralizing 78% of primary HIV-1 isolates. In a single-dose clinical trial, similar to the experience with the other antibodies, baseline

viral resistance to the antibody, when present, limited the decline in viremia, although a decline was seen in most study participants, and viral resistance and rebound developed within 2 weeks of antibody administration in those with initially sensitive virus[19].

To date, monotherapy with a single broadly-neutralizing anti-HIV antibody has resulted in only transient suppression of initially sensitive virus. As with antiretroviral drugs, pre-treatment knowledge of the antibody sensitivities of the patients' viral isolates was demonstrated to be an important predictor of response. And, as with drugs, combinations of at least 3 antibodies known to be active at baseline against the patients' HIV-1 isolates will probably be needed for durable suppression of viremia.

Other Antibodies and Antibody Modifications in Development—Additional broadly-neutralizing monoclonal anti-HIV antibodies have been identified and are in pre-clinical development. These include other antibodies targeting the CD4-binding site of the HIV-1 envelope glycoproteins (gp), as well as antibodies directed at the gp120 apex, the high-density mannose patch, the gp120/gp41 interface, and the membrane proximal external region of gp41[27]. Combinations of antibodies targeting different sites on the HIV-1 envelope are likely to provide better potency and breadth of response, and better protect against the evolution of resistance, than combinations of antibodies targeting the same site. Bispecific antibodies are also being designed to increase the breadth of activity, to target both the HIV-1 envelope and an HIV-1 cell receptor, or to target HIV-1 antigen and a receptor of effector immune cells in order to enhance antibody-mediated killing of infected cells[28].

It is noteworthy that the Fc region and glycosylation sites of antibodies can be altered to affect their functions, such as the ability to engage lymphocytes, macrophages, and neutrophils for antibody-dependent cellular cytotoxicity and phagocytic activities, as well as the ability to fix complement[20,29,30]. Mounting evidence suggests that non-neutralizing Fc functions of antibodies may be more effective at preventing HIV-1 infection[31] and could be more critical in eliminating latent cell reservoirs of HIV-1[32]. For example, viral kinetic modeling and *in vitro* studies in a humanized mouse model determined that 3BNC117 accelerated the clearance of HIV-infected cells[32]. Antibodies could also be isolated and refined from the beginning specifically for such non-neutralizing Fc activities.

Finally, and perhaps most importantly, mutations can be introduced by site-directed mutagenesis within the C-terminus of the heavy chain constant region away from the antigen-binding site of a monoclonal antibody to increase its binding affinity for the neonatal Fc receptor (FcRn), and thus prolong the clearance rate *in vivo* such that terminal half-lives of several months can be achieved[20]. A long-acting formulation of VRC01, VRC01-LS, has been constructed in this manner and a single dose study of its pharmacokinetics and antiviral activity is underway[NCT02840474; ClinicalTrials.gov].

Antibodies that Inhibit Cell Entry

Ibalizumab—Antibodies targeting the cell receptors for HIV-1 entry have been demonstrated to have anti-HIV activity in humans, and are also in clinical development. These antibodies are more rapidly cleared by intracellular uptake after binding to the cell

receptors, and have terminal half-lives of 3-4 days[33,34]. They need to be administered every 1-2 weeks. The monoclonal antibody ibalizumab is a humanized IgG4 antibody that inhibits HIV-1 entry by binding to the extracellular domain 2 of CD4, rather than to the binding site for HIV-1, but prevents subsequent entry of the virus into CD4 T cells through allosteric effects[35]. The binding site is also distant from major histocompatibility complex (MHC) binding sites. In phase 1 and 2 studies, ibalizumab demonstrated antiviral activity in antiretroviral therapy–experienced subjects, followed by early rebound of viremia associated with resistance[33,36]. After two, as yet unpublished, 24-week phase 2B trials[37,38], a phase 3 clinical trial in patients viremic on ART with multiple drug resistant (MDR) HIV-1 was conducted recently. Ibalizumab 2000 mg IM was administered initially, followed by 800 mg IM every two weeks for 24 weeks. A clinically appropriate optimized background antiretroviral drug regimen (OBT) was started at day 7. At day 7, 83% of participants attained a viral load reduction of >0.5 $\log_{10}$ copies/ml. The median viral load decrease at 7 days was 1.1 $\log_{10}$ copies/ml. After 24 weeks, 43% of participants had viral loads <50 copies/ml when combined with OBT[39].

PRO 140—PRO 140 is a humanized CCR5 monoclonal IgG4 antibody that potently inhibits R5 viruses by binding to the extracellular HIV-I binding domain of the CCR5 receptor[40]. This attachment site is different from the transmembrane helices where maraviroc binds, and PRO 140 is active against maraviroc-resistant viruses. It inhibits HIV-1 at concentrations that do not block the natural activity of CCR5 *in* vitro. Single doses of 5mg/kg of an intravenous form of PRO 140 and 324 mg of a subcutaneous preparation given weekly for 3 weeks in HIV-infected individuals with exclusively R5-tropic virus demonstrated potent antiviral activity[34,41,42] Anti-PRO 140 antibodies developed in some patients, but they did not appear to affect pharmacokinetics, antiviral responses, or susceptibility to adverse events. Current studies are evaluating PRO 140 as maintenance monotherapy after initial viral suppression with standard combination ART, and as salvage therapy for patients with viremia on their current ART regimen. A major drawback of PRO 140 as a component of universal ART is the requirement to demonstrate that the patient's HIV uses the CCR5 coreceptor exclusively prior to initiating therapy.

Conclusions

Currently available oral antiretroviral regimens are extremely potent at providing viral suppression and restoring the prospect of relatively normal lives with minimal toxicity and the simplicity of once daily single-tablet dosing. Other regimens or routes of delivery, for example weekly oral or long-acting parenterally administered agents, whether they be in combinations of small molecules or antibodies or both, may be useful for treatment in circumstances where daily oral therapies are difficult to administer, and when adherence may be deficient. In these situations, alternatives to oral therapy could be life-saving and reduce the transmission of infection to others. Issues to be addressed that could limit their use include the management of toxicities, given that exposure to the agents is not as easily reversed, and prevention of drug resistance when these drugs are discontinued and drug concentrations slowly wane. Substantial primary resistance and the promotion of secondary resistance on therapy present major hurdles for treatment with anti-HIV monoclonal

antibodies. Clearer prospects for the value of agents with long-acting anti-HIV-1 activity are in the prevention of acquisition of HIV-1 infection in persons at-risk, and where adherence to taking daily oral drugs by otherwise healthy individuals has proven to be a barrier to success. If alternative regimens and routes of drug delivery prove to be highly efficacious, safe, well-tolerated, and economical, they may gain broader appeal for more widespread, if not universal, use.

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Key points

Long-acting injectable or implantable antiretrovirals could be an effective alternative for patients not succeeding with oral antiretroviral regimens.

Long-acting nanocrystal formulations of two antiretrovirals, carbotegravir and rilpivirine, have been studied in combination in clinical trials and found to be well tolerated and effective at suppressing HIV thus far.

Extended-release polymer implants of antiretrovirals, with the advantages of removability and more consistent, predictable drug release, are also being developed.

Monotherapy with a single broadly-neutralizing anti-HIV antibody has resulted in only transient suppression of virus because of substantial primary resistance and the development of secondary resistance on therapy, pointing to the need for combinations of active antibodies for durable suppression of viremia.

Antibodies targeting the cell receptors for HIV-1 entry have been demonstrated to have anti-HIV activity in humans, and are also in clinical development.

Table 1

Novel Approaches to Universal ART

Antiretroviral Drugs
Less Frequent Administration of Current Oral Drugs
Tenofovir
Efavirenz
New Orally Administered Drug
EFdA (MK-8591)
Long-Acting Injectables
Carbotegravir
Rilpivirine
Polymer Implants
Tenofovir
EFdA (MK-8591)
Monoclonal Antibodies
Broadly Neutralizing Antibodies
VRC01, VRC01-LS
3BNC117
10-1074
Antibodies that Inhibit Cell Entry
Ibalizumab
PRO 140