

Lifetime HIV Treatment: Strategies for Success (TRUNCATED)

Abstract

The primary goal of human immunodeficiency virus type 1 (HIV-1) therapy has shifted from eradication of the virus to suppression below detectable levels (<50 copies/mL). Today, avoiding resistant HIV-1 variants represents the single most important challenge driving the directions of HIV-1 research. The shortcomings of HAART have changed practices such as 'hit hard/early' and stimulated increased interest in immune enhancement through vaccines and immunomodulators. Current and future research on immunological enhancement includes antigen stimulation, induction of HIV-1 specific memory and CTL responses, and activation of resting CD4 cells with latent reservoirs of HIV-1. New classes of antiretroviral agents, such as entry inhibitors and nucleotide reverse transcriptase inhibitors, and new formulations including once-daily agents are forming the basis of new HAART regimens in treatment -naive and -experienced patients. The article discusses the status of successful HIV-treatment strategies for life, including new treatment practices, new antiretrovirals, new immune enhancement agents, and developments to facilitate increased regimen adherence.

Introduction

In the past decade, the primary goal of human immunodeficiency virus type 1 (HIV-1) therapy has shifted from eradication of the virus to suppression below detectable levels (<50 copies/mL). {16,20} (**Gallant, 2002, p. 318, Dybul, 2002, abstract**) However, as HIV-1 treatment has evolved, drug resistance has become increasingly recognized as a paramount challenge to successful HIV therapy. Today, avoiding the emergence of resistant HIV-1 variants represents the single most important challenge driving the direction of contemporary research, drug development, and therapy guidelines for HIV-1 treatment. A broad-stroke presentation of new therapeutics and new strategies that address resistance issues and other critical challenges is provided in the following article. The sum of these novel approaches provides the greatest potential for successful lifetime HIV-1 treatment strategies.

Highly active antiretroviral therapy (HAART) for treatment of HIV-1 infection and AIDS has become standard practice. {5} (**Pollard, 2002, p. 1**) However, the durability of HAART is often limited for reasons that include poor pharmacokinetics, drug toxicity, inadequate regimen adherence, and resistance development. *Antiretroviral pharmacokinetics.* The pharmacokinetic parameters most highly correlated with maximal suppression of HIV-1 are trough levels (C_{\min}) at the end of a dosing period and drug potency, expressed as the amount of drug needed to inhibit viral replication by 90% (IC_{90}). The ratio of the inhibitory quotient ($IQ=C_{\min}/IC_{90}$) expresses the relative ability of a compound to suppress HIV-1 replication. Higher index values correspond to lower probabilities of developing viral resistance due to poor drug exposure. This is especially true of protease inhibitors (PI) and nonnucleoside reverse transcriptase inhibitors. (NNRTIs). However, with nucleoside reverse transcriptase inhibitors (NRTIs), the drug must be intracellularly metabolized (such as phosphorylated) to be activated. Hence, with NRTIs plasma concentrations are less useful for assessing

antiretroviral activity. Instead, antiretroviral activity may be more dependent on the ‘intracellular half-life of these compounds. (Gallant, 2002, p. 320)

Suboptimal exposure to HAART increases the likelihood of developing drug resistance. {5} (Pollard, 2002, p. 1) Different anatomical sites may experience suboptimal exposure because of inefficient transport and/or accelerated drug metabolism in these compartments. Evidence of suboptimal drug exposure in various tissue and intracellular compartments comes from studies that have identified genetically distinct HIV-1 variants, isolated from different anatomical sites of the same person. {1} (Delwart, 1998, p. 2420)

Poor bioavailability and accelerated metabolism of antiretrovirals may cause the reduction of viral suppression. For instance, the bioavailability of the gel capsule formulation of saquinavir is approximately 4% when taken with food, but nearly 0% when taken on an empty stomach. {16} (Gallant, 2002, p. 320)

Metabolism of antiretrovirals can be accelerated by certain drugs such as efavirenz and nevirapine, which reduce plasma concentrations of antiretrovirals by causing the induction of hepatic P450 CYP3A isoenzymes. {5} (Pollard, 2002, p. 4)

Genetics of resistance development. The fundamental reason for the development of HIV-1 resistance stems from the inability of the HIV-1 reverse transcriptase enzyme to proofread errors in deoxynucleotide incorporation. {14} (McColl, 2003, p. 219) In the case of PIs, the primary mutation occurs near the active site of HIV-1 viral protease. Secondary mutations may confer goodness of fit that compensates for the initial decrease in viral fitness caused by the primary mutation, thereby restoring efficiency of HIV-1 replication and increasing the degree of drug resistance. Secondary mutations may also confer additional resistance to a second antiretroviral in the same drug class or confer additional resistance to a second class of antiretrovirals. {2} (Masquelier, 2002, p. 1) For each replication cycle of HIV-1, an error in one base pair can be expected. Throughout several replication cycles, resulting mutations may eventually lead to drug resistant HIV-1 variants, especially when HIV-1 suppression is suboptimal. {14} (McColl, 2003, p. 219) The rate at which drug-resistant HIV-1 variants emerge is dependent on several factors, including the antiretroviral’s genetic barrier to resistance.

Genetic barriers to resistance differ among antiretrovirals. For instance, NRTIs such as 3TC and nevirapine have a low barrier, requiring only a single *pol* mutation to develop high-level resistance. In contrast, ritonavir has a higher barrier to resistance, requiring multiple *pro* mutations to develop resistance. {1} (Delwart, 1998, p. 1)

Regimen adherence. The rate at which drug-resistant HIV-1 variants emerge is associated with the degree of patient adherence to a drug regimen. {2} (Masquelier, 2002, p. 1506) Adherence to HAART is often made difficult—both physically and emotionally—by the complexity of the regimen, pill burden, and reduced quality of life that stems from frequent toxicity, tolerability, and safety issues. Adverse events and safety issues may include lipodystrophy, dyslipidemia, lipoatrophy, hepatotoxicity, nephrolithiasis, neuropathy, {16} (Gallant, 2002, p. 320, 322, 323, 324) risk of myocardial infarction, impaired glucose tolerance, insulin resistance, diarrhea, rash, nausea, and others. {13} (Moyle, 2002, p. 589, 590, 591) Masquelier found that

mechanisms of early viral failure (VF) in a cohort of antiretroviral-naive patients were more often shown by genotyping data, PI plasma concentrations at VF, and adherence measurements and patterns characteristic of the prescribed PI. {2} (**Masquelier, 2002, p. 1506**) Contemporary definitions recognize that adherence is a multidimensional parameter comprised of dosing adherence, timing adherence, and the number of drug holidays. Reductions in adherence caused by HAART complexity can be dramatic. Adherence is inversely correlated with daily dose frequency. {4} (**van Vaerenbergh, 2002, p. 238**) In one study, an adherence rate of 79% for drugs taken once-daily dropped to 69%, 65%, and 51% for drugs taken twice, 3 times, and 4 times daily, respectively. {5} (**Pollard, 2002, p. 2**)

Symptomatic patients are more likely to tolerate treatment side effects than are asymptomatic patients, because symptomatic patients are likely to experience reduced symptoms. Asymptomatic patients may be less conscious of the reality of their illness and the clinical benefit of treatment. {16} (**Gallant, 2002, p. 320**)

Patient/caregiver issues. Inadequate HIV education, difficulties in physician-patient communication and poor physician estimates of regimen adherence may contribute to poor adherence. Studies of regimen adherence in non-HIV-1-infected people demonstrate that physician's predictions of patient adherence are poor. One study determined the sensitivity of clinical judgment for detecting non-adherence to be only 10%. {3} (**Murri, 2002, p. 158-159**)

In patients treated with HAART, studies found startling discordance between physician estimates and actual adherence, as determined by Medication Events Monitoring System (MEMS). For instance, physicians overestimated adherence in 30% of patients and underestimated it in 11% of patients, compared with MEMS data. {3} (**Murri, 2002, p. 159**) Other data showed that low sensitivity (40%) and specificity (85%) of providers' estimates of adherence was worse than patient self-report, confirmed by undisclosed pill-count verifications. {3} (**Murri, 2002, p. 159**) This is problematic in HIV-1 treatment because adherence estimates often form the basis of treatment decisions, such as initiating treatment, switching treatment, withholding treatment, or not prescribing treatment when non-adherence is anticipated. Misjudgment of patient adherence can have adverse consequences such as unnecessary changes in therapy or unnecessary laboratory testing.

Murri et al. has described a number of opportunities for increased HIV education and promotion of regimen adherence within the context of the physician-patient relationship. They observed that patient characteristics, such as lower educational level and unemployment, and clinic characteristics such as absence of a social worker and unavailability of afternoon visits, were significantly and independently related to discordance between physician estimates and patient reports of treatment adherence. Therefore, recommendations include greater availability of nontraditional clinic hours, flexible visit lengths, provision of transportation and childcare services, and access to social support and translation services. Providing information in an empathic manner so that patients feel heard and respected may help facilitate the trust and understanding necessary for patients to appreciate and accept the importance of discomfiting queries on adherence. {3} (**Murri, 2002, p. 160,161**) Finally, concerns about social desirability, reluctance to disappoint

the physician, or fears of having medication withheld may prevent patients from disclosing non-adherence to physicians, or discussing lifestyle issues that prevent adherence.

Successful Antiretroviral Therapies: Where We are Today

It has become increasingly clear that the interplay of antiretroviral pharmacokinetics, HIV-1 viral suppression, host immunological behavior, regimen adherence, HIV-1 genetics, and the development of HIV-1 resistance are all mechanistically connected. So intimate is the relationship among these various mechanisms that cause and effect are often indistinguishable. Our heightened awareness of the intimate interplay among these factors has informed current therapy strategies and guided the research direction of future HIV-1 treatments. This has led to the development of novel drugs, reformulations, new technologies, new HAART combinations, and enhanced immunological approaches.

Ritonavir-boosted PIs and first-line dual PI therapy. Success with many current PIs is limited by significant variability in pharmacokinetics. Many clinicians now use a ritonavir-boost to improve the pharmacokinetic characteristics of antiretroviral regimens. The coadministration of a ritonavir booster also reduces dosing schedules, regimen complexity, and pill burden. Low doses of ritonavir are commonly administered with other PIs, such as saquinavir, indinavir, and amprenavir. The coadministration of ritonavir raises the plasma concentrations of the primary PI by inhibiting its hepatic metabolism by the P450 isoenzyme, CYP3A4. {5} **(Pollard, 2002, p. 3)** Ritonavir boosting primarily increases the C_{min} , and in some cases, increases the C_{max} of the primary PI. Modest reductions in interpatient variability and increases in PI half-life may also be achieved from ritonavir boosting. The increased drug exposure that results from higher PI plasma levels may potentially inhibit the development of HIV-1 drug resistance. {13} **(Moyle, 2002, p. 586)** Monitoring for side effects is necessary because of increased toxicity that may accompany coadministration of ritonavir. Metabolic changes in lipid and glycemic levels are associated with lipodystrophy, dyslipidemia, and loss of glycemic control in patients using PI-containing HAART regimens. {13} **(Moyle, 2002, p. 588-591)**

Dual PI regimens. Two dual PI regimens, atazanavir-saquinavir and ritonavir-saquinavir, were evaluated in a study of antiretroviral-experienced patients who had failed an approved prior regimen. At 48 weeks of treatment, HIV-1 RNA levels had decreased by a mean of 1.44 \log_{10} copies/per mL (atazanavir 400 mg/saquinavir 1200 mg), 1.19 \log_{10} copies/mL (atazanavir 600 mg/saquinavir 1200 mg), and 1.66 \log_{10} copies/mL (ritonavir 400 mg/saquinavir 1200 mg). While marked lipid increases characterized the ritonavir-saquinavir combination, decreases from baseline in fasting low-density lipoprotein (LDL) cholesterol was reported for both atazanavir-saquinavir combinations. Potential first-line dual PI regimens with atazanavir may eliminate the dyslipidemia associated with other PIs, and provide reduced risk of cardiovascular events. {13} **(Moyle, 2002, p. 587)** The combination of lopinavir-ritonavir is currently administered twice-daily with food at a dosage of 400 mg lopinavir and 100 mg ritonavir. In a comparison of once-daily lopinavir-ritonavir (800 mg/200 mg) with twice-daily dosing (400 mg/100 mg), HIV-1 RNA levels below 50 copies/mL were reached in 74% of patients (once-daily) and 79% of patients (twice-daily) after 48 weeks of treatment. {5} **(Pollard, 2002, p. 5)** While dual PI regimens may provide such benefits as reverse transcriptase inhibitor (RTI) sparing,

and in some cases reduced risk from dyslipidemia, regimens typically add unneeded complexity and, because of the development of cross-resistance, patients choosing dual PI regimens may be sacrificing future salvageability options.

Evolving strategies for immunological enhancement of HAART. The ability of CD4 T-cells to coordinate the CD8 cytotoxic T-lymphocyte (CTL) responses and B-cell effector responses to viral antigens is critical to the functional integrity of the immune system. However, HIV-1 infection destroys the CD4 T-cells that would otherwise provide help to CD8 T-cells and B-cell effector responses. During HIV-1 infection, the resulting dysregulation of CD4 T-cell-dependent immune responses is complex. Moreover, the behavior of these responses during HAART is even less clear. Nonetheless, studies demonstrate that enhancing these immunological responses may be possible. {7,8} **(Binley, 2000, p. 1, 2, 9,11, Hardy, 2002, p.40, 41)**

Markowitz et al. found that early pharmacologic control of viremia, within 90 days of patient symptoms of acute infection, was generally associated with decreasing levels of CTL activity. Although the reduction in HIV-specific CTL activity could possibly be due to a direct inhibitory effect of the antiretroviral therapy, they hypothesized that this reduction in CTL activity was most likely due to a reduced antigen load to suboptimal levels, too low to sustain maximal immunologic stimulation. Although early control of viremia was associated with preservation of normal absolute CD4 cells and increased CD4/ CD8 cell ratio, HIV-1-specific immune responses were diminished. In light of these findings, immunological enhancement with antigen may be necessary to activate latently infected resting CD4 T-cells. {6} **(Markowitz, 1999, p. 527, 536)**

In a study of untreated HIV-1 infected individuals, Binley et al. found that the emergence of the HIV-1 viral replication during short periods of intermittent HAART therapy was capable of promoting generalized activation of T-helper lymphocytes, indicated by increased T-cell proliferative responses to HIV-1 Gag and recall antigens. The study examined the relationship between the CD4 T-cell proliferative response and plasma viremia using a standard antigen-stimulated T-lymphoproliferative assay. In this study, observations indicated that CD4 T-cell responses might be regenerated if viral load (VL) was suppressed to allow partial immune recovery, and antigenic stimulation was provided afterwards. Thus, the restoration of sustained active cellular immune responses and memory responses may be possible if antigens are continuously generated *in vivo*, or if vaccine regimens frequently boost antigen loads. {7} **(Binley, 2000, p. 1, 2, 9, 11)**

Other lines of evidence testify to the immune system's real potential for (1) aborting the establishment of HIV-1 infection and (2) containing HIV-1 infection to subpathological levels after establishment of infection. Two distinct clinical populations of HIV-1-exposed individuals provide this evidence: (1) highly exposed, persistently seronegative individuals, and (2) long-term non-progressors. Seronegative sex workers in sub-Saharan Africa have shown that sterilizing immunity to HIV-1 occurs naturally in individuals exposed to HIV-1 at a very high frequencies. Surprisingly, infection does not occur. These individuals display a robust and aggressive CTL response to HIV-1 *gag* proteins and mucosal envelope-specific neutralizing IgA. {8} **(Hardy, 2002, p. 41)**

Containment of established infection also occurs naturally. This is demonstrated by long-term non-progressors (LTNPs) with chronic HIV-1 infection, who lack clinical progression defined by the absence of surrogate disease markers such as typical CD4 T-cell counts or VL. LTNPs constitute approximately 1% of the total population of HIV-1 infected individuals. Non-progression is accompanied by strong HIV-1 *gag*-specific CD4 T-cell responses, absent from individuals with normal HIV-1 disease progression. Protection from disease progression is long-term and may be maintained indefinitely. {8} (**Hardy, 2002, p. 41**)

Vaccine development. There are several obstacles to developing effective vaccines with adequate antigenic stimulation. The primary challenge at the molecular level resides in the intrinsic properties of the external envelope glycoprotein, gp120. The heavy glycosylation of the outward-facing domains of gp120 shields the functional, conserved domains from antibody recognition. {9} (**Ho, 2002, p. 136**) Additionally, access to the CD4-binding domain is sterically blocked by the tertiary structure of this protein. {8} (**Hardy, 2002, p. 40**) The standard complexities of vaccine development are further compounded by HIV-1 immunopathogenicity and the absence of an appropriate animal model. {10} (**Hu, 2003, p. 638**)

Another potential obstacle in the development of an HIV-1 vaccine is HIV-1 diversity. Considerable debate has taken place on whether any HIV-1 sequence will suffice for broad population coverage or if the use of an ancestral or consensus sequence for all HIV-1 subtypes will be adequate. Regardless of what viral sequence is ultimately selected, the vaccine strain should be matched to the dominant virus in the target community(s). Efficacy testing of current vaccine candidates in high-incidence HIV-1 populations will also be challenging, since many candidate vaccines are made using subtype-B viruses, the dominant strain in the U.S., as opposed to virus subtypes in developing countries such as Africa, where subtypes A, C, and D are prevalent. Evaluating efficacy of a vaccine in a test population where the prevailing viruses are genetically distant from the vaccine strain may be problematic. Political opposition based on apparent or real exploitation may also pose an obstacle to testing. {9} (**Ho, 2002, p. 138**)

Candidate vaccines. The vaccine Remune is a clade G *gag* immunogen isolated from the plasma of an HIV-1 infected patient in 1976. The purification process causes the envelope gp120 antigen to disassociate, depleting the immunogen of gp120, followed by degradation of viral nucleic acids. {8} (**Hardy, 2002, p. 41**) Although this HIV-1 immunogen showed promise throughout several previous trials, the most recent findings have shown otherwise. Remune failed to cause changes in VL or CD4 percentage and did not increase HIV-1 progression-free survival, when evaluated in a large, placebo-controlled U.S. study of 2,527 patients on unrestricted HAART, with or without HIV-1 immunogen. {8} (**Hardy, 2002, p. 42**)

In addition to the Remune vaccine, other extensively tested vaccines include VaxSyn and p24-virus-like particle. VaxSyn is a recombinant gp160 preparation that has shown large gp160-specific proliferative responses and CTL responses throughout several trials including a five-year study of VaxSyn monotherapy. However, none of these trials demonstrated effects on CD4 T-cell counts or VL. The p24-virus-like particle is a yeast organism vector expressing *gag* proteins p24 and p17. In phase II studies of p24-virus-like particle, vaccination also failed to alter CD4 T-cell counts or VLs. {8} (**Hardy, 2002, p. 42**)

The use of adenovirus as vectors for HIV-1 vaccines has been proposed, although pre-existing immunity to adenovirus presents a problem. Neutralizing antibodies may eradicate the vector before the HIV-1 immunogen has had enough time to cause an immune response. Solutions to this problem include using a higher vaccine dose or using a DNA vaccine to prime responses to the antigen. An adenovirus construct containing the clade B *gag* gene is currently undergoing dose-escalation studies, prime boost studies, and DNA-primed adenovirus-boosted studies in both HIV-1–infected and non-infected individuals.

The DNA vaccine, DermaVir delivers replication- and integration- defective simian envelope (S) HIV DNA to dendritic cells after topical skin application. DermaVir is thought to transduce Langerhans' cells on the surface of the skin and stimulate CD4, CTL, and naive CD4 cell growth. Once the (S) HIV DNA is present in the Langerhans' cells, these cells are expected to migrate to the lymph node, mature to antigen-expressing dendritic cells, and elicit (S) HIV-specific T-cell immunity. {8} **(Hardy, 2002, p. 43)** DermaVir was evaluated in 10 macaques chronically infected with simian immunodeficiency virus (SIV) that were randomized to receive either continuous HAART or 10 cycles of intermittent structured treatment interruptions (STI) of HAART (3-weeks on/3-weeks off) plus DermaVir (last 4 cycles). Following subsequent immunizations with DermaVir, VL was increasingly suppressed with each STI, from a VL of 4,292,260 to <200 copies SIV RNA/mL of plasma. Induction of robust SIV-specific T-cell responses accompanied the VL suppression. {8} **(Hardy, 2002, p. 44)**

Vaccination programs. Initial implementations of an HIV-1 vaccination program will be met with unprecedented public health challenges. Studies indicate that the first generation of HIV-1 vaccines will most likely be of moderate viral efficacy, with perhaps 30% efficacy in preventing the establishment of infection. However, preliminary modeling studies indicate that widespread administration of HIV-1 vaccines with low efficacy could still reduce the severity of HIV-1 epidemics in countries with high incidence of HIV-1 infection. {10} **(Hu, 2003, p. 639)** In the U.S., a vaccine with low to moderate efficacy may likely be directed toward persons at higher risk of HIV-1 infection, such as with injection drug users, men who have sex with men, heterosexuals at high risk for infection, and high-risk adolescents. {10} **(Hu, 2003, p. 640)** Although modeling studies indicate potential success using low- to moderate- efficacy vaccines, increased risk behavior due to a false sense of protection among immunized individuals could nullify any gains from vaccination. {10} **(Hu, 2003, p. 641)** Implementation of an HIV-1 vaccination program will also require the development of new technologies for distinguishing true HIV-1 infection from vaccine-induced seropositivity. {10} **(Hu, 2003, p. 642)**