New Paradigms in the History of Highly Active Antiretroviral Therapy for HIV-1 Infection

Grand Rounds

Gary Sinclair MD
Associate Professor of Medicine
UTSouthwestern

September 11, 2009

INTRODUCTION: THE HISTORY OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART)

The introduction of protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs) in the 1990s, now known as Highly Active Antiretroviral Therapy or HAART, dramatically changed the lives of patients with HIV-1 infection. With the advent of these new highly potent agents, it became possible to suppress viral replication to levels below the limits of laboratory detection. It was hoped that this shut-down in viral replication would prevent the development of resistance and that failure would no longer be the inevitable outcome of therapy. With the possibility of permanent viral suppression, hopeful experts began to calculate the rate of decay of the latent viral pool and to estimate the amount of time before "HAART" would effect a "cure".

Unfortunately, the availability of these new therapies did not solve the problems of drug resistance, subsequent treatment failure, and the latent viral reservoir. Many patients starting HAART were already highly resistant to NRTIs due to prolonged use of monotherapy and dual therapy. Resistance testing was still considered experimental, and there was still a limited understanding of cross-resistance within classes. The practice of adding single new agents to failing NRTI regimens became common, as patients and physicians were desperate to take advantage of new therapeutic modalities. This strategy often resulted in a transient response followed by the emergence of resistance to the new agent. As new agents became available, "good drugs were thrown after bad", and many patients developed extensive multi-class resistance due to what was effectively serial monotherapy with the new drug of the day. Perhaps most disappointing, experimental evidence began to reveal that the latent viral pool decays slowly, if at all, meaning that while HAART has the potential to prolong life significantly, it will never lead to total eradication of HIV and thus will never serve as a cure.

In the early years of the HAART era, physicians began to adapt principles learned in the treatment of other chronic infectious diseases that cannot be effectively treated with a single drug, such as tuberculosis, to the treatment of HIV infection. Such principles included:

- The goal of treatment should be to achieve long term suppression of replication in order to avoid the development of drug resistance, rebound, and subsequent clinical failure.
- Since monotherapy is known to lead to drug resistance, combinations of at least two (preferably three) active drugs with dissimilar genetic resistance patterns should be used at all times.
- The addition of any single drug to a failing regimen should be avoided as it will likely be ineffective and resistance to the new agent will typically emerge.
- Today's wonder drug is tomorrow's poison (except in Africa)

Experienced HIV clinicians learned these principles quickly. However, the application of these principles to HIV clinical practice required extensive knowledge, experience and judgment on the part of treating clinicians. New agents became available at an average rate of only 1 to 2 per year, making it challenging to form fully active regimens in

patients with drug-resistant virus. Moreover, when several drugs did become available at the same time, the degree of cross-resistance within existing drug classes was often underestimated. For example, prior to their approval, efavirenz, abacavir, and adefovir dipivoxil could be prescribed together through expanded-access programs. However, many of the patients placed on this combination had prior failed treatment experience with zidovudine/lamivudine and nevirapine, which engenders cross resistance to abacavir and efavirenz respectively. The combination of these 3 new active agents led to the appearance of adefovir (and sister drug tenofovir) resistance in the HIV positive population even before the drugs were ever formally considered for approval by the FDA.

It is now well recognized that the use of a new agent, without waiting for other active drugs to be used in combination, can do more harm than good. However, waiting for these new agents can be very difficult for clinicians and life threatening for patients.

This review attempts to summarize the evolution of HAART therapy. There are three parts:

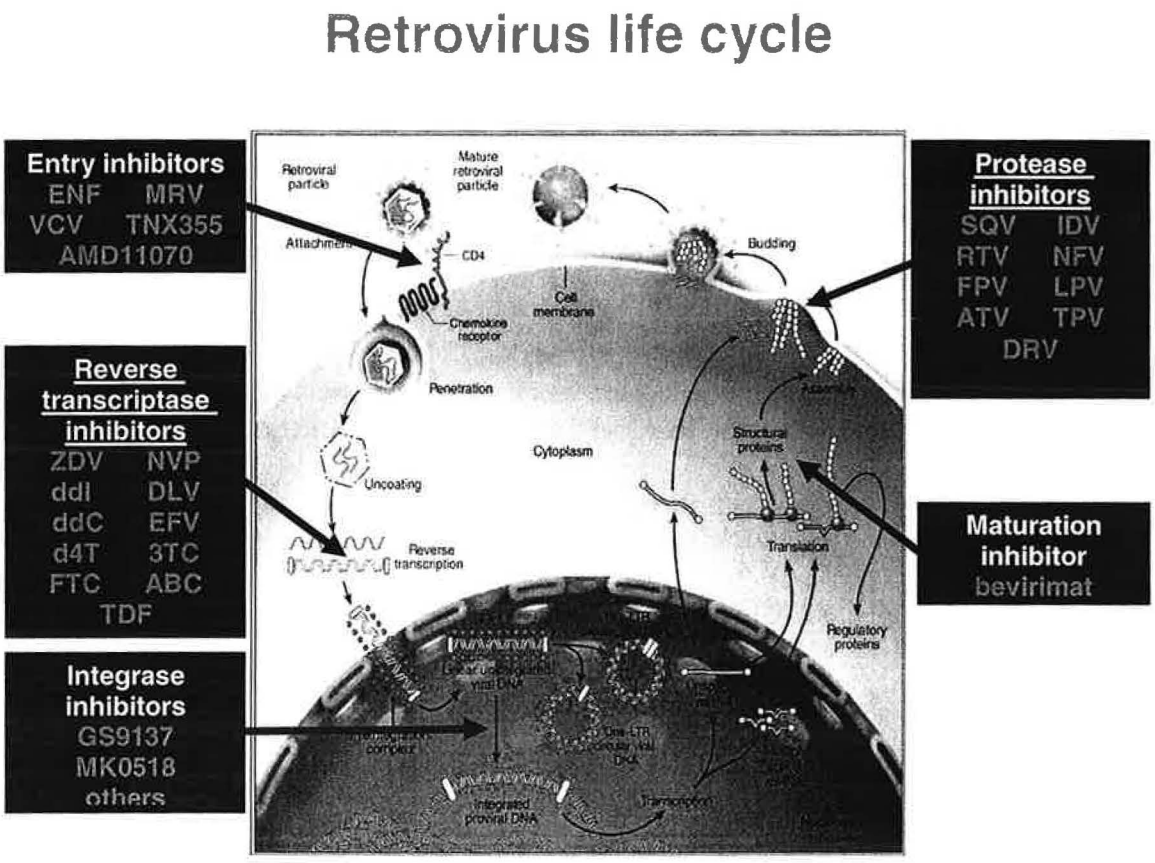
1. The Start of the Revolution: Nucleoside/Nucleotide Reverse Transcriptase Inhibitor (NRTI), Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI), and Protease Inhibitors.
2. The Second Wave of the War: Integrase inhibitors (II) and Entry Inhibitors (EI)
3. The Cutting Edge of the Battlefield: Anti-CD4 and Anti-HIV antibodies

A case study of a single patient hereafter referred to as Patient #9 will be used to illustrate principles throughout all three sections.

1. The Start of the Revolution

Figure 1 represents the lifecycle of HIV-1 as a function of the actual and potential therapeutic targets.

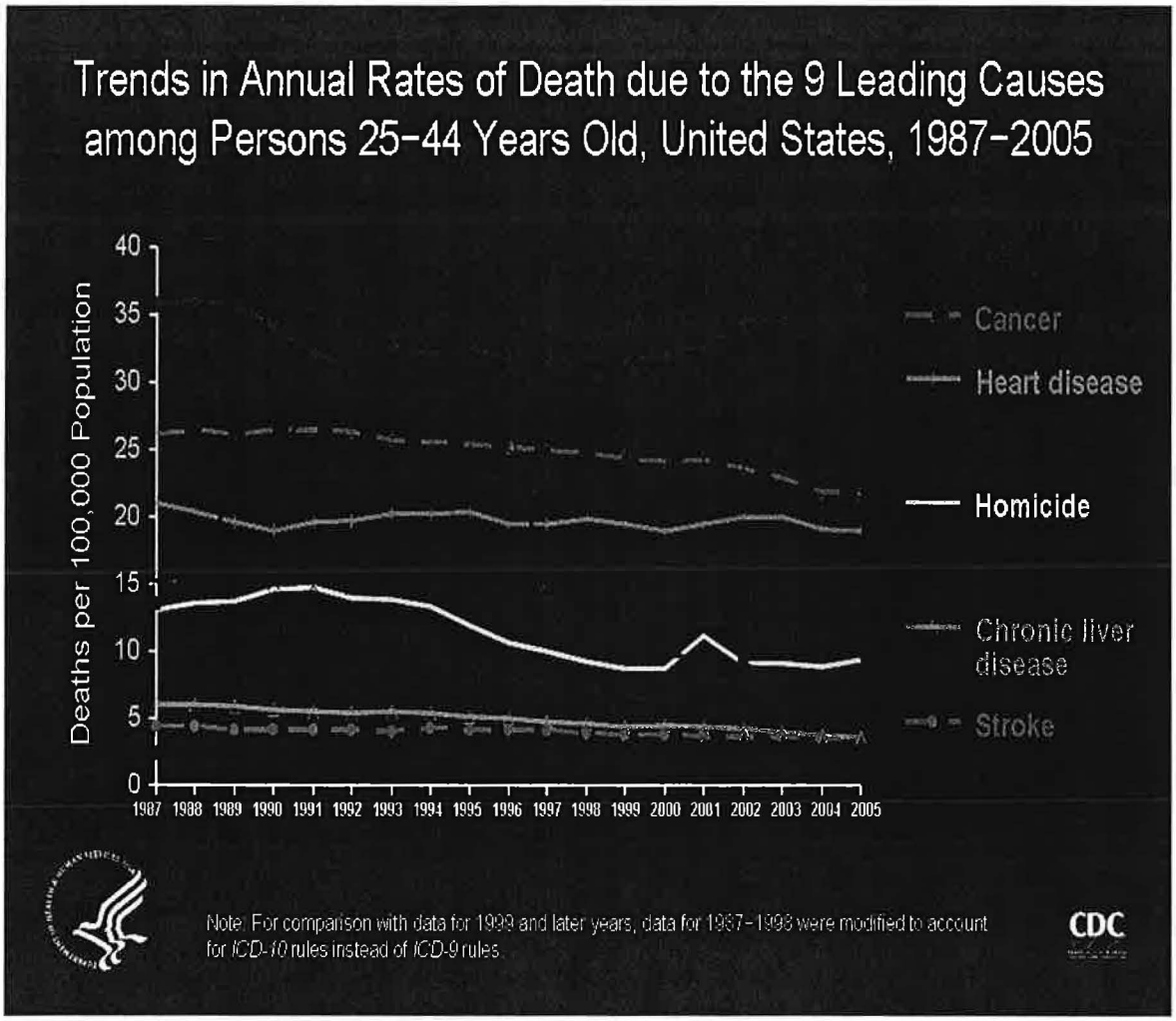
Figure 1



The three classes of drugs that became available during the mid-1990s and comprised the cocktails that constituted Highly Active Antiretroviral Therapy are NRTI, NNRTI, and Protease Inhibitor. There are 20 drugs approved by the FDA for the treatment of HIV-1 infection in these three classes, not including 4 patented co-formulations (Atripla, Truvada, Combivir, and Epzicom).

The proper use of these agents led to dramatic decreases in the age adjusted HIV related mortality of people infected with HIV and is considered one of the major successes of 20th century medicine. Some have argued that this highlights the ability of society to mobilize large sums of resources in response to a grave threat. Others have argued that this is proof that greed, not compassion, is our savior. Figure 2 illustrates the affect that these three initial categories of drugs had on the morbidity and mortality of HIV.

Figure 2



By the middle of the beginning of the second decade of HAART, concerns that the respite period was over began to emerge. Though new agents within the above classes continued to be added to the armamentarium, cross resistance, drug interactions, and pill fatigue began to threaten the efficacy of this new mode of therapy. Pharmaceutical companies began to divide patients into 5 tiers:

1. Treatment Naïve
2. First treatment failure
3. Late treatment failure
4. Deep salvage
5. No active agents available.

It was estimated that the HIV positive population divided approximately evenly among the 5 groups. Amongst deep salvage and no active agents available patients, opportunistic infections reminiscent of the earlier portions of the epidemic began to re-merge, as HIV related hospitalization rates were reported to begin to rise.

Case History: Part I

Patient #9 is an African American Male born in 1954, the 11th of 11 children, to sharecropper parents in the rural southern United States. His early life was characterized by no unusual illnesses though he had a strong personal and family history of type 2 diabetes. He completed high school and 2 years of vocational training. He has been a licensed practical nurse since 1976.

In 1985, Patient #9 was one of the first people to test positive for HIV-1 antibodies by the newly available Elisa and Western blot system. His risk factor for HIV acquisition was unprotected intercourse with males. He does not recall his CD4 count at the time, and viral load testing was not available until about 11 years later. He wanted to be pro-active with regard to his healthcare, and therefore enrolled in some of the early trials of AZT.

His treatment history has been pieced together as follows:

1. *AZT monotherapy*
2. *AZT + 3TC*
3. *AZT + 3TC +saquinavir (virologic failure)*
4. *d4t + ddi + indinavir (virologic failure)*
5. *abacavir + 3TC + kaletra +efavirenz (first and only time every undetectable)*
6. *tenofovir + 3TC + efavirenz (at provider's advice—virologic failure).*
7. *d4t + 3tc + tenofovir + atazanavir+ ritonavir+ Fuzeon injectable on expanded access protocol (virologic failure)*
8. *Duet Trial: Truvada + darunavir + ritonavir +etravirine +fuzeon (briefly undetectable followed by virologic failure)*

He presents because the Duet Trial is now over, he continues to take the same medications on the compassionate use rollover arm of the trial, and he wants to discuss his options . He has lost 20 pounds, complains of "no energy", and he has weaned himself off of insulin and oral hypoglycemics because his blood sugars have been too low. His CD4 count is 82 cells/mL (6.4%) and his HIV-1 Viral Load is 316,000 copies/mL.

The appropriate next step in this patient's therapy is to

A. Continue current therapy as patients on partially suppressive regimens tend to do better than patients on non-suppressive regiments.
B. Offer patient drug holiday, as he suffers from severe pill fatigue, and he has already told you that he is going to do this anyway.

C. Discuss funeral arrangements.
D. Look for another clinical trial
E. Obtain some more information about the virus which patient number 9 is harboring.
F. All of the above

More to follow.

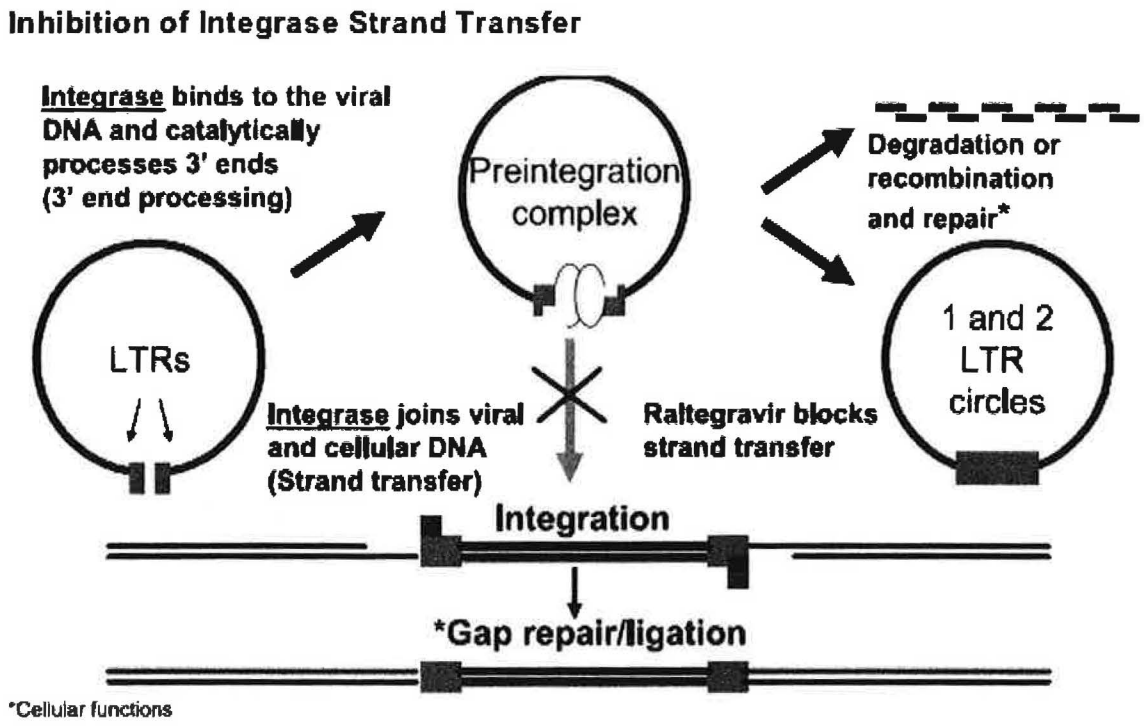
II. The Second Wave of the War: Integrase Inhibitors and Entry Inhibitors

Integrase Inhibitors

The notion that the viral gene integrase would be an excellent target for an antiretroviral drug actually preceded the development of reverse transcriptase inhibitors (see Figure 3). Integration was known to be an essential, rate limiting step in the HIV viral lifecycle, and since the enzyme that catalyzes integration (integrase) bears little if any similarity to any human enzymes, it seemed likely that a clinically effective integrase inhibitor would play a role in the treatment of HIV-1 infection.

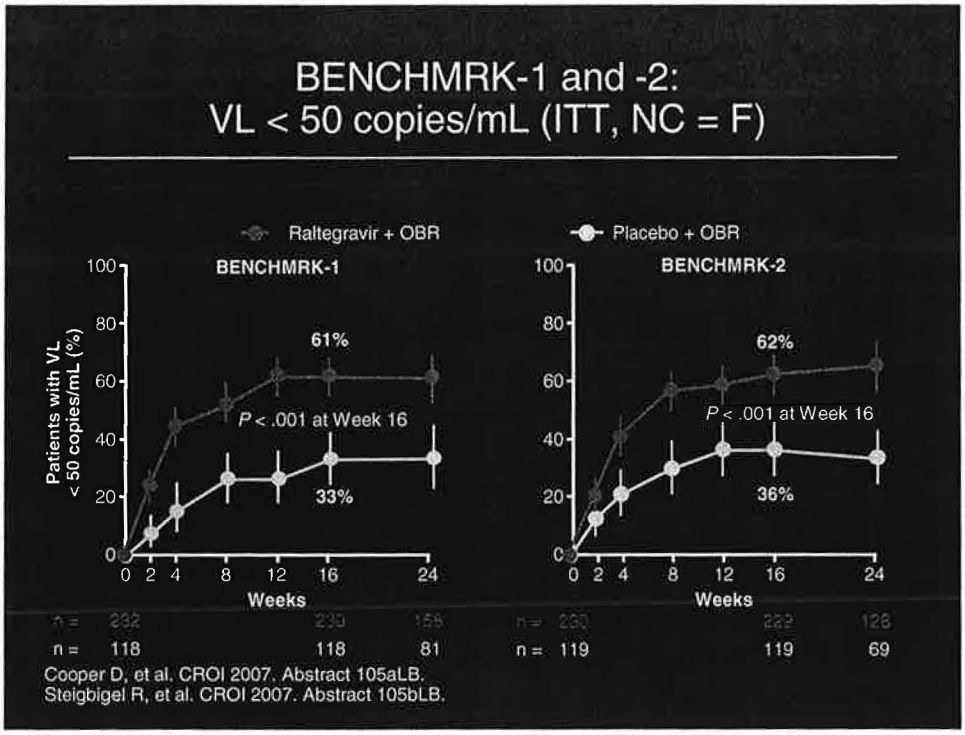
However, despite many promising candidate drugs, it took many years to find a compound deemed safe enough for human trials. The small molecule, raltegravir (formerly MK-0518) was first used in a human subject in 2004, and became the first FDA approved integrase inhibitor (brand name Isentress) in the fall of 2007, after a 3 year period of clinical development, one of the fastest development programs on record. The mechanism by which raltegravir inhibits the replication of HIV-1 is illustrated in Figure 3 and the video.

Figure 3



Efficacy of raltegravir was demonstrated in the Benchmrk Studies, two identical randomized, double blinded, trials of raltegravir vs. placebo each in combination with an optimized background regimen. Because of time and space considerations, a detailed review of these trials cannot be provided, but the published references have been placed in the appendix. The pivotal results are shown below in Figure 4.

Figure: 4



Entry Inhibitors (Co-receptor Inhibitors and Fusion Inhibitors)

The HIV-1 entry process consists of three major steps:

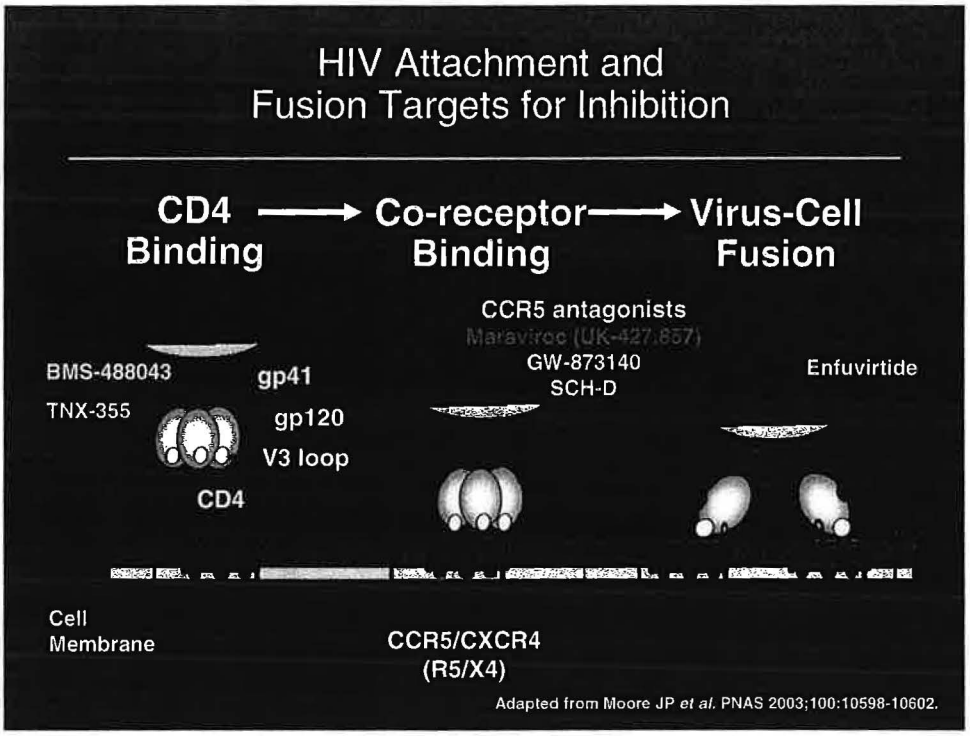
1. The attachment of the viral envelope (Env) surface glycoprotein 120 (gp120) to the CD4 receptor on the surface of T-cells

2. The subsequent interaction of the Env-CD4 complex with a co-receptor (usually CCR5 or CXCR4)

3. Virus-cell membrane fusion mediated by the Env transmembrane (TM) gp41 subunit

These three steps are illustrated in Figure 5 and the movie.

Figure 5



Fusion Inhibitors

Only one FDA approved drug exists in the class known as fusion inhibitors, enfuvirtide. Enfuvirtide works by disrupting the gp 41 subunit of the viral surface glycoprotein thus preventing fusion of the HIV virion with the CD4 positive cell (see figure 5).

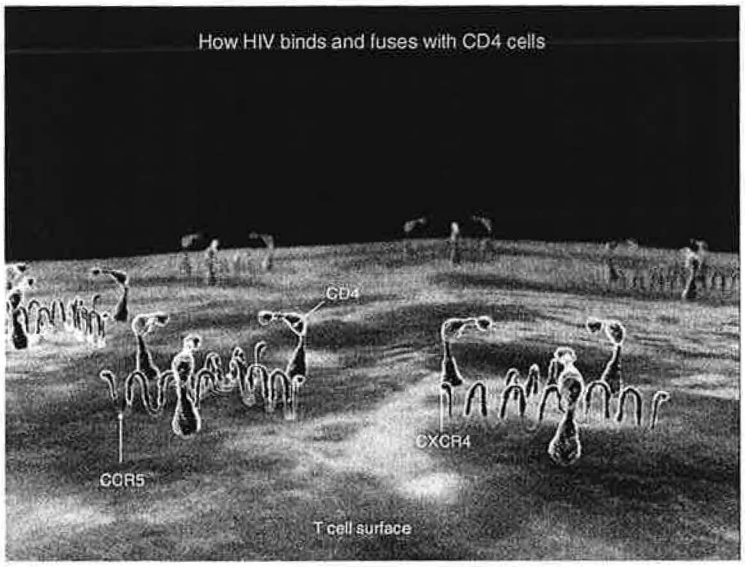
Co-receptor/CCR5 Inhibitors

Early in the course of the HIV epidemic, it was realized that HIV predominately infects cells in the human body which obtain a CD4 cell surface receptor, including CD4 positive lymphocytes, macrophages, and dendritic cells. While CD4 positivity is necessary for infection with HIV-1, it is not sufficient, and infectable cells have been found to have one of two co-receptors, CCR5 and CXR4. It appears that about half of all HIV-1 positive patents are infected with virus that is CCR5 "tropic", with patients at the early part of infection showing about 80% CCR5 tropism. The vast majority of the remainder of patients have virus that is either CXCR4 trophic (~2%) or mixed dual trophic (the majority). As a general rule, earlier infections tend to be CCR5 positive and later infections tend towards CXCR4 tropism. Currently there is only one FDA approved drug which has a mechanism of action that takes advantage of the need for a co-receptor, the CCR5 inhibitor maraviroc. While maraviroc is currently approved for use in

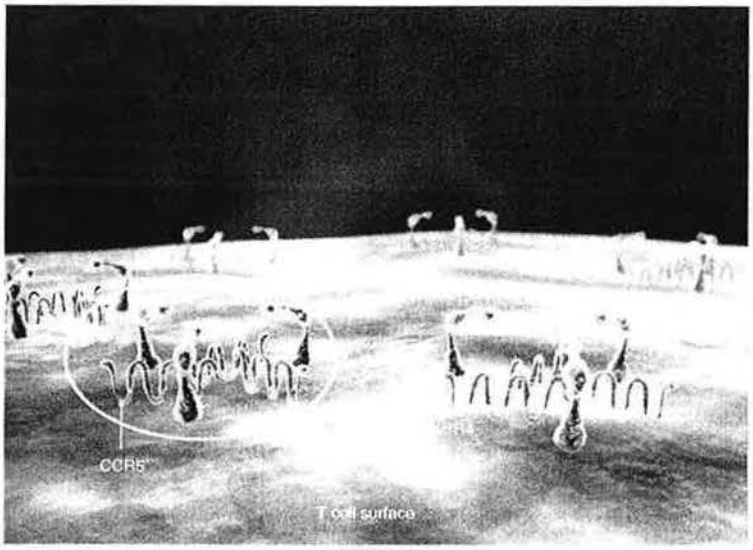
treatment experienced patients, the fact that treatment naïve patients are more likely to be purely CCR5 tropic has raised interest in using maraviroc as a first line agent. It is also important to note that maraviroc as well as other potential CCR5 inhibitors are the first HIV medications whose intended site of action are receptor complexes on human cells, as opposed to viral antigens. Given that human DNA sequences tend to be much more conserved than viral sequences, resistance, while not impossible, should be very different for these new medications as compared to older medications. The primary mechanism of HIV-1 resistance to maraviroc, appears not to be any one or set of point mutations, but a genetic shift involving many HIV-1 genes, in which the virus changes from being CCR5 tropic to mixed dual tropic.

The following set of slides (figure 6) demonstrates normal HIV-1 infection through the use of CD4 and CCR5 co-receptors, and the mechanism by which maraviroc blocks the infection in CCR5 trophic cells. CXCR4 blockers remain in early clinical development.

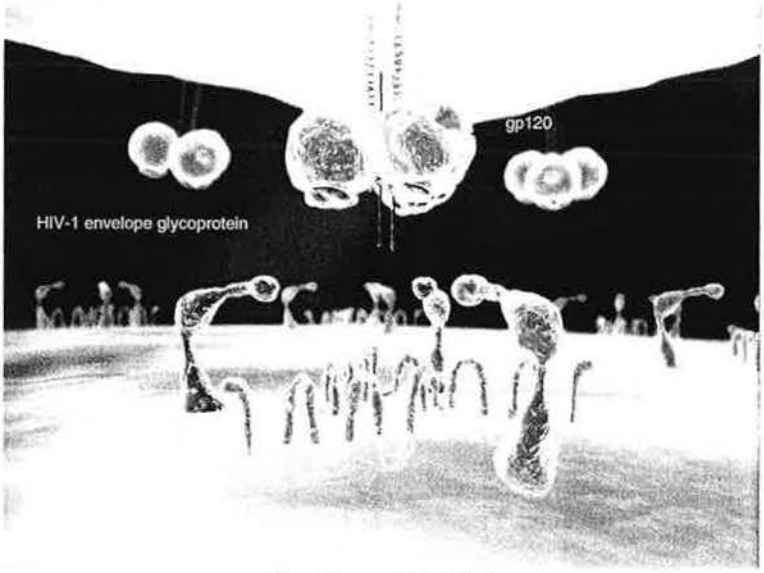
Figure 6



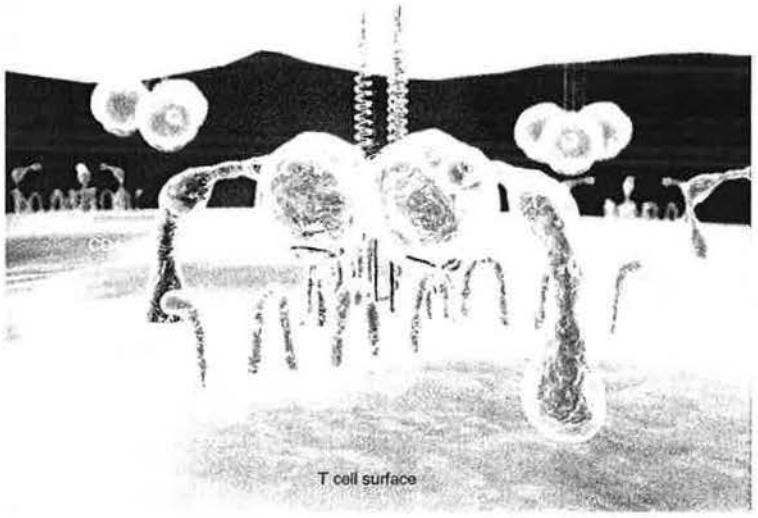
Dual Mixed Trophic

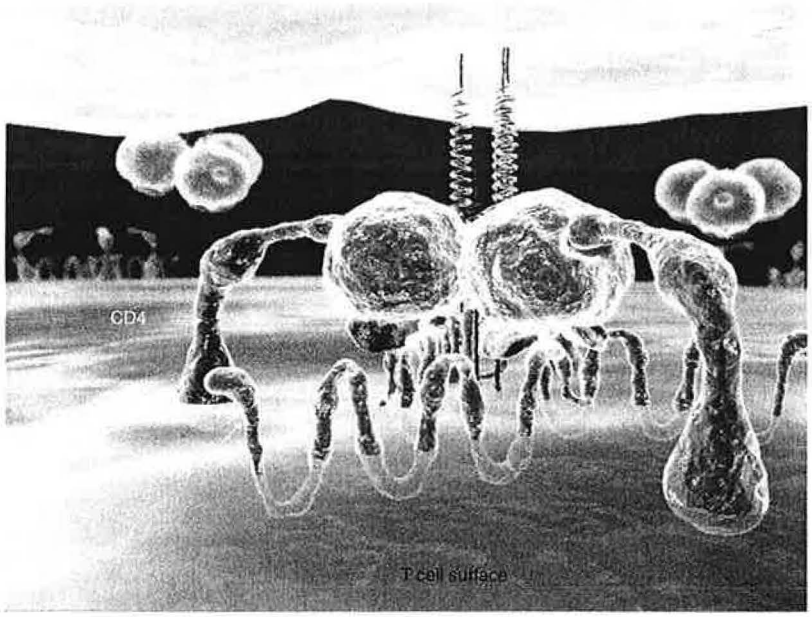


CCR5

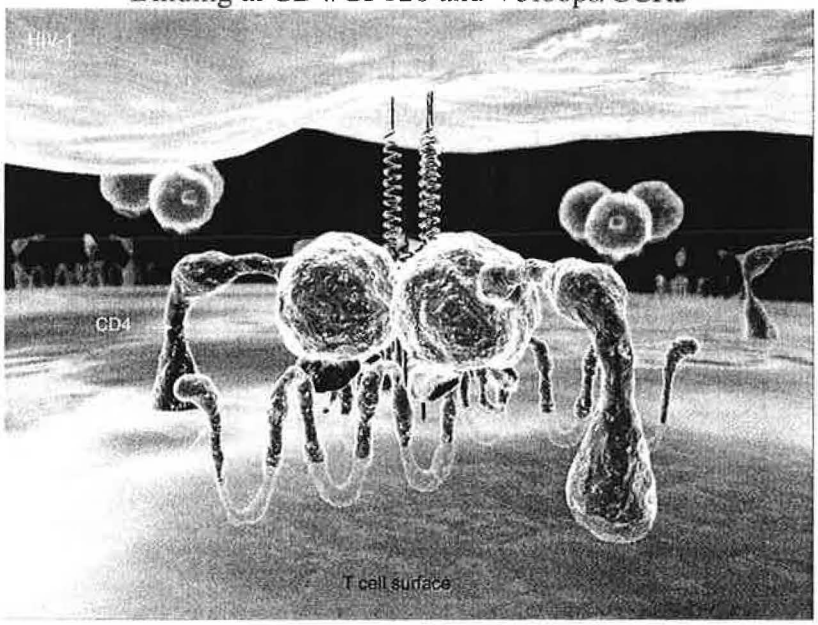


Gp 41 and Gp120

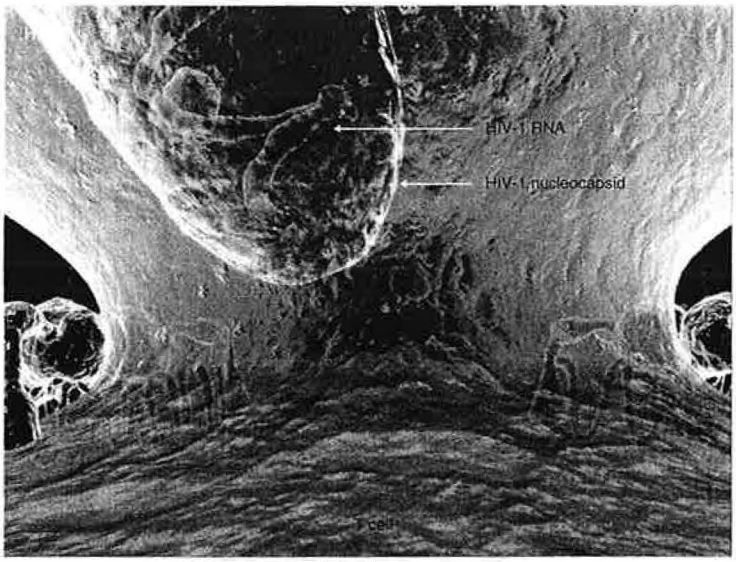




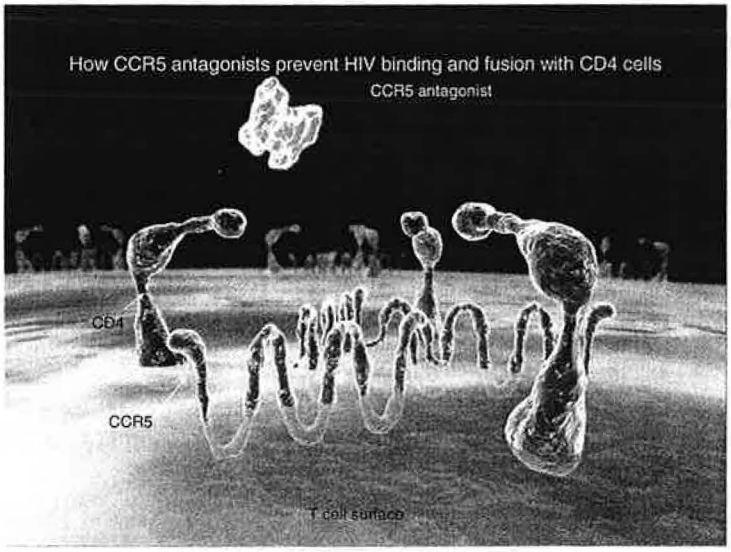
Binding at CD4/GP120 and V3loops/CCR5



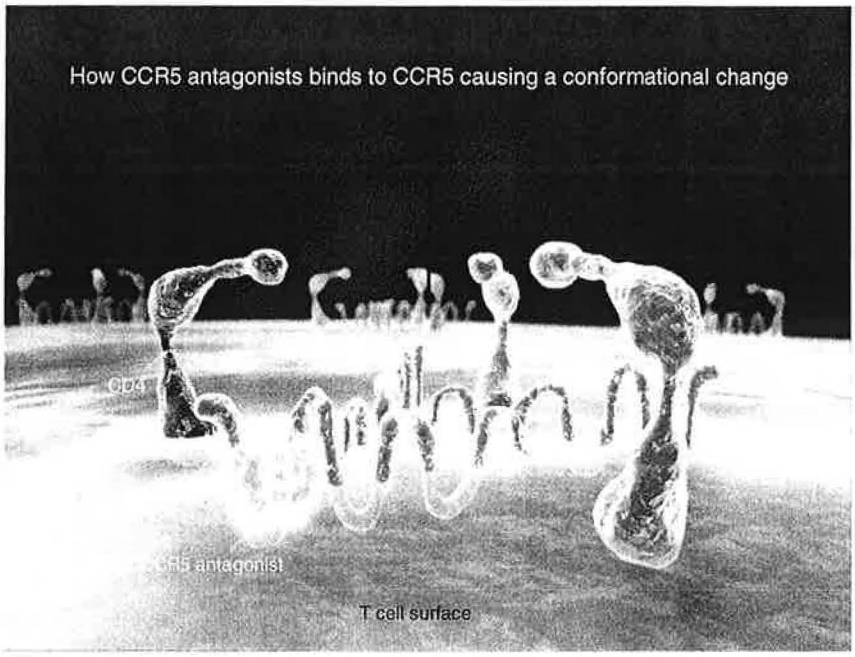
Conformational change of GP41



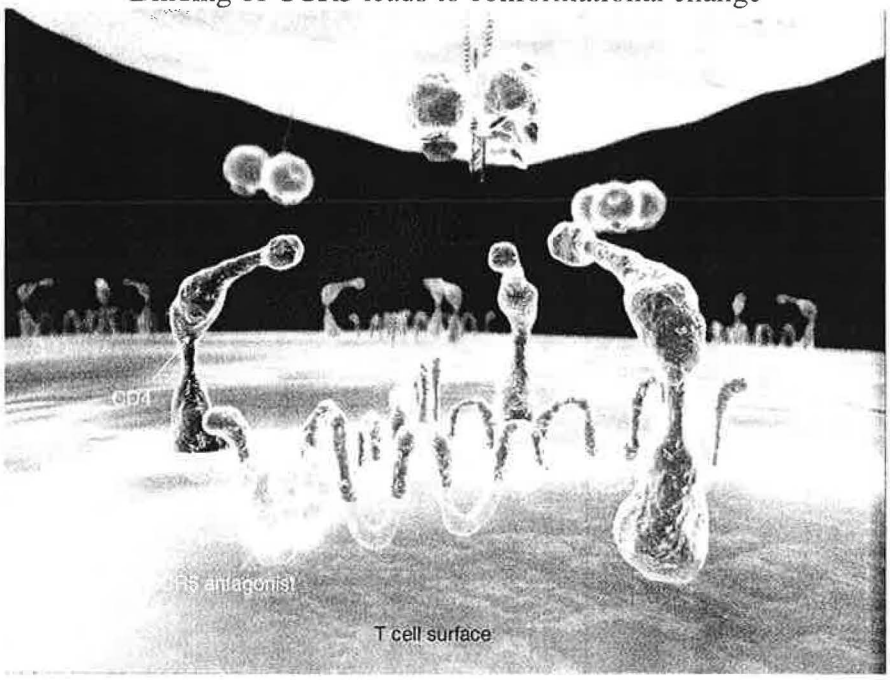
Fusion



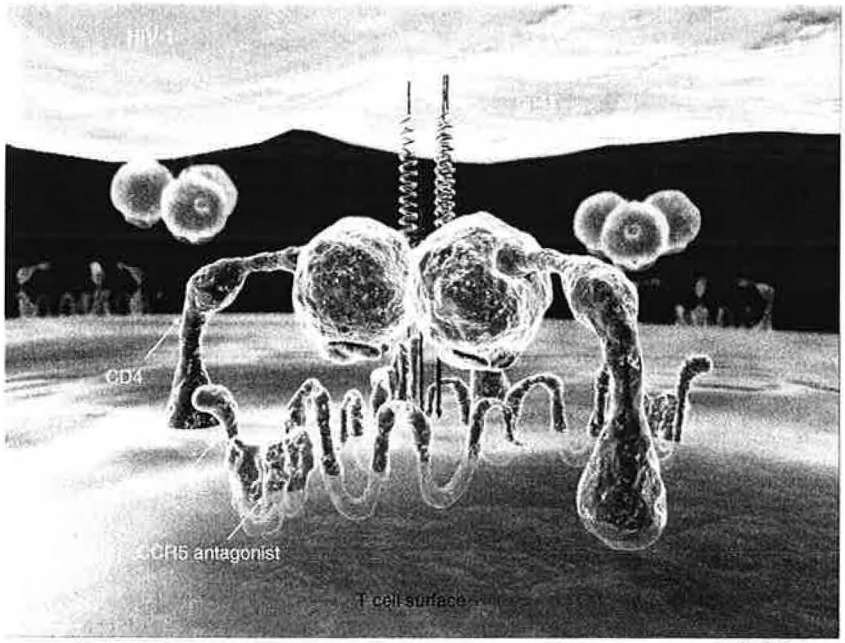
CCR5 Inhibitor



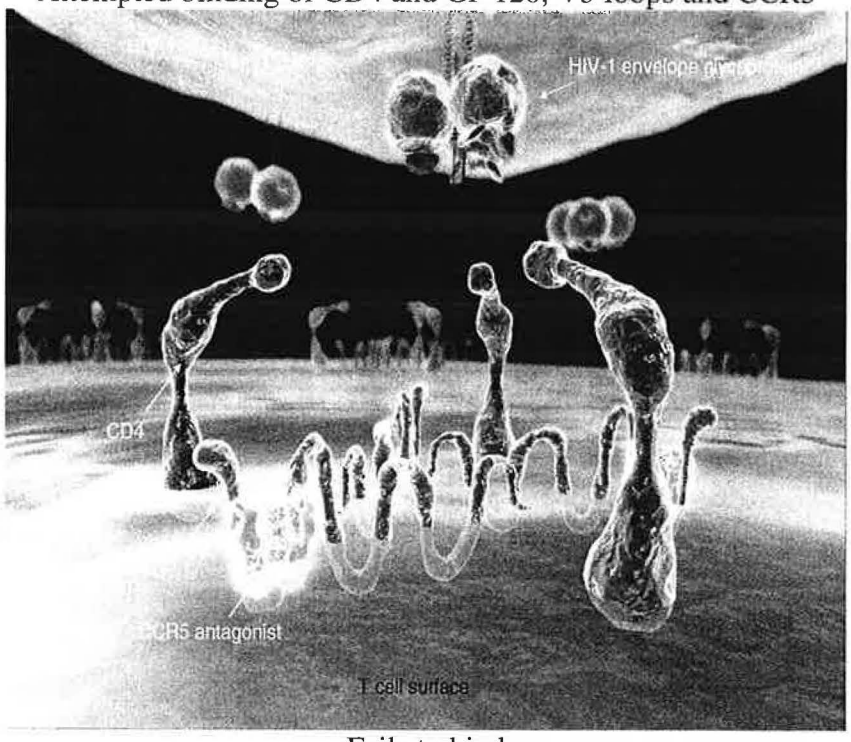
Binding of CCR5 leads to conformational change



Approaching Virion



Attempted binding of CD4 and GP 120, V3 loops and CCR5



Fails to bind

Case History: Part 2

You have elected to obtain some more information on Patient #9.

1. ***HIV -1 Resistance Genotype:***
   - *12 RT mutations;*
   - *19 protease mutations;*
   - ***Resistant to all licensed NRTI;***
   - ***Resistant to all licensed NNRTI;***
   - ***Resistant to all licensed protease inhibitors;***
   - ***Resistant to enfuvirtide.***
   - *Raltegravir (integrase inhibitor) not tested.*
2. ***Trofile Assay:***
   - ***Dual mixed CCR5/CXCR4 tropism.***

You should

A. *Start patient on raltegravir containing regimen*
B. *Start patient on raltegravir and maraviroc containing regimen*
C. *Plan funeral*
D. *Arrange to have patient infused with increasing doses of polyclonal caprine anti-HIV-1 IgG antibodies.*

IIIa. The Cutting Edge of the Battlefield

The Goat Study: A phase 1b observational, dose escalation trial to establish the pharmacokinetics and safety of HRG214, in patients with advanced HIV-1 disease.

HRG214 (a patented preparation owned by the Vironyx Corporation Limited) represents a new biological approach (passive immunotherapy) for patients infected with HIV who are failing their current regimen and have progressed onto AIDS. It is produced by immunization of goats with purified HIV proteins, synthetic peptides, and recombinant proteins based on HIV sequences detected by caprine but not human anti-HIV antibodies. The selected peptides and recombinant proteins contain highly conserved HIV sequences that have been chemically identified, synthesized and individually conjugated to muramyl dipeptide micro particles for immunization. **The resultant polyclonal antibodies have in vitro HIV inhibition of infection activity and, in the presence of complement, virion lytic activity.** This is the first known therapeutic agent with the potential for "virocidal" versus "virostatic" activity against HIV.

The antibodies in this formulation react with highly conserved and non-mutating regions on HIV-1 resulting in complement dependent lysis of free infectious viral particles, reduction of infectivity, and discriminative lysis of infected CD4+ cells, possibly addressing the issue of the latent viral compartment.

HRG214 had been given to 79 humans with HIV in non-IND studies. This patient, was

the ninth patient enrolled in this registrational trial. There was no control arm.

The trial involved approximately 3 infusions weekly, each lasting 2-4 hours, under physician supervision. Each dose was given 12 times before moving on to the next highest dose. Patients were monitored for the development of "HAGAR" (human anti-goat antibody response) which has been deemed to be a possible predictor of anaphylactic reactions.

Case Study: Part 3

Patient number 9 received treatment as follows. He continued taking all of the medicines that he had been taking previously on the Duet trial.

Date	*Dose HRG214*	*CD4 (cells/mL)*	*Viral Load (c/mL)*	*Glyburide/insulin*
2/25/08	*2mg/kg*	*46*	*125,000*	*No*
4/2/08	*4mg/kg*	*36*	*389,000*	*No*
5/7/08	*8 mg/kg*	*26*	*39,400*	*Yes*
7/14/08 (missed doses 7/14-8/18	*12 mg/kg*	*21*	*15,157*	*Yes*
8/18/08	*16 mg/kg*	*23*	*29,399*	*Yes*
8/29/08	*16mg/kg*	*Not done*	*Not done*	*Yes*
Trial indefinitely suspended due to "lack of investment potential".				
9/30/08	*1 mo f/u*	*6*	*11,807 (lowest viral load since July 2000)*	*Yes*
10/28/08	*2 mos f/u*	*17*	*13,312*	*Yes*

By 2/6/09, patient had begun to lose weight, developed intractable itching, recurrent ca-MRSA abscesses, low grade fever, and had weaned himself off insulin again. His CD4 count was 6 cells/mL and his viral load had risen to 45,609 copies/mL.

The best course of action for this patient at this point in time is:

A. *Referral to a different tertiary care center.*
B. *Storm Vironyx and demand immediate resumption of the research program.*
C. *Add Isentress to patient's Duet medications.*
D. *Infuse the patient with a mouse IgG4 monoclonal antibody directed against a conformational epitope in domain 2 of the human CD4 receptor which inhibits post attachment steps required for HIV entry while allowing for physiologic CD4 functioning.*

IIIb. The Cutting Edge of the Battlefield

A Phase 2b, Randomized Double-Blinded , 48-week, Multicenter, Dose-Response Study of Ibalazumab Plus an Optimized Background Regimen in Treatment-Experienced Patients Infected with HIV-1.

The scientific rationale for this project starts with the premise that the CD4 molecule is an excellent place to intervene in the HIV-1 lifecycle for the purpose of preventing intracellular infection. Many groups have developed antibodies against CD4 which are capable of blocking the entry of HIV-1, but most of these antibodies are directed against an epitope in domain 1 of the CD4 molecule, and have as a side effect the inhibition of the physiologic function of CD4, which is to signal and enhance the cell mediated immune response when properly stimulated though the secretion of Il-2 as well as other signaling pathways.

Ibalazumab is directed against an epitope in domain 2. While still effective at blocking the entry of HIV-1, Ibalazumab appears to allow for relatively normal and physiologic functioning of CD4 and thus does not appear to be by itself immunosuppressive.

The most challenging inclusion criteria for this study involves the fact that while restricted to heavily treatment experienced subjects, subjects must retain full susceptibility to at least one currently licensed antiretroviral agent.

In the case of patient #9, we had been saving raltegravir for "a rainy day". Randomization in this study is to either an 800mg IV infusion every 2 weeks versus a 2000mg IV infusion every 4 weeks, with no subjects receiving placebo only. It seemed reasonable to use raltegravir in combination with this likely active second agent.

While still resistant to all other licensed antiretrovirals, patient #9 proved to harbor virus with full susceptibility to raltegravir only. He has been on the trial for approximately 2 months, and reports that his weight is up, that he feels well, and that his diabetes is wildly out of control.

References:

Hammer SM, Yeni P. Anti-retroviral therapy: where are we? AIDS. 1998; 12 (suppl A): S181-8.

Lazzarin A, Clotet B, Cooper D, Reynes J, Arasteh K, Nelson M, et al. Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. N Engl J Med. 2003;348(22):2186-95.

Sattenau QJ, Moore JP. The role of CD4 in HIV binding and entry. Phil Trans R Soc London Biological Sciences. 1993;342(1299):59-66.

Jacobson JM, Kuritzkes DR, Godofsky E et al. Phase 1b study of the anti-CD4 monoclonal antibody (mAb) ibalizumab in HIV-1 infected patients: safety and

antiretroviral activity of multiple doses. 11th Conference on Retroviruses and Opportunistic Infections. 2004. Feb 8-11; San Francisco California.

Verity EE, Williams LA, Haddad DN, Choy V, O'Loughlin C, Chatfield C, Saksena NK, Cunningham A, Gelder F, McPhee DA. Broad neutralization and complement mediated lysis of HIV-1 by PEHRG214, a novel caprine anti-HIV-1 polyclonal antibody. AIDS. 2006 Feb 28:20(4):505-15.

Zhang L, Huang Y, Cao Y, Ho DD. HIV-1 subtype and second –recpetor use. Nature 1996;383:768.

Schuitemake H, Koot M, Kootsra NA, Derckse MW, de Goede RE, van Steenwijk RP, et al. Biological phenotype of human immunodeficiency virus type 1 clones at different stages of infection: progression of disease is associated with a shift from monocytotropic to T cell tropic virus population. J Virol 1992; 66:1254-60.

Koot, van't Wout AB, Kootsra NA, de Goede RE, Tersmette M, Schuitemaker H. Relation between changes in cellular load, evolution of viral phenotype, and the clonal composition of virus populations in the course of human immunodeficieny virus type 1 infection. J Infect Dis 1996;173:349-54.