TAG

NEW DRUG DILEMMAS

Scientific and Regulatory Issues in the Era of Antiretroviral Polytherapy and a Viral Load-Driven Standard of Care

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A Report to the FDA Antiviral Drugs Advisory Committee

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The Treatment Action Group (TAG) fights to find a cure for AIDS and to ensure that all people living with HIV receive the necessary treatment, care, and information they need to save their lives. TAG focuses on the AIDS research effort, both public and private, the drug development process, and our nation's health care delivery systems. We meet with researchers, pharmaceutical companies and government officials, and resort when necessary to acts of civil disobedience, or to acts of Congress. We strive to develop the scientific and political expertise needed to transform policy. TAG is committed to working for and with all communities affected by HIV.

Acknowledgements are due to all TAG board members, staff, volunteers, committee members, our generous donors, and our many researcher friends, without whom our work would not be possible.

TAG's website address is *http://www.aidsnyc.org/tag*, updated versions of this and other TAG reports may be accessed and downloaded from that site.

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This report is dedicated to

Dr. James C. Hill
Deputy Director of NIAID, 1987-1995

A proud gay man, an early activist ally
and an unceasing fighter against AIDS

d. 26 June 1997

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NEW DRUG DILEMMAS

Scientific and Regulatory Issues in the Era of Antiretroviral Polytherapy and a Viral Load-Driven Standard of Care

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1. PREFACE & INTRODUCTION

by Spencer Cox

PREFACE

Two comparisons seem to come inevitably to the minds of writers when they survey the past two years of AIDS research, with the enormous advances that have been made in the theory and practice of AIDS therapy: the first is the miraculous recovery of the biblical Lazarus, and the second is Alice in Wonderland, desperately trying to make sense of a world in which everything changes by the minute. These conflicting metaphors might also describe the position of advocates for people with HIV, trying to determine how patients can get maximal benefit from new drugs and new data, without entirely giving up our ability to continue to get more information about the optimal use of therapies.

This report summarizes development of several selected new anti-HIV drugs, both recently approved (delavirdine and neflinavir) and currently in advanced development (abacavir, adefovir dipivoxil, DMP-266 and GW141). In addition, comments are offered regarding proposed changes in the process by which anti-HIV therapies are regulated by the US Food & Drug Administration (FDA). No pretense is made that this report is comprehensive; indeed, the authors do not believe that, at present, enough data are available to make comprehensive judgements about how clinical trials ought to be conducted in this rapidly-changing era of polypharmacy and quantitative viral load measurements. In general, we endorse the trend towards assessment of new therapies based on HIV RNA levels. However, we believe that much work still needs to be done to define regulatory standards which will meet the needs of people living with HIV.

This policy shift represents a significant change for the Treatment Action Group (see Cox 1994), and it has occasioned much discussion amongst our membership. We recognize that there are important arguments both for and against RNA-based assessment of therapeutic efficacy, and we believe that those arguments need to be seriously examined in open public fora. For that reason, we are seriously concerned that the FDA has chosen not to arrange for presentations to the Antiviral Drugs Advisory Committee regarding the historic failures of surrogate markers, including the recent finding that, despite increased clearance of MAC bacteremia, high-dose clarithromycin prophylaxis increased mortality among people at risk for *Mycobacterium avium* complex (MAC). Safety concerns must be one of the primary issues in considering this transformed regulatory standard.

Nonetheless, we have confidence that these vital discussions can occur, that protections against unsafe and ineffective drugs can be maintained, and that the relevant standards for approval can be altered in ways that improve the utility of data generated by clinical trials. We do not elieve that this will be an easy task, but we look forward to working with FDA, industry, researchers and AIDS advocates to ensure that HIV-inrected individuals can expect continued improvements in their prospects for disease-free survival.

INTRODUCTION

Last month, the Public Health Service published a new draft set of "Guidelines for the Use of Antiretroviral Therapies in HIV-infected Adults and Adolescents." This document marks the consolidation of a revolution in HIV therapy that has occurred over the past several years (HHS 1997). The improved precision in therapeutic decision-making offered by quantitative viral load tests, and the increased efficacy of treatment have led most researchers to agree that treatment should be initiated considerably earlier in the course of disease, and should aim to reduce plasma HIV RNA to levels as low as possible, ones not detectable by current assays (NIH 1997).

These changes in clinical care necessarily impact the design and conduct of AIDS-related clinical trials. However, the catch is that researchers have broad disagreements about how, specifically, studies need to change: for example, in Jon Cohen's recent article from *Science* Magazine, Dr. Douglas Richman, from the University of California/San Diego asserted that "Anything that is not designed to completely suppress viral replication is suboptimal." As a consequence, Dr. Richman and other have opined that studies using two-nucleoside control arms are unethical, exposing patients to undue risk of drug resistance. Their arguments, based on new data about the biology and quantitative dynamics of HIV infection, are often compelling. However, other leading researchers, such as Dr. Michael Saag from the University of Alabama/Birmingham have suggested that only long-term studies, looking at the clinical effects of different "strategies" for treatment of HIV infection, using different combinations of drugs (including, possibly, two-nucleoside regimens) in different sequences, can truly determine how best to treat the disease. Dr. Saag argues that the biology of the disease is only one consideration in determining optimal use of anti-HIV therapy, and that the safety and efficacy profiles of the different therapies, the biological and behavioral variations among patients, and the possible negative sequalae of therapy need to be accounted for in determining how best to make use of potent new drugs (Cohen 1997).

This dilemma was starkly highlighted not long ago when the AIDS Clinical Trials Group (ACTG) set out to design it's first "strategy trial," known as the "Strategic Timing of Antiviral Therapy" or START trial. The ACTG leadership agreed that a strategy trial was called for. However, the study proposal, which was designed by Dr. Saag and other top ACTG investigators, was rejected when the leadership could not agree on which strategies for initiation of therapy should be evaluated. Indeed, some investigators felt that the biology of HIV infection had already answered the question: treatment should be initiated as soon as an HIV-infected patient could be persuaded to begin.

Historically, regulatory requirements for new therapies and the clinical care of HIV-infected patients have not diverged greatly. Sequential monotherapy was the clinical standard, and tools for monitoring therapeutic success or failure were extremely limited. In patients with relatively advanced HIV infection, clinical events were likely to occur with depressing frequency, even in the face of antiviral therapy, ensuring that the benefits of therapy could be measured with clinical endpoints.

Now, however, a great divergence has begun to occur. Therapy appears to be becoming capable of delaying illness and death for substantial periods of time, and viral load assays allow an individual patient's

response to therapy to be evaluated rapidly. Drugs are used earlier in the course of infection, and in combinations, which imposes difficulty in assessing the contributions of particular product to therapeutic efficacy. Maintenance of patients on randomized, blinded, properly-controlled trials long enough to evaluate therapeutic effects has become severely problematic -- especially when control arms include suboptimal therapy. The requirements of patient care have come into conflict with the goal of substantiating claims about particular treatments.

For some researchers, such as Dr. Joep Lange from the University of Amsterdam, this conflict necessarily implies that the regulatory goals should be abandoned. Dr. Lange believes that the goal of future research should be to "identify maximally suppressive therapeutic strategies that will confer the greatest and longest immunological and clinical benefit at lowest toxicity and cost." (Lange 1997). Unfortunately, while Dr. Lange has given us an excellent description of current thinking about how to assess optimal care for patients, he has not described an algorithm for assessing the claims made by pharmaceutical companies about their products. The US regulatory system has evolved as it has in order to ensure that companies are not able to make false or misleading claims about the particular health technologies that they manufacture. As we have recently seen with several anti-HIV drugs, such as the cross-resistance profile of Invirase™ brand saquinavir, and the prophylactic effects of high-dose Biaxin™ brand clarithromycin against Mycobacterium *avium* Complex (MAC), such evaluation remains important. Had the companies been allowed indefinitely to make claims based on preliminary data about these drugs, the products would continue to be misused, causing harm to patients.

In response to the changing clinical arsenal, many researchers, regulators, and patient advocates have proposed to move towards a regulatory standard based on quantitative measurements of plasma HIV RNA levels and circulating CD4 cell counts. Dr. Richman observes, "All this talk of HIV RNA and CD4 being surrogate markers, that has always bothered me. They are not surrogate markers. They are the measurement of the disease."

Such a change seems inevitable given the limitations imposed by today's standard of care. The conduct of ACTG 320-style studies, in which patients are maintained on treatment regimens while showing virologic -- and later clinical -- failure seems both practically and ethically untenable. However, alterations in the regulatory standard should account not only for the needs of patient care, but also for the requirements of sound product regulation. As such, these changes need to be carefully thought out, with a close eye on the law of unintended consequences. Changes in the regulatory standard that are ostensibly intended to be responsive to patient care could have the consequence of damaging patient care by permitting unsubstantiated claims about products, leading to misuse of drugs based on preliminary data.

After discussions with industry and AIDS advocates, FDA has suggested a proposal that would permit full marketing approval based on evidence of a durable virologic response to therapy. This proposal seems to change with some rapidity, however a number of suggestions were made during a meeting with AIDS advocates on May 16th, 1997:

1. Evidence that a drug confers a reduction of 0.5 log10 in plasma HIV RNA levels at 16-24 weeks would be sufficient for accelerated approval.
2. Evidence that a drug, when used in an appropriate combination regimen, confers a sustained reduction in plasma HIV RNA levels to 48 weeks would be sufficient for full approval.
3. Trials demonstrating surrogate response would need to include at least 200 patients treated with the study drug.
4. Evidence of safety would be required in at least 300 patients followed for at least six months.

The proposal at the time did not discuss various alternatives for designing RNA-based confirmatory studies. However, various alternatives for such studies address different areas of concern with current trial design, and impose differing obstacles to optimal implementation. For instance, although in May it seemed that FDA had settled on magnitude of virologic response as the optimal measure of therapeutic efficacy, many researchers believe that time to virologic failure may be the appropriate measure of therapeutic efficacy. Depending on how virologic failure is measured, studies may need to become larger and longer, rather than smaller and faster as industry desires. The Antiviral Advisory Committee should carefully consider the different aspects of this proposal, as the implications of particular choices will be important to the design and conduct of future studies.

In particular, the Treatment Action Group believes that the Committee should carefully consider the following questions:

1. How should virologic response be measured? During the period in which FDA relied on CD4+ cell count changes to assess response to therapies for accelerated approval, the measures of CD4 cell count differed from therapy to therapy – in particular, companies looked at both absolute CD4 cell count changes and changes in Area Under the Curve (AUC). Because the agency did not define a standard measure of immunologic response, companies were allowed to perform a number of tests, and to selectively rely on measurements supporting their proposed claims. Before moving to an RNA-based standard for clinical efficacy, the agency needs to define what it means by a virologic response.

    a. A number of different measures are available to determine therapeutic effects on plasma HIV RNA levels, including:

        i. Magnitude of initial virologic decline
        ii. Percentage of patients with at least an 0.5log10 decline in plasma HIV RNA levels
        iii. Percentage of patients who achieve plasma HIV RNA levels below the limits of detection
        iv. Percentage of patients with undetectable plasma HIV RNA levels at a defined time point, or for a defined duration

v. Time to nadir of virologic decline
vi. Time to re-appearance of detectable virus

Each of these measurements have different implications for trial design. For instance, FDA has also suggested that "time to virologic failure" may be the most appropriate measure of clinical response. However, the recent PHS Guidelines list four criteria for virologic failure:

i. Less than a 10-fold (1.0 log) reduction in plasma HIV RNA by 4 weeks following initiation of therapy.
ii. Failure to suppress plasma HIV RNA to undetectable levels within 4-6 months of initiating therapy.
iii. Repeated detection of virus in plasma after initial suppression to undetectable levels, suggesting the development of resistance.
iv. Any reproducible significant increase, defined as 3-fold or greater, from the nadir of plasma HIV RNA not attributable to intercurrent infection, vaccination, or test methodology;

In addition, the guidelines also note that persistently declining CD4 T cell numbers as measured on at least two separate occasions, or clinical deterioration may also suggest therapeutic failure in some cases, even in the face of apparent virologic success. These different measures need to be considered, along with their implications for trial design. For instance, measurement of the absolute magnitude of the initial virologic response may have the advantage of being measurable over the short-term in a relatively small number of patients, but may lack long-term predictive capacity, and may be confounded by the assay limits of detection.

RECOMMENDATION 1: FDA should define a standard measure of changes in HIV RNA levels to be used in assessing clinical efficacy.

1. What is the minimal evidence of virologic response needed to imply efficacy? Again, the historical failure of FDA to define minimal criteria for evaluating a CD4+ cell response to treatment meant that therapies were approved based on as little as a ten-cell improvement over AZT monotherapy in a patient population that had been heavily pre-treated with AZT. Assuming that RNA changes are partially predictive of clinical response, the benefit offered by large virologic improvements over acceptable control arms – such as those offered by AZT/3TC/indinavir as compared to AZT/3TC – is unlikely to be overwhelmed by minor or infrequent adverse events. On the other hand, when virologic improvements are small, those differences may easily be swamped by a rare, serious adverse event. FDA would be well-advised to begin by setting minimal criteria for virologic response that is well above the estimate of meaningful clinical changes, allowing a "buffer zone" to account for unidentified adverse events. Therapies that do not meet this minimal standard would still be eligible for approval based on evidence of decreased rates of illness and death in treated patients.

RECOMMENDATION 2: FDA should define a rigorous minimal standard for evidence of virologic response suggesting clinical efficacy.

What is the minimal size of the safety database? Disease and death are responsive not only to therapeutic efficacy, but also to the impact of serious adverse events. Clinical endpoint studies allow us to measure the aggregate effects of diverse biological properties of therapy. If FDA is prepared to sacrifice this measure, then adverse event monitoring needs to be carefully considered. Randomized, controlled trials should be supplemented by an observational database, possibly conducted in the context of an expanded access program, to provide longer-term and potentially more detailed information about serious adverse events associated with therapy. The Treatment Action Group does not believe that 300 people followed for six months is sufficient to allow for the kind of safety assessment required in the absence of clinical endpoint studies, as early experience with ddI pancreatitis and more recent discoveries about protease inhibitor-associated diabetes indicate.

RECOMMENDATION 3: FDA should define minimal standards for the size of the safety database required for approval that is more rigorous that what has been proposed.

What supportive data are needed? In the absence of clinical endpoint data, FDA should use this opportunity to increase the amount of supportive data required – particularly data regarding interactions between the regulated product and products with which it is likely to be coadministered. For instance, both approved non-nucleoside reverse transcriptase inhibitors were approved without substantive safety data on use in combination with HIV protease inhibitors, and Glaxo-Wellcome is currently testing GW-1592 mainly in combination with other products manufactured by Glaxo-Wellcome. If, as is expected, anti-HIV drugs will be used in combination with a diverse array of other anti-HIV products, then minimal pharmacokinetic interaction studies need to be conducted with those products, and more substantial safety and activity data should be generated when an interaction is identified, unless the combination is clearly contraindicated. In addition, interaction data should be available on drugs commonly used to prophylax and treat opportunistic infections that afflict HIV-infected patients, as well as on anti-anxiety and anti-depressive medications, birth control medications, and methadone.

RECOMMENDATION 4: FDA should require a more comprehensive package of interaction data for drugs approved based on plasma HIV RNA improvements.

What incentives exist to encourage follow-up studies? While FDA's primary mission is the evaluation of claims regarding the safety and efficacy of particular products, the agency has also recognized the proper safety evaluation continues in the post-marketing setting. If the quantity of data available at the time of approval is to be reduced, then the agency should clearly consider mechanisms, such as limitations on labeling at the time of initial approval, to encourage the conduct of post-marketing studies that will continue to elucidate the safety and efficacy of products as components of different therapeutic "strategies."

RECOMMENDATION 5: FDA should shape regulations to encourage post-marketing evaluation of therapeutic safety and efficacy.

What decisions should be made in public? Historically, decisions regarding the approval of particular products have influenced overall interpretation of regulations. For instance, when ddC was approved, both the manufacturer and members of the Antiviral Drugs Advisory Committee cited the earlier approval of ddI to support the approval of ddC: both argued that, because allowances had been made for ddI, justice demanded that it be made for ddC. However, ddC was a different drug, with a different safety and efficacy profile from ddI. The willingness of the Antiviral Drugs Advisory Committee to make commitments regarding acceptable minimal requirements for approval (as was done with 3TC) in private meetings with the company compromises the ability of patient advocates to effectively support patient interests.

RECOMMENDATION 6: Substantive commitments regarding the adequacy of a data set for marketing approval should be made in open public hearings.

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II. The Birth of a New Treatment Paradigm: Maximal Viral Suppression as the Goal of Antiretroviral Therapy

by Mark Harrington

In June the Federal government published twelve 'Principles of HIV Therapy' and 'Clinical Practice Guidelines for Treatment of HIV Infection', developed by two HHS committees over the last eight months to provide guidance for physicians, people with HIV and third-party payers about how best to use new antiretroviral drugs and viral load tests.

Turning the treatment revolution of 1996 into new standard of care for 1997 was no picnic. After Vancouver, it was obvious that the previous Public Health Service (PHS) guidelines for treating HIV, published in 1993, were antiquated, dating from the era of AZT as first-line monotherapy, when there was still no clinical evidence of benefit for combination therapy, let alone of the dramatic impact protease-inhibitor containing regimens can have on prolonging health and life. Sophisticated, accurate viral load testing was experimental in 1993, but is now the basis for clinical management. While some self-appointed blue ribbon panels in 1996 promulgated interim treatment guidelines -- notably the International AIDS Society, USA (an oxymoronic cognomen) -- these were based more on expert guesswork than on a thorough review of the rapidly changing field.

With a sublimity only a dysfunctional government bureaucracy could have devised, two branches of the US Department of Health & Human Services (HHS) set up not one, but two panels to codify the new approach to anti-HIV therapy. Under the aegis of the Office of AIDS Research (OAR), the National Institutes of Health (NIH) set up the NIH Panel to Define Principles of Therapy of HIV Infection, chaired by Chuck Carpenter of Brown University, with OAR's Mark Feinberg as executive secretary. The NIH panel held hearings in November 1996 to update its members on the latest data (see *TAGLine*, February 1997), and subsequently a series of twelve principles of HIV therapy were developed (see appendix I).

Simultaneously, the Office of HIV/AIDS Policy (OHAP) in HHS, administered by Eric Goosby, set up the Panel on Clinical Practices for Treatment of HIV Infection, co-chaired by John Bartlett of Johns Hopkins University and Anthony S. Fauci, director of the National Institute of Allergy & Infectious Diseases (NIAID). The HHS panel met in four contentious working sessions over four months to work out how best HIV should be treated in the era of viral load testing, protease inhibitor polytherapy, and 'undetectability'.

It took six months for the panel leaders to define their respective roles. Eventually, the bureaucrats worked out a stunningly simple solution: the NIH panel wrote principles of HIV therapy, which are expected to endure, and the HHS panel wrote clinical practice guidelines, which are expected to change as new studies finish, new drugs become available, and new information emerges about pathogenesis and treatment. Pulling would-be practice guidelines out of the principles document and vice versa was like pulling teeth.

It was not easy to be part of a process which will impact on treatment decisions made by hundreds of thousands of people living with HIV. Along with fellow activists Cornelius Baker of NAPWA, David Barr (formerly at GMHC, now with the Forum for Collaborative HIV Research), Spencer Cox of TAG, Martin Delaney of Project Inform, and community advocate Sallie Perryman, I felt the crushing responsibility of getting it right in a rapidly changing field, curbing the excessive impulses of certain gun-happy virologists, and bringing a reality check to the proceedings. For there were many who wanted to add triple-combination therapy to the drinking water, or so it seemed. Concerns about adherence, convenience, cost, toxicity and hassle were relegated to a lower priority, and some researchers seemed unaware that, though the treatment options of 1997 are broader than they were before, they are still quite limited, and the risk of cross-resistance remains quite real. Data are still inadequate on when to start therapy, and what to start with. However, after six months of work, helped along by the emergence of new data from studies such as ACTG 320, and only after a last-minute effort to substitute bias for data by some prominent researchers, blocked by the community representatives, the HHS panel came to some strong conclusions.

WHEN SHOULD THERAPY BE STARTED?

This proved to be the most controversial part of the Guidelines. The April draft was based on risk thresholds derived from ACTG 175 and the MACS study. In early May, a group of ACTG investigators hijacked the draft and recommended starting therapy in about 97% of the HIV-infected population. The community representatives to the Panel responded by threatening to pull out unless a semblance of rationality was restored. Later in May this controversy appeared to be resolved, and the final Guidelines provide more information about the risk of progressing to AIDS at various CD4 and RNA levels, which may assist doctors and people with HIV in making treatment decisions. A comparison of the April and early May draft Guidelines follows:

April draft Recommendations for Initiating Therapy

CD4<350, any HIV RNA level	"Treat"	[Based on 175]
CD4 350-500, bDNA (corrected) >20,000	"Treat"	[Based on MACS]
CD4 350-500, bDNA (corrected) <20,000	"Treat or observe"	"
CD4 >500, bDNA (corrected) >60,000	"Treat"	"
CD4 >500, bDNA (corrected) 20-60,000	"Treat or observe"	"
CD4>500, bDNA (corrected) <20,000	"Observe or treat"	"

Early May draft Recommendations for Initiating Therapy

CD4<500, any detectable HIV RNA	"Treat"
CD4 351-500, undetectable HIV RNA	"Treat or observe"
CD4 >500, HIV RNA >10-20,000 (bDNA)	"Treat"
CD4 >500, HIV RNA <10-20,000 (bDNA)	"Treat or observe"
CD4 >500, HIV RNA undetectable	"Observe"

To effectively guide clinical management, support appropriate access and reimbursement, and set the

scientific agenda for future research, the Guidelines should at least attempt to be honest about what we know and what we don't.

The April draft, which based when-to-start decisions on the MACS cohort and ACTG 175, was data-driven, scientifically credible, and defended physician-patient autonomy. The early May draft subverted this autonomy, discarded MACS and ACTG 175, and set up the very real possibility of overtreating a healthy asymptomatic population including many who may not be ready for treatment, may not need it, may lack the requisite motivation, and may benefit from waiting.

A few ACTG investigators -- despite having missed most Panel meetings -- exerted overwhelming pressure behind the scenes to discard the April draft and adopt a more aggressive, less data-driven approach.

It was ironic, to say the least, that the leadership of the world's largest AIDS trials network was so sure of when we should start therapy that they are not only unwilling to conduct studies to prove their belief (in spite of having been wrong many times before), but also appeared determined to foreclose the possibility that *anyone* could conduct studies to answer this question by moving it beyond the realm of research into the realm of certainty?

According to one researcher, the early May draft would have placed 97% of the HIV-infected population on therapy -- completely disregarding the difficulty of adherence to a life-long treatment regimen, the possibility of creating widespread cross-resistance, low risks of immediate progression, and the toxicity and cost of overly aggressive treatment guidelines.

The drug companies are already doing a good job of scaring providers and patients into considering early therapy -- perhaps too early. Is it the role of the Public Health Service to provide them with yet another, ostensibly objective, promotional tool?

Three very different prospects open out before HIV-infected individuals with access to treatment -- eradication, lifelong suppression, or delayed progression to AIDS.

If eradication of HIV infection proves possible, then all infected should start eradicative treatment regimens as soon as possible. However, eradication may remain a chimera.

If chronic lifelong suppression of HIV proves possible, it becomes very important indeed to determine whether in fact there is an immunological "point of no return," so people could start treatment before then. It may be important to intervene as early as possible, or it may be just as good, and less expensive or toxic, to wait until some yet-to-be-defined trigger point to start therapy. Until we know more, the April Guidelines seemed a good place to start.

Because we can be sure that better, more convenient, less toxic, and perhaps more potent regimens will be available in coming years, at least some people may gain from waiting.

If all maximally suppressive therapy can do is delay progression to AIDS, it is still critical to determine the best time to initiate therapy. If resistance is sure to develop to any regimen, no matter how potent, it is by no means clear that earlier is always better, both for individuals on treatment and for the public health, when widespread transmission of resistant HIV may make the epidemic uncontrollable again.

In the early May draft, physician-patient autonomy was sidelined by a strong bias towards initiating therapy in all infected individuals regardless of CD4 count or viral load.

Luckily, the Panel co-chairs responded to the threatened walk-out by the community representatives and restored some semblance of rationality to the Guidelines by providing more detailed information about risks of progression, enabling people at all stages of HIV infection to make informed decisions about whether and when to start, while preserving the necessity for third-party reimbursement when someone decides to start treatment (HHS 1997).

WHO SHOULD BE TREATED?

"For acute primary HIV infection: While many experts would recommend treatment with maximally-suppressive antiretroviral therapy for an indefinite period of time, there is no evidence yet of clinical benefit or altered long-term disease progression.

For asymptomatic HIV infection, CD4 T cells <500 or HIV RNA >10,000 (bDNA) or >20,000 (RT-PCR): Treatment should be offered. Strength of recommendation is based on readiness of patient for therapy and prognosis for disease-free survival as determined according to Table IV (*see below*).

"For asymptomatic HIV infection, CD4 T cells >500 or HIV RNA <10,000 (bDNA) or <20,000 (RT-PCR): Most experts would delay therapy and observe; however, some experts would treat.

"For symptomatic HIV infection: Treat."

For salvage therapy (anyone on suboptimal therapy or failing potent combination therapy): Switch to another potent regimen to which the virus has not already become resistant (f this is feasible), recognizing that little or no clinical information is available for this population, and options will vary by treatment history (see ACTG 333).

Viral load risk thresholds for disease progression. The HHS Guidelines provide detailed information on the risk of progression to AIDS first presented by John Mellors at Vancouver, derived from follow-up on 1,604 HIV-infected men from the Multicenter AIDS Cohort Study (MACS) whose blood was drawn in 1985, measured by bDNA in 1995. Their risk of progression over that decade was strongly correlated with their baseline viral load. The MACS is the biggest, longest study to demonstrate that baseline viral load predicts the rate of progression, but the bDNA values given for the 1985 samples suffer from several distorting factors. The blood was stored at room temperature for several hours, and stored in heparinized tubes. Heparin degrades HIV RNA. Therefore, the Mellors 1985 numbers must be *at least doubled* to get a realistic picture of the risk of progression associated with a given viral load measurement

taken today. Similarly, values given by bDNA must be *doubled again* if they are given for PCR. For example, a comparison of the risk of AIDS in several groups of men from the MACS shows the risk of developing AIDS within three, six and nine years using adjusted bDNA and RT-PCR values:

MACS Study: Progression Rates by CD4 and Viral Load Category

Adjusted bDNA	RT- PCR	N	% developing AIDS 3 years	6y	9y
CD4 ≤ 350					
<1,000	<2,000	3	0	0	0
1,000-6,000	2,000-12,000	30	0	18.8	30.6
6,001-20,000	12,001-40,000	51	8.1	42.2	65.6
20,001-60,000	40,001-120,000	73	40.1	72.9	86.2
>60,000	>120,000	174	72.9	92.7	95.6

Thus, if a recent bDNA test showed CD4 under 350 and viral load over 60,000, one's risk of progression over three years might be as high as 73%, and similarly for an RT-PCR result over 120,000. By contrast, none of the three MACS participants with low CD4s but undetectable (<500 bDNA) viral load progressed over nine years.

Adjusted bDNA	RT- PCR	N	% developing AIDS 3 years	6y	9y
CD4 350-500					
<1,000	<2,000	NA	NA	NA	NA
1,001-6,000	2,001-12,000	47	4.4	22.1	46.9
6,001-20,000	12,001-40,000	105	5.9	39.8	60.7
20,001-60,000	40,001-120,000	121	15.1	57.2	78.6
>60,000	>120,000	121	47.9	77.7	94.4

Higher viral load (over 20,000 by bDNA or 40,000 by RT-PCR) distinguishes a medium-risk (32% at three years) from a low risk (5% over three years) group in this group with medium CD4 counts.

Adjusted bDNA	RT- PCR	N	% developing AIDS 3 years	6y	9y
CD4 > 500					
<1,000	<2,000	110	1.0	5.0	10.7
1,001-6,000	2,001-12,000	180	2.3	14.9	33.2
6,001-20,000	12,001-40,000	237	7.2	25.9	50.3
20,001-60,000	40,001-120,000	202	14.6	47.7	70.6
>60,000	>120,000	141	32.6	66.8	76.3

People with over 500 CD4 cells whose bDNA is over 60,000, or PCR over 120,000, appear to have

a 33% risk of progression over three years -- the same as those with 350-500 CD4 cells and over 20,000 bDNA or 40,000 PCR HIV copies. For those with high CD4s and high viral loads, starting treatment might be more urgent than for those with low viral loads -- especially as treatment options will improve over the next few years. Some asymptomatic persons with high CD4s and low to moderate viral load may do better by waiting.

WHAT TO START WITH?

What are the optimal first-line therapeutic regimens? After ACTG 320 proved the superiority of AZT/3TC/indinavir to AZT/3TC in an AZT-experienced population starting with under 200 CD4 cells, the panel decided it was time to abandon partially-suppressive regimens such as double-nucleoside combinations. After one year of treatment, such regimens render fewer than 10% of recipients undetectable (viral load <400 copies per milliliter), compared with 65-85% on triple-drug therapy including at least one new nucleoside and a potent protease inhibitor. Therefore, the new standard of care for *anyone starting anti-HIV therapy* should include a regimen designed to give a high likelihood that virus will become undetectable and stay that way for at least a year. This will minimize the chance of developing resistance, thereby prolonging immune function and delaying progression to AIDS.

"AI Preferred: Strong evidence of clinical benefit and sustained suppression of plasma viral load. One highly active protease inhibitor and two nucleoside reverse transcriptase inhibitors (NRTIs) (one drug from column A and two from column B):

Column A	Column B
Indinavir	AZT+ddI
Nelfinavir	AZT+3TC
Ritonavir	d4T+3TC
	d4T+ddI
	AZT+ddC

BII. Alternative: Less likely to provide sustained virus suppression; clinical benefit is undetermined:

* Two NRTIs + nevirapine, *or*
* Two NRTIs + saquinavir"

Unlike the protease combinations, only one study, INCAS, has shown nevirapine-containing regimens can render over 50% of participants undetectable after one year, with AZT/ddI/nevirapine. An AZT/ddC/nevirapine study conducted by the Inter-Company Collaboration (ICC), however, found no such benefit. Unlike the protease inhibitors, nevirapine has yet to demonstrate clinical benefit. Other NNRTIs such as delavirdine are even less impressive virologically, while more powerful candidates such as DMP-266 are moving rapidly through the pipeline. There is no firm evidence that the current FDA-approved saquinavir formulation can render even 40% of treatment-naive people undetectable when

used with two NRTIs.

"CI. Not generally recommended. Clinical benefit demonstrated, but initial virus suppression is not sustained in most patients.

* Two NRTIs, as listed above.

DI. Not recommended. Evidence against use, virologically undesirable:

All monotherapies
d4T+AZT
ddC+ddI
ddC+d4T
ddC+3TC"

WHAT TO SWITCH TO?

What drugs should be used in changing an antiretroviral regimens [a.k.a. "Never-Never Land"? A subgroup of the HHS Panel held discussions in March and April to discuss treatment options for this large and important group of people living with HIV. According to the CDC, 225,000 Americans are living with AIDS, and the number can be expected to grow as the death rate drops and people live longer on potent antiretroviral combinations. However, data on optimizing treatment in this population are scanty at best, and most of the recommendations were based on guesswork, or on small surrogate marker studies.

"Suggested New Regimens for Patients Who Have Failed Antiretroviral Therapy*

Prior regimen	Consider switching to
2 NRTIs + NFV + RTV + IDV + SQV	2 new NRTIs + RTV, or IDV, or SQV/RTV, or NVP/RTV, or NVP/IDV SQV/RTV or NFV/NVP NFV, or RTV, or RTV/SQV, or NVP/IDV
2 NRTIs + NVP	2 new NRTIs + a PI
2 NRTIs	2 new NRTIs + a PI
1 NRTI	2 new NRTIs + a PI 2 new NRTIs + NVP

* These suggested alternative regimens have not been proved to be clinically effective.

NRTI = nucleoside analogue RTI; NNRTI = non-nucleoside RTI; IDV = indinavir; NFV = nelfinavir; NVP = nevirapine; PI = protease inhibitor; RTI = reverse transcriptase inhibitor; RTV = ritonavir; SQV = saquinavir."

Use of viral load testing for HIV management. Viral load testing is key to assessing a given HIV-infected individual's prognosis, rate of progression, and need for antiretroviral therapy. Higher viral load means more rapid disease progression. Countless studies presented at and after Vancouver demonstrate this, and other studies (ACTG 116B, 175, 320) demonstrate that treatment-induced viral load reductions reduce the risk of disease progression as well. Consequently, periodic viral load monitoring is critical in HIV management for 1) diagnosis of acute or chronic HIV infection, 2) assessing prognosis in chronic infection, and 3) making decisions to start or switch treatment. Viral load should be tested before starting treatment, at one month and every three months after starting treatment, and be measured twice before switching, to reduce the risk of measurement error. Viral load should be taken in clinically stable individuals who have not had an intercurrent infection or recent immunization, which can cause transient spikes in viral load. It is important to stress that different viral load tests given different values. Few people know that the Chiron bDNA assay yields numbers about one half those given by the Roche RT-PCR kit, although both kits, used consistently, are equally predictive of prognosis and demonstrative of virological response to treatment. Therefore, it is important for people to always get their blood tested at the same lab, with the same kit.

Turning the new clinical practice guidelines into reality. However tortuous, writing the new treatment guidelines was the easy part. Turning them into reality will be another thing altogether. While a recent CDC study showed that last year, for the first time, the AIDS death rate fell by 12% nationwide, *it fell by fifty percent in ACTG 320.* Unequal access to state-of-the-art HIV care clearly reduces the impact of the new therapies on AIDS and death. AIDS deaths actually increased in 1996 among women and heterosexuals, barely dropped (by just 2%) in African-Americans, and dropped less in Hispanics than among non-Hispanic, non-African-Americans. It dropped by just 8% in the south, whereas in New York City, endowed with a generous state AIDS Drug Assistance Program (ADAP) and major Ryan White AIDS care funding programs, it dropped by 30%. In places with province-wide health care, such as British Columbia, by contrast, the death rate dropped by 50% or just as much as in ACTG 320.

Making the new treatment regimens available to all will be an enormous undertaking. Advocacy groups will have to focus on systemic health care reform, defending Medicaid and Medicare from Federal budget cutters, expanding coverage of state ADAPs through Ryan White titles I and II, pressuring health insurance companies and HMOs to cover viral load testing and combination therapy regimens, and working to force drug companies to charge fair prices for their drugs. After all, the taxpayer subsidized some of their pivotal clinical trials, such as ACTG 229 for saquinavir or ACTG 320 for indinavir, and the accelerated approval process greatly reduced development costs. Another enormous task will the construction of professional treatment education programs within AIDS service providers and community-based organizations to educate clients and communities about the complicated new treatment strategy, and to assist people with HIV in making treatment decisions, maintaining adherence to complex regimens, and staying abreast of a field in rapid evolution. Perhaps new federal program will be necessary to support broadened treatment education by community organizations in the era of potent polytherapy. TAG is

working with other advocacy groups in the ADAP Working Group, the Patients' Coalition, and with organizations such as the AIDS Treatment Data Network (ATDN), Gay Men's Health Crisis (GMHC), the National Association of People with AIDS (NAPWA), the National Minority AIDS Council (NMAC), Project Inform, and the People with AIDS Coalition (PWAC) to ensure that all people with HIV get the information and support they need to make informed treatment decisions in the new era.

PRINCIPLES OF HIV THERAPY (SUMMARY)

BACKGROUND

* HIV infection leads to progressive immune system damage in nearly all infected persons.
* HIV replication rates in infected persons can be accurately gauged by measurement of plasma HIV concentrations.
* The magnitude of HIV replication in infected individuals determines their rate of disease progression.
* HIV replicates actively at all stages of the infection.
* Active HIV replication continuously generates viral variants that are resistant to antiretroviral drugs.
* Combination antiretroviral therapy that suppresses HIV replication to undetectable levels can delay or prevent the emergence of drug resistant viral variants.
* Antiretroviral therapy-induced inhibition of HIV replication predicts clinical benefit.
* Repair of immune system function may be incomplete following effective inhibition of continuing HIV replication and damage by antiretroviral drug therapy.

PRINCIPLES

1. Ongoing HIV replication leads to immune system damage and progression to AIDS. HIV infection is always harmful and true long-term survival free of clinically significant immune dysfunction is unusual.

2. Plasma HIV RNA levels indicate the magnitude of HIV replication and its associated rate of CD4 T cell destruction, while CD4 T cell counts indicate the extend of HIV-induced immune damage already suffered. Regular, periodic measurement of plasma HIV RNA levels and CD4 T cell counts are necessary to determine the risk of disease progression in an HIV-infected individual and to determine when to initiate or modify antiretroviral treatment regimens.

3. As rates of disease progression differ among individuals, treatment decisions should be individualized by level of risk indicated by plasma HIV RNA levels and CD4 T cell counts.

4. The use of potent combination antiretroviral therapy to suppress HIV replication to below the levels of detection of sensitive plasma HIV RNA assays limits the potential for selection of antiretoviral-resistant HIV variants, the major factor limiting the ability of antiretroviral drugs to inhibit virus replication and delay disease progression. Therefore, maximum achievable suppression of HIV replication should be the goal of therapy.

5. The most effective means to accomplish durable suppression of HIV replication is the simultaneous initiation of combinations of effective anti-HIV drugs with which the patient has not been previously treated and that are not cross-resistant with antiretroviral agents with which the patient has been treated previously.

6. Combination antiretroviral therapy should be initiated and maintained using optimum schedules and dosages of each of the components of the treatment regimen.

7. The available antiretroviral drugs are limited in number and mechanism of action, and cross-resistance between specific drugs has been documented. Therefore, any change in antiretroviral therapy always increases future therapeutic constraints.

8. Women should receive optimal antiretroviral therapy regardless of pregnancy status.

9. The same principles of antiretroviral therapy apply to both HIV-infected children and adults, although the treatment of HIV-infected children involves unique pharmacologic, virologic and immunologic considerations.

10. Persons with acute primary HIV infections should be treated with combination antiretroviral therapy to suppress virus replication to levels below the limit of detection of sensitive plasma HIV RNA assays.

11. Antiretroviral treatment of persons who have experienced occupational exposure to HIV should be encouraged.

12. Until there are data to suggest otherwise, HIV-infected persons, even those with viral loads below detectable limits, should be considered infectious and should avoid sexual and drug-use behaviors that are associated with transmission or acquisition of HIV and other infectious pathogens.

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III. PROBLEMS WITH NEW ANTIRETROVIRAL DEVELOPMENT PLANS

This spring, we undertook to conduct a review of recently-approved antiretrovirals and experimental agents entering phase II/III trials, with a view towards exploring how the new RNA-based standard of care and potential regulatory changes might impact their development, and what sorts of information people with HIV and their physicians would want about new antiretrovirals. We found considerable confusion and disarray amongst industry about how the new standard of care and approval standard would affect their drug development plans, and indeed, believe that uncertainty about this impact may actually be slowing down development in some cases. We wrote to the sponsors of the new antiretrovirals and, again, found a spectrum of responses. Some companies, such as Agouron, DuPont Merck, Gilead, and Vertex, were forthcoming about their development plans, while others -- such as Glaxo Wellcome -- were downright obstructive, refusing to provide us with the information we needed to develop policy. While Hoffmann-LaRoche appeared initially interested in initiating a more open policy with the community, its motives for appearing to do so appeared linked to the plight of saquinavir rather than a fundamental change in the company's notoriously tight-fisted and tight-lipped corporate culture. Nonetheless, we hope that the larger pharmaceutical sponsors will take note of the greater openness of their smaller biotechnology competitors and enter into good-faith negotiations about their development plans in this exciting and confusing era.

We have focused on several examples from the three major classes of antiretroviral agents:

1. The nucleoside and nucleotide analogues, with Glaxo's abacavir (1592) and Gilead's adefovir dipivoxil (bis POM-PMEA);
2. The non-nucleoside reverse transcriptase inhibitors, with Pharmacia & Upjohn's Rescriptor brand delavirdine mesylate, and DuPont Merck's DMP-266: and
3. The protease inhibitors, with Agouron's VIRACEPT brand nelfinavir, Hoffmann-LaRoche's new saquinavir soft gel cap, and Glaxo Wellcome/Vertex's GW141/VX.

Things are moving too rapidly in the field for this to be a comprehensive overview, and we have not developed enough information about many interesting new approaches, such as ABT-538, CCR5 receptor blockers, F-ddA, integrase inhibitors, lobucavir, PMPA, or zinc finger inhibitors, to include them in our analysis here. We hope that the coming months will see an evolving consensus about how best to study new antiretroviral agents in the era of polytherapy and viral load-driven HIV treatment.

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IIIA. NUCLEOSIDE & NUCLEOTIDE ANALOGUES

i. Abacavir / 1592U89 (Glaxo Wellcome)

by Theo Smart

Abacavir (formerly known as 1592U89 and commonly referred to as '1592') is a lipophilic carbocyclic guanosine analog with good oral absorption and CNS penetration. Limited preliminary data suggest it also may be the most potent nucleoside analog antiretroviral yet tested in treatment-naive patients. The dramatic reductions in viral load (in the range of 1.4-1.8 logs below baseline) reported in one twelve-week dose-ranging study have led many activists to call for rapid development of and compassionate use access to the compound. Unfortunately, the pace of development has been excrutiatingly slow, and no further clinical data have been publicly released from any study of the drug, other than updates from the dose-ranging study, in over a year. The slow development of the drug stems from a number of factors, including Glaxo Wellcome's indecision over how it will market the drug, supply problems, and confusion about how to design of clinical studies of a new agent in the era or highly active antiretroviral therapy and utilization of viral load in the clinical management of people with HIV.

BACKGROUND

Glaxo has long seemed somewhat ambivalent about the abacavir. Several years ago, Glaxo used to own the rights to carbovir, a chemical antecedent to abacavir, but dropped the compound reportedly because of toxicity observed in animal studies. At this point, chemists from the old Burroughs Wellcome (BW) made slight structural modifications to carbovir that altered its toxicity profile, and took the new drug into clinic in late 1996. Shortly afterward, Glaxo and Wellcome (GW) merged, and the future of the compound plus two other nucleoside analogs under study by BW was in jeopardy, as the merged company already owned AZT and 3TC, a combination which would soon dominate the market. Some corporate decision-makers may have felt that there would be little advantage to GW in marketing yet another nucleoside analog.

Indeed, GW wasted little time in dropping one of the old BW drugs, a cytosine analog very similar to but reportedly more potent than 3TC, and then axed 935, a novel uridine analog, when its antiviral activity -- roughly equivalent to AZT's -- was deemed disappointing. Abacavir was next on the chopping block, but the company found itself in a bind when the early data on abacavir far exceeded anyone's expectations -- the drug's potency seemed similar to that of a protease inhibitor.

What could the company do? It would have been unwise to sell the drug because in a competitor's hands it might cut into sales of AZT / 3TC. So GW instead chose to develop the compound slowly, emphasizing the clinical evaluation of abacavir in combination with its own drugs, AZT, 3TC and 141W94. This was despite *in vitro* data suggestive of some cross resistance between abacavir and 3TC.

STRUCTURE & MECHANISM OF ACTION

Abacavir is a lipophilic carbocylic 2',3'-ene nucleoside analog, activated intracellularly to a triphosphate (TP) carbocyclic guanine analog, that acts as a reverse transciptase inhibitor. Guanine is one of the nucleotide bases of DNA. By acting as a defective decoy of this nucleotide, abacavir-TP is inserted by the HIV reverse transcriptase enzyme into the growing chain of HIV proviral DNA (K 2OnM). No additional nucleotides can be placed next to this defective guanine which disrupts viral DNA chain synthesis, aborting infection of the cell.

ANTIRETROVIRAL POTENCY

In vitro studies. Abacavir inhibits HIV clinical isolates in peripheral blood lymphocyte cultures with an average IC_{50} of 0.26 μM. This *in vitro* potency is similar to AZT's, which partly accounts for the surprise with which the clinical results were met. The increased *in vivo* potency is now explained by unusually efficient intracellular absorption and activation of the drug.

In vitro, abacavir is synergistic with the thymidine analog AZT, the non-nucleoside reverse transcriptase inhibitor, nevirapine, and Glaxo Wellcome's protease inhibitor 141W94.

CLINICAL DATA

Data presented in Vancouver AIDS Conference, and at the Drug Therapy for HIV Infection Conference in Birmingham, England, established that abacavir has unprecedented potency. Those data were drawn from study 2001, in which patients were treated with 200 mg tid, 300 mg bid, 400 mg tid or 600 mg tid of 1592 (twenty patients per arm). After four weeks of monotherapy, viral load fell by 1.48-1.84 logs (from a baseline range of 4.5-5.1 logs), and CD4 cell counts increased by 63 to 83 cells (from a baseline of 356 to 396 cells).

Patients then were randomized to continue monotherapy or to add AZT. At 12 weeks, viral load reductions ranged between 1.7-2.2 logs, and CD4 count increases were between 90-145 cells. There was no significant difference between the 1592 monotherapy and 1592/AZT combination arm in absolute reduction of viral load, but a higher percentage of patients on combination therapy (60% versus 20%) had viral load reductions that fell below the limit of detection (200 copies per ml).

In combination with 141W94: In one arm of a dose-ranging study of GW's protease inhibitor, 141W94, nine patients received abacavir, 300 mg bid in combination with 141W94 900 md bid. Two patients dropped out due to adverse events: one because of rash and dysarthria (difficultly speaking) and one because of nausea. After four weeks of therapy, the median decrease in viral load experienced by the remaining patients was 2.08 log (from a baseline of 4.19 log). CD4 counts increased by a median of 79 cells over a baseline of 223. Five of seven (71%) patients achieved viral load reductions that fell below 400 copies per ml.

ONGOING STUDIES

Protocol 2002 is a 24-week dose-evaluation study currently underway in Europe comparing 100, 300 and 600 mg bid. The study has enrolled sixty antiretroviral naive patients with CD4 cell counts> 100, and viral loads above or equal to 30,000 copies per ml. Subjects may elect to discontinue the blinded portion of the study and continue on AZT/ 3TC with abacavir if they reach one of a set of pre-defined criteria based on CD4 cell count, viral load or disease progression. Preliminary analysis of data from this study (out to week 4) and data from 2002 suggest that doses above 600 mg are roughly equivalent.

Protocol 2003 is being conducted in patients with extensive prior nucleoside analog therapy, CD4 cell counts above 100 and loads above 10,000 copies per ml. The 40 patients enrolled have one of four treatment histories: 1) at least 6 months prior d4T monotherapy; 2) six or more months of ddI with or without AZT; 3) twelve or more months or prior AZT monotherapy; or 4) at least 12 months of AZT/ 3TC combination therapy. Data analysis is pending.

RESISTANCE & CROSS RESISTANCE

Dr. Richard Harrigan from Glaxo Wellcome reported on the resistance profile of 1592 at the Fourth Conference on Retroviruses and Opportunistic Infections. *In vitro*, after four serial passages in the presence of increasing concentrations of drug, a mutation arises at the 184 codon on the reverse transcriptase enzyme. Dr. Harrigan noted that this is "the same mutation that causes high level resistance to 3TC, but interestingly, it only confers a marginal decrease in 1592 susceptibility." After several more passages, mutations at positions 65, associated with ddC resistance; 74 associated with ddI resistance; and/or 115 occur, which together with the 184 mutation confers a ten to twelve-fold decrease in susceptibility to 1592. Such isolates remain susceptible to AZT and d4T, however, and are only five-fold less susceptible to ddI and ddC. Any virus containing the 184 mutation is resistant to 3TC however.

The resistance profile may be slightly different in humans, particularly when the drug is used in combination with other antivirals. In fact, when the virus was passaged in vitro in the presence of both 1592 and AZT, only the mutation at position 65 was observed. (This combinatorial effect on resistance did not extend to the combination of abacavir and 3TC, however, as the same mutations occurred when abacavir was sequenced alone.)

In study 2001, after twelve weeks nearly 60% of viral isolates that could be assessed from patients on 1592 monotherapy had some mutation or combination of mutations at positions 65, 74 or 184 compared to roughly 13% in the virus taken from patients treated with AZT/ 1592. But perhaps the most promising observation from the study was that one patient who had the 184 mutation at baseline, experienced a one log reduction in viral load on 1592, and an additional log reduction when AZT was added. This suggests that 1592 may be active in some patients who have become resistant to 3TC.

This single patient anecdote may be misleading, however. Investigators (who wish not to be quoted at present) in 2003 privately report mixed results using abacavir in combination with stable antiretroviral therapy. Some of these patients appear to benefit from the addition of abacavir; some do not. As this

study includes patients with a history of prior AZT, AZT + 3TC, d4T, ddI (with or without AZT) treatment, final results may show whether pretreatment with any particular regimen prejudices against benefitting from abacavir.

The dreaded 151 mutation. A recently reported mutation in the reverse transcriptase enzyme at codon 151 that reportedly causes resistance to all marketed nucleoside analogs, apparantly defeats abacavir as well. Thus, abacavir therapy will be of no avail in pretreated patients with this mutation. How often the 151 mutation might occur in people taking abacavir is unknown.

The 184 mutation. That abacavir and 3TC share the 184 mutation should be a cause of concern, particularly to Glaxo Wellcome. It is possible that the use of abacavir in combination with AZT/3TC may only serve to speed the development of resistance to 3TC, and loss of both drugs' antiretroviral activity. In the patients pretreated with 3TC, the 184 mutation, particularly when combined with other mutations, may render abacavir useless. And if abacavir commonly causes the 184 mutation when used as a first-line treatment, it will render subsequent 3TC therapy useless. GW may find itself marketing a drug that competes with 3TC, anyway, and will not increase the company's market share. This again helps to explain the slow development of the compound.

An even more frightening scenario may emerge if all three or four mutations evolve in people treated with abacavir. First-line treatment with abacavir thus may destroy the likehood of subsequent benefit from any currently marketed nucleoside analog except perhaps AZT.

ADVERSE EVENTS

Animal and cell culture toxicology. The toxicity of abacavir in animal studies has been characterized by Dr. Steve Lafon of GW as "unremarkable." In laboratory studies, abacavir was relatively non-toxic to human bone marrow progenitor cells (BFU-E and CFU-GM cells; ICSO 110μM) and to human leukemic and liver tumor cell lines.

Human toxicology. Despite the positive press, abacavir treatment was associated with significant side effects in study 2001. These included nausea, headache, asthenia, diarrhea, insomnia, dizziness, vomiting, abdominal pain, rash and other conditions. Eleven of 80 patients experienced adverse events and laboratory abnormalities which were treatment-limiting or led to treatment discontinuation. These adverse events included suspected acute allergic reactions in two patients (symptoms included fever and rash, and in one subject, parasthesias); rash in one participant, dizziness, palpitations and photophobia in one patient; and nausea and/or vomiting in three subjects (one of whom also complained of fatigue). Laboratory abnormalities included one case of neutropenia, grade 3/4 ALT in one subject, decreased platelets in one patient and hypoglycemia in another.

In the European study 2002, the safety profile has been reportedly similar to that seen in 2001. The most common adverse events have been nausea, headache, asthenia, diarrhea, and abdominal pain.

PHARMACOKINETICS, FOOD & DRUG INTERACTIONS

In a placebo controlled phase I dose-escalation study (Protocol 131001), twelve out of eighteen patients were randomized to receive five escalating doses of abacavir (100, 300, 600, 900 and 1200 mgs) separated by a washout period of at least one week. The average T_{max} was 1.0-1.7 hours and the C_{max} was ranged between from 0.6-9.6 g/ml. The intracellular halflife of the drug's active metabolite is presently unknown. Food decreases the abacavir AUC by 5% and the C_{max} by 35%

Central nervous system penetration. Abacavir was designed to enter the central nervous system. In animals, its CNS penetration is comparable to AZT's. In HIV-infected adults, the average CSF:plasma ratio was 0.19, one- hour post-dose.

Drug interactions. Unlike the protease inhibitors, abacavir is not metabolized by the cytochrome p450 liver enzyme system. It is therefore less likely to have significant interactions with other drugs, save, perhaps other nucleoside analogs, as the drug may effect the intracellular triphosphorylation of other nucleosides.

NEW & PLANNED STUDIES

A number of abacavir studies started recently, and a few others are slated to begin this month or in August. GW is still putting the final touches on several of the protocols. In particular, the total number of patients to be enrolled, site selection and precise definition of virologic progression remain to be decided. In most of the studies, patients will have the option of going on open-label treatments if they meet this protocol defined criteria of progression after sixteen week on study. In some studies, this has been defined as two consecutive detectable viral loads (200 or 400 copies per ml); other options under discussion have been consecutive viral loads over 5000 copies per ml.

Antiretroviral-naive studies

Abacavir/Protease combination trial. Abacavir's potency and its CNS penetration provide clear rationale to evaluate it in combination with protease inhibitors. Study 2004 is a 48 week open label study in treatment-naive patients of abacavir plus the five major protease inhibitors: indinavir, ritonavir, saquinavir, nelfinavir and 141W94. There will be sixteen patients randomized to each arm of the study at eight different sites in the US. Participants must have at least 100 CD4 cells and a viral load of above 5,000 copies to enroll. Patients who progress virologically, as defined by the protocol (see below), prior to week sixteen may continue on randomization or discontinue the study. Patients who meet failure criteria after this point have the option of continuing abacavir with any approved antiretroviral regimen of their choice in addition to the options of quitting or remaining in randomization.

The 'three is better than one study': Abacavir versus AZT/3TC/abacavir. Study 3003 is an international study in antiretroviral therapy-naive patients with at least 100 CD4 cells. Patients will be randomized to receive abacavir alone or the incestous combination of Glaxo's three nucleosides for forty-eight weeks in a blinded fashion. Patients who meet protocol defined switch criteria after sixteen

weeks will have the option of continuing blinded in the trial (not bloody likely), quitting the study, or receiving abacavir in combination with any approved antiretroviral therapy.

Given that 60% of the patients in 2001 developed mutations conferring decreased susceptibility to abacavir by week twelve, the inclusion of an abacavir monotherapy arm would appear to be unethical, especially given the possibility that resistance-associated failure on abacavir could render subsequent therapy with most other nucleoside analogs useless. Furthermore, the result appears to be a foregone conclusion. Note also that GW chose to compare the monotherapy, and not an abacavir dual therapy, with the three sisters. The company clearly does not want to risk a study result in which AZT/ abacavir is found to be equivalent to the combination including 3TC. Nor is there a AZT/ 3TC arm lest abacavir monotherapy outperform GW's leading earners. What would be the profit in that?

Study 3005, the indinavir/combivir/abacavir trial. One of the more useful GW studies will try to show the equivalence of at least 48 weeks of indinavir plus combivir (the new combination AZT/3TC tablet) to the combivir/abacavir combination. To qualify patients must be over 16 years old, antiretroviral naive, with more than 100 CD4 cells and more than 10,000 copies of HIV RNA per ml. Patients who meet the protocol defined criteria, (two consecutive HIV RNA counts of over 400 copies per ml) after week sixteen will again be allowed to either drop out of the study, continue on blinded randomization, or receive open label study drugs plus any other currently licensed therapy.

Treatment experienced studies

The AIDS dementia complex trial. Study 3001 is a phase III international trial of abacavir in combination with antiretroviral therapy (stable for at least eight weeks prior to study entry). Subjects may not change or add to their background antiretroviral therapy during the randomized phase of the study. Patients will be randomly assigned to receive either abacavir (600 mg bid) or placebo for twelve weeks. CSF sampling is required at screening. Additional CSF sampling will be performed on consenting patients. Neurological, neuropsychological assessments as well as patient and caregiver questionaires will be collected for all participants. At the end of the 12 week randomization phase (or at the time of ADC progression, or after six weeks on study if the patient experiences severe drug toxicity related to background therapy and not abacavir) patients may continue open-label abacavir.

ACTG 320 rollover study: ACTG 368. This trial includes patients originally randomized to AZT/3TC on ACTG 320 or anyone with a CD4 cell count below 200 cells and more than three months prior therapy with AZT (or d4T) plus 3TC. All patients must be receiving AZT/3TC at the time of study entry and be protease and NNRTI-naive. Patients with over 50 CD4 cells will be randomized and followed for at least forty-eight weeks on:

* indinavir (tid or bid) + DMP 266, or
* indinavir (tid or bid) + DMP 266 + abacavir.

Patients with CD4 cell counts below 50 will be randomized only to either of the two indinavir tid regimens. Patients with confirmed detectable plasma HIV RNA (two consecutive viral loads above or

equal 200 copies/ml) will be offered open label indinavir/DMP 266/ abacavir.

The European antiretroviral-experienced study 3002. In this European study, patients with more than 12 weeks, and less than 18 months of prior antiretroviral therapy will be randomized to standard of care therapy with or without abacavir.

Pediatric studies. Study 3006 is a study in treatment-experienced children less than 13 years old and with less than 100,000 copies per ml. Patients will be randomized to receive abacavir or placebo plus AZTI 3TC for forty-eight weeks. Patients who meet a protocol defined switch criteria at 8 weeks or thereafter will have the option or receiving abacavir in addition with any approved antiretroviral therapy. Neurodevelopment assessments will be collected on all patients.

ACTG 321 is single and multiple dosing pharmacokinetic dose-escalation study in HIV-infected infants. All patients will receive standard postnatal AZT therapy in addition to single or multiple doses of abacavir. Results from the single dosing phase will be used in the multiple dosing part of the study.

To qualify, infants must be 0-72 hours old or 21-28 days old depending on which part of the study they enter. The treatment duration for patients in the multiple dosing phase of the study will be six weeks.

Compassionate use & expanded access. Glaxo Wellcome's current compassionate use! expanded access plans have deservedly come under much fire from the AIDS treatment advocate community. It is clear that the company had long planned to open a small token compassionate use program and then a much larger expanded acccess program only a few months before marketing approval. Glaxo may indeed have supply problems there was some trouble in formulating the drug that appears to have slowed GW's development plans by at least six to nine months. Glaxo says that it takes six months to produce each batch of drug. Nevertheless, activists last winter informed the company that a compassionate use program that did not supply drug to all people with very limited options would be unacceptable. The company has had more than enough time to find a way to address this need.

Rather than providing the drug to patients through their healthcare provider, as has traditionally been done, the abacavir compassionate use program distributes the drug only through selected sites worldwide (62 in the US). The program comprises three open label studies.

Pediatric study 3007. This program will be open to pediatric patients (between 6 months of age up to the 14th birthday) at high risk of progression or mortality as defined by viral loads of at least 100,000 copies/ml, a CD4% < 15% of total lymphocyte count despite therapy with commercially available antiretrovirals for at least 4 weeks. Patients intolerant to AZT, 3TC and ddI, or who have HIV-associated encephalopathy refractory to a AZT-containing regimen also will qualify. Size: 250 pts worldwide.

Dementia study 3010. To qualify for this program, patients must have severe dementia yet to be defined and diagnosed by a neurologist. All patients must have previously tried AZT. Size: 250 patients worldwide.

Study 3008. The program is open to anyone over 13 years old with a CD4 cell count < 100 cells, viral loads of at least 30,000 copies/ml who have been treated with at least two nucleoside analogs and one protease inhibitor. Patients who are intolerent to all commercially available therapy may also attempt to enroll. The company plans to gather data on surrogate markers, and adverse events through the selected sites.

The program's size is extremely limited. Initially, GlaxoWellcome wanted to offer drug for 2,000 patients worldwide. This has now been increased to nearly 4,000, by rolling out drug to 100 patients a week in the US, and at varying rates in other countries. There currently is no committment from Glaxo to triage the patients into the program based upon severity of illness. There is no plan to offer the drug to patients who cannot reach the clinical trial site, or who are homebound.

Expanded access. In March of 1998, Glaxo plans to release drug to up to nine thousand more patients. At present, the criteria for this program have yet to be defined. As the drug is expected to be approved and reach market only a few months after this date, it is clear that this expanded access is merely a premarketing program.

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IIIA. NUCLEOSIDE & NUCLEOTIDE ANALOGUES

ii. Adefovir dipivoxil / bis-POM PMEA (Gilead Sciences)

by Theo Smart

BACKGROUND

Adefovir dipivoxil is a nucleotide analog which has in vitro activity against HIV, HBV, HSV-1 and -2, EBV, HHV-6 and CMV. Despite the drug's broad spectrum activity, it has fallen through the cracks, overlooked by most activists and clinicians. The half log (70%) reduction in viral load that this drug achieved in studies of mostly antiretroviral-experienced people last year was overshadowed by the potency of abacavir, the protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Adefovir's potency also has been overshadowed by another Gilead drug further back in the pipeline, PMPA. The newer agent does not share adefovir's broad spectrum activity, but its anti-HIV potency is impressive. Well-publicized reports that dramatic potency — for example a single dose of PMPA blocked SIV infection in primates when given up to 24 hours after exposure, a feat not matched by any other agent — have led many activists to call for Gilead, a small company with limited resources, to drop the adefovir in favor of rapid development of PMPA. However, the oral formulation of PMPA has only recently entered phase I/II studies, and has yet to show antiviral activity in people.

Meanwhile, adefovir is now in phase III pivotal studies for HIV, as a CMV prophylaxis, and in phase IIs for HBV. Though not the most potent of agents, aside from abacavir and perhaps 3TC, the drug appears to be as potent as any of the nucleoside analogs in the treatment-experienced population. Few would dispute that agents such as AZT, d4T and ddI still have a role in combination regimens. And adefovir may be particularly useful in treatment experienced patients, since it has a unique resistance profile.

Structure and Mechanism of Action. PMEA (9-[2phosphonomethoxy)ethyl]adenine) is a nucleotide analog, which differs from a nucleoside analog by virtue of a phosphate — the drug is one step closer to activatation when it enters a cell. When fully phosphorylated, PMEA is an inhibitor of viral polymerases (and HIV's reverse transcriptases) with submicromolar K_i values versus HIV reverse transcriptase (K_i 0.01μM), HCMV, HSV, and HBV polymerase. The fully phosphorylated nucleotide competes with adenosine, one of the building blocks of DNA, for incorporation into DNA. In the case of HIV, once added to the growing chain of HIV proviral DNA, no additional nucleotides can be placed next to this defective adenosine, which disrupts viral DNA chain synthesis, and aborts infection of the cell.

Adefovir or bis(POM) PMEA (bis(pivaloyloxymethyl)-9-[2-(phosphonomethoxy)-ethyl]adenine) is actually the prodrug of PMEA with improved oral bioavailability, tolerability and antiviral activity (by virtue of improved intracellular metabolism).

ANTIRETROVIRAL POTENCY

In vitro studies. Adefovir potently inhibits HIV in a number of cell lines including monocytes and macrophages. The IC_{50} values are listed below.

IC_{50} (μM), HIV-1

Cell type	PMEA	Adefovir	AZT	Reference
MT-2	16	0.5	0.1	Srinivas
Lymphocyte C8166	3.5	--	--	Perno
M/M	0.025	--	--	Perno
PBMC				
activated	0.4	--	0.008	Shirisaka
resting	0.023	--	17.5	Shirisaka

In vitro, adefovir is synergistic with d4T, ddC, AZT, nelfinavir, ritonavir, and saquinavir.

Clinical data. Activity data have been reported from two dose-ranging studies of adefovir.

Study 402 was a double-blind placebo-controlled study that enrolled 36 patients with CD4 cell counts above 100, p24 Ag >50 pg/mL. Concurrent antiretroviral therapy was forbidden. Participants were randomized to take adefovir 125, 250, 500 mg or placebo for fourteen days (9 active/3 placebo per dose group). Results are shown below.

Antiretroviral Potency of Adefovir: Median HIV RNA Change

		Median log	Median log change from baseline	
Dose Group	N	Baseline	N	Week 2
Placebo	8	5.2	8	-0.1
125 mg	9	4.6	9	-0.4
250 mg	8	4.9	8	-0.6
500 mg	9	4.8	9	-0.6
All active	26	4.8	26	-0.5

p=0.03, comparison of dose groups.

There was no significant difference between the antiviral activity of dose groups, although further study of the 500 mg dose was discontinued because of a higher rate of adverse events (see below).

Gilead conducted a further study to determine whether there was a difference between the doses over time. Study #403 randomized seventy patients (75% nucleoside experienced) with CD4 cell counts over 200 to twelve weeks on adefovir monotherapy 125 and 250 mg or placebo. There was no difference

in viral load changes between the two doses (median reduction 0.5 log) during the initial phase of the study. There was a median increase of 45 CD4 cells over the twelve week period.

After four weeks of washout, patients were allowed to restart adefovir in combination with concomitant antiretrovirals for six months. Sixteen patients who continued adefovir as a monotherapy had a 0.6 log reduction at week 24 of the maintenance phase in viral load from their new baseline, as did eleven patients who took adefovir with other antiretrovirals. It is unclear why there was no additional increase in viral load among the patients on other drugs, although it is possible that they may have initiated the other agents during the washout period. Also, adefovir does not have synergistic activity with all other nucleoside analogs, such as 3TC, and coadministration may even be slightly antagonistic.

RESISTANCE & CROSS RESISTANCE

As noted above, adefovir's effect as a monotherapy appears to be fairly durable with antiviral activity sustained out to a least nine months in patients who have been in long-term follow-up for that long. Most importantly for people who have exhausted most of the other antiretrovirals options, viral isolates resistant to almost all of the other nucleoside analogs and NNRTIs remain susceptible to adefovir.

Gilead has conducted a number of in vitro studies to predict what mutations might be associated with decreasing susceptibility to adefovir. In one experiment, the virus (HIV IIIb) was grown in MT2 cell cultures in the presence of drug. The drug concentrations were aggressively increased with each serial passage. After 8-12 passages a unique mutation at codon 70 occurs which causes a 9-fold decrease in susceptibility to adefovir. In another experiment in H9 cell lines with HIV_{LAI}, concentrations of drug were increased more gradually. After more than thirty serial passages, a mutation was detected at position 65, which decreased susceptibility to adefovir by sixteen-fold. This mutation has been observed in 10-15% of patients treated with ddC. Aside from this, adefovir retains its activity against isolates resistant to all other reverse transcriptase inhibitors, including those containing the 151 mutation with confers resistance to AZT, ddI, ddC, d4T, 3TC and abacavir.

Over long-term follow-up of the ongoing clinical studies, researchers from Gilead have had little success in finding mutations in the reverse transcriptase enzyme in patients treated with adefovir (abstract 216). The mutation at position 70 was observed in some viral isolates from one patient on adefovir monotherapy. Even so, at this timepoint the patient had a 0.9 reduction of viral load from baseline. Virus containing this mutation is 3- to 4-fold less competent than wild type virus, which could explain the continued suppression of viral load. Alternatively, Gilead may simply have caught the beginning of resistance and drug failure. Only a few other conserved mutations were observed, but in patients on concurrent therapies, all of whom continued to sustain reductions in viral load.

ADVERSE EVENTS & DRUG INTERACTIONS

The adverse events experienced on adefovir are primarily gastrointestinal.

In study 402, there were few adverse events in the two lower doses. Four out of 18 patients

experienced nausea, one case of vomiting, and two cases of eructation. At the discontinued higher dose, nausea, anorexia, vomiting, and flatulence were all observed. More adverse events occurred during the longer follow-up of study 403 (below).

Adverse Events: Study 403

Grade 2-4 events	Placebo	125 mg	250 mg
N	24	24	24
Nausea	0	3	6
Diarrhea	1	2	4
Asthenia	2	1	4
Headache	1	2	1
Pain	1	2	1
Sinusitis	2	3	0

A number of other events and laboratory abnormalities have been reported in a study #408, an ongoing 48-week pivotal phase II/III study with a targeted enrollment of 400, that began last June. This study is using the 120 mg dose. As of the beginning of March, at least twenty of 283 patients enrolled have discontinued study drug, seven due to patient/investigator request, six due to GI complaints, two because of fatigue, one case each of elevated creatinine and ALT, and three because of events unrelated to study drug. A total of 29 patients have experienced serious and grade 3/4 events. Thirteen events in eleven patients that were considered by the investigator to be possibly related to study drug included: 8 ALT/AST elevations, 2 CPK elevations, 1 bilirubin elevation, 1 elevation of creatine and 1 hospitalization due to fever, dyspnea, and weakness.

The creatinine elevation is of some certain because of the severe renal toxicity associated with another Gilead nucleotide analog, cidofovir. Gilead notes that each case of elevated creatinine observed has been reversible. However, the company has instituted more conservative guidelines for creatinine monitoring and dosing adjustments.

Adefovir metabolism also depletes levels of L-carnitine, necessitating supplementation with oral L-carnitine 500 mg per day.

PHARMACOKINETICS, FOOD & DRUG INTERACTIONS

Adefovir has a long intracellular halflife that allows for once-daily dosing. Adefovir has a terminal serum half-life of approximately 5 hours. Its Cmax is dose proportional at the doses tested. It is renally excreted in unchanged form. There appears to be no drug accumulation over time.

Food effects. In a fasted state, adefovir is approximately 30% orally bioavailable. Food increases the oral bioavailability to 40%.

Dosing requirements. Based upon the dose-evaluation studies, Gilead chose to use 120 mg dose in a

number of its major pivotal. However, no dose-response was noted in the dose-ranging studies. Thus, it may be possible to use an even lower dose without losing antiviral activity. Several upcoming small studies, and perhaps a compassionate use program will compare 60 to 120 mg per day.

ONGOING & PLANNED TRIALS

Gilead has outlined an ambitious clinical development plan for adefovir. Most of these studies are currently underway, except where noted.

Study 408: Pivotal surrogate marker trial. Study 408 began last June at 35 centers across the US. It is now almost fully enrolled with 400 patients with CD4 cell counts between 200-500, and viral load over 2,500 copies per ml. Participants are randomized to adefovir 120 mg daily or placebo in combination with continued stable antiretroviral therapy for 24 week, followed by twenty four weeks of open label adefovir. Primary endpoints are CD4 and HIV RNA $DAVG_{24}$.

Study 407, the CPCRA clinical endpoint study. This study is particularly ambitious, seeking to randomized 2,160 patients, with AIDS or with 100 cells or less, to adefovir (120 mg daily) or placebo both in combination with concommitant antiretroviral therapy (with change of concurrent therapy permitted). Unfortunately, since opening in January, the study has only enrolled 200 patients. The slow accrual may be due to more intensive safety and virologic monitoring required for the first 400 patients. Dr. Jim Rooney of Gilead says that he believes that enrollment should pick up after these patients are enrolled, since only clinical events (including progression of CMV disease) will be monitored in the remaining patients. The current plan is for the study to last around two and a half years (12 months after the last patient is enrolled). Given the slow accrual, the potency of current antiretroviral therapies, and the ability to switch or add drugs in this study, it is unclear when or whether the study will be able to show a statistically significant clinical result.

Gilead may be able to prove a statistically signicant benefit with a meta-analysis, by combining the CPCRA study results with a virtually identical trial being conducted in Europe and Australia. Study 410, or the ADHOC trial will also randomize ~2,000 patients with 100 CD4 cells or less to standard therapy plus adefovir or placebo. The study's endpoints will be survival and end-organ disease.

Lest adefovir come to market with no specific information about how to use it with other antiretrovirals, Gilead is initiating a number of smaller surrogate marker studies of specific combinations in early, intermediate, and advanced disease, including studies in protease failures.

Study 411 will be an open label, randomized 48-week trial comparing triple and quadruple combinations in 100 antiretroviral-naive patients with more than 100 CD4 cells, and viral loads over 5,000 copies per ml. Endpoints will be changes in HIV RNA, CD4s and safety. There will be five arms with 20 patients each: adefovir + indinavir + AZT/3TC; adefovir + indinavir + AZT; adefovir + indinavir + 3TC; adefovir + indinavir + d4T, and indinavir + AZT/3TC.

Study 415 (ADHAART) will evaluate whether adefovir can extend the durability of highly active

antiretroviral therapy (HAART). The trial will include around 60-120 patients on 3 months of stable HAART, CD4 cell counts over 200, and viral loads below 500 copies per ml. Participants will be randomized to continue HAART alone, or add adefovir, and will continue for 48 weeks. Study endpoints are time to return of viral load to detectable, and time to eradication of tissue burden.

Study 417 will be a blinded dose comparison and triple combination 48-week study in at least 120 patients (Gilead is considering increasing the sample size to 200). The study will randomize subjects with CD4 cell counts over 100 and no prior protease inhibitor therapy to receive adefovir (60 or 120 mg daily) plus 1) nelfinavir/saquinavir (soft gel), 2) nelfinavir plus a nucleoside analog, or 3) saquinavir (soft gel) plus a nucleoside analog. The study will compare changes in viral load and CD4 cell counts between both doses, and between the three treatment arms.

ACTG 359 is a blinded triple/quadruple combination study in 400 indinavir failures, with viral loads over 5,000 copies per ml. Changes in HIV RNA and safety will be monitored for 24 weeks, with a possible 24 week extension. The study arms are 1) saquinavir/ritonavir + adefovir, 2) saquinavir/ritonavir + adefovir + delavirdine, 3) saquinavir/ritonavir + adefovir + DMP 266, 4) saquinavir/ritonavir + DMP 266, and 5) saquinavir/ritonavir + delavirdine. [what's the current status on nelfinavir???]

Study 419 (the Stanford study) will be in thirty patients with over 100 CD4 cells, viral loads over 5,000 and with more than six months prior protease and nucleoside analog therapy. Participants in the 48 week study will be randomized to adefovir + nelfinavir + saquinavir + nevirapine, or nelfinavir + saquinavir + d4T + ddI.

Study 418, the Pediatric study. In this 24-week trial, 30-40 protease inhibitor-naive HIV positive children over 20 kg in weight and able to swallow pills will be randomized to adefovir (1.5 or 3.0 mg/kg) for two weeks. Then patients will add nelfinavir and another nucleoside analog. The study will monitor adefovir pharmacokinetics, and multiple dose safety, and changes in HIV RNA and CD4 cells.

Expanded access & compassionate use. Gilead has made a committment to open an expanded access program before the end of the year. Just when is currently the subject of negotiation. Aside from using such a program to compare the 60 and 120 mg dose, the company is unsure how to design a program that does not interfere with the adefovir pivotal clinical endpoint study. This study is enrolling very slowly, and randomizes volunteers with less than 100 CD4 cells to receive adefovir or placebo in addition to standard of care medications. As it is currently designed, patients who have exhausted all or most therapeutic options may enroll in the study, and be randomized to either placebo or what is almost certainly suboptimal therapy. The most ethical solution would be to exclude such individuals and through expanded access offer them adefovir and possibly other experimental antiretrovirals such as abacavir and DMP 266. Word of an expanded access program also might increase interest in the drug, and patients who qualify for the ongoing clinical endpoint study could be referred to their local trial sites, expediting accrual. As Gilead plans to file for approval sometime next summer (1998), the company needs to reach a decision quickly. The company claims it is interested in a program that allows access with other antiretrovirals, but it is not clear whether the necessary negotiations can be completed at this late a date.

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IIIB. NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)

i. Delavirdine Mesylate / Rescriptor™ (Pharmacia & Upjohn)

by Spencer Cox

BACKGROUND

Delavirdine mesylate is an inhibitor of the HIV reverse transcriptase enzyme. Unlike the nucleoside analogue reverse transcriptase inhibitors (RTIs), non-nucleoside RTIs (NNRTIs) such as delavirdine do not act as DNA chain terminators. Instead, delavirdine binds directly to reverse transcriptase and blocks RNA- and DNA-dependent DNA polymerase activities. Delavirdine is the second NNRTI to receive marketing approval from the US Food & Drug Administration (FDA), after Boehringer Ingelheim's Viramune™ brand nevirapine.

NNRTIs have a spotty history as anti-HIV therapies. The earliest products to enter the clinic were abandoned when monotherapy trials showed that, while the drugs were initially very potent, resistance developed rapidly and surrogate effects were short-lived following initation of therapy. Even today, with two NNRTIs approved and several others in development, the role of these drugs in the treatment of HIV remains unclear: most have major interactions with protease inhibitors that have not yet been well-characterized, and controversies remain about their potency and capacity to produce cross-resistance within the class.

Indication. The Rescriptor® labeling indication is confusing, due to the failure of studies to suggest efficacy or, in some studies, antiviral activity after four weeks. According to the label, "Rescriptor tablets are indicated for the treatment of HIV-1 infection in combination with appropriate antiretroviral agents when therapy is warranted. This indication is based on surrogate marker changes in clinical studies. Clinical benefit was not demonstrated for Rescriptor based on survival or incidence of AIDS-defining clinical events in a completed trial comparing Rescriptor plus didanosine with didanosine monotherapy. Resistant virus emerges rapidly when Rescriptor is administered as a monotherapy. Therefore, Rescriptor should always be administered in combination with appropriate antiretroviral therapy." (Pharmacia & Upjohn, 1997). The recommended dosage for Rescriptor tablets is 400mg (four 100mg tablets) three times daily. Rescriptor has not been evaluated in children under 16 years of age, and no pediatric dosing recommendations are offered.

About the sponsor. Pharmacia & Upjohn, Inc., is a research-based, pharmaceutically focused company formed by the 1995 merger of Pharmacia AB (Sweden) and The Upjohn Company (US). Pharmacia & Upjohn has more than 30,000 employees and, in 1995, had annual sales of approximately $7 billion. Pharmacia & Upjohn is the ninth largest pharmaceutical company in the world. Its key areas of research focus include infectious diseases, oncology, inflammatory diseases, metabolic diseases, and nervous-

system diseases. Key products manufactured by Pharmacia & Upjohn include the antibiotics clindamycin (Cliacin/Dalacin) and cefpodoxime (Vantin), the anti-TB and MAC drug rifabutin (Mycobutin), Genotropin (rHGH) for treatment of dwarfism, Halcion for insomnia, Xanax for anxiety, and adriamycin for various cancers. After an accelerated NDA was submitted to the FDA for Pharmacia & Upjohn's Rescriptor® brand delavirdine in the second quarter of 1996, the agency's Antiviral Drugs Advisory Committee split evenly on a recommendation to approve the drug. Approval was finally granted in March of 1997. Pharmacia & Upjohn is also working on a new line of antibiotics that may be effective against drug-resistant gram-positive bacteria, and is currently in phase II testing.

Mechanism of activity. HIV is a retrovirus, which means that it stores its genetic material as RNA, rather than as DNA. In order to infect a human cell, HIV's RNA must be converted to DNA. This conversion is accomplished by a viral enzyme called reverse transcriptase. NNRTIs, including delavirdine, bind to reverse transcriptase, blocking its activity. HIV-2 is not inhibited by delavirdine, and HIV-1 group O, a group of highly divergent strains that are not common in North America, may not be inhibited by delavirdine.

ANTIRETROVIRAL POTENCY

Test-tube studies. In vitro, delavirdine is effective against infected monocytes, lymphoblasts, and plasma lymphocytes from both laboratory and clinical (wild-type) HIV-1 strains. Its 50% inhibitory concentration (IC_{50}) for clinical isolates ranged from 0.001 to 0.69 micromolars (FM). The mean 90% inhibitor concentration (IC_{90}) in clinical isolates ranged from 0.04 to 0.10 FM respectively. *In vitro*, delavirdine is additive or synergistic with AZT, ddI, ddC, 3TC, interferon-α, and protease inhibitors. However, these results may not be relevant *in vivo*, since test-tube cultures lack the hepatic cytochrome p450 system through which all protease inhibitors (as well as the NNRTIs) are metabolized, leading in some cases to *in vivo* pharmacokinetic synergy or antagonism which would not be predicted *in vitro*.

Clinical trials. Three major clinical trials have been conducted to assess the *in vivo* effects of delavirdine on CD4 cell counts, plasma HIV RNA levels, and rates of clinical disease and death.

Study 0021 compared delavirdine plus AZT to AZT monotherapy in 718 HIV-infected patients who were treatment-naïve or who had received less than six months of prior AZT reatment. Mean baseline CD4 cell count was 334 and baseline plasma HIV RNA was 5.25 $\log_{10}$ copies/mL. Participants were treated with 200 milligrams (mg) of AZT thrice daily (tid), or with delavirdine at doses of 200, 30, or 400 mg tid in combination with AZT. At 24 weeks, there was no significant difference in CD4 counts between the delavirdine-containing arms and the AZT arm. Patients treated with delavirdine in combination with AZT experienced a reduction of approximately one log in plasma HIV RNA levels at week four, as compared to a reduction of only about 0.5log in patients treated with AZT monotherapy. By week 24, the combination therapy arm had about an 0.7 log drop in HIV RNA levels, while the AZT monotherapy arm had an 0.4log reduction.

Study 0017 compared ddI monotherapy to combination treatment with delavirdine and ddI in 1,190 HIV-infected patients who had received up to four months of prior ddI therapy. Mean baseline CD4 cell

count was 142 and mean baseline plasma HIV RNA was 5.77 log copies/mL. Patients were treated with ddI (dosing adjusted for body weight), with or without 400 mg delavirdine tid. At week eight, patients treated with the combination therapy arm experienced a CD4 increase of about 30 cells, while patients treated with ddI monotherapy had a CD4 cell increase of about 15. By week 24, there was essentially no difference in CD4 cell counts. Patients treated with the ddI/delavirdine combination experienced an average reduction of 0.9log HIV RNA copies/mL at week four, as compared to a reduction of about 0.5 log copies in patients treated with ddI alone. By week ten there was essentially no difference between the treatment arms. At 24 weeks, no difference could be seen between rates of clinical illness and death between the two treatment arms.

ACTG 261 was a study comparing four treatment regimens (delavirdine/ddI vs. delavirdine/AZT vs. delavirdine/ddI/AZT, vs. AZT/ddI) in 544 HIV-infected patients who were either treatment naïve, or who had fewer than six months prior treatment with either AZT or ddI. Thirty-seven percent of patients reported prior therapy. Mean baseline CD count was 296 and median baseline plasma HIV RNA was 4.45 log copies/mL. Treatment doses were 400 mg delavirdine tid, 200mg AZT tid, and ddI dosing adjusted by body weight. Through week 32, no significant difference was seen in CD4 cell counts or in plasma HIV RNA between the three-drug combination of delavirdine, AZT and ddI as compared to the two-drug combination of AZT and ddI.

Pediatrics. The pharmacokinetics of delavirdine have not been studied in patients younger than 16.

Gender. In study 021, which enrolled 139 (19%) women among its 718 participants, the mean delavirdine area under the curve (AUC) was 31% higher in women than in men, and the mean trough concentration is 80% higher in women than in men. However, no dose adjustment is recommended (Pharmacia & Upjohn 1997b).

Pregnancy. No studies of delavirdine have been conducted in pregnant women. Delavirdine has been categorized as pregnancy category C, which means that the drug has been shown to cause birth defects in animals. In particular, the drug caused heart defects in rats when administered early in pregnancy at doses that produced systematic exposure comparable to expected human exposure to the drug at normal doses. Additionally, reduced pup survival was seen in rats at exposure levels approximately equal those expected in humans.

High doses of delavirdine (approximately six-fold higher than expected human concentrations) also induced miscarriages in rabbits.

Of seven unplanned pregnancies in women taking delavirdine, three were ectopic pregnancies, three were normal births, and one infant was born prematurely with a heart defect similar to those seen in rats treated with delavirdine.

Race & ethnicity. No significant differences were seen in delavirdine pharmacokinetics across different racial or ethnic groups.

Hepatic or renal impairment. The pharmacokinetics of delavirdine have not been studied in patients with hepatic or renal impairment.

RESISTANCE & CROSS RESISTANCE

Following treatment with delavirdine, rapid emergence of HIV strains that are cross-resistant to other non-nucleoside reverse transcriptase inhibitors (NNRTIs) has been observed *in vitro*, including mutations at positions 103 and 181. Delavirdine may confer cross-resistance to other NNRTIs, although the various manufacturers offer conflicting claims in this regard.

ADVERSE EVENTS & TOXICITY MANAGEMENT

Studies 0017 + 0021 : Pooled Data on Moderate or Severe Adverse Events Occurring in ≥2% of Study Participants (%)

	Study 0017		Study 0021	
	ddI	ddI+DLV	AZT	AZT+DLV
Headache	4.7	5.6	4.8	5.6
Fatigue	2.7	2.9	4.8	5.2
Nausea	3.4	4.9	6.6	10.8
Diarrhea	4.4	4.5	2.2	3.5
Vomiting	1.2	2.4	1.1	2.8
Increased SGPT	3.6	5.2	0.7	2.4
Increased SGOT	3.0	4.5	0.7	1.7
Rash	3.0	9.8	1.5	12.5
Maculopapular rash	2.0	6.6	1.1	4.5
Pruritis	1.7	2.2	1.5	3.1

Clearly rash, a side effect shared by the entire class of NNRTIs, is the most common serious toxicity, occurring in 18% of all patients in combination regimens in phase II or III studies who received the recommended dose of delavirdine. Forty-two to fifty percent of patients treated with 400 mg delavirdine tid in studies 0021 and 0017 experienced a rash. 4.3% of these patients discontinued treatment due to rash. Serious rashes occurred in 10-12% of patients receiving the approved dose. The manufacturer notes that "the majority of rashes ... occur within 1 to 3 weeks after initiating treatment... The rash normally resolves in 3 to 14 days and may be treated symptomatically while therapy ... is continued. Any patient experiencing severe rash or rash accompanied by symptoms such as fever, blistering, oral lesions, conjunctivitis, swelling, muscle or joint aches should discontinue medication and consult a physician." Unofficially, the company notes that , in most patients, the rash can be treated through using an antihistamine such as Benadryl to treat symptoms.

The mechanism of the rash remains unknown.

In general, no laboratory abnormalities occurred more frequently in patients taking nucleosides in combination with delavirdine than occurred in patients taking nucleosides alone. The one exception was study 0021, in which patients treated with AZT were about twice as likely to develop neutropenia as patients taking AZT in combination with delavirdine.

*Frequency (%) * of Clinically Important Laboratory Abnormalities*

	Study 0017		Study 0021	
	ddI	ddI+DLV	AZT	AZT+DLV
N	591	594	271	287
Neutropenia (ANC <750/ mm^3)	6.7	5.7	7.7**	3.5
Anemia (Hgb <7.0g/dL)	0.2	0.7	1.1	1.0
Thrombocytopenia (platelets <50,000/mm^3)	1.4	1.5	0.0	0.0
ALT (>5.0 x ULN)	4.6	6.7	3.7	3.8
AST (>5.0 x ULN)	4.9	5.6	3.0	2.1
Billibrubin (>2.5 ULN)	0.7	0.5	0.4	1.0
Amylase (>2.0 ULN)	6.5	5.2	1.1	0.0

[ANC = absolute neutrophil count; ULN = upper limit of normal]

* Percentage was based on the number of patients for which data on that laboratory test was available.

** Significant ($p<.05$) delavirdine + AZT vs. AZT.

PHARMACOKINETICS, FOOD & DRUG INTERACTIONS

Delavirdine is easily absorbed when given in oral form, with peak steady-state plasma concentrations of $35\pm20\ \mu M$ at one hour after dosing. Trough concentrations was $15\pm10\ \mu M$, and area under the curve was approximately $180\pm100\ \mu M/hr$. Bioavailability of the drug can be increased by about 20% by dissolving tablets in water. The plasma half-life of delavirdine increases with dose; mean half-life following 400 mg tid is 5.8 hours.

Delavirdine may be taken with or without food. Although a high-fat meal may lower the peak plasma concentration and area under the curve of a single delavirdine dose significantly, during multiple-dose studies, trough concentrations and area under the curve were not significantly affected by normal diet.

In the bloodstream, approximately 98% of delavirdine binds to pplasma proteins (primarily albumin). Delavirdine levels in the CNS fluid, saliva and semen are generally about 20%, 6% and 2% respectively of plasma delavirdine concentrations. Approximately 44% of a dose is excreted in the stool, and approximately 51% in the urine.

The main physicological interaction of delavirdine is with a family of liver enzymes known as the cytochrome p450 isoforms. Delavridine is primarily metabolized by the CYP3A isoform, but *in vitro* data also suggest metabolism by CYP2D6. Delavirdine inhibits CYP3A activity, slowing its own metabolism. *In vitro* studies have also shown that delavirdine reduces CYP2C9 and CYP2C19 activity.

Because this liver enzyme system is also responsible for metabolizing a number of other commonly-used drugs, delavirdine can have a significant effect on their plasma half-life and plasma concentration.

Interactions between Delavirdine & Other Commonly Used HIV/AIDS Drugs

Drug	DLV Dose	N	Interaction
Antacids (alumina and magnesia oral suspension)	300 mg single-dose	12	41±19% reduction in delavirdine AUC
Clarithromycin (500 mg bid)	300 mg tid	6	44+50% increase in delavirdine AUC; 100% increase in clarithromycin AUC, 75% decrease in 14-hydroxyclarithromycin AUC
ddI (125 or 250 mg bid)	400 mg tid	9	20% decrease in both ddI and delavirdine AUC
Fluconazole (400 mg/qd)	300 mg tid	8	No change
Fluoxetine	Not given	36	50% decrease in delavirdine trough levels
Indinavir (400 mg single-dose)	400 mg tid	14	Increases indinavir AUC to levels resembling 800mg IDV alone. Dose reduction to 600mg IDV tid is recommended.
Indianvir (600 mg single-dose)	400 mg tid	14	Increases indinavir levels to +40% of standard 800mg IDV dose levels. Dose reduction to 600mg IDV tid is recommended.
Ketoconazole	Not given	26	Increases delavirdine trough levels by 50%
Pheytoin, phenobarbital & Carbamazepine	Not given	8	Substantial reduction – comadministration is not recommended
Rifabutin (300 mg qd)	400 mg tid	7	80±10 decrease in delavirdine AUC, ≥100% increase in rifabutin AUC. Coadministration is not recommended.
Rifampin (600 mg qd)	400 mg tid	7	96+4% decrease in delavirdine AUC. Coadministration is not recommended.
Ritonavir (300 mg bid)	400 or 600 mg bid	13	No change in ritonavir or delavirdine pharmacokinetics.
Ritonavir (600mg bid)	NA	0	Not available
Saquinavir (600mg tid)	400 mg tid	7	500% increase in saqinavir AUC, 15±16% decrease in delavirdine AUC
TMP/SMX (Bactrim, Septra)	400 mg tid	311	No effect
Zidovudine (AZT)	NA	NA	No effect

[NA = not available.]

Safety Considerations: A number of drugs should *NOT* be taken with delavirdine:

* The anticonvulsants phenytoin, phenobarbital, and carbamazepine
* The Antimycobacterial drugs rifabutin and rifampin
* The anti-ulcer drugs cimetidine, famotidine, nizatidine and ranitidine.

Safety considerations. A number of drugs have not been tested for use with delavirdine, but are expected to have major interactions that could result in "potentially serious and/or life-threatening adverse events":

* The antihistamines terfenadine and astemizole
* The sedatives alprazolam, midazolam and triazolam
* The digestive aid cisapride

Fnally, ddI and antacids should be taken at least an hour before or after taking delavirdine.

PRICING

At $2,250 per year, delavirdine's cost is comparable to the nucleoside analogs, and to that of nevirapine.

CURRENT & PLANNED POST-MARKETING STUDIES

0063	A 24-week study of AZT/3TC/indinavir vs. AZT/delavirdine/indinavir in 90 HIV-infected patients with CD4<500, HIV RNA >20,000 copies, and <6mos of prior AZT
0073	A 24-week study of two nucleoside analogs (2NAs) + nelfinavir, vs. NA/delavirdine/nelfinavir vs. 2NAs/nelfinavir/delavirdine in 160 PI & NNRTI-naïve patients with >60,000 HIV RNA copies and ≥50 CD4+ cells.
0074	A 24-week study of AZT/3TC/indianvir, vs. AZT/delavirdine/indiinavir, vs. 3TC/delavirdine/indinavir vs. AZT/3TC/indinavir/delavirdine in 160 treatment-naïve patients with ≥50 CD4 cells and >60,000 HIV RNA copies.
Interaction studies	Studies are planned or underway to evaluate delavirdine in combination with ritonavir and saquinavir.
Dosing	Several studies may evaluate BID dosing of delavirdine in combination with protease inhibitors.

Pediatrics	Studies are planned to evaluate delavirdine in pediatric patient populations.

DISCUSSION

In general, the optimal use of NNRTIs has not been determined. However, of this class, the potential utility of delavirdine is particularly difficult to classify. The drug is weakly potent, with no demonstrated clinical benefit, and virologic activity is seen generally for only four to eight weeks when the product is used in combination with one nucleoside analog. While pharmacokinetic interactions with protease inhibitors might be exploited to increase the efficacy of both delavirdine and of modestly active drugs such as saquinavir, these interactions have only been described at the grossest pharmacokinetic level, with no data available regarding safety or activity. Anecdotes have abounded, ranging from tales of miraculous responses effected by the combination of delavirdine with Crixivan, to horror stories about serious liver toxicity caused by the same combination.

Because of concerns about cross-resistance to DMP-266, an NNRTI in development by DuPont Merck which seems much more potent than either delavirdine or nevirapine, the current marketed NNRTIs seem to be relegated to a role in salvage therapy in patients who have failed at least one protease inhibitor, and who , due to extensive pre-treatment, have limited options for combinations with multiple nucleoside analogs.

To some extent, Pharmacia & Upjohn are clearly victims of the rapid changes in clinical care for HIV-infected patients: their studies were designed before the protease revolution, and even before the clinical validation of combination therapy. As a consequence, most of their registration trials involved use of delavirdine in combination with a single nucleoside analog. It may be that, in combination with more potent drugs, delavirdine can make a substantial contribution to virologic suppression. However, in the absence of more useful empirical data, doctors are left to prescribe the drug based on a combination of theory and intuition – a poor rationale for prescribing anti-HIV medication, and one that can be harmful by compromising the utility of drugs used in combination and producing cross-resistance to other, more potent drugs.

Perhaps the most problematic aspect of delavirdine is its interaction profile: the drug has serious pharmacokinetic interactions with several important therapies used in the treatment of HIV-infected patients, of which only a few have been well-characterized. While there is great interest in combining NNRTIs with protease inhibitors, Pharmacia & Upjohn presented spotty interaction data on these combinations, mostly from studies of HIV-negative patients (who may differ in absorption from HIV-infected patients), in single-dose studies, or at doses that differ from current recommended doses. Anecdotally, these combinations may be associated with serious side effects, and longer-term studies are needed to define the potency of delavirdine in combination with protease inhibitors. Pharmacia & Upjohn have planned several such studies.

However, the FDA's decision to approve the drug based on very limited data on clinical activity (let alone efficacy) raises troubling questions about the standard of approval: the agency should define more clearly

how changes in HIV RNA levels are to be measured, and promulgate guidelines for the design and conduct of clinical trials to evaluate the contribution of a particular drug used in combination to a change in the measurement.

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REFERENCES

Pharmacia & Upjohn, Rescriptor™ brand delavirdine mesylate package insert, 4 April 1997a.

Pharmacia & Upjohn news release, "New AIDS Drug Tested in Women with HIV Drug Trough Concentrations Higher in Women Than Men," 7 May 1997.

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IIIB. NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)

ii. DMP-266 (DuPont-Merck)

by Spencer Cox

BACKGROUND

DMP-266, like delavirdine, is a non-nucleoside reverse transcriptase inhibitor (NNRTI). The chemical was first synthesized by Merck in 1995, which licensed the drug to DuPont-Merck when it decided to focus on development of indinavir. However, unlike delavirdine, DMP-266 seems to be a relatively potent drug which is easy to administer and has a promising resistance profile.

About the sponsor. The DuPont Merck Pharmaceutical Company was formed in 1991 as a research-based, independent joint venture between the DuPont Company and Merck & Company, Inc. Dupont Merck has approximately 4,000 employees worldwide, and 1996 sales and revenue totaled $1.4 billion. Overall, the company invests more than 20% of revenue into research and development. Key research foci include HIV, cardiovascular disease, radiopharmaceuticals, central nervous system diseases, and cancer. Its leading products include a series of radio-imaging agents, as well as treatments for Parkinson's disease and alcoholism.

Mechanism of activity. DMP-266 , like other NNRTIs, inhibits reverse transcriptase by binding to the enzyme and blocking polymerase activity.

ANTIRETROVIRAL POTENCY

Test-tube studies. In vitro, DMP-266 is effective against a wide range of laboratory and clinical HIV isolates. Its IC_{95} for the inhibition of HIV-1 is 1.5nM. In addition, the drug could inhibit *in vitro* viruses with single mutations that confer resistance to other NNRTIs.

Clinical trials. In preliminary results from a Phase II study (DMP-003), a cohort of 16 patients with CD4 counts of 100-500 and plasma HIV RNA levels of >20,000 copies/mL were treated with two weeks of DMP-266 monotherapy, resulting in a mean reduction in HIV RNA of 1.68 logs, and a 96-cell increase in CD4 cell counts. Indinavir was then added, resulting in a mean reduction of -3.2 logs in HIV RNA, with 55% having RNA levels below 400 copies/mL. A mean CD4 cell count increase of more than 100 cells was also observed.

In another arm from this complicated study, 30 patients with 100-500 CD4 cells and HIV RNA levels of >20,000 copies were treated with two weeeks of indinavir monotherapy, and then randomized in a 2:1 fashion to receive DMP-266 or a placebo in combination with indinavir. Investigators rapidly found that DMP-266 caused a 35% decrease in the indinavir AUC, and so increased the dose of indinavir from 800mg every eight hours (q8h) to 1,000 mg q8h early in the course of the trial. After 24 weeks, patients

on combination therapy had a 2.2 log reduction in HIV RNA levels, compared to a 1.5log reduction in patients treated with indinavir monotherapy. CD4 cell counts increased by approximately 100 cells in both groups. Viral load was less than 400 copies/mL in 82% of patients treated with the combination therapy, versus 38% of patients treated with indinavir monotherapy.

To further explore the pharmacokinetic interaction between DMP-266 and indinavir, researchers tested DMP-266 at a dose of 400 and 600 mg with indinavir at a dose of 1200 mg three times a day. Twelve patients were treated in each dose group. In the lower-dose DMP-266 group, a mean decrease was seen in plasma HIV RNA of 2.2 logs was seen at four weeks. The high-dose DMP-266 arm had a mean decrease of 2.6 logs at four weeks; no data from later time-points are yet available.

RESISTANCE & CROSS RESISTANCE

In vitro studies have suggested that, unlike other NNRTIs, virus requires multiple mutations in the reverse transcriptase to develop resistance to DMP-266, and the emergence of highly resistant virus only develops after multiple passages in tissue culture. The primary *in vitro* mutations conferring loss of sensitivity were L100I alone or in combination with either V108I or V179D/Y181C. The K103N mutation is the single observed mutation most resistant to DMP-266, conferring a 10-fold reduction in sensitivity. Normal dosing should produce concentrations sufficient to suppress replication of virus with K103N.

In vivo genotyping results were obtained from thirteen patients in study DMP 266-003 who were treated for sixteen weeks with DMP-266 200 mg/day + indinavir 800/1000 mg tid. All of these patients had initially responded to treatment, but failed between weeks eight and twelve. No Y181C, K101E, or L100I single mutants were seen. Seven patients had K103N, one had K103N/G190S, one had K103N/L100I, one had Y188L, and data are pending in 3/13. No indinavir-related mutations associated with high-level resistance were seen in the protease.

ADVERSE EVENTS & TOXICITY MANAGEMENT

In general, the main side effects associated with DMP-266 seem to involve central nervous system (CNS) symptoms. According to the manufacturer, these CNS symptoms – possibly resembling those associated with ritonavir, such as dizziness and parasthesias – have been reported after doses of 200, 400 and 600 mg. Episodes recur on daily dosing. Intensity decreases with continued dosing, and seem to pass after about two weeks. Intensity of these symptoms is dose dependent, and may be minimized with dosing in the evening just before sleep.

Because large-scale trials of DMP-266 have not yet been completed, toxicity data is somewhat scattered, and differs somewhat between studies.

Drug-Related Adverse Events in Two Phase One Studies of DMP-266

Adverse events	Number of cases (N=117)
Headache	5
Dizziness	4
Nausea	5
Diarrhea	2
Vomiting	4
Increased GGT	1
Increased ALT	1
Somnolence	1

In phase II studies combining DMP-266 and indinavir, including now more than 200 patients, the most frequent adverse events reported included diarrhea, headache, rash, dizziness, lightheadedness, nausea, dry skin, insomnia, cough, abdominal pain and fatigue. It is not possible at present to determine which of these side effects are related to DMP-266.

Unlike nevirapine and delavirdine, DMP-266 is not clearly associated with a rash.

Incidence of Drug-Related Rash in DMP 266-003

	Monotherapy Period			Combination Period	
	DMP-266	Placebo	IDV	DMP-266+IDV	IDV
N	22	10	30	90	51
N (%) w/ rash	1 (5%)	1 (10%)	3 (10%)	22 (24%)	16(31%)
Discontinued drug.	0	0	0	1 (DMP-266) 1 (IDV)	1(Placebo)

[IDV=indinavir.]

DRUG INTERACTIONS

Like other NNRTIs and the protesae inhibitors, the main physiological interaction of DMP-266 is with a family of liver enzymes known as the cytochrome p450 isoforms. Clinical data show that DMP-266 is an inducer of the CYP3A isoform, which may result in interactions between the drug and many other common AIDS treatments.

DuPont-Merck has already determined that DMP-266 has no effect on levels of AZT, 3TC, or fluconazole. Clarithromycin levels are lowered by 20% during coadministration with DMP-266.

A pharmacokinetic drug interaction study of DMP-266 and nelfinavir was conducted in 20 healthy volunteers, divided into two treatment groups. Group one received 750 mg nelfinavir every eight hours

for fourteen days, and 400 mg DMP-266 every day for seven days starting on study day eight. Group 2 received 400 mg DMP-266 a day for 14 days and 750 mg nelfinavir every eight hours for seven days starting on day eight. The preliminary results for DMP-266 suggest no difference in peak concentration or AUC values between days seven and fourteen in group 2, or between the two groups on day 14. For nelfinavir, the group 1 day 14 peak concentration was 26% higher and AUC value was 15% higher than the day 7 values. There were no differences between groups in nelfinavir peak concentration or AUC values on day 14.

Studies have been completed and are currently being analyzed looking at interactions between DMP-266 and saquinavir, famotidine and Mylanta. Other interaction studies are planned, including interactions with ritonavir, rifampin, azithromycin, ethinyl estradiol, midazolam, lorazepam, paroxetine, methadone, abacavir (1592) and 141W94.

EXPANDED ACCESS

DuPont Merck has committed to develop an expanded access program for DMP-266, beginning in January, 1998 at the latest. The design of this program is currently being planned.

PEDIATRICS

DuPont Merck is finalizing a pediatric formulation of DMP-266, and plans to file for approval in conjunction with their adult approval.

CURRENT & PLANNED POST-MARKETING STUDIES:

ACTG 364	DMP-266 + nucleoside analogs reverse transcriptase inhibitors (NRTIs) vs. nelfinavir + NRTIs vs. DMP-266 + nelfinavir + NRTIs, N=300
ACTG 368	DMP-266 + indinavir + abacavir vs. DMP-266 + indinavir in 300 NRTI-experienced, protease inhibitor-naïve patients
DMP-266-007	DMP-266 + indinavir + NRTIss vs. indinavir + NRTIss in 2400 NRTI-experienced, protease inhibitor-naïve patients. (This clinical-endpoint study may be abandoned if FDA eliminates requirements for evidence of clinical benefit).
Combination Studies:	Studies are planned of DMP-266 in combination with all marketed protease inhibitors and NAs, as well as experimental drugs such as abacavir, adefovir and 141W94.
Interaction studies	Multiple interaction studies are planned for drugs process through the P450 isoform system

Pediatrics	Studies are planned to evaluate DMP-266 in pediatric patient populations.

DISCUSSION

So far, DMP-266 looks like an extremely promising drug. The company believes that once-a-day dosing may be possible, although this has not yet been confirmed. In addition, exploitation of pharmacokinetic interactions with protease inhibitors may improve administration of those drugs by reducing dosing schedules. In general, the drug appears to be potent and associated with few adverse events. The company has planned a wide variety of interaction studies that should illuminate the optimal use of this drug. Development of a pediatric formulation in tandem with the adult formulation is a good sign of the company's commitment to all people with HIV. However, it is important to remember that DMP-266 is still in an early stage of development, and that new information may become available as testing continues that limits the rosy picture currently suggested by the very limited available data.

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REFERENCE

DuPont Merck, personal communication to author, spring 1997.

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IIIC. PROTEASE INHIBITORS

i. Nelfinavir Mesylate (VIRACEPT™, Agouron Pharmaceuticals)

by Mark Harrington

We're convinced [nelfinavir] *is the best of the four approved protease inhibitors.*

-- Peter Johnson
President, Agouron
(Mascolini 1997)

It's good for marketing.

-- Douglas Richman, UCSD,
speaking of the D30N mutation,
(Mascolini 1997)

BACKGROUND

Nelfinavir mesylate, an inhibitor of the HIV protease enzyme, is the first protease inhibitor simultaneously approved for adults and children with HIV.

Indication. The VIRACEPT™ labeling indication is broad and vague, as has become typical for an antiretroviral drug licensed through accelerated approval: "VIRACEPT is indicated for the treatment of HIV infection when antiretroviral therapy is warranted. This indication is based on surrogate marker changes in patients who received VIRACEPT in combination with nucleoside analogues or alone for up to 24 weeks. At present, there are no results from controlled trials evaluating the effect of therapy with VIRACEPT on clinical progression of HIV infection, such as survival or the incidence of opportunistic infections." (Agouron 1997). For adults the recommended dose is 750 milligrams (mg) taken three times daily (tid). For children over two years old the dose is 20-30 mg/kg, not to exceed 750 mg.

About the sponsor. Agouron Pharmaceuticals was founded in 1984. In 1987 it was awarded an NIH grant to determine the structures of HIV proteins. It began working with Eli Lilly in 1988 on drug discovery. By 1989, investigators had resolved the structure of the HIV protease complexed with (bound to) lead compound protease inhibitors. First named AG-1343 and identified as a development candidate in 1993, nelfinavir mesylate was licensed by Lilly to Agouron (Appelt 1993, Babine 1995), which initiated clinical trials in 1994 with funding from Japan Tobacco, Inc. (JTI) (Agouron 1996). Agouron filed for approval on Christmas Eve, 1996, and the drug received accelerated approval from the US Food & Drug Administration (FDA) on 14 March 1997. Its development time was just 38 months -- the quickest yet

for an HIV protease inhibitor. VIRACEPT™ is Agouron's first FDA-approved drug. Other compounds in the pipeline are targeting protease enzymes of cytomegalovirus (CMV), hepatitis C virus (HCV) and rhinovirus. The company has a partnership with Roche to market the drug in Europe. While Roche has apparently filed for marketing approval, it is dragging its feet on a previous commitment made by Agouron to provide nelfinavir on expanded access to 2,000 Europeans (Broekhuizen 1997). Rumors are circulating that Roche may be interested in buying Agouron. It would not be surprising if this led to an exodus of some of La Jolla's best and brightest, as happened when Glaxo bought Wellcome.

Mechanism of activity. Protease is an enzyme which enables HIV to cleave its proteins from the *gag-pol* polyprotein-- a long precursor protein chain -- into smaller functional units essential to HIV infectivity. All inhibitors of HIV protease block the action of this enzyme through binding within the active proteolytic (protein-cleaving) site. If you imagine the protease enzyme as a pair of hands joined at the wrists whose fingers open and shut like crab's claws, you can envision a protease inhibitor as a long protein which jams the claws and prevents them from slicing into their prey -- the *gag-pol* polyprotein -- rendering the virions non-infectious. Protease inhibitors are bigger molecules than the nucleoside analogue or non-nucleoside reverse transcriptase inhibitors (RTIs), which means they must be taken in larger amounts to be active inside the body.

ANTIRETROVIRAL POTENCY

Test-tube studies. In vitro, nelfinavir is active against both laboratory and clinical (wild-type) HIV-1 strains and against the HIV-2 strain ROD. Its 95% effective concentration (EC_{95}) ranges from 7-196 nanomolars (nM). *In vitro* it is synergistic with the nucleoside analogue reverse transcriptase inhibitors (NRTIs) AZT, 3TC and ddC, and additive with ddI and d4T. Test tube interactions with other protease inhibitors were more variable, ranging from antagonistic to synergistic. These may not be relevant *in vivo*, since test tube cultures lack the liver cytochrome P450 system through which all protease inhibitors (as well as the non-nucleoside RTIs delavirdine, nevirapine, and DMP-266) are metabolized, leading in some cases to *in vivo* synergy which would not be predicted *in vitro*.

Clinical trials. Nelfinavir has been studied clinically in over 1,500 individuals. The three pivotal studies enrolled 696 individuals. The pediatric trial enrolled 38 children aged two to thirteen.

Monotherapy. In a study of thirty people who received either 500, 750, or 1000 mg of nelfinavir monotherapy tid after a two-week antiretroviral washout period, mean HIV RNA reductions were 75%, 94% and 97% (0.6 1.2 and 1.5 logs) respectively after sixteen weeks of therapy (Agouron 1996a); these results were described in Vancouver as reductions of 1.4, 1.9 and 1.7 logs using the cutoff of 500 RNA copies/ml (bDNA), and 1.5, 2.4 and 2.3 logs using the cutoff of 100 RNA copies. 20% on 500 mg tid and 50-60% on 750 and 1000 mg tid fell below the limit of detection. "The most frequently reported adverse events were loose stool and mild to moderate diarrhea" (Conant 1996). Agouron study 505 randomized 97 (or 91; the Retrovirus Conference abstract says 97, the FDA package insert 91) HIV-infected individuals to receive either 750 or 500 mg nelfinavir tid (one third of the participants received placebo for the first four weeks). Of these, 37 were antiretroviral naive and 57 were experienced. The median baseline CD4 was 264 and HIV RNA was 5 logs (Powderly 1997).

Nelfinavir's spectacular debut. Nelfinavir first made its dramatic debut in the collective consciousness of the global AIDS research elite on July 11, 1996, when it was lucky enough to have been included in the triple-combination study at Aaron Diamond AIDS Research Center in which David Ho for the first time showed that viral levels in eleven individuals which were undetectable using a lower threshold of detection of 400 copies/mL were also undetectable using an even lower threshold, measured with a new, super-sensitive bDNA assay, of 25 HIV RNA copies/mL. The trial, Agouron 509, enrolled twelve chronically-infected, treatment-naive individuals with baseline CD4 counts of 245 (range 26-501) and viral load of 56,000/mL (range 14,000-618,000). One patient was lost to follow-up. Within two weeks, viral levels dropped 99%, and descended further towards 400 copies/mL over time. CD4 counts rose by an average of 100 cells. At eight weeks, all eleven participants still on study had plasma RNA below 400 copies/mL, and HIV could not be cultured from up to 10 million peripheral blood mononuclear cells (Ho 1996, Markowitz 1996).

Acute primary infection. Another study carried out at the Aaron Diamond Center enrolled twelve recently-infected individuals with acute primary infection. The median entry CD4 count was 253 and viral load was 81,000 copies. One patient developed a grade 4 CPK elevation and withdrew from the study. The remaining eleven all had viral loads become undetectable within 12 weeks. The median CD4 count rose by 109 cells (Markowitz 1996).

Pivotal studies. In presentations at the Fourth Retrovirus Conference in January 1997, Agouron scientists described 2.5 log viral load reductions observed among individuals receiving nelfinavir in combination therapy regimens. Pooling data from three randomized pivotal studies (505 -- two doses of nelfinavir; 506 -- d4T/nelfinavir vs. d4T; and 511 -- AZT/3TC vs. AZT/3TC/nelfinavir), the sponsor claimed that nelfinavir-containing combination regimens reduced HIV RNA an average of 2.5 logs in over 700 individuals entering with a baseline viral load of just under 100,000 copies/mL. In those on triple therapy in study 511, the sponsor stated that the average HIV RNA reduction was 2.5 logs, and that 65-81% of recipients' viral levels became undetectable ($\leq$500 copies/mL). Reductions on d4T/nelfinavir were said to be 2.5 logs and 76% became undetectable.

In the package insert, these reductions have been described more conservatively. Agouron used a detection threshold of $\leq$400 copies/mL with the Chiron 2.0 bDNA assay. The FDA, however, insisted on using a higher cutoff of $\leq$1200 copies/mL, stating that "values below an estimated 1,200 copies/ML could not be reliably quantified," resulting in apparently less dramatic viral load reductions. This, however, is an artifact of whichever cutoff is used:

Agouron 511: Impact of Viral Load Detection Threshold on Reported Potency of Nelfinavir

	Definition of "Undetectable": Six Month Data		
HIV RNA (copies/mL, bDNA)	<1,200	<500	<100
Agouron 511: AZT/3TC/nelfinavir 750	-1.7 $\log_{10}$	-2.0 $\log_{10}$	-2.5 $\log_{10}$

Double therapy in treatment-experienced individuals. Agouron study 506 randomized 308 HIV-infected individuals to two doses of nelfinavir (750 or 500 mg tid) plus d4T versus d4T alone. 89% of the participants were male and 75% were white. 20% were antiretroviral naive. The mean duration of antiretroviral experience in the previously-treated individuals was two years, eight months. Mean baseline CD4 count was 279 and mean plasma HIV RNA was 141,396 copies/mL (4.86 $\log_{10}$). By 24 weeks, 43 of 109 (39.4%) d4T monotherapy recipients switched to combination because of inadequate surrogate marker responses (Pedneault 1996, Agouron 1997a).

Agouron 506: HIV RNA Changes from Baseline

		Weeks of Therapy			N/% UD (<1200/mL)[1]
Regimen	N	Two	Twelve	24	at 24 weeks
d4T	109	-0.6 log	-0.5 log	-0.6 log	13 (12%)
d4T/NFV 500	99	-1.4 log	-1.1 log	-0.9 log	24 (24%)
d4T/NFV 750	107	-1.45 log	-1.25 log	-1.0 log	22 (21%)

Agouron 506: CD4 Cell Changes from Baseline

		Weeks of Therapy		
Regimen	N	Two	Twelve	24
d4T	109	+35	+ 30	+ 40
d4T/NFV 500	99	+75	+110	+ 95
d4T/NFV 750	107	+75	+120	+100

The data on nelfinavir plus a single nucleoside RTI are not as impressive as those with two RTIs.

Triple therapy in treatment-naive individuals. Agouron study 511 randomized 297 antiretroviral-naive, HIV-infected individuals to AZT/3TC alone or with either 500 or 750 mg tid of nelfinavir. The median age was 35. 89% were male and 78% white. Mean baseline CD4 count was 288 and plasma HIV RNA was 153,044 copies/mL (4.86 $\log_{10}$).

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[1] UD = undetectable. The limit of detection of the plasma HIV RNA using the Chiron version 2.0 bDNA assay was $\leq$1,200 HIV RNA copies/mL.

Agouron 511: HIV RNA Changes from Baseline

Regimen	N	Weeks of Therapy Two	Twelve	24	N/% UD (<1200/mL) at 24 weeks
AZT/3TC	101	-1.5 log	-1.25 log	-1.25 log	30 (30%)
AZT/3TC/NFV 500	97	-1.7 log	-1.6 log	-1.6 log	59 (61%)
AZT/3TC/NFV 750	99	-1.6 log	-1.6 log	-1.6 log	73 (74%)

Unsurprisingly, triple combination in naive individuals is more potent than double combination in experienced ones. Moreover, there is a trend suggesting that the higher dose of nelfinavir -- 750 mg as opposed to 500 mg tid -- is more potent virologically. Presumably this was the basis for Agouron's choice of the higher dose for the FDA-approved labeling.

Agouron 511: CD4 Cell Changes from Baseline

Regimen	N	Weeks of Therapy Two	Twelve	24
AZT/3TC	101	+80	+ 80	+ 80
AZT/3TC/NFV 500	97	+80	+140	+130
AZT/3TC/NFV 750	99	+80	+120	+140

In both studies, the CD4 changes are indistinguishable between the two doses of nelfinavir.

Triple-therapy with Bristol-Myers Squibb nucleosides. At the Fourth Retrovirus Conference, Bristol-Myers Squibb researchers presented preliminary data from a pilot study of ddI/d4T/nelfinavir in 22 protease-naive HIV-infected individuals, of whom 11 were antiretroviral naive. Median baseline CD4 count was 315 and viral load was 4.75 $\log_{10}$. Changes over first eight weeks of therapy were:

ddI/d4T/nelfinavir: Pilot Data

Parameter	2 weeks	4 weeks	8 weeks
CD4 change	+ 75 cells	+103 cells	+218 cells
HIV RNA change	-1.4 log	-1.7 log	-2.1 log

The lower limit of detection in this study was 500 HIV RNA copies/mL. After eight weeks viral load had become undetectable in three of eight (37.5%) participants. Seventeen participants (77.3% -- note the higher figure cited by a company which doesn't manufacture the drug in question) reported "occasional episodes of loose stools," and there was one case each of grade 3 thrombocytopenia and one of grade 3 allergic reaction to nelfinavir (Pedneault 1997).

Pediatric indication. 38 children ranging from two to 13 years of age were given nelfinavir in an open-label, uncontrolled trial. The recommended pediatric dose is 20-30 mg/kg thrice daily, not to exceed

750 mg tid. Similar toxicity was seen in children and adults. Oral clearance appears higher in children than in adults, which is seen with other drugs metabolized by cytochrome P450 (Krogstad 1997). Antiviral activity analyses are ongoing. At the time of its approval, nelfinavir had not yet been evaluated in children less than two years old.

Recommendation 1: Agouron should develop a neonatal formulation and study nelfinavir in pregnant women, infected neonates, and infants less than two years old.

In response to an inquiry from TAG, Agouron's Joy Schmitt wrote that "At the time the NDA was submitted, no children... [younger than 2] had been enrolled. Study 524 is ongoing and has since [NDA approval] recruited infants as youngg as 3 months. Data are being collected on the approximately 50 children now enrolled with the intent of eventual marketing clearance in children less than two years of age. Based on our experience to date, the current powder formulation, which may be combined with water, milk, and formula, is suitable for neonates... We are currently working with the PACTG to finalize Study 353, which will evaluate the safety, tolerance, and antiviral efficacy of the triple drug regimen, nelfinavir/AZT/3TC." (Schmitt 1997)

RESISTANCE & CROSS-RESISTANCE

Nelfinavir-resistant HIV strains were selected by *in vitro* passage. Observed point mutations were compared with point mutations observed in isolates drawn from nelfinavir-treated individuals. After 22 passages, the D30N mutation was observed to confer a nine-fold increase in the effective dose (ED_{90}). No cross-resistance was observed with other licensed protease inhibitors.

Genotypic resistance analysis was performed on samples from 55 individuals treated with nelfinavir alone or with other antiretroviral agents, and phenotypic analysis was performed on 19 such individuals. The percentage of patients with genotypic resistance after 16 weeks of treatment was 56% on monotherapy, 6% on AZT/3TC/nelfinavir and 0% on AZT/3TC. Among the HIV protease mutations observed in more than 10% of individuals with evaluable isolates were amino acid substitutions at positions 30, 35, 36, 46, 71, 77 and 88. Among the 19 individuals from whose clinical isolates both genotypic and phenotypic analysis was performed, 9/19 (47.4%) showed five-to-93-fold reduced susceptibility to nelfinavir *in vitro.* All nine had at least one mutation in their protease gene. The most frequent mutation site was at position 30 (Patick 1997). Subsequently the researchers looked for the D30N mutation in 64 individuals on monotherapy and 49 individuals on AZT/3TC/nelfinavir combination:

D30N Mutation at 12-16 Weeks of Therapy

	N	Total (%) with D30N mutation
Nelfinavir monotherapy	64	36 (56%)
AZT/3TC/nelfinavir	49	3 (6%)

Of note, some individuals were undetectable at 12-16 weeks of therapy -- particularly, one presumes,

in the triple-therapy group -- and by definition virus could not be isolated and amplified from these individuals.

Clinical viral isolates from five nelfinavir-treated individuals exhibiting five-to-93-fold reduced susceptibility to nelfinavir *in vitro* remained susceptible to indinavir, ritonavir, saquinavir and GW141 (the Vertex/Glaxo-Wellcome protease inhibitor) *in vitro*.

A single isolate from a saquinavir-experienced individual which showed seven-fold decreased susceptibility to saquinavir *in vitro* remained sensitive to nelfinavir *in vitro*. However, six of seven HIV isolates which exhibited eight-to-113-fold decreases in susceptibility to ritonavir also exhibited decreased five-to-40-fold susceptibility to nelfinavir *in vitro*. The company did not report on experiments with isolates from individuals receiving indinavir. However, since indinavir is generally cross-resistant with ritonavir, it may be expected that indinavir-resistant HIV is likely to be resistant to nelfinavir as well.

While Agouron is to be commended for performing these resistance analyses, which are certainly more detailed than those shown at the time of approval for indinavir, ritonavir or saquinavir, the number of isolates sampled is small -- particularly phenotypically -- and the need for clinical studies of virologic responses to various protease sequencing regimens is critical.

Nelfinavir Cross-Resistance: Phenotypic Analysis of 13 Clinical Isolates

Protease Exposure	N	Resistant to	Susceptible to
Nelfinavir	5	NFV (100%, 5-93-fold)	IDV, RTV, SQV, 141
Indinavir	-	Not reported	Not reported
Ritonavir	7	NFV (85%, 8-113-fold)	Not reported
Saquinavir	1	Not reported	NFV (1 of 1)
GW141	-	Not reported	Not reported

In a table published in the VIRACEPT "Backgrounder", Agouron presented handy chart proclaiming that nelfinavir-resistant HIV strains remained susceptible to all three other licensed protease inhibitors. The total number of individuals from whom viral isolates were drawn was six (Agouron 1997b). Agouron also presented its analysis of mutational overlap between protease inhibitors:

Protease Cross-Resistance: Agouron's Version

	HIV Protease Point Mutation Site										
Saquinavir	10				***48***		63	71			***90***
Ritonavir	10	20	36	46		54	63	71	***82***	***84***	***90***
Indinavir	10	24	36	46		54	63 65	71	***82***	***84***	***90***
Nelfinavir		***30*** 35	36	46				71	77	88	

[Clinically observed mutations correlating with phenotypic resistance are shown in ***bold italics***.]

With so much hype, such pressure for market share, and so little clinical data, it is good to remain skeptical about pharmaceutical sponsor claims about resistance, as Mike Barr reminds us:

> When it comes to corporate positioning for protease inhibitor market share, every company has a yarn to spin. Merck loyalists insist that theirs be used first-line because it's so powerful and, "after all, really requires *multiple mutations* in order to significantly alter viral sensitivity." Roche (and later, Agouron, in lock step) claim that their protease is the only one to deserve a first-line indication because the mutations elicited with saquinavir and nelfinavir are unique and not nearly as predisposing to cross-resistance as are, say, the indinavir mutations. Since scientists at all the protease outfits seem capable of pulling whatever color rabbit out of their hats is deemed most conducive to a successful marketing campaign (and since all cross-resistance analyses to date have been conducted in test tube experiments), trying to sort through the morass of claims and counter-claims has been at times Herculean; at others, Sisyphean (Barr 1997).

Recommendation 2: It is critical for Agouron to work with the manufacturers of other HIV protease inhibitors to assess clinically the virologic effect of:

2a. Treating individuals virologically resistant to nelfinavir with other protease inhibitors;

2b. Treating individuals virologically resistant to indinavir, ritonavir, saquinavir, and GW141 with nelfinavir;

2c. Studying genotypic and phenotypic resistance in clinical isolates from far greater numbers of individuals than heretofore studied participating in prospective, randomized, controlled studies of various protease sequences.

Eight studies including nelfinavir are being conducted in saquinavir and indinavir failures; see below under "current & planned studies."

Agouron's resistance work to date has largely focused on genotypic analyses. It should expand this work to cover phenotypic analyses in the future.

ADVERSE EVENTS & TOXICITY MANAGEMENT

Just 11% of patients discontinued nelfinavir in the two pivotal studies -- a proportion which Agouron claims is "a very low incidence for clinical trials" (Agouron 1997). Just 1.6% discontinued for diarrhea, and 4% for side effects overall.

Agouron 511 + 506: Pooled Data on Moderate or Severe Adverse Events

	Agouron 506 Naive Patients			Agouron 511 Experienced Patients		
	Placebo AZT/3TC	NFV 500 AZT/3TC	NFV 750 AZT/3TC	Placebo d4T	NFV 500 d4T	NFV 750 d4T
N	101	97	100	109	98	101
Abdominal pain	1%	0	0	3%	2%	4%
Asthenia	2%	1%	1%	4%	3%	1%
Diarrhea	3%	14%	20%	10%	28%	32%
Nausea	4%	3%	7%	1%	3%	2%
Flatulence	0	5%	2%	4%	8%	3%
Rash	1%	1%	3%	0	4%	3%

Clearly diarrhea is the most common serious toxicity, occurring in between 20-32% of individuals receiving the FDA-approved dose. (Anecdotes from people actually on the drug report a much higher occurrence of less severe diarrhea, which the sponsor likes to refer to as "loose stools", and which investigators are wont to dismiss with an airy, "Take Imodium!")

All the licensed protease inhibitors cause some degree of gastrointestinal discomfort, with symptoms ranging from mild GI upset to gastric reflux (heartburn) to gas and flatulence to "loose stools" to severe nausea and diarrhea. Little study has occurred into the cause of these GI toxicities, which impair quality of life and reduce adherence, risking the emergence of resistant HIV.

On 11 June 1997 the FDA released a public health advisory warning that 83 cases of diabetes mellitus or hyperglycemia (elevated blood sugar) had been reported among individuals receiving protease inhibitors. Additional cases may be reported to FDA's MEDWATCH program at 1.800.FDA.1088 or faxed to 1.800.FDA.0178 (FDA 1997).

Recommendation 3: Agouron, along with other protease inhibitor manufacturers, should collaborate with academic gastroenterologists experienced in treating HIV disease to discover the molecular, cellular or physiologic basis for protease inhibitor-induced GI toxicity and diabetes, and study interventions to reduce or eliminate these side effects.

Few laboratory abnormalities were seen among individuals taking nelfinavir, with the most frequent abnormalities including decreased neutrophils in 5% of participants receiving AZT/3TC/nelfinavir -- probably due to the AZT -- and elevated creatine kinase seen in 2-6% of participants.

Expanded Access Program. In September 1996 Agouron opened an Expanded Access Program to provide nelfinavir free of charge to HIV-infected individuals who for whom approved, available protease

inhibitors were failing, unacceptably toxic, or contraindicated. Originally the program was open only to those with fewer than 50 CD4 cells. In January 1997 the entry criteria were liberalized to include those in whom fewer than 100 CD4 cells had been measured at any time point. Also in January, Expanded Access was extended to children over two years of age. About 3,000 people enrolled in the program by the time of approval. Those in the Program will receive one month of free nelfinavir after approval, and assistance in transition to third-party payment. A resistance sub-study of the Expanded Access Program will continue for one year. Safety data from the Expanded Access Program are not yet available.

Recommendation 4: Agouron should analyze and publish data on mild, moderate, severe, and life-threatening adverse experiences, including drug interactions, from its adult and pediatric Expanded Access Programs.

Agouron has indicated that it will present these data at the 1997 ICAAC in Toronto during September.

Note on Hemophilia. Special caution may be warranted when administering protease inhibitors, possibly including nelfinavir, to people with hemophilia. "There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors. In some patients, additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship has not been established." (Agouron 1997).

Recommendation 5: Agouron should carry out safety studies to ensure that nelfinavir is safe for use among individuals with type A or B hemophilia.

In response to this concern, Agouron confirmed that "the safety data to date with hemophiliacs has been limited. There was [only] one hemophiliac enrolled in the US pivotal trials. Of the 39 patients currently enrolled in the clinical trials conducted by Japan Tobacco, 23 are hemophiliacs... We are currently unaware of any increased bleeding episodes attributable to nelfinavir in patients with hemophilia." (Schmitt 1997).

PHARMACOKINETICS, FOOD & DRUG INTERACTIONS

Pharmacokinetics is the study of how a drug is absorbed from the stomach, processed through the liver, transported through the body and into cells by the bloodstream, and excreted by the kidneys (through urine) or the GI tract (through feces). There are two ways of measuring how much of a drug gets into the body -- how *long* it stays there [its half-life in the blood, or plasma area under the curve (AUC)], and how *much* of it gets into the blood at its peak (maximal concentration, or C_{max}). Nelfinavir has a longer half-life and a greater area under the curve (AUC) than other protease inhibitors. Peak plasma concentrations occur after two to four hours when 500 to 750 milligrams (mg) of nelfinavir is taken with food. The approved dosing regimen is 750 milligrams thrice daily (750 mg tid). After four weeks of this regimen, peak plasma concentrations (C_{max}) averaged 3-4 micrograms per milliliter (μg/mL. Plasma concentrations before the morning dose were 1-3 μg/mL (drawn an average of 11 hours after the previous evening dose).

It is essential to eat nelfinavir with food, which increases the drug's C_{max} and AUC by two-to-three-fold. The impact of food on absorption was assessed in 14 individuals who ate meals containing 517-759 kilocaolories (Kcal), with 153-313 Kcal derived from fat.

Agouron is very happy that its drug can be taken with food, and on a less restrictive time schedule (with meals thrice daily -- the half-life is longer than indinavir's, and so adhering to a strict every eight hourly regimen is not as critical with nelfinavir, as long as three doses are taken each day). "VIRACEPT's half life is between 3.5 and 5 hours which means that blood levels stay elevated long after eight hours. Comparatively, Crixivan's half life is 1.8 $\pm$ 0.4 hours, making it critical for patients to take their medications on time... Taking VIRACEPT with food, as opposed to an empty stomach as recommended with Crixivan, may aid in the difficult task of adhering to a dosing regime," hints Agouron, helpfully (Agouron 1997b). On the other hand -- who knows? -- perhaps the hunger pangs associated with Crixivan dosing actually stimulate the brain to remember "Time for my Crix! In an hour I can eat!"

In the blood, nelfinavir is highly protein-bound. 82-86% of the drug in the plasma is unchanged. Its terminal plasma half-life is 3.5 to five hours. 87% of an oral 750 mg dose containing radioactive (Carbon 14, C^{14}) labeled nelfinavir was excreted in the stool. Only one to two percent of the dose was recovered in urine.

Nelfinavir pharmacokinetics have not been measured in individuals with liver or kidney dysfunction. Because just two percent of the drug comes out in the urine, kidney dysfunction should not affect drug metabolism.

The company studied between-gender differences in pharmacokinetics and found none. It did not study racial or ethnic differences in pharmacokinetics.

Agouron "currently [has] no human data on CNS penetration with nelfinavir. However, tissue distribution studies were performed in rats... After a six hour infusion... at a dose of 40 mg/kg, penetration into the brain was found. The brain levels recorded for this study were higher than required for antiviral activity of the drug." (Schmitt 1997). Greatnews for rats with AIDS dementia, but human data are still needed.

The main physiological interaction of nelfinavir is with the family of liver enzymes known as human cytochrome P450 isoforms, which include the proteins CYP3A, CYP2C19, CYP2D6, CYP2C9 and CYP2E1. Only CYP3A was inhibited by nelfinavir at concentrations in the therapeutic range. K_i is a measure of enzyme inhibition. A higher K_i concentration means a lower inhibition. Compared with ritonavir, which has a K_i of 0.1, and indinavir, which has one of 0.7, nelfinavir is a milder inhibitor, with a K_i of 4.8 (Agouron 1997b).

Because this liver enzyme system is also responsible for metabolizing a number of other commonly-used drugs, nelfinavir has significant effects on their plasma half-life (AUC) and plasma concentration (C_{max}):

Effect of Nelfinavir (750 mg tid) on Concomitant Drug Plasma AUC + C_{max}

Concomitant drug	N	AUC (95% CI)	C_{max} (95% CI)
3TC 150 mg	11	Up 10% (1-20%)	Up 31% (5-62%)
d4T 200 mg	8	No change	No change
AZT 200 mg	11	Down 35% (28-41%)	Down 31% (8-49%)
IDV 800 mg	6	Up 51% (25-83%)	No change
RTV 500 mg	10	No change	No change
SQV 1200 mg	14	Up 392% (271-553%)	Up 179% (105-280%)

Effect of Nelfinavir (750 mg tid) on Concomitant Drug Plasma AUC + C_{max} (continued)

Ethinyl estradiol 35 μg	12	Down 47% (41-63%)	Down 28% (14-39%)
Norethindrone 35 μg	12	Down 18% (12-27%)	No change
Rifabutin 300 mg	10	Up 207% (151-276%)	No change
Terfenadine 60 mg	12	Transiently measurable	Transiently measurable

Effect of Concomitant Drug on Nelfinavir (750 mg tid) Plasma AUC + C_{max}

Concomitant drug	N	AUC (95% CI)	C_{max} (95% CI)
ddI 200 mg	9	No change	No change
AZT 200 mg / 3TC 150 mg	11	No change	No change
IDV 800 mg	6	Up 83% (34-150%)	Up 31% (13-52%)
RTV 500 mg	10	Up 152% (86-242%)	Up 44%
SQV 1200 mg	14	Up 18% (5-33%)	No change
Ketoconazole 400 mg	12	Up 35% (21-49%)	Up 25% (8-44%)
Rifabutin 300 mg	10	Down 32% (10-48%)	Down 25% (6-38%)
Rifampin 600 mg	12	Down 82% (77-86%)	Down 76% (67-83%)

[3TC = lamivudine; AZT = zidovudine; d4T = stavudine; ddI = didanosine; IDV = indinavir; RTV = ritonavir; SQV = saquinavir]

These pharmacokinetic interaction data -- more than we have ever had for any HIV protease inhibitor at the time of approval -- raise some safety concerns and suggest several follow-up studies for enhancing protease inhibitor efficacy through synergy.

Safety considerations. Several drugs should *NOT* be taken with nelfinavir:

* The antihistamines astemizole (Hismanal) and terfenadine (Seldane)
* The antimycobacterial rifampin (Rifadin, Rifamate, Rifater, Rimactane)
* The benzodiazepines midazolam (Versed) and triazolam (Halcion)
* The GI motility agent cisapride (Propulsid)

Use of these drugs in combination with nelfinavir may cause "serious and/or life-threatening cardiac arrhythmias or prolonged sedation" (Agouron 1997, Kerr 1997).

* Persons on nelfinavir should *CUT THEIR DOSE OF RIFABUTIN (Mycobutin) IN HALF.*

Use of full-dose rifabutin with nelfinavir may increase the risk of rifabutin-induced uveitis (eye inflammation).

* The anticonvulsants carbamazepine (Atretol, Tegretol, Epitol), phenobarbital (Arco-Lase, Bellergal, Donnatal, Quadrinal, Mudrane, Solfoton) and phenytoin (Dilantin) may decrease nelfinavir plasma concentrations, rendering the drug ineffective or HIV resistant to it.
* Nelfinavir may decrease plasma concentrations of the oral contraceptives ethinyl estradiol and norethindrone (two drugs sold together as Brevicon, Demulen, Levlen, Lo/Ovral, Modicon, Nordette, Norinyl, Ortho-Cept, Ortho-Cyclen, Ortho-Novum, Ovral, Tri-Levlen, Tri-Norinyl, Triphasil, Nelova, Norethin), rendering them ineffective in preventing conception.

Efficacy considerations

* The protease inhibitors indinavir (Crixivan) and ritonavir (Norvir) may increase nelfinavir half-life by 83-152% and its plasma concentrations by 31-44%, respectively (Yuen 1997).
* Nelfinavir may increase the half-life of indinavir by 51% (Yuen 1997).
* Nelfinavir may increase the half-life of saquinavir (Invirase) by up to 400%, and its plasma concentration two-fold (179%) (Kravcik 1997).

Recommendation 6a: It is critical that Agouron work with Merck to quickly undertake studies of the combination of indinavir and nelfinavir.

Recommendation 6b: It is critical that Agouron work with Roche to quickly undertake studies of the combination of nelfinavir and saquinavir.

At least three protease-protease studies with nelfinavir are currently underway; see under "current & planned studies".

Nelfinavir/NNRTI interactions. Not listed in the package insert, but tantalizingly hinted at in presentations at the Fourth Retrovirus Conference in January 1997 is the possibility of positive interactions between nelfinavir and the non-nucleoside reverse transcriptase inhibitor delavirdine (Rescriptor, a CYP3A inhibitor). Note: the other NNRTIs, nevirapine (Viramune) and DMP-266 are CYP3A *inducers* and so *speed* metabolism of protease inhibitors, shortening their half-life and reducing their plasma concentration.

Recommendation 7: Agouron should work with Boehringer-Ingelheim, Dupont-Merck, and Pharmacia & Upjohn to study *in vivo* the safety and activity profile of nelfinavir in combination with their NNRTIs.

Agouron confirms that studies of nelfinavir with nevirapine, DMP-266 and delavirdine are all underway, with 24, 54 and 14 patients, respectively. Several larger planned studies -- e.g., ACTG 364 and 374 -- involve nelfinavir/NNRTI combinations (Schmitt 1997).

Methadone. Not addressed in the package insert was the concomitant use of nelfinavir and methadone. All the protease manufacturers have been negligent in studying this interaction and, as a result, many drug users taking methadone are prohibited from taking protease inhibitors (Ken Fornataro, personal communication). In Europe, some researchers in France have undertaken to study the interaction of ritonavir and indinavir, respectively, with methadone (ARCAT SIDA 1997), but they are not studying nelfinavir, and ultimately this should be the responsibility of the sponsor.

Recommendation 8: Agouron should assess the pharmacokinetic interaction of nelfinavir and methadone.

Agouron claims that "conducting a small study is currently being considered. However, CYP2E1, CYP3A4, and possibly CYP2D6 are involved in the metabolism of methadone. While possible that nelfinavir may inhibit methadone metabolism by CYP3A4, the extent of inhibition will be limited, since nelfinavir would not impair metabolism of methadone by CYP2E1 and CYP2D6" (Schmitt 1997).

CURRENT & PLANNED POST-MARKETING STUDIES

Agouron 509 — Agouron 509 (the Aaron Diamond study conducted by Martin Markowitz) is continuing to follow eleven individuals after 52 weeks. At month ten, 10/11 individuals (91%) had HIV RNA levels below 500 copies/mL. Viral levels are being measured in lymph nodes and semen.

Protease-Protease Studies

Agouron 534 — Will enroll 60 women, give them d4T/3TC, and randomize them to receive nelfinavir + saquinavir twice or thrice daily.

Agouron 535 — Two nucleosides (at least one of which is new) with nelfinavir, saquinavir, and nelfinavir/saquinavir vs. the two proteases alone; 158 people have enrolled in this study to date.

Agouron 547 — In collaboration with Merck will combine nelfinavir (500 and 750 mg) in combination with indinavir (1000 mg tid) (Schmitt 1997).

Protease/NNRTI Studies

Nelfinavir/nevirapine Boehringer Ingelheim has enrolled 24 patients.

Nelfinavir/DMP-266 DuPont Merck has enrolled 24 patients in study 019 and 30 will enroll in 024.

Nelfinavir/delavirdine Pharmacia & Upjohn has enrolled 14 patients.

Studies with Nucleosides

Agouron 542	d4T/3TC/nelfinavir, N=240.
ATLANTIC	ddI/d4T/3TC vs. ddI/d4T/indinavir vs. ddI/d4T/nelfinavir, N=?.
AVANTI III	AZT/3TC/nelfinavir vs. AZT/3TC/placebo, entry CD4 150-500, protease naive, N=100, main endpoint is virological; sites include Australia, Belgium, Canada, Denmark, Germany, Holland, Italy, Spain, UK (ARCAT SIDA 1997).
BMS 062/063	ddI/d4T/nelfinavir/hydroxyurea, N=30, sponsored by Bristol-Myers Squibb.
CPCRA 042	Nelfinavir plus nucleoside analogues versus ritonavir plus nucleoside analogues in 1,300 treatment-experienced, HIV-infected adults with CD4<100. The study began enrollment in January and will continue for at least one year. Endpoints are progression to AIDS and death.
NV15436A	A Roche study randomizing 150 patients to receive saquinavir enhanced oral formulation (EOF, N=25), nelfinavir (N=25), SQV EOF + NFV (N=100), all with combination nucleosides. The main endpoint is RNA PCR at 16 weeks. Follow-up will be for 48 weeks. The study is taking place in Belgium, Germany, Holland, Switzerland and the UK (ARCAT SIDA 1997).
1592 + Nelfinavir	A 48-week, open-label study is comparing abacavir (1592) plus either indinavir, saquinavir, ritonavir, nelfinavir, GW14194 or DMP266 (ATDN 1997).
Interaction studies	Discussions are underway with Boehringer-Ingelheim, Dupont-Merck, and Pharmacia & Upjohn about testing nelfinavir with nevirapine, DMP-266, and delavirdine, respectively. Protease-protease studies are being planned.
Women's study	60 women taking nelfinavir + nucleoside analogues will be studied.
BID dosing study	A European study is comparing 1000 to 1250 mg nelfinavir twice daily (bid); it should be complete later in 1997.

Resistance

A substudy of the Expanded Access Program is following 100 protease-experienced individuals to assess their response to nelfinavir after failing other protease inhibitors. Agouron claims that, "Anecdotally, many patients have responded," without giving qualitative or quantitative specifics (Agouron 1997b). Which drugs were the responders taking previously? How *much* resistance did they have? Which mutations were associated with a response, or with failure? Seven other studies are giving nelfinavir to protease failures: 1) treatment of saquinavir failures with nelfinavir or ritonavir, each with nucleosides, in CPCRA 042; 2) treatment of indinavir failures with abacavir/DMP-266/nelfinavir in ACTG 372; 3) treatment of indinavir failures with ddI/d4T/nelfinavir/saquinavir or adefovir/nelfinavir/nevirapine/saquinavir in a Stanford study; 4) treatment of indinavir failures with abacavir/d4T/nelfinavir/saqunavir or ddI/d4T/nelfinavir/saquinavir in a study conducted by Steven Deeks; 5) treatment of indinavir failures with ddI/d4T/nelfinavir in a Bristol-Myers study carried out by Martin Hirsch and Douglas Richman; 6) treatment of 141W94 failures with a nelfinavir-containing regimen in an ACTG study; and 7) ongoing follow-up of study 511 (Schmitt 1997).

PRICE & ACCESS

VIRACEPT costs $15.48 per day or $5,650 per year at the recommended dose *wholesale*. This is more expensive than Crixivan (indinavir) and less expensive than Invirase (saquinavir) or Norvir (ritonavir). Still, the price is too high. While it's Agouron's first drug, it reached market in unprecedented time, so development costs were surely much lower than the typically-cited figure of $500-700 million, which reflects an industry average assuming *ten years* of development time and several large, long phase III trials. VIRACEPT took just 38 months from phase I testing to FDA approval.

Recommendation 9: Agouron should consider a price for VIRACEPT more in line with that for Crixivan, the market leader, if it wants to be a widely-used contender for first-line protease therapy.

Agouron responds, "While we appreciate your comments, current pricing will remain. Please remember that this is Agouron's first commercially available product after being in existence for thirteen years. We have additional products in our pipeline that obviously require developmental dollars..." (Schmitt 1997).

Agouron established a patient assistance program to assist people in obtaining reimbursement for nelfinavir. The company says it will "provide drug free of charge to people who are unable to pay for drug or find appropriate reimbursement sources." Agouron has also agreed to provide Medicaid and state AIDS Drug Assistance Programs (ADAPs) the standard Medicaid discount (17.5% off), and will provide nelfinavir free of charge to all children under the age of 12 not covered by public or private health insurance. "No child will go without drug." (Agouron 1997b). The patient assistance program for adults and children can be reached at 1.888.777.6637. Product information can be obtained at 1.888.847.2237.

COMMENT

Agouron conducted what was in many respects a model antiretroviral drug development program, with rapid development and a database which clearly merits accelerated approval. Particularly praiseworthy were the development of nelfinavir for children and the expanded access program. Its postmarketing development plan seems both ambitious and reasonable. Its marketing campaigns have been no more egregious than those of its competitors[2], and yet one cannot help wishing that they would all subject their products to head-to-head and sequencing studies, with standardized resistance assays carried out by academic researchers not beholden to individual sponsors, rather than engaging in the currently fashionable sport of rival assay-bashing and rampant speculation.

However, we remain concerned that FDA approved the drug without a public hearing of the Antiviral Drugs Advisory Committee. While clearly the package merited approval, public hearings are essential for researchers, clinicians, HIV community representatives and treatment information providers to have a chance to see that data critically assessed by FDA staffers, Advisory Committee members, and experts speaking in public session. The approval of nelfinavir without a public hearing sets a poor precedent, especially as the drug is likely to be widely used.

Recommendation 10: The FDA should always convene Antiviral Drugs Advisory Committee hearings when considering licensing for a new antiretroviral agent.

TAG appreciated Agouron's rapid and comprehensive response to our letter sent this spring in anticipation of this report. Few other sponsors (among them Gilead and Vertex) has been as forthcoming. The larger companies -- and particularly Abbott and Glaxo Wellcome -- have stonewalled our requests for information at every point. It is interesting that small, innovative biotech companies seem to have a more forthcoming, forthright corporate culture than many of the more established big pharma behemoths, despite the greater experience in AIDS drug development of the latter.

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[2] FDA scolded Agouron for a press release released on April 11 which was "misleading... lacks balance and implies that the results of this study are more representative than they really are," (*Wall Street Journal* 1997); perhaps this slap on the wrist reflects Agouron's relative inexperience with advertising, since it's never before had a licensed product.

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IIIC. PROTEASE INHIBITORS

ii. Saquinavir Soft Gel Capsules / Invirase™ (Hoffmann-LaRoche Co.)

by Mark Harrington

Some [activists] *say lives were endangered by Roche's aggressive marketing of an inferior drug and then hyping it without solid scientific basis. What's more, the FDA's accelerated approval process, fought for by AIDS activists to help save lives, fails to provide a safety net for consumers after drugs are approved.*

-- Enid Vázquez (1997)

We really believed what [the activists] *said at the* [May 1997] *meeting and wanted no more confusion about the two drugs.*

-- Jeff Winton, director of public affairs, Hoffmann-LaRoche, quoted in *Positively Aware* (Vázquez 1997)

BACKGROUND

One of the most interesting potent new antiretrovirals in development is the *soft gel capsule (SGC) formulation of saquinavir.* For the purposes of this report, we are treating it as a qualitatively new and different drug from Invirase™ brand saquinavir mesylate, which was approved in a hard gel capsule (HGC) formulation at 600 milligrams (mg) thrice daily (tid) by the US Food & Drug Administration (FDA) in December 1995; it was the first licensed HIV protease inhibitor.

About the sponsor. This is the house that Valium built. Hoffmann-LaRoche Inc.is a Swiss-based global giant with far-flung investments in pharmaceutical and biotechnology research. "Cynical", "greedy", "manipulative", "opportunistic", "penny-pinching", "short-sighted", "slipshod" -- do these words come to mind when you think of Hoffmann-LaRoche's AIDS drug development efforts? They should. Examples of such behavior are legion, from the fiasco that was ddC to the joke that is the current formulation of saquinavir to the curious decision by the Basel-based pharmaceutical giant to drastically curtail development of valganciclovir, the oral ganciclovir prodrug which offered the hope for finally being an effective prophylaxis for cytomegalovirus (CMV) disease. As one high-placed Federal official noted (off the record, of course) of the latter decision, "Roche finally has a decent drug, and they're thinking of dropping it." Some feel that Roche's HIV program gives the "ethical" pharmaceutical industry a bad name.

ANTIRETROVIRAL POTENCY

Saquinavir, like ddC, is the most potent drug of its class -- *in vitro*. However, only 4% of the drug gets into the bloodstream in the licensed HCG formulation. Hoffmann-LaRoche was in such a hurry to get its drug licensed as the first protease inhibitor that it never bothered doing the dose-ranging studies which could have defined a maximum tolerated dose (MTD) for saquinavir.

CLINICAL TRIALS & TRIBULATIONS

I was a member of the ACTG's Primary Infection Committee when Roche approached them to conduct the phase II study, dubbed ACTG 229. The dose chosen was 600 milligrams (mg) thrice daily, based, they claimed, on three European phase I studies, or, as others thought, on a limited drug supply which made higher doses impractical -- or not worth Roche's investment. While the Primary Infection Committee was never known as a bastion of open scientific debate, ACTG 229 was swaddled in a secrecy unusual even for them. Roche declined to present the results of its phase I studies to the committee as a whole. Rather, they allowed Thomas Merigan of Stanford University and Ann Collier of the University of Washington at Seattle to take a peek at the alleged phase I virological response to saquinavir.

The study would take place in AZT-experienced patients, then the favorite population for trials of new antiretrovirals (remember ACTG 155?). They would be randomized to receive either AZT and ddC, AZT and saquinavir, or AZT, ddC and saquinavir. This was one of the first of the so-called "incestuous combination" studies recently pilloried by Joep Lange, in which a company's own drugs are studied together as much as possible, regardless of the scientific rationale for doing so[3].

Preliminary review of the study design by the Division of AIDS (DAIDS) and Harvard's Statistics & Data Analysis Center (SDAC) raised several concerns, which I mentioned to Dr. Collier (the principal investigator of ACTG 229) in a letter on 30 September 1992:

> I remain perplexed about the current design of ACTG 229. *In particular, I share the CTRC's concern "about the selection of 600 mg tid as the dose of Ro 31-8959* [saquinavir] *since there is no established maximum tolerated dose"* [NIAID Clinical Trials Review Committee letter, 27 August 1992]. Doses as high as 1200-1800 mg tid have been tested in HIV-negative patients and found to be safe... but people with HIV have only been given doses up to 600 mg tid. I would concur with the CTRC that "the need for the pharmaceutical sponsor to be forthcoming with data from their European trials" is pressing as we proceed towards opening ACTG 229...
>
> I became even more concerned when I read David Schoenfeld's SDAC review. His bottom line was that *"the proposed study will not be able to detect whether Ro 31-8951 has*

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[3] Lange JMA. Current problems and the future of antiretroviral drug trials. *Science* 1997;276:548-50. Based on "Tribulations of Trials: Where Do We Go From Here," at Fourth Conference on Retroviruses & Opportunistic Infections, Washington, D.C., 25 January 1997.

moderate activity." (Harrington 1992)

Needless to say, the ACTG brushed aside the concerns of statisticians and activists and conducted the study as Roche wished it to. 300 AZT-experienced individuals were enrolled and followed for 18 months.

By June 1994, Roche had detected the surrogate marker response it hoped for (triple drug combination proved superior to either two drug combination as measured by CD4 cell response and, less impressively, by viral load). As Schoenfeld predicted, the study failed to show whether saquinavir was any more potent than ddC, the weakest of the nucleoside analogues *in vivo* (Collier 1996).

Undeterred by this minor annoyance, Roche promptly petitioned the FDA to consider an accelerated new drug application (NDA) for saquinavir.

Worried by the precedent this would set for the protease inhibitors as a class, TAG then wrote to FDA Commissioner David Kessler requesting that accelerated approval for saquinavir be placed on hold until a full and open public debate could take place to assess how much data would be required for accelerated approval of protease inhibitors, and how post-marketing confirmatory studies should be designed (Cox 1994).

In the controversy that ensued, Roche quietly agreed to double the size of its pivotal efficacy trials, thereby increasing their ability to determine whether saquinavir provided any clinical benefit. Unfortunately, the study which was eventually to provide such evidence -- Roche NV14256B -- compared saquinavir to ddC to the combination in AZT-experienced patients. Since the role of ddC in this population is far from clear, and its benefit dubious in any population, such a control arm must be regarded as questionable. Nonetheless, to no one's surprise, the combination of these two drugs, each the weakest in its class, proved to be more potent than either one alone.

This led to accelerated approval for saquinavir, now dubbed INVIRASE™, by the FDA in November 1995. The drug was licensed at the dose studied in ACTG 229, 600 mg thrice daily, despite the fact that there was *already* evidence at the time that a dose twice as high was more potent and equally tolerable (Schapiro 1995). Moreover, it was already known at the time that suboptimal doses of protease inhibitors might predispose HIV towards the development of resistance and possibly even cross-resistance to other protease inhibitors (Condra 1995).

RESISTANCE & CROSS-RESISTANCE

Thus, ever since saquinavir's licensure at the end of 1995, Roche has known that the licensed dose was suboptimal and that its use could well result in widespread cross-resistance to multiple protease inhibitors.

Had saquinavir rapidly become the drug of choice for people who were failing on nucleoside analogue monotherapy or double therapy, a public health disaster might well have resulted. If cross-resistance became widespread through broad and prolonged use of saquinavir, many people would not have been

able to benefit from the later introduction of more potent protease inhibitors.

Luckily, help was not long in coming. Within three months, both Abbott's NORVIR™ brand ritonavir and Merck's CRIXIVAN™ brand indinavir were licensed, at doses which were able, when given in combination with new reverse transcriptase inhibitors, to drive viral load beneath the limit of detection in over 75% of patients who could tolerate them for up to one year (Merck 035, etc.), and could prolong health and life when compared with standard of care (Abbott study, ACTG 320). Of note, Roche's survival study used ddC monotherapy, which no one, even then, regarded as standard of care.

None of this deterred Roche from charging $5,800 wholesale for a year's supply of INVIRASE™, an inexplicably high price for such a weak drug.

Yet Roche faced a quandary. Despite its slipshod, post-haste development plan, two more potent protease inhibitors reached the market within three months of its own accelerated NDA, and even those unversed in the intricacies of retrovirology could tell that they were far more potent. How could Roche redeem its drug?

Two opportunities presented themselves. The first was to use the ability of other protease inhibitors -- and particularly ritonavir -- to inhibit cytochrome p450 metabolism, thereby increasing the bioavailability, exposure, half-life, and maximum concentration of saquinavir to therapeutic levels. The other, more prosaic, approach was to finally begin addressing the need for a more bioavilable formulation and higher dose of saquinavir itself, unassisted by complex hepatometabolic pathways. Roche proceeded to follow both leads.

As for those participants lucky enough to survive ACTG 229, they were given the chance to enroll in ACTG 333, the first-ever randomized study in protease failures. ACTG 333 randomized 72 SQV-experienced individuals to continue on hard gel cap (HCG) saquinavir at 1.8 grams/day, switch to the more bioavailable soft gel capsule (SGC) formulation at 3.6 grams/day, or switch to indinavir at 2.4 grams/day. They were asked *not to switch underlying nucleoside analogues* for the first eight weeks of the study. The primary endpoint was virologic response. The study would stop early if no arm achieved greater than a 0.7 $\log_{10}$ reduction in HIV RNA. After an interim analysis conducted when 72 patients reached 8 weeks of follow-up showed that no arm did in fact achieve such a reduction, ACTG 333 was terminated.

Participants had received an average of 112 weeks of prior saquinavir therapy. 86% were male, 75% white, non-Hispanic, and the median age was 43. Median baseline HIV RNA was 20,911 copies/mL; 6% had fewer than 200 RNA copies/mL at entry. Median baseline CD4 was 220 cells/mm^3. Follow-up for the first 72 subjects was a median 18 weeks (range 12-22 weeks).

ACTG 333: 8 Week RNA + CD4 Results

	HIV RNA (log_{10}) reduction	% undetectable (<200/mL) ever*	at week 8	CD4 change (/mm^3)
SQV-HGC	+0.04 log	2/24 (8%)	2/22 (9%)	- 0.4 cells
SQV-SGC	-0.23 log	4/22 (18%)	2/20 (10%)	+ 37 cells
IDV	-0.58 log	9/21 (43%)	7/19 (37%)	+ 22 cells

* Undetectable at one or more of the week 2, 4, 6, or 8 timepoints.

The study team commented that, "while there was variability in the RNA responses in individual subjects in both the IDV and SQVsgc arms, the mean decreases in RNA and mean CD4 cell increases in both arms was [sic] less than seen in other trials of protease inhibitor[s] used in combination with nucleosides." (ACTG 1997).

Based on these disappointing results, accrual to ACTG 333 was terminated. Already enrolled patients were allowed to remain on assigned therapy or switched based on virological response. Genotypic resistance analyses are underway. The study ends on 14 July 1997 (Bastille Day).

Several things are notable about ACTG 333:

1. These were sequential monotherapy patients, many given first AZT, then AZT/ddC or AZT/saquinavir (in ACTG 229), then given SQV-HCG, SQV-HCG or indinavir, without regard to treatment history or virological status at baseline. Certainly the trial would be designed differently if it were begun today.
2. ACTG 333 participants had almost two years (112 weeks) of previous saquinavir experience upon enrolling into 333.
3. Most participants switched to SQV-SGC did not experience much of an antiretroviral benefit. The minority who did probably had not been receiving therapeutic doses of SQV-HGC, and hence had not developed SQV resistance.
4. Most participants switched to indinavir experienced far less of a viral load reduction than typical with this drug when given as a first protease inhibitor[4]. However, results are given for indinavir patients *as a group.* Most likely they fall into three subgroups: a) fully susceptible to indinavir; b) partially susceptible to indinavir (as suggested by the group average); and c) wholly resistant to indinavir. What proportion of patients fall into each category is an intriguing question which may be answered, at least in part, by the ongoing resistance analyses.

After the ACTG 333 fiasco, Roche called various community groups in a series of anxious conference calls

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[4] In Merck 028, protease-naive patients given indinavir as monotherapy experienced a 1 log reduction in HIV RNA at two weeks which was sustained for 24 weeks, by which point 37% of them had HIV RNA levels below 500 copies/mL. CRIXIVAN (indinavir sulfate) package insert, Merck & Co., 1996.

to try and squelch doubts raised by the study. Roche's whole marketing campaign for INVIRASE™ was based on the drug's alleged tolerability and the presumption that you could use it as a first-line protease inhibitor and then go on to use others without fear of cross-resistance[5]. ACTG 333 called this notion into doubt. Moreover, on one of these calls, Roche representatives revealed that saquinavir HGC, when used with AZT and 3TC in antiretroviral-naive individuals, lowered viral load beneath the limit of detection in fewer than 40% of patients -- less than AZT/ddI/nevirapine in INCAS/BI 1046.

Roche's anxieties were deepened when it apparently received a preliminary draft of the HHS Clinical Practice Guidelines for Treatment of HIV Infection and discovered that -- *quelle surprise!* -- saquinavir did not make the cut as a first-line protease inhibitor.[6]

Spurred by the prospect of being left off formularies across the country, Roche decided to accelerate its filing for FDA approval of the new saquinavir formulation.

Thus it was that on 14 May 1997 Roche convened a conclave of treatment advocates from the East Coast and the Midwest to hear the exciting new data on its new formulation, soft gel capsule (SGC) saquinavir. The meeting took place at the chic, sleek, postmodern Soho Grand Hotel in lower Manhattan.

They had a new team of eager young investigators and public relations experts who, they earnestly explained, wanted to "open doors", "start an ongoing dialogue" -- even "set up a community advisory board". Gasps emanated from the activists who remembered the fiasco of Roche's previous CAB, which resigned *en masse* amidst screams and spilled shrimp cocktail at a *melee* at the Times Square Marriot Marquis in summer 1992 over ddC. Roche's new team, unaware of its predecessors' plight, quickly redubbed the proposed CAB a "task force".

Clinical team manager Laurent Fischer presented preliminary data on new (SGC) saquinavir and asserted that SGC provided *eight to nine times* the exposure of the licensed hard gel capsule (HGC) formulation (Roche 1997).

Activists at the meeting were skeptical, assailing Roche's failure to define an MTD before bringing saquinavir to market, and said since the drug company had made its bed, now it must lie in it. Some asked the company to reduce the price of the current formulation by 7/8 (to approximately $875 per year) to reflect Roche's new assessment of its potency.

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[5] See its advertisements which until recently ran in such journals such as *Genre*, *Out*, *Poz*, etc., "When considering and HIV protease inhibitor... Consider a protease inhibitor you can live with," and "What's your strategy...?"

[6] The HHS Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents comment on the role of saquinavir with two nucleosides as first-line therapy with a footnote in Table VI which reads, "The current hard gel capsule formulation of saquinavir is not recommended do to poor bioavilability..." (HHS 1997). The company is furiously lobbying to change this rational and, indeed, restrained, comment.

Key studies of the soft gel cap saquinavir include NV15107, a dose finding study which "identified 1200 mg three times daily as the preferred dose," NV15182, a safety study, and NV15355C, a virological equivalency study comparing hard to soft gel caps in 160 treatment naive patients in the USA and Canada. They will be randomized to receive (open-label):

* SQV-HGC 600 mg tid + 2 new nucleosides, *or*
* SQV-SGC 1200 mg tid + 2 new nucleosides

Note that, just to be sure, Roche is giving *twice the dose* of the new formulation compared with the old (1200 vs. 600 mg tid) -- which would likely make it superior even if the new formulation were no more bioavailable (remember Schapiro 1995?). The company claims SGC saquinavir is 12% bioavailable (compared with 4% for hard gel caps), and stated that a monotherapy study among 22 volunteers demonstrated a 1.43 $\log_{10}$ (96.3%) reduction in HIV RNA. The primary "efficacy' comparison in NV15355C will be HIV RNA and CD4 changes over the first 16 weeks, after which SQV-HGC patients will be rolled over to SQV-SGC and followed for a further 32 weeks. The 16 week analysis is due to be complete by summer 1997 and will presumably be the basis for the FDA filing.

Ongoing & Planned Studies of SQV-SGC

	PI + RTIs	2 PIs/2 RTIs	PI/NNRTI/RTI	N
Antiretroviral naive	2 studies	2 studies	1 study	437
RTI experienced, protease naive	2 studies	3 studies	2 studies	845
Protease experienced	--	2 studies	2 studies	370
N	330	692	630	1,652

Needless to say, several additional studies continue to follow patients on hard-gel cap saquinavir. Most recently, Roche announced triumphantly the successful conclusion of its European study in antiretroviral naive patients, SV14604C (AZT vs. AZT/ddC vs. AZT/saquinavir vs. AZT/ddC/saquinavir). 3,485 antiretroviral naive (no more than 16 weeks AZT experience), HIV-infected individuals enrolled in 22 countries. Baseline CD4 was around 200 and median baseline HIV RNA was 5 logs. The triple drug regimen scored a 50% reduction in clinical endpoints compared with either two drug arm (Roche 1997b):

SV 14604: AZT/ddC vs. AZT/saquinavir HGC vs. AZT/ddC/saquinavir HGC

	AZT/ddC	AZT/SQV HGC	AZT/ddC/SQV/HGC
AIDS or death	142	116	76

At the May meeting, Roche had the effrontery to claim that in ACTG 333, "patients switching protease inhibitor showed benefit" and attributed the disappointing results to "evolving treatment strategies".

This evoked considerable outrage. In fact, at the New York meeting and at a subsequent one in

California, activists demanded that Roche immediately stop running its "Strategy" advertisements for INVIRASE™, and stop advertising the drug as first-line therapy until FDA approves the soft gel caps.

Roche pulled the ads (Vázquez 1997).

We look forward to seeing whether the FDA concurs with Roche's assessment of the potency of saquinavir SGC, and to its use in creative and novel antiretroviral combinations.

As for those who have believed Roche and taken saquinavir HGC at the approved dose, the company has announced no plans to compensate them for whatever options this therapeutic choice may have foreclosed.

In summary:

1. Roche went to market in November 1995 knowing that the dosage and formulation of saquinavir for which it sought approval were suboptimal and might lead to resistance or cross-resistance.
2. Roche promoted saquinavir as a first-line protease option for 18 months while studying higher doses and a new formulation.
3. ACTG 333 reveals that individuals who took saquinvir HGC are less likely to experience a maximal response from either saquinavir SGC or indinavir.
4. Individuals considering starting combination therapy with a potent protease inhibitor should avoid starting with saquinavir at least until the new formulation is licensed by FDA, and then only if data support Roche's assertion that it is much more potent than the HGC.
5. In the interim, the only way to achieve maximal doses of saquinavir (HGC) is to double the dose and take it with a potent cytochrome p450 inhibitor such as ritonavir or nelfinavir. Even among those whose insurers will cover this, it will cost $14,000 per year for the saquinavir alone (never mind the nukes), which is unconscionable.
6. It's time for activists to start monitoring and critiquing the ads placed by drug companies in consumer magazines.
7. Roche should consider some form of compensation for individuals who have taken saquinavir HGC and may have developed cross-resistance to other, more potent protease inhibitors from which they may not now benefit.

After the meeting, Roche invited the activists upstairs for cocktails and "refreshments". Let us hope that the Soho Grand's cocktails were more potent than those being hawked by the unscrupulous pharmaceutical giant. I wouldn't know; I didn't go.

*

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IIIC. PROTEASE INHIBITORS

iii. 141W94 / VX-478

(Vertex Pharmaceuticals, Glaxo Wellcome, Kissei Pharmaceuticals)

by Paul Dietz

Most disturbingly, some AIDS doctors fear that even before GW141 hits the market, some patients may have acquired resistance to it because they have fared poorly with the already-available protease inhibitors.

-- Michael Waldholz (*WSJ* 1997)

BACKGROUND

141W94 / VX-478 is an experimental HIV protease inhibitor formulated by Vertex Pharmaceuticals and licensed for clinical development to Glaxo Wellcome (outside of Asia) and Kissei Pharmaceuticals (for the Asian market). Though expanded Phase II/III trials have just gotten underway, 141W94 / VX-478 holds the promise of exceptional pharmacokinetic attributes and potency, twice-per-day dosing without dietary limitation, and a resistance profile that may be distinctive from one or more of the approved protease inhibitors. While this early lab data has lifted the hopes of Vertex's faithful cadre of researchers (in addition to its stock price), a great multitude of questions remain unanswered in the clinic. Fortunately or not, depending on one's perspective, the course of clinical trials plotted out by Glaxo Wellcome is a long and winding road.

About the sponsors. Vertex Pharmaceuticals is a small drug discovery company started by a former lead chemist from the research lab where Merck developed its HIV protease inhibitor. The company uses structure-based "rational" design methods to create small molecule drug candidates for the treatment of HIV, multidrug-resistant cancer, autoimmune diseases, and hepatitis C. VX-478 is currently Vertex's most advanced drug candidate.

"Structure-based" or "rational" drug design gained interest in the 1980s as the availability of powerful computer-based modeling tools offered an alternative to the traditional "trial and error" drug screening process. Structure-based design begins with the use of X-ray crystallography and nuclear magnetic resonance to establish the three-dimensional structure of a therapeutic target, most often a protein. Using this information, scientists "design" a chemical compound that binds with the target protein in a way that either blocks or enhances the protein's natural activity. Once a lead compound is identified, additional design work is performed in an iterative manner to optimize the drug's potency and

pharmacokinetic attributes.

Given its dearth of resources and development experience, Vertex has partnered with Glaxo Wellcome and Kissei Pharmaceuticals to guide VX-478 through clinical trials. Glaxo and Kissei will fund a large portion of the development cost and will provide technical and marketing expertise in exchange for distribution rights in their respective territories. Glaxo Wellcome is one of the world's largest pharmaceutical company, and through its ownership of rights to AZT and 3TC™, has a leading market share in the market for HIV antivirals. Glaxo's license includes the US, Europe, and certain other territories outside of Asia. Kissei, a mid-size Japanese drug company, has the rights for Japan, China, and other markets in the far east. Vertex will receive a royalty on the sales of VX-478 should the compound pass all regulatory hurdles.

As if three companies holding financial stakes in 141W94 / VX-478 aren't enough, Glaxo and Vertex deemed it prudent to acquire a license from Searle, filer of certain patent applications over a broad class of protease inhibitors that apparently cover 141W94 / VX-478. Vertex and Glaxo paid Searle the astronomical sum of $25 million up-front, and will also pay a royalty on future sales. Though in theory, the drug's price (should it pass all regulatory hurdles) will be more a function of its competitive characteristics than its development cost, you can bet that the price will in some way reflect the daisy chain of stakeholders associated its development.

Mechanism of activity. Protease is an enzyme that enables HIV to cleave its proteins from the gag-pol polyprotein precursor chain, into smaller functional units essential to HIV infectivity. All inhibitors of HIV protease alter the action of this enzyme through binding within the protein-cleaving site, resulting in genesis of morphologically-altered noninfectious virus.

ANTIRETROVIRAL POTENCY

In vitro studies. 141W94 / VX-478 is a potent inhibitor of HIV *in vitro* with a mean IC_{50} of 0.08 uM in HIV-infected MT4 cells and peripheral blood lymphocytes, and 0.012 uM against a diverse set of clinical isolates (St Clair). The IC_{90} is 40uM in CEM cells infected by HIV-IIIB (Kim). These inhibitory concentrations are known to increase by 1.5 fold in plasma due to the binding of 141W94 to alpha-1 acid glycoprotein (Livington).

C_{min} levels above the IC_{90} (adjusted for plasma protein binding) can be achieved with doses as low as 300mg twice per day (bid). Doses of 1200mg BID result in concentrations of 8-10 times the IC_{90} (ACTG). According to the protocol from an ongoing ACTG trial, "results of animal and single-dose human studies have led some researchers to believe that a 600mg bid dose of 141W94 / VX-478 would result in blood levels that are comparable to (the approved dose of) indinavir in terms of their relationship to IC_{90} for the compound" (ACTG).

In vitro, 141W94 / VX-478 is synergistic with the nucleoside analogs AZT, DDI and 1592U89 (St Clair), and with the protease inhibitor saquinavir (St Clair). In addition, 141W94 / VX-478 shows additivity with indinavir and ritonavir (St Clair).

Summary of clinical data. Data have been reported from two small clinical trials involving a total of forty-nine patients. In both cases, the duration of study was just four weeks.

Monotherapy. Preliminary results of a dose-ranging study were presented at the 36th ICAAC (Schooley). The study included forty-two protease-naive patients with between 150 and 400 CD4 cells/mm^3 at baseline.

4 Week HIV RNA + CD4 Changes on GW141

Dosage (bid)	300 mg	600 mg	900 mg	1200 mg
N	9	12	9	7
Baseline HIV RNA	4.72 $\log_{10}$	4.84 $\log_{10}$	4.75 $\log_{10}$	5.04 $\log_{10}$
HIV RNA change	-0.58 $\log_{10}$	-1.025 $\log_{10}$	-1.69 $\log_{10}$	-1.95 $\log_{10}$
N	10	9	10	7
Baseline CD4	254	303	305	266
CD4 change	+64	+85	+35	+110

(Schooley 1996)

The viral load suppression and CD4 response at the 1200mg bid dose is extremely good for monotherapy. The discontinuity in CD4 cell increases seen at the 900 mg dose might simply reflect natural variability in such a small number of study patients. Three patients (7%) discontinued the study due to adverse events - two with rash, one due to worsening chronic colitis. This trial may have been influential in Glaxo Wellcome's decision to pursue development using the 1200mg bid dosing regimen.

GW141 + abacavir (1592U89) in protease-naive patients. Nine patients were enrolled in a four week pilot study testing the safety and activity of 141W94 / VX-478 (900mg BID) in combination with abacavir (1592U89), an experimental nucleoside analogue also in development at Glaxo Wellcome. Patients began the study with between 150 and 400 CD4 cells/mm^3.

GW141 (900 mg bid) + Abacavir (300 mg bid): 4 Week HIV RNA + CD4 Changes
(4th Conference on Retroviruses and Opportunistic Infections, January, 1997)

	N	Baseline	Change *
HIV RNA	7	4.17 $\log_{10}$	-2.08 $\log_{10}$
CD4 cells/mm^3	7	223	+79log

In this study, five of seven patients had their viral load drop below the limits of detection (400 copies/mL). Two of nine patients withdrew from the trial due to adverse events - one due to dysarthria (difficulty with speech) and rash, and the other because of nausea.

While these preliminary data justify the expanded study of 141W94/VX-478 with abacavir, we should

keep in mind that very early potent data reported from pilot studies in the past has often led to disappointment when data from a larger body of patients has shown more modest effects. Cases in point would include the preliminary data reported at the 1995 ICAAC for the d4T/ddI combination, and the early results reported on nelfinavir plus d4T (see "Nelfinavir", above).

One might be tempted to question Glaxo's pretext in conducting a trial of two of its development drugs in combination. This same nepotistic pairing strategy with 3TC, another compound not developed but controlled by Glaxo, and AZT helped drive increases in sales of AZT boosting its position relative to d4T which also works well with 3TC. However, the combination of 141W94 / VX-478 and abacavir is intriguing in that it pairs two of the seemingly more potent and best penetrating HIV drugs in their respective classes. In addition, the twice-per-day dosing schedule, and potentially lower cost, offered by the dual combination would be a welcome addition to the HIV arsenal. Since it is hoped that both drugs may benefit some antiretroviral-experienced patients, a similar trial is planned for patients that have failed triple therapy.

RESISTANCE & CROSS-RESISTANCE

In vitro resistance. It's become sadly apparent that the HIV protease can withstand multiple mutations in the face of selective pressure while maintaining, or regaining through compensatory mutations, most or all of its ability to function. Though resistance patterns to 141W94 / VX-478 have yet to be well characterized in the clinic, lab studies have determined that this agent is vulnerable to resistance just like all the other drugs that have come before.

141W94's habitual triple mutation. In vitro serial passage with 141W94 / VX-478 has spotlighted a predominant triple-mutation at the 46, 47, and 50 residues. The mutation at codon 50, a key bonding point for the molecule, confers a moderate three-fold reduction in sensitivity to 141W94. The second mutation, M46 to I/L, produces a double mutant with up to 7 times reduced sensitivity. Typically the third mutation to arise, I47V, produces a triple mutant with a 20-fold reduction in sensitivity. Despite improved growth properties over the single mutation virus, the triple variant is slightly growth impaired compared to the wild type (Painter).

To date, the 46/47/50 triple mutation has not emerged from exposure to other protease inhibitors, and such variants remain susceptible *in vitro* to saquinavir and to a lesser degree indinavir (Painter). However, we must caution that the cross-resistance equation is complex. Variables include, but are certainly not limited to the duration of HIV infection, virulence and fidelity of the HIV strain, the intensity and duration of current and previous antiretroviral drug exposure, host factor variability, etc. As a result, promising early lab data for other drugs has often been contradicted in the clinic (for more information refer to "Saquinavir SGC" above). We therefore advise caution in drawing early inferences from this lab data on cross resistance.

Other recurring mutations. Additional mutations have been also been observed with 141W94 *in vitro* including L10F, D60V, and I84V. While the role of these mutations is unclear at the moment, the fact that mutations at 10 and 84 are seen with other protease inhibitors is somewhat alarming. While some

believe that these mutations may have only compensatory effects on enzyme stability and growth kinetics (Painter), they seem to arise rather early and appear able to confer resistance *in vitro.*

GW141 Resistance Profile

Exposure*	Mutation	IC90		Fold Increase in IC_{90} After Serial Passage GW141	Crixivan	Saquinavir
0 / none	None	23		1	1	1
7 / 800	L10F, I84V	880		38	2	1
8 / 1600	L10F, I50V	2,000	87	NA	NA	
9 / 1600	L10F, M46I, I47V, I50V	3,400	150	3	1	
10 / 3,200	L10F, M46I, I47V, I50V, D60V	4,000	170	6	1	

(Partaledis)

* Number of serial passages / selecting concentration (nM); NA = data not available assay not performed.

The mutation at codon 84 which emerges early *in vitro* but is then replaced by the more assertive I50V is unsettling in that it is associated with resistance to other protease inhibitors including indinavir and ritonavir.

Adding 141W94 / VX-478 to the Protease Resistance Roster

HIV Protease Point Mutation Site

Saquinavir	10			***48***		63	71					***90***
Ritonavir	10	20	36	46	54	63	71		***82***	***84***		***90***
Indinavir	10	24	36	46	54	63 65	71		***82***	***84***		***90***
Nelfinavir		***30*** 35	36	46			71	77			88	***90***
141W94	10			46 47 50						84		

[Clinically observed mutations correlating with phenotypic resistance are shown in ***bold italics***. *In vivo* resistance data on 141W94/VX-478 are not available.]

Cross resistance to 141W94 / VX-478 after indinavir. HIV-infected cells that have been pretreated *in vitro* with indinavir are reportedly four fold less sensitive to 141W94 / VX-478 (Tisdale).

Resistance in vivo. At the Fourth Conference on Retroviruses and Opportunistic Infections in January 1997, Glaxo Wellcome reported the results of genotypic (amino acid sequence) and phenotypic (drug sensitivity) resistance analysis from the previously-described four week dose-escalating trial of 141W94 / VX-478 monotherapy.

Not surprisingly, some patients receiving low doses of 141W94 / VX-478 began to experience a rebound in viral load by week four. However, no consistent pattern of amino acid substitutions were noted

(Tisdale 1997) and researchers dismissed any sporadic mutations as the result of "natural genetic drift" (Vertex). With regard to the phenotypic analysis, one allegedly noncompliant patient demonstrated a shift in viral sensitivity of 4-5 fold during the study (Vertex).

Based on this data, Vertex issued a rosy press release stating that test results "showed that resistance does not appear to develop to 141W94 / VX-478 during four weeks of monotherapy, whether at the lower sub-optimal doses or at higher doses where potent antiretroviral activity was observed". In addition, the release stated that "phenotypic analyses showed no reduction in drug sensitivity after four weeks".

Though the wording of this release was carefully chosen to exclude the noncompliant patient, Vertex's statement borders on hyperbole. Instead of such naive extrapolations, we need clinical trials that test the effect of 141W94 / VX-478 in patients that have failed other protease inhibitors and vice versa.

ADVERSE EVENTS & TOXICITY MANAGEMENT

Animal toxicology. Administration of 141W94 / VX-478 for 28 days was well tolerated in rats at doses up to 1,000 mg/kg/day, and in dogs at up to 400mg/kg/day (ACTG 342 Protocol). Adverse events included reversible increases in the size of liver cells and liver weight in the rat, though this was not noted in the dog (ACTG 342).

Human toxicology. Doses of between 150-1200mg BID were well tolerated in the Phase I/II dose-ranging study. Adverse events occurring in more than 10% of patients were rash, diarrhea / loose stools, and headache.

The most frequent adverse experience associated with 141W94 / VX-478 is clearly rash. In pooled clinical trial data, approximately 20% of patients developed rash, with 3% experiencing severe (grade III/IV) rash. One case of Stevens Johnson syndrome was noted in a patient who was receiving a number of drugs in addition to his or her antiretroviral regimen, including a sulfa-based drug which are known to cause of Stevens Johnson Syndrome. The study drop out rate resulting from rash is said to be about 6%, though there are reports that use of antihistamines such as Benedryl have allowed a number of patients with less severe rash to be treated through until the condition resolves (personal conversation). The rash usually appears between day nine and twenty of starting the drug, but as the risk of rash does not appear to be dose-related, the use of a titration schedule is not currently under consideration.

Note on hemophilia. Special caution may be warranted when administering protease inhibitors to people with hemophilia. "There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors. In some patients, additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship has not been established." (Agouron 1997).

Note on diabetes. Through June, 1997, approximately 80 cases of diabetes had been reported in patients taking HIV protease inhibitors. As a result, the FDA advised doctors to monitor patients for

abnormal blood sugar levels. Elevated blood sugar levels were found in some animal toxicology studies of 141W94 / VX-478, so the situation will have to be closely observed as with other protease inhibitors.

Recommendation 1: Glaxo Welcome should carry out safety studies to determine the risk factors and causes of diabetes in protease inhibitor recipients.

PHARMACOKINETICS, FOOD & DRUG INTERACTIONS

141W94 / VX-478 is one of the smaller and more soluble protease inhibitors to reach clinical evaluation. Its bioavailability ranges between 40% and 90% in animals and is estimated to be 70% in humans, though the latter estimate is based upon algorithm rather than the complex tests required to achieve an accurate measure. According to Glaxo Wellcome, the C_{min} is 0.17 micrograms/mL for the 900 g dose and the C_{max} is 5.00 micrograms / mL. The C_{max} for the 1200mg dose reportedly ranges between 3.9 um and 18.0 um, but information on the C_{min} for this dose was not obtainable.

The area under the curve (AUC) is said to be linear within the 300 mg to 1,200 mg dosing range, and interpatient variability for AUC, C_{max} and C_{min} has been "minimal". The drug's half-life varies between seven hours at the 150 mg dose and ten hours at the highest tested dose (1200 mg). This compares favorably with Crixivan's relatively short half-life of about two hours. The average plasma concentrations of 141W94 / VX-478 at eight and twelve hours after dosing were greater than 10 times the IC_{50} (Painter). As a result, the twice daily 1200 mg dosing regimen is being employed in prospective clinical trials.

Dosing requirements. Fortunately, the absorption of 141W94 / VX-478 is not dependent on food intake and it may therefore be taken with meals or on an empty stomach. The disadvantage with 141W94 however, is that the 1,200 mg bid dose requires swallowing eight large capsules twice daily. Vertex is considering use of the pediatric liquid formation (at a 70 ml bid dose -- equal to roughly one-third of a soda can twice daily) as an alternative for adults that have difficulty swallowing the required number of pills. They are also working to reduce the 16 pill daily requirement.

Protein binding. The binding of HIV protease inhibitors to human serum proteins has caused the failure of a number of promising drug candidates (remember the Searle, Dupont Merck, and early Upjohn drugs?). However, it is important to consider not only whether the drug is protein bound, but also whether the binding is strong or weak -- the latter permitting the drug to free itself and go on to impede the replication of HIV. This is illustrated by the cases of ritonavir and nelfinavir which are highly protein bound and yet have shown potent efficacy *in vivo*. In plasma, 141W94 / VX-478 is approximately 90% protein bound, mainly to alpha 1 acid glycoprotein. However, the off rate is extremely fast -- suggesting that this should have little effect on antiviral activity -- though the protein binding is probably the reason that such a large dose of 141W94 / VX-478 is required. *In vitro* antiviral assays have shown that the addition of human plasma causes only a modest two-fold increase in the IC_{90} (Livington).

Lymph system penetration. The mesenteric (central body) lymph node tissue-to-blood concentration ratio in rats and mice was found to be more than 11 time based on AUCs with similar disappearance as in the blood (Painter).

Central nervous system (CNS) penetration. Tissue distribution studies indicate that the brain to blood AUC ratio is about 1.7 in rat (Painter). However, studies recently carried out at Vertex, also in the rat, indicate a lower brain tissue concentration. Brain tissue concentrations were found to be twice that of the CSF levels. A clinical trial is underway to assess the drug's penetration into the CSF (ACTG 342).

Seminal penetration. Semen is believed to be a major HIV transmission vector, and there has been concern that penetration of protease inhibitors into the testes may be suboptimal. As a result, this is being examined in clinical trials (see description of ACTG 342 below).

Drug Interactions. In general, HIV protease inhibitors inhibit the cytochrome-450 family of liver enzymes. Such inhibition is known to alter the levels of certain of other protease inhibitors and nonnucleoside reverse transcriptase inhibitors in the human body. Unfortunately, very little information regarding 141W94 / VX-478's interactions is available at the present time. According to a personal conversation with Glaxo Wellcome, the interactions are expected to be similar to indinavir.

Recommendation 2: Glaxo Welcome should consider undertaking a study to determine the safety, interactions, and efficacy of 141W94 / VX-478 in combination with methadone.

ONGOING TRIALS

A wide array of clinical trials are underway or planned for 141W94 / VX-478.

Phase II study with AZT and 3TC™. In September, 1996, Glaxo initiated a Phase II open label 12 week dose ranging study of 141W94 / VX-478 in combination with AZT and 3TC™ in 80 patients. The duration of this study has been extended to 24 weeks.

Phase III study with AZT and 3TC™. Even before obtaining the results of the Phase II trial, Glaxo lunged 141W94 / VX-478 into a multinational 30-site Phase III white elephant that was originally intended to be the pivotal trial but is now unlikely to provide meaningful data. In this trial, 240 adults were randomized to receive either 141W94 / VX-478 in combination with AZT and 3TC™ or to AZT and 3TC™ alone.

You will recall that a similar indinavir trial, ACTG 320, was stopped early when it was determined that the lack of complete viral suppression offered by the dual nucleoside arm was reconsidered unethical under the current treatment goal of suppressing viral load below the limits of detection. Since we are now fairly certain that three drugs are better than two, this trial will hopefully be stopped as quickly as was ACTG 320. In the meantime, Glaxo has reportedly returned to the drawing board to plan a trial comparing 141W94 / VX-478 to triple therapy with indinavir or nelfinavir in drug experienced patients.

ACTG 342. The NIH-sponsored AIDS Clinical Trials Group (ACTG) is conducting a perilous but interesting double-blind 24-week multi-center study that will randomize 84 protease naive patients to either the triple combination of 141W94 / VX-478 with AZT and 3TC™ or 141W94 / VX-478

monotherapy + nucleoside placebo. In addition to measuring the relative safety and changes in CD4 count for each arm, the trial will compare the proportion of patients whose plasma HIV RNA is suppressed below the limit of detection after 24 weeks of therapy. Genotypic and phenotypic resistance data will be gathered from patients who do not achieve full viral suppression.

Two interesting substudies will be conducted in conjunction with ACTG 342.

i. In substudy ACTG 847, a subset of patient volunteers from ACTG 342 will contribute cerebrospinal fluid (CSF) samples one hour after taking the first dose and at one other point during the 24 week treatment period. The patient's CSF will be evaluated for drug levels to assess the ability of the study drugs to enter and reduce HIV viral load in the CSF. It is hoped that HIV levels in the CSF are representative of brain tissue which is a known reservoir for HIV. Exaltations are due to the 35 trial participants who have volunteered for this intrusive substudy.

ii. In substudy ACTG 850, a subset of male patients from ACTG 342 will provide seminal fluid samples. The objective of this substudy is to assess the ability of the drugs to reach and reduce HIV levels in the semen. The testes are also a known biologic compartment for HIV and the semen is believed to be a medium for sexual transmission of the virus. Praise of a slightly different sort goes out to these unblushing patient volunteers as well, since the seminal donations are required to be imparted on site.

Hopefully the HIV isolated from CSF and semen can be quantitated and analyzed for phenotypic and genotypic resistance to the study drugs.

There are obvious ethical questions associated with this trial as well. The use of a single agent has come to be viewed as unethical under the presumption that monotherapy would encourage drug resistance and therefore treatment failure within a relatively short period of time; while antiretroviral drug combinations have been shown to slow resistance. However, ethics come into play only if the monotherapy arm is known or strongly suspected to be incapable of maximal viral suppression or likely to lead to drug resistance within the study period. Apparently, the ACTG feels that the potent antiviral activity and lack of drug-induced mutations witnessed in the four-week monotherapy trial provide adequate rationale for this study.

The potential gains from this study should also be considered. If it is found that monotherapy with 141W94 / VX-478 is able to achieve the same virological and immunological effects as triple therapy in all or a certain subgroup of patients, it could lead to more practical and less costly treatment strategies.

As a safeguard, subjects with detectable HIV RNA at weeks 16 and 20 will be offered open-label triple drug therapy as a consolation, though it is certainly questionable whether such "serial" triple therapy would be a wise choice at that point. Unfortunately, like other studies, the viral load measurements for this study will incorporate a minimum level of detection of 500 copies. It is unclear why a lower minimum could not be employed given that more precise tests with minimums of 400, 200, and even 20 are available.

Recommendation 3: The ACTG should consider using a viral load threshold of 200 rather than 500 copies per ml and a lower limit of 20 should be employed at the twenty-four week point for patients returning undetectable results at week 16.

This author feels that the monotherapy application of 141W94 / VX-478 in this trial has come a bit before its time. One would argue that this trial should have waited until the drug's long term (24 week) efficacy in triple combination is established. Moreover, it might have helped to alleviate concerns if 141W94 VX-478's propensity to cause cross-resistance to other protease inhibitors has been established prior to the trial as well. Then, a small monotherapy trial could have been initiated in a few patients with relatively low viral load.

Double protease combinations. In early 1997, Glaxo began a Phase II 24-week study to test the safety, pharmacokinetics and antiretroviral efficacy of 141W94 / VX-478 in combination with either indinavir, nelfinavir, and saquinavir. The trial will be conducted at three sites in the United States and will include a total of 48 patients. A fourth "control" arm will receive GW141-VX478 along with AZT and 3TC. Entry criteria will include a CD4 count in excess of 200 cells/mm^3 and baseline viral load or more than 20,000 copies per mL. No prior protease therapy is permitted.

In recent seroconverters. This study is being conducted in the Aaron Diamond Research lab of David Ho. It will compare 141W94 / VX-478 in combination with AZT, 3TC and abacavir with other so-called potential eradication arms in recent seroconverters.

PLANNED STUDIES

Comparison with indinavir and nelfinavir in drug experienced patients. Thankfully, this study will provide a head-to-head comparison of 141W94 / VX-478 with the approved protease inhibitors indinavir and nelfinavir in patients with previous antiviral exposure. As plans have not been finalized, details were not obtainable.

Pediatric study. A pediatric (sweet liquid) formulation has been developed and a clinical study in children is expected to commence during the summer of 1997. The study will compare the current standard of care (SOC) for pediatric treatment (presumably a pair of nucleoside analogues) to the SOC plus GW141. If the data warrants, Glaxo intends to file the pediatric and adult applications with the FDA simultaneously.

European study with abacavir. A study will take place in Europe that tests the combination of 141W94 / VX-478 and 1592U89 in approximately 30 patients for 48 weeks.

With abacavir in indinavir failures. This study will test the combination of GW141 and abacavir in ten patients who have failed indinavir. This study will include 48 patients and run for 24 weeks.

Twice vs. thrice daily. Presumably concerned that the marketing objective of twice per day dosing convenience took precedence over optimal efficacy, it is rumored that the FDA has required Glaxo to plan a study that compares twice per day dosing versus three times per day dosing.

AIDS dementia study. As the design for this trial appears to be awaiting cerebro-pharmacokinetic data from ACTG 342, detailed information was not available. It is likely that this study will be conducted in combination with abacavir, which is known to have good CNS penetration.

What's missing? Though the array of clinical trials in progress and planning is broad, there are no trials planned to test 141W94 / VX-478 in combination with nonnucleoside reverse transcriptase inhibitors.

Recommendation 4: Glaxo Welcome should consider undertaking a study to determine the safety, interactions, and efficacy 141W94 / VX-478 in combination with the nonnucleoside reverse transcriptase inhibitors.

TIMETABLE, PRICE & ACCESS *(assuming all goes well)*

Why has 141W94 / VX-478 been so late in getting to this point? In 1993, Vertex and Agouron were in a virtual dead heat in the race to develop and market the first highly potent "second generation" protease inhibitor. In very divergent strategies, Vertex used aggressive public relations to increase the bidding stakes in negotiations with potential development partners, while Agouron in contrast, pursued nelfinavir's development along at a steady pace on its own. With nelfinavir now on the market, its obvious who won the race and to a lesser extent why. Reportedly, the development of 141W94 / VX-478 was retarded further when key scientific defections occurred at Wellcome in the wake of the Glaxo merger (WSJ). Further, with 3TC, abacavir and other drugs also in Glaxo's pipeline, some feel that competition for project staffing and funding caused delays in the development of 141W94.

With so many unanswered questions, the lost time appears to be just that. We must not be tempted to grab too quickly for drug regimens with fewer pills and less frequent dosing intervals. This is not the time for demanding short cuts. With HIV's hideous ability to outwit multiple drugs with one set of mutations, it's possible that people with HIV will get just one or maybe two shots at achieving maximal suppression of the virus. The primary objective should be drug efficacy and survival.

We therefore need an adequate body of data regarding the long term relative safety and durability of response for 141W94 / VX-478 before it can be regarded as an alternative first line therapy.

The issue of cross resistance is an entirely other matter. A fast track should be established for a new drug that has shown the ability to help to people who have failed indinavir and / or nelfinavir. Therefore, the most pressing issue to settle regarding 141W94/ VX-478 is its propensity to either cause or suffer from cross resistance.

Recommendation 5: Glaxo Welcome should consider undertaking a small pilot study to determine the safety and efficacy of 141W94 / VX-478 in patients who have failed multiple protease inhibitors.

The expanded access program for 141W94 / VX-478 is only in early planning stages, and we do not know whether 141W94 / VX-478 will ever receive approval. However, at the current pace, if all goes

well, the NDA for 141W94 / VX-478 will be filed in the third quarter of 1998. As no less than the twelfth AIDS drug to reach the market and the fifth protease inhibitor (counting saquinavir only once), Glaxo would behoove itself to price 141W94 / VX-478 competitively.

Recommendation 6: Glaxo Wellcome should consider a price for GW141 more in line with that for Crixivan, the market leader, if it wants to be a contender for first-line protease therapy. Reportedly, the simple chemical structure makes 141W94 / VX-478 a less expensive drug to manufacture.

It was hoped that increased sales volume from more people seeking and staying on treatment would bring price reductions, but this will depend on the intensity of competition. By this time, however, Glaxo may have a tight grip on the market for HIV antiretrovirals. Should 141W94/VX-478 and 1592U89 both be approved, no less than four of 13 HIV antivirals will be controlled by Glaxo. With such a shrewdly assembled Gang of Four, Glaxo will undoubtedly wield a wide degree of market power. While HIV drugs accounted for just 5% of Glaxo's 1996 revenues, they should grow proportionately to account for 12% of the total by 2000, according to Lehman Brothers' Stewart Atkins (Business Week). With such a large portion of its profits at stake, we can expect Glaxo to be aggressive in this market.

Competition from the other nine drugs will be divided among seven companies including: Roche (2), Bristol Myers Squibb (2), Merck (1), Abbott (1), Agouron (1), Boehringer Ingelheim (1), and Upjohn (1). We can only wonder what commitment these companies will show in the face of Glaxo's fearsome machine.

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