HIV TREATMENT FAILURE:

A REVIEW OF CURRENT CLINICAL RESEARCH

A REPORT FROM THE
FORUM FOR COLLABORATIVE HIV RESEARCH

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The Forum for Collaborative HIV Research, (FCHR) situated within the Center for Health Policy Research (CHPR) at The George Washington University Medical Center, is an independent public-private partnership composed of representatives from multiple interests in the HIV clinical research arena. The FCHR primarily facilitates ongoing discussion and collaboration between appropriate stakeholders on the development and implementation of new clinical studies in HIV and on the transfer of the results of research into clinical practice. The main purpose of the FCHR is to enhance collaboration between interested groups in order to address the critical unanswered questions regardingthe optimal medical management of HIV disease. By encouraging coordination among public and private HIV/AIDS clinical research efforts, the FCHR hopes to integrate these efforts into HIV/AIDS medical care settings. Therefore, studies performed by these various research entities, separately or in cooperation, can begin faster; duplication of efforts can be reduced; patient enrollment and retention can be further facilitated; and costs of getting answers to the critical questions can be shared. At present,the FCHR is staffed by three persons and consists of over one hundred members, representing all facets of the field. These include pharmaceutical companies; public and private third-party payors; health care delivery system groups; government agencies; clinical research centers; and patient advocacy groups. The Director of the FCHR is David Barr.

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I. REPORT FROM THE DIRECTOR AND EXECUTIVE SUMMARY

In 1996, we experienced a revolution in HIV treatment. New tests that could accurately measure levels of HIV in blood became commercially available. Resulting data showed that plasma viral load was the strongest predictor of the risk of progression to AIDS and death. New drugs, including potent protease inhibitors (PI's) also became available. Strategies such as the simultaneous initiation of 2- or 3- drug regimens, including a potent PI or a non-nucleoside reverse transcriptase inhibitor (NNRTI) plus two nucleoside reverse transcriptase inhibitors (RTI) were found to inhibit HIV production more profoundly and more durably than previous antiretroviral strategies and without the rapid development of drug resistance. The value of these new drugs and diagnostic tests is made clear through dramatic decreases in rates of new cases of AIDS, hospitalizations and incidence of AIDS-related deaths over a two-year period.

This new treatment strategy, however, is not a cure for HIV disease. While many patients are benefiting from treatment, others are not or have experienced only a temporary benefit. There are many reasons why treatment fails. Poor patient adherence to therapy is the most cited reason, and, indeed, is a probable cause for much treatment failure. The treatment regimens are extremely complex and inflexible and must be taken for a lifetime.* However, adherence is not the only reason for treatment failure. Inability to tolerate therapy because of side effects is another. Also, sub-optimal treatment prior to the availability of potent protease inhibitors has created a group of patients who were already resistant to several drugs and, therefore, not able to initiate a regimen that significantly and durably suppresses viral replication. Some patients will fail therapy because they were never placed on an appropriate treatment regimen to begin with because of poor physician education about a very complex treatment strategy. Differences in patients' abilities to absorb and metabolize drugs may also cause treatment to fail. Finally, the new treatment strategy is still in its infancy and we have no long-term data about its durability or possible long-term side effects. Therefore, the study of HIV antiretroviral treatment failure is important to understand why and how therapy fails patients and what strategies can be developed to treat patients for whom therapy is failing.

The Forum for Collaborative HIV Research (FCHR) commissioned this report on HIV antiretroviral treatment failure as a way of compiling what is currently understood from clinical research in order to help define and prioritize questions for further research and discussion. This report focuses on four central issues:

How is treatment failure defined in current clinical research?

How are estimates of treatment failure developed for the design of clinical studies?

What factors may predict treatment failure?

What strategies are being examined for managing treatment failure?

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0The report seeks to provide an overview of research currently underway in the rapidly changing, dynamic milieu ofantiretroviral treatment. Rather than attempting to be definitive and comprehensive, we attempt to provide a broad outlook without encompassing the entire universe of ongoing studies. We have selected examples of the types of studies that are underway tohelp identify key issues for further discussion by the FCHR. Literature reviews were conducted by FCHR staff using Medline, AEGIS and ACTIS, as well as the abstracts from recent meetings of the Infectious Disease Society of America (IDSA), the InterscienceConference on Antimicrobial Agents and Chemotherapy (ICAAC) and the recent Conference on Retrovirus and Opportunistic Infections. We also secured protocols in development from the NIAID AIDS

* The Forum for Collaborative HIV Research, along with the National Minority AIDS Council and the NIH Office of AIDS Research recently published its report from *Adherence to HIV Therapy – A Research Conference*. The report provides an overview and bibliography of literature on patient adherence to treatment, discussion on issues specific to HIV treatment adherence and a research agenda to learn more about what factors effect a patient's ability to adhere to treatment, what interventions may assist patient adherence and methods to effectively measure patient adherence. The report is available through the FCHR website at:

Clinical Trial Group (ACTG) and the CPCRA (full name??). Further, the FCHR conducted a survey of on-going studies by those pharmaceutical companies that are members of the FCHR. The report examines both prospective and population-based studies.

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0The report is not meant to be a critique of HIV clinical research, but an analysis of the research that has been accomplished to date to identify the gaps in knowledge. It is our hope that the report will be a useful tool in further discussions about the both the questions that must be answered and the best methods to answer them to ensure that the promise of these remarkable treatment developments can be fully realized. The FCHR will facilitate some of those discussions over the coming year.

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0The new developments in HIV treatment are the result of extraordinarily hard work on the part of scientists, researchers and administrators from academia, government, industry, health care providers, and patients. The Forum for Collaborative HIV Research applauds the work of all these participants in the research and drug development process for their tireless efforts.

Below are some of the salient findings from our investigation:

There have been significant changes in clinical trial design over the past few years, including: (1) the use of virologically based entry criteria, (2) shorter length of follow-up time, (3) the use of virological, rather than clinical endpoints.

Most reports of successful treatment of individuals who failed a PI-containing regiment do not report very long follow up, ranging from several weeks to months.

There is little, if any data available on people starting HAART regimens with over 200 CD4 cells/mm.

Other than the ACTG, there is no mechanism for "roll over" studies which would assist with long-term follow up of patients. Even within the ACTG, this mechanism is in development.

Many studies in PI treatment failure are assessing four-drug regimens.

It is unclear how rapidly patients who develop virologic failure will progress immunologically or clinically. While some studies are looking at what regimens may be best to switch to, few studies are examining when to switch treatment after virological failure has occurred. However, some data shows that patients who switch rapidly after virological failure appear to have a better virologic response to a second PI-containing regimen.

There do not appear to be any generally accepted methods to measure the causes of virologic failure.

We identified only one study comparing different strategies for switching therapy based on the results of genotypic and phenotypic antiretroviral resistance assays.

Several studies of the relationship between antiretroviral therapy use and survival and mortality are examples of the value of population-based observational databases in studying clinical failure.

Multi-site population-based studies can provide important information, however, these studies also have important limitations, including: (a) incomplete medical histories of study participants make it difficult to accurately interpret the collected data, (b) it is unclear as to whether findings from one collection site are applicable elsewhere, and (c) populations in these studies are often homogenous and it is, therefore, difficult to apply the findings to a general population of HIV-infected patients.

Single-site population-based studies also have limited value because: (a) it is unclear whether sample-sizes in the study are based on statistical power tests or because they represent all patients with complete medical records treated at the site, (b) some of the sample sizes may be to small to be statistically reliable, (c) the value of laboratory testing in these studies is compromised if the data are collected at non-uniform times or from multiple laboratories, and (d) it is

often unclear whether patients were continuously in care at the study location for the duration of the study.

Varying degrees of success have been achieved by researchers using population-based data sets to estimate the rate of opportunistic infections in patients receiving HAART. Similarly, observational databases have been used with varying success to study disease progression in the children born to HIV-infected women.

While case studiesof adverse events are clinically interesting and may form the basis for larger systemic evaluations of adverse events among patients on HAART, their commonly small patient cohorts make the results unreliable in estimating the rate of clinical adverse events.

Several observational databases have demonstrated the direct relationship between HAART on service utilization and associated costs. Studies conducted in "closed care systems" (e.g., Department of Veteran's Affairs, managed care systems) have been particularly successful in accounting for all services and related costs generated by their patients.

Although population-based studies have contributed to our understanding of treatment failure in clinical practice, the studies' methodological limitations leave wide research gaps. Larger samples and longer observational periods among some existing projects address some of these gaps. Other gaps remain unfilled, however, and include:

a. Recognition that randomized clinical trials are limited in their ability to estimate treatment failure rates in clinical practice and that well designed population-based studies have utility in evaluating some aspects of treatment failure. Clinical trial and population-based research have not been integrated to benefit from their varied strengths.

b. Formal and consistent definitions of treatment failure have not been used to design and conduct scientifically rigorous population-based treatment failure studies. Studies using population-based approaches have not been explicitly designed to measure treatment failure. Existing study designs have been expanded or refined to address new analytic questions, often without application of sufficient measurement precision, adequate sample sizes or observational periods, or appropriate statistical methods.

c. Some large observational and administrative databases do not directly link indicators of treatment failure (e.g., virologic or immunologic measures, onset or recurrence of opportunistic infections, resource use) with actual use of a treatment intervention. Rather, they hypothesize that changes in these indicators among populations are the result of treatment failure or success.

d. Population-based treatment failure studies tend to focus on HIV-infected adults late in the spectrum of HIV disease, with few studies addressing failure among recently infected adults.

e. Few population-based treatment failure studies have been conducted in children or adolescents.

f. Little is known about treatment failure in pregnant women using HAART, despite its growing use.

g. Population-based studies that estimate treatment failure rates and evaluate factors associated with those rates have not been conducted with sufficiently large and heterogeneous populations. Even large-scale multi-site studies tend to use small numbers of clinical sites that do not represent various regional, socio-demographic, economic, and cultural sub-populations of children and adults across the clinical spectrum of HIV. Heterogeneous clinical settings are also not well represented to account for variation in prescribing and practice patterns (such as the timing of diagnostic testing and initiation of HAART) among clinicians caring for HIV-infected patients.

h. Existing observational databases (such as those sponsored by CDC, Canadian government agencies, European governments, and/or manufacturers) have not been systematically reviewed to determine the feasibility of linking them to address aspects of treatmentfailure that require large and generalizable population samples.

i. The feasibility has not been assessed of linking databases maintained by "closed service systems" (e.g.,

Veterans Administration, armed services, or managed care plans) to study treatmentfailure. Such studies might address design problems encountered in studying patients in open systems in which patients may seek care at several clinical sites during an observational period.

j. Clinical site-based studies usually do link their records with other providers to assure that endpoint and other important data are gathered. Findings of single-site studies may be heavily biased by missing or censored data.

k. Although the utility of supplementing clinical databases with administrative databases (e.g., Medicaid and commercial insurance claims systems) has been demonstrated, such a linked data system has not been used in studies of treatment failure. Administrative databases are valuable in identifying the various sites and sequencing of clinical endpoints and other important data.

II. INTRODUCTION

In the fall of 1997, the FCHR commissioned a review of current research on 3 critical emerging issues in antiretroviral therapy:

Estimating treatment failure rates;
Predictors of treatment failure; and
Strategies for managing treatment failure.

The report also provides some analysis as to what methodology is being used and how failure is defined. This report attempts to provide an overview of research currently underway in the rapidly changing, dynamic milieu of antiretroviral treatment. Rather than attempting to be definitive and comprehensive, we attempt to provide a broad outlook without encompassing the entire universe of ongoing studies. We have selectedexamples from various types of studies underway and possible approaches to help identify key issues (e.g., definitions of treatment failure or methodology) for further discussion by the Forum.

A. Evolving Definitions Of Antiretroviral Treatment Failure

From the dawn of the antiretroviral era, with the success of AZT in BW-02 during 1986, the drawbacks and strengths of clinical endpoint studies have been apparent. In chronic diseases such as HIV infection, the drawback was their great length and the small numbers of individuals who progressed clinically in spite of the widespread belief that immune suppression proceeded relentlessly. This belief turned out to be true, once understanding of pathogenesis caught up with theory. The strengths of defining failure by clinical progression lay in the fact that it was the clearest and most direct measurement of therapeutic success or failure.

Nonetheless, most antiretrovirals developed after AZT were licensed based on changes in surrogate markers. The nucleosides ddI, ddC and d4T were approved based on changes in CD4 counts measured shortly after the initiation of therapy. These modest and transient changes reflected the characteristic activity of the nucleoside monotherapy approach. Furthermore, CD4 measurement is highly variable and an indirect estimation of antiretroviral activity.

For many years, efforts to develop effective measurements of viral activity were stymied. Such putative surrogates as HIV p24 antigen proved useful only in a subset of infected subjects, and assays such as lymphocyte co-culture were labor-intensive and hardly suited for widespread clinical use.

By 1993, however, the first generation of a series of HIV ribonucleic acid (RNA) assays became available for use in research settings. Tests such as the quantitative competitive polymerase chain reaction (QT-PCR), reverse transcriptase PCR (RT-PCR), and branched chain DNA (bDNA) were developed and applied in prospective trials and also to retrospective epidemiologic studies such as the Multicenter AIDS Cohort Study (MACS) (Kaslow 1987). By early 1996, it became clear that the plasma HIV RNA test (i.e., viral load) yielded both strong prognostic information about an individual's risk of progressing to AIDS and relatively direct feedback on the activity of an antiretroviral drug or regimen (Mellors 1996).

Later nucleosides such as 3TC and the first 4 PIs, along with the first 2 NNRTIs were approved by the FDA in part based on their ability to directly reduce plasma HIV RNA levels. One of the PIs, ritonavir, was fully approved based on a clinical endpoint study, Abbott 247, which ushered in a new era of optimism about the prospects for successful treatment of HIV disease.

By mid-1996 all the elements were in place for a revolution in HIV treatment:

New tests such as the Roche Amplicor HIV-1 RT-PCR could measure to 400 copies of HIV per milliliter (L) of plasma.

The Chiron Quantiplex branched-chain DNA test could measure to about 1,200 HIV copies/ L.

New data from the MACS and elsewhere showed that plasma viral load was the strongest predictor of the risk of progression to AIDS and death.

New drugs including potent PIs and less potent but still useful NNRTIs were becoming available.

New strategies such as the simultaneous initiation of 2- or 3-drug regimens (including a potent PI or NNRTI plus 2 nucleoside analogues) were found to inhibit HIV production more profoundly and more durably, as well as inhibit the rapid evolution of antiretroviral drug resistance.

Following the July 1996 AIDS conference in Vancouver, triple combination antiretroviral therapy was adopted as the standard of care in most developed countries when the new treatments became available. The subsequent 18 months saw a profound and prolonged decrease in the number of AIDS diagnoses and deaths. For the first time, antiretroviral therapy was making a clear and obvious difference in the AIDS epidemic (Chiasson 1998, McNaughten 1998, Moore 1998, Muthumbi 1998).

The new treatments and strategies do not work for everyone. This report considers the state of current research on antiretroviral treatment failure. The report examines:

Various definitions of treatment failure;

Studies that estimate rates of antiretroviral treatment failure; and

Predictors of failure and studies of new strategies that are underway to address treatment failure both by more completely understanding it and, most importantly, by developing effective new treatment regimens for individuals experiencing treatment failure.

B. Methodology and Information Sources

FCHR staff systematically reviewed literature searches for relevant key words using AEGIS. They secured protocols from the NIH AIDS Clinical Trials Group (ACTG), published literature, and abstracts and posters presented at recent meetings of the Infectious Disease Society of American (IDSA) and the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), as well as the annual Conference on Retrovirus and Opportunistic Infections. Since this is a rapidly evolving field, the most recent available information from the Fifth Conference on Retroviruses and Opportunistic Infections, held in Chicago during February 1998 has proved a veritable gold-mine of provocative and intriguing, though not always definitive, information.

The Federal AIDS Clinical Trials Information Service (ACTIS) and other ACTG databases were made available for our research. FCHR requests to the industry were less successful in obtaining complete current data about research that is currently underway. The industry sponsors who responded to the FCHR query include Abbott, Agouron, Boehringer Ingelheim, Hoffmann-LaRoche, Merck, and Pharmacia and Upjohn.

We then completed a matrix of completed, ongoing, and planned randomized studies of therapies for individuals previously treated with antiretrovirals (i.e., “antiretroviral-experienced individuals”) and those who had experienced treatment failure (see Appendix I). Many phase I/II studies of new antiretroviral treatments were not included in the analysis because they are carried out most often in antiretroviral-naive individuals, so as to optimize the chance that the drug will appear active, and to minimize the effects of potential cross-resistance.

Several interesting trends in antiretroviral study design appeared from this matrix (see Appendix I):

As antiretroviral trials have evolved, clinical endpoints such as AIDS and death have become less practical, while laboratory measurements and treatment history have become more important factors in trial design and analysis.

Studies that once used CD4 thresholds for entry or exclusion criteria are moving increasingly to the use of viral load thresholds.

Many studies have restrictions related to prior therapy (e.g., PI-naive, NNRTI-naive, naive to study drug or others in its class, etc.).

As the use of laboratory measurements has increased and the incidence of clinical endpoints has declined, studies are becoming smaller and their duration shorter.

Studies appear to be attempting to answer several questions at once. For example, they are simultaneously attempting to validate the use of new doses, new treatment combinations, and new diagnostic tests (such as genotypic or phenotypic resistance assays).

Additional commentary on recent trends in study design will be found in the Conclusion Section.

C. Definitions Of Treatment Failure

There are several possible definitions of treatment failure, including:

Clinical failure (e.g., HIV progression, opportunistic infections, death);

Empirical failure (e.g., decision to switch therapies);

Immunological failure (e.g., CD4 decline or starting *Pneumocystis carinii* pneumonia or MAC prophylaxis);

Virological failure;

Failure to achieve significant viral load decrease;

Viral load rebound from nadir or undetectable; and

Genotypic or phenotypic resistance.

In current studies, primary endpoints are often virologic and clinical, with secondary endpoints being immunological or assay-dependent (e.g., on resistance). Study sample sizes are most often based on the need to detect differences in the magnitude or duration of the virologic effect, rather than clinically significant differences.

It is important to note that virologic failure and clinical failure are not equivalent. Virologic failure may precede immunological and clinical failure by months or years. No one yet knows how quickly, on average, a person experiencing a viral load rebound will progress. In a poster presentation from the Fifth Conference on Retroviruses and Opportunistic Infections, Deeks and his colleagues in San Francisco carried out a retrospective analysis of 79 individuals who experienced virologic failure on highly active antiretroviral therapy (HAART) (viral rebound to above 500 copies/ L on 2 subsequent occasions after at least 20 weeks of treatment) (Deeks 1998). Of note, these patients had *not* changed underlying nucleosides when they added a PI. Thus, they were not on the regimen defined by the Department of Health and Human Services (HHS) Guidelines as a preferred, likely maximally suppressive regimen.

Despite a median of 8.9 months since evidence of virologic failure, the median CD4 T cell count in the San Francisco cohort remained 101 cells above baseline (Deeks 1998). Among the 58 patients with an available baseline viral load, 9 (16%) had no virologic response (<0.5 log RNA reduction), 26 (45%) had a potent but transient response (i.e., greater than 1 log decrease followed by a return to 0.5 log of baseline), and 15 (26%) had a durable response (persistent viral load reduction of at least 1 log). A total of 37 patients achieved an undetectable viral load (<500 copies/ L) for a median of 7 months

(range 2.4-16.5). It is unclear why CD4 counts increased in the face of virologic failure. Most patients continued to have clinical benefit without clinical progression (Deeks 1998).

III. CLINICAL EVIDENCE FOR TREATMENT FAILURE RATES ON HAART

A. Randomized, Controlled Trials

Two pivotal clinical studies patients (Abbott 247 and ACTG 320) conducted in nucleoside-experienced validated the clinical superiority of PI-containing regimens versus 2 nucleosides. These regimens are often, though not always consistently, referred to as HAART. Ideally a HAART regimen involves the simultaneous initiation of at least 2 new drugs including either a potent PI with 2 nucleosides (NRTIs) or a NNRTI plus 2 NRTIs. The literature, particularly observational studies, is often inconsistent with regard to the use of this term.

In Abbott 247, 1,090 individuals withCD4 counts below 100 were randomized to receive ritonavir or placebo over a background of any combination of AZT, ddI, ddC or d4T (Cameron 1996). Use of 3TC was prohibited. After 1 year, the clinical superiority of the regimen containing ritonavir was clear. Six-month viral load data, however, suggest that there was a virologic rebound in at least some individuals randomized to the ritonavir-containing regimen. These findings suggest that despite initial impressive results, viral resistance was developingin this study of what was essentially sequential monotherapy, albeit with a new, powerful PI.

Results of Abbott Study 247

Endpoint	***Ritonavir***	***Placebo***	***p-value***
N	543	547	
AIDS or death	119 (21.9%)	205 (31.1%)	<0.0001
CMV, all sites	24	32	<0.05
CMV retinitis	19	18	
CMV – other	5	14	
Esophageal candidiasis	19	40	<0.05
MAC	9	11	
PCP	12	22	<0.05
Wasting	2	9	<0.05
Kaposi's sarcoma	8	19	<0.05
Non-Hodgkin's lymphoma	4	9	
Others	17	30	<0.05

(Cameron 1996)

At the Retrovirus Conference in January 1996, however, investigators presented preliminary results from a study which appeared to resolve the issue of sequential monotherapy by simultaneously adding 2 drugs (3TC and indinavir) to AZT monotherapy (Gulick 1996, 1997). Study subjects had at least 6 months' prior AZT experience, a CD4 count between 50-400/mm^3, and at least 20,000 copies of HIV RNA/ L. They were randomized to receive AZT/3TC, indinavir monotherapy, or AZT/3TC/indinavir. Merck 035 was the first study to show that such a strategy could produce durable suppression of viral load, and corresponding increases in CD4 count. Data for the first year are shown below. Recent data indicate that 80% of participants remaining on the triple drug arm of Merck 035 continue to have undetectable viral loads out to over 100 weeks of follow-up (R. Gulick, personal communication).

Merck 035: Viral Load and CD4 Changes

	AZT/3TC	***IDV***	***AZT/3TC/IDV***	***p-value***

N	33	31	33	
Prior AZT (median)	31.2 months	32.2 months	28.2 months	
Prior AIDS	3 (9%)	5 (16%)	5 (15%)	
Baseline CD4 (median)	144 (34-400)	155 (51-480)	133 (35-433)	
Baseline HIV RNA median)	44,040	39,910	41,900	
HIV RNA change at week 12	-0.6 $\log_{10}$	-1.5 $\log_{10}$	-2.0 $\log_{10}$	
HIV RNA change at week 24	-0.5 $\log_{10}$	-1.0 $\log_{10}$	-2.1 $\log_{10}$	
HIV RNA change at week 52	-0.0 $\log_{10}$	-1.3 $\log_{10}$	-2.3 $\log_{10}$	
RNA <500/mL at week 12	1/33 (3%)	12/31 (40%)	25/31 (80%)	
RNA < 50/mL at week 12	0/33 (0%)	6/31 (20%)	12/31 (40%)	
RNA <500/mL at week 24	0/30 (0%)	11/28 (40%)	28/31 (90%)	<0.001
RNA < 50/mL at week 24	0/30 (0%)	8/28 (30%)	19/31 (60%)	
RNA < 500/mL week 52	0/5 (0%)	1/5 (20%)	5/5 (100%)	
RNA < 50/mL at week 52	0/ 5 (0%)	0/ 5 (0%)	4/ 5 (80%)	
CD4 change, week 12 (median)	+30	+95	+100	
CD4 change, week 24 (median)	+20	+100	+125	<0.01
CD4 change, week 52 (median)	+35	+100	+200	

(Gulick 1997)

Merck 039 adopted a similar strategy in more advanced patients, randomizing 320 HIV-infected individuals with fewer than 50 CD4 cells/mm^3 and a history of at least 6 months' AZT use to receive AZT/3TC, indinavir monotherapy, or AZT/3TC/indinavir. After 24 weeks, all participants were offered open-label indinavir. A total of 249 individuals participated in the open-label extension. Of these,33 (14.5%) added only indinavir, 10 (4.4%) added 1 antiretroviral, 182 (79.8%) added 2 antiretrovirals, and 3 (1.3%) added 3 or more antiretrovirals. Encouragingly, durable viral load suppression out to 84 weeks, and persistent CD4 increases out to 72 weeks, have been seen even in this advanced, heavily pre-treated population. Moreover, many of those initially randomized to AZT/3TC or indinavir experienced a viral load suppression to below the limit of quantification once they entered the open-label phaseof the study and were free to add other antiretrovirals.

Merck 039: Sixty-Week Viral Suppression in Patients with CD4 ≤ 50/mm³				
	N	***AZT/3TC***	***IDV***	***AZT/3TC/IDV***
N -- Merck 039 overall	320	108	107	105
N -- Open-label extension	247	71	87	91
Still in follow-up	143	36	43	64
Baseline HIV RNA/μL (median)	74,353	70.742	85,010	68,151
Baseline CD4 (median)	15	14	17	15
RNA < 500/μL at week 24		0/92 (0%)	0/101 (0%)	57/95 (60%)
RNA < 50/μL at week 24				43/90 (48%)
CD4 change at week 24 (median)		+5	+75	+90
RNA < 500/μL at week 36*		28/92 (30%)	9/98 (10%)	53/95 (56%)
RNA < 50/μL at week 36				42/91 (46%)
CD4 change at week 36 (median)		+48	+100	+125
RNA < 500/μL at week 60		21/84 (25%)	14/89 (16%)	43/84 (51%)
RNA < 50/μL at week 60		10/74 (13%)	6/81 (7%)	25/66 (38%)
CD4 change at week 60 (median)		+54	+74	+131

* After cross-over to open-label IDV, with or without other antiretrovirals. *(Hirsch 1998)*

The strategy of changing at least one other antiretroviral when starting a PI received additional support at the 1996 International AIDS Conference in Vancouver. Before the conference, many clinicians simply added PIs to an underlying RTI regimen (as in Abbott 247). After the conference, the standard of care evolved to improve the chances for maximal suppression with the simultaneous initiation of at least 2 new antiretrovirals. Thus, the two- nucleoside era was succeeded, in the wake of studies such as Merck 035 and 039 and ACTG 320 by the HAART era. This approach was codified in the HIV treatment guidelines developed by a panel convened by the HHS (Bartlett 1997).

In February 1997, investigators prematurely terminated ACTG 320, after an interim analysis by the Data and Safety Monitoring Board (DSMB) revealed that AZT-experienced patients entering with CD4 counts below 200/mm^3 fared dramatically better if they added 3TC and indinavir simultaneously, rather than simply adding 3TC. This study helped validate the notion that one must switch at least 1 underlying RTI when adding a potent PI, for there were some among the ritonavir group in Abbott 247 who developed resistance and clinical failure after initially benefiting.

ACTG 320 enrolled 1,156 people with a history of AZT use who were naive to 3TC and indinavir. Most subjects (83%) were male and 52% were white, 28% black and 18% Hispanic. Less than one-fifth (16%) of subjects were injecting drug users and were 3% hemophiliacs. The median age was 39 years, median CD4 count at baseline was 87, and median viral load 5.0 $\log_{10}$. Average duration of prior AZT use was 21 months. If they became intolerant to AZT, they could switch to d4T.

Triple therapy proved to reduce the risk of death by 50% and the risk of AIDS or death by 57%. At the Conference on Retroviruses in February 1998, Currier presented the opportunistic infection (OI) events from ACTG 320 (Currier 1998). A total of 91 OI events occurred, with 60 in the AZT/3TC arm and 31 in the AZT/3TC/indinavir arm. Of note, the CD4 lymphocyte count 8 weeks after starting treatment was a strong indicator of risk for development of an OI. Patients whose CD4 counts rose by at least 50 cells/mm^3 had an 80% reduced risk of developing an OI compared with those whose CD4 cells rose by less than 10. Lack of starting *Pneumocystis carinii* pneumonia (PCP) prophylaxis increased the risk of PCP 13-fold. The authors concluded that early rises in CD4 number appear to protect against the development of OIs.

Results of ACTG 320					
	N	***AZT/3TC***	***AZT/3TC/IDV***	***HR (95% C.I.)***	***p-value***
N	1,156	575	579		
First event (AIDS or death)	96	63 (11%)	33 (6%)	0.50 (0.33,0.76)	
Death	26	18 (3%)	8 (1.4%)	0.43 (0.19,0.99)	
AIDS	91	60	31		
PCP	23	17	6		<0.05
CMV	16	11	5		0.55
MAC	12	5	7		NS
HIV RNA at week 24 (log_{10})		-1.0	-2.1		
HIV RNA BLQ at week 24		3%	51%		
CD4 increase at week 24		+40	+121		

BLQ = below limit of quantification (<500/μL); HR = hazard ratio *(Hammer 1997, Currier 1998)*

B. Estimation of Treatment Failure Rates and Predictors of Treatment Failure

A review of the recent literature reveals that virological treatment failure appears to be more common among individuals with an extensive history of treatment and experience with sequential monotherapy (Deeks 1997, 1998). Some studies report that a high baseline viral load or low baseline CD4 count is also associated with a lower rate of successful treatment (Demeter 1998). Nonetheless, recent evidence suggests that even in an AZT-treated population such as that of the Merck 035 and ACTG 320 studies, profound and durable suppression of viral load beneath the limits of quantification is possible in a majority of individuals. After 100 weeks, over 80% of subjects in the triple-therapyarm of Merck 035 continue to have a viral load below 400 copies/ L (Gulick 1998). Similar reports are available of regimens including nelfinavir/AZT/3TC (Agouron 511), ritonavir/AZT/3TC and others. Among the infrequently measured cofactors affecting treatment success or failure are 1) non-adherence, 2) drug-drug interactions and 3) malabsorption.

Demeter and colleagues carried out a virology substudy of ACTG 320 to determine predictors of virologic response (Demeter 1998). Plasma samples for viral load testing were taken at baseline and weeks 0, 4, 8, 24 and 40. Virologic suppression was defined as plasma RNA below 500 copies/ L at weeks 24 and 40. A total of 1,083 subjects with baseline and at least 1 follow-up HIV RNA value were studied. Their mean baseline CD4 count was 87, and log_{10} HIV RNA was 4.95. About one-half (51%) achieved virologic suppression in the triple combination group compared with 3% of those in the AZT/3TC group ($p<0.001$). In the triple therapy group, 39% of those with baseline CD4 below 50 cells/mm^3 and 58% with baseline CD4 between 51-200 achieved virologic suppression ($p<0.001$). For only 7 clinical events was the last RNA value prior to the event less than 500 copies/ L; for the other 119 events, it was greater. The authors conclude that HIV RNA at week 4 was the strongest predictor of virologic suppression at weeks 24 and 40 in this study.

Early Predictors of Later (24-40 Week) Virologic Response		
	Odds ratio (O.R.)	***p-value***
Baseline RNA	1.9 for each log_{10} decrease	<0.001
Baseline CD4	1.4 for each 50 cell increase	<0.001
Week 4 RNA	3.4	<0.001

(Demeter 1998)

These results are consistent with those from a meta-analysis of earlier nucleoside analogue studies carried out by Hughes and colleagues (Hughes 1998). All nucleoside studies with over 6 months of follow-up, HIV RNA measurements, and over

1 clinical progression event were analyzed. Preliminary results were given for10 trials involving single or double nucleoside therapy with AZT, ddI, ddC and 3TC.

Early Surrogate Predictors of Later Clinical Response from Ten Nucleoside Trials	
	Risk reduction (95% C.I)
0.5 log_{10} RNA drop, 0-24 weeks	-22% (+1%,-41%)
50 CD4 cell rise, 0-24 weeks	-23% (-13%,-31%)

(Hughes 1998)

C. Treatment Failure And Switching

The new HIV clinical practice guidelines released by the HHS reflect the current confusion over what constitutes treatment failure, and when switching therapy is warranted, as described in Appendix I. Although work addressing the pressing issue of"when to switch" is in its infancy, theoretical models (Richter 1998) and at least 1 clinical trial (Haubrich 1998) indicate that switching early based on viral load, rather than waiting for a CD4 decline or clinical progression, is likely to be both cost-effective and clinically beneficial. Richter and colleagues performed a Monte Carlo simulation for a group of imaginary patients who initiated therapy according to the recent HHS guidelines (Bartlett 1997) withCD4 counts between 350-500 and a mean HIV RNA of 25,000 copies/µL (Richter 1998). Using a computerized model, they "followed" these patients for 15 years. Three switching strategies were compared, with drug costs, laboratory tests, and other medical care costs factored in:

Switching when viral load reached 10,000 copies/µL;

Switching when CD4 count dropped by 30% from peak; or

Switching when CD4 dropped by 20% from peak.

The regimens included various triple regimens. The authors conclude that "managing patients with viral load switching rules is cost-saving within 5 years." Lifetime cost savings were estimated to be as much as $43,700.Five-year and life-time costs were computed for the three switching rules.

Combination Regimens in Five-Year Monte Carlo Simulation			
Regimen	***Chance of VL < BLQ***	***Duration of Suppression***	***CD4 Increase (Range)***
AZT/3TC/IDV	90%	18 months	100-120
NVP/NFV/ddI	80%	13 months	80-100
RTV/SQV/ddC	70%	10 months	50-80
RTV/SQV/ddC/d4T	50%	6 months	20-50
AZT (salvage therapy)	0%	--	0

(Richter 1998)

Viral Load Switching More Cost-Effective than CD4-Based Switching Rules				
Switching Rule	***Five-year Cost***		***Lifetime Cost***	
	Drug & Lab Tests	***Total Costs***	***Drug & Lab Tests***	***Total Costs***
Viral Load	$53,845	$67,484	$76,304	$141,497
CD4, 30%	$55,588	$71,800	$116,959	$185,214
CD4, 20%	$55,733	$71,360	$106,650	$174,171

(Richter 1998)

The California Clinical Trials Group (CCTG) study 570 enrolled 204 patients with HIV RNA over 5,000 copies/μL and at least 2 agents available for treatment switches to receive CD4 measurements every 2 months (Haubrich 1998). They were randomized to two groups: Group A received viral load monitoring every 2 months (Amplicor) and Group B received a maximum of two RNA measurements per year.

Baseline RNA and CD4 were 4.7 log and 140 cells, respectively. Patients in both arms had a median 17 months of prior therapy. One-tenth (10%) of patients were antiretroviral naive and about one-fourth (29%) were on PIs. The authors conclude that"patients randomized to intensive HIV RNA monitoring had a greater proportion of undetectable HIV RNA at month 6 than those with less intensive monitoring."

CCTG 570: Bimonthly Versus. Six-Monthly HIV RNA Monitoring Compared

Viral load frequency	***Two months***	***Six months***	***p-value***
6 month VL	-0.85 log	-0.43 log	0.002
6 month VL BLQ	40%	16%	0.009
10 month CD4	+137	+34	0.002

(Haubrich 1998)

IV. CLINICAL TRIALS ADDRESSING TREATMENT FAILURE

A. Studies In Antiretroviral-Naive Individuals

While not directly germane to a discussion of treatment failure, starting regimens in antiretroviral naive individuals obviously affects later treatment options and the subsequent likelihood of success in second-line and salvage therapy trials. Among the first-line regimens which appear to produce durable antiretroviral suppression in 75% to 90% of subjects are indinavir, nelfinavir, ritonavir, and ritonavir/saquinavir plus 2 NRTIs (Bartlett 1997). There are alsonew, experimental regimens that appear to produce impressive short-term benefit and may well soon join the current preferred regimens. These data should be viewed with some skepticism, as there is a tendency to lose drop-outs to observation (i.e., individuals who are virologic non-responders), so as the weeks roll on, the on-study group is more and more comprised of responders, which tends to exaggerate the treatment effect. Most of the data appear to be presented by the authors in the form of on-treatment analysis rather than by intent-to-treat.

Potential New Antiretroviral Regimens in Naive Subjects					
Regimen	***N***	***Follow-up***	***% with VL BLQ****	***CD4 Change***	***Ref.***
Two NRTIs plus					
Amprenavir	46	24w	63%	+?	*Murphy 1998*
Abacavir/amprenavir	25	20w	5/8 (62.5%)	+149	*Kost 1998*
Efavirenz	137	16w	?	+?	*Hicks 1998*
Nelfinavir/SQV-SGC	51	32w	28/40 (70%)	+130	*Opravil 1998*
SQV-SGC	42	32w	31/36 (90%)**	+200	*Sension 1998*
SQV-SGC	63	24w	14/14 (100%)	+300	*Borleffs 1998*
Two-drug regimens					
Abacavir/PI	56	16w	31/56 (55%)***	+>110	*Mellors 1998* *Lederman 1998*
Abacavir/amprenavir	35	24w	9/11 (80%)	+200	*Bart 1998*
Amprenavir/PI	33	16w	13/16 (81%)§	+?	*Eron 1998*
Efavirenz/indinavir	59	60w	91%	+267	*Kahn 1998*
Nelfinavir/ritonavir	20	20w	6/8 (75%)	+85	*Gallant 1998b*
Nelfinavir/SQV-SGC	14	52w	7/9 (80%)	+100	*Kravcik 1998*
Nelfinavir/SQV-SGC	54	32w	14/36 (40%)	+160	*Opravil 1998*
Additional new regimens					
d4T/efavirenz/indinavir	42	60w	79%	+210	*Kahn 1998*
3TC/indinavir/nevirapine	22	52w	45% (10/22)	+?	*Harris 1998*
d4T/nelfinavir/nevirapine	25	29w	84% (19/23)	+95	*Skowron 1998*
d4T/ddI/hydroxyurea	144	12w	39/72 (54%)	+28	*Rutschmann 1998*
ddI/hydroxyurea/indinavir	8	20w	8/8 (100%)	+116	*Lori 1998a*
ddI/hydroxyurea/indinavir	10	8-52w	10/10 (100%)«	+?	*Lori 1998b*

* VL BLQ = viral load beneath limit of quantification (<400 copies/μL); PI = protease inhibitor; SQV-SGC = saquinvir soft gel capsules (Fortovase™)

** 14 of 42 subjects (33%) terminated prematurely; 8/42 (19%) were not included in the analysis.

*** PI success rates included 7/10 (70%) ABC/IDV, 7/13 (54%) ABC/IDV, 9/11 (82%) ABC/RTV, 7/9 (78%) ABC/NFV, 11/13 (85%) ABC/amprenavir. Four rebounded on ABC/SQV and 1 on ABC/IDV. 5% of subjects developed abacavir hypersensitivity.

§ At 16 weeks mean viral load reductions were -1.84 log on AMP/NFV, -2.49 on AMP/SQV, -2-79 log on AMP/AZT/3TC and -3.75 log on AMP/IDV.

« Acute primary infection, prior to seroconversion.

B. Studies in Nucleoside Analogue Failures

In Madrid, 96 patients who had received over 6 weeks of AZT therapy and had CD4 counts below 350 were randomized to receive d4T/indinavir with either 3TC or ddI (400 mg once daily) (Villalba 1998). Patients developing an undetectable viral load were monitored and genotypic resistance analysis was conducted among patients experiencing treatment failure.

Randomized Comparison of d4T/Indinavir with 3TC or ddI		
	3TC/d4T/IDV	***DdI/d4T/IDV***
VL BLQ at month 1	52/69 (75%)	16/26 (62%)
VL BLQ at month 3	35/56 (63%)	13/18 (72%)
VL BLQ at month 6	23/38 (61%)	6/7 (86%)
VL BLQ at month 9	7/12 (58%)	1/2 (50%)
Stopped due to toxicity	8/69 (11%)	5/26 (19%)

VL BLQ = viral load beneath limit of quantification (<400 copies/μL); *(Villalba 1998)*

25% of 3TC recipients and 28% of ddI recipients failed to reach an undetectable viral load, and additional patients failed after temporarily developing an undetectable viral load (Villalba 1998). Of these failures, 67% of the 3TC failures had the RT codon mutation associated with 3TC resistance,while none of the ddI failures developed the RT codon 74 mutation associated with ddI. The authors concluded that approximately 70% of AZT-pretreated patients could achieve an undetectable viral load within one month and that, while 3TC was better tolerated than ddI, high-level resistance to 3TC emerged more readily than to ddI among treatment failures, removing 3TC from the arsenal in these individuals' potential future treatment regimens.

A study of 147 patients is Barcelona who experienced immunologic failure (defined as a return of CD4 count to baseline) on nucleoside analogues were randomized to d4T/3TC with either indinavir, ritonavir or saquinavir (hard gel capsules) (Martinez 1998). There were 49 individuals in each arm. Primary endpoints were clinical progression, immunologic failure (lack of a CD4 increase), virologic failure (less than 0.5 $\log_{10}$ reduction in viral load), or a refusal to continue on study medications. The authors concluded that "saquinavir [hard gel capsules] is better tolerated but less potent than ritonavir or indinavir [which] appear to be similar in terms of tolerability and efficacy."

Randomized Comparison of 3TC/d4T with Indinavir, Ritonavir or Saquinavir				
	3TC/d4T/IDV	***3TC/d4T/RTV***	***3TC/d4T/SQV***	***p-value***
N	49	49	49	
Endpoint by 30 weeks	9 (18%	6 (12%)	22 (50%)	
Adverse event	57%	51%	10%	0.0001
Mean viral load response at 3m	-1.9	-1.8	-1.1	0.0001
Mean viral load response at 6m	-1.7	-2.2	-1.3	0.01
Mean CD4 response at 3m	+92	+100	+59	
Mean CD4 response at 6m	+100	+167	+100	

(Martinez 1998)

Harris and colleagues treated 22 individuals with advanced HIV infection who had previously failed or developed toxicity to combination nucleoside analogues with a combination of 3TC, indinavir (at the standard dose, despite fears of a negative interaction with nevirapine) and nevirapine (Harris 1998). Advanced HIV disease was defined as median CD4 count of 30 and viral load of 5.16 $\log_{10}$. All individuals studied were naive to indinavir and nevirapine and were followed for 1 year. A total of 20 were men, 15 had a prior AIDS diagnosis, 19 were experienced with 3TC, 2 were experienced with loviride, and 1 was experienced with ritonavir. A total of 4 patients withdrew by week 8 due to adverse events, 2 withdrew for personal reasons, and 5 withdrew due to virologic failure (i.e., HIV RNA above 5,000 copies/ L). At 12 months, 11 patients remained on study treatment. At 1 year, 10 of 22 originally assigned to d4T/IDV/NVP (45%) had undetectable viral load (<400 copies/ L, Amplicor), 7 (32%) had viral load below 20 copies/ L (Ultra-Direct), and 1 (5%) had a viral load of 1,635 copies/ L. The results are intriguing because 19 of the 22 participants were 3TC experienced and presumably had baseline resistance to 3TC. The finding suggests that in spite of this, the addition of 2 new drugs (an NNRTI and a potent PI)

succeeded in about one-half the patients as a salvage regimen.

C. Studies Assessing Rate of Failure on an Initial Protease Inhibitor Containing Regimen

Cross resistance among HIV PIs was first seen *in vivo* three years ago (Condra 1995), and its importance is underlined by an accumulationof new clinical and laboratory data. Hertogs and colleagues subjected over 500 clinical HIV-1 isolates to phenotypic resistance testing using the PR-RT Antivirogram™ (made by Virco, Belgium) (Hertogs 1998). They found that 77% to 95% of the isolates with10-fold or greater resistance to IDV, NFV, RTV *or* SQV also had four-fold or greater cross-resistance to all 3 other PIs. Subsequently, PI genes from samples with greater than10-fold phenotypic resistance revealed that over 30% of isolates had mutations at residues 10, 36, 46, 54, 71, 77, 82 and 90. Compensatory mutations at the *gag* cleavage site were found in 52% of the isolates.

Phenotypic Resistance to One PI is Associated with Cross-Resistance to Three Others

>Ten-fold resistance to		***% Cross-Resistant To***							
		IDV		**NFV**		**RTV**		**SQV**	
	N	***4-fold***	***10-fold***	***4-fold***	***10-fold***	***4-fold***	***10-fold***	***4-fold***	***10-fold***
IDV	224	--	--	86%	78%	95%	78%	83%	66%
NFV	277	87%	63%	--	--	90%	70%	77%	63%
RTV	261	93%	67%	87%	74%	--	--	78%	62%
SQV	220	90%	67%	89%	79%	95%	74%	--	--

(Hertogs 1998)

Several retrospective observational studies suggest that people who have failed on 1 PI frequently have difficulty obtaining virologic success on a second PI, regardless of which PI the patientstarted with or switched to. Of course, randomized studies testing rational sequences of PI-containing regimens are in their infancy. In the meantime, we rely on suggestive patterns that appear to emerge from small, uncontrolled, retrospective surveys.

Fessel and Hurley assessed almost 2,500 HIV-infected patients in a large health maintenance organization (Kaiser Permanente) who took triple therapy including a PI (Fessel and Hurley1998). At the Retrovirus Conference in February 1998, they noted that Kaiserhas observed a 70% decrease in the annual incidence of PCP and MAC since the introduction of PIs, and an 83% reduction in the annual incidence of CMV retinitis. Viral loads (Chiron bDNA) were conducted for 906 subjects within 30 days of starting HAART, and 280 patients (23%) had the additional analysis criteria of a baseline viral load over 3.7 $\log_{10}$, and over 180 days of follow-up. They measured virologic success in 2 ways: (1) whether viral load fell by greater than 1 log or (2) below the quantification limit (<2.7 log). Immunologic success was defined as either (1) if starting with over 300 CD4 cells/mm^3 , by double or at least 50 cells, or (2) if starting with fewer than 300 CD4 cells, by over 200 cells. The strongest predictor of virologic success was starting 1 or more new RTIs within 30 days of starting a PI. Mean follow-up was 273 days.

Predictors of Virologic Success among 280 Patients Starting a Protease Inhibitor w/ over 180 days follow-up

	No new RTI	***One new RTI***	***2 new RTIs***
Viral load decreased $\leq$1 $\log_{10}$	48%	57%	74%
Viral load decreased BLQ*	39%	52%	66%
CD4 increased >50-200	34%	--	50%
Viral load went BLQ and CD4 rose >50-200	20%	24%	39%

Predictors of Virologic Success among 280 Patients Starting a Protease Inhibitor w/ over 180 days follow-up			
Mean durability of VL BLQ (days)	140	155	160

BLQ = below limit of quantification (1,200 copies/μL for bDNA) *(Fessel 1998)*

A Belgian group studied 52 patients who failed indinavir, ritonavir, or saquinavir (Cassano 1998). Failure was defined as inability to decrease HIV RNA by 1 log, or a 1 log RNA rise from the nadir, any detectable RNA after going below the limit of quantification, or viral load above 5,000 copies/ L. Median duration of prior PI-containing therapy was 270 days. Just 7 to16% of these patients had switched an underlying nucleoside when they took their first PI, so this group (like that studied by Deeks in San Francisco) reflects the first use of PIs before the codification of HAART. After failing their first PI regimen, the 52 individuals were given ritonavir plus saquinavir in combination with 2 nucleoside analogues. After 9 months, just 3 of the 6 patients (50%) with prior saquinavir experience had an undetectable viral load, compared to 7 of the 21 patients (33%) with prior indinavir or ritonavir experience. The saquinavir group appeared to do better when assigned ritonavir/saquinavir/2 NRTIs, perhaps because they had not reached therapeutic levels of saquinavir or developed resistance (unlike the prior IDV or ritonavir group).

Rachlis and colleagues assessed predictors of virologic treatment failure in 36 HIV-infected men starting an indinavir-containing regimen with fewer than 50 CD4 cells/mm^3 (median 26 cells) (Rachlis 1997). Mean viral load at baseline was 5.2 log_{10} (range 3.8-6.0). Twenty of 36 (55%) of patients had a viral load decrease of 0.5 log_{10} or greater at 24 weeks. The mean decrease was 1.3 log_{10} and the mean CD4 increase was 105 cells. The strongest predictors of having a greater than 0.5 log viral load decrease were CD8 count at study entry (p=0.03) and not having prior treatment with saquinavir (p=0.04).

Rozenbaum and colleagues assessed incidence and predictors of failure in 500 pre-treated patients with advanced HIV disease who started taking indinavir between April and October 1996 (Rozenbaum 1998). The mean age was 39, 54% had prior AIDS, and the median duration of prior treatment was 18.4 months. Median follow-up after starting indinavir was 13.7 months. Only 24 (2%) of patients added at least 1 new RTI when they started indinavir. Treatment was interrupted in 167 patients (33%), 29 for intolerance, and 70 for failure. Forty-five patients died and 28 were lost to follow-up. The strongest predictor of treatment success was changing other antiretroviral treatment at baseline (RR 3.53, 95% C.I. 2.04,6.11). The authors concluded that "change in combined NRTI at initiation of IDV improved virological results at10 months independently of baseline CD4 count and viral load."

Predictors of Indinavir Failure in 500 Pre-Treated Patients with CD4 < 200/mm^3			
	Median CD4 (N)	***Median VL (N)***	***% with VL BLQ***
Baseline	34 (498)	5.11 log10 (447)	3.0%
Month 10	130 (402)	3.6 log10 (399)	40.6%

BLQ = below limit of quantification (<500 copies/ L); VL = viral load. *(Rozenbaum 1998)*

The follow-up to Merck 039 (described previously) provides a snapshot of the likelihood of responding to new regimens after failing indinavir monotherapy. As noted, at 24 weeks all participants were offered open-label indinavir (Hirsch 1998). One-third of patients (101), however, were randomized to indinavir monotherapy. None of these patients had an undetectable viral load at week 24. At the cross-over, all patients were able to add additional non-study drugs, and 28 (30%) of the original AZT/3TC groupreached undetectable viral load by week 36, as compared with only 9 of the 98 individuals (10%) in the indinavir monotherapy group. By week 60, these figures were 10 out of 74 (13%) versus 6 out of 81 (7%), respectively. This finding suggests that indinavir monotherapy patients are limited in their future (PI) treatment options compared to those pre-treated only with nucleoside analogues.

Another approach to indinavir monotherapy attempted to use it (or AZT/3TC) as maintenance therapy after 6 months of AZT/3TC/indinavir. In ACTG 343, Havlir and colleagues randomized 309 patients with over 200 CD4 cells, over 1,000 HIV

RNA copies and no PI experience to this induction/maintenance scheme (Havlir 1998). They were only randomized to maintenance if their viral load had been undetectable (less than 200 copies/ L) at weeks 16, 20 and 24. Viral load was measured weekly for 4 weeks, then every 4 to 8 weeks during the maintenance phase. The primary endpoint was virologic failure (i.e., 2 consecutive HIV RNA measurements of at least 200 copies/ L). The study was prematurely terminated after interim review indicated that either 1 or 2 drug maintenance therapy was inferior to triple combination therapy.

ACTG 343: Triple-Drug Induction followed by Maintenance with One, Two or Three Drugs				
	Maintenance Regimen			
	AZT/3TC	***IDV***	***AZT/3TC/IDV***	***p-value***
N	104	101	104	
Baseline CD4	437	458	463	
Baseline HIV RNA	22,011	18,970	17,273	
Virologic failure	18	16	3	0.0012 (3 vs IDV) 0.0003 (3 vs. 2)

(Havlir 1998)

The Trilege trial (ANRS 072) studied the same strategy, randomizing 379 people after 3 months of AZT/3TC/indinavir to receive AZT/3TC, AZT/indinavir, or all 3. Study subjects were then followed to measure re-emergence of viral load (Raffi 1998). All individuals were initially antiretroviral naive, with CD4 counts below 600 and viral load below 5 logs. A total of 306 out of 356 patients (86%) achieved undetectable viral load by 2 months of triple therapy. A total of 277 patients were randomized to maintenance, with 44 patients (15.8%) experiencing a viral load rebound. It appears that maintenance therapy with just 1 or 2 currently licensed drugs is unlikely to maintain durable viral suppression.

ANRS 072/TRILEGE: Triple-Drug Induction, then Maintenance with Two or Three Drugs				
	AZT/3TC	***AZT/IDV***	***AZT/3TC/IDV***	***p-value***
VL rebound	22/92 (24%)	16/93 (17%)	6/92 (6.5%)	<0.01
Detectable VL at month 6	38%	24%	10%	<0.01

(Raffi 1998)

Agouron 511 is one of the pivotal licensing studies on the basis of which Viracept™ brand nelfinavir received FDA approval in spring 1997 (Clendeninn 1998). Beginning in February 1996, 297 antiretroviral-naive subjects were randomized to receive 500 or 750 mg tid of nelfinavir plus AZT/3TC, or elseAZT/3TC/placebo. 89% of participants were male. Mean baseline viral load and CD4 were 4.9 $\log_{10}$ (153,000 copies/ L) and 283 cells/mm^3, respectively. HIV RNA values were measured using the Chiron Quantiplex™ bDNA kit, the Roche Amplicor™ RT-PCR kit, and the Roche Ultra-Sensitive Amplicor™ RT-PCR assay, with lower quantification limits of 1,200, 400 and 50 HIV RNA copies/ L, respectively. After 6 months, nelfinavir was added to the AZT/3TC arm. At 12 months, 80% of patients randomized to receive AZT/3TC and 750 mg tid of nelfinavir developed an undetectable viral load according to the bDNA and Amplicor tests; 60% were undetectable according to the Ultra-Sensitive assay. By 21 months, about 75% remained undetectable according to the Amplicor test. CD4 counts rose by 150 cells at month 6 and 200 cells by month 12, with the rise persisting out to month 21.have risen by 200.

Agouron 511: Two Doses of Nelfinavir plus AZT/3TC vs. AZT/3TC			
	AZT/3TC	***AZT/3TC/NFV 500***	***AZT/3TC/NFV 750***
VL BLQ at month 6			
bDNA (<1,200)	21%	67%	83%
Amplicor (<400)	8%	62%	81%
Ultra-Sensitive (<50)	5%	37%	66%

Agouron 511: Two Doses of Nelfinavir plus AZT/3TC vs. AZT/3TC			
VL BLQ at month 12			
BDNA	53%	59%	79%
Amplicor	37%	54%	75%
Ultra-Sensitive	23%	37%	61%

BLQ = below limit of quantification; VL = viral load *(Clendeninn 1998)*

In a smaller study carried out by Markowitz and colleagues, 3 of twelve (25%) subjects initially given AZT/3TC and 750 mg tid of nelfinavir developed treatment failure at months 7, 15 and 17 based on 2 consecutive HIV RNA measurements above the quantification limit (Markowitz 1998). All 3 subjects had the M184V mutation in reverse transcriptase, 2 had D30N in the PI gene, and 1 had L90M. "No resistance-associated point mutations were detected in isolated non-sustained increases in HIV-RNA of persistent responders." Of the 3 non-responders, 1 who had 4,232 HIV RNA copies/ L at month 18 was switched to d4T/ddI/ritonavir/saquinavir, and 1 who had 2,330 RNA copies at month 12 was given delavirdine (DLV)/d4T/ddI/ritonavir/saquinavir. The third did not return forfollow-up, but was salvaged (presumably by a primary care physician) with a similar regimen. Nelfinavir trough levels did not predict subsequent treatment failure. The authors conclude that after 20 months of therapy, 12/12 evaluatable subjects have HIV RNA below 500 copies/ L and a mean CD4 increase of 160 cells. Interestingly, the number of putative "naive" CD4 lymphocytes, with a CD45RA+62L+ phenotype, increased in 10 evaluatable subjects from 63 cells/mm^3 at baseline to 120 cells at 18 months ($p<0.002$). The authors conclude that the nelfinavir-containing triple regimen is durable, but that in those demonstrating virologic failure, switching should occur early.

A total of 9 monotherapy patients in the quaintly designed ACTG 347 (amprenavir alone versus AZT/3TC/amprenavir) failed virologically by 88 days and the study was stopped prematurely (Murphy 1998). The virologic failures were given the chance to sign up for ACTG 373, a study of d4T/3TC/indinavir/nevirapine for PI failures. Within the first months of treatment 32/36 (88.9%) of the amprenavir failures developed a viral load below 500 copies/ L. Of the ACTG 347 subjects who stayed on AZT/3TC/amprenavir, 63% remained undetectable at 24 weeks. Investigators stated that most of those who failed by 24 weeks took a drug holiday or interrupted treatment due to adverse events. Three subjects stopped therapy altogether, due to rash (2) or nausea (1).

D. Studies of Second-Line Protease Regimens after Failure on a First PI-Containing Regimen

Hellinger and colleagues conducted a retrospective chart review of 14 individuals who added saquinavir (400-600 mg bid) to ritonavir and 2 nucleosides after taking ritonavir/2 NRTIs for at least 8 months. (Hellinger 1997). All subjects adding saquinavir had detectable viral load when they did so, and thus may be characterized as ritonavir virologic failures. Of note, just 2 of 4 individuals (50%) who changed a nucleoside when they added saquinavir developed a viral load below the limit of quantification. Overall, the addition of saquinavir was associated with a modest (0.42 $\log_{10}$) reduction in HIV RNA. The authors conclude that "protease experienced individuals should not add 1 single drug to intensify combination therapy."

Adding Saquinvir to Ritonavir and 2 NRTIs		
	Group 1	***Group 2***
N	10	4
CD4 count	58 (17-192)	527 (460-749)
Viral load	56,200 (1,310-179,600)	4,215 (529-41,000)
Median prior Ritonavir	11 months (8-17)	20 months (18-22)
CD4 change at 12 weeks (median)	+50 (-104,+138)	-43 (-27,-160)
HIV RNA change at 12 weeks (median)	-11,340 (-179,100-+270,000)	-2,380 (-29,-7,812)
HIV RNA BLQ at 12 weeks	3/10 (30%)	2/4 (50%)

BLQ = below limit of quantification *(Hellinger 1997)*

Lawrence and colleagues treated 16 saquinavir failures (viral load over 5,000 copies/ L) with nelfinavir and 2 NRTIs (Lawrence 1998). The median baseline CD4 was 156 (range 21-306) and HIV RNA was 16,716 (range 2,915-878,461). The individuals had extensive nucleoside analogue pre-treatment (mean=4 agents), limiting their therapeutic options. The introduction of nelfinavir produced only a transient viral load drop (0.59 log at 2 weeks), and viral load returned to baseline by week 12 in most patients. Abouttwo-thirds of patients (n=11, 69%) were subsequently given indinavir (1,000 mg tid), nevirapine, and 2 NRTIs after failing nelfinavir. This led to a median viral load drop of 1.58 log by week 4. Six of 11 (55%) developed an undetectable viral load (<400 copies/ L), but only 3 (27%) maintained maximal suppression beyond week 20. Genotypic analyses are ongoing. This study is not the first to suggest a significant degree of clinical cross-resistance among the PIs, although this heavily nucleoside-pretreated population may not have provided the optimal means of assessing PI cross-resistance in isolation.

ACTG 333 was the first randomized study in PI failures. A total of 72 saquinavir-experienced individuals to continue on hard gel cap (HCG) saquinavir at 1.8 grams per day, switch to the more bioavailable soft gel capsule (SGC) formulation at 3.6 grams per day, or switch to indinavir at 2.4 grams per day. They were asked *not to switch underlying nucleoside analogues* for the first 8 weeks of the study. The primary endpoint was virologic response. The study was slated to 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. Most participants (86%) were male, 75% white, non-Hispanic, and the median age was 43. Median baseline HIV RNA was 20,911 copies/ L; 6% had fewer than 200 RNA copies/ L 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: Eight Week RNA and CD4 Results				
	HIV RNA reduction	**% ever BLQ**	**% BLQ @ week 8**	**CD4 change**
SQV-HGC	+0.04 $\log_{10}$	2/24 (8%)	2/22 (9%)	-0.4 cells/mm^3
SQV-SGC	-0.23 $\log_{10}$	4/22 (18%)	2/20 (10%)	+37 cells/mm^3
IDV	-0.58 $\log_{10}$	9/21 (43%)	7/19 (37%)	+22 cells/mm^3

BLQ=below limit of quantification (<200 HIV RNA copies/ L, RT-PCR). *(Para 1997)*
IDV=indinavir (Crixivan™); SQV-HGC=saquinavir hard gel caps (Invirase™); SQV-SGC=saquinavir soft gel caps (Fortovase™)

The study team commented that, "while there was variability in the RNA responses in individual subjects in both the indinavir and saquinavir arms, the mean decreases in RNA and mean CD4 cell increases in both arms was [sic] less than seen in other trials of PIs used in combination with nucleosides" (ACTG 333 1997). Based on these results, accrual to ACTG 333 was terminated. Already enrolled patients were allowed to remain on assigned therapy or switched based on virological response. Several things were notable about ACTG 333:

> These were sequential monotherapy patients, many given first AZT, then AZT/ddC or AZT/saquinavir (in ACTG 229), then given saquinavir hard gel caps, saquinavir soft gel caps, or indinavir, without regard to treatment history or virological status at baseline. Certainly the trial would be designed differently if it were begun today.
>
> ACTG 333 participants had almost 2 years (112 weeks) of previous saquinavir experience upon enrolling into 333.
>
> Most participants switched to saquinavir soft gel caps did not experience much of an antiretroviral benefit. The minority who did may not have been receiving therapeutic doses of saquinavir hard gel caps, and hence had not developed saquinavir resistance.
>
> Most participants switched to indinavir experienced far less of a viral load reduction than typical with this drug when given as a first PI[In Merck 028, protease-naive patients given indinavir as monotherapy experienced a one 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/ L. CRIXIVAN (indinavir sulfate) package insert, Merck and Co., 1996].

The ACTG 333 results, however, were given for indinavir patients *as a group.* They were likely to have fallen within 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 fell into each category was an intriguing question which many had hoped would be answered, at least in part, by analysis of resistance at baseline. Unfortunately, this analysis, which was presented at the Retrovirus Conference in February 1998, was less informative than many had hoped. Para and colleagues sequenced the PI gene from baseline HIV isolates taken from 81 subjects enrolled in ACTG 333 (Para 1998). Theyfound multiple PI and reverse transcriptase mutations. Mutations or mixtures of mutations and wild-type sequences were found at 42/81 (52%) baseline isolates at position 90 and at 6/81 (7%) isolates at position 48. (48 and 90 are the PI codons most frequently associated with HIV resistance to saquinavir.) They presented RNA and resistance data on 43 subjects:

Baseline Protease Mutations and Viral Load Response in ACTG 333				
	Protease Position			
	48		90	
Regimen	**WT**	**M (or mix)**	**WT**	**M (or mix)**
IDV *(N)*	10	10	17	3
Viral load reduction	-0.95	-0.51	-0.78	-0.41
SQV-SGC *(N)*	10	13	21	2
Viral load reduction	-0.32	-0.30	-0.30	–0.31

(Para 1998)

In this study, baseline genotypic mutations associated with resistance to saquinavir did not appear to predict virologic response or failure to switching from saquinavir hard gel caps to saquinavir soft gel caps or to indinavir (Para 1998). The study raises the possibility that genotypic analysis for PI response may be of limited use. Perhaps phenotypic analysis would be more useful. Perhaps we need better assays.

In Australia, Bodsworth and colleagues also tried to correlate the incidence of baseline genotypic saquinavir-associated mutations with subsequent virologic response to indinavir or ritonavir (Bodsworth 1998). The study involved 3 groups:

> *Group 1*: 34 subjects who received Invirase™ brand saquinavir and either added ritonavir at 400 or 600 mg bid while adjusting the saquinavir dose;
>
> *Group 2*: 14 individuals who initially received Invirase™ and switched to indinavir;
>
> *Group 3*: 14 PI-naive individuals who initiated therapy with ritonavir/saquinavir

The men in Groups 1 and 2 had a median age of 42-47 and a median prior duration of saquinavir use of 31-35 weeks.

Effect of Adding Ritonavir or Switching to Indinavir in Saquinavir-Experienced Patients			
	SQV->RTV/SQV	***SQV->IDV***	***1st-line RTV/SQV***
N	34	14	14
Baseline RTI (%)	20%	56%	86%
Baseline VL (log_{10})	4.27	5.23	4.98
Baseline CD4 (mm^3)	216	142	265
Prior SQV (weeks)	31	36	--
N (%) changing 2nd drug	8 (20%)	9 (56%)	--
28 week VL change	-1.28 log_{10}	-1.82 log_{10}	-2.32 log_{10}
28 week VL BLQ	52%	50%	80%
28 week CD4 change	+77	+76	+72
Genotyping substudy			
N	16	8	8
Responders	12/16 (75%)	5/8 (62.5%)	6/8 (75%)
Non-responders	3/16 (19%)	2/8 (25%)	2/8 (25%)
Relapsers	1/16 (6%)	1/8 (12.5%)	0/8 (0%)
Protease mutations at baseline p-value			
L10I/F	3/19 (15.8%)	3/5 (60%)	0.07
M48L/I	0/19	2/5 (40%)	0.04
G48V	0/19	1/5 (20%)	0.21
I54L	0/19	2/5 (40%)	0.04
L63P/A/H/T	16/19 (84%)	4/5 (80%)	0.46
A71T/V	6/19 (31.5%)	3/5 (60%)	0.21
L90M	4/19 (21%)	3/5 (60%)	0.11

(Bodsworth 1998)

Of the 5 non-responders (2 indinavir "switchers" and 2 ritonavir "adders"), all but 1 switcher did not switch underlying nucleosides. Three non-responders (60%) had the L90M mutation at baseline, 1 of whom also had G48V and 1 of whom had M46L. Two non-responders had no known saquinavir mutations at baseline. By week 24, however, all 5 non-responders had some combination of M46L (2), L90M (3), G48V (2), V82A (2), I84I/V (1), I54V (1), or A71V (1). The authors concluded that "all failures can be explained by looking at the genotype of the virus population," either at baseline or at week 24. This small study concluded that ritonavir adders and indinavir switchers both benefited (with -1.7 and -1.8 log_{10} reductions, respectively); switching a second drug (NRTI) resulted in a further reduction of 0.4 log_{10}.

The authors concluded that patients failing on saquinavir-containing regimens are more likely to respond to a second protease inhibitor-containing regimen if they switch earlier rather than later. They cited two other saquinavir failure studies. The 3 studies, taken together, suggest that the longer a patient received saquinavir, the smaller the likelihood of responding to a second PI:

Duration of Prior Saquinavir May Predict Reponse to Subsequent Protease Inhibitor			
Duration of prior SQV-HGC	***New rx***	***VL reduction (log_{10})***	***Reference***
36 weeks	IDV, RTV/SQV	-1.83	*Bodsworth 1998*
52 weeks	IDV, SQV-SGC	-1.20	*Schapiro 1997*
112 weeks	IDV, SQV-SGC	-0.58	*Para 1997 (ACTG 333)*

In Baltimore, 29 patients with indinavir or nelfinavir failure were treated with ritonavir/saquinavir and followed for 30 weeks. Responders (those whose RNA went below the limit of quantitation) were more likely to have switched underlying RTIs than non-responders (Gallant 1998a). The researchers deliberately tried to switch people early, rather than waiting for multiplePI mutations to occur or for viral load to return to baseline (it was 1 log below baseline when these patients switched). Clearly, switching underlying RTIs increases the likelihood that ritonavir/saquinavir salvage therapy will work, at least for 27 to 29

weeks. The authors suggest that switching earlier improves the likelihood of responding to ritonavir/saquinavir after indinavir or nelfinavir failure.

HIV RNA Response to Ritonavir/Saquinavir among Indinavir or Nelfinavir Failures				
	Indinavir failed		***Nelfinavir failed***	
	Responders	***Non-responders***	***Responders***	***Non-responders***
N	10	6	6	1
RNA at switch	12,562	22,367	9,665	78,200
CD4 at switch	240	258	335	257
Weeks on failed regimen	44	30	41	38
RNA went BLQ (<400/mL)	10/16 (63%)	6/16 (37%)	6/7 (86%)	1/7 (14%)
Durability of new regimen	>29 weeks	0 weeks	>27 weeks	0 weeks
Switched RTIs	11/12 (92%)	3/5 (60%)	6/6 (100%)	1/1 (100%)

(Gallant 1998a

Henry and colleagues followed 27 patients from the phase II nelfinavir trials (Agouron 506, 511 and 525) at two sites who failed virologically and developed two consecutive viral loads over 5,000 copies/μL (Chiron bDNA). They were switched to the four-drug combination of d4T, 3TC, ritonavir and saquinavir. The median prior nelfinavir use was 52 weeks. 33% (9) subjects originally had a complete virologic response to the nelfinavir-containing regimen. 20 of the 27 patients were antiretroviral-naive or had limited prior experience. Of these 20, one discontinued at three weeks, and 19/19 (100%) of the remaining subjects reached undetectable viral loads (<500 copies) which were sustained out to 9/10 (90%) subjects at week 16. Only 3/7 (43%) of patients with extensive prior therapy in Agouron 525 developed a viral load below the limit of quantification. The most frequent baseline protease gene mutations in the study group prior to switching were D30N (17/25, 68%) and L90M (5/25, 20%). These mutations were did notappear to predict the likelihood of a short-term virologic response to the quadruple therapy salvage regimen. The authors concluded that most nelfinavir-failing patients responded to subsequent quadruple, double PI therapy, and that the likelihood of a subsequent response was increased if the patients were antiretroviral naive before starting nelfinavir (Henry 1998).

E. Ongoing and Planned Studies of Regimens For Treatment Failure

Appendix II presents in table form a sampleof completed, currently ongoing, or planned studies of regimens for people who have experienced antiretroviral treatment failure. The information sources for this included the NIH AIDSACTIS and results of a survey carried out by the FCHR. The pharmaceutical sponsors who responded to the Forum query were Agouron, Boehringer Ingelheim, Abbott, Hoffmann-LaRoche, Merck, and Pharmacia & Upjohn.

V. POPULATION-BASED STUDIES OF TREATMENT FAILURE

Several types of population-based methods have been used to study treatment failure including: observational databases, case studies, and administrative databases. Population-based study methods differ substantially from clinical trials in the scientific rigor used in their study design, data collection, and analysis. Randomized clinical trials have been widely used to compute rates of treatment failure. Clinical trials commonly randomize individuals to several treatment alternatives. The objectives of the trials are identified and data collection methods are developed before initiation of treatment and data collection. Sample sizes are commonly estimated prior to initiation of the study, with an effort made to control for other factors that may influence the outcome measures. Study subjects are identified prior to the initiation of the project and give their informed consent to participate. Following enrollment, the study subjects' identities are usually blinded to the researchers. Data are collected prospectively, at fixed points in time, and in a standardized manner. Sequencing of data collection (e.g.,

laboratory test results, physical examinations, etc.) is timed to be consistent among study subjects. Both cross-sectional and longitudinal statistical analyses of clinical endpoints are conducted.

In contrast to clinical trials, population-based observational databases, case studies, and administrative databases are formed from existing secondary data such as medical, billing, and administrative records. In applying pre-existing data to study treatment failure, these studies are constrained by the collection methods used and resulting data quality. The complexity of the study design is limited by the size, characteristics, and generalizability of the populations represented in the database and the data's completeness, accuracy, reliability, timeliness, and breadth. The study designs are also influenced by factors that may shape clinical service use such as prescribing behavior, other practice patterns, insurance coverage, access to care, and patient care seeking and adherencebehavior. Population-based studies of treatment failure often have several common design characteristics:

- The studies consider drugs following their FDA approval. These post-approval studies afford an opportunity to compute treatment failure rates and evaluate factors associated with failure in "real world" settings among a variety of HIV-infected individuals.
- Many of the studies reviewed for this report were not explicitly designed to directly assess treatment failure. If the studies' goal had been assessing treatment failure they may have been designed differently.
- Patients are usually not formally "enrolled" in the database. Their care seeking and adherence behavior may not be similar to patients voluntarily enrolling in a clinical trial. Patients observed in observational or administrative databases, however, may be more clinically, socio-demographically, and economically heterogeneous than patients volunteering to participate in clinical trials.
- Several studies have been conducted in relatively large populations in several European countries or US regions and represent large numbers of practice sites. Most studies, however, tend to be conducted at single or multiple participating clinical settings by clinicians practicing at those sites. The patients' individual records are not always blinded to the researchers. As a result, clinicians may directly evaluate the impact of their own practice behavior on their patients. In practice-based observational databases and case studies the sample sizes tend to be small and it is often unclear what proportion of the general practice population is represented.
- Researchers conducting practice-based studies usually do not obtain the clinical, prescribing, or laboratory records of their study subjects from other practices that treated the patients during the observation period. As a result, a complete profile of the patient is not available.
- The studies tend to be descriptive with no formal study questions posed, hypotheses tested, or control groups used. Statistical analyses are often cross-sectional and small sample sizes limit the rigor of statistical analyses.
- Some clinical and empirical studies do not directly measure the impact of a treatment on the outcomes studied. Rather, they extrapolate a relationship between the treatment and the outcome, such as studies of morbidity, mortality, and inpatient admissionrates and their potential links to use of therapeutics.

A. Examples of Methods Used To Estimate The Rates of Treatment Failure

In this section we describe recent studies conducted to estimate the rates of virological, immunological, clinical, and empiricalfailure. In addition to describing the methods used to estimate treatment failure rates, we summarize the results of the studies and briefly discuss their limitations. This review represents key examples of recent treatment failure studies, rather than acomplete review of the literature.

1. Virological and Immunologic Failure

Multi-site and single-site observational studies have been used recently in the US and Europe to study virologic and immunologic failure. Virologic and immunologic failure are commonly assessed together in these studies.

a. Multi-Site Observational Studies

Several multi-site observational studies have studied aspects of virologic and immunologic failure among segments of the HIV-infected US population. The CDC Viral Load Project has retrospectively collected viral load, CD4 count, and morbidity data from the medical charts of over 2,000 adolescents and adults newly reported with AIDS in Los Angeles and San Francisco or with HIV infection or AIDS in New Jersey (Denning 1998). Viral loads were significantly lower among patients receiving more aggressive anti-retroviral therapy. Viral loads were lowest for patients receiving PI and RTI combinations (median viral load=20,200) compared to patients receiving combination RTIs (median viral load=39,500), antiretroviral therapy monotherapy (median viral load=72,000), or no therapy (median viral load=134,100). Patients treated with PI and RTI combinationswere also significantly more likely to have a viral load below 500 than those treated with combination RTIs. While a benefit was documented for patients receiving HAART, it should be noted that 42% of patients studied had not received any antiretroviral therapy and 53% had not received viral load testing despite their advanced HIV disease.

Several large observational databases are based on the clinical records of HIV multi-site hospital-based clinic or private practices. The HIV Outpatient Study (HOPS) Group is a cohort of over 3,000 patients treated at 7 private and 2 public HIV clinics in 8 US cities (Moorman 1998). Changes in viral load and CD4 count over time have been measured prospectively through analysis of automated medical records. Most HOPS participants are male (85%) and most are white (73% white, 18% black and 9% Hispanic). About two-thirds (65%) of participants are men who have sex with men, 15% are injection drug users, and 4% contracted HIV heterosexually. Almost one-half (49%) of participants have private insurance and 25% are enrolled in Medicare or Medicaid. Among patients recently receiving HAART, CD4 counts rose in 48% of patients and viral loads declined in 59%. A striking trend in this study appears to be the growing use of antiretrovirals, viral load testing, and regimens which would later be designated “preferred” by the HHS guidelines panel (Bartlett 1997), although they had not been released by the second quarter of 1997.

Changing Patterns of Antiretroviral Use in the HIV Outpatient Study (HOPS), 1996-97

	3rd quarter 1996	***2nd quarter 1997***
N	1,919	1,850
Used antiretroviral therapy	1,470 (77%)	1,593 (86%)
Used PI	1,086 (56%)	1,150 (61%)
Used VL test	1,347 (70%)	1,698 (92%)
Started ART at CD4>500	14%	14%
Started ART w/ VL < 1,000/µL	26%	28%
Started ART w/ VL 1,000-9,999/µL	20%	21%
Started ART w/ VL 10,000-99,999/µL	23%	31%
Started ART w/ VL > 100,000/µL	31%	21%
Started PI at CD4 > 500	10%	10%
Started PI w/ VL < 1,000/µL	36%	33%
Started PI w/ VL 1,000-9,999/µL	46%	41%
Started PI w/ VL 10,000-99,999/µL	10%	19%
Started PI w/ VL > 100,000/µL	8%	7%
Used PPI + 2 NRTIs	36%	50%
VL decreased on ART	57%	66%
CD4 increased on ART	43%	43%
VL decreased on PI	54%	59%

Changing Patterns of Antiretroviral Use in the HIV Outpatient Study (HOPS), 1996-97		
CD4 increased on PI	49%	48%

ART = antiretroviral; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PPI = potent protease inhibitor (indinavir, nelfinavir or ritonavir); VL = viral load *(Moorman 1998)*

The Pacific Oaks Population Study (POPS) is a longitudinal cohort study of HIV-infected patients treated at 1of the largest private multi-site medical groups specializing in HIV in the US (Shaefer 1998). Patients are followed prospectively and their charts reviewed each quarter forantiretroviral therapy and other medication use, HIV-related conditions, viral load, and CD4 and CD8 lymphocyte counts. Specimens are stored for genotypic and phenotypic HIV virology analysis. In a recent study, use of mono and combination antiretroviraltherapy including PIs was studied in the first 249 patients and changes in viral load and CD4 counts were measured for a 1-year period. HAART resulted in decreased viral load and an increase in CD4 counts. Although the patients studied had been heavy pretreated with antiretroviral therapy, two-thirds of those switching to triple combination therapy had undetectable viral load levels.

In a small multi-site study, the charts of 14 patients participating in the Community Research Initiative of New England were reviewed retrospectively to assess the effect on viral load and CD4 count of adding saquinavir (400-600 mg bid) to an existing ritonavir and nucleoside combination regimen (Hellinger 1997). Adding saquinavir among patients with detectable viral loads was associated with increased CD4 counts and decreased viral load for some patients. Of note, just 2 of 4 individuals (50%) who changed a nucleoside when they added saquinavir developed a viral load below the limit of detection. Overall, addition of saquinavir was associated with a modest (0.42 $\log_{10}$) reduction in HIV RNA. The authors conclude that"protease experienced individuals should not add one single drug to intensify combination therapy." The Initiative also conducted a study to determine if patients switching to nelfinavir from indinavir or a ritonavir and saquinavir combination continued to have viral load suppression (Cohen 1998). About three-quarters (74%) of the patients switched to nelfinavir had continued suppressed viral load at 6 weeks of follow-up.

Adding Saquinvir to Ritonavir & 2 NRTIs		
	Group 1	***Group 2***
N	10	4
CD4 count	58 (17-192)	527 (460-749)
Viral load	56,200 (1,310-179,600)	4,215 (529-41,000)
Median prior RTV	11 months (8-17)	20 months (18-22)
CD4 change at 12 weeks (median)	+50 (-104,+138)	-43 (-27,-160)
HIV RNA change at 12 weeks (median)	-11,340 (-179,100-+270,000)	-2,380 (-29,-7,812)
HIV RNA BLD at 12 weeks	3/10 (30%)	2/4 (50%)

BLD = below limit of detection *(Hellinger 1997)*

Studies conducted using multi-site observational databases generally concluded that HAART was associated with significant declines in viral load and increases inCD4 counts. While the findings of the Community Research Initiative of New England study were more equivocal, this may be in part due to the small number of individuals studied (Hellinger 1997).

b. Single Site Observational Studies

Several large single site observational studies have been conducted to assess the impact of antiretroviral therapy on virologic and immunologic measures. For example, clinicians at the Kaiser Permanente Medical Center in San Francisco have studied outcomes associated with triple combination therapy, including a PI, on viral load and CD4 cell levels over time in a cohort of 2,139 patients (Fessel 1998). Virologic success or failure were defined as whether viral load fell greater or at 1 $\log_{10}$ or below detectable. Among patients with no new RTI, virologic success was observed in 48% of individuals; with 1 new RTI success was found in 57%, and with 2 new RTIs success was found in 52%. Virologic success was associated with the number of new RTI prescribed within 30 days of the initiation of PI therapy. Immunologic success or failure was also

defined as whether or not CD4 cells rose if starting: (1) less than or equal to 300/mm by double but greater than 50 cells or (2) greater than or equal to 300/mm by greaterthan or equal to 200 cells. Immunologic success was observed in 41% of individuals but was also associated with use of new RTIs. Immunologic success was observed in only 34% among individuals with no new RTI, compared to 50% among individuals receiving 2 new RTIs. Total treatment success was defined as HIV viral load falling more than 1 $\log_{10}$ to below detection and a CD4 rise as defined in the immunologic success criterion. Total treatment success was also associated with initiation of a new RTI, with 20% of patients achieving total success with no new RTI, 24% with 1 new RTI, and 39% with 2 new RTIs. Durability of virologic suppression to below detectable was also measured, with rebound occurring in 140 days in patients with no new RTI, 155 days with 1 newRTI, and 160 days with 2 new RTIs. Additional studies conducted in large single sites are described in the clinical failure section of this report.

In a study specifically designed to assess changes in viral load and CD4 count in patients failing PI therapy, the medical records of 79 patients treated at the University of California San Francisco were reviewed retrospectively (Deeks 1998). Virologic failure was defined as the 2 most recent viral load assays greater than 500 copies/µL after at least 20 weeks of treatment. Although the patients studied were found to have ongoing viral replication for more than 6 months, their CD4 cells were elevated in most patients failing PI therapy. A sustained virologic response to PIs was observed. Despite a median of 8.9months since evidence of virologic failure, the median CD4 T cell count remained 101 cells above baseline. Fifty-eight patients had a baseline viral load available. About one-tenth of patients (n=9, 16%) had no virologic response of less than 0.5 $\log_{10}$ RNA reduction, almost one-half (n=26, 45%) had a "potent but transient response" of greater than 1 $\log_{10}$ decrease followed by a return to 0.5 $\log_{10}$ of baseline, and about one-fourth (n=15, 26%) had a durable response with persistent viral load reduction of at least one $\log_{10}$. Thirty-seven patients achieved an undetectable viral load of less than 500 copies/µL for a median of 7 months (range=2.4-16.5). Reasons for the persistent CD4 increase in the face of virologic failure are not yet clear. Most patients continued to have clinical benefit without clinical progression.

The impact of HAART on viral load was measured in several moderate or small-sized single site adult cohorts in the US and Europe. Assessment of treatment failure was not an explicit goal of thesestudies. A subset of 273 subjects were selected from a longitudinal cohort of 4,800 patients treated at a United Kingdom HIV clinic (Youle 1997). In this study, the effect of stavudine (in combination with or without a PI) on viral load and CD4 count wasmeasured. Patients receiving stavudine in combination with a PI had a significant positive CD4 response. In a retrospective review of the medical charts of 250 women treated at Brown University, the predictors of undetectable viral load were studied (Flanigan 1998). Receipt of HAART and private insurance were the greatest predictors of viral loads. About 90 heavily pretreated patients seen at an outpatient clinic at the Hospital Ramon in Madrid were observed over a twelve-month period to evaluate the effectiveness and safety of indinavir and ritonavir (Perez-Elias 1997). In addition to measuring the impact of these therapies on viral load over time, CD4 count, onset of OIs, resource use, adverse events, and mortality were assessed. In a study conducted at the same Spanish hospital, the impact of indinavir, saquinavir, and ritonavir on viral load and CD4 count were compared. Adherence to these drug regimens and associated resource use and adverse events were also compared (Moreno 1997). CD4 counts were sustained above baseline levels 12 months after initiation of PI treatment and a 1 $\log_{10}$ average decrease in viral load after 9 months was observed. The percentage of patients with undetectable viral load was moderate in each of the 3 PI regimen groups. The clinical records of 33 patients with previous PI experience who were treated at the Albany Medical College and receiving ritonavir and saquinavir were reviewed to assess the impact on viral load and CD4 count (Piliero 1997). The ritonavir and saquinavir combination produced a significant or sustained reduction in viral load in 42% of patients studied. Over one-half (58%) of patients discontinued therapy due to toxicity or lack of CD4 response.

The Swiss Cohort Study database (Ledergerber 1994) has been used to assess the toxicity, efficacy, and viral load concentrations of ritonavir and saquinavir in 16 patients with advanced HIV disease treated in university clinics and community hospitals (Lorenzi 1997). Short to moderate-term response to the 2 PI combination was unpredictable, with a

minority of patients with viral load rendered undetectable. In most patients, however, mutations developed and mitigated the benefit of the regimen even in cases of good adherence and relatively high plasma drug levels.

In Germany, 52 antiretroviral therapy naïve or experienced patients were studied over a 6-month period to evaluate the efficacy of a combination regimen of stavudine, lamivudine, and indinavir (Knechten 1997). Viral load and CD4 counts were serially measured at 3 points during the observational period. Substantial reduction in viral load was achieved in both pretreated and treatment naïve patients at least for 24 weeks. Treatment naïve patients, however, had a more rapid and greater therapeutic benefit than did pretreated patients. In Australia, the efficacy of a regimen including saquinavir, ritonavir, and either zidovudine and lamivudine or stavudine and lamivudine was studied in 51 males who were heavily pretreated with PIs and nucleosides (Kaufmann 1997). Although a significant effect on the CD4 counts was observed, 41% of patients had virologic treatment failure by the sixth month of observation.

A small cohort of patients treated at the Johns Hopkins University Moore Clinic was studied retrospectively to assess the effectiveness of ritonavir and saquinavir as a salvage therapy after failure of an initial indinavir or nelfinavir regimen (Gallant 1998). Failure of the initial regimen was defined as any detectable viral load after 16 weeks of therapy confirmed on 2 occasions. Viral load was measured at the time of the switch to the ritonavir and saquinavir combination and in prospective follow-up. Almost two-thirds (62.5%) of the patients responded (i.e., with an average viral load of less than 400 copies/µL) to the new regimen after a 27 to 29 week follow-up period. Responders were more likely to have switched underlying RTIs than non-responders. The Hopkins group deliberately attempted to switch people early, rather than waiting for multiple protease mutations to occur or for viral load to return to baseline (it was one log below baseline when these patients switched). Switching underlying RTIs appears to increase the likelihood that ritonavir and saquinavir salvage therapy will work, at least for the period observed. The authors suggest that switching earlier may improve the likelihood of virologic response to ritonavir and saquinavir after indinavir or nelfinavir failure.

HIV RNA Response to Ritonavir/Saquinavir Among Indinavir or Nelfinavir Failures

	Indinavir failed		***Nelfinavir failed***	
	Responders	***Non-responders***	***Responders***	***Non-responders***
N	12	5	3	1
Baseline HIV RNA	285,000	227,000	139,000	333,000
RNA at switch	24,000	25,000	13,000	40,000
CD4 at switch	240	258	335	257
Weeks on failed regimen	44	30	41	38
RNA went BLD (<400/µL)	10/16 (63%)	6/16 (37%)	6/7 (86%)	1/7 (14%)
Switched RTIs	11/12 (92%)	3/5 (60%)	6/6 (100%)	1/1 (100%)

(Gallant, 1998)

Several observational studies have been conducted in small cohorts to evaluate the use of HAART by children. At the University of Maryland, 113 perinatally infected children were studied to assess the efficacy and adherence to HAART (Watson 1998). Treatment failure was defined as the inability to achieve a clinically meaningful drop in viral load. While HAART was found to be effective in reducing viral replication in children and increasing CD4 counts, only 10% of children's families were able to adhere to the regimen. A case study was conducted in Puerto Rico among 54 HIV-infected children over 8 years of age and adolescents to measure the impact on viral load of ritonavir and 1 or 2 nucleoside RTIs (Febo 1998). Over three-quarters (78%) of patients receiving ritonavir experienced a positive virologic response, however, only 9% of patients has sustained viral levels at 10 months of follow-up. CD4 count, side effects, survival time, and mortality were also studied. The impact of triple therapy regimens, including PIs, on viral load and CD4 count has also been studied in 34 children treated at 2 hospitals in Chicago and 1 hospital in Boston (Pelton 1998). Treatment failure was defined as changing the regimen following initiation of the original triple combination. Triple combination therapy including a PI was effective in

reducing viral load and CD4 in most children.

Although observational databases have not been widely used to study genotypic or phenotypic resistance, the Veterans Administration Medical Center in Atlanta has described baseline HIV genotypic resistance and its association with mortality and time to onset of a new OI in 95 treatment naïve or treated patients (Rimland 1997). Baseline genotypic markers of resistance in plasma virus did not predict mortality. The POPS cohort has also been studied to identify viral mutation associated with use of several combinations of antiretroviral therapy (Ross 1998). The only PI mutation identified was associated with indinavir.

2. Clinical Failure

a. Duration of Survival and Death

The Multicenter AIDS Cohort Study (MACS) population is a prospectively studied group of over 500 US homosexual men who seroconverted between 1984 and 1997 (Kaslow 1987). The MACS cohort has been used recently to assess the impact on survival time to AIDS and death of monotherapy during 1990 to 1993, combined RTI therapy in 1993 to mid-1995, and RTI in combination with PIs between the last half of 1995 and 1997 (Detels 1998). HAART was found to significantly extend survival time from HIV infection to onset of AIDS, as well as survival from infection to death. The association of viral load with survival time in MACS subjects with severe immunosuppression and the impact of antiretroviral therapy on these measures has also been studied (Jacobson 1998). Viral load was significantly related to survival, after controlling for CD4 count, CD8 cells, and hemoglobin level. Even among severely immunocompromised patients with the highest viral loads, antiretroviral therapy use extended time to death.

The Women's Interagency HIV Study (WIHS) is a prospective study of over 2,500 HIV-infected and uninfected women in 5 US cities who were initially recruited in 1995 (Kanastos 1998). Clinical, virologic, and immunologic evaluations are performed every 6 months. A recent study using data from the WIHS cohort assess the relationship between viral load and other factors associated with survival among the HIV-infected subjects. Women with CD4 counts below 50 and viral load greater than 500,000 had the greatest risk of death. Data regarding the antiretroviral therapy failure was not presented.

Duration of survival and mortality have been studied in several European cohorts. EuroSIDA is a prospective, multi-center cohort study of about 4,500 HIV-infected patients in the Northern, Central, and Southern regions of Europe (Vella 1998). In a recent study using EuroSIDA data, regional mortality rates were computed to identify differences associated with antiretroviral therapy (including PIs), CD4 counts, and PCP prophylaxis. Regional mortality rates varied substantially, based in part on difference in use of RTIs and PIs. The Swiss Cohort Study database has been used to assess the impact of combination antiretroviral therapy on mortality and progression to AIDS-defining events in about 5,200 Swiss patients treated at 7 HIV units in university clinics and community hospitals between 1988 and 1996 (Egger 1997). Comparing the 1988-1990 and the 1995-1996 cohorts, risk of progression to AIDS dropped by 73% and mortality declined 62%. Compared to individuals with no antiretroviral therapy, risk of an initial AIDS diagnosis (after CD4 counts fell to less than 200) dropped by 16% for patients receiving monotherapy, 24% for those with combination therapy, and 65% with triple therapy. Compared to persons with no antiretroviral therapy, mortality dropped by 23% for patients receiving monotherapy, 31% for those with double combination therapy, and 65% for those with triple therapy.

A population-based cohort enrolled in the Drug Treatment Program of the British Columbia Centre for Excellence in HIV/AIDS are beingfollowed prospectively (Hogg 1997, 1998, 1998, 1998; Forrest 1998). Several indicators of treatment failure have been studied using this cohort, including time to AIDS diagnosis, incidence and spectrum of AIDS-defining illnesses, and death. All British Columbians prescribed antiretroviral therapy are enrolled in the cohort. Their physicians enrolling HIV-infected patients into the Drug Treatment Program must complete an initial application that includes HIV-specific drug history, CD4 cell counts, and current drug requests. On an annual basis, patients are asked to complete an

enrollment survey and their physicians must prepare a clinical staging form. These data are supplemented by information from linked provincial and national AIDS and death registries. An initial significant decline in mortality observed in the British Columbian cohort coincided with availability of lamivudine and expanded dissemination of double combination therapy (Hogg 1997). In a subsequent follow-up study, the effect of the dissemination of newly emerging antiretroviral therapy drugs was shown. Patients receiving an initial regimen of stavudine or lamivudine had significantly lower mortality rates and a longer period before onset of an AIDS-defining condition than those who received initial treatment with zidovudine, didanosine, and zalcitabine. The virological response to double nucleoside combination therapy has also been measured in a sub-set of the cohort who were antiretroviral therapy naïve (O'Shaughnessy 1998).

The Ontario HIV Project Center's Drug Distribution Program collects data on antiretroviral therapy use, CD4 counts, and clinical history at enrollment and at 3 to 6 month intervals for all Ontario patients receiving government subsidized antiretroviral therapy (Rachlis 1998). Over 10,000 individuals have enrolled in the program. Trends in survival have been studied, controlling for factors such as patient age, CD4 count, and clinical status. Median survival time increased from 9 to 30 months for persons with AIDS over 35 years and with CD4 counts below 100. Median CD4 counts also rose significantly after the initiation of antiretroviral therapy in program participants.

Vital records systems also may contribute to our understanding of factors associated with clinical failure.In a series of studies conducted by the New York City Department of Health, death records of 71,289 persons with AIDS were analyzed for the period between 1980 and 1997 (Muthambi 1998). Mortality rates and survival time from AIDS diagnosis to death were computed for individuals diagnosed with AIDS and factors associated with temporal changes were assessed. A sub-analysis compared AIDS mortality in New York City for the last half of 1996 with the first half of 1997 (Chiasson 1998). The most dramatic drop inmortality during 1997 in New York City was observed among black women, whose mortality decline doubled form 16% in 1996 to 30% in 1997. The impact of antiretroviral therapy was not directly measured in either study. In a supplemental study, however, 150 deceased randomly selected AIDS cases was compared to 150 controls who were not known to have died to determine if PI use was associated with likelihood of the decline in death rates in AIDS cases (Reggy 1998). Cases and controls were matched for age, race, HIV risk factors, and receipt of publicly funded medical care. Data were obtained from the AIDS registry, death certificates, and medical charts. Death following AIDS diagnosis was strongly associated with absence of PI therapy.

Accelerating Decline in NYC AIDS Deaths, 1995-1997

	Annual deaths	***Daily deaths***	***Change***	***Change since '95***
1995	7,046	19.3	--	
1996	4,998	13.7	-29%	-29%
1997	(incomplete)	7.0 (first 9m)	-48%	-64%

(Chiasson 1998)

Reduction in NYC AIDS Death Rate by Risk Group, 1996-1997			
	Men	***Women***	***Difference***
Overall	-33%	-32%	1%
Whites	-41%	-33%	8%
Blacks	-28%	-30%	2%
Hispanics	-34%	-37%	3%
Gay/bisexual men	-40%	NA	NA
Injecting drug users	-30%		?
Heterosexuals	-30%		?

(Chiasson 1998)

A cohort of 500 patients treated at the Hospital Rothschild in Paris was followed from initiation of indinavir to measure changes in viral load and CD4 counts over time and associated survival time and mortality rates (Le Pen 1998). A continuous Markov model was used to describe the significant short-term effect of antiretroviral therapy on CD4 and viral load levels. A separate analysis of these patients' clinical records was conducted to determine the efficacy, tolerance, and factors that predict viral load below 500 copies/μL ten months after initiation of indinavir (Rozenbaum 1998). Results of the study suggest that a change in non-RTIs in combination with initiation of indinavir following treatment failure improve virologic results, controlling for CD4 count and viral load at baseline. Discontinuation, failure of the new non-RTI and indinavir combination, and mortality rates were also measured.

b. Opportunistic Infections and Other Conditions Related To HIV Infection

Several multi-site studies have evaluated the association between antiretroviral therapy failure and the onset or recurrence of OIs and other conditions related to HIV infection. The CDC's Adult Spectrum of Disease Project is designed to measure and describe HIV-infected persons at various stages of immunologic function who are treated at 10 US inpatient and outpatient centers (CDC 1998). The medical records of all individuals treated at ASD sites are abstracted every 6 months. ASD data have been used to study the effect of mono and combination antiretroviral therapy, including triple combination therapies with a PI on the survival time and mortality rates of persons with AIDS (McNaughten 1998). Mono, double combination, and triple combination antiretroviral therapy were all associated with reduced mortality risk, although triple combination therapy had the most profound effect on survival (i.e., 2.5 times lower than for patients on monotherapy). Risk of death declined for patients receiving any type of antiretroviral therapy and PCP and/or, *Mycobacterium avium* complex (MAC) prophylaxis. Factors influencing survival in HIV-infected individuals with progressive multifocal leukoencephalopathy (PML), including use of PIs and other antiretroviral therapy, have also been studied in the ASD cohort (Dworkin 1998). PI use was found to have a significant and positive impact on survival time following diagnosis of PML.

The French Clinical Epidemiology Database contains abstracted clinical records compiled since 1989 on over 66,000 HIV-infected patients treated in more than 60 French hospitals from 1992 to 1997 (Costagliola 1998). The author notes that double nucleoside therapy became frequent after the results of ACTG 175 and Delta. In the first half of 1995, 16% of patients were on double NRTIs; this rose to 315 in the second half, and 44% in the first half of 1996. By April 1996, PIs became available, and were used in 17% of subjects. By the end of 1996, this rose to 34%. Beginning in the second half of 1996, significant reductions by 40% or more were observed in the incidence of esophageal candidiasis, bacterial pneumonia, MAC, PCP, Kaposi's sarcoma, cytomegalovirus (CMV) disease, cryptosporidiosis, and cryptococcosis at these facilities. Moderate decreases of about 25%were observed in tuberculosis and toxoplasmosis, while slight decreases were measured in PML, encephalopathy, and lymphoma. Although combination therapy (including the use of PIs) became common during that period, no direct relationship between treatmentfailure and reduction in the incidence of OIs was measured.

Rapidly Declining OI Rates in France, 1996-1997 *(Rate Per Thousand Patient Years)*			
	1996, 1st half	***1997, 1st half***	***% change***
Cryptosporidiosis	10	2	-82%

CMV	40	8	-80%
Atypical mycobacteria	26	7	-73%
Cryptococcosis	6	2	-70%
Esophageal candidiasis	34	10	-69%
PCP	18	6	-68%
Encephalopathy	16	5	-67%
Kaposi's sarcoma	23	8	-65%
Toxoplasmosis	15	5	-64%
Tuberculosis	11	6	-50%
Lymphoma (NHL, CNS)	12	7	-44%
Bacterial pneumonia	29	17	-41%
PML	3	5	0.28

CNS = central nervous system; NHL = non-Hodgkins lymphoma *(Costagliola 1998)*

A study of over 1,700 patients treated at participating HOPS sites found dramatically reduced incidence of AIDS OIs from 26.9 per 100 person years in 1995 to 3.0 per 100 person years in the second quarter of 1997 (Palella 1998). The death rate dropped from 30.3 per 100 person years in 1994 to 6.4 per 100 person years in the second quarter of 1997. Significant reductions in viral load were also observed in patients receiving PIs. Multivariate analysis of morbidity and morality rates demonstrated substantialsurvival benefit associated with PI use; a benefit that significantly exceeded that contributed by non-PI combination therapies. Declines in morbidity and mortality and increases in PI use were seen across all groups regardless of gender, race, age, risk, method of payment, or type of clinic. Concomitant with these changes in morbidity and mortality rates, the HOPS has documented a dramatic reduction in the incidence of AIDS-defining events among people with HIV infection and fewer than 100 CD4 cells.

Declining AIDS and Death in the Hospital Outpatient Study (HOPS), 1995-1997
(Quarterly Rate Per 100 Person Years)

	Died	***OI Rate***	***Rx Included PI***
1995	30.7	26.9	20 % (4th qtr.)
1996 overall	17.6	18.1	
4th quarter 1996	11.3	4.8	
2nd quarter 1997	6.4	3.0	84%

(Palella 1998)

Several large clinic-based observational databases have been used to study the onset of OIs among patients receiving antiretroviral therapy. The clinical records of patients treated at Hopkins have been retrospectively analyzed for OI and other studies (Moore 1996). The incidence of secondary PCP, cryptococcal meningitis, and herpes zoster were found to have declined in the early 1990's. The incidence of CMV and other OIs among 1,500 patients receiving mono or combination antiretroviral therapy, including a PI, has been studied (Moore 1997; Moore 1998). Reduced risk for OIs was associated with HAART, as well as with CD4 count and viral load level. No patients receiving HAART developed an OI if their CD4 count was greater than200. Patients treated at San Francisco General Hospital have been followed prospectively since 1994 (Holtzer 1998). Decline in the number of patients diagnosed with CMV retinitis, PCP, meningitis due to cryptococcus neoformans, and MAC has been observed and is associated in recent periods with use of HAART.

Declining Event Rates at Johns Hopkins University Moore Clinic, 1994-1997
(Event Rate Per 100 Patient Years At Risk)

	1994	***1995***	***1996***	***1997***	***Relative reduction, 1994-97***

Death	38	35	27	22	-42%
Bacterial pneumonia	26	22	13	9	-65%
PCP	11	11	7	4	-64%
Dementia	11	11	5	1	-91%
MAC	9	11	5	4	-56%
CMV	7	7	7	1	-86%
Toxoplasmosis	3	3	1	1	-67%
Kaposi's sarcoma	3	2	0.5	0.5	-83%
PML	1.75	1.75	1.75	0.5	-71%
Non-Hodgkins lymphoma	1	1	0.8	0.6	-40%
Cryptosporidiosis	1	1	0.4	0.3	-70%

(Moore 1998)

Several studies using moderate or small sized cohorts have evaluated the occurrence of OIs following initiation of PIs. The AIDS Research Consortium of Atlanta surveyed 53 participating physicians to identify cases of HIV-related OIs occurring at higher than usual CD4 counts in patients receiving PIs (Thompson 1997). The records of over 10,000 patients were reviewed to retrieve CD4 counts, viral load, identify onset of OIs, and OI prophylaxis data. Development of OIs at relatively high CD4 levels among patients receiving PIs was observed in a small number of patients. A retrospective chart review study was conducted in 7 hospitals in western France to determine the incidence of CMV infections, MAC, cerebral toxoplasmosis, PCP, cryptococcal meningitis, and esophageal candidiasis among 452 patients receiving either ritonavir or indinavir when preventive treatment was either suspended or ongoing (Michelet 1997). CMV infections were observed during the first 2 months of PI treatment, despite a rapid increase inCD4 count. A review of the medical records of patients treated at the Louisiana School of Medicine for an 18-month period before (n=1,181) and following (n=1,284) availability of PIs demonstrated significant to moderate reductions in the incidence of OIs and other AIDS-related conditions (Michaels 1998). The most significant decreases were found in PCP and wasting, while moderate drops were found in Kaposi's sarcoma, MAC, and CMV retinitis. It is unclear if the decline in the conditions studied is directly associated with PIs or other factors.

Declining OIs in the Adult Spectrum of Disease Cohort, 1994-1998			
	Jan 94 - Dec 96	***Jan 96 - Jan 98***	***p-value***
N	1,181	1,284	
PCP	18.0%	11.7%	<0.01
Wasting	9.5%	4.8%	<0.01
MAC	8.5%	6.1%	<0.05
CMV	4.6%	3.0%	<0.05
Kaposi's sarcoma	4.3%	2.5%	<0.05
Toxoplasmosis	2.9%	1.9%	<0.15
Dementia	3.8%	2.8%	<0.20
Esophageal candidiasis	9.5%	8.0%	<0.20
Cryptococcal meningitis	3.3%	2.7%	<0.35
Cryptosporidiosis	3.8%	3.2%	<0.45

(Michaels 1998)

Several studies report the impact of HAART and individual OIs. The positive impact of PIs to delay or stave off the onset of dementia is reported in a case study of 16 patients with advanced AIDS and abnormal MRI brain scans that revealed multifocal or severe white matter disease (Skolnick 1998). Rates of stabilization of encephalopathy (8 out of 9 patients) and complete regression of encephalopathy (4 out of 9 patients) are reported. Time to progression of CMV retinitis following anti-

CMV therapy is reported in a cohort of 102 AIDS patients receiving HAART and being treated at the University of California San Diego (Freeman 1998). Inflammatory responses and non-progression of CMV retinitis following discontinuation of anti-CMV medication was described among a small group of patients. Survival improvement of PML patients receiving PIs has also been found in French (Gasnault 1998) and Spanish cohorts (Miralles 1998). Clinicians at the Albany Medical College reported that 2 patients died due to PML despite HAART, interferon-alpha 2b, and Peptide T (Piliero 1998).

The rate of onset or recurrence of PCP among patients using antiretroviral therapy has been calculated in several studies of hospital-based HIV clinic populations. Factors associated with the onset of PCP while receiving HAART were studied in a cohort of 289 patients followed at the University of Colorado Health Sciences Center (Grodesky 1998). Almost one-half (47%) of patients were receiving HAART at the time of PCP onset, although other factors such as use of trimethoprim-sulfamethoxazole (TMP-SMX), non-adherence, and low CD4 count were identified as confounding factors. A retrospective study of PCP cases treated at San Francisco General Hospital found no patients who report antiretroviral therapy at the onset of PCP and whose CD4 count was greater than 200/µL but who previously had a CD4 count of less than 200/µL (Huang 1998).

c. Adverse Clinical Events

Administrative databases are useful in measuring various aspects of clinical failure. The clinical records of individuals participating in the Viracept Expanded Access Program were studied to assess the rate and nature of adverse effects among 2,366 heavily pretreated patients with advanced HIV disease (Becker 1997). One-quarter (25%) ofpatients reported adverse events, with diarrhea being the most commonly reported (14%), rash reported by 5% of patients, nausea (3%), and other events reported by 2% or less of patients. Reasons for discontinuation of the therapy were also reported, with 5% discontinuing due to adverse events.

Practice-based case studies have been used to observe side effects associated with PI use. Urinary stones were characterized in a study of 29 French clinic patients treated with indinavir (Daudon 1997). Indinavir-related nephropathy was reported among Austrian women (Sarcletti 1998). Severe illness associated with initiation of indinavir was described in 5 patients with advanced HIV disease and sub-clinical MAC infection treated at the Beth Israel Deaconess Medical Center (Race 1998). Symptoms including fever, leucocytosis, and lymphadenitis were observed in patients with CD4 counts below 50 cells/µL and subclinical MAC infection. Recurrence of TMP-SMX hypersensitivity has also been reported in a case study of 4 patients treated at Deaconess Medical Center (Race 1997). The incidence of development of cervical fat pad following treatment with PIs was studied in a group of over 7 of 800 patients followed at the Ottawa General Hospital (Roth 1998) and in a group of 58 patients treated in Chicago (Berger 1997). The incidence of hyperglycemia and diabetes associated with use of PIs was assessed in a cohort of 290 patients treated at the Johns Hopkins Moore Clinic (Keruly 1998). Hyperglycemia was found to be uncommon among patients using PIs, but was severe when it occurred.

d. Disease Progression

In this section we review studies of treatment failure resulting in disease progression in children. We have discussed studies of disease progression in earlier sections of this report.

Several recent studies have been conducted among pregnant HIV-infected women. The impact of prenatal and perinatal zidovudine on disease progression was studied in vertically infected infants born to a cohort of over 400 mothers treated at the University of Miami (DeSouza 1998). The mothers had initiated zidovudine at different points during in the prenatal, interpartum, and post-partum periods. Outcome measures studied include perinatal infection, a CDC Class C clinical event, or AIDS-related death by 18 months of age. The impact of antiretroviral therapy was also measuredamong 65 women receiving care at a British Columbia provincial referral center (Forbes 1998). A significant decrease in HIV-infected infants was found among pairs in which antiretroviral therapy was used orally during pregnancy and intravenously during delivery

(3.6%) compared to pairs in which no antiretroviral therapy was received (20%). The infection rate was high (23.5%) among infants in which only partial antiretroviral therapy in which zidovudine was administered intra and/or post-partum.

3. Empirical Failure

Factors associated with the decision to switch to an alternate HAART regimen have yet to be well documented. A study of PI use among patients treated at the University of Maryland Medical System, however, documents some of those factors in a retrospective review of the medical records of 86 randomly selected patients in treatment for at least 12 months who had received a PI (Bozek 1998). About one-half (51%) of patients remained on their original PI regimen at the end of 1 year. Non-adherence and poor patient understanding were identified as the reason for switching in 51% of patients and lack of efficacy in 25%. Switch rates for individual PIs and the subsequent treatment regimens selected following switching are described.

Health services utilization and associated costs have been associated in earlier generations of HIV health services research with treatment failure and lack of access to services. With the introduction of combination antiretroviral therapy, these measures have taken on importanceas indices of treatment success. They continue to be important indicators of differential treatment success or failure, variable access among sub-populations of HIV-infected individuals, or in where HAART has been slower to be adopted than elsewhere in the US or in developed countries.

The association between use of PI and nucleoside analogues and hospital inpatient, clinic, and emergency room use and costs has been studied in patients treated at the Southwestern Medical Center (Keiser 1998). Inpatient admission rates, lengths of stay, inpatient mortality, and the reason for hospitalization (e.g., OI-related stays) have been measured at New York Hospital (Paul 1998). Similar studies were conducted at Cook County Hospital, St. Vincent's Hospital and Medical Center, and the Department of Veteran Affairs New Jersey Health Care System using clinical and AIDS inpatient unit data (Sherer 1998; Torres 1998; O'Donovan 1997). Costs of inpatient bed days, outpatient prescriptions, and clinic visits were studied in a group of patients receiving HAART at the Denver Veterans Affairs Medical Center (McCollum 1998) and in a group of over 7,700 patients treated at 10 French AIDS referral centers (Mouton 1997). The Mid-Atlantic Permanente Medical Group has also studied costsassociated with outpatient prescriptions, inpatient admissions, lengths of stay, and laboratory services of patients receiving antiretroviral therapy (Melnick 1998). Utilization of inpatient, skilled nursing/hospice care, and home health services, as well as outpatient specialist referrals among patients receiving triple combination therapy were assessed by clinicians at a Los Angeles private practice managed care specialty clinic (Ruane 1997).

B. Strategies Being Studied To Address Treatment Failure

Several strategies are being adopted to apply population-based approaches to the study of treatment failure. Most of the observational databases described in this report are conducting on-going data collection and analysis. As a result, their ability to directly evaluate the relationship between therapeutic use and the various measures of treatment failure described in this report are being enhanced. Since data collection is ongoing, the failure (or success) of HAART is being directly observed and measured in avariety of populations throughout the US, Canada, and Europe. These studies are also increasing their cohort sizes; thus addressing limitations arising from earlier small sample sizes. Observational periods are also being extended so that there is sufficient time to observe the duration of patient experience with HAART and the time-dependent aspects of treatment failure (e.g., viral load rebounds from undetectable, downward turns in CD4 count following initial increases, progression to disease, mortality, etc.). Increases in sample sizes and observational periods also will afford an improved ability to accurately measure rare occurrences associated with treatment failure, such as onset of uncommon OIs or adverse clinical events.

In addition to these ongoing efforts, the federally-funded HIV Cost and Services Utilization Study (HCSUS) will provide useful data linking clinical outcomes (including some treatment failure measures) with service use and costs. HCSUS is a national

probability sample of 3,100 adultsreceiving HIV care from 58 major providers and about 100 providers who treat small numbers of HIV-infected individuals. An additional 100 patients are included in a rural over-sample. The longitudinal, person-based study measures variations in the use of clinical and support services, quality of life and clinical care, social supports, and service use and costs among patients in various regions of the US, health care systems, and patient populations. Patient and provider surveys are augmented with medical,billing, and pharmacy record reviews. A supplemental data collection project has been undertaken to obtain virologic and immunologic data among study subjects with high CD4 counts. The project is jointly supported by the Agency for Health Care Policy and Research, the Health Resources and Services Administration, the National Institute of Mental Health, the National Institute of Drug Abuse, the Office of Research on Minority Health, and the National Institute on Aging. Published summaries of preliminary findings from HCSUS are forthcoming.

V. CONCLUSIONS

A. Prospective Studies

Several things are striking about the changes that have occurred in study design of clinical trials since the first of these completed studies were initiated:

1. Most of the original studies used CD4 entry criteria, while most of the new studies use virological (HIV RNA-based) entry criteria.
    a. For first-line studies, virologic entry criteria usually require a viral load high enough to measure a greater than 2 log reduction ($\geq$5,000 copies/ L).
    b. For second-line studies, virologic entry criteria usually require a viral load rebound over the limit of quantification ($\geq$500 copies/ L), and some require a rebound over 5,000.
2. Most of the original studies used clinical endpoints, while most of the new studies use virological endpoints.
    a. Virologic failure is usually described as either a failure to develop viral load below the limit of quantification (usually below 500 copies/ L), or a rebound from levels BLQ measured at least twice.
    b. Most studies do not rigorously assess reasons for virologic failure. Non-adherence is most frequently given as the cause of virologic failure, but the evidence for this claim is rarely spelled out.
    c. There are virtually no clinical, and only short-term virological, data on people initiating HAART with over 200 CD4 cells/mm^3.
3. Most of the original studies anticipated 1 to 2 years of follow-up, while most of the new studies are planned to follow participants for 16, 24 or 48 weeks.
    a. Most reports of successful treatment of individuals who failed a PI-containing regimen do not report very long follow-up, ranging from several weeks to months.
4. Most of the original studies were stand-alone, while many of the new studies are roll-over studies from previous trials. For example, in ACTG 320 participants may rollover into any of 4 substudies of ACTG 372, based on their current regimen and viral load.
    a. Outside of the ACTG, there does not appear to be a mechanism for following trial participants from study to study. Even within the ACTG, this mechanism is very new and its completeness of follow-up is yet to be determined.
5. Several recently completed studies (ACTG 343, ANRS 072/TRILEGE) recently assessed a strategy of intense induction followed by less intense maintenance therapy (Havlir 1998; Raffi 1998). These studies yielded disappointing results, and now several other studies are addressing a strategy of treatment *intensification* among individuals whose viral load remains below the limit of quantification (usually <500 copies/ L). For example, ACTG 372A is randomizing

ACTG 320 participants with a viral load BLQ to stay on AZT/3TC/indinavir *or* to add abacavir to their triple regimen. CPCRA 052 will add a second PI or an NNRTI to a successful triple regimen in half of its 500 participants.

6. Many studies in PI treatment failures are assessing four-drug regimens--either 2 NRTIs plus 2 PIs or 2 NRTIs, a PI, and an NNRTI. Additionally, some studies are assessing unconventional combinations with just 1 or no NRTIs (e.g., efavirenz/indinavir, abacabir/amprenavir).

    a. Most regimens used in studies of treatment failure appear to be chosen for pragmatic reasons (e.g., availability of new drugs that appear, on theoretical grounds, not to have too high a likelihood of cross-resistance).

7. Only 1 study is assessing a head-to-head comparison of 2 PI-containing regimens as first-line therapy. CPCRA 042 is comparing nelfinavir versus ritonavir/indinavir (indinavir is substituted for ritonavir if ritonavir cannot be tolerated). The usefulness of this study is questionable, as ritonavir is the least-commonly used PI as a stand-alone; indinavir, nelfinavir and saquinavir soft-gel capsules are allmore widely used (K. Anastos, personal communication, November 1997).

8. Building on this observation, there appear to be few or no studies that the following questions:

    a. When is the best time for an antiretroviral naive individual with greater than 200 CD4 cells/mm^3 to begin therapy?

    b. What is the optimal antiretroviral-starting regimen?

    c. What is the optimal antiretroviral regimen to switch to when an optimal starting regimen has failed?

9. Since there is a clear temporal disconnect between virologic failure and clinical failure (Deeks 1998), it is unclear how rapidly individuals who develop virologic failure will progress immunologically or clinically.

    a. Only a few studies (e.g., ACTG 372C) evaluate whether it is better for patients with low but detectable HIV RNA levels (500-2,000 copies/ L) to stay on their regimen, while ACTG 372B randomizes such patients to 4 *new* regimens, and ACTG 372D follows patients on 4 new drugs. None of these 3 substudies randomizes patients to stay or switch regimens based on low but detectable viral load.

10. Individuals developing virologic failure who switch rapidly appear to have a better virologic response to a second PI-containing regimen than those who switch after viral load levels have rebounded to baseline (Para 1997, Schapiro 1997, Bodsworth 1998). These data are limited to individuals failing on saquinavir hard gel capsules, however, who never received a true "HAART" regimen. Moreover, the virologic response to the second regimen has not been measured for a very long period of time.

11. Many of the studies (e.g., ACTG 333) whose results are now available for interpretation were carried out early in the PI era, and participants did not switch underlying NRTIs when they started PI-containing regimens. Therefore, the rates of virologic failure from these studies may not match rates of virologic failure among individuals who begin at least 2, and preferably 3, new non-cross-resistant drugs at the same time.

12. The current standard of care, based on starting 1 potent PI and 2 NRTIs at the same time, is likely to be rapidly eclipsed by an even more confusing time when starting regimens may well include double PI combinations (presumably with 2 NRTIs) or combinations of a PI inhibitor with a potent NNRTIs such as efavirenz, whenever it is licensed.

13. There do not appear to be any widely-used, easy-to-use ways to measure different reasons for virologic treatment failure (e.g., non-adherence, drug-drug interactions, pharmacokinetics, etc.) and nor is it clear that the current generation of trials is investigating such issues.

14. There do not appear to be any widely-used ways to measure tolerability and ease of use of different measurements, as seen from the patient's perspective.

15. Little information is available about:

    a. How much accrual rates in new studies may have been affected by the widespread availability of combination

therapies;

b. Whether new study design entry criteria are capturing sufficient numbers of eligible individuals; or

c. Whether individuals are willing to be followed through multiple studies involving randomization to multiple regimens over multiple years.

16. There do not appear to be any studies comparing the clinical or long-term virological efficacy of changing therapy at different viral load or CD4 thresholds.

17. With the exception of the CPCRA GART [genotypic antiretroviral resistance testing] versus no-GART study, there do not appear to be any studies comparing different strategies for switching therapy based on the results of genotypic and phenotypic antiretroviral resistance assays.

B. Population-Based Studies

1. Despite their important findings, studies using multi-site observational databases have some important limitations.

   a. The CDC Viral Load Project is conducted in only three sentinel sites and gathers data on newly reported AIDS or HIV cases (Denning 1998). Such a cross-sectional study may not adequately account for use of antiretroviral therapy before being treated by the reporting clinician-- particularly important in studying AIDS cases with potentially many years of antiretroviral therapy experience. It is also uncertain if the findings are biased because it may be difficult to track and link all medical records to reconstruct individuals' antiretroviral therapy and viral load testing experience—data not collected by the CDC.It is also unclear if sub-analyses comparing the three sites support the general findings of the study and if the findings are similar for AIDS cases in Los Angeles and San Francisco compared to the HIV cases in New Jersey. More over, it is unclear how generalizable these findings are to other parts of the US. Finally, the authors conclude that almost one-half of the subjects had not received antiretroviral therapy and over one-half had not received viral load testing. Absence of these important data significantly impairs the reliability of the findings. It is unclear if in part, these low utilization rates reflect incomplete historical data on the subjects that might be obtained through review of all their medical records (rather than their records at thetime of HIV or AIDS diagnosis). It is also uncertain if systematic bias in some sub-populations exists in the absence of drug and viral load data.

   b. The HOPS and POPS databases provide important examples of large multi-site observational databases. Their populations, however, tend to be white, male, commercially insured, and have access to community-based clinicians (Moorman 1998; Shaefer 1998). As a result, it is unclear what bias these factors may introduce and the impact of that bias on the generalizability of the patients being followed. Inability to capture data on patients that use other sources of health care may also impact the completeness of the database.

2. Studies conducted in single clinical settings share common methodological characteristics that may limit their value.

   a. In these studies, relatively small cohorts of patients are observed whose medical records are easily accessible. It is unclear if the sample sizes used in the study are based on statistical power tests or because they represent all patients with complete medical records treated in the setting. It is likely that some of the sample sizes are too small to be statistically reliable.

   b. Review of retrospective medical records is the principal data collection strategy, it is unclear what impact missing clinical data have on the results. The timing of laboratory testing is associated with physician practice behavior, as well as the patients' ambulatory care seeking behavior, acute clinical events, ability to pay, and third party payers' policies. The value of laboratory testing used in virologic and immunologic failure studies is likely to be compromised if the data are collected at non-uniform times or from multiple laboratories with varying degrees of testing experience. Moreover, it is unclear if the patients studied were continuously in care in the study location for

the duration of the study period. RTI, virologic, and immunologic data representing care received from other clinicians may provide more complete patient profile andimpact the study results.

3. Several studies of the relationship between antiretroviral therapy use and survival and mortality are examples of the value of population-based observational databases in studying clinical failure.

   a. Both the EuroSIDA and Swiss Cohort link survival and mortality records with virologic, immunologic, and treatment data in large cohorts (Vella 1998; Egger 1997). It is unclear, however, how representative these cohorts are of populations residing in the countries studied and howcomplete the person-based data is in each databases.

   b. The British Columbia Drug Treatment Program is an important example of the application of a "closed-system" population-based observational database, since the database can account for the therapeutic, diagnostic testing, and mortality data of the individuals receiving HIV-related therapeutics in the province (Hogg 1998; Forrest 1998). Unlike analyses of the British Columbia database, a recent study using data from the Ontario HIV Project Center's Drug Distribution Program does not link antiretroviral therapy failure with duration of survival or mortality rates (Rachlis 1998). These analyses may be forthcoming.

   c. The Parisian hospital studies conducted by Le Pen (1998) and Rosenbaum (1998) are examples of the utility of facility-based clinical records to assess the impact of indinavir failure on survival, mortality, immunologic, and virologic outcomes. It is unclear, however, if the database captures the patients' data from all care sites.

   d. Mortality studies conducted in New York City demonstrate the complexity of assessing the relationship between mortality and antiretroviral therapy failure in large populations (Muthambi 1998; Chiasson 1998; Reggy 1998). While several recent studies compute survival times and mortality rates of New Yorkers, these analyses do not directly account for the effect of therapeutics on the outcomes due to the lack of linked vital status and clinical records (Muthambi 1998; Chiasson 1998). In the sub-analysis conducted by Reggy (1998), only 300 decedents were studied. It is unclear if this sample size is large enough to achieve statistical power. It is also unclear if the clinical records obtained by the researchers were complete enough to profile the individuals studied. The study demonstrates the resource-intensive nature of linking vital status records with complete multi-site clinical records.

   e. The WIHS offers a unique opportunityto study treatment failure in women. Vital status, duration of survival, antiretroviral therapy use, virologic, and immunologic data are being collected longitudinally among a large group of US women. The recent study by Kanatos and colleagues (1998) using WIHS data does not link these data, however, to assess the relationship between antiretroviral therapy failure and mortality.

4. Varying degrees of success have been achieved by researchers using population-based data sets to estimate the rate of OIs in patients receiving antiretroviral therapy.

   a. A HOPS study demonstrated a link between PI use and OI rates (Palella 1998). The generalizability of HOPS may be limited, however. Several single and multiple-site observational databases have also been used to assess OI rates in patients receiving HAART in Baltimore, San Francisco, Atlanta, Denver, and France (Moore 1998; Holtzer 1998; Huang 1998; Thompson 1997; Grodesky 1998; Michelet 1997). The cohorts studied at these sites tend to be large to moderate in size-- an important characteristic of studies measuring relatively rare events such as onset of OIs. The reliability of these data may be affected, however, by the lack of data from other clinical sites that may have treated the study subjects during the observational period.

   b. Some studies have been less successful in detecting OIs in antiretroviral therapy-treated patients. The Costagliola (1998) study of over 61,000 patients in French hospitals computes OI rates. It does not directly link hospitalization for OIs, however, with changes in the rate of antiretroviral therapy failure. The Louisiana study also did not directly link inpatient admissions with PI use (Michaels 1998). Therefore, it is unclear if drops in inpatient OI admissions resulted from antiretroviral therapy use or shifts in treatment of OIs from inpatient to ambulatory settings. In studies

of small cohorts (ranging from 2 to 102 patients), it is likely that an insufficient number of individuals were studied to observe rare OIs (Skolnick1998; Freeman 1998; Gasnault 1998; Miralles 1998; Piliero 1998).

5. Observational databases have been used with varying success to study disease progression in the children born to HIV-infected women. Clinic-based studies conducted in British Columbia andMiami have demonstrated the utility of the use of these databases and serve as models for studies in larger multi-site cohorts (DeSouza 1998; Forbes 1998).

6. Administrative databases, such as those generated by manufacturers' expanded access programs, are useful in describing adverse clinical events. Results of these studies have significant generalizability and reliability limitations, however. These limitations result from factors associated with program eligibility requirements, such as patient income, pending eligibility for third party payment, and willingness to contribute information into the database. Moreover, patients applying for these programs must be in the care of a clinician willing to assist the patient's enrollment and to contribute clinical information to the database.

7. Case studies of adverse events are clinically interesting and may form the basis for larger systematic evaluations of adverse events among patients receiving antiretroviral therapy. Their commonly small patient cohortsmake the results unreliable in estimating the rate of clinical adverse events, particularly since adverse events are relatively rare (Daudon 1997; Race 1998).

8. Several observational databases have demonstrated the direct relationship between HAART or other antiretroviral therapy treatment regimens on service utilization and associated costs.

    a. Studies conducted in "closed care systems" such as the Department of Veterans Affairs and managed care systems have been particularly successful in accounting for all services and related costs generated by their patients (O'Donovan 1997; McCollum 1998; Melnick 1998).

    b. Studies conducted in single-site settings have been less successful in directly measuring the relationship between treatment failure and resource use and costs (Keiser 1998; Paul 1998; Sherer 1998; Torres 1998; Mouton 1998). For example, it is unclear if drops in inpatient admissions for OIs result from antiretroviral therapy use or from shifts in treatment of OIs from inpatient to ambulatory settings. Additionally, declines in inpatient lengths of stay may not be related to use of antiretroviral therapy but result from the impact of day limits set by insurers.

9. Although population-based studies have contributed to our understanding of treatment failure in clinical practice, the studies' methodological limitations leave wide research gaps. Larger samples and longer observational periods among some existing projects address some of these gaps. Other gaps remain unfilled, however and include:

    a. Recognition that randomized clinical trials are limited in their ability to estimate treatment failure rates in clinical practice and that well designed population-based studies have utility in evaluating some aspects of treatment failure. Clinical trial and population-based research have not been integrated to benefit from their varied strengths.

    b. Formal and consistent definitions of treatment failure have not been used to design and conduct scientifically rigorous population-based treatment failure studies. Studies using population-based approaches have not been explicitly designed to measure treatment failure. Existing study designs have been expanded or refined to address new analytic questions, often without application of sufficient measurement precision, adequate sample sizes or observational periods, or appropriate statistical methods.

    c. Some large observational and administrative databases do not directly link indicators of treatment failure (e.g., virologic or immunologic measures, onset or recurrence of OIs, resource use) with actual use of a treatment intervention. Rather, they hypothesize that changes in these indicators among populations are the result of treatment failure or success.

    d. Population-based treatment failure studies tend to focus on HIV-infected adults late in the spectrum of HIV disease, with few studies addressing failure among recently infected adults.

e. Few population-based treatment failure studies have been conducted in children or adolescents.

f. Little is known about treatment failure in pregnant women using HAART, despite its growing use.

g. Population-based studies that estimate treatment failure rates and evaluate factors associated with those rates have not been conducted with sufficiently large and heterogeneous populations. Even large-scale multi-site studies tend to use small numbers of clinical sites that do not represent various regional, socio-demographic, economic, and cultural sub-populations of children and adults across the clinicalspectrum of HIV. Heterogeneous clinical settings are also not well represented to account for variation in prescribing and practice patterns (such as the timing of diagnostic testing and initiation of HAART) among clinicians caring for HIV-infected patients.

h. Existing observational databases (such as those sponsored by CDC, Canadian government agencies, European governments, and/or manufacturers) have not been systematically reviewed to determine the feasibility of linking them to address aspects of treatment failure that require large and generalizable population samples.

i. The feasibility has not been assessed of linking databases maintained by "closed service systems" (e.g., Veterans Administration, armed services, or managed care plans) to study treatment failure. Such studies might address problems in open systems in which patients may seek care at several clinical sites during an observational period.

j. Clinical site-based studies usually do link their records with other providers to assure that endpoint and other important data are gathered. Findings of single-site studies may be heavily biased by missing or censored data.

k. Although the utility of supplementing clinical databases with administrative databases (e.g., Medicaid and commercial insurance claims systems) has been demonstrated, such a linked data system has not been used in studies of treatment failure. Administrative databases are valuable in identifying the various sites and sequencing of clinical endpoints and other important data.

Clearly the study of effective regimens for the treatment of HIV disease has become exponentially more complex. It is far less clear how studies should be designed to take advantage of new discoveries in HIV pathogenesis, viral quantification, (at least partial) immunologic reconstitution, the deployment of potent new anti-HIV agents, and the changing prognosis for HIV-infected individuals with access to treatment.

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Appendix I: Guidelines for Changing an Antiretroviral Regimen for Suspected Drug Failure

Criteria for changing therapy include a suboptimal reduction in plasma viremia after initiation of therapy, re-appearance of viremia after suppression to undetectable, significant increases in plasma viremia from the nadir of suppression, and declining CD4 T cell numbers:

- When the decision to change therapy is based on viral load determination, it is preferable to confirm with a second viral load test.
- Distinguish between the need to change a regimen due to drug intolerance or inability to comply with the regimen versusfailure to achieve the goal of sustained viral suppression; single agents can be changed or dose reduced in the event of drug intolerance.
- In general, do not change a single drug or add a single drug to a failing regimen; it is important to use at least 2 new drugs and preferably to use an entirely new regimen with at least 3 new drugs.
- Many patients have limited options for new regimens of desired potency; in some of these cases it is rational to continue the prior regimen if partial viral suppression was achieved.
- In some cases, regimens identified as sub-optimal for initial therapy are rational due to limitations imposed by toxicity, intolerance or non-adherence. This especially applies in late stage disease. For patients with no rational alternative options who have virologic failure with return of viral load to baseline (pretreatment levels) and a declining CD4 T cell count, there should be consideration for discontinuation of antiretroviral therapy.
- Experience is limited with regimens usingcombinations of 2 PIs or combinations of PIs with nevirapine or delavirdine; for patients with limited options due to drug intolerance or suspected resistance these regimens provide possible alternative treatment options.
- There is limited information about the value of restarting a drug that the patient has previously received. The experience with zidovudine is that resistant strains are often replaced with "wild-type" zidovudine sensitive strains when zidovudine treatment is stopped, but resistance recurs rapidly if zidovudine is restarted. While there is preliminary evidence that this occurs with indinavir, it is not known if similar problems apply to other nucleoside analogues, PIs, or NNRTIs, but a conservative stance is that they probably do.
- Avoid changing from ritonavir to indinavir or vice versa for drug failure, since high level cross resistance is likely.
- Avoid changing from nevirapine to delavirdine or vice versa for drug failure, since high level cross-resistance is likely.
- The decision to change therapy and the choice of a new regimen requires that the clinician have considerable expertise in the care of people living with HIV. Physicians who are less experienced in the care of persons with HIV infection are strongly encouraged toobtain assistance through consultation with or referral to a clinician with considerable expertise in the care of HIV-infected patients (Bartlett 1997).

APPENDIX II: Completed, Ongoing & Planned Studies of Combination Antiretroviral Therapy in Antiretroviral-Experienced Individuals

Completed Randomized Studies of Triple Regimens in Antiretroviral-Experienced Patients

		Entry Criteria					
Trial No.	**PI**	**HIV RNA**	**CD4**	**Rx History**	**Treatment Regimens**	**N**	**Length**
ACTG 193	Henry		?	>?m AZT	AZT + ddI AZT + ddI + NVP	?	?
ACTG 229	Collier	--	?	>?m AZT	AZT + ddC AZT + SQV (Invirase, 600 mg tid) AZT + ddC + SQV	?	?
NCAS / BI .046	Montaner	--	?	>?m AZT	AZT + NVP AZT + ddI AZT + NVP + ddI	?	?
ACTG 261	**?**	--	100-500	<6m AZT or ddI (but not both)	AZT + ddI AZT + DLV ddI + DLV AZT + ddI + DLV	544	48w
Merck 035	Gulick	--	≤200	>?m AZT	AZT + 3TC AZT + 3TC + IDV	?	?
Merck 039	Hirsch	--	≤50	>6m AZT, PI/3TC naive	AZT + 3TC AZT + 3TC + IDV	320	24w
Abbott 247	Cameron	--	≤100	?	RTV + 1 or 2 NRTIs (no 3TC) Placebo + 1 or 2 NRTIs (no 3TC)	?	?
ACTG 320	Hammer	--	≤200	<3m AZT, PI/3TC naive	AZT + 3TC AZT + 3TC + IDV	?	?
ACTG 333	Para	--	--	Pts from ACTG 229 or on SQVhgc	SQVhgc (Invirase, 600 tid) SQVsgc (Fortovase, 1200 tid) IDV	72	8w
Agouron 601	Merigan	≥ 5,000	Any	≥6m SQV	NFV + 2 NRTIs	?	24w
Agouron 605	Merigan	≥ 5,000	Any	IDV intolerant or failure	SQVsgc + NFV + d4T + ddI vs. SQVsgc + NFV + ADF + NVP	42	48w

Ongoing Randomized Studies of Three- and Four-Drug Regimens in Antiretroviral-Experienced Patients

		Entry Criteria					
Trial No.	**PI**	**HIV RNA**	**CD4**	**Rx History**	**Treatment Regimens**	**N**	**Length**
ACTG 364	Fischl	Any	Any	ACTG 302/303 rollover study	NFV + 2 NRTIs* EFZ + 2 NRTIs NFV + EFZ + 2 NRTIs *	300	48w
ACTG 372A	Hammer	<500 @ screening for 372	<200 @ 320 start	ACTG 320 pts, pVL BLQ, NNRTI naive	AZT (or d4T) + 3TC + IDV vs. AZT (or d4T) + 3TC + IDV + ABC	200	--
ACTG 372B	Hammer	>500 @ screening for 372	>200 @ 320 start	ACTG 320 pts, pVL not BLQ, NNRTI naive	EFZ + ADF + NFV + ABC + 1 NRTI EFZ + ADF + NFV + 2 NRTIs EFZ + ADF + ABC + 1 NRTI EFZ + ADF + 2 NRTIs	80	--
ACTG 372C	Hammer	500-2K	>200 @ 320 start	ACTG 320 pts who stay on 320 regimen	AZT + 3TC AZT + 3TC + IDV	40	--
ACTG 372D	Hammer	≥500	>200 @ 320 start	ACTG 320 pts with pVL >500	ABC + EFZ + ADF + NFV (observational, non-randomized)	40	--
ACTG 373	Gulick	>5000	--	Pts on 141	AMP + AZT + 3TC IDV + NVP + 3TC + d4T	94	--
ACTG 375	Valdez	--	--	ACTG 315 pts	AZT + 3TC + RTV (6 weeks); if pVL not BLQ, may switch to HAART regimen containing AZT, 3TC, d4T, ddI, DLV, RTV or SQV	34	--