

## II. Maximal Viral Suppression as the Goal of Antiretroviral Therapy

*by Mark Harrington*

Three very different prospects open out before HIV-infected individuals with access to treatment -- eradication, lifelong suppression, or delayed progression to AIDS. Current clinical research indicates that eradication of HIV is unlikely, at least with currently available agents (Harrington 1997).

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

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

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

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

In April 1998 the CDC's *Morbidity & Mortality Weekly Report* published "Principles of Therapy of HIV Infection" and "Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents" (MMWR 1998:45:RR-5). These contained the latest version of a set of Federal treatment recommendations developed and continually updated by a panel of researchers, clinicians and treatment advocates. The guidelines were first released on line in June 1997 with the objective of providing guidance to physicians, people with HIV and third-party payers about how best to use new antiretroviral drugs and viral load tests.

After Vancouver, it was obvious that the previous Public Health Service (PHS) guidelines for treating HIV, published in 1993, were antiquated, dating from the era of AZT as first-line monotherapy, when there was still no clinical evidence of benefit for combination therapy, let alone of the dramatic impact protease-inhibitor containing regimens can have on prolonging health and life. Sophisticated, accurate viral load testing was experimental in 1993, but is now the basis for clinical management. While some self-appointed blue ribbon panels in 1996 promulgated interim treatment guidelines -- notably the International AIDS Society, USA (an oxymoronic cognomen) -- these were based more on expert guesswork than on a thorough review of the rapidly changing field. For example, the viral load threshold for treatment (10,000 copies/ml) was based on a rushed colloquy after a presentation at the Third Retrovirus Conference in Washington, D.C., during February 1996 (John Mellors, personal communication), rather than on firm data.

The US Department of Health & Human Services (HHS) set up two panels to codify the new approach to anti-HIV therapy. Under the aegis of the Office of AIDS Research (OAR), the National Institutes of Health (NIH) set up the NIH Panel to Define Principles of Therapy of HIV Infection, chaired by Charles C.J. Carpenter of Brown University, with OAR's Mark Feinberg as executive secretary. The NIH panel held hearings in November 1996 to update its members on the latest data (see *TAGLine*, February 1997), and subsequently a series of eleven principles of HIV therapy were developed.

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

The NIH panel wrote principles of HIV therapy, which are expected to endure, and the HHS panel wrote clinical practice guidelines, which are expected to change as new studies finish, new drugs become available, and new information emerges about pathogenesis and treatment. Now that the guidelines are out, the HHS panel has an Antiretroviral Working Group which meets by phone monthly to consider new data.

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

## **WHEN SHOULD THERAPY BE STARTED?**

This proved to be the most controversial part of the Guidelines. The original draft was based on risk thresholds derived from ACTG 175 and the Multicenter AIDS Cohort Study (MACS) study. ACTG 175 provided clear evidence that combination antiretroviral therapy (albeit with double nucleosides, since the study was conducted in the pre-protease era) provides clinical benefit among individuals with fewer than 350 CD4 T cells (the study was open to those with fewer than 500 CD4 cells, but very little progression occurred in those with 350-500 CD4 cells at baseline). And the MACS study indicated clearly that those with a CD4 count below 350 and viral load over 10,000 (bDNA) or 20,000 (RT-PCR) had a 40% chance of progressing to AIDS within three years; those with viral load over 30,000 (bDNA) or 55,000 (RT-PCR) had a 73% chance of progression within that period (Mellors 1997).

However, in a later draft version of the guidelines, some researchers slipped in new language advocating treatment for all individuals with over 10,000 HIV RNA copies in their plasma. This would have led to the treatment of perhaps 97% of the HIV-infected population, a conclusion for which compelling clinical data were certainly lacking, especially given concerns over adherence, long-term safety, the emergence of resistance, and the number of new agents or regimens in the pipeline.

The community representatives to the Panel responded by threatening to pull out unless a semblance of rationality was restored. Later this controversy appeared to be resolved, and the final Guidelines provide more information about the risk of progressing to AIDS at various CD4 and RNA levels, which may assist doctors and people with HIV in making treatment decisions.

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

### **Background to Principles of Therapy of HIV Infection**

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

### **Summary of the Principles of Therapy of HIV Infection**

1. Ongoing HIV replication leads to immune system damage and progression to AIDS. HIV infection is always harmful and true long-term survival free of clinically significant immune dysfunction is unusual.
2. Plasma HIV RNA levels indicate the magnitude of HIV replication and its associated rate of CD4 T cell destruction, whereas CD4 T cell counts indicate the extent of HIV-induced immune damage already suffered. Regular, periodic measurement of plasma HIV RNA levels and CD4 T cell counts is necessary to determine the risk for disease progression in an HIV-infected individual and to determine when to initiate or modify antiretroviral treatment regimens.
3. As rates of disease progression differ among individuals, treatment decisions should be individualized by level of risk indicated by plasma HIV RNA levels and CD4 T cell counts.
4. The use of potent combination antiretroviral therapy to suppress HIV replication to below the levels of detection of sensitive plasma HIV RNA assays limits the potential for selection of antiretroviral-resistant HIV variants, the major factor limiting the ability of antiretroviral drugs to inhibit virus replication and delay

disease progression. Therefore, maximum achievable suppression of HIV replication should be the goal of therapy.

5. The most effective means to accomplish durable suppression of HIV replication is the simultaneous initiation of combinations of effective anti-HIV drugs with which the patient has not been previously treated and that are not cross-resistant with antiretroviral agents with which the patient has been treated previously.
6. Each of the antiretroviral drugs used in combination therapy regimens should always be used according to optimum schedules and dosages.
7. The available effective antiretroviral drugs are limited in number and mechanism of action, and cross-resistance between specific drugs has been documented. Therefore, any change in antiretroviral therapy increases future therapeutic constraints.
8. Women should receive optimal antiretroviral therapy regardless of pregnancy status.
9. The same principles of antiretroviral therapy apply to both HIV-infected children, adolescents and adults, although the treatment of HIV-infected children involves unique pharmacologic, virologic and immunologic considerations.
10. Persons identified during acute primary HIV infections should be treated with combination antiretroviral therapy to suppress virus replication to levels below the limit of detection of sensitive plasma HIV RNA assays. ***[Note that this differs from the recommendation in the HHS guidelines, below.]***
11. HIV-infected persons, even those with viral loads below detectable limits, should be considered infectious. Therefore, they should be counseled to avoid sexual and drug-use behaviors that are associated with transmission or acquisition of HIV and other infectious pathogens.

## **WHO SHOULD BE TREATED?**

According to the HHS treatment guidelines, treatment decisions should be made on an individualized basis by physician and person with HIV, taking into consideration the potential risks and benefits of early initiation of antiretroviral therapy and the available data, which strongly indicate that the benefits of treatment outweigh the risks for those who are symptomatic. The HHS panel differed from the NIH panel with respect to treatment of acute primary infection.

***For acute primary HIV infection:*** Some would recommend treatment with maximally-suppressive antiretroviral therapy for an indefinite period of time, but there is no evidence yet of clinical benefit or altered long-term disease progression, and others would wait until more data are available.

***For asymptomatic HIV-infected individuals with fewer than 500 CD4 cells or HIV RNA above 10,000 bDNA) or 20,000 (RT-PCR):*** Treatment should be offered. The strength of the recommendation is based on readiness of patient for therapy and prognosis for disease-free survival as determined by monitoring viral load and CD4 count and by the willingness of the patient to accept therapy.

**For asymptomatic HIV-infected individuals with over 500 CD4 cells and fewer than 10,000 (bDNA) or 20,000 (RT-PCR) HIV RNA copies per milliliter of plasma:** Most experts would delay therapy and observe; however, some experts would treat.

**For symptomatic HIV infection:** All individuals with symptomatic HIV infection should be given antiretroviral therapy.

**For salvage therapy** (anyone on suboptimal therapy or failing potent combination therapy): Switch to another potent regimen to which the virus has not already become resistant (if this is feasible), recognizing that little clinical data are available for this population, and options will vary by treatment history.

**Viral load risk thresholds for disease progression.** The HHS Guidelines provide detailed information on the risk of progression to AIDS first presented by John Mellors at Vancouver, derived from follow-up on 1,604 HIV-infected men from the Multicenter AIDS Cohort Study (MACS) whose blood was drawn in 1985, measured by bDNA in 1995. Their risk of progression over that decade was strongly correlated with their baseline viral load. The MACS is the biggest, longest study to demonstrate that baseline viral load predicts the rate of progression. However, because the RT-PCR test is more sensitive than the bDNA test, a given RT-PCR measurement will count twice as many copies as an equivalent bDNA test. Thus, a comparison of the risk of AIDS in several groups of men from the MACS shows the risk of developing AIDS within three, six and nine years using bDNA and RT-PCR values (Mellors 1997):

**MACS Study: Progression Rates by CD4 and Viral Load Category**

I.	CD4 ≤ 350 and HIV RNA by		N	% developing AIDS		
	bDNA	RT- PCR		3 years	6 years	9 years
	< 500	<1,500	3	0	0	0
	501- 3,000	1,501- 7,000	30	0	18.8	30.6
	3,001-10,000	7,001-20,000	51	8.1	42.2	65.6
	10,001-30,000	20,001-55,000	73	40.1	72.9	86.2
	>30,000	>55,000	174	72.9	92.7	95.6

Thus, if a recent bDNA test showed CD4 under 350 and viral load over 30,000, one's risk of progression over three years might be as high as 73%, and similarly for an RT-PCR result over 55,000. By contrast, none of the three MACS participants with low CD4s but undetectable (<500 bDNA) viral load progressed over nine years.

II.	CD4 350-500 and HIV RNA by		N	% developing AIDS		
	bDNA	RT- PCR		3 years	6 years	9 years
	< 500	<1,500	--	--	--	--
	501- 3,000	1,501- 7,000	47	4.4	22.1	46.9
	3,001- 10,000	7,001- 20,000	105	5.9	39.8	60.7
	10,001- 30,000	20,001- 55,000	121	15.1	57.2	78.6
	>30,000	>55,000	121	47.9	77.7	94.4

Higher viral load (over 30,000 by bDNA or 55,000 by RT-PCR) distinguishes a high-risk (48% at three years) from a medium risk (15% over three years) group in this cohort with medium CD4 counts.

III.	CD4 > 500 and HIV RNA by		N	% developing AIDS		
	bDNA	RT- PCR		3 years	6 years	9 years
	< 500	<1,500	110	1.0	5.0	10.7
	501- 3,000	1,501- 7,000	180	2.3	14.9	33.2
	3,001- 10,000	7,001- 20,000	237	7.2	25.9	50.3
	10,001- 30,000	20,001- 55,000	202	14.6	47.7	70.6
	>30,000	>55,000	141	32.6	66.8	76.3

People with over 500 CD4 cells whose bDNA is over 30,000, or PCR over 55,000, appear to have a 33% risk of progression over three years. For those with high CD4s and high viral loads, starting treatment might be more urgent than for those with low viral loads -- especially as treatment options will improve over the next few years. Some asymptomatic persons with high CD4 counts and low to moderate viral load may do better by waiting.

### WHAT TO START WITH?

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

## Recommended Antiretroviral Agents for Treatment of Established HIV Infection<sup>1</sup>

**Preferred:** Strong evidence of clinical benefit and/or sustained suppression of plasma viral load.

One choice each from column A and column B. Drugs are listed in random, not priority order:

Column A	Column B
Indinavir (AI)	AZT + ddI (AI)
Nelfinavir (AII)	d4T + ddI (AII)
Ritonavir (AI)	AZT + ddC (AI)
Saquinavir-SGC* (AII)	AZT + 3TC <sup>§</sup> (AI)
Ritonavir + SQV-SGC* <sup>†</sup> (BII)	(d4T + 3TC <sup>§</sup> (AII))

**Alternative:** Less likely to provide sustained virus suppression:

- \* One NNRTI (nevirapine or delavirdine)<sup>¶</sup> + 2 NRTIs (column B, above)
- \* Saquinavir-HGC [hard gel capsules; Invirase<sup>™</sup>] + 2 NRTIs

**Not generally recommended.** Strong evidence of clinical benefit, but initial virus suppression is not sustained in most patients.

- \* Two NRTIs (column B, above)

**Not recommended.** Evidence against use, virologically undesirable, or overlapping toxicities:

- \* All monotherapies (DI)
- \* d4T + AZT (DI)
- \* ddC + ddI<sup>††</sup>
- \* ddC + d4T<sup>††</sup> (DII)
- \* ddC + 3TC (DII)

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<sup>1</sup> The HHS panel used the following rating system for strength of recommendation and quality of evidence supporting the recommendation:

Categories reflecting the strength of each recommendation:

- A Strong; should always be offered
- B Moderate; should usually be offered
- C Optional
- D Should generally not be offered
- E Should never be offered

Categories reflecting the quality of evidence supporting the recommendation:

- I At least one randomized trial with clinical endpoints
- II Clinical trials with laboratory endpoints
- III Expert opinion

- \* Virologic data and clinical experience with saquinavir-*sgc* [soft gel capsules; Fortovase™] are limited in comparison with other protease inhibitors.
- † Use of ritonavir 400 mg b.i.d. with saquinavir soft-gel formulation (Fortovase™ 400 mg b.i.d. results in similar areas under the curve (AUC) of drug and antiretroviral activity as when using 400 mg b.i.d. of Invirase™ in combination with ritonavir. However, this combination with Fortovase™ has not been extensively studied, and gastrointestinal toxicity may be greater when using Fortovase™.
- § High-level resistance to 3TC develops within 2-4 weeks in partially suppressive regimens.
- ¶ The only combinations of 2 NRTIs and one NNRTI that have been shown to suppress viremia to undetectable levels in the majority of patients are AZT + ddI + nevirapine [in BI 1046/INCAS] and AZT + 3TC + delavirdine [in ACTG 261]. These combinations were studied in antiretroviral-naïve persons.

## WHAT TO SWITCH TO?

**What drugs should be used in changing an antiretroviral regimens?** According to the CDC, at least 225,000 Americans are living with AIDS. The number can be expected to grow as the death rate drops and people live longer on potent antiretroviral combinations. However, data on optimizing treatment in this population are scanty at best. Most of the recommendations were based on guesswork, or on small surrogate marker studies. [For a fuller discussion of existing data on second-line and salvage anti-HIV regimens, see *HIV Treatment Failure: A Review of Current Clinical Research -- A Report from the Forum for Collaborative HIV Research* (Harrington & Hidalgo, 1998)].

### Suggested New Regimens for Patients Who Have Failed Antiretroviral Therapy\*

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

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

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

**Use of viral load testing for HIV management.** Viral load testing is key to assessing a given HIV-infected individual's prognosis, rate of progression, and need for antiretroviral therapy. Higher viral load means more rapid disease progression. Countless studies presented at and after Vancouver demonstrate this.



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

***Turning the new clinical practice guidelines into reality.*** However tortuous, writing the new treatment guidelines was the easy part. Turning them into reality will be another thing altogether. While a recent CDC study showed that in 1996, for the first time, the AIDS death rate fell by 12% nationwide, *it fell by fifty percent in ACTG 320* (Hammer 1997). Unequal access to state-of-the-art HIV care clearly reduces the impact of the new therapies on AIDS and death. AIDS deaths actually increased in 1996 among women and heterosexuals, barely dropped (by just 2% ) in African-Americans, and dropped less in Hispanics than among non-Hispanic, non-African-Americans. It dropped by just 8% in the south, whereas in New York City, endowed with a generous state AIDS Drug Assistance Program (ADAP) and major Ryan White AIDS care funding programs, it dropped by 30%. In places with publicly-financed health care, such as British Columbia, and in France, by contrast, the death rate dropped by 50% or just as much as in ACTG 320. More recent data (see Introduction above) indicate that the AIDS death rate continues to drop wherever people with HIV have access to HAART regimens.

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