Terapia Antirretroviral II:
Estado Actual de las Combinaciones y Futuras Terapias

GORDON DICKINSON, M.D.
University of Miami

Introduction

The ideal drug for treatment of HIV infection –one which is safe, convenient to use, has excellent bio-availability, good pharmacokinetics, potent and cidal activity against all HIV strains and is not subject to the emergence of resistance– is not yet available. In its absence, we have moved from single drug to multidrug regimens to achieve potent and effective therapy. As imperfect as current regimens are, they represent a significant gain –one which we have not yet fully explored. Today combination therapy with three or more drugs, including a protease inhibitor or non-nucleoside reverse transcriptase inhibitor, has become the standard of care.[1] Monodrug therapy is no longer acceptable.

What have we achieved with the potent combinations of antiretroviral drugs, the so-called HAART (highly active antiretroviral therapy)? This question is not yet fully answered. HIV has been isolated from patients with no detectable virus following treatment for one to two years,[2-4] suggesting that eradication will be difficult if not impossible. Yet Dr. David Ho, an advocate of aggressive therapy, has argued that these reports do not preclude the possibility of eradication of HIV.[5] Ongoing studies started more than two years ago show that continued suppression of replication is possible in up to 80% of patients.[6,7,8] Others have pointed out that results in clinical trials are typically not reproducible in the clinic and that long term suppression is difficult to maintain.[9] No one can deny, however, the major impact of triple combination therapy on HIV disease.[10,11] In many centers across the United States hospital beds in dedicated AIDS units stand largely empty. At the same time, we know that restoration of the immune system is significant but incomplete.[12-14] The impressive rebound in CD4 cells in adults occurs without the benefit of the thymus gland, and the majority of the restored cells are committed memory cells rather than the naïve cells necessary for combating new pathogens. Until the functional capacity of the new CD4 cells has been demonstrated, most experts advise continuation of primary and secondary prophylaxis initiated at a time of low CD4 cells until data currently being accumulated shows at what point the prophylaxis can be dropped.

Antiretroviral Drugs, 1998

1. Nucleoside analogue reverse transcriptase inhibitors (NRTIs)

A. Zidovudine

B. Didanosine

C. Zalcitabine

D. Lamivudine

E. Abacavir (1592U89)

F. F-ddA (BCH-10652)

2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

A. Nevirapine

B. Delaviradine

C. Efavirenz (DMP-266)

3. Nucleotide analogue reverse transcriptase inhibitors (NTRTIs)

A. Adefovir (bis-POM PMEA)

4. Protease inhibitors (PIs)

A. Saquinavir

B. Ritonavir

C. Indinavir

D. Nelfinavir

E. Amprenavir (141W94 or VX-478)

F. ABT-378

G. PNU-140690 (Pharmacia & Upjohn)

H. PD-178390 (Parke-Davis)

Each class has certain characteristics relevant to their clinical use

The NRTIs are the group with which we have the most experience. In general, they are well absorbed, are widely distributed and have a well defined toxicity profile. As a class they have modest antiretroviral therapy. Resistance, although frequently encountered because of

their wide usage in the pre-combination era, is variable and may or may not apply to all agents.

The NNRTIs are potent drugs but are characterized by rapid emergence of high-level resistance through single point mutations which convey resistance to all members of the class. For this reason, the NNRTIs should never be used in a regimen which is unlikely to produce complete suppression of replication. These drugs are well absorbed, have good pharmacokinetics but have significant toxicity profile.

The NTRTI class is represented by just one agent, adefovir, which is newly released in the US (see below).

Protease inhibitors include some of the most potent of the ARTs, and they have become the mainstay of combination drug regimens. There is considerable variation between members of this class in terms of tolerability, adverse reaction profile and pharmacokinetics. They have impressive potential for drug interaction because of their metabolism by the P450 cytochrome oxidase enzymes in the liver and their tendency to inhibit the activity of the CYP3A4 pathway.

Treatment with combination ART

Treatment is recommended for any patient with: A) established HIV disease and symptoms; B) <500 CD4 cells/mm3 (some experts prefer to wait until levels are <350 cells/mm3); and C) HIV copies >10,000 regardless of CD4 cell count. Patient adherence is critical, so therapy should be initiated only for the committed patient.

Which regimen to use is a matter of some subjectivity: two NRTIs plus a protease inhibitor is one such regimen, for example zidovudine, lamivudine and indinavir. Other combinations may be comparable in efficacy and better tolerated. As noted, there is not much data from head-to-head studies. Most of the information we have is from comparative studies of triple vs single or double drug regimens. Although there is less experience with combinations in which a NNRTI was substituted for a PI, a three drug regimen including two NRTIs and nevirapine or delaviradine may ultimately prove to be comparable to the regimen with a PI.

Combination therapy is proving to be a complex and challenging endeavor. Although differences in efficacy from definitive head-to-head studies of various combinations are lacking, there are important differences in toxicity and pharmacokinetic profiles. Using multiple drugs in combination is expensive. All of these drugs are expensive and when given together the drug cost alone ranges from $7,000 to $8,000 US. The expense puts these drugs beyond the reach of virtually all patients unless they have third party support (insurance or governmental funding). And the drug expense is but one component of treatment: physician visits and expensive laboratory monitoring easily double the cost.

New Directions

The near term future holds several developments: new classes of drugs, new drugs in one of the classes already discussed, and new ways in administering current drugs.

New Dosage Regimens and Combinations

Multidrug regimens they are cumbersome to use and few patients are able to strictly adhere to them. As noted above, attempts to simplify the regimens by reducing the frequency of dosing and the number of pills have already reduced the frequency of dosing of one popular combination, zidovudine and lamivudine, from a total of eight pills taken in three or five divided doses to one capsule twice daily. Preliminary results from a number of ongoing studies with the potent protease inhibitors indinavir and nelfinavir suggest that twice a day dosing is comparable to the standard every eight hour dosing schedule.[15,16] Because non-compliance (non-adherence) is recognized as a major obstacle to successful, durable treatment, there will be further efforts to identify regimens which require only once or twice daily dosage. On the other hand, because of suboptimal efficacy with present regimens in some patients, new combinations also are being explored.[17-19]

New agents in existing classes

In the table listed above, a non-inclusive listing of new agents was included. Of these several are in clinical trials and are likely to be available in the near future.

Abacavir is a carbocyclic NRTI which is being positioned as an agent for salvage therapy because of its potency and activity against HIV virus resistent to one of the current NRTIs. Although it generally retains its activity against strains resistant to or two NRTIs, Mellors et al reported that only 1 of 7 strains of multi-NRTI-resistant HIV was fully sensitive and 3 were resistant.[20] So abacavir may not be the answer for patients who cycled through all previous NRTIs. Additionally, abacavir has the potential to cause a hypersensitivity reaction characterized by fever, malaise and rash (the rash may be absent). One patient died on rechallenge, so this reaction is considered an absolute contraindication to further treatment with abacavir.

Efavirenz is an NNRTI (available in the US) with good bioavailability unaffected by food with a long half life (~50 h). Because of metabolism via CYP3A4 isozyme there is interaction with PIs. It is administered in a dose of 400 mg once daily and as with other members of this class it is inactive against NNRTI-resistant strains.

Adefovir dipivoxil is phosphorylated (i.e., it is a nucleotide). It has a half-life of 16-18 hours and is given once daily. Elevated creatinine and proteinuria have been reported in small % of recipients, but is reportedly well tolerated. Its role vs. NRTIs-resistant is unclear but it will likely be used interchangably with members of NRTI class.

Amprenavir is the PI closest to competing clinical trials.[21] It possesses favorable activity compared to other PIs, although susceptibility to resistance will likely be similar. With a half life of 7 hours and good bioavailability uncompromised by food, it will a twice daily drug.

PNU-140690 and PD-178390 are being developed because they retain activity against some (many?) PI-resistant strains of HIV.[22, 23]

New Classes of antiretrovirals

There are three classes receiving attention: Fusion inhibitors,[24] Integrase inhibitors[25] and Zinc finger inhibitors.[26]

The Future

We will continue to search for the mythical "ideal" drug for HIV. This search will provide more drugs with enhanced potency and improved pharmacokinetic profiles. The silver lining to the HIV story, if there is such a silver lining, are the tremendous leaps in our knowledge about viral pathogenesis and the methods developed to exploit the weaknesses of the retroviruses.

References

1. Carpenter C.C.J., Fischl M.A., Hammer S.M., *et al,* for the International AIDS Society-USA. Antiretroviral therapy for HIV infection in 1997: recommendations of the international panel. JAMA. 1997; 277:1962-1969.

2. Wong J.K., Hezareh M., Gunthard H.F., *et al.* Recovery of Replication-Competent HIV despite prolonged suppresion of Plasma Viremia. Science.1997; 278:1291-1295.

3. Finzi D., Hermankova M., Pierson T., *et al*. For Identification of a Reservoir for HIV-1 in patients on highly active Antiretroviral Therapy. Science.1997; 278:1295-1300.

4. Balter M. HIV survives drug onslaught by hiding out in T Cells. Science. 1997; 278:1227.

5. Ho D. Residual pool of HIV after prolonged combination therapy. Lecture #S16, 5th Conference on Retroviruses and Opportunistic Infections. February, 1998, Chicago, IL.

6. Montaner J.S.G., Reiss P., Cooper D., Vella S., *et al*. Long-term follow-up of patients treated with Nevirapine (NVP) based combination therapy with the INCAS trial. 5th Conference on Retroviruses and Opportunistic Infections. 1998, Chicago, IL. Abst. 695.

7. Gulick R.M., Mellors J.W., Havlir D., *et al.* Treatment with Indinavir, Zidovudine, and Lamivudine in Adults with Human Immunodeficiency Virus infection and prior Antiretroviral Therapy. N Engl J Med. 1997; 337:734-739.

8. Cameron D.W., Japour A., Mellors J., *et al*. Antiretroviral Safety and Durability of Ritonavir (RTV)-Saquinavir (SQV) in Protease Inhibitor-naïve Patients in Year Two of Follow-up. Conference on Retroviruses and Opportunistic Infections, 1998, Chicago, IL. Abst. 388.

9. Bozek P.S., Perdue B.E., Forrest-Smith M. Maintaining protease inhibitor therapy in a clinic setting. . 5th Conference on Retroviruses and Opportunistic Infections. 1998, Chicago, IL. Abst 148.

10. Hogg R.S., Heath K.V., Yip B. *et al*. Improved survival among HIV-infected individuals following initiation of antiretroviral therapy. JAMA 1998;279:450-454.

11. Verheught F.W.A., Effect of HAART on natural history of AIDS-related opportunistic disorders. The Lancet. 1998; 351:228-230.

12. Hengel R.L., Jones B.M., Kennedy S.M., Hubbard M.S., McDougal J.S. Reconstitution of "naïve" CD4+ T-cells after potent anti-HIV-1 Therapy. 5th Conference on Retroviruses and Opportunistic Infections. 1998, Chicago, IL. Abst. 157.

13. Levacher M., Bouscarat F., Chau F., *et al.* One year follow-up of CD4 and CD8 cytokine secreting lymphocytes in HIV infected patients treated with stavudine + didanosine + ritonavir. 5th Conference on Retroviruses and Opportunistic Infections. 1998, Chicago, IL. Abst. 161.

14. Majchrowicz M.A., Hultin L.E., Hultin P., *et al.* Reversal of immune activation during potent antiretroviral therapy. 5th Conference on Retroviruses and Opportunistic Infections. 1998, Chicago, IL. Abst. 171.

15. Sension M., Elion R., Farthing C., *et al*. Open-Label Pilot Studies to Assess the Safety and Efficacy of Bid Dosing Regimens of Viracept (nelfinavir mesylate) Combined with NRTI's in HIV-Infected Treatment-Naïve Patients. 5th Conference on Retroviruses and Opportunistic Infections 1998, Chicago, IL. Abst.387a.

16. Petersen A., Johnson M., Clendeninn N., *et al.* Comparison of BID and TID Dosing of Nelfinavir (NFV) in Combination with Stavudine (d4T) and Lamivudine (3TC): An Interim Look. 5th Conference on Retroviruses and Opportunistic Infections. 1998, Chicago, IL. Abst. 373.

17. Gallant J.E., Heath-Chiozzi M., Raines C., *et al*. Safety and Efficacy of Nelfinavir-Ritonavir Combination Therapy. 5th Conference on Retroviruses and Opportunistic Infections. 1998, Chicago, IL. Abst. 394a.

18. Polis M.A., Schrager L., Yoder C., *et al.* Virologic, immunologic and histologic responses to a 4-drug combination therapy in antiretroviral naïve, HIV-infected persons. 5th Conference on Retroviruses and Opportunistic Infections. 1998, Chicago, IL. Abst. 394.

19. Havlir D.V., Riddler S., Squires K., *et al.* Co-administration of indinavir and nelfinavir in a twice daily regimen: preliminary safety, pharmacokinetic and antir-viral activity results. 5th Conference on Retroviruses and Opportunistic Infections. 1998, Chicago, IL. Abst. 393.

20. Mellors J.W., Hertogs K., *et al*, Susceptibility of clinical HIV-1 Isolates to 15927U89. The 5th conference on Retroviruses and Opportunistic Infections. 1998, Chicago, IL. Abst. 687.

21. Bart P.A., Rizzardi G.P., Gallant S., *et al.* Combination Abacavir (1592)/Amprenavir (141W94) Therapy in HIV-1-Infected Antiretoroviral-Naïve Subjects with CD4+ Counts >400 cells/ul and Viral Load >5000 copies/mL. 5th Conference on Retroviruses and Opportunistic Infections. 1998, Chicago, IL. Abst. 365.

22. Borin M.T., Wang Y., Schneck D.W., Li H., Brewer J.E., Denzer C.L. Multi-dose safety, tolerance, and pharmacokinetics of the protease inhibitor PNU-140690 in healthy volunteers. 5th conference on Retroviruses and Opportunistic Infections. 1998, Chicago, IL. Abst. 648.

23. Domagala J.M., Boyer F., Ellsworth E., *et al.* PD178390: a novel potent non peptide HIV protease inhibitor of the 5,6-dihyro-4-hydroxy-2-pyrone class. 5th conference on Retroviruses and Opportunistic Infections. 1998, Chicago, IL. Abst. 638.

24. Dezube B.J., Wong T.K., Dahl T.A., *et al.* A fusion inhibitor (FP-221399) for the treatment of HIV infection: a phase I study. 5th conference on Retroviruses and Opportunistic Infections. 1998, Chicago, IL. Abst. 650.

25. Goglioptti R.D., Ellsworth E.L., Holler T.P., *et al.* Quinolones as novel HIV integrase inhibitors. 5th conference on Retroviruses and Opportunistic Infections. 1998, Chicago, IL. Abst.641.

26. Huang M., Turpin J.A., Graham L., *et al*. Anti-HIV agents that selectively target the retroviral nucleocapsid protein zinc fingers without affecting cellular zinc finger proteins. 5th conference on Retroviruses and Opportunistic Infections. 1998, Chicago, IL. Abst. 643.