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Combination Therapy of AIDS

Edited by E.D.A. De Clercq and A.-M.I. Vandamme

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NRTIs: nucleoside reverse transcriptase inhibitors (zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, emtricitabine)

NtRTIs: nucleotide reverse transcriptase inhibitors (tenofovir, disoproxil fumarate)

NNRTIs: non-nucleoside reverse transcriptase inhibitors (nevirapine, delaviridine, efavirenz)

FIs: fusion inhibitors (enfuvirtide)

PIs: protease inhibitors (saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir, atazanavir)

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Contents

List of contributors	VII
Preface	IX
<i>Erik De Clercq</i> Anti-HIV agents to be used in drug combination regimens	1
<i>Deborah Konopnicki and Nathan Clumeck</i> A perspective of the history of HAART	25
<i>Cécile L. Tremblay and Martin S. Hirsch</i> The basic principles for combination therapy	41
<i>Roger Paredes, Bonaventura Clotet and Lidia Ruiz</i> Comparison of the efficacy of HAART: single, dual or triple-class antiretroviral therapy	53
<i>Michael Kurowski</i> Pharmacokinetics and pharmacodynamics of HAART	73
<i>Luc Perrin and Marie-Charlotte Bernard</i> Primary HIV infection: from diagnosis to treatment	87
<i>Marianne Harris and Julio S.G. Montaner</i> Salvage therapy	99
<i>Felipe García, Joan Joseph and José M. Gatell</i> Structured therapy interruptions (STIs): lessons from a therapeutic strategy	115
<i>Brigitte Autran</i> Immune reconstitution in HIV infection	127
<i>Nicole H. Tobin and Lisa M. Frenkel</i> Highly active antiretroviral treatment (HAART) of pediatric HIV-1 infection	141
<i>Roy M. Gulick</i> Causes of HIV treatment failure	159

Christopher Holtzer and Mike Youle

Economic implication of HIV-1 resistance testing in
overall clinical care 195

Charles C.J. Carpenter

Guidelines for antiretroviral therapy 205

Ume L. Abbas and John W. Mellors

Visions for the future of antiretroviral therapy 225

Index 239

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Preface

HIV infection has been a greater challenge to current medicine than any other viral disease of modern times. HIV leads to a persistent infection and the virus has an immense genetic flexibility under selective pressure. During its replicative cycle in patients, HIV accumulates mutations at such a high rate that the selective pressure inflicted on the immune system, or generated by antiviral drugs rapidly triggers the appearance of escape mutants. Currently available drugs, when used singly, are not capable of suppressing virus replication in patients to such a level that the generation of mutations, from which a variant resistant to immune attack or antiviral drugs can be selected, is prevented. This is the main reason why combination therapy, usually of three drugs, has become the standard procedure for the treatment of AIDS.

It is obvious that virus eradication will not readily be achievable, so that drugs have to be taken for a prolonged time or even lifelong so as to keep the viral load as low as possible. Whether the currently used drug combinations will be able to control virus replication in a particular patient for such a prolonged period of time depends on many factors, most of which are addressed in the different chapters of this book.

The aim of antiviral drug combination therapy for AIDS is ultimately to restore full function of the immune system. The expected immunological benefit is one of the major determinants driving the decision when to start therapy. In principle, treatment should be started sufficiently early, so as not to compromise too much immune competence. However, in the past the traditional drug regimens have been compounded by a number of side-effects which often caused patients to not adhere to drug intake. It could be argued therefore that therapy should not be started too early, so as not to weaken motivation for life-long compliance in the face of more harm from side-effects of the drugs than of the disease itself. Shifting treatment guidelines reflects this difficult balance. In addition, the potency of the individual drugs also contributes to the choice of the drugs to be incorporated in the combination regimens.

Current clinical tools to evaluate the success of antiretroviral combination therapies are still based on viral load, reflecting virus replication, and CD4 count, reflecting the status of the immune system. A new tool has recently emerged: drug resistance testing. It is logical that knowledge of drug resistance will help in therapy decisions; however, scientific evidence was only recently firmly established, so that guidelines now include resistance testing. Other parameters such as drug level monitoring and drug adherence are considered very valuable, but have not been evaluated sufficiently thoroughly in prospective studies to warrant their use in routine clinical practice.

In the introduction chapter of the book, Erik De Clercq provides an overview of the four different classes of compounds that are now available for the treatment of AIDS, the so-called NRTIs (nucleoside reverse transcriptase inhibitors), NtRTIs (nucleotide reverse transcriptase inhibitors), NNRTIs (non-nucleoside reverse transcriptase inhibitors) and PIs (protease inhibitors). A fifth class, that of the virus-cell fusion inhibitors, is represented by a single compound (enfuvirtide) that has recently been approved and that, together with the NRTIs, NtRTIs, NNRTIs and PIs, could be included, when available and desirable, into combination drug regimens.

How antiviral drug therapy of AIDS evolved from a single drug (zidovudine) therapy in 1987 to what today is commonly referred to as highly active antiretroviral therapy (HAART) is chronicled by Deborah Konopnicki and Nathan Clumeck.

Cécile L. Tremblay and Martin S. Hirsch then describe the basic principles for combining different drugs in the treatment of HIV infection. Simply stated, triple drug combinations do better than dual drug combinations, which, in turn, score better than single drug monotherapy. Roger Paredes, Bonaventura Clotet and Lidia Ruiz have assessed different forms of multiple-drug regimens from a comparative viewpoint.

The drug levels achieved at the site(s) of virus replication are of paramount importance to predict the efficacy of any drug regimen, and this should become clear from the chapter of Michael Kurowski on the pharmacokinetics and pharmacodynamics of the therapeutic regimens used.

Luc Perrin and Marie-Charlotte Bernard discuss HAART treatment for primary HIV infection, an indication which today is recommended only within the scope of formal clinical trials. This chapter is followed by the chapter of Marianne Harris and Julio S.G. Montaner on salvage therapy for which, as for first-line therapies, sustained immunological and clinical benefit has been demonstrated only when complete suppression of plasma viral load is achieved.

Felipe García, Joan Joseph and José M. Gatell tell us what to expect from structural therapy interruptions (STIs) as a strategy to re-activate or reconstitute immunity, a provocative approach towards the therapeutic management of HIV infections. The kinetics of immune reconstitution and the current limitations thereof are further analyzed by Brigitte Autran.

Specific aspects have to be considered when dealing with HAART in children infected with HIV-1, and suggestions on how to treat such pediatric HIV-1 infections are proposed by Nicole H. Tobin and Lisa M. Frenkel.

Treatment failure continues to occur commonly because of a multitude of reasons and, when assessing remedies to prevent or overcome treatment failures, discontinuation of drug therapy for toxicity, non-adherence or other reasons must be distinguished from virologic, immunologic and clinical treatment failures, as pointed out by Roy M. Gulick.

One of the major reasons for treatment failure is the development of HIV resistance towards the antiretroviral medications. The sensitivity of HIV-1 to

antiretrovirals can be monitored by either genotyping or phenotyping, or both. The economic impact, i.e., costs of medical care, for HIV-1 drug resistance testing is analyzed by Christopher Holtzer and Michael Youle.

Taken all the foregoing considerations together, a number of issues could be raised, as to when antiretroviral therapy should be indicated, which drug regimens are likely to be the most efficacious, how antiretroviral therapy, once it has been initiated, should be monitored, and when drug regimens need to be changed in individual patients. Charles C.J. Carpenter has formulated the guidelines for optimal antiretroviral therapy, ultimately aimed at providing the most effective and durable virologic, immunologic and clinical response.

In the final chapter, Ume L. Abbas and John W. Mellors envision the future of antiretroviral therapy. They describe a number of new promising antiretrovirals that are in development, addressing, in particular, new NRTIs (among which emtricitabine has in the mean time been approved for clinical use (EmtrivaTM)), NNRTIs, PIs (such as atazanavir, now also approved for clinical use (ReyatazTM)), viral entry and integrase inhibitors, as well as some important procedures, such as therapeutic drug monitoring (TDM) and strategies, such as immune-based therapies (including therapeutic vaccines), cytokines (i.e. IL-2) and intermittent therapy with once-daily dosing regimens, that should keep pace with globally growing AIDS pandemic.

Combination therapy of AIDS is a complex matter. Many things can go wrong, and clinicians need sufficient training and expertise to be able to make the wisest decision in any particular setting. Continued education is a must, and comprehensive coverage is needed to bring this complex matter to the clinical and medical practice in a sufficiently elaborated way. Also researchers, whether basic or clinical, should familiarize themselves with all aspects of treating HIV patients, in order to grasp where the needs are for continued progress and extended knowledge. Drug designers should be aware of the complexities associated with the ultimate use of their potential new drugs. This is why this book will fill the needs of clinicians, healthcare workers, researchers and drug designers. It aims at delineating the complexity of combination therapy for AIDS, thereby providing guidance on the optimal use of the anti-HIV drugs.

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