Summary
Erik De Clercq
Anti-HIV agents to be used in drug combination regimens

Virtually all the compounds that have been approved, and are currently used, for the treatment of HIV infections, belong to one of the following classes: (i) nucleoside reverse transcriptase inhibitors (NRTIs: zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir) and nucleotide reverse transcriptase inhibitors (NtRTIs: tenofovir disoproxil fumarate); (ii) non-nucleoside reverse transcriptase inhibitors (NNRTIs: nevirapine, delavirdine, efavirenz); and (iii) protease inhibitors (PIs: saquinavir, ritonavir, indinavir, nelfinavir, amprenavir and lopinavir). As these compounds are specifically targeted at viral enzymes [reverse transcriptase (RT) or protease], they inevitably lead to the emergence of mutations in the RT or protease that are associated with diminished drug susceptibility (resistance). To reduce the risk of virus-drug resistance development, and also to obtain synergistic activity (between drugs targeted at different molecular events) and diminish the potential for toxic side effects, the existing NRTIs, NtRTIs, NNRTIs and PIs have been administered in various three- or four-drug combination regimens. Also additional events in the HIV replicative cycle, other than RT and protease, have been envisaged as potential targets for chemotherapeutic intervention: (i) viral adsorption, through inhibition of the viral envelope glycoprotein gp120 with its receptor CD4; (ii) viral entry, through blockade of the viral coreceptors CXCR4 and CCR5; (iii) virus-cell fusion, through binding to the viral envelope glycoprotein gp41; (iv) viral assembly and disassembly, through NCp7 zinc finger-targeted agents; (v) proviral DNA integration, through integrase inhibitors; (vi) viral mRNA formation, through inhibitors of the transcription (transactivation) process. Also, various new NRTIs, NNRTIs and PIs have been developed that possess either higher potency or lesser toxicity and/or a more favorable resistance profile (i.e. better activity against resistant virus strains) than the "older" NRTIs, NNRTIs or PIs. Given the multitude of molecular targets with which anti-HIV agents can interact, any future strategies for the treatment of HIV infections should be based upon multiple-drug combinations targeted at different specific events in the HIV replicative cycle.

Key words: HIV (human immunodeficiency virus), NRTIs (nucleoside reverse transcriptase inhibitors), NtRTIs (nucleotide reverse transcriptase inhibitors), NNRTIs (non-nucleoside reverse transcriptase inhibitors), PIs (protease inhibitors), virus-drug resistance.

Summary
Deborah Konopnicki and Nathan Clumeck
A perspective of the history of HAART

This chapter reviews the development of antiretroviral drugs targeted against HIV infections in adults: nucleoside analogues were the first class used, initially in monotherapy then in dual regimens. Protease Inhibitors (PIs) appeared in the mid nineties and led to the concept of highly active antiretroviral therapy which brought a dramatic improvement in patient mortality and morbidity. Non-nucleoside reverse transcriptase inhibitors represent the third class of antiretroviral licensed today bringing also their contribution to the 16 drugs currently available. The toxicity and difficulties linked to long-life therapy have led to the implementation of different strategies discussed in this chapter. Switch therapy, PI-sparing regimens and structured therapy interruption have been designed both to decrease the exposure to PIs and to facilitate the patients' compliance. Pharmacological progresses have allowed the development of boosted PIs with better pharmacokinetic profiles, new compounds such as fusion inhibitors and once daily therapy. Studies on salvage treatment

based on resistance testing, immune based therapy and vaccination are other more recent approaches that are also (briefly) included in this review.

Key words: NRTI; PI; NNRTI; monotherapy; dual therapy; HAART; boosted PI; switch therapy; PI-sparing; structured therapy interrruption; NRTI-sparing; salvage; immune based therapy; vaccine; lipodystrophy

Summary
Cécile L. Tremblay and Martin S. Hirsch
The basic principles for combination therapy

Combining antiretroviral agents is an effective strategy against HIV-1 infection as indicated by dramatic declines in HIV-associated morbidity and mortality since the introduction of this approach. Combination therapy can take advantage of synergistic or additive antiviral interactions or favorable pharmakokinetic interactions to increase regimen potency. Combinations can also increase benefit by broadening tissue penetration or cell spectrum. Together these effects can lead to greater antiviral suppression and possibly reduced toxicity. In vitro techniques have been developed to measure drug interactions and help identify which combinations should be further evaluated clinically. As new targets for antiretroviral agents are identified and new classes of drugs are developed, a better understanding of drug interactions will be essential to design the best possible combination regimens.

Key words: Antiretroviral therapy, combination therapy, combination indices, drug toxicity, synergy, antagonism, additivity, pharmacokinetics, drug targets, reservoirs, cellular targets, HIV-1 replication

Roger Paredes, Bonaventura Clotet and Lidia Ruiz
Comparison of the efficacy of HAART: single, dual or triple-class antiretroviral therapy
(No summary & key words available)

Michael Kurowski
Pharmacokinetics and pharmacodynamics of HAART
(No summary & key words available)

Summary
Luc Perrin and Marie-Charlotte Bernard
Primary HIV Infection: from diagnosis to treatment

Over the last five years there has been a change in therapeutic guidelines reflecting in some way the limited activity of available anti-retroviral drugs which display short and long term toxicities and are unable to eradicate the infection. This context has obvious consequences for initiation of treatment in primary HIV infection (PHI) which is today recommended only within clinical trials. HAART treatment in PHI patients is associated, as in chronic patients, with a rapid decrease of viremia and CD4 recovery. Moreover, virological markers decrease more rapidly and HIV specific immune responses are preserved. However , as in chronic patients, long term HAART is associated with drug induced toxicities. This limits the possibility to pursue HAART for years. The intensity of symptoms at the time of the acute

retroviral syndrome predicts the long term disease outcome. We, however, still have few predictors of the viremia set point which will be achieved in PHI patients on long term HAART who stop treatment. This set point results from the interaction of viral replication and specific immune defense mechanisms. As the specific immune defense mechanisms affording protection from disease are still poorly characterized, we are in an exploratory phase which will be best explored within control trials. Acute HIV infection presents biological characteristics such as homogeneity of the virus and preserved immune system which translate into a unique opportunity to explore new avenues for a better containment of HIV replication. In addition to HAART, a number of trials has been or will be exploring the impact of immune interventions from controlled re-exposure to the patient's virus to therapeutic vaccination and use of immuno-modulating agents. In this context PHI may help to define new leads which may benefit at a later stage to patients with established infection.

Summary
Marianne Harris and Julio S.G. Montaner
Salvage therapy

Despite the established success of current combination antiretroviral regimens, treatment failure remains an important clinical issue for which appropriate management may be challenging. As for first-line therapies, for second-line and later salvage treatments, sustained immunologic and clinical benefit have only been demonstrated with complete suppression of plasma viral load below detectable levels. Appropriate timing, drug selection, and optimal adherence are critical determinants for the success of salvage therapy. Expert interpretation of resistance testing may be helpful in selecting the components of the salvage regimen, and monitoring of plasma drug levels may help optimizing potency and tolerability, especially of complex, multiple drug regimens. Still to be defined with ongoing clinical studies are the potential roles of newer antiretroviral agents, adjuvants, treatment interruptions, and immune-based therapies in the context of salvage therapy.

Key words: salvage therapy; rescue therapy; treatment failure, management; drug sequencing; multiple drug rescue therapy, virtual virus

Summary
Felipe García, Joan Joseph and José M. Gatell
Structured therapy interruptions (STIs) lessons from a therapeutic strategy

Current treatment guidelines for HIV infection recommend a relatively late initiation of highly active antiretroviral therapy [59,60]. However, what should be recommended to those patients who started therapy with CD4+ T cell counts above the current recommendation or to those patients whose CD4+ T cell counts increased and are stabilized even for years above a given level (i.e. 500 cells/mm^3) after initiating HAART remains to be answered. It would be helpful to implement strategies with lesser potential for side effects than the current "HAART for life" to avoid the natural evolution of the disease in patients with a high level of CD4 T cell counts. STI by itself will rarely be sufficient to attain the goal of low viremia without anti-retroviral therapy. Alternative or complementary approaches such as therapeutic vaccines are being explored.

Key words: structured therapy interruption, auto-vaccination, helper responses, CTL responses, anti-HIV-specific responses, viral reservoirs, hydroxyurea, mycophenolate mofetil, toxicity; cost

Summary
Brigitte Autran
Immune reconstitution in HIV infection

Combination of HIV reverse transcriptase and protease inhibitors allow the immune system damaged by years of infection with HIV to reconstitute the CD4 cell pools and to restore the host's protection against pathogens, at any stage of the disease. The condition required for such immune reconstitution is an efficient and durable inhibition of virus replication and still now represents a real breakthrough in the clinical management of HIV-infected patients. The lack of restoration of immunity against HIV itself, however, is a major limitation of these treatment regimens which cannot eradicate the virus and have to be administered for life. New therapeutic strategies based upon immune interventions to restore an immunity to HIV have thus to be developed. This chapter reviews the kinetics of immune reconstitution and its various mechanisms as well as the current limitations of immune reconstitution.

Summary
Nicole H. Tobin and Lisa M. Frenkel
Highly active antiretroviral treatment (HAART) of pediatric HIV-1 infection

Administering highly active antiretroviral therapy (HAART) effectively to HIV-1-infected children poses several unique challenges. There is a paucity of data on the optimal time to initiate HAART and on which therapeutic regimen to prescribe. Administration of antiretrovirals to HIV-1-infected children can be difficult. Careful consideration of multiple factors may assist in maximizing both the level and duration of virologic efficacy of HAART in children. This chapter summarizes studies of 3- and 4- drug HAART and salvage regimens in children. In addition, the pharmacokinetics of antiretrovirals in children including absorption, distribution and rationale for monitoring drug levels is discussed. The transmission and treatment of drug-resistant viruses is reviewed, as are strategies to avoid the selection of drug-resistant mutants. The chapter concludes with suggestions regarding treatment of HIV-1-infected children.

Key words: HAART, Children, Neonates, Infants, Adolescents, HIV-1, Resistance, Pediatric HIV-1, Antiretroviral Therapy, Salvage Therapy, Pharmacokinetics of Antiretrovirals, Concentration-controlled therapy

Summary
Roy M. Gulick
Causes of HIV treatment failure

HIV treatment failure encompasses a number of different causes, including toxicity, non-adherence, and virologic, immunologic or clinical failure. Treatment failure occurs commonly with rates as high as 63% reported from clinical cohorts. Factors associated with an increased risk of virologic failure include patient characteristics (e.g., AIDS diagnosis, prior antiretroviral treatment, HIV RNA level, CD4 cell count, non-adherence), viral characteristics (e.g., drug-resistance mutations, virologic response) and treatment characteristics (e.g., potency, toxicity, convenience, pharmacokinetics). One of the most challenging aspects of HIV treatment failure is that multiple factors may play a role in an individual patient. Patient factors, viral factors, and treatment factors all must be carefully assessed. Addressing the cause of treatment failure in a given patient is critical to

determining the optimal next step in patient management. Successful management of the treatment-experienced patient who has experienced treatment failure currently is one of the most challenging areas of HIV medicine.

Key words: antiretroviral therapy; treatment-naïve HIV-infected patients; treatment-experienced HIV-infected patients; antiretroviral treatment failure; HIV RNA response; virologic failure; CD4 cell count response; drug resistance; drug toxicity; drug adherence; pharmacokinetics; drug-drug interactions

Christopher Holtzer and Mike Youle
Economic implication of HIV-1 resistance testing in overall clinical care
(No summary & key words available)

Summary
Charles C.J. Carpenter
Guidelines for antiretroviral therapy

Effective combination antiretroviral therapy (HAART) has dramatically decreased the mortality of HIV infection whenever these medications have been available. Durable interruption of disease progression and improved immune function can now be achieved in almost all patients who have received no prior antiretroviral drugs. Although serious toxicities may result from HAART, careful tailoring of the medications for each individual, and close monitoring for early signs of adverse effects have decreased the magnitude of this problem. Development of resistance to antiretroviral drugs remains a major long-term challenge, even when adherence to a HAART regimen is optimal. This problem may be ameliorated, but will not disappear, when new classes of antiretroviral agents (viral entry inhibitors, integrase inhibitors) become available.

Key words: Antiretroviral therapy, CD4 cell count, plasma viral load, protease inhibitors, reverse transcriptase inhibitors, medication adherence, resistance mutations, treatment failure, structured treatment interruption

Summary
Ume L. Abbas and John W. Mellors
Visions for the future of antiretroviral therapy

As the HIV pandemic continues in its third decade, antiretroviral therapy remains our most effective weapon against HIV-induced morbidity and mortality. Many research efforts are focused on the development of new drugs against novel and known targets, optimization of existing agents and standardization and simplification of therapeutic regimens. However, in order to make a significant global impact, formulation of new and enhanced antiretrovirals must be complemented by advances in vaccine research and innovations in methods of treatment administration. This chapter looks into the future highlighting promising new and anticipated breakthroughs in HIV treatment research.

Key words: Antiretroviral therapy, new antiretrovirals, drug resistance, treatment strategies, biomedical informatics

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