Fabric of the future

Abstract Book

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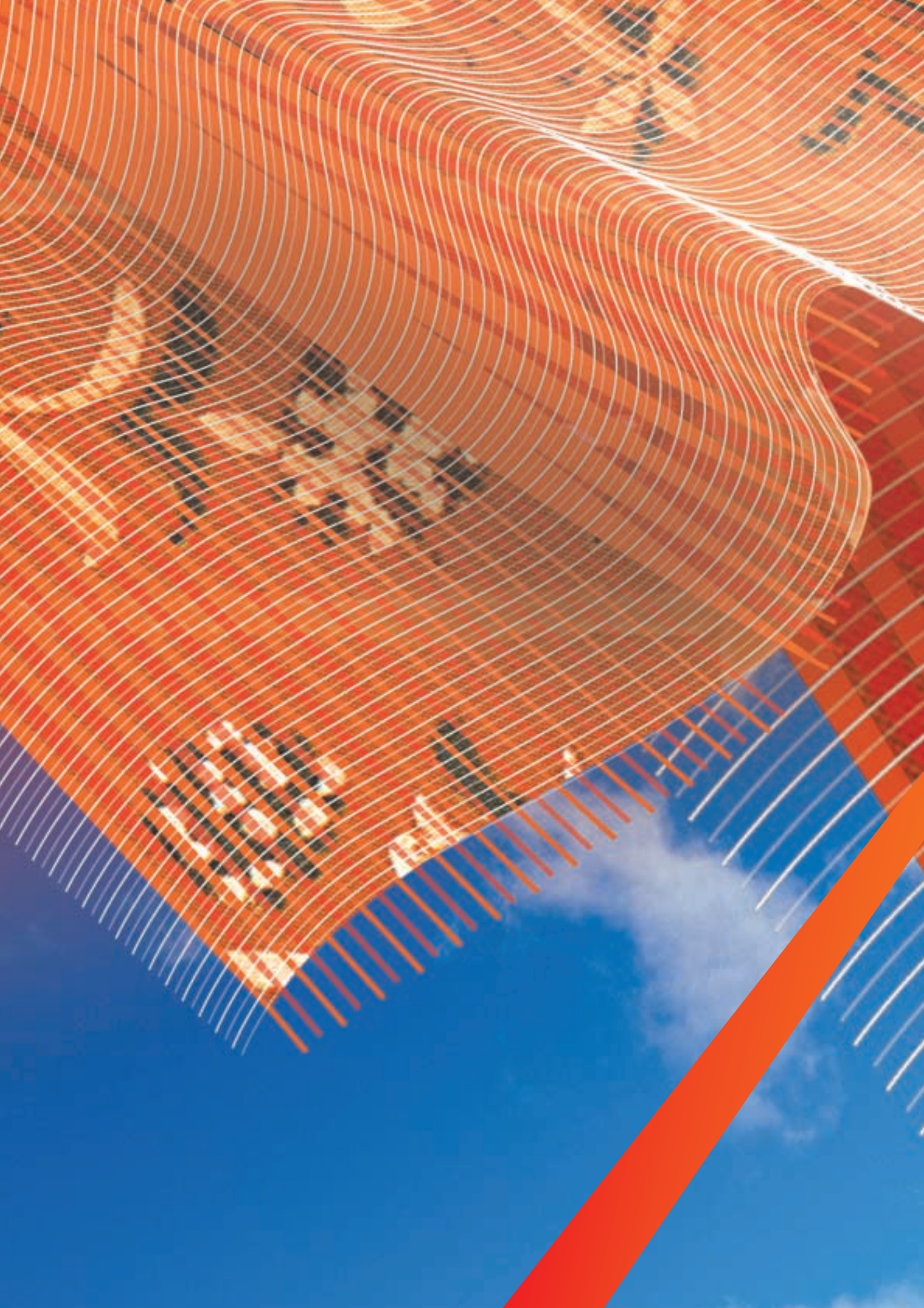
Fabric of
the future



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Introduction from the Chairmen

Peter N Mugyenyi
Deputy Chairman, Mbarara University of Science and Technology, and Secretary, UNAIDS-Uganda HIV Drug Access Initiative, Uganda

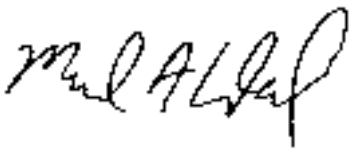
Mark A Wainberg
President, International AIDS Society and Director of the McGill University AIDS Centre, Jewish General Hospital, Montreal, Canada

Mark A Wainberg is an internationally recognized scientist in the field of HIV/AIDS who has made important independent contributions to the study of antiviral drug development and HIV drug resistance.
He is well known for his initial identification of 3TC as an antiviral drug, in collaboration with BioChem Pharma Inc. in 1989, and has contributed numerous papers to the literature on drug action and drug resistance in AIDS. His laboratory continues to work in the area of new drug discovery, and Dr Wainberg has now turned his attention to novel concepts in HIV vaccine development and prevention of HIV infection.
Dr Wainberg is a strong advocate of measures that will enhance prevention of HIV infection in developing countries and is a microbicide activist. He was recently Chair of the Microbicides 2000 Conference held in Washington, DC, and will be Chair of the XV International AIDS Conference to take place in Toronto during the summer of 2004.

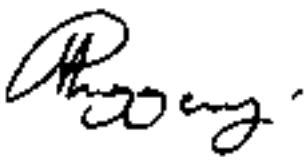
Dr Mugyenyi is the Director of the Joint Clinical Research Centre – a Centre of excellence for AIDS research in Uganda. A pioneer of HIV/AIDS research in sub-Saharan Africa, Dr Mugyenyi has participated in a number of AIDS research projects including the first HIV vaccine trial in Africa. He campaigns to facilitate the use of antiretrovirals in Uganda, a resource constrained country.
Dr Mugyenyi is a consultant to various international organisations working on HIV/AIDS. He has contributed to many scientific papers on HIV treatment and made numerous presentations on both the clinical and social aspects of the disease. At present, Dr Mugyenyi is involved in studies on the development of vaccines for HIV and is an active member of a group of scientists involved in development of ethical and scientific guidelines for conducting research in developing countries.
Dr Mugyenyi advocates that the millions of sub-Saharan Africans already infected with HIV/AIDS should gain access to the treatments available in industrialised countries. He is the Secretary to the UNAIDS HIV Drug Access Initiative in Uganda pursuing this goal.

Fabric of the future

We are delighted to welcome you to the symposium, 'Fabric of the future' which has been sponsored by F Hoffmann-La Roche. This symposium will focus on three of the 'strands' that makes up the 'fabric' of HIV disease – the diagnosis, surveillance and management of the virus and opportunistic infections. Although the controversies surrounding prevention of, and intervention for, HIV are multi-fold, the intention of the faculty in our capacity as physicians and researchers actively concerned with the everyday lives of people with HIV is to focus on the scientific advances to combat HIV. We will seek to describe the 'gold standard' of treatment excellence – as determined through clinical experience in the developed world. We have considered the appropriateness of this content and believe it is our responsibility to acknowledge, advise and update delegates at the conference of our understanding about the treatment of HIV. We are confident that this approach will secure the improvement and development of effective intervention strategies that will benefit as many people living with HIV as possible. As such, we have a distinguished assembly of international experts who will present persuasive clinical and research data to outline the contributions made by the pharmaceutical and medical strands. It is our hope that by weaving these advances with the political, social and economic strands we can produce an optimistic 'fabric' or outlook of the future. We look forward to a positive and interesting exchange of experience, suggestion and opinion.



Mark A Wainberg



Peter N Mugyenyi

David Katzenstein

Vertical Transmission of HIV in Africa: Diagnostic Testing Can Facilitate New Studies and Improve Outcomes

David Katzenstein
Associate Professor, Division of Infectious Diseases, Stanford University, Stanford, California, USA

Since 1985 David Katzenstein has been a Principal Investigator for HIV/AIDS research and clinical trials and is currently Associate Medical Director of the Stanford University AIDS Clinical Trial Group and Co-Director of the Diagnostic Virology Laboratory at Stanford University Hospital.
Professor Katzenstein has presented at many international conferences and has published extensively in the field of HIV and infectious diseases. He is a member of the American Society for Microbiology, the Infectious Disease Society of America, the Society for General Microbiology and the International AIDS Society and has made valuable contributions to further understanding of and education about HIV.

The United Nations Programme on HIV/AIDS and the World Health Organization have estimated that the number of people infected with the human immunodeficiency virus (HIV) rose by 10% during 1998–1999, to 33.6 million people.[1,2] This increase is not uniformally distributed worldwide, as at least 95% of infections and related deaths are now in developing countries; Africa has by far the greatest burden (Fig. 1). Additionally, while there has been a marked decline in mother-to-infant (vertical) transmission in developed countries such as the USA,[3] the opposite has been observed in developing countries.

Globally, the molecular diversity and epidemiology of HIV display different patterns. The two HIV groups, HIV-1 and HIV-2, and the HIV-1 groups (O and M) and HIV-1 M subtypes (A to K) exhibit ever-increasing genetic variability.[4] HIV-1 occurs worldwide,[2] while HIV-2 is found mainly in Africa and Southeast Asia.[5,6] In Southern Africa, the predominant virus remains subtype C. In West Africa, subtype A is most common while in Central and East Africa there is an increasing diversity of recombinant viruses. A number of biological and behavioural variables contribute to these marked differences in the epidemiology of the virus. HIV-1 is currently spreading at varying rates in different countries.[7–9] Furthermore, recent statistics show that in sub-Saharan Africa, the proportion of HIV-infected adults who are women has risen to 55% which is considerably higher than all other regions of the world.[2] This large increase in HIV-infected women makes the problem of vertical transmission even greater; consequently, improving diagnosis and care in these women, and their children, is vital.

Developing countries have different diagnostic criteria than developed countries. The case definition of AIDS by Centers for Disease Control and Prevention (CDC) criteria requires quantification of HIV RNA and CD4+ cells. However, among African countries, only the Ivory Coast requires a positive test to support the diagnosis of HIV infection or AIDS. The cost of equipment and the need for well-trained personnel often prohibit the use of certain diagnostic techniques in developing countries. Serological tests are the 'gold standard' in the African HIV/AIDS case definition, but their positive predictive value is not as accurate as the tests required by CDC definition.

A major area for concern in developing countries is the absence of treatment for HIV-infected women during pregnancy; this is especially important considering the high rates of vertical transmission. Many women only seek assistance in the late stages of pregnancy and may not have prenatal care or sufficient follow-up regarding laboratory results. The use of rapid, accurate and practical diagnostic assays in these countries would promote faster initiation of antiretroviral therapy and counselling, as well as safe and effective prophylaxis against opportunistic infection.

Some recent diagnostic advances in this area include innovations in enzyme-linked immunosorbant assays (ELISAs) and polymerase chain reaction (PCR) techniques. ELISAs are the most widely used screening tests for HIV antibodies, but they may not detect highly divergent subtypes. Additionally, local test conditions must be taken

Adults and children estimated to be living with HIV/AIDS as of end of 1999

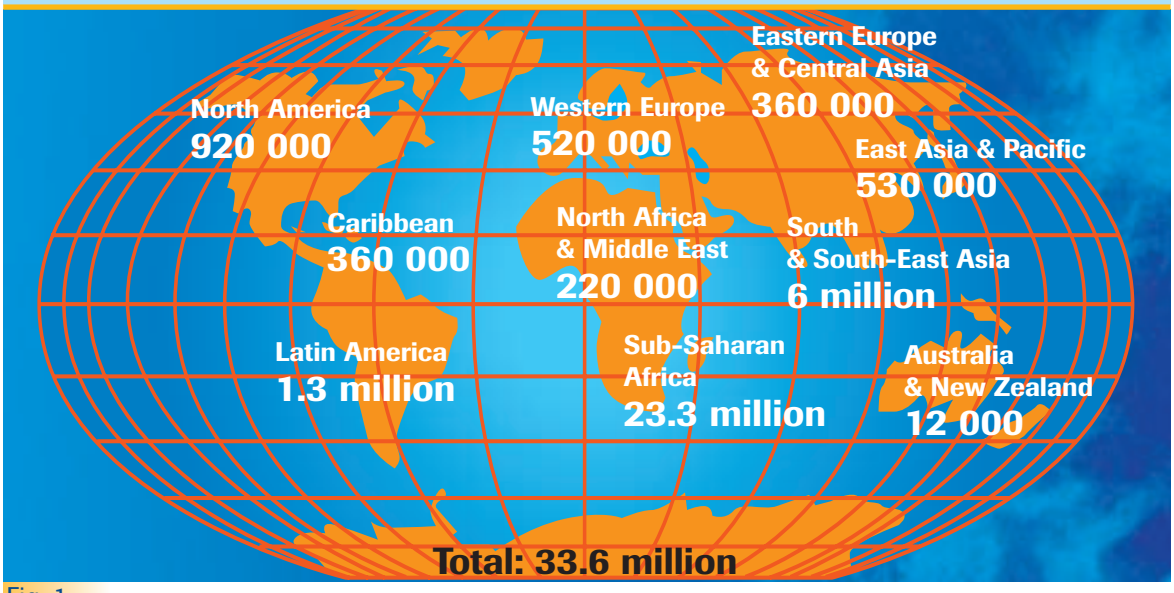


Fig. 1

into account; this was demonstrated by a test of 14 commercially available HIV-1/2 antibody assays.[10] All 14 showed high specificity (99.2–100%) against Swedish blood donor sera but lower specificity (91.9–99.6%) when used against African specimens. The ideal technique for HIV antibody confirmation is western blot analysis, but this procedure is expensive and requires well-trained personnel. Most studies rely on the high sensitivity of ELISA assays, using two different ELISAs to confirm infection. Acknowledgement of the need for affordable and simpler confirmatory strategies led Urassa et al.[11] to assess consecutive testing of sera by a recombinant antigen-based sandwich ELISA followed by a recombinant antigen-based competitive ELISA. In a field test of 1558 sera conducted in Tanzania, this approach was highly successful, with a sensitivity and specificity of 100%.

Another method of HIV detection that does not involve antibody technology is PCR. The PCR-based diagnostic assays currently in development provide accurate, rapid, simple and relatively inexpensive diagnosis of HIV infection. However, given the wide genetic diversity of HIV, detection depends on the ability of the chosen primers to detect all strains. Therefore, research has focused on the development of a standardized PCR assay with universal primers for the detection of all strains. For example, Roche Molecular Systems recently introduced a modified, semi-automated PCR assay that incorporates primers for all HIV-1 subtype M viruses.[12] Furthermore, data were presented recently documenting the development of highly sensitive assays for the detection of HIV-1 group O and HIV-2 viruses.[13] The ultimate aim is to combine these technologies to produce a single, multiplex assay capable of detecting all three HIV targets.

Our own experience in Zimbabwe and South Africa with predominantly subtype C virus isolates demonstrates high levels of sensitivity and specificity with qualitative HIV DNA assays. In a test conducted in Zimbabwe on 202 whole blood samples from adults immediately postpartum, the assay had 100% sensitivity for the detection of HIV-1 DNA and a specificity of 100%.[12] Another study sought to address the large variation in the capacity of different assays, antibody based and PCR, to differentiate between HIV-1 and HIV-2.[14] The researchers found that it was possible to achieve a high concordance between antibody and PCR testing through careful selection of the diagnostic tools.

Early detection of HIV perinatally is vital for effective treatment or for prevention in uninfected HIV-exposed infants. Antibody-based technologies such as ELISAs and western blot analyses are unsuitable for the diagnosis of HIV infection in children younger than 18 months of age primarily due to the presence of maternal antibodies. The most effective methods for the detection of infection in infants younger than 18 months are HIV DNA PCR or HIV culture. Compared with PCR, HIV culture is laborious and expensive; consequently, PCR is the method of choice for early diagnosis.[15] The PCR methods outlined previously have proved effective in detecting HIV infection in adults.[12,14] A few studies examining perinatal infection have demonstrated the effectivenes of PCR in detecting HIV. Using PCR testing, approximately 93% of HIV-infected infants have markers of HIV infection by 14 days postpartum and essentially 100% by 30 to 90 days after birth.[16–19] However, more studies are required using the newly developed PCR-based diagnostic assays in infants.

Rapid diagnosis of HIV infection in infants, followed by prompt intervention, is vital to improve therapy outcome (Fig. 2). The impact of different therapeutic strategies has been addressed by several HIV perinatal studies. For example, the PETRA trial, involving 1447 women in Uganda, Tanzania and South Africa, assessed the potency of regimens considerably shorter than the USA standard.[20] This randomised, placebo-controlled study

Availability of rapid diagnostic tests, suitable for use in developing countries, may help reduce vertical HIV transmission rates

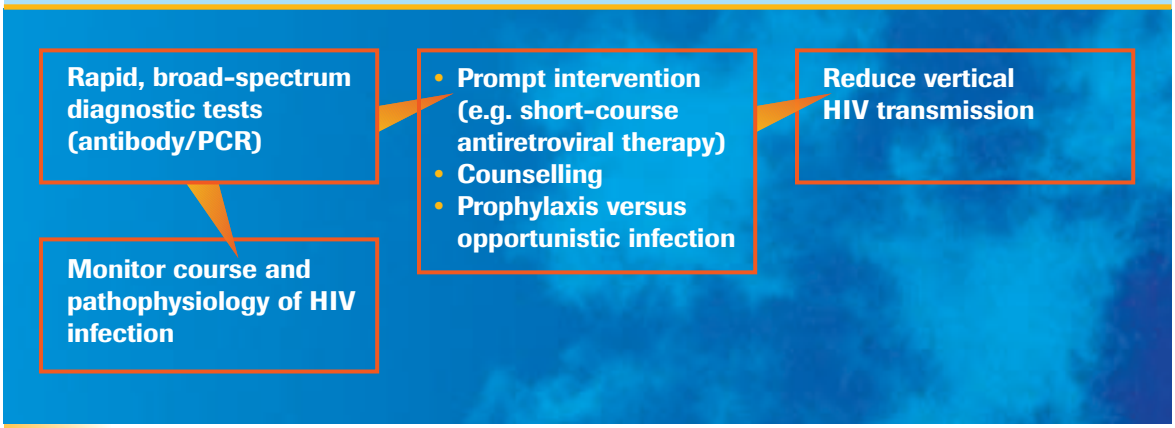


Fig. 2

measured the efficacy of zidovudine in combination with 3TC given before birth (starting at 36 weeks of pregnancy), during labour and/or after birth. Over 60% of the women taking part breast-fed their infants.

Transmission rates at 6 weeks were as follows: 7.8% for the group receiving therapy before birth and during labour, with the infant receiving treatment for 1 week; 10.2% when treatment was started intrapartum and the infant received 1 week of therapy; 15.7% in the group that received only intrapartum treatment and 16.5% in the placebo group. These results suggest that short-course antiretroviral therapy is beneficial in reducing vertical HIV transmission. However, cost–benefit analyses using regional data are required to determine if implementation of this therapy is feasible at a local level.[21,22] The recent results from the HIVNET 012 trial in Uganda, where single-dose nevirapine, administered to women and their infants at the onset of labour and birth, respectively, demonstrate the capacity of inexpensive antiretroviral regimens to reduce mother-to-infant transmission.[23]

In addition to reducing transmission of HIV from mother to infant, the early identification of HIV-infected infants may allow the use of less-expensive chemoprophylaxis for common pathogens (Fig. 2). Most prominent among these is *Pneumocystis carinii*, increasingly recognized as a cause of infant morbidity and mortality in Africa. For pennies a day, it is possible to administer effective prophylaxis to infected infants, yet the costs and logistics of HIV detection in newborns may limit the administration of co-trimoxazole among those who would most benefit.

In conclusion, the use of rapid HIV diagnostic tests followed by effective prophylactic as well as therapeutic regimens may help reduce vertical transmission and infant mortality in the developing world. It will require intense efforts and innovative use of existing drugs to achieve infant survival rates comparable with those now observed in developed countries. However, improved diagnostic testing will also assist in assessing the impact of various interventions aimed at reducing the risk of vertical transmission further and in monitoring the course and pathophysiology of HIV infection.

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Andrew Zolopa

Establishing the Gold Standard: The Critical Choice of Initial Antiretroviral Regimen

Andrew Zolopa
Assistant Professor of Medicine,
Stanford University, School of Medicine,
Stanford, USA

Andrew Zolopa, M.D., is Assistant Professor of Medicine at the Stanford University School of Medicine. He is also Director of the Stanford Positive Care Program and Chief of the AIDS Medicine Division at Santa Clara Valley Medical Center. Dr Zolopa received his M.D. from the University of California Los Angeles School of Medicine, was a Robert Wood Johnson Clinical Scholar, and completed a Postdoctoral Fellowship in Infectious Diseases and Geographic Medicine at the Stanford University Medical Center. He is board certified in infectious diseases and maintains an active HIV clinical practice at Stanford University Medical Center. Past research interests of Dr Zolopa include population-based studies of HIV and TB prevalence and risk factors in homeless populations. This work has led to ongoing studies of HIV treatment, adherence to antiretrovirals, and drug resistance in inner-city urban populations in which he collaborates. Since 1996, Dr Zolopa has been actively involved in the evaluation and use of HIV-1 resistance testing in the care of HIV-infected patients. His study documenting the prognostic value of HIV-1 genotyping was published in a recent issue of the *Annals of Internal Medicine*.

The established goal of antiretroviral therapy is the long-term suppression of viral replication below the limit of quantification of the most sensitive available assays. This recommendation is based on recent evidence showing that the achievement of a plasma viral load (pVL) nadir less than 50 copies/ml is associated with a lower risk of subsequent viral rebound compared with substantial but incomplete viral suppression (pVL nadir between 50 and 400 copies/ml).[1]

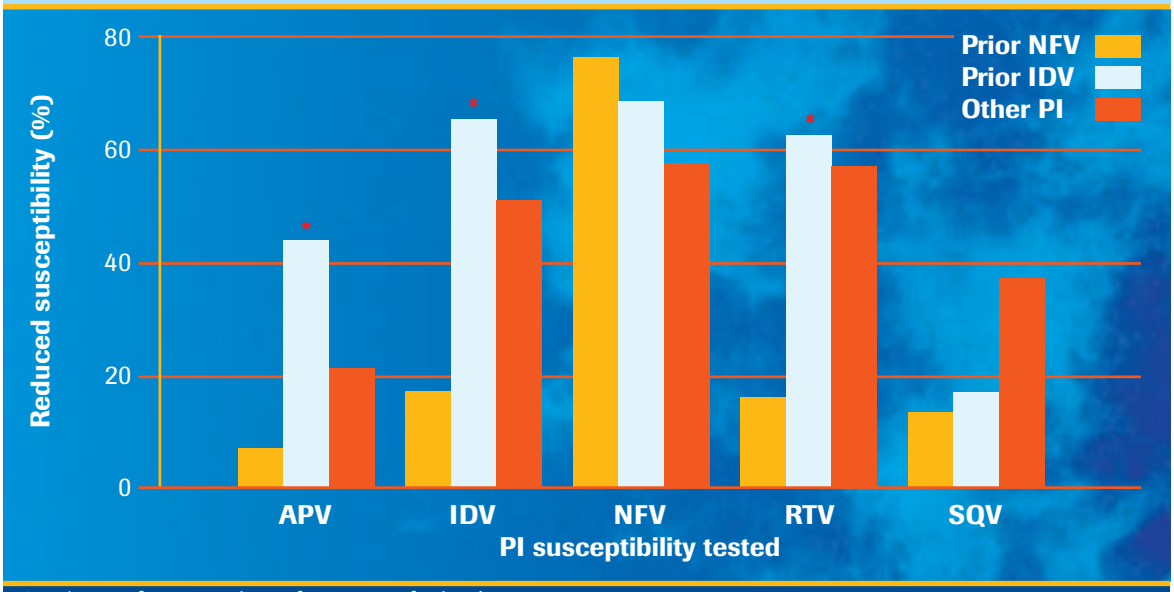
The choice of initial antiretroviral regimen is critical to attaining the goal of successful management of HIV in the long term. The first-line regimen must not only provide potent and durable suppression of HIV replication, but also be easy to take and well tolerated. An important strategic consideration for the initial antiretroviral regimen is that it must also leave open subsequent therapy options to regain control of HIV replication after eventual rebound.

Nelfinavir has demonstrated a number of characteristics that warrant consideration as the PI of choice in an initial antiretroviral regimen. It is a highly potent PI that provides durable viral suppression in antiretroviral-naïve patients.[1–6] Treatment with nelfinavir (1250 mg twice daily) in combination with stavudine (d4T) and lamivudine (3TC) sustained HIV RNA levels below 50 copies/ml up to 96 weeks in approximately 65% of patients using an on-treatment analysis (approximately 45% by intention-to-treat) in preliminary results from a subset of patients.[2] In comparison to triple therapy with zidovudine (ZDV)/didanosine (ddI)/nevirapine (NVP), treatment with nelfinavir or indinavir in combination with ZDV and 3TC produced longer viral suppression among patients with pVL between 20 and 400 copies/ml.[7]

The unique resistance profile associated with nelfinavir and infrequent cross-resistance arising to other PIs when used as first-line therapy is a further benefit that substantiates the inclusion of nelfinavir in initial regimens. In Study CCTG 575, the frequency of phenoypic cross-resistance after initial nelfinavir therapy was significantly less compared with indinavir (16% vs 60%, $p<0.001$) and ritonavir (14% vs 56%, $p<0.001$) (Fig. 1).[8] These findings have been confirmed recently in the VIRA 3001 trial.

The replicative fitness of HIV mutants selected by different PIs has been determined in vivo. The relative fitness of the drug-resistant HIV mutants, D30N and the mutant L90M with the wild type, has been compared. Resulting data indicate that the replicative capacity of the D30N and L90M mutants were substantially and moderately decreased respectively.

CCTG 575: Reduced phenotypic susceptibility by prior protease inhibitor



* *$p < 0.001$ for comparison of 3 groups of prior therapy.*

Fig. 1

Furthermore, the fitness of the clones with the D30N mutation was not improved by the addition of a L63P 'compensatory' mutation as was the case with the L90M-containing clones. It thus appeared from these experiments, that D30N-containing viral clones would require more extensive compensatory mutations to improve fitness as compared to other primary protease inhibitor resistance mutations.

The genetic basis for the lack of phenotypic cross-resistance seen in clinical trials is likely due to the fact that the D30N mutation is unique to nelfinavir and this mutation does not, by itself, cause resistance to other PIs. Moreover, the impaired ability of viruses with the D30N to replicate efficiently may also provide a basis for an improved response to second-line PI-based therapy.

The infrequent cross-resistance associated with initial nelfinavir therapy may help maintain options for subsequent ART regimens and provide a strategic first step in a long term treatment plan. For example, a number of clinical studies have demonstrated the efficacy of ritonavir–saquinavir combination therapy in patients who had previously experienced virological failure on a nelfinavir-containing regimen.[10–13]

Tebas et al.[11,12] demonstrated the efficacy of an antiretroviral regimen containing saquinavir, ritonavir, stavudine and lamivudine in 26 patients who had previously experienced failure of a nelfinavir-containing regimen. Long-term follow-up of the 24 patients evaluated showed that HIV suppression (plasma HIV RNA <500 copies/ml) was sustained up to week 48 in 58% (14) of patients.[12] In addition, 58% maintained this antiretroviral response for a median duration of 60.9 weeks, determined using the last observation carried forward analysis method.

A multicenter clinical cohort study also showed that over half (52%; 57) of the nelfinavir-failing patients (n=109) achieved HIV RNA <500 copies/ml up to week 48 on a ritonavir/saquinavir-containing regimen (Fig. 2).[10] A subset of these patients sustained this HIV suppression for up to 61 weeks.

Improved patient adherence through simpler, lifestyle-friendly regimens is an additional factor that may deter the development of antiretroviral resistance. Recent studies have demonstrated the comparable safety and efficacy of a convenient twice-daily nelfinavir (1250 mg) dosing regimen to the three times daily (750 mg).[2]

Response to SQV / RTV following nelfinavir (Percentage of patients with HIV RNA <500 [OT])

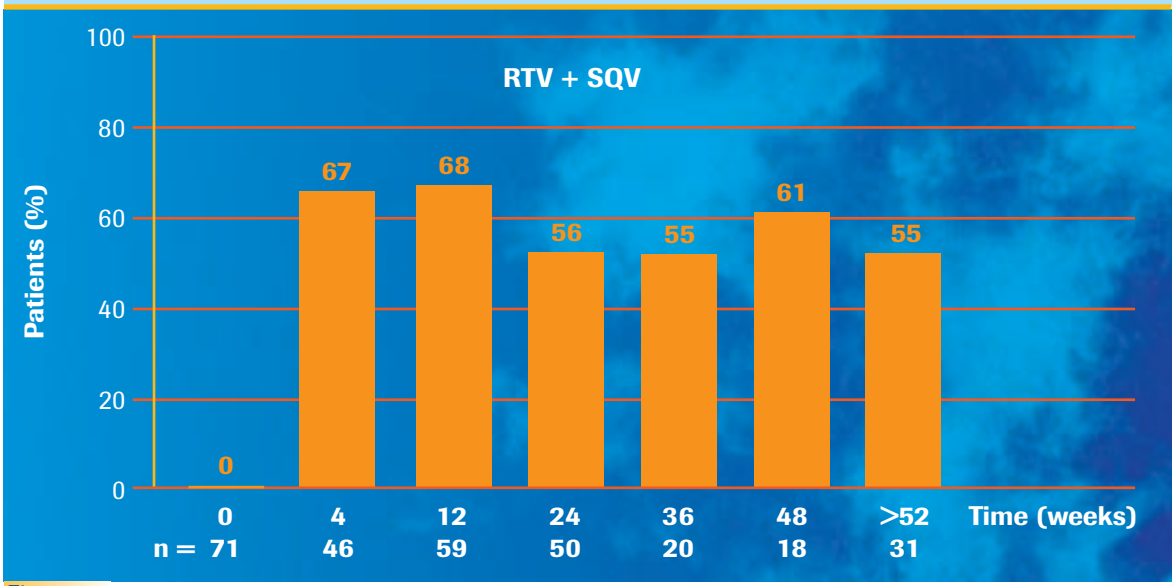


Fig. 2

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Malaki Dundu Owili

Challenges of Adherence – African Experience

Malaki Dundu Owili
Consultant Dermatologist, Venereologist and Cosmeologist
Aga Kahn Hospital,
Nairobi, Kenya

Currently Secretary General of the Society on AIDS in Africa, immediate past Chairman of the Kenya National AIDS Committee, Chairman and Founder of the Kenya Herpes Management Forum and Vice-President of the Task Force on AIDS Research in Africa, Malaki Dundu Owili has 30 years' clinical experience as a dermatologist and venereologist.
Dr Owili has presented at numerous international conferences, is on the editorial board of many journals (including the *International Journal of Human Immunodeficiency Syndrome*) and is a member of the International Society for Infectious Diseases and the Network of AIDS Research of Eastern and Southern Africa.

It has been suggested that a contributory factor to the development of resistance to antiretroviral therapy, and the subsequent failure of viral suppression, is the failure of patients to sustain strict adherence to multidrug regimens.[1,2] There is no 'gold standard' method for measuring adherence, or a definition for 'good' adherence. Therefore, a number of studies have attempted to rationalise the effect of different levels of adherence, and assess methods in which to determine it. These studies are essential to identify the level of adherence required to prevent development of resistant virus and virological failure, and to evaluate ways in which to improve it.

The adherence to protease inhibitors by 84 HIV-infected patients was assessed using an electronic device called MEMSCaps.[3] This study demonstrated that successful virological suppression (pVL <400 copies/mL) was associated with >95% adherence after three months of protease inhibitor therapy (Fig. 1). Virological failure was increasingly apparent with decreasing levels of adherence. In addition, this study showed that physician judgement and the patient self-report method of assessing adherence were unreliable.

The REACH cohort study also examined different methods of determining patient adherence.[4,5] Adherence, viral suppression and resistance mutations were assessed in 34 low-income or homeless, HIV-infected individuals on protease inhibitor-containing combination therapy over a median duration of 66 days. Methods used to determine adherence were self-reporting, pill count and electronic monitoring. Median adherence was determined as being 89% (range: 16–100%) for self-reporting, 73% for pill count (range: 3–100%) and 67% (range: 0–100%) for electronic monitoring. Adherence was demonstrated to be related to the 36–65% variation in HIV-1 viral load. A doubling of the HIV RNA level was associated with a 10% decrease in adherence. In addition, drug resistance was rare in those individuals who had failed to follow the drug regimen well. It was concluded that adherence may be a better indicator of viral suppression than tests for viral resistance.[5]

A number of factors are thought to contribute to poor adherence by patients including pill burden, complex dosing regimens and interruptions to routine (e.g. holidays) (Table 1). Paterson et al. reported that active depression (p=0.02) and alcoholism (p=0.069) were both associated with poor adherence.[3] An additional study has implicated poor literacy skills as a significant barrier to adherence.[6]

Adherence *vs* response

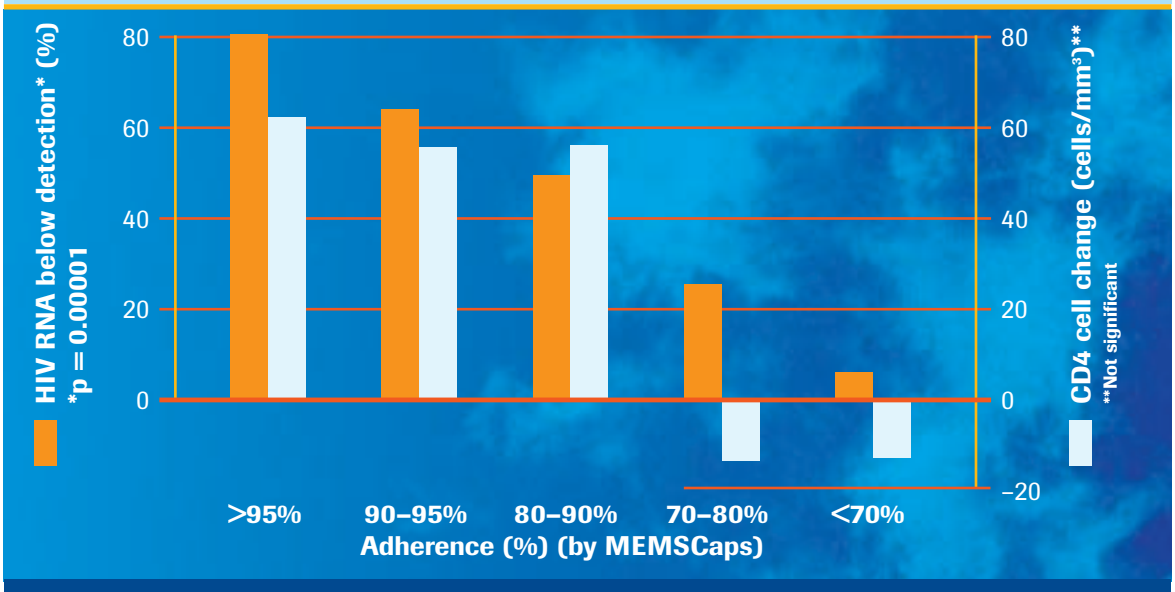

Fig. 1

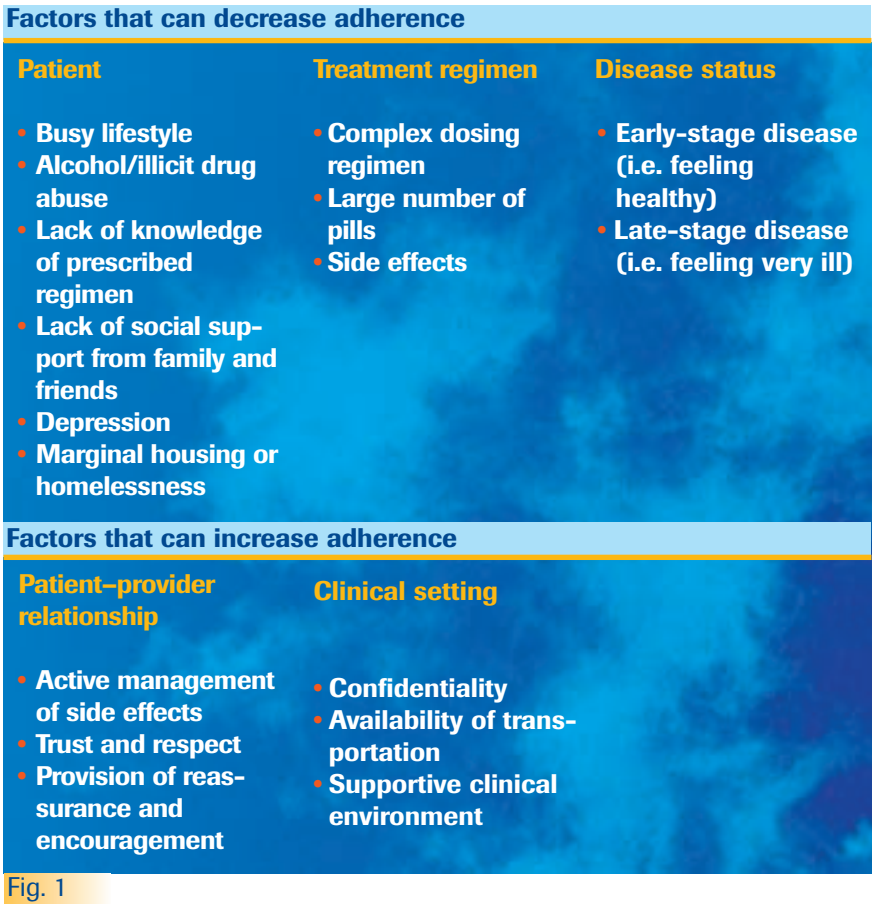

Fig. 1

As indicated in Table 1 many of the factors that can decrease adherence in the West may differ from those in the developing world. For example, many antiretroviral drugs require administration with food or fluid. A lack of adequate clean water or food supplies may lead to non-adherence. The effective management of HIV in developing countries is also limited by the lack of a basic healthcare infrastructure to deliver an un-interrupted supply of medication.

It has been shown that potentially preventable infections are the main causes of hospital morbidity and mortality among HIV-infected patients in Abidjan.[7] In these developing countries the survival of HIV-1 infected patients may be improved by the prevention of opportunistic infections with antibiotic prophylaxis.[8] Prophylaxis of opportunistic infections is advantageous due to the low cost and ease of implementation. Studies of successful adherence to conditions such as tuberculosis may identify ways in which to improve adherence to HIV regimens. In a programme run by the African Research Foundation (sponsored by Hoffmann-La Roche) the daily administration of trimethoprim-sulphamethoxazole (800 mg/1600 mg) (co-trimoxazole) prophylaxis was shown to decrease the rates of death and hospital admissions among HIV-infected, tuberculosis patients in Abidjan by half.[8] The adherence to this drug was reported to be good with 85% of patients in the co-trimoxazole group taking at least 75% of their medication. Co-trimoxazole is administered to immunocompromised patients, however in most clinical settings in Africa CD4-lymphocyte testing is unavailable. Therefore, co-trimoxazole may be administered to all HIV-infected patients with tuberculosis. This exemplifies the lack of diagnostic and testing facilities in these countries that may be a potential problem for assessing adherence to antiretroviral therapy.

In Africa, only one-third of the population has regular access to basic, essential drugs. The growing HIV/AIDS problem has critically overloaded the African health care system, which is already stressed. Therefore care for people with HIV should focus on symptomatic relief, prophylaxis of opportunistic infections, good nutrition, counseling and psychological support for patients and their families. Despite the high cost of antiretroviral drugs, their use in Africa is inevitable; although recent collaborations are seeking to reduce these costs, there is temptation that financial pressures will restrict patients to use suboptimal or intermittent doses which may lead to the development of HIV-resistant strains. Patients must be assessed for their ability to afford long-term antiretroviral therapy and to determine whether their psychological state and social environment will permit adherence to complicated regimens. Effective use of these drugs also necessitates access to laboratories where adverse reactions, development of resistance and T-cell counts can be monitored.

In summary, adherence is critical for the long-term management of HIV infection. The ideal regimen to promote adherence would be well tolerated and consist of a low pill burden with once- or twice-daily administration, no food or fluid restrictions and a favourable pharmacokinetic profile.

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Julio Montaner

Optimising Protease Inhibitor Therapy

Julio Montaner
Professor of Medicine,
University of British Columbia,
Canada

Julio Montaner received his M.D. with Honours in 1979. He completed a residency in Internal Medicine and Respiratory Medicine at the University of British Columbia, where he was Chief Resident for the Department of Medicine before joining the faculty at St Paul's Hospital/University of British Columbia (SPH/UBC) as Director of the AIDS Research Program and the Infectious Disease Clinic. He is currently Director of the Clinical Activities of the BC Centre for Excellence in HIV/AIDS and a founding co-Director of the Canadian HIV Trials Network. He held a National Health Research Scholarship of Health Canada for 10 years and received the Endowed Chair on AIDS at SPH/UBC. In 1997 he was appointed Professor of Medicine at the University of British Columbia.

Dr Montaner has published extensively about the respiratory complications of AIDS and antiretroviral therapy. He pioneered the use of adjunctive corticosteroids for AIDS-related *Pneumocystis carinii* pneumonia and contributed significantly to establishing the relationship between the development of HIV resistance to nucleoside analogues and clinical progression of the disease. Recently Dr Montaner has participated in several important international studies including the AVANTI trials, CAESAR and INCAS and has evaluated several alternative therapeutic approaches, such as Acemannan, Hydroxyurea and GP160. Currently focussing on simplification of antiretroviral therapy and the management of multiple drug resistant HIV, Dr Montaner has also initiated a new effort to characterize the long-term safety of antiretroviral therapies. Dr Montaner is Editor of the BC Centre Therapeutic Guidelines, where he is also responsible for sections of the Drug Distribution Program for the BC Centre for Excellence in HIV/AIDS. He is an organising member of several conferences, a member of the International AIDS Society (USA) Expert Panel on Antiretroviral Therapies, Treasurer of the Canadian Association for HIV Research and an elected member of the Council of the International AIDS Society.

HIV protease inhibitors (PIs) represent an effective class of antiretroviral agents for the treatment of HIV disease. However, they are associated with the disadvantages of relatively large pill burdens and complex dosing regimens, plus wide-ranging bioavailability between patients.[1] These factors can reduce adherence to treatment regimens, which can lead to poor long-term virological suppression and the development of viral resistance to treatment.

Current research aims to improve the long-term therapeutic efficacy of PI-containing regimens and, hence, encourage adherence to treatment. The main focus of this research is the improvement of PI bioavailability by co-administration with ritonavir. As a potent inhibitor of the major cytochrome P450 drug-metabolising enzyme CYP3A, ritonavir substantially increases the bioavailability of other, co-administered PIs.[2] With indinavir, nelfinavir and amprenavir the effect of ritonavir seems to be focussed predominantly on increasing the half-life of the boosted PI (Fig. 1). Whereas, with saquinavir the predominant effect seems to be on C_{max} (Fig. 2). This allows the dose and dosing frequency of the co-administered PI to be reduced and may help prevent the emergence of drug-resistant strains as suppressive plasma levels of PIs are maintained. Also, the variability in bioavailability among individuals may be reduced.

Main effect of ritonavir on indinavir, nefinavir or amprenavir – half-life boosting

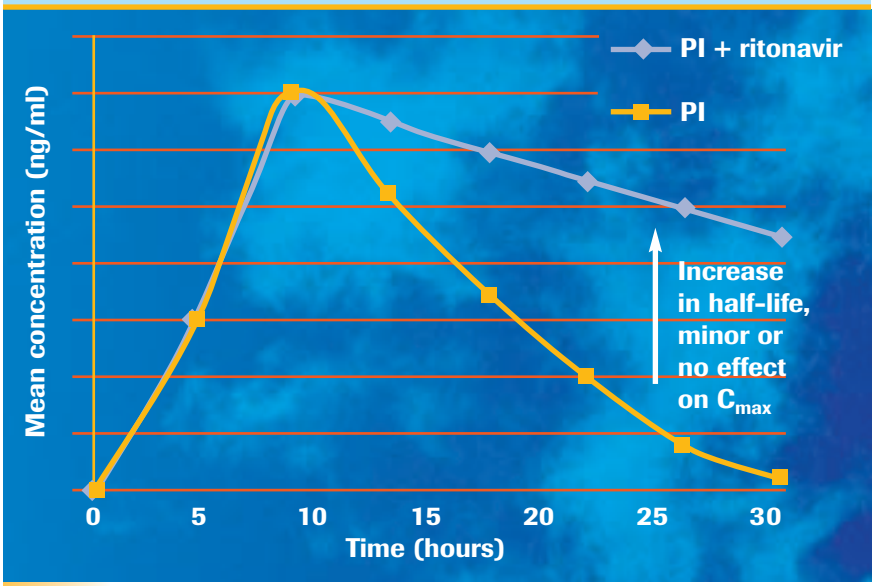

Fig. 1

For most PI/ritonavir combinations, there are no available data on relative clinical benefits. Indeed, most comparisons have been based on the results of in vitro 'modelling' studies, which can only give an estimation of the likely clinical efficacy of these regimens. Recent studies have used ratios of in vitro inhibitory drug concentration (IC_{95}) to minimum plasma concentration (C_{min}) to

Main effect of ritonavir on saquinavir (and ABT-378) – C_{max} boosting

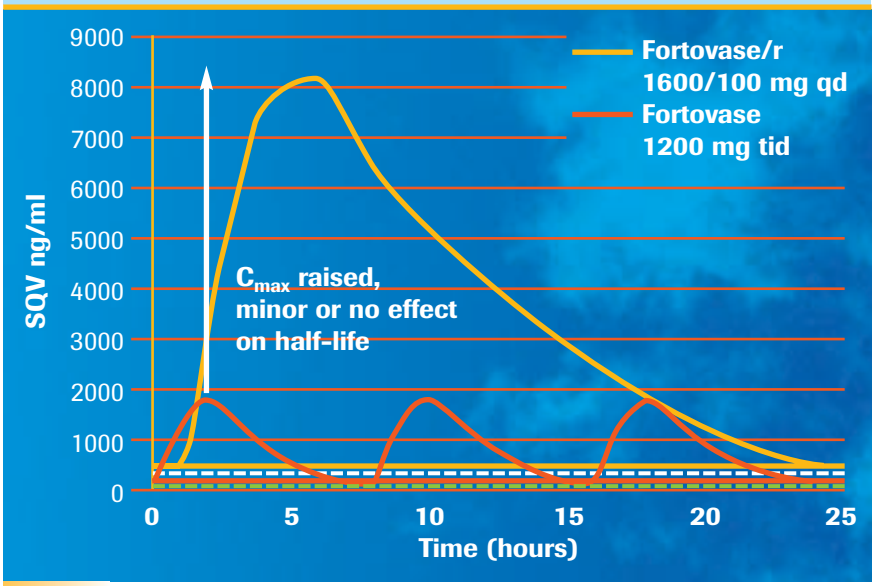

Fig. 2

predict the clinical success of boosting various PIs with ritonavir.[3] These in vitro estimates, however, do not provide a substitute for randomised clinical trials, as they fail to account for factors such as in vivo viral diversity, gastrointestinal absorption, protein binding and intracellular absorption.

Data generated in vivo indicate that the 'pharmacokinetic boosting' effect with ritonavir is largest in combination with saquinavir compared with other licensed PIs in healthy[4,5] or HIV-infected individuals[6] (subject information not provided in Nelfinavir prescribing information[7]). Pharmacokinetic and clinical data on the saquinavir/ritonavir combination have been available to physicians for several years, unlike other PI combinations. Its clinical efficacy was established using the 400/400 mg twice-daily dosing regimen,[8] but this combination is associated with relatively high levels of adverse events. As lowering the dose of ritonavir reduces the incidence of side effects,[9,21] research has focused on determining the optimal combination of reduced ritonavir dose ('mini dose') with increased saquinavir dose.[10]

For example, Saag et al.[9] showed that in healthy volunteers, ritonavir doses of 100 mg once daily are able to decrease the metabolism of saquinavir sufficiently to enable saquinavir-SGC (1600 mg) to be given once daily (Fig. 2). Trough concentrations were reported to be around five-fold higher than those in the group receiving saquinavir-SGC monotherapy at the recommended dose of 1200 mg three times daily. Furthermore, the authors reported that the tolerability of the once-daily regimen was similar to that of the standard regimen. This factor, combined with the expected efficacy and convenience of the regimen, makes it particularly suitable for use in antiretroviral-naïve or minimally pre-treated patients. For example, with indinavir/ritonavir 800/100 mg twice daily, estimates of the C_{min}/IC_{95} ratio range from 0.5 to 44.5, depending on the assumptions made in the calculations and the sources of data used. It is essential that new standards be created which allow more meaningful reporting of such data.

Various other studies have investigated the feasibility of administering saquinavir in combination with conventional doses of ritonavir as a twice-daily regimen in antiretroviral-naïve or minimally pre-treated patients[11-15] or as salvage therapy.[16-19] Recently, Piketty et al.[20] investigated the use of 'mini dose ritonavir' treatment in patients who had failed a conventional triple-drug regimen including indinavir or ritonavir. Patients received saquinavir-HGC/ritonavir 1000/100 mg twice daily plus efavirenz and nucleoside reverse transcriptase inhibitors. After 24 weeks, 71% and 45% of patients achieved a plasma viral load <500 copies/ml and <50 copies/ml, respectively. It is expected that such twice-daily saquinavir/ritonavir regimens, which generate higher saquinavir exposures, will be particularly useful in multiple anti-

Actual and predicted C_{min} & C_{max} for BID doses of saquinavir/r

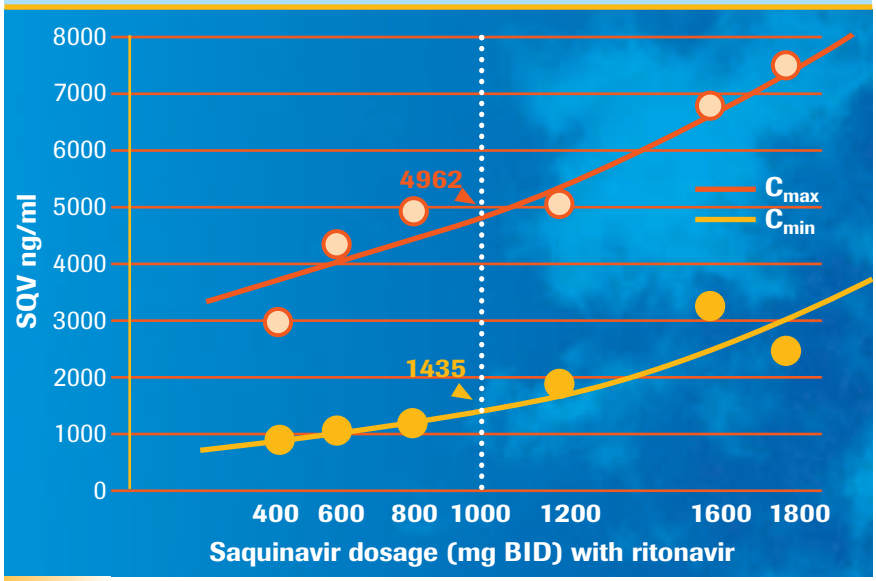

Fig. 3

Geometric mean (95% CI) $\log_{10}$ C_{min} for BID doses of saquinavir/r

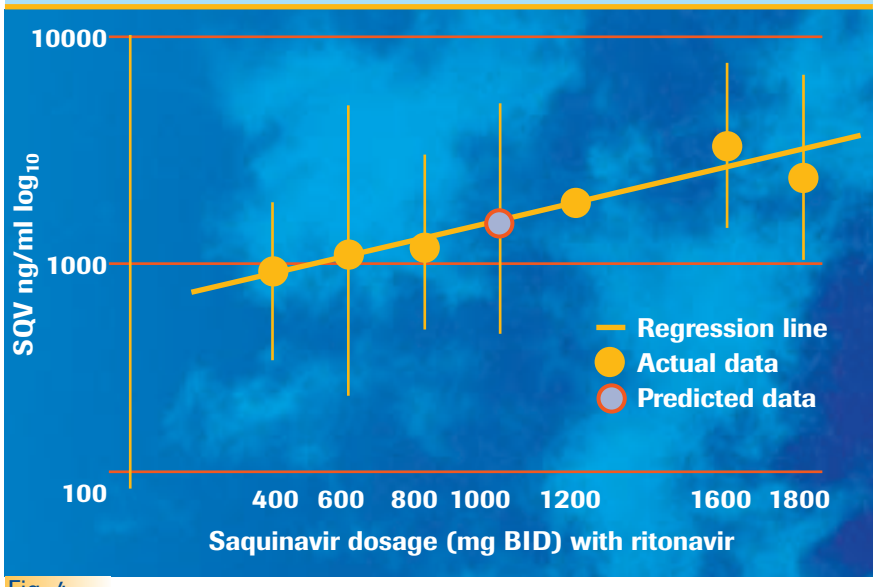

Fig. 4

retroviral-experienced patients. The very high drug exposure achieved with saquinavir/ritonavir may be necessary to re-establish virological control. Furthermore, the high drug exposure and elevated C_{min} levels when saquinavir is combined with ritonavir (Figs. 3 and 4), allow once-daily saquinavir/ritonavir dosing[9]; this is especially useful in antiretroviral-naïve and minimally pre-treated patients. Previous studies have shown that when saquinavir and non-nucleoside RTIs (NNRTIs) are combined, saquinavir C_{min} is reduced. However, saquinavir/ritonavir dosing maintains adequate saquinavir C_{min} values, even in combination with NNRTIs.[20] Thus, saquinavir/ritonavir dosing is a flexible combination that can be used effectively with other classes of antiretroviral agent.

In conclusion, 'pharmacokinetic boosting' of PIs with ritonavir has the potential to improve patient outcomes. At present, however, there have been no comparative clinical trials for the different combination regimens. Saquinavir/ritonavir is the most extensively studied combination, and its clinical efficacy is now well established. Studies are ongoing to investigate its comparative efficacy and tolerability against other combinations, and different saquinavir/ritonavir dosing regimens are being assessed further. This combination promotes flexibility in providing what is expected to be a highly potent twice-daily or once-daily regimen designed to maximize long-term adherence. Moreover, the flexibility of this combination allows it to be adapted for use in a wide range of patient populations from antiretroviral naïve to salvage.

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Nick Cammack

New Targets – New Agents to Treat HIV Infection

Nick Cammack
Department Head and HIV Disease Area Head,
Viral Diseases, Roche Discovery,
Welwyn Garden City, UK

Following a first degree in Microbiology at Leeds University and an MSc in Virology at Reading University, Nick Cammack received an Medical Research Council Postgraduate Fellowship to study the differences between vaccine and virulent envelope proteins of yellow fever virus at the London School of Hygiene and Tropical Medicine. He was awarded a PhD in 1986. He continued his intensive training in Virology during a postdoctoral position with Dr Phil Minor at the National Institute for Biological Standards and Control before joining Glaxo Group Research in 1989, where he played a key role in the development of Epivir™ for the treatment of HIV infection.
Dr Cammack joined Roche in February 1997 and has strengthened his research interests in HIV through a broad range of drug discovery and development projects.

Drug therapies for HIV infection have been aimed at stages in the HIV lifecycle where replication may be prevented by selectively targeting viral enzymes critical for virus replication and maturation. Current antiretroviral agents inhibit two viral enzymes of the HIV lifecycle, reverse transcriptase and HIV protease. The incomplete long-term virological suppression and cross-resistance amongst existing drugs, in addition to concerns regarding long-term safety and potential adverse pharmacokinetic interactions, limit the therapeutic options for extensively pre-treated patients. As an increasing number of pre-treated patients harbour multiply resistant virus, there is a need for a new generation of drugs active against these resistant strains. New drugs are needed that are aimed at established targets, as are new classes of drugs aimed at new viral targets, including immune-based therapies, that are unlikely to be cross-resistant with existing therapies.

To address the need for new therapies, two Roche discovery programmes (HIV PI and HIV RTI) have focused on developing new protease inhibitors (PI) and reverse transcriptase inhibitors (RTI). The aim of the HIV PI programme is to produce a compound with an optimal pharmacokinetic profile and activity against resistant isolates of the virus selected by the existing PIs. The activity of these novel compounds against recombinant clones of HIV is used to determine their activity against mutant viruses (Table 1). In addition to bioavailability studies in animals, a number of in vitro tests are used to simulate the pharmacokinetic profile of these compounds. These tests include the use of the Caco-2 cell line and human liver microsomes to assess the contribution of P-glycoprotein and cytochrome P-450 metabolism to intestinal and hepatic clearance respectively.

Adherence issues are also being considered with the aim of developing a compound with a convenient once- or twice-daily dosing schedule and a low tablet load. Modern informatics is used to perform a multidimensional analysis of candidate compounds to determine the best agent for further development. The HIV RTI programme has a similar focus: to identify compounds with activity against resistant virus which have improved safety profiles (i.e. no mitochondrial toxicity) and convenient dosing schedules.

Existing therapies (PIs and RTIs) target the virus once it has entered the host cell. However, potential targets for antiretroviral intervention exist prior to viral entry, as the HIV virion must first attach and subsequently fuse with the host cell membrane. The HIV attachment and fusion process consists of many defined stages that may be targeted, including the interaction of HIV with its co-receptors CXCR4 or CCR5[1] and gp41-mediated fusion (Figs 1 and 2).[2]

The CCR5 co-receptor is an attractive target, as macrophage tropic (M-tropic) strains of HIV (now known as R5 viruses), which predominate in early- and mid-stage infection and are involved in sexual transmission of the virus, use this co-receptor.[3] A research collaboration between Roche Discovery, UK, and Progenics Pharmaceuticals Inc., USA, is currently underway to discover an orally bioavailable inhibitor targeted against R5 clinical isolates. This project takes advantage of a novel cell-based assay using a natural CCR5-bear-

Profiling lead and competitor compounds against resistant viruses

	IC_{50} (nM)				
Inhibitor	Wild type	10/48/82/90	20/46/63/82/84	20/46/54/63/82/84	0/84/90
Saquinavir	5	>156	12	29	38
AG1776	12	8	43	ND	ND
BMS 232, 632	1	47	43	ND	ND
ABT-378	8	35	242	ND	ND
Ro-X	6	14	5	10	8
Ro-Y	5	14	7	11	9

Table 1

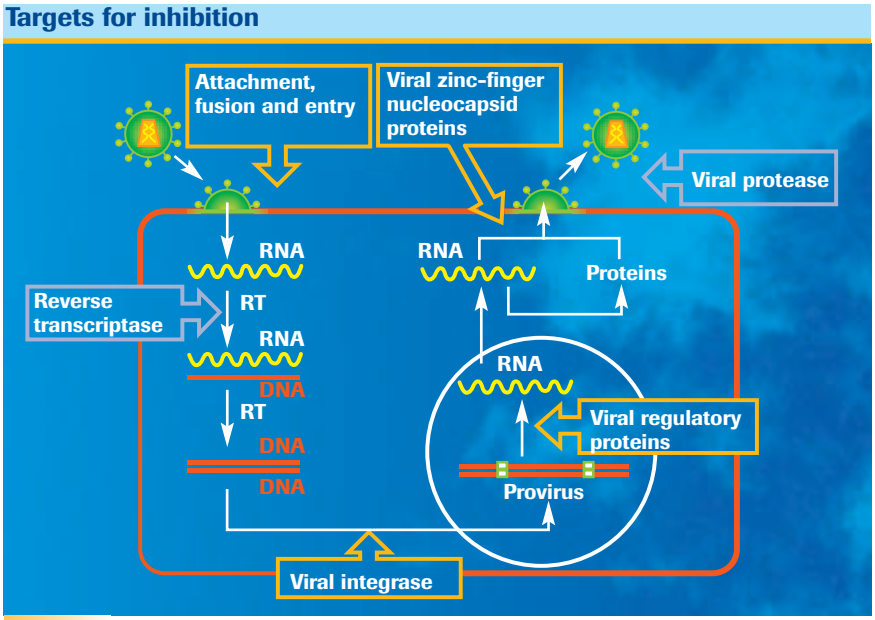

Fig. 1

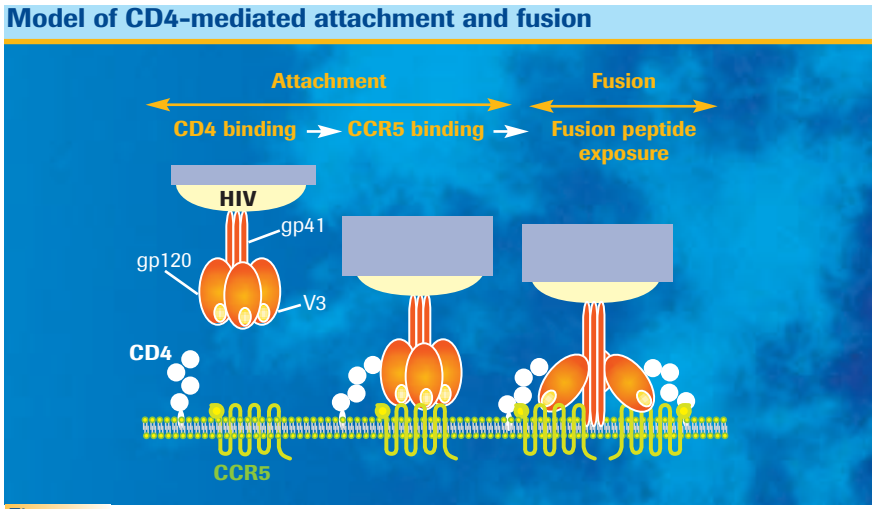

Fig. 2

ing cell line to simulate the virus infection process. Current efforts are focusing on identifying the best chemical 'hits' to advance for drug development.

In 1999 Roche and Trimeris entered into a collaboration to develop T-20 and T-1249, the first two drugs in a new class of antiretrovirals called fusion inhibitors. The fusion inhibitors T-20 and T-1249 are synthetic peptides that target gp41 and prevent the virus from fusing with the host cell by preventing the conformational change in gp41 necessary to facilitate fusion prior to virus entry (Fig. 3). T-20 and T-1249 act outside the host cell and therefore circumvent some of the potential problems associated with other antiretroviral agents such as intracellular absorption into the host cell and intracellular activation. The significant advantage of these agents is their potential activity against viruses resistant to existing therapies. Therefore, clinical studies with these agents have primarily targeted heavily pre-treated patients.

In vitro and in vivo studies have demonstrated the potent antiviral activity of T-20[4-8] when administered intravenously as monotherapy[5] or by subcutaneous injection/continuous infusion in combination with oral antiretroviral salvage therapy.[6,7] T-1249 has a similar mechanism of action to that of T-20 but binds to a different region of the HIV gp41 protein. Pre-clinical studies have demonstrated the potent inhibition of HIV infection using HIV laboratory strains and clinical isolates. These studies have also shown that T-1249 is active against zidovudine-, saquinavir- and T-20-resistant isolates of the virus. A phase I dose-escalation trial has commenced, involving up to 60 patients, to assess once-daily versus twice-daily subcutaneous administration. Clinical studies are planned or ongoing to further characterise the long-term safety and efficacy of these novel agents in combination with other anti-HIV drugs. In addition, active drug discovery programmes in collaboration with Trimeris will focus on the next generation of fusion inhibitors to identify follow-up 'peptide-like' molecules that address issues such as convenience of administration, potency, potential

immunogenicity and activity against T-20/T-1249-resistant viruses.

In conclusion, Roche aims to provide a balanced portfolio of discovery programmes in both proven and novel target classes to increase the range of therapeutic options available for the management of HIV, with an emphasis on overcoming virus resistant to current therapeutic approaches.

T-20 mechanism of action

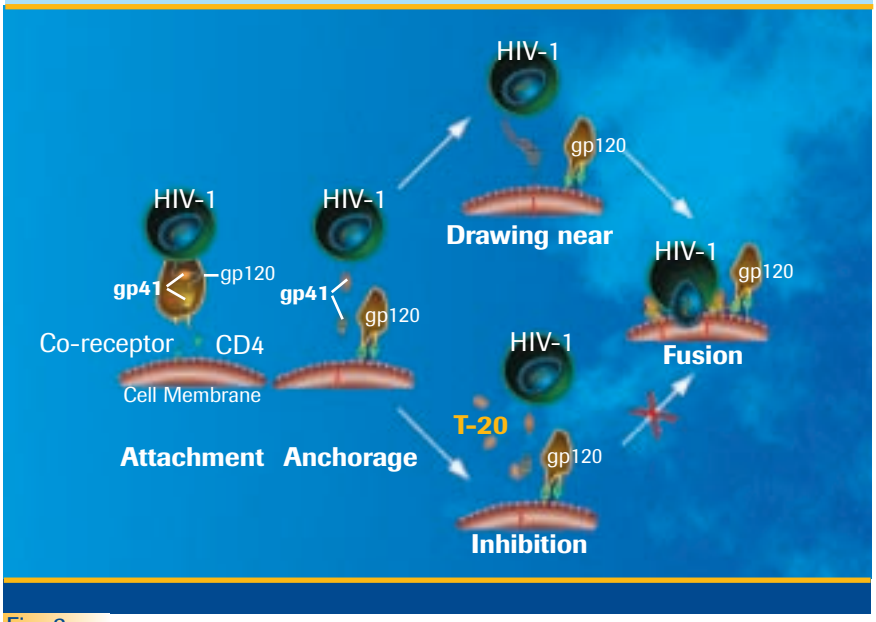

Fig. 3

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Francesca J Torriani

New Developments in the Management of HIV Co-Infections: HCV and CMV

Francesca J Torriani
Assistant Professor of Medicine,
University of California,
San Diego (UCSD), USA

Francesca J Torriani graduated with an MD degree from the Lausanne University School of Medicine, Lausanne, Switzerland, in 1985. She performed her postdoctoral training in Internal Medicine at the Centre Hospitalier Universitaire Vaudois (CHUV) in Lausanne, Switzerland. In 1989 Dr Torriani was appointed Internal Medicine Chief Resident/Attending for three years with direct supervision of more than 40 residents involved in the care of 500 to 600 acute inpatients and then in the divisions of Infectious Diseases, Cardiology and Endocrinology and in the Emergency Department and intensive and critical care units. In 1992 she took up an Infectious Diseases Research Fellowship in the Division of Infectious Diseases at UCSD.

Since 1995 Dr Torriani has been an active member of the UCSD faculty in the Division of Infectious Diseases/Department of Medicine. In March 2000 she was nominated Clinical Service Chief for the Internal Medicine Specialties and in July 2000 will also become responsible for directing the clinical research effort in hepatitis C virus at the Veterans Administration Medical Center, San Diego.

Dr Torriani is an active member of the AIDS Clinical Trials Group (Cardiovascular Focus Group, Immunology Research Agenda Committee, Protocol Chair) and the California Collaborative Treatment Group as well as the Studies of Ocular Complications in AIDS Steering Committee. She has published extensively in HIV research, often serves as advisor in clinical trial design and is a regular speaker at national and international conferences.

A number of opportunistic infections/co-infections may occur in the presence or absence of antiretroviral treatment of HIV infection. Both hepatitis C (HCV) and cytomegalovirus (CMV) infection are associated with significant morbidity in immunocompromised patients. In particular, CMV retinitis is estimated to affect 25–40% of AIDS patients.[1] In this abstract, recent progress in the treatment of two common viral infections occurring in HIV-positive individuals, hepatitis C virus and cytomegalovirus is reviewed.

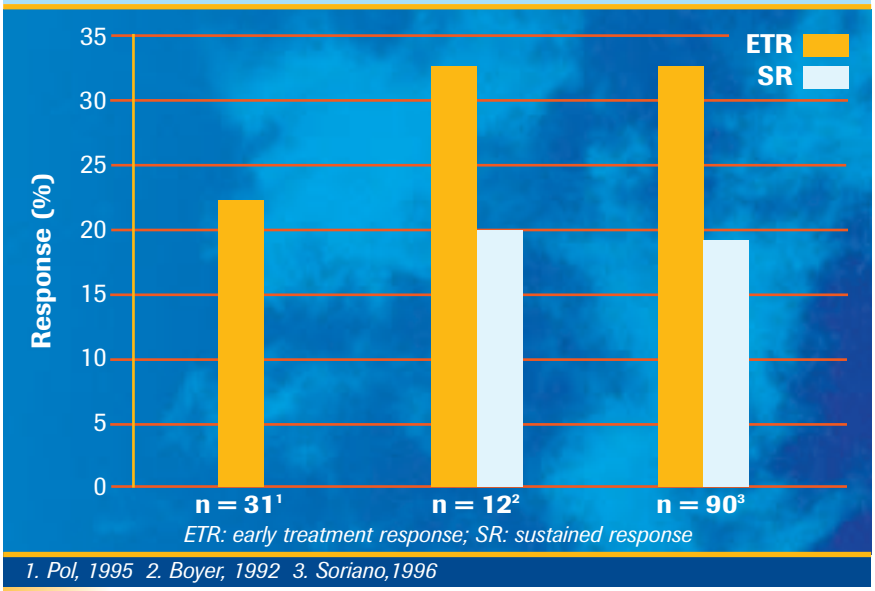
Hepatitis C virus

Infection with hepatitis C virus (HCV) is prevalent, with an estimated 170 million infected individuals world-wide.[2,3] Transmission usually occurs via contact with contaminated blood. In developed countries, this most commonly occurs by the sharing of contaminated needles for intravenous drug use, while in developing countries, nosocomial infection (due to lack of needle availability for vaccination), sharing of household products tainted with infected blood and receiving contaminated blood products are the most frequent sources of infection. Only 20% of persons infected with HCV are successful in eradicating the virus spontaneously, while up to 80% of individuals develop chronic infection. In about 20% of chronic HCV infections, progressive liver disease will lead to cirrhosis and (in a proportion of these) to hepatocellular carcinoma.

The similar routes of transmission make co-infection with HIV common, and between 30% and 50% of HIV-infected individuals are estimated to be co-infected with HCV. Several patient groups are at high risk for co-infection with HCV and HIV, with the highest incidence among injection drug users and nosocomially infected individuals (approximately 90%); among homosexual men the incidence is estimated to reach 10%. While HCV does not appear to affect the natural history of HIV, it has been clearly established that HIV infection accelerates the progression of HCV liver disease. In fact, age at HCV infection, CD4 counts and alcohol intake were independent predictors of progression to cirrhosis.[4] In patients with CD4 counts below 200 cells/mm^3, cirrhosis occurred 20 years after HCV infection, compared with 36 years after infection in patients with CD4 counts above 200 and a daily alcohol intake of less than 5 drinks.

In addition to the increased morbidity and mortality secondary to HIV co-infection, moderate to severe hepatic toxicity has been observed in a proportion of HCV co-infected individuals soon after initiation of potent antiretroviral therapies. This effect is thought to reflect an immune recov-

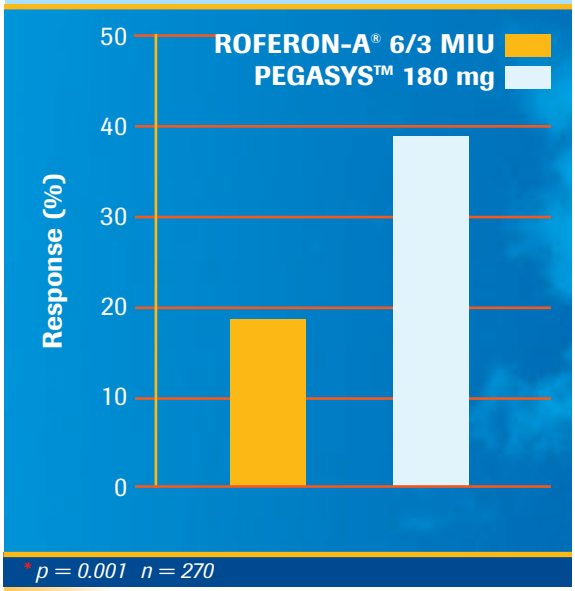
Response to IFN–α in HCV/HIV co–infection



1. Pol, 1995 2. Boyer, 1992 3. Soriano,1996

Fig. 1

Sustained virologic response at week 72 (ITT)



* *p = 0.001 n = 270*

Fig. 2

ery disease, secondary to restoration of immune function, and similar inflammatory reactions have been observed with other co-infections including *Mycobacterium* and cytomegalovirus. This inflammatory response has serious implications when choosing an effective and durable antiretroviral regimen. However, immune reconstitution following the introduction of HAART leads to the control of HCV replication.[5,6]

In the past year these findings have prompted HIV specialists to consider treating HCV infection in spite of the risk of treatment limiting toxicities, the possibility of a lower response rate in HIV co-infection and the decrease in quality of life.

In the treatment of chronic HCV infection uncomplicated by HIV co-infection, a combination of IFN alpha (3MU three times daily) with oral ribavirin (1000–1200 mg/daily) significantly improves sustained response rates compared with IFN monotherapy both in naïve patients (35–45% of sustained response vs 13% on IFN monotherapy) and 49% vs 5% on IFN alone in relapsed patients (of sustained response).[7] Dual therapy has therefore become the standard treatment for naïve and relapsed patients.[8,9]

Despite the improved response obtained with combination therapy, more than half of the patients with chronic hepatitis C do not eradicate the infection with currently available drugs. Treatment failure is high for patients infected with genotype 1b, in those with a high HCV viral load and/or liver cirrhosis. New formulations of interferons and new types of combinations, allowing for slower elimination, constant levels and thus stable antiviral pressure, are currently under evaluation for these patients.

Promising results have been obtained with pegylated IFN alpha 2a (PEGASYS™) a once-weekly preparation which has a greatly improved pharmacokinetic profile compared to conventional IFN given tiw. Available data indicate that a 12-month course of PEGASYS™ alone is associated with sustained response rates comparable to those of standard combination therapy.[10] Preliminary results from a small pilot safety trial suggest that the virological response can be optimised by a combination of PEGASYS™ and ribavirin: plasma HCV RNA was below the limits of detection in 80% of patients after 24 weeks of treatment with similar adverse event rates.[11]

In HIV/HCV co-infection, small non-randomised trials have shown that combination therapy with interferon alpha-2 and ribavirin is superior to interferon alone, with plasma HCV RNA below the limits of detection in up to 50% of patients at 12 weeks. The effects of pegylated interferon on plasma HIV RNA have not been studied to date, but it is possible that an antiretroviral effect could be observed. In studies to date, PEGASYS™ produces sustained response rates that are about 2- to 3-fold better than those for standard interferon alpha-2a. Therefore, as in singly infected patients, optimal treatment for the HCV/HIV co-infected population may be combination therapy with pegylated interferon and ribavirin.

To test this hypothesis a large international trial in HCV/HIV co-infected patients on antiretroviral therapy is currently being planned to test the safety and efficacy of PEGASYS™. Participants will be randomised to one of three treatment arms: 1) PEGASYS™ 180 µg once weekly; 2) PEGASYS™ 180 µg once weekly plus daily oral ribavirin 800 mg/day; 3) interferon alfa 3 MU three times weekly plus daily oral ribavirin 800 mg/day. Clearance of HCV viremia will be assessed at 48 weeks (end of treatment response) and at six months after completion of treatment.

These studies suggest that pegylated interferon may offer an alternative to standard and combination therapies for HCV co-infected patients.

Cytomegalovirus

Cytomegalovirus (CMV) infection causes significant morbidity in immunocompromised HIV-positive patients. Up to 40% of HIV-positive patients with CD4 counts below 50 cells/mm^3 will develop CMV end-organ disease, 90% of which will manifest as CMV retinitis in the absence of prophylaxis.[1] Once end-organ disease is established, morbidity and mortality from this infection are considerable.

Ganciclovir (GCV) is commonly used in the treatment and prevention of CMV disease. However, the use of oral GCV is limited by its poor bioavailability (6–9%) and saturable absorption rates,[12] and accordingly GCV is usually administered intravenously (IV).

Valganciclovir (VGCV) is an orally bioavailable (60%) prodrug that is rapidly hydrolysed to the active nucleoside analogue GCV.[13]

The safety and efficacy of VGCV (900 mg bid for 3 weeks, followed by 900 mg qd), was compared with that of IV GCV (5 mg/kg bid for 3 weeks followed by 5 mg/kg daily qd) as induction treatment in 160 HIV-infected patients with newly diagnosed CMV retinitis.[14] The primary efficacy endpoint was CMV retinitis progression, determined on masked review of retinal photographs as opposed to funduscopic examination within 4 weeks of initiating treatment. Secondary endpoints included the achievement of a prospectively defined 'satisfactory response' to induction therapy and the time to progression of CMV retinitis.

The two treatment groups were balanced for initial CD4 cell count and use of potent antiretroviral therapy. An equivalent number (7) and proportion (10%) in each group progressed during the first 4

CMV retinitis progression by week 4 (photography – efficacy analysis)

	IV Ganciclovir	Valganciclovir
	n = 73	n = 73
Progression	7 (10%)	7 (10%)
No progression	63 (86%)	64 (88%)
Unevaluable*	3 (4%)	2 (3%)
Type of progression		
Movement	6	7
New lesion	1	

* *Unevaluable = 'missing', 'cannot grade' or 'no CMV at baseline'*

Table 1

weeks. Seventy-seven percent and 72% of evaluable patients in the IV GCV and VGCV groups respectively achieved the prospectively defined 'satisfactory' response to induction therapy at 4 weeks. Median (mean) times to first CMV retinitis progression were 120 (210) days in the IV GCV induction group and 198 (226) days in the VGCV induction group. Adverse event frequency and severity were similar among treatment groups.

In conclusion, VGCV may provide a convenient and effective alternative to IV GCV for the treatment and prevention of end-organ CMV disease.

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F. Hoffmann-La Roche Ltd
Basel, Switzerland

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