



Highlights from the latest  
papers in HIV research

# RESEARCH HIGHLIGHTS

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## Macrophage-targeted nanocarriers for anti-HIV therapy

Mansoor M Amiji

Evaluation of: Wan L, Pooyan S, Hu P, Leibowitz MJ, Stein S, Sinko PJ: Peritoneal macrophage uptake, pharmacokinetics and biodistribution of macrophage-targeted PEG-fMLF (I-formyl-methionyl-leucyl-phenylalanine) nanocarriers for improving HIV drug delivery. *Pharm. Res.* 24(11), 2110–2119 (2007).

Despite significant progress in understanding the disease pathology and developments in preventive and therapeutic approaches over the last 25 years, HIV/AIDS continues to affect millions of individuals, especially in sub-Saharan Africa. One of the most challenging aspects of clinical HIV therapy, even with the antiretroviral cocktail, is the ability of the virus to sequester and isolate in select cellular and anatomical sites in the body. These so-called 'HIV reservoirs' can maintain viable latent viral particles despite aggressive antiretroviral therapy showing undetectable viral load in the systemic circulation. Peripheral phagocytic cells including monocytes and macrophages have been identified as important cellular HIV reservoirs. The phagocytic cells act as 'shuttles' to transport viral load to anatomical sites including the CNS, lymphatic system, lungs and the urinogenital tract. The cellular and anatomical HIV reservoirs can also significantly contribute to resistance development.

We and others have proposed that nanotechnology-based drug delivery systems can significantly influence antiretroviral therapy by specific localization to the cellular and anatomical viral reservoir sites upon systemic administration. Based on the physicochemical and biological properties of engineered nanoparticle-based delivery systems, a wide vari-

ety of single and multiple therapeutic payloads can be encapsulated and the biodistribution and pharmacokinetic profiles of the drug(s) are influenced by the nanocarrier system. Labile molecules are protected from degradation in the systemic circulation or upon cellular entry. Lastly, nanocarrier systems can be designed preferentially to deliver the payload inside the phagocytic cells or at specific anatomical site for optimum therapeutic outcomes.

In the article by Wan *et al.*, the authors propose to have developed formyl methionine-leucine-phenylalanine (fMLF) peptide-targeted nanocarrier systems for macrophage-directed anti-HIV therapy. Multiple peptide functionalities were attached through a poly(ethylene glycol) (PEG) linker. The peptide-modified PEG derivatives were incubated with murine macrophage and the preferential receptor-mediated association was examined. In addition, the biodistribution and pharmacokinetic profile of the constructs was examined *in vivo* in Sprague–Dawley rats. The results showed that fMLF-modified PEG derivatives (5K and 20K) accumulated to a greater degree in liver, kidneys, lung and spleen than the corresponding unmodified PEG. The authors concluded that the enhanced uptake of the peptide-PEG conjugates in these organs was due to preferential association with macrophages.

## Cardiovascular implications of HIV treatment in pediatric patients

Jintanat Ananworanich

McComsey GA, O'Riordan M, Hazen SL et al.: Increased carotid intima media thickness and cardiac biomarkers in HIV infected children. *AIDS* 21(8), 921–927 (2007).

Life used to be simple before the Strategy for Management of Antiretroviral Therapy (SMART) Trial announced its results in late 2005 that instead of decreasing the risk, stopping antiretroviral therapy (ART) caused more cardiovascular events [1]. We know that long-term antiretrovirals, particularly ritonavir-boosted protease inhibitors, lead to metabolic syndrome and coronary heart disease (CHD) [2,3]. But why stopping ART causes CHD is unknown. It is postulated that certain proinflammatory markers rise with HIV viremia that in turn trigger CHD. HIV viremia correlated with levels of endothelial markers, vascular cell adhesion molecules, von Willebrand factors and D-dimer [4]. Carotid intima media thickness (IMT) in adults was related to time on ART, and HIV infection, inflammation and metabolic parameters [5]. Studies in children are limited.

McComsey et al. [6], performed carotid ultrasound on, and measured metabolic and cardiovascular biomarkers in 31 children with HIV infection and 31 controls that were matched for age, gender, race and body mass index. Children with CHD risks (hypertension, diabetes, family history of premature CVD and smoking) were excluded. Overall, the children had a median age of 9 years (range: 2–21 years), 65% were females and 70% were African–Americans. All were on ARV and almost all had well controlled HIV. Half were on protease inhibitors and stavudine was used in 35%. Compared with their controls, the HIV group had higher systolic blood pressure, waist–hip ratio, serum cholesterol and triglycerides and insulin resistance. HIV children had significantly higher

IMT than the controls as well as higher myeloperoxidase and a trend towards a higher C-reactive protein while the homocysteine levels were lower. These biomarkers did not correlate with IMT. The only predictor for IMT was the duration of ART.

This study suggests that compared with their matched controls, HIV-infected children on ART display the typical adult risk factors for CHD. The long-term effect is unknown. Both HIV and ART likely play a role in the pathogenesis of CHD. Early initiation of ART with a metabolic-friendly drug regimen may be the key to lowering CHD risk together with lifestyle modification. Longitudinal studies in children before and after ART are necessary to understand CHD risk.

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## Reducing resistance in the prevention of mother-to-child transmission of HIV

Elise Arrivé

Evaluation of: Chi B, Sinkala M, Mbewe F et al.: Single-dose tenofovir and emtricitabine for reduction of viral resistance to non-nucleoside reverse transcriptase inhibitor drugs in women given intrapartum nevirapine for perinatal HIV prevention: an open-label randomised trial. *Lancet* (2007) (Epub ahead of print)

Single-dose nevirapine administrated to the mother at the beginning of labor and to the neonate is the main regimen used to prevent mother-to-child transmission of HIV-1 in many resource-limited settings. However, it results in viral

resistance mutations with an estimated frequency of 36% in women (+/- also receiving also antenatal short-course zidovudine prophylaxis) and 52% in children, to the class of non-nucleosidic reverse transcriptase inhibitor (NNRTI) drugs, due to cross resistance [1]. These mutations have been shown to impair the virological response of subsequent therapy with antiretroviral combinations that include a NNRTI in women initiating such treatment 6 months or less after nevirapine exposure and in children, infected despite the intervention [2,3]. To reduce the resistance occurrence, postpartum administration of lamivudine and ziduvudine during 3 to 7 days is currently

recommended, resulting in a more complex intervention [4]. A strategy consisting of one intrapartum single dose of 300 mg tenofovir disoproxil fumarate and 200 mg emtricitabine in addition to antenatal short-course zidovudine and intrapartum nevirapine was thus evaluated in the context of a randomized trial conducted in Zambia. There were a total of 399 pregnant women, not eligible for antiretroviral therapy, randomized to receive or not to receive the intervention, in addition to standard antiretroviral prophylaxis. The primary outcome was NNRTI viral resistance mutations in women at 6 weeks postpartum. Women given the intervention were 53% less likely than controls to have NNRTI resistance mutation at 6 weeks postpartum (20/173 [12%] vs 41/166 [25%]; risk ratio: 0.47, 95% confidence interval: 0.29–0.76). Postpartum anemia was the most common serious adverse event in mothers and septicemia and pneumonia were those in infants. These events did not differ between groups and none were judged to be caused by the intervention. It is not known whether these findings can be extrapolated to pregnant women who cannot receive antiretroviral therapy while they are eligible to, or to women who

did not receive antenatal zidovudine or to children. However, this regimen, while not improving PMTCT efficacy compared with standard antiretroviral prophylaxis represents a feasible approach to reducing maternal NNRTI resistance.

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## A new class of HIV inhibitors maturing in the pipeline

Nicolas Sluis-Cremer

Evaluation of: Salzwedel K, Martin DE, Sakalian M: Maturation inhibitors: a new therapeutic class targets the virus structure. *AIDS Rev.* 9, 162–172 (2007).

2007 has been a significant year in the development of novel antiretroviral inhibitors that target HIV-1 replication. Following the discovery in 1983 that HIV was the infectious agent responsible for AIDS, 22 drugs belonging to only one of four distinct therapeutic classes of inhibitors had been approved by the US Food and Drug Administration for the treatment of HIV-1 infection. These included the nucleoside reverse transcriptase inhibitors, the protease inhibitors, the nonnucleoside reverse transcriptase inhibitors and a fusion inhibitor that were first introduced into therapy in 1987 (zidovudine), 1995 (saquinavir), 1996 (nevirapine) and 2003 ( enfuvirtide), respectively. This year, however, drugs from two new classes of HIV inhibitors were approved for treatment-experienced patients who have strains that are resistant to multiple antiretroviral drugs. These include the integrase inhibitor raltegravir and the CCR5 chemokine co-receptor antagonist maraviroc. Despite the hope that raltegravir and maraviroc bring to the therapy table, there is still a continuing need for new drug options to overcome problems with tolerability and the emergence of viral resistance. Enter the maturation inhibitor bevirimat, which is currently being developed by Panacos Pharmaceuticals, and is elegantly reviewed by Salzwedel *et al.* in *AIDS Reviews* [1].

Bevirimat (or PA-457) is a natural product derived from *Syzygium claviglorum* that has been found to specifically block a late step in the processing of the HIV Gag protein [2,3]. The clinical efficacy of bevirimat has been demonstrated in two small clinical trials [4,5]. In the first, a single-dose, double-blind, placebo-controlled Phase I/II monotherapy study was carried out in which different doses of bevirimat was administered as an oral solution to HIV-positive patients [4]. This study showed a statistically significant, dose-dependent reduction in mean viral load in the bevirimat group as compared with the placebo group. Bevirimat was then assessed in a multiple-dose, randomized, double-blind, placebo-controlled Phase IIa monotherapy study in which the inhibitor was again given once daily for 10 days as an oral solution to HIV-positive patients [5]. At the primary end point of the study, a statistically significant reduction in median viral load was observed for the two highest dose groups (100 and 200 mg), with median reductions in viral load of -0.48 and -1.03 log for the two dose groups, respectively. A Phase IIb monotherapy study of bevirimat in a solid tablet form was then initiated in 2006 in HIV-positive patients, in which it was added to the patients existing background regimen that had failed. However, at the primary end point of the trial it was discovered that plasma inhibitor concentrations were much lower than expected, and as a result the tablet formulation was discontinued. Despite this setback, the Phase IIb study of bevirimat is still ongoing using the original liquid formulation, with development of an optimized formulation for Phase III studies continuing in parallel.

The clinical data briefly described above serves as proof-of-principle that maturation inhibitors, such as bevirimat or second generations thereof, represent an attractive class of inhibitors for development of anti-HIV therapeutics. In this

regard, we should all hope that this class of inhibitors will continue to mature and that, like raltegravir and maraviroc, they will become available for HIV treatment in the near future.

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## Metabolic effects of protease inhibitor-sparing antiretroviral regimens in treatment-naïve subjects

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Evaluation of: Shikuma CM, Yang Y, Glesby MJ *et al.*: Metabolic effects of protease inhibitor-sparing antiretroviral regimens given as initial treatment of HIV-1 infection (AIDS Clinical Trials Group Study A5095). *J. Acquir. Immune Defic. Syndr.* 44, 540–550 (2007).

Dyslipidemia, insulin resistance and body composition changes are common complications in HIV-infected subjects on potent antiretroviral (ARV) therapy. The likely long-term metabolic consequences of ARV medications are important factors in selecting the optimal initial regimen for these patients. The ACTG study 5095 was a randomized, placebo-controlled, double-blind trial designed to compare the metabolic effects of three protease inhibitor-sparing regimens consisting of zidovudine/lamivudine/abacavir (ZDV/3TC/ABC), zidovudine/lamivudine (ZDV/3TC) plus efavirenz (EFV), and ZDV/3TC/ABC+EFV in treatment-naïve subjects [1]. The ZDV/3TC/ABC arm was discontinued early because of virologic inferiority [2]. Subjects on these arms with HIV-RNA less than 200 copies/ml received intensification with Efavirenz or tenofovir. Overall, there were 857 subjects with suitable data for metabolic analyses. Over the first 24 weeks, all initial arms of the study, irrespective of the inclusion of Efavirenz, demonstrated a modest increase in glucose and insulin resistance (HOMA-IR). The similarity of

changes for glucose and insulin resistance observed among the arms suggest that disorders of glucose metabolism may be related to the nucleoside backbone rather than to the drug influence of Efv.

So far, the bulk of evidence is consistent with the notion that protease inhibitors are primarily responsible for glucose metabolism abnormalities in ARV-treated HIV-infected patients [3]. The data observed in this study support newer evidence suggesting that cumulative exposure to nucleoside analogues is associated with insulin resistance and increased incidence of diabetes mellitus [4,5].

From week 0 to week 96, the levels of triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) showed a modest increase in all arms of the study. The inclusion of Efv was associated with a higher lipid elevation compared with the use of the nucleoside backbone alone. Lipid changes of all study participants compared with the NHANES general population norms showed that LDL-C levels increased but remained lower, triglyceride level was higher at baseline and even higher at the end of 96 weeks, and HDL-C improved but remained lower. The data observed in this study suggest that the lipid dysregulation of concern in HIV-infected patients treated with protease inhibitor-sparing regimens are increased rates of hypertriglyceridemia and continued low (also improved) HDL-C. Further studies are needed to clarify pathogenesis of dyslipidemia observed in HIV-infected patients treated with ARV as well as efficacy of intervention strategies.

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