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Antiretroviral nanoparticles: the future is now: authors' response to editorial comments

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We appreciate the insights and comments made by Martínez and Blanco [1] in their editorial accompaniment to our recent article entitled 'Long-acting three-drug combination anti-HIV nanoparticles enhance drug exposure in primate plasma and cells within lymph nodes and blood' [2]. We fully agree that development of long-acting anti-HIV therapies utilizing the enormous potential of lipid nanoparticles (LNPs) will be a milestone in the fight to eradicate HIV. Martínez and Blanco [1] highlighted outstanding results we achieved in developing long-acting three-drug combination LNPs that produced elevated drug levels in blood plasma and cells that remained detectable for 7 days in primates. They also raised some important issues that require further clarification.

Although loading or incorporation efficiency of the three drugs in our LNP formulation are not identical, all provide plasma and drug levels that extend for at least 7 days. In our multidrug LNPs, two hydrophobic drugs, lopinavir and ritonavir, were predominantly associated with LNPs, and about 12% of tenofovir was bound to LNPs in the admixture. Yet, to our surprise, the 12% LNP-associated tenofovir resulted in over 90% of total drug exposure occurring between 8 and 168 h (from days 1 to 7), whereas only 8% of drug exposure occurred after 8 h with free drug [2]. These data suggest an additional fraction of tenofovir-LNP association or interaction which has yet to be elucidated. It is possible that the degree of bound and unbound tenofovir characterized with equilibrium dialysis method may not reflect how tenofovir associates or dissociates from the LNP drug admixture formulation in primates. Regardless, the combination of hydrophobic and hydrophilic drugs demonstrates the versatility of the lipid nanoparticle admixture platform, which we are now evaluating with other anti-HIV drug combinations with proven clinical effectiveness.

A relatively high dose of drug combination LNPs was administered to show safety and ensure sufficient plasma and cellular drug concentrations were available for detailed pharmacokinetic analysis. The tested dose should not be considered as a recommended therapeutic dose. Additional studies including dose escalation and multidose studies are needed to develop a dose-range likely to be well tolerated and effective in humans. However, it is important to note that these HIV drugs, targeted to HIV enzymes, have been shown to delineate HIV infected and uninfected host cells by 100-fold or more. Thus, while the safety

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Conflicts of interest

There are no conflicts of interest.

of a high peak in plasma tenofovir concentration shortly after subcutaneous injection of the anti-HIV nanoparticle formulation (presumably on a weekly basis) needs consideration, we believe it could and should be addressed with formulation optimization and dose–response studies.

The editorial commentary also raised the concern that patients may be resistant to injectable medications, citing the HIV patient experience with enfuvirtide, a twice daily and chronic injection therapy. However, a recent survey indicates a high degree of patient interest in weekly administered injectable antiretroviral therapy [3]. In addition to physician and patient preference, a key factor contributing to enfuvirtide's low clinical use is related to the high rate of injection site reactions [4]. Multiple HIV drugs associated with LNPs constructed with biocompatible lipid excipients not only reduced the risk of injection site reaction, but also provided feasibility for weekly dosing (as opposed to twice daily dosing with enfuvirtide). Clinical potential of this long acting anti-HIV drug combination strategy is highlighted in a recent NIH Funding Opportunity Announcement (FOA number RFA-AI-14-008) soliciting for development of sustained release strategies, including injectable dosage forms for the treatment of HIV. The clinical feasibility of weekly to monthly self-administered subcutaneous injectable monoclonal antibody therapeutics has already been demonstrated with other diseases, such as rheumatoid arthritis [5].

We appreciate Martínez and Blanco [1] highlighting our achievements and raising these important points for discussion. Although it may be desirable to have equal loading efficiencies of all drugs in a combination nanoparticle, our anti-HIV nanoparticle formulation in its current form is sufficient to provide long lasting intracellular lopinavir, ritonavir, and tenofovir levels in lymph nodes and in plasma for 7 days. Given the safety profile of these anti-HIV drugs, and our understanding of patient preferences, a weekly dosing schedule is likely to be well tolerated and acceptable for patients. Further innovation and critical analysis is needed to capitalize on the enormous potential of antiretroviral nanoparticles. Despite the long road ahead, nanoparticle-based therapeutics may provide the gateway to finding a cure for HIV.

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