HIV treatment

We have come a long way from when the first cases of HIV infection were reported, towards prevention, management, and treatment of HIV. According to the HIV Surveillance Report published by the Centre for Disease Control in November 2017, the number of new annual HIV cases has reduced by nearly 18% in a span of six years from 2008 to 2014.

Today, people infected with HIV can live normal, longer, and healthy lives thanks to the various forms of treatments modes available today. One such form of treatment is the HIV antiretroviral therapy (Palella, F. J. et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N. Engl. J. Med. 338, 853–860 (1998). Antiretroviral drugs help manage HIV in infected individuals by hindering the duplication process of the HIV virus. Various antiretroviral drugs are used in a combination with each other to accomplish maximum suppression of the HIV virus. Between 1996 and 2010, life expectancy in 20-year-old patients starting ART increased by about 9 years in women and 10 years in men.

Despite the availability of novel treatments like ART to manage HIV, studies have shown that nonadherence to antiretroviral therapy by individuals infected by the HIV virus can significantly affect the positive outcome of antiretroviral therapy (Mills, E. J. et al. Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. JAMA 296, 679–690 (2006), and, Lima, V. D. et al. The combined effect of modern highly active antiretroviral therapy regimens and adherence on mortality over time. J. Acquir. Immune Defic. Syndr. 50, 529–536 (2009)). Factors like high cost and low accessibility or availability of drugs, unforeseen personal situations, and societal acceptance of HIV patients can cause nonadherence to antiretroviral therapy. Patients have also been known to adhere to their therapy schedule during the early sessions of the therapy. As therapy progresses, patients become less adherent. Chesney MA et al. (2000) reports the Adult AIDS Clinical Trials Group (AACTG) Adherence Instruments to obtain data about drug adherence. The AACTG Adherence Instruments consists of two sets of questionnaires each about 10 minutes long. 75 HIV positive individuals undergoing ART participated in this study at 10 AACTG locations across the USA. The study reported "11% of patients reported missing at least one dose the day before the interview, and 17% reported missing at least one dose during the two days prior. The most common reasons for missing medications included 'simply forgot' (66%) and a number of factors often associated with improved health, including being busy (53%), away from home (57%) and changes in routine (51%)."

Thus, stemmed the need to develop a stable drug delivery system that allowed long-term, consistent, and timely delivery of antiretroviral drugs with HIV patients (Fasano, A. Innovative strategies for the oral delivery of drugs and peptides. Trends Biotechnol. 16, 152–157 (1998). Such a drug delivery system would greatly alleviate the stress experienced by patients who are on a daily drug consumption schedule by reducing the chances of patients forgetting to consume the antiretroviral drugs prescribed to them and patients having to keep a track of their drug consumption.

An oral antiretroviral drug delivery system, while efficient and used widely, cannot tolerate the low pH of stomach acids for long times (Mojaverian, P. Evaluation of gastrointestinal pH and

gastric residence time via the Heidelberg radiotelemetry capsule: pharmaceutical application. Drug. Dev. Res. 38, 73–85 (1996). A.R. Kirtane et al. (2018) developed and studied a weekly, oral HIV drug delivery model in a pig. This "modular drug delivery system which folds and recoils, enabling oral dosing, which retains its integrity in the stomach for prolonged residence, and which can be loaded with up to six different drug formulations resulting in desired pharmacokinetics" and "is capable of delivering three highly-potent antiretrovirals— dolutegravir (DTG), raltegravir (CAB) and rilpivirine (RPV)— for a week after a single dose in a swine model."

The antiretroviral drug delivery system studied in A.R. Kirtane et al. (2018) is a start shaped model. This model has "six arms", capable of delivering six different drugs at desired rates, connected by a "central core" (Fig. 1a).

The six arms in this model, connected at the core, fold upon each other. This system is then enclosed within a shell to form an orally ingestible capsule. Once the capsule comes in contact with stomach acids, the shell disintegrates, and the six arms unfold into a star shape and begin releasing the drug loaded onto each arm.

The materials used for constructing the arms of the model had to have "rigidity for gastric residence and adjustability of drug release". A.R. Kirtane et al. (2018) reports using various "mechanical tests" whose results yielded "a thermoplastic polyurethane Elastollan®R6000" that "displayed an ultimate flexural stress."

The early drug models consisted of just one type of polymer constituting the central core as well as the arms of the model. Thus, this one polymer was responsible for providing rigidity to the structure as well as dispense drugs. This became a problem while designing a model that could release drugs at varying rates because the rigidity of the model was compromised when the polymer configuration was altered (New drug capsule may allow weekly HIV treatment Replacing daily pills with a weekly regimen could help patients stick to their dosing schedule, Anne Trafton, MIT News Office January 9, 2018 http://news.mit.edu/2018/new-drug-capsule-may-allow-weekly-hiv-treatment-0109).

A.R. Kirtane et al. (2018) reports utilizing "tensile testing" methods to select polymers for the construction of the central cores. "A thermoplastic polyurethane Elastollan®1185" was selected because it had an "elastic modulus of ~27.7 ± 2.2 MPa."

Ultimately the structural polymer Elastollan®R6000 and elastomeric core polymer Elastollan®1185 were selected for construction of the model because they demonstrated "the highest value for maximum stress (~12.1 ± 1.2 MPa) (n = 3)" and tolerated gastric acid without disintegration for up to 7 days.

A.R. Kirtane et al. (2018) tested antiretroviral drugs "DTG (an integrase inhibitor), CAB (an integrase inhibitor), RPV (a non-nucleoside reverse transcriptase inhibitor), and tenofovir alafenamide (TAF, a nucleotide reverse transcription inhibitor, and pro-drug of tenofovir)" "at acidic pH (for gastric release) and high temperatures (for manufacturing at elevated temperatures)." low pH were = 50 mg/day, allowing us to load sufficient mass onto the structure for weekly dosing. To further determine if these drugs were suitable for use in our system, we tested their stability Unless indicated otherwise, all experiments described in this manuscript were performed with the salt forms of the drugs. Only drugs DTG, CAB and RPV did not disintegrate in low pH conditions and remained stable after being heated to 150°C for 2 hours.

These drugs were thus, administered onto the polymer arms of the model.

Both the drugs DTG and RPV had a detectable plasma concentration within 15 minutes of administration but could not be detected after day 2 while CAB could not be detected on and after day 3.

Future directions:

The drug delivery system developed in this study can deliver three antiretrovirals DTG, RPV, and CAB, used alone or together, for 7 days after ingestion. The model used in this study is "non-invasive" with long-term drug release mechanism. The study utilized "mathematical modeling frameworks" to see the effect of long-term antiretroviral therapy. Better adherence was found in patients on a weekly drug schedule.

Some limitations to the model used in this study need further research and investigation to develop a more efficient drug delivery system. The plasma-drug concentration data of the drugs used in this study was different from that obtained from the actual clinical trial of the antiretroviral drugs. A.R. Kirtane et al. (2018) attributes this to the anatomical difference between humans and pigs. Helpful data can be gathered if this model is tested on humans and primates. The "gastrointestinal transit time" in humans is about 5 hours (Davis, S. S. et al. The effect of density on the gastric emptying of single- and multiple-unit dosage forms. Pharm. Res. 3, 208–213 (1986), and 9 hours in pigs (Snoeck, V. et al. Gastrointestinal transit time of disintegrating radio-opaque pellets in suckling and recently weaned piglets. J. Control Release 94, 143–153 (2004). Certain diets or can also alter the drug release or "gastric residence" of the drug delivery system. Furthermore, only drugs with about 50mg daily dosage amount can be used with this model for it to release drugs efficiently.

If these drawbacks can be addressed to construct a better oral, weekly, drug delivery model, we might be on the brink of revolutionary HIV treatment and management.