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ADVANCED IN NANOMEDICINE DRUG DELIVERY APPLICATION FOR HIV THERAPY

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ABSTRACT

Despite remarkable advance with the current Highly active antiretroviral therapy (HAART) for HIV (Human immunodeficiency viruses) there remain challenges. HIV is a long term disease and patient adherence therapy is critical over a lifetime. Poor therapy adherence is associated with less effective viral suppression which risks the immediate health of the patient ,but also risk creating permanent treatment resistance to that particular group of agent within a given complication therapy regimen. Poor aqueous drug solubility is a vital limitation, negatively impacting oral bioavailability for many ART. Complete destruction resulting in recovering has been a center of research intention but the existence of cellular & anatomical regions. Where the virus can continue to replicate therapeutic drug concentration create sanctuary sites. Which reseed the blood when treatment is detached. Nanomedicine application can improve a variety of pharmacological problem from increasing bioavailability to specific targeting to the site of action. Often reducing the dose of drug need for the therapeutic activity. The application of nanomedicine to present & future HIV treatment may offer bespoke solution to the problem faced by established formulated drug. In this review we are discuss about the advance in nanomedicine drug delivery application for HIV therapy.

KEYWORDS: Nanomedicine, HIV, HAART, ARV, Bioavailbility.

INTRODUCTION

1) Convention oral nanomedicine is effective at achieving concentration of ARV & control suppressing of viral replication. The application of oral nanomedicine, action such as reduced drug concentration low toxicity & rise bioavailability. Subtherapeutic

concentration of ARV in sanctuary site continue viral replication key cellular &anatomical area against viral suppression in the plasma.

2) Targeted nanomedicine action to drug distribution of therapeutics concentration of ARV. poor patient compliance may produce subtherapeutic concentration of ARV which causes rebound of viral replication.
3) Long acting nanomedicine may reduced the risk impact of poor patient adherence.

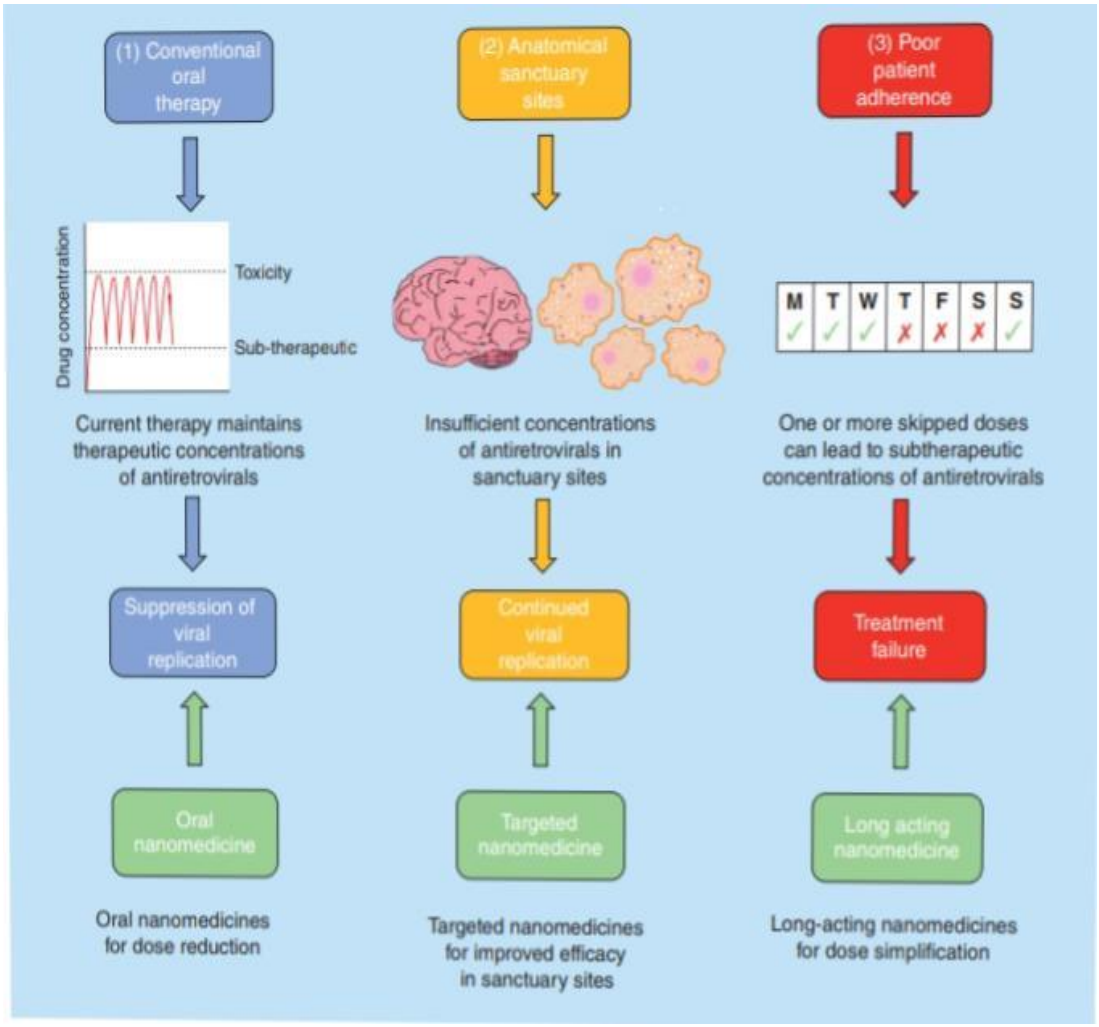

Fig. Shows some of the limitation of current antiretroviral therapy and opportunity to address these limitation via nanomedicine.

Oral Nanomedicine: A lot of nanomedicine system have been explored for oral distribution of ARV drugs are reviewed already. The solid drug nanoparticle formulations (SDNF) in this formulation the present system to rise bioavailability of poor Solubility in water. Solid drug nanoparticle are freshly develop using a single step emulsions -templated freeze drying.

Techniques. In vitro -in vivo ADME extrapolation predicted that the SDN formulations could achieve complimentary pharmacokinetic to the standard Sustiva ©pediatric formulation with a 50% dose reduced. To determine the rate of standard preclinical formulations is considered a greater Concentration max concentration min. &AUC.

Drug	Formulation (mg)	Comments
DRUGS NEEDED FOR PMTCT		
NVP	20 mg scored tablet	Used for infant prophylaxis from 6 weeks onwards
DRUGS NEEDED FOR PAEDIATRIC ART		
LPV/RTV	40/10 mg sprinkle	Heat-stable formulation that will be equivalent to 0.5 ml of liquid and used to treat infants and children who are unable to take the paediatric tablet
ABC/3TC	Scored adult 300/150 mg tablet	Used in children >25 kg
ABC/3TC/NVP	60/30/50 mg	Triple FDC to align with the dual FDC
RTV	50 mg heat-stable sprinkle or tablet	Useful for co-administration with unboosted PIs and for super boosting when PIs need to be dosed with rifampicin
TDF/3TC	75/75 mg tab	
	Scored 300/300 mg tab	
DRV/RTV	Unclear	Current labelling calls for different ratios of DRV to RTV for different age brackets. It is unclear what the correct ratio should be to produce a co-formulated FDC, but this is a priority formulation
Raltegravir	Unclear	Raltegravir is not yet approved for paediatric use but this is high-priority formulation

Oral nanomedicine for pediatric for mulations

Presently, the ritonavir (RTV) -boosted lopinavir (LPV) oral liquid formulation is WHO recommended as a4 1 (RTV): (LPV) combination. It includes 42% ethanol &15.03% propylene glycol these are certainly unwanted. In vivo pharmacokinetic Profiles for lopinavir without the need of any organic solvent. SDN techniques in industrial scale for spray dry manufacturing they use recently license vaccine combine with US FDA Center for evaluation &research (CDER'S) note pharmaceutical active ingredient. They may be possible to produce very defined personalized tablet easily &cheaply. Combination with solid drug loaded nanoparticles may create effective future therapy.

Long acting injectable nanomedicine: Long acting antiretroviral drug may improve compliance to therapy. the need for combination ART &physicochemical &dosing limitation of presents ARV drug impede attempt to redevelop them as long acting injectable Formulations. The non- nucleotide reverse transcriptase inhibitor rilpivirine has been available for oral administration, since 2011.

Newly rilpivirine has been nanoparticle formulation to produce an long acting injectable (LAI) rilpivirine was administered in rat &dog as single subcutaneously or intramuscularly. Rilpivirine plasma concentration time profile show sustained and dose proportional release over 2 month in rat and 6 month in dog. Where effective plasma concentration remained 10 ng/ml for up to 26 week. The combination of drug is most successful to HIV treatment the integrase inhibitor cabotegravir is an currently development as both oral and long acting injectable formulation. The cabotegravir was administered subcutaneous or intramuscular injection. Plasma drug concentration increased early over a first week with sustained up to 24weeks. Multiple long acting injectable ART system are under investigation .the most advanced long acting injectable remained prepared a two drug combination an integrase inhibitor (cabotegravir) and non nucleotide reverse transcriptase inhibitor (rilpivirine) administered as a separate injection. Multiple antiretroviral drug are potentially improve patient compliance. Recently multiple drug lipid nanoparticles encapsulating the ARV lopinavir (LPV) and ritonavir (RTV) and tenofovir were developed. The lipid formulation was administered subcutaneous injection to rhesus macaque to favorably, tenofovir plasma concentration and peripheral blood mononuclear cell concentrations were perceptible over 2weeks peripheral blood mononuclear cell exposure of all tenofovir and tenofovir diphosphate was higher marketed in compared with standard oral tenofovir disoproxil fumarate.

Mechanistic drug class	Agents	Formulation	Stage of development
Nucleoside reverse transcriptase inhibitors	EFdA (MK-8591)	Implant	Preclinical
	Tenofovir alafenamide	Implant	Preclinical
	GS-9131	Implant	Preclinical
Nonnucleoside reverse transcriptase inhibitors	Rilpivirine	Injectable	Phase III
	Elsulfavirine	Injectable	Preclinical
Protease inhibitors	Atazanavir	Injectable	Preclinical
	Ritonavir	Injectable	Preclinical
Integrase inhibitors	Cabotegravir	Injectable	Phase III
	Raltegravir	Injectable	Preclinical
Entry inhibitors	Ibalizumab	Intravenous	US FDA approved
	PRO 140	Intravenous	Phase II
	Albuvirtide	Intravenous and subcutaneous	Approved in China
	Broadly neutralizing antibodies	Intravenous	Phase II/III
	Combinectin	Intravenous	Preclinical
Capsid inhibitors	GS-CA1	Injectable	Preclinical

Long acting antiretroviral drug

Targeted nanomedicine: As notice previously a remarkable barrier to HIV removed in the presence of sanctuary sites. Systemically available drugs need to cross biological mistakes for distribution to cellular and anatomical site which most presently available ARV formulation could not. CNS availability of most ARV drug is very low because poor permeability across the blood brain barrier. li wan and colleagues was investigation of macrophage up take pharmacokinetic and distribution of macrophage targeted PEG –(FLMF) nanoparticle for improve HIV drug distribution. PEG based drug had been investigated for distribution of ARV to the brain in US. The nanomaterial based strategies explored for HIV therapeutics are liposome, nanoparticle, mannose receptors, polymeric micelles, vaccine most suitable for HIV therapy. We highlights both immune mediated system and those targeted endogenous immune cell involved in HIV. HIV sanctuary sites are also able to go undetected by the immune system. which increases the risk of viral replication. Targeted nanoparticle use ligand such as mannose galactose, FLMF p peptides have been utilize by target macrophage, major HIV reservoirs ln future targeted distribution of two or more ARV drug in nanoparticle strategies.

Could radically improve therapy of viral reservoirs

S. No	Nanoparticles	Targeting moiety	Therapeutic agent
1	Gelatin	Mannose	Didanosine
2	Gelatin	Mannan	Didanosine
3	Dendrimer	Tuftsin	Efavirenz
4	Conjugate	Tuftsin	AZT
5	PLGA	Transferrin	Nevirapine
6	Albumin	Transferrin	AZT
7	PLA	TAT	Ritonavir
8	Liposome	Anti-HLA-DR	Indinavir
9	Liposome	Anti-HLA-DR	Amphotericin B
10	Liposome	Anti-gp120	P11
11	Liposome	LFA-1	RNAi
12	Dendrimer	Mannose	Lamivudine
13	Lipid nanoparticles	CD4 binding peptide	Indinavir
14	Liposome	CD4-IgG	-
15	Liposome	CCR5	EDTA
16	Chimeric	Anti-gp120 aptamer	RNAi
17	Liposome	Galactose	AZT
18	Liposome	Mannose	Zidovudine
19	Liposome	Mannose	Stavudine
20	Liposome	Galactose	Stavudine

Targeted Nanoparticles

Future perspective: The application of nanomedicine to HIV current many existing opportunities. HIV has reached pandemic level. Because the complexities of both the HIV infection cycle and the target for distribution of drug intended to cure this disease. Most effective drug distribution system are necessary. Different forms of nanoparticle have been Investigate the effective delivery of ARV drug for to treat HIV. The application of nanoparticle strategies for distribution of ARV drug can achieve more efficient distribution, provide a mechanism to cross the BBB, or tissue and provide a mean to overcome innate barrier to delivery such as mucus. The combination of drugs are more effective treatment of HIV infection. Further analysis regarding the safety and efficacy of the ARV nanoparticle must be performed. Minimum information is presently available regarding the short &long term toxicity of nanoparticles .against increasing interest in nanomedicine there are remarkable gap in knowledge in underlying mechanism. For example. A better understanding of drug release following long acting injectable injection is necessary. The deeper knowledge and understanding of the real interactions involved in the diseases tissue is fundamental for

the development new therapeutic approach and protocol base on employment of smart nanoparticles.

CONCLUSION

In summary ,a greater understanding of the mechanisms underpinning nanoparticles action will enable rational design of nanomedicines with better efficacy and improve safety to the preclinical promise can be recognize for infected patient ,across the various nanotechnology being explored.

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