Prakash, J Virol Antivir Res 2020, 9:2
DOI: 10.37532/jva.2020.9(2).195

Journal of Virology & Antiviral Research

Research Article

a SciTechnol journal

Immunological and Virological Effects of Novel Prakasine Nanomedicine in HIV-Infected Patients in South India: A Preliminary Study

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Abstract

Objectives: While HIV remains incurable, one method of eliminating latent virus is, sensing dormant HIV then target the infected cells. The Cytotoxic T-Lymphocytes (CTL) play a major role in it. Several nanoparticles were reported to induce CTL, renewal of stem cells, immune cells and cytokines as well. It is hypothesised, if CTL is stimulated with nanoparticles HIV reservoir would be eradicated. To test this hypothesis this study was performed. This is the modification of 500 years old traditional medicine.

Methods: Prakasine (PRK-NP) is the 10 - 50 nm size, spherical shape, nanoparticle. Consenting ART-naive (n=14), male and female, aged between 25 - 50 years, with weight loss about average 5 kgs, lethargic, HIV RNA ≤ 100000 copies/ml, CD4~500 cells /µl HIV patients and healthy individuals (n=4) were enrolled in this study and divided as positive control (n=4), treatment group (n=10) and negative control (n=4). The treatment group only administered 1gram of PRK-NP thrice daily for three years in Naval AIDS Research centre, Namakkal. Body weight (BW), viral load (VL), HIV-1 proviral DNA, CD4, CD8, complete blood cell (CBC), liver function tests (LFT), kidney function tests (KFT) and physical neurological examination were analysed once in three months. Wald chi-square test was performed for statistical analysis.

Results: In all patients in treatment group (n=10) clinical symptoms disappeared. The mean BW gain about 10 kgs, mean rise of CD4 and CD8 are 296 and 225 respectively (p=0.0001, Wald chi-square test) show that the PRK-NP has induced immune cells growth in treatment group. The VL came to Less than Detectable (LDL) level, but HIV-1 proviral DNA detected in five patients and in another five patients, the Proviral DNA not detected. Whereas in positive control VL raised from 27250 to 181500, CD4 decreased from 827 to 402 and CD8 reduced from 750 to 467, the Proviral DNA is detected in all the times. In negative control, all the time, the VL is LDL, proviral DNA is not detected and there are no significant changes in CD4 and CD8. In all patients in treatment group and in both positive and negative control, CBC, LFT, KFT and physical neurological examination are normal.

Discussion: PRK-NP reveals no side-effects and possesses therapeutic efficacy.

Keywords

Nanomedicine, Prakasine, HIV Cure, HIV treatment, alternative to ART, Immunotherapy and Immunostimulant drug

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Received: April 20, 2020 **Accepted:** July 02, 2020 **Published:** July 08, 2020

Introduction

Mercury has been shown as miraculous metal in Tamil Traditional Medicine (TTM) [1-5]. It has various kinds of physical and chemical properties than any other metals [6-13]. Mercury and its compounds have medicinal properties and it is being used for various diseases in various preparations in TTM [14-19]. Several countries banned mercury in medicine due to its toxicity and side effects [20-33]. Mercury is still in use in dentistry in many countries [34]. Mercury was used for syphilis treatment from 16th - 20th century [35]. Mercury is still being used in alternative medicine systems especially in Chinese, Ayurvedic and Siddha (Traditional Tamil Medicine) effectively. Even though, modern medicine says that mercurial preparations are toxic, the traditional medicines play an effective role in the treatment of ailments in humans, animals and birds. Hence, the question is being raised! Which produces the real mercury toxicity-only single compounds or only certain type of mercurial compounds? Can we produce a non-toxic or less toxic mercury compounds like anti-snake venom from venom, vaccines from same viruses by using nanotechnology and biotechnology? This is the million- dollar question. If we can produce less toxic or non-toxic mercury compound, certainly, it will be useful for therapeutics because from 16th century to 20th century, the whole world was depended only on mercurial for incurable diseases then stopped because of its toxicity. If we nullify the toxicity by nano-biotechnological strategies again it will come into existence for the treatment of diseases. As an author, I have been observing last two decades in my TTM practice to various diseases and admired about mercurial preparations comprising plant extracts, minerals in TTM did not produce any side effects rather they have given only beneficial effects. Unfortunately, no publications available for that, but there is separate department available in Tamilnadu government and this kind of preparations are desperately prescribed and supplied to the patients suffering with several ailments in each and every government hospital of Tamilnadu, India. With this background, unpublished reports, results from my patients, my experience and observations of various combinations and its apparent chemical molecules present in it to produce therapeutic effects have given me an enthusiasm to explore this and produce non or less toxic mercurial nano medicine based on hypothesis and my proposed modern scientific theory.

When we look into insight of toxicity and side effects, these will fall under only two categories. One is, the mercury atom attaches with the sulphur atom of the biomolecules and causes toxicity. The another one is stagnation of metal compounds in to the cells or cellular compartments without getting eliminated after ingestion by any route. Here, based on reaction of molecules *In-vivo* and observations made among many reactions and various compounds, a wide scientific theory is proposed on hypothesis, that is,

1. If metal atoms are attached with sulphur atoms with co-ordinated covalent bond gives raise to metallic sulphur complex, if this metallic sulphur complex is attached further with organic compound (ligand), the organometallic complex will be formed, which will not produce any toxicity or less toxicity.

2. This metallic sulphur complex will form di-sulphide bond in *In-vivo* and evince therapeutic action with less adverse effect.

doi: 10.37532/jva.2020.9(2).195

3. Some metals particularly mercury attaches with sulphur and form covalent bond even when more other elements present in a biochemical reaction. The bond between Hg and S cannot be broken by biochemical reactions both *In-vivo* and*In-vitro*.

This proposed theory is here after called as "Prakash Theory of Metal Drugs". Thus, the synthesised metal nano medicine would have potential for exploitation in the biomedical field. To test this hypothesised theory, the highly toxic metal mercury was selected and the present study was performed. Mercury and sulphur atom were covalently attached, again this molecule was attached with one sulphur containing biomolecule in *Ex-vivo* made into nanoscale level and has been developed as drug. As per the theory the mercury gets into system and come out as HgS or its complexes after evincing the biological role. So, there will be no toxicity by this drug. My previous works proved this theory and Prakasine plays in the immunotherapy as well [36-39].

Materials and Methods

Ethical Statement

The particular regimen of Prakasine nanomedicine is from the approved system being under medical practice more than 500 years in my state and the formulation is already in our country's Traditional Knowledge Digital Library (TKDL). I obtained informed consent and this study was performed as per Helsinkideclaration.

Nano medicine Synthesis

Prakasine (PRK-NP) nanoparticle was synthesised with processed mercury, processed sulphur and methionine (ligand) according to patent application number CHE/5776/2014 and as reported in my previous works [36-39] and employed for this presentstudy.

Nano medicine Therapy

The HIV individuals those who voluntarily sought the treatment from Naval AIDS Research center, Namakkal were randomlyselected. Some 14 individuals who were not ready to go for HAART due to its adverse effects were enrolled in this longitudinal study. Among the 14, four HIV individuals neither to take PRK-NP nor to takeHAART due to their various situations were kept as positive control as per their request to monitor the HIV status in the absence of any treatment. Some four HIV negative individuals having sexual exposure with unknown persons psychologically demanded the PRK-NP were kept as negative control to monitor their status with the intention of initiating treatment if they become positive.

The inclusion criteria are both male and female, aged between 25 - 50 years, with weight loss about average 5 kgs, lethargic, HIV RNA ≤100000 copies/ml, CD4~500 cells /µl and four were non-HIV infected individuals. The exclusion criteria are paediatric age group, pregnant women, opportunistic infections, diabetics, hypertension, any other diseases and HAART. They were administered with PRK-NP at the dose level of one capsule containing 1000 mg thrice in a day for 36 months. The viral load, HIV proviral DNA, CD4, CD8 profile, Complete Blood Count (CBC), Liver Functions Tests (LFT), Renal Function Tests (RFT) and physical neurological examination were performed every three months once for all. All assays were performed in triplicate. Wald chi-square test was performed for statistical analysis.

Results

The results of PRK-NP nano medicine therapy have shown that the clinical symptoms like lethargies disappeared completely in all patients of treatment group, in positive control the clinical symptoms increased. Whereas in negative control no significant changes noticed. The mean BW gain about 10 kgs in treatment group, whereas in the positive control the BW average 5 kgs reduced but in negative control no significant changes.

Viral load

In treatment group the VL has reduced from 59330 (mean value) (Table 1) to Less than detectable limit (LDL) when compare to the before treatment. In positive control the VL has increased from 27250 (mean value) to 181500 (mean value) when compare to the before treatment. Whereas in negative control all the time were LDL.

CD4 cells

The CD4 counts of the treatment group has increased from the 632 (mean value) to 928 (mean value) (Table 2) compare to before

Table 1: Quantification of of viral load (Copies of Viral RNA per ml of Serum).

PATIENT NUMBER	BEFORE TREATMENT	AFTER TREATMENT		18th month	24th month	36th month
		6 MONTHS	12 MONTHS			
1.Treatment group	90000	53000	11000	5500	770	LDL
2	94300	69500	15400	9000	1500	LDL
3	43000	21500	10300	5500	900	LDL
4	52000	23000	14000	7000	1400	LDL
5	63000	29000	17000	9000	1000	LDL
6	15000	6700	2900	1100	700	LDL
7	80000	18000	11000	6500	900	LDL
8	90000	35000	17500	7000	600	LDL
9	16000	7500	300	LDL	LDL	LDL
10	50000	25000	12500	5000	500	LDL
11.Positive Control	27000	110000	145000	130000	160000	230000
12	19000	49000	63000	78500	110000	150000
13	29000	55000	85000	111000	148300	201000
14	34000	57000	76000	111500	126600	145000
15.Negative Control	LDL	LDL	LDL	LDL	LDL	LDL
16	LDL	LDL	LDL	LDL	LDL	LDL
17	LDL	LDL	LDL	LDL	LDL	LDL
18	LDL	LDL	LDL	LDL	LDL	LDL

doi: 10.37532/jva.2020.9(2).195

treatment but in positive control it has reduced from 827 (mean value) to 402 (mean value). In the negative control there is no significant changes

CD8 Cells

The CD8 counts of the treatment group has increased from the 769 (mean value) to 994 (mean value) (Table 3) compare to before treatment but in positive control it has reduced from 750 (mean value) to 467 (mean value). In the negative control there is no significant changes.

Complete Blood Cell Counts (CBC)

The hemogram (Table 4) shows the CBC values of all the patients of treatment group, positive control and negative control. There are no significant changes of CBC before and after the treatment of all groups.

Proviral DNA

The HIV-1 Proviral DNA is detected in all the 10 patients in treatment group before the initiation of the treatment (Table 5) but after the treatment 5 patients that is patient numbers 1, 4, 5, 9 and 10 has come to the level of "not detected". This is due to the significant effect of the treatment with PRK-NP.

Neurological Study

The neurological studies were performed for all the patients in all the group (Table 6) to assess the neurotoxicity of PRK-NP. The study reveals that there is noneurotoxicity.

Table 2: CD4 cell counts of patients before and during the course of treatment (cells/ ul of blood).

PATIENT NUMBER	BEFORE TREATMENT	AFTER TREATMENT		18th month	24th month	36th month
		6th month	12th month			
1 Treatment group	690	710	990	980	1000	1010
2	680	880	1080	950	1000	1050
3	510	940	950	930	960	980
4	890	1100	1100	950	1000	1090
5	580	990	990	980	999	1000
6	670	1010	1000	1020	1000	1100
7	690	980	950	800	800	800
8	510	760	760	770	750	750
9	520	790	750	750	760	750
10	580	800	770	770	760	750
11 Positive Control	1000	850	750	700	600	500
12	750	560	510	490	410	360
13	760	750	680	569	448	360
14	800	750	590	550	480	390
15 Negative Control	1000	980	1000	1020	1000	990
16	900	990	910	900	990	970
17	950	1000	950	1000	980	990
18	1100	1080	1100	1200	1000	1010

Table 3: CD8 cell counts of patients before and course of treatment (cells/ ul blood).

PATIENT NUMBER	BEFORE TREATMENT	AFTER TREATMENT		18th month	24thmonth	36thmonth
		6thmonth	12thmonth			
1 Treatment group	760	770	1000	790	750	1000
2	750	770	780	770	1030	990
3	800	810	750	750	760	890
4	760	770	760	1200	760	1000
5	759	767	768	768	787	980
6	800	810	820	810	1810	1000
7	769	750	1300	750	760	1050
8	770	760	780	760	780	980
9	760	760	800	1000	1320	1020
10	770	760	1050	780	750	1030
11 Positive Control	740	770	810	760	770	550
12	750	760	770	780	800	410
13	760	800	860	850	630	400
14	750	770	770	810	450	510
15 Negative Control	1020	760	770	780	770	1000
16	800	790	780	890	798	790
17	890	900	1000	1000	770	900
18	910	1080	910	900	800	900

doi: 10.37532/jva.2020.9(2).195

Table 4: Haemogram of the HIV-1 infected and normal individuals before and after treatment (36 months). The patients 1-10 are treatment group, patients 11-14 are positive control and 15-18 are negative control.

PIN	W.B.C	P	L	E	M	HB	RBC	PC	PCV	E.S.R	W.B.C	P	L	E	M	HB	RBC	PC	PCV	E.S. R
		%	%	%	%			$X10^5$	%			%	%	%	%			$X10^5$	%	
1	7500	50	40	6	4	13	5	3	40	5	9000	41	45	4	10	14	6	4.2	40	5
2	4000	60	30	7	3	10	4	1.3	27	7	10000	45	40	6	9	13	5	2.3	40	5
3	5500	55	35	5	5	11	4	2	45	6	9000	46	44	4	6	14	4	3	45	4
4	4500	60	35	7	5	12	4	3	30	6	10000	45	45	2	8	15	5	4	45	5
5	5000	55	37	7	4	12	3	3	30	6	10000	50	40	3	7	14	5	3.6	40	4
6	7000	60	30	7	3	12	4	2	30	7	9000	40	45	5	10	15	6	4	50	4
7	4000	60	30	6	4	11	3	3	28	7	9000	40	45	5	10	14	5	4	40	4
8	5500	55	35	5	5	12	4	2	30	6	8500	47	40	3	10	15	5	3.5	50	5
9	6000	60	30	6	4	12	4	3	30	7	9000	45	42	3	10	14	6	4	45	4
10	7000	60	30	5	5	11	3	2	27	6	9500	45	42	3	10	14	5	4	50	5
11	4000	60	30	6	4	11	4	3	30	6	9000	43	45	3	9	15	5	3	45	4
12	6500	65	27	4	4	12	4	3	30	6	9000	43	45	4	8	14	5	4	50	5
13	7000	60	30	5	5	12	4	3	30	6	9500	43	45	4	8	15	6	4	45	5
14	6000	65	25	5	5	12	3	2	30	5	9000	42	45	3	10	14	4	4	45	4
15	6000	61	23	5	6	11	3	2	29	5	6000	41	44	2	11	13	3	4	45	4
16	6500	60	24	5	5	12	4	3	30	5	7000	43	45	4	10	15	6	4	45	5
17	7000	61	30	5	5	12	4	3	30	6	7000	43	45	4	11	15	6	4	45	5
18	6000	60	30	5	5	12	4	3	30	6	6000	43	45	5	12	14	6	4	30	3

Table 5: Status of the HIV-1 proviral DNA of infected and normal individuals before and after treatment (36 months). The patients 1-10 are treatment group, patients 11-14 are positive control and 15-18 are negative control.

Patients Numbers	Before Treatment	After Treatment				
		6th month	12th month	18th month	24th month	36th month
1. Treatment Group	Detected	Detected	Detected	Detected	Not Detected	Not Detected
2	Detected	Detected	Detected	Detected	Detected	Detected
3	Detected	Detected	Detected	Detected	Detected	Detected
4	Detected	Detected	Detected	Not Detected	Not Detected	Not Detected
5	Detected	Detected	Detected	Detected	Not Detected	Not Detected
6	Detected	Detected	Detected	Detected	Detected	Detected
7	Detected	Detected	Detected	Detected	Detected	Detected
8	Detected	Detected	Detected	Detected	Detected	Detected
9	Detected	Detected	Detected	Not Detected	Not Detected	Not Detected
10	Detected	Detected	Detected	Detected	Detected	Not Detected
11.Positive control	Detected	Detected	Detected	Detected	Detected	Detected
12	Detected	Detected	Detected	Detected	Detected	Detected
13	Detected	Detected	Detected	Detected	Detected	Detected
14	Detected	Detected	Detected	Detected	Detected	Detected
15.Negative control	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected
16	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected
17	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected
18	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected

doi: 10.37532/jva.2020.9(2).195

Table 6: Neurological examination (mental status, cranial nerves, motor, sensory, reflexes, coordination, gait and for neurological clinical symptoms).

Patients Numbers	Before Treatment	After Treatment
1.Treatment Group	Normal	Normal
2	Normal	Normal
3	Normal	Normal
4	Normal	Normal
5	Normal	Normal
6	Normal	Normal
7	Normal	Normal
8	Normal	Normal
9	Normal	Normal
10	Normal	Normal
11.Positive control	Normal	Normal
12.	Normal	Normal
13.	Normal	Normal
14	Normal	Normal
15.Negative Control	Normal	Normal
16	Normal	Normal
17	Normal	Normal
18	Normal	Normal

As the measure of another safety study, in all the patients, in treatment group, positive control and negative control, LFT and KFT are normal in all the times. The results are statistically significant (p=0.0001, Wald chi-square test).

Discussion

Even though the existing state of art mercury compounds are toxic, the PRK-NP was developed by novel theory, strategy and also by TTM protocols as nontoxic by its elemental articulations, particle sizes and administered to humans since it did not produce any toxicity in animal studies conducted in my previous works [36-39]. My previous studies in birds, zebrafish, mice and in human had revealed that the PRK-NP is able to increase the humoral immunity against Newcastle disease, increases the immunostimulatory (IL1α, IL1β, IL2, IL6, IL8, IL12, TNFα, IFNγ) cytokine gene expressions, the maximum tolerance dose is 900 mg/kg body weight and potential immunotherapy for HIV respectively.

The PRK-NP is the combination of TTM molecules and biomolecules; therefore, these are novel chimeric molecules for therapeutic use. Since the TTM is the oldest system of medicine in Tamilnadu and approved by government of India, the references cited in this manuscript are in India's Traditional Knowledge Digital Library (TKDL) website (http://www.tkdl.res.in/tkdl/LangDefault/siddha/Sid_Advancesearch.asp?GL=Eng) both in translated version of English and prior art version of Tamil including its formulatory preparations and therapeutic uses, so no need of present regulatory approvals to use in human beings. Many of the TTM ingredients possesses methionine, therefore, methionine was directly added in pure form to make this chemical complexes easily in this synthesis. The TEM, XRD and SEM studies revealed these particles are in nanoscale, the sizes are about 5 nm -50 nm [36-39].

There are other metal complexes already produced in nanoscale level and reported to have therapeutic effect [40-45]. Already several nanoparticles were employed in HIV research both for diagnostic and treatment purposes but none of them have given encouraging results to treat HIV patients alternative to ART successfully [46-50]. Different micronized HAART drugs are heavily toxic that is being administered to HIV patients since there is no alternative for them [51-53]. Since there are no available regulatory bodies for nano medicines only few drugs in Nano form are under Human clinical trials [54]. Already methionine metal complexes had been synthesised and reported but they are not nanoparticles [55,56].

Even though many nanoparticles used as medicine there is no specific theory to synthesis like Prakash theory of metal drugs. From zero side effects of PRK-NP and its appreciable results in human HIV patients, the theory is proven to be effective. This study shows that the nano mercury locked with sulphur atom or atoms will not produce any toxicity, side effects rather beneficial effects. Before this study there is one evidence with mercury preparations developed by TTM protocols were administered to HIV/AIDS patients in government Tambaram Sanatorium Hospital by Dr. Deivanayagam and the patients were recovered successfully without any adverse effects [57].

We could understand from results of this study that the PRK-NP possesses the effects to reduce the viral load and eliminate HIV proviral DNA in some patients with increase of CD4 and CD8 cells. Also, we could observe that the PRK-NP has increased the weight gain and reduced the symptoms. It is assumed since there are no significant changes in the parameters like liver profile, renal profile, CBC, neurological examination that the PRK-NP does not have any adverse effects as they are novel and in nanoscale level. PRK-NP was tested for anti-HIV activity but they did not possess the same *In-vitro* (unpublished data) but they are producing good immunological anti-HIV results during the treatment to HIV patients due to immunostimulatory cytokines gene expression. They might evince the anti-HIV action *In-vivo* by sensing dormant HIV then target the infected cells. The Cytotoxic T-Lymphocytes (CTL) might play a major role in it (Figure1). Several nanoparticles were reported to induce CTL, renewal of stem cells, immune cells and cytokines as well. Further studies to be warranted to confirmthis.

It is very important in this study that the mercury atoms were detoxified with sulphur locks and again attached with sulphur containing amino acid DL-Methionine *Ex-vivo* to prevent the adverse and toxic effects by arresting the reactions of mercury with sulphur

doi: 10.37532/jva.2020.9(2).195

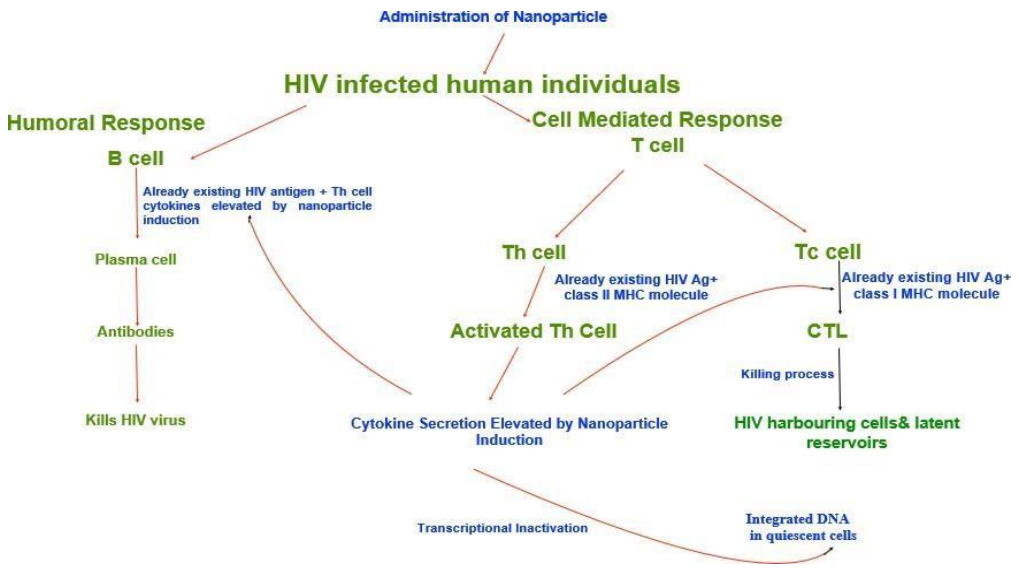

Figure 1: Proposed mechanism of action of Prakasine nanoparticle towards HIV elimination.

atoms of sulphur containing amino acids because all the mercury compounds reacts with sulphur containing amino acids *In-vivo* particularly the mercury atom attaches with sulphur atom and disturb the functions of that amino acid that is why the mercury toxicity is being developed by inactivating sulphur or sulfhydryl groups of enzymes and thus interfering with cellular metabolism and function as mercury readily forms covalent bond with sulphur [58]. The PRK-NP is not interfering with cellular metabolism and function as other mercury compounds. Therefore, this is safe and has the potency to treat HIV patients with further studies.

Conclusion

Since no drugs have the potency so far towards the HIV cure, this PRK-NP may be useful for the HIV patients as an alternative to ART and cure as well with numerous furtherstudies.

Acknowledgement

This is to acknowledge Dr.P.Revinselvan MBBS, Naval AIDS Research Centre general physician for supporting this study

Conflict of Interest

This is to declare that this study does not have any conflict of interest.

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