Randomized trial of impact of multiple interventions on HIV reservoir: SPARC-7 trial

Ricardo Sobhie Diaz,[1] Leila B Giron[1,2], James Hunter[1], Juliana Galinskas[1], Danilo Dias[1], Paulo Roberto Abrão Ferreira[1], Gisele Gosuen[1], Sadia Samer[1,3], M Shoaib Arif[1,4], Ermelindo Dela Libera[1], Maria Juliano[1], Edecio Cunha Neto[5], Maria Cecilia Sucupira[1], Luiz Mario Janini[1], Andrea Savarino[6] Luis Travassos[1], and SPARC Working Group

1.Federal University of São Paulo, São Paulo, SP, Brazil; 2.Wistar Institute, Philadelphia, PA, US; 3.Yerkes National Primate Center, Emory Vaccine Center, Atlanta, GA, US; 4.Northwestern University Feinberg School of Medicine, Chicago, IL, US; 5. University of São Paulo, São Paulo, SP, Brazil; 6.Department of Infectious Diseases, Italian Institute of Health, Rome, Italy.

Presentation: *0399*

Introduction:

- Recognized barriers for HIV persistence among individuals with suppressive antiretroviral therapy (ART) are *(i)* residual HIV replication [Maldarelli F, et al. PLoS Pathog. 2007], *(ii)* virus/cell latency, and *(iii)* viral sanctuaries.
- In this sense, multiple interventional strategies may be fundamental to decrease the size of HIV-1 reservoir along with ART.
- To measure the impact of isolated and combined strategies in decreasing viral persistence and inflammation, we investigated the effect of treatment intensification with **Dolutegravir (DTG)** with and without Maraviroc (MVC) in order to decrease HIV residual replication, **Nicotinamide (NAM)** in order to disrupt HIV latency, **auranofin** in order to induce lymphocyte apoptosis, especially in the memory compartment of lymphocytes, encompassing the viral reservoir, and an **autologous dendritic cell vaccine** to target HIV resident in latent cells and/or in sanctuaries.
- Dolutegravir was chosen as a drug for treatment intensification due to its unprecedent potency [Min S et al, AIDS 2011]
- Maraviroc was chosen for treatment intensification due to its added value in decreasing inflammation and apoptosis [van Lelyveld et al, Plos One, 2015], and its capacity of latency interruption [Madrid-Elena N, J Virol 2018]
- Nicotinamide, an Histone Deacetylase (HDAC Class) II inhibitor is being explored as an anti-proliferative agent [Audrito et al. Cancer Res 2011] and an anti-HIV latency agent [Samer et al. EACS 2017], as shown in the pre-clinical investigation following.
- The gold salt auranofin used in combination with intensified antiretroviral therapy induced a remarkable decay in viral DNA in peripheral blood of SIVmac251-infected macaques [Lewis et al., AIDS 2011]. Gold salts decrease lymphoproliferation by inhibiting synthesis of cytokines such as IL-2 [Vint et al., Agents Actions 1993] and induce viral reactivation from latency in some cell types [Fronteh & Meyer, BMC Infect Dis. 2014]. As mentioned, auranofin induces lymphocyte apoptosis, especially in the memory compartment of lymphocytes, encompassing the viral reservoir [Chirullo et al., Cell Death Dis, 2013].
- Autologous dendritic cell (DC) vaccine was used here to booster cellular immunity.

Innovation:

First time that:

- 2 ARVs were used for antiretroviral treatment intensification: Dolutegravir and Maraviroc.
- Dolutegravir was used for antiretroviral treatment intensification (first patient screened on August 21, 2015, and last patient ended week 48 on August 7, 2017).
- The HDAC inhibitor Nicotinamide was used as a Latency Reversal agent *in vivo*.
- The gold salt Auranofin was used in Humans as HIV curative strategy.
- A Dendritic cell vaccine was used among antiretroviral suppressed individuals to boost cellular immunity.

Methods:

Study design: Randomized open label pilot proof of concept clinical trial [www.clinicaltrials.gov; ID: NCT02961829]. Study subjects were all male (this choice was done given the potential teratogenicity of one of the study drugs [Gao XY et al, J Appl Toxicol 2017]).

Randomized patients were distributed within six arms with 5 patients each followed every 4 weeks for a total of 48 weeks, followed by additional time for patients subjected to DC vaccine. Selected patients were ART suppressed for >2 years, with CD4+ T cell count nadir >350, harboring R5 HIV strains. Patients were randomized to distinct Intervention Groups as followed:

1) Continuation of ART (control group)
2) intensified ART (Continuation of ART+DTG and MVC; Group 2)
3) intensified ART and HDACi (ART+DTG+MVC+NA; Group 3)
4) intensified ART and Auranofin (ART+DTG+MVC+Auranofin; Group 4)
5) partially intensified ART (ART+DTG), followed by DC vaccine (Group 5)
6) partially intensified ART (DTG)+NA+Auranofin, followed by DC vaccine (Group 6).

Auranofin was used for the first 24 weeks of the study in G4 and G6. Sera, plasma, PBMCs, saliva, urine were collected every month. Rectum biopsies were performed at baseline and at 48 weeks in groups 1, 2, 3, and 4, and at the end of DC vaccine protocol in groups 5 and 6.

Proviral DNA quantitation in PBMCs and Rectum biopsies tissues:

Viral DNA was measured as an estimate of the viral reservoir by published qPCR techniques [Komninakis et al., 2012; Buzón et al., 2010; Kumar et al. 2009] following in-house analyses aimed at ruling out the effect of PCR inhibitors.

HIV-1 Episomal DNA Detection and Quantitation was performed according to [Buzon et al, Nat Med 2010, Sharkey et al Nat Med. 2000]. The qPCR quantitation values were normalized based on cell numbers estimated by CCR5 quantitation and are expressed as the number of DNA copies per 106 PBMC.

T Cell activation markers:

PBMCs were labeled with anti-CD3 APC and anti-CD4 PercP (for the lymphocytic subpopulation) and anti-CD38 FITC and anti-HLA-DR PE (for cellular activation). At this moment, cell activation markers were performed only in the groups 1, 2 and 6 at baseline and week 20.

DC vaccine preparation:

HIV Gag256-367 characterization from each patient using Next Generation Sequencing and single genome amplification. Design of autologous GAG peptides (nanomers) according to the best immunogenicity (biding affinity > 100) based in the specific HLA profile of each individual to elicit MHC class 1 [Kai et al 2015; Benito et al 2004]. Between 2 and 6 peptides for each patient were prepared. Monocytes of each patient were obtained by cytapheresis and transformed into DCs. Exposure of DCs to autologous peptides and preparation of 3 doses of vaccine injected into axillar and inguinal subcutaneous region every 2 weeks.

Antibodies (Abs) quantitation:

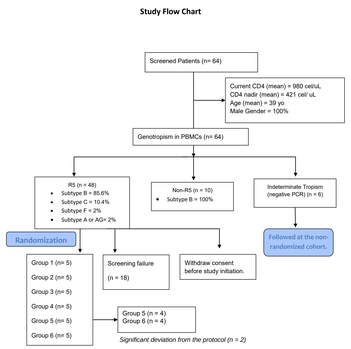
We have earlier shown that HIV antibodies quantitation relates to the efficacy of ART and levels of HIV replication [Cimerman S et al, AIDS Patient Care and STDs, 2007]. We therefore hypothesize that the decay/slope of Abs level will indicate constant suppression and directly relates to the size of the reservoir. We have performed Abs quantitation using the Abbott ARCHITECT HIV Ag/Ab Combo assay (Abbott, IL, USA)l.

Statistical Analysis:

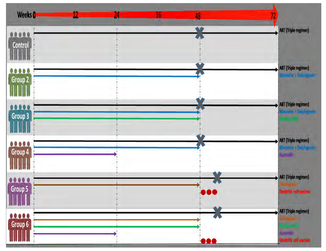
Data were analyzed by repeated-measures ANOVA and linear regression (to show trends over time) following an appropriate transformation where necessary.

Presented at CROI 2019 – Seattle, Washington

Study Flow Chart:



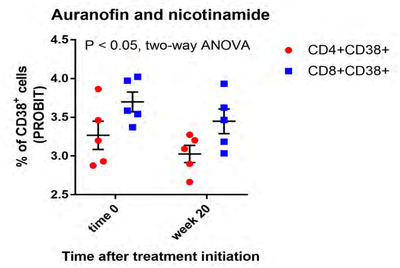
Distribution of patients according to specific intervention:



Results:

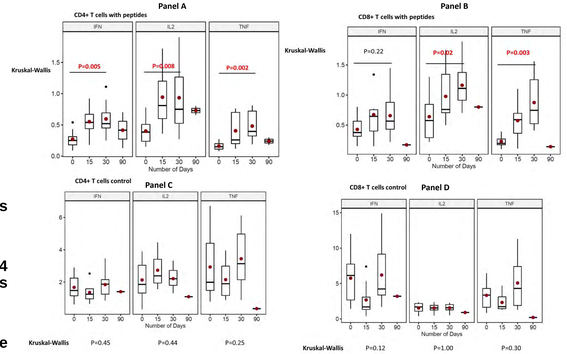
- **Viral Loads were below detection limits during all study period for for all patients.**
- **No significant differences were found for CD4 or CD8+ T cell counts or CD4/CD8 rations during study period.**
- **No grade 3 or 4 adverse events were observed.**

Changes in the mean % of CD4+ T cells CD38+, and CD8+ T cells and CD38+ among individuals of Group 6 :



in vitro immunogenicity of vaccine :

Median in vitro values reflecting the in vitro immunogenicity of vaccine in the CD4+ T cells (Panel A) and CD8+ T cells (Panel B). Samples from patients of G5 and G6 were collected at the time of the first vaccine dose (day 0), at the time of the 2nd vaccine dose (day 15, reflecting the impact of first vaccine dose), at the time of the 3rd vaccine dose (day 30, reflecting the impact of the 2nd vaccine dose), and 2 months after the 3rd vaccine dose (day 90). Patient's cells were pulsed with autologous peptides used to sensitize DC, and IL2, TNF and interferon (IFN) were measured by flow cytometry in the CD4+ T cells and CD8+ T cells. There was a significant increase in these interleukins measurement from day zero to day 30 at CD4+ T cells, and a significant increase in IL2 and TNF measurements from day zero to day 30 (Kruskal-Wallis). As for the control experiment, patient's cells were pulsed with S aureus enterotoxin type B (SEB) and brefaldine (BFA), and IL2, TNF and interferon (IFN) were measured by flow cytometry in the CD4+ T cells (Panel C) and CD8+ T cells (panel D). There was a no significant changes in these interleukins measurement over time (Kruskal-Wallis).



Qualitative results of total HIV DNA in PBMCs and Rectal biopsy tissues over time:

	ID	PBMC w0	PBMC w24	PBMC w48	PBMC After DC vaccine	Rectal Tissue Baseline (BX1)	Rectal Tissue End (BX2)
G1	P1	+	+	+		NR	+
	P2	+	+	+		NAS	+
	P3	+	+ / -	+		NAL	+ / -
	P4	+	+	+		ACCAP	+
	P5	+	+	+		CCAP	+ / -
G2	P6	+	+	+		NP	+ / -
	P7	+ / -	+ / -	+		NP	+ / -
	P8	+	+	BLOL		NAS	+ / -
	P9	+	+	+		NAS	+
	P10	+ / -	+	+		NAE	+
G3	P11	+	+	+		JPC	+
	P12	+	+ / -	+		JADN	+
	P13	+ / -	+ / -	+		NAD	+
	P14	+	+	+		DSA	+
	P15	+ / -	+	+		JDVC	+
G4	P16	+	+	+		DVP	+
	P17	+	+	+		DG	+
	P18	+ / -	+	+ / -		ACVC	+ / -
	P19	+	+	+		ACVD	+
	P20	+	+	+		PPE	+ / -
G5	P21	+	+	+	+	NATB	+
	P22	+	+ / -	+	+	DAP	+ / -
	P23	+	+	+	+	LVC	+ / -
	P24	+	+	+	+	NCVI	+
	P25	+	+	+	+	PHD	+
G6	P26	+ / -	BLOL	BLOL	BLOL	PAAS	+
	P27	+	+	+	+	NRA	+
	P28	+	+	+	+	NVV	+
	P29	+	+ / -	BLOL	BLOL	QVHS	+
	P30	+	+	+	+	NS	+

Results from 2 patients that interrupted antiretrovirals and became viremic marked in yellow. (protocol violators)

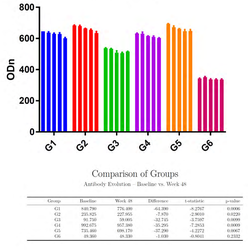
«Intention-to-treat» risk analysis (recommended by CONSORT)
$P = 0.0640$ (Fisher's exact test)

Effect size	Value	95% CI
Relative Risk (positive or dubious HIV DNA in both PBMC and RB of subjects receiving the complete protocol)	0.6250	0.2397 to 0.9428
Reciprocal of relative risk	1.600	1.061 to 4.171
Attributable risk (P1 - P2)	0.3600	-0.07125 to 0.7352

«Per protocol» risk analysis (without protocol violators who significantly altered the treatment outcome; also recommended by CONSORT)
$P = 0.0452$ (Fisher's exact test)

Effect size	Value	95% CI
Relative Risk (positive or dubious HIV DNA in both PBMC and RB of subjects receiving the complete protocol)	0.5217	0.1562 to 0.9041
Reciprocal of relative risk	1.917	1.106 to 6.401
Attributable risk (P1 - P2)	0.4583	0.04833 to 0.9083

Antibodies quantitation means using the Abbott ARCHITECT HIV Ag/Ab Combo assay (Abbott, IL, USA) by group:



The SPARC-7 Patients:

- Two subjects (P26 and P29) from Group 6's showed an undetectable DNA in PBMCs at the end of the treatments. We thus decided to subject the PBMC samples and rectal biopsies (RB) from these subjects to external validation.
- DNA quantifications were repeated following another RT rtPCR method [Viard et al, AIDS 2004] by an operator independent from the institutions involved in the study*.
- Results showed that both P26 and P28 displayed a detectable viral DNA both in PBMC and RB at baseline and, at the end of the study, an undetectable viral DNA in both duplicate analyses in PBMCs and RB (p29), or a dubious positivity (negative in one of the duplicate analyses) in PBMC and undetectable viral DNA in both duplicates in RB. These results confirmed the analysis conducted in Sao Paulo by our group.

Qualitative episomal HIV DNA in PBMCs over time. Tests have been performed in duplicates, and +/- represents presence of positive and negative results at the same sample tested*

	ID	Episomal DNA week0	week4	week20	week24	week48
G1	P1	-	-	-	-	-
	P2	+ / -	-	+ / -	-	+
	P3	+	+ / -	-	+	-
	P4	-	+	-	-	+
	P5	-	-	-	-	-
G2	P6	+	+	-	-	-
	P7	-	+	-	+	-
	P8	+	+	-	+	-
	P9	+	-	-	+	-
	P10	-	-	-	-	-
G3	P11	-	-	-	-	-
	P12	-	-	ND	+	+
	P13	-	-	-	-	-
	P14	-	-	-	-	-
	P15	-	-	-	-	-
G4	P16	-	-	-	-	-
	P17	-	-	-	-	-
	P18	+	+	-	+	-
	P19	∞	-	-	-	-
	P20	-	+ / -	-	-	-
G5	P21	+	+	-	-	-
	P22	+	+	-	-	-
	P23	+	+	-	-	-
	P24	+	+	+ / -	+	+ / -
	P25	-	-	-	-	∞
G6	P26	-	-	+	-	-
	P27	-	-	-	-	-
	P28	+	-	+	-	+ / -
	P29	-	-	-	-	-
	P30	-	-	+	-	+ / -

Conclusions:

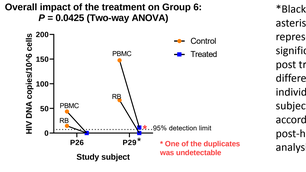
- A significant reduction of viral DNA as analyzed by a more conservative qualitative analysis was detected only in the group that received all proposed interventions: treatment intensification, HDACi, auranofin and DC- vaccine (G6).
- A reduction of the immune inflammation marker CD38 among individuals already in suppressive ART was also detected in G6, suggesting a decrease in production of viral proteins and/or bacterial translocation.
- Subjects displaying a negative HIV DNA at the end of follow up started from a low viral reservoir at baseline
- The dendritic cell vaccine administered is immunogenic, and patient P29 evolved to total PBMC DNA below detection limits only after vaccination.
- Treatments were well tolerated
- Only a portion of patients showed a clear response SPARC-7 patients
- Undetectable viral DNA may in some cases be a consequence of ART-only regimens (one study subject treated with intensified ART only showed an undetectable viral DNA)
- It is as yet unclear whether undetectable HIV DNA may lead to long-term control/cure of the infection in the absence of drugs: undetectable viral DNA resulted in Sustained HIV Remission without Antiretrovirals (Berlin patient, SPARTAC, and VISCONTI patients) but some studies show that at least in some cases it was not the case (see Boston patients and Mississippi baby)
- Analytical Treatment Interruption is being planned for study participants.

Demographic, virologic, immunologic characteristics :

Group	ID	Nadir CD4	Gender	age	VL before treatment	ARV	Treatment initiation (year)
G1	P1	395	MALE	30	78,753	TDF/3TC/EFV	2013
G1	P2	534	MALE	49	17,188	TDF/3TC + FPV-r	2002
G1	P3	480	MALE	34	110,000	TDF/3TC + NVP	2004
G1	P4	658	MALE	54	52,312	TDF/3TC/EFV	2013
G1	P5	758	MALE	34	9,736	TDF/FTC + RAL	2014
G2	P6	492	MALE	29	11,762	TDF/3TC/EFV	2013
G2	P7	566	MALE	61	97,000	AZT/3TC + NVP	2013
G2	P8	604	MALE	40	7,512	AZT/3TC + ATV-r	2013
G2	P9	661	MALE	36	55,000	TDF/3TC/EFV	2012
G2	P10	683	MALE	45	13,715	TDF/3TC/EFV	2013
G3	P11	398	MALE	40	18,500	TDF/3TC/EFV	2012
G3	P12	731	MALE	28	3,340	ABC+3TC+ATZ-r	2012
G3	P13	372	MALE	34	20,221	TDF/3TC/EFV	2012
G3	P14	490	MALE	52	90,000	AZT/3TC + EFV	2010
G3	P15	506	MALE	35	5,361	TDF/3TC/EFV	2013
G4	P16	412	MALE	41	15,931	AZT/3TC + EFV	2010
G4	P17	372	MALE	32	20,221	ABC + 3TC + EFV	2012
G4	P18	873	MALE	48	22,300	AZT/3TC + EFV	2007
G4	P19	434	MALE	35	88,000	TDF/3TC + FPV-r	2011
G4	P20	448	MALE	28	154,504	TDF/3TC + ATV-r	2012
G5	P21	749	MALE	32	98,000	TDF/3TC + FPV-r	2008
G5	P22	552	MALE	55	364,000	AZT/3TC + EFV	2011
G5	P23	490	MALE	27	527,795	TDF/3TC + ATV-r	2013
G5	P24	161	MALE	56	480,000	TDF/3TC/EFV	1996
G5	P25	400	MALE	44	102,000	TDF + VPV-r	1997
G6	P26	530	MALE	38	12,859	AZT/3TC + EFV	2012
G6	P27	766	MALE	25	172,029	TDF/3TC/EFV	2015
G6	P28	685	MALE	45	57,800	TDF/3TC/EFV	2012
G6	P29	505	MALE	50	3,300	TDF/3TC/EFV	2010
G6	P30	460	MALE	61	278,000	TDF/3TC/EFV	2005

Total HIV DNA quantitation in PBMCs and Rectal biopsy tissues over time:

	ID	w0	w24	w48	After DC vaccine	DNA in Rectal tissue at baseline (BX1)	DNA in Rectal Tissue at end (BX2)
G1	P1	1.49	11.40	2.12		9.63	2.13
	P2	4.80	9.95	14.65		19.49	1.19
	P3	0.51	0.75682	12.84		0.75	2.22
	P4	2.42	2.80	5.41		2.74	6.57
	P5	3.71	2.40	17.04		5.48	3.29
	mean	2.44	4.26	10.37		7.81	3.08
G2	P6	4.71	1.08	12.82		0.89	9.12
	P7	0.67	1.56	2.98		4.39	0.28
	P8	1.29	2.49	BLOL		1.33	4.28
	P9	6.50	1.85	28.35		40.47	1.25
	P10	0.18	19.42	11.39		27.53	6.52
	mean	2.67	5.48	13.64		15.03	4.29
G3	P11	0.89	3.14	3.32		4.31	0.76
	P12	4.70	8.35	18.14		4.87	4.48
	P13	0.98	6.62	1.16		4.93	3.27
	P14	2.93	26.78	42.16		56.49	10.07
	P15	4.84	7.17	10.05		9.97	5.05
	mean	2.97	10.41	14.57		16.11	4.72
G4	P16	1.92	0.02	20.91		20.60	5.82
	P17	13.59	30.64	15.62		14.45	66.06
	P18	0.26	2.47	2.48		3.44	0.89
	P19	7.84	35.87	24.24		18.43	42.70
	P20	1.62	7.65	2.43		0.98	7.24
	mean	5.04	15.34	13.14		11.58	24.34
G5	P21	9.77	27.57	12.13	124.81	26.06	25.47
	P22	7.70	28.62	0.41	13.96	5.28	10.93
	P23	13.00	13.00	24.92	15.63	0.29	10.23
	P24	21.32	28.21	18.51	46.75	27.00	25.78
	P25	27.12	19.78	19.41	31.94	21.86	35.43
	mean	15.79	23.44	15.08	46.22	16.09	21.17
G6	P26	0.31	BLOL	BLOL	BLOL	4.49	0.96
	P27	33.31	4.36	34.36	63.52	30.76	16.09
	P28	36.30	70.37	18.09	20.37	21.19	13.65
	P29	11.71	7.65	0.83	BLOL	2.46	BLOL
	P30	0.32	0.25	0.82	15.37	0.56	6.36
	mean	28.79	20.66	13.52	33.09	11.93	9.27



*One of the duplicates was undetectable

*Black asterisks below represent the significant pre-post treatment differences in individual subjects according to post-hoc analysis

References

- Audrito V, Vaisitti T, Rossi D, Gottardi D, D'Arena G, Laurenti L, Gaidano G, Malavasi F, Deaglio S. Nicotinamide blocks proliferation and induces apoptosis of chronic lymphocytic leukemia cells through activation of the p53/miR-34a/SIRT1 tumor suppressor network. Cancer Res. 2011 Jul 1;71(13):4473-83. doi: 10.1158/0008-5472.CAN-10-4452. Epub 2011 May 12.
- Buzón MJ, Massanella M, Llibre JM, Esteve A, Dahl V, Puertas MC, Gatell JM, Domingo P, Paredes R, Sharkey M, Palmer S, Stevenson M, Clotet B, Blanco J, Martinez-Picado J. HIV-1 replication and immune dynamics are affected by raltegravir intensification of HAART-suppressed subjects. Nat Med. 2010 Apr;16(4):460-5. doi: 10.1038/nm.2111.
- Chirullo B, Sgarbanti R, Limongi D, Shytaj IL, Alvarez D, Das B, Bor A, Dal Corso S, Chomont N, Liotta L, Petricoin EI, Nowell S, Pelosi E, Garaci E, Savarino A, Palamara AT. A candidate anti-HIV reservoir compound, auranofin, exerts a selective 'anti-memory' effect by exploiting the baseline oxidative status of lymphocytes. Cell Death Dis. 2013 Dec 5;4:e944. doi: 10.1038/cddis.2013.473.
- Cimerman S, Sucupira MC, Janini DS, Diaz RS. Less-sensitive HIV-1 enzyme immunoassay as an adjuvant method for monitoring patients receiving antiretroviral therapy. AIDS Patient Care and STDs, 2007, 21(2):42-54
- Fonteh P, Meyer D. In vitro reactivation of latent HIV-1 by cytostatic bis(thiosemicarbazonato) gold(III) complexes. BMC Infect Dis. 2014 Dec 11;14:680. doi: 10.1186/s12879-014-0680-3.
- Gao XY, Li K, Jiang LL, He MF, Pu CH, Kang D, Xie J. Developmental toxicity of auranofin in zebrafish embryos. J Appl Toxicol. 2017 May;37(5):602-610
- Komninakis S, Santos D, Santos C, Oliveros M, Sanabani S, Diaz RS. HIV-1 Proviral DNA load (qPCR) in patients subjected to Structured Treatment Interruption (STI) after antiretroviral therapy failure, J Clin Microbiol. 2012 Jun;50(6):2132-3.PMID:22423851.
- Kumar AM, Fernandez JB, Singer EJ, Commins D, Waldrop-Valverde D, Ownby RL, Kumar M. Human immunodeficiency virus type 1 in the central nervous system leads to decreased dopamine in different regions of postmortem human brains. J Neurovirol. 2009 May;15(3):257-74. doi: 10.1080/13550280902973952.
- Lewis MG, Dal Conso S, Chomont N, Palamara AT, Tardugno M, Mai A, Collins M, Wagner WL, Valley-Ogunro J, Greenhouse J, Chirullo B, Norelli S, Garaci E, Savarino A. Gold drug auranofin restricts the viral reservoir in the monkey AIDS model and induces containment of viral load following ART suspension. AIDS. 2011 Jul 17;25(12):1547-56. doi: 10.1097/QAD.0b013e32834784d7.
- Madrid-Elena N, García-Bermejo ML, Serrano-Villar S, Díaz-de-Santiago A, Sastre B, Gutiérrez CI, Dronda F, Coronel Díaz M, Domínguez E, López-Huertas MR, Hernández-Novoa B, Moreno S. Maraviroc is associated with latent HIV-1 reactivation through NF-κB activation in resting CD4+T cells from HIV-infected individuals on Suppressive Antiretroviral Therapy. J Virol. 2018 Feb 14. pii: JVI.01931-17. doi: 10.1128/JVI.01931-17.
- Maldarelli F, Palmer S, King MS, Wiegand A, Polis MA, Mican J, Kovacs JA, Davey RT, Rock-Kress D, Dewar R, Liu S, Metcalf JA, Rehm C, Brun SC, Hanna GJ, Kempf DJ, Coffin JM, Mellors JW. ART suppresses plasma HIV-1 RNA to a stable set point predicted by pretherapy viremia. PLoS Pathog. 2007 Apr;3(4):e46.
- Min S, Sloan L, DeJesus E, Hawkins T, McCurdy L, Song I, et al. Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of dolutegravir as 10-day monotherapy in HIV-1-infected adults. AIDS 2011;25:1737-1745.
- Samer S, Arif MS, Giron LB, Zukurov JPL, Hunter J, Galinskas J, Janini LM, Sucupira MC, Diaz RS. Sirtuin1 Inhibitor Nicotinamide Activates Latent HIV Ex Vivo in ART Suppressed Individuals. 16th European AIDS Conference, Milan, Italy. 25–27 October, 2017. Abstract PE153
- van Lelyveld SF, Drylewicz J, Krikke M, Vent EM, Otto SA, Richter C, Soetekouw R, Prins JM Brinkman K, Mulder JW, Kroon F, Middel A, Symons J, Wensing AM, Nijhuis M, Borghans JA, Tesselaar K, Hoepelman AI; MIRS study group. Maraviroc Intensification of cART in Patients with Suboptimal Immunological Recovery: A 48-Week, Placebo-Controlled Randomized Trial. PLoS One. 2015 Jul 24;10(7):e0132430. doi: 10.1371/journal.pone.0132430. eCollection 2015.
- Viard JP, Burgard M, Hubert JB, Aaron L, Rabian C, et al. (2004) AIDS 18: 45-49.
- Vint IA, Chain BM, Forman JC. The effects of auranofin on activation and interleukin-2 release from human peripheral blood mononuclear cells.Agents Actions. 1993 Nov;40(3-4):209-14.
- Sharkey ME, Teo I, Greenough T, Sharova N, Luzuriaga K, Sullivan JL, et al. Persistence of episomal HIV-1 infection intermediates in patients on highly active anti-retroviral therapy. Nat Med. 2000;6(1):76-81.

Acknowledgements:

- The authors are thankful to Dr. Iart Luca Shytaj (Ruprecht Karol Universität Heidelberg, Germany), and Drs. Roberto Cauda and Francesca Lombardi (Universita Cattolica del Sacro Cuore, Roma, Italy) for external validation of the results.
- The study was funded by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP, Brazil, #2013/11323-5), Conselho Nacional de Pesquisa (CNPq, Brazil, #403558/2012-3), and an Investigator Sponsored Study Programme from ViiV Healthcare (Brentford, UK). Torino Pharma (San Diego, CA) donated some of the study drugs.
- The funders had no role in study design, data collection and analysis, decision to present the data, or preparation of the paper.