Effects of IM28 on HIV-1 and Metabolic Disorders-induced Highly Active Antiretroviral Therapy in Gabonese Patients

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Abstract

Highly active antiretroviral therapy (HAART) was recently associated with disturbance of lipid metabolism, fat mass distribution and insulin resistance, known to be partly regulated by steroid hormones. Nevertheless, complementary or adjunctive wide used of dehydroepiandrosterone (DHEA) in fully suppressed HIV patients appeared to have no beneficial antiviral, immuno modulatory, hormonal or body composition effects. Herein, we tested *in vivo* safety and efficacy of IM28, a potent analog of DHEA, on volunteers HIV positive patients from Gabon, randomly organized as followed: IM28 alone (15 patients + 30 healthy individuals), IM28+HAART (150 patients), HAART alone (13 patients) and DHEA+HAART (23 patients). All patients were evaluated three times: M0 (pre-treatment with IM28), M1 (after six months of treatment with IM28) and M2 (after 12 months of treatment with IM28). No noticeable side effects were observed for IM28 as evaluated by measuring hepatic, cardiac, renal functions and body weight progression. Compared to HAART therapy, combinations DHEA+HAART, IM28+HAART or IM28, quickly rescued patients from anxiety, restored their appetite and normalized their body weight. However, only patients receiving IM28 alone or in combination with HAART showed normalization of body temperatures and increase in the levels of CD4 lymphocytes ($p<0.01$) and haemoglobin ($p<0.001$), as well as significant reductions of platelets antigenemia p24 ($p<0.001$) and viral load ($p<0.01$). Moreover, only cardiovascular, obese and hypertensive disease-induced HAART therapy patients under IM28 showed restoration of body levels in lipids, glucose and normalization of blood pressure. These data unequivocally suggest therapeutic proprieties to IM28 for HIV-1 and cardiovascular-induced HAART therapy. These open new promising insights for IM28.

Keywords: IM28; DHEA; HAART; Hypertension; HIV-1 patients; Opportunistic diseases

Introduction

Despite remarkable improvements of the survival and quality of life style in HIV patients with the use of highly active antiretroviral therapy (HAART), cross-sectional and prospective studies have reported chronically complications including hyperlipidemia, lipodystrophy and impaired glucose metabolism, qualified as metabolic syndrome. The later result in cardiovascular disorders such as diabetes, hypertension, abdominal obesity, low HDL, hypercholesterolemia, hypertriglyceridemia (see Jevtović et al., 2009; Carper et al., 2008; Chanu and Valensi, 2005; Lee et al., 2005; Lee et al., 2004). Metabolic syndrome arise earlier within the first third months of treatment with HAART along with chronic headache that may also result from opportunistic infections or side-effects of HAART, or from the HIV in the central nervous system itself (see Segerer et al., 1999; Koppel et al., 2000; Ferrando and Freyberg, 2008a; Manfredi and Chiodo, 2001; Geraix et al., 2006; Sattler et al., 2001; Cattelan et al., 2001; Chow et al., 2003). However, pain induced by AIDS therapy and other symptoms very often cover depressive episodes represent progressive problems and induce the necessity to alter the HAART (Ferrando and Freyberg, 2008b).

On a clinical note, not only the long-term effect of current HAART still limited by resistance generation (Hoffmann and Jaeger, 2003) due to the latent HIV reservoir, but also, the association of HAART with some classes of drugs entail special considerations including potential drug-drug interactions as is the case for antidepressants which use similar metabolic pathways with the panoply of AIDS drugs (Farber and McDaniel, 2002; Penzak et al., 2000). Likewise, whereas prospective study with low doses of the statin rosuvastatin has provided interesting avenues on the treatment of hyperlipidemia in HIV patient under HAART (Calza et al., 2005a; Calza et al., 2005b), previous data have reported that some potential protease inhibitors interacting with statins metabolism through the cytochrome P450, family 3, subfamily A, polypeptide (CYP3A4) pathway can inhibit this pathway thereby increasing the concentration of statins several times with the higher risk of skeletal muscle and hepatic toxicity (Dube et al., 2000). Another interesting approach was proposed by the supplementation with alpha-lipoic acid, a potent antioxidant that had positively impact patients with HIV and acquired immune deficiency syndrome by restoring blood total glutathione level and improving functional reactivity of lymphocytes to T-cell mitogens, but without any impact on body lipid (Jariwalla et al., 2008). In the same way, the widely use of dehydroepiandrosterone (DHEA) as complementary therapy among people with HIV infection has shown

beneficial effects in depressive HIV1 patients (Ferrando and Freyberg, 2008a; Carrico and Antoni, 2008), particularly in women, in which DHEA provided positive potential effects on mood and energy (Davis et al., 2008; Poretsky et al., 2009). Indeed, DHEA has provided increase of AZT uptake by changing the affinity of AZT orphan transporter (Nishimura et al., 2008), appears to stimulate a significant immune response in elderly (May et al., 1990; Khorram et al., 1997) and to alter body composition by increasing lean body mass (Nestler et al., 1988; Morales et al., 1998). But, DHEA still limited as no helpful antiviral, hormonal, or body composition has been noticed in fully suppressed HIV patients (Abrams et al., 2007).

However, the approach of DHEA in HIV therapy was relevant as an association has been established between cortisol and (DHEA) ratio, with lipid alteration and lipodistrophy in HIV positive patients since the imbalance of the synthesis and the degradation of lipid or increase metabolism are regulated by cortisol and DHEA (Christeff et al., 1999a; Christeff et al., 1999b). We then thought to prospect *in vivo* effects of IM28, an analog of DHEA which demonstrates *in vitro* antiviral potency including inhibition of the reverse transcriptase activity, the restriction of the envelop proteins mediating cell-cell fusion (gp120/gp41) between infected and healthy cells and the suppression of 3TC/AZT resistant in clinical isolate (Diallo et al., 2000; Mavoungou et al., 2005). Indeed, if in addition of DHEA positive effects, IM28 demonstrates efficacy against the reservoir of latently infected cells in the body, it could be used adjunctively with HAART or alone as alternative solution for opportunistic diseases-induced HAART therapy or for HIV.

Patients and Experiment Design

Study groups

The study was a prospective randomized, double-blind, controlled study on 201 HIV-1 positive patients and 30 healthy individuals. All patients were required to be at 18 years of age and over. Volunteers HIV positive patients were confirmed by ELISA and western blot with Lymphocytes greater than 150/mm³; adequate hematology parameters: absolute count equal or greater than 1500/mm3 for neutrophil, 150000/mm3 for platelets and 9g/dl for hemoglobin.

186 patients among 201 (93%) involved in the study were CDC 2 and 3, already treated with HAART combivir, ép ivir and retrovir when the study started. These patients were already under HAART since 6 to 24 months at le centre de traitement ambulatoire (CTA). 45% of these patients under HAART carried one or various metabolic opportunistic patholo-

gies such as Diabetes, hypertension, tuberculosis, malaria, skin rash, digestive rash, urinal rash, facial paralysis, language troubles, memory deficit, anorexia and anxiety; most of them complained from violent headache.

Additional 15 HIV positive naïve volunteers recently diagnosed at the Anyambyè and 30 healthy volunteers were used to test the safety and the tolerability of IM28.

All patients must have adequate renal and liver functions and must be able to receive medicine per os. Exclusion criteria included; active substance abuse (e.g., alcohol or injection drugs); pregnancy or breast-feeding.

Study design

To address the question of efficacy and tolerance of IM28 or it in-vivo efficacy, we enrolled 15 naïve patients and 30 healthy volunteers. The adjunctive efficacy of IM28 or its effects on opportunist disease and metabolic syndrome was tested on 150 patients already under HAART for 6-24 months. As control groups we kept 13 patients kept HAART therapy only and enrolled 23 patients on DHEA+HAART. All these volunteers were evaluated three times: M0 (pre-treatment with IM28), M1 (after six months of treatment with IM28) and M2 (after 12 months of treatment with IM28). The Drug Product Services at the CRPH, Libreville, Gabon, provided pharmaceutical grade DHEA was furnish by Delpech lab (France) and IM28 (50 mg capsules) produced locally from DHEA as specified in its data sheet (INPI 0990847; Fr2792201; Wo0106666; CRPH, Gabon).

Procedures

Patients received a dose of 50 mg/day/70Kg of DHEA or IM28, respectively. They had to take simultaneously their medicines and their blood samples. Their urine where collected weekly according to the research guidelines of our institution (CRPH). Laboratory measurements included CD4+ T lymphocyte cell count, Haemoglobin, and platelets levels were measured using and Cobas instrument from Biomerieux (France). The antigenemia P24 was measured using Mini Vidas from Biomerieux (France). Hepatic, renal and cardiac functions were evaluated using UV-VIS spectrophotometer. Body Weights were measured on a calibrated scale Zumba balance. Viral load was mesured by DNA technique.

Statistical analysis

Data are Mean ± SEM. Statistical analysis performed using student t-test or one-way analysis of variance (ANOVA) followed by Newman-keuls post hoc multiple comparison tests using Graph pad Prism software (4, San Diego). Only $p < 0.05$

Parameters	Baseline	IM28	P <
UREA (2.5-7.5 mmol)	3.73 ± 0.12	4.07 ± 0.25	NS
Creatinine 562-120 µmol/L	77.50 ± 2.50	105.20 ± 6.04	0.001
GOT (<37 UI/L)	12.10 ± 0.60	15.90 ± 1.11	0.01
TGP (<40 UI/L	10.50 ± 0.98	11.70 ± 1.03	NS
Cholesterol (3.6-7 mmol/l)	4.15 ± 0.98	4.09 ± 0.12	NS
Lymphocytes (mm³)	2202 ± 100.40	2377 ± 156.69	NS
Body weight (Kg)	59.70 ± 1.45	61.10 ± 1.36	NS
Haemoglobin (g/dl)	12.88 ± 0.18	12.87 ± 0.16	NS
Glucose (4.6-6.1 mmol/l)	3.50 ± 0.09	4.70 ± 0.14	0.001

Table 1: Evaluation of IM28 Toxicity. Values are Mean±SEM of 10 HIV patients under IM28 alone. Statistical analysis was done using a student t test.

was considered as significant.

Results

In vivo IM28 toxicity evaluation

We tested the safety of IM28 on 30 healthy volunteers and 15 naïve patients freshly diagnose with HIV1. Data from the baseline (M0) for hepatic, cardiac and renal functions measured to M2 on healthy volunteers (not shown) or 15 patients under IM28 alone did not shown dramatics variations from the baselines values for urea (3.73 ± 0.12 vs 4.70 ± 0.25 mmol), TGP (10.50 ± 0.98 vs 11.70 ± 1.03 UI/I), Cholesterol (4.15 ± 0.98 vs4.09 ± 0.12) (see table 1) albeit significant increases seen for creatinine (77.50 ± 2.50 vs 105.20 ± 6.04 mmol), oxaloacetic transaminase (GOT) (12.10 ± 0.60 vs 15.90 ± 1.11UI/I), which remained in the range of normal values. Interestingly, whereas the overall level of blood glucose baseline averaged 3.50 ± 0.09 mmol/I, under the accepted values, IM28 induced a normalization in treated patients by significantly shifting the baseline glucose value at 4.70 ± 0.14 mmol/I ($p<0.05$) that rep-

resents a normal admitted value (see Table 1). Healthy and HIV positive volunteers tolerated IM28 adequately. Healthy individuals reported increasing of their appetite and libido, two weeks after the beginning of the treatment. Patients under IM28 treatment presented a clear well being. Some of them complaining about violent headaches at their admission felt better.

In addition, compare to the cardio vascular values of healthy subjects at M0, HIV positive patient developed evident hypertension. When treated healthy subjects with IM28, the later was without effects on cardio vascular rate (Figure 1). Altogether, these data showed that no noticeable toxic effects could be associated to IM28 which can be considered as safe for patients.

In vivo effects of IM28 on HIV reservoir, immune and non immune factors

In the group treated with HAART + IM28, there was increase in body weight ($P<0.01$), in the levels of CD4+ ($p<0.01$), lymphocytes and hemoglobin ($p<0.001$) at M2 (Table 2). Concomi-
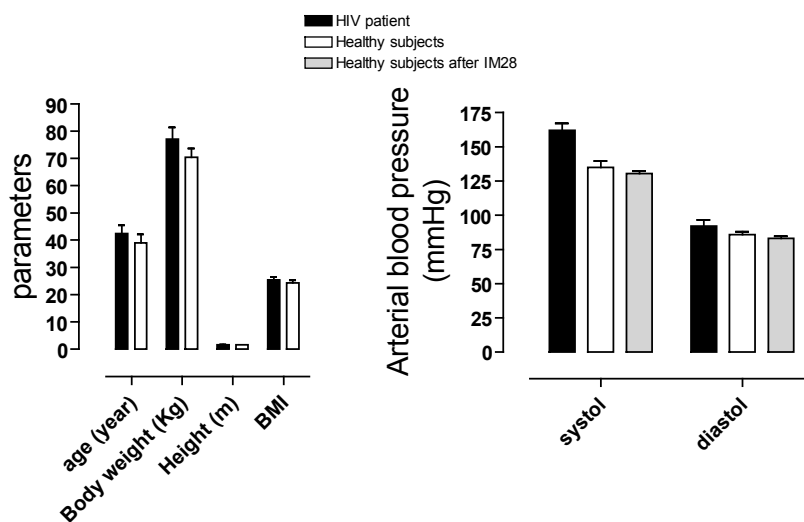

Figure 1: The left panel represent the Age, Body weight, Height and Body max index (BMI) of HIV positive (■) and healthy (?) subjects at M0. The right Panel presents cardiovascular values of HIV positive treated with HAART and healthy subject treated with IM28 (■) at M2. As seen, IM28 did not affect cardiovascular values in healthy subjects. Values are Mean±SEM of 10 HIV positives patients and 30 healthy volunteers.

Parameters	Baseline (HAART only) at Mo	HAART + IM28 at M2	P <
Lymphocytes (mm^3)	2103 ± 160	2460 ± 40	0.05
Body weight (Kg)	59.37 ± 2.075	60.05 ± 4.49	NS
Haemoglobin (g/dl)	13.50 ± 0.40	14.75 ± 0.44	0.05

Table 2: Effects of IM28 on Body weight, Hemoglobin & Lymphocytes levels. Values are Mean ± SEM of 150 HIV positives patients under HAART + IM28. Statistical analysis was done using a student t test.

%	DHEA + HAART		IM28 + HAART		
	Base line	M2	Base line	M2	
Tuberculosis	11.71	9.68	7.8	2.2	
Malaria	80.02	79.72	76.70	3.5	
Skin rash	27.03	22.58	20.44	7.80	
Digestive rash	98.20	94.622	92.20	20.09	
Urinary rash	15.32	15.02	15.32	3.30	
facial paralysis	-	-	0.03	0.01	
Language and memory troubles	-	-	0.10	0.00	
Stroke	-	-	0.06	0.02	
Anxiety	-	-	0.80	0.10	

Table 3: Percentage of opportunistic diseases and their evaluation from M0 to M2. As noticed, IM28 clearly reduced the percentage of opportunist disease.

tantly, the increased levels of CD4+ in IM28-treated patients were accompanied by significant decrease in their platelets, antigenemia p24 ($p < 0.001$) and viral load ($p < 0.01$) (Figure 2) confirming the anti-viral effects of IM28 documented in previous *in vitro* studies.

Effects of IM28 on opportunistic diseases

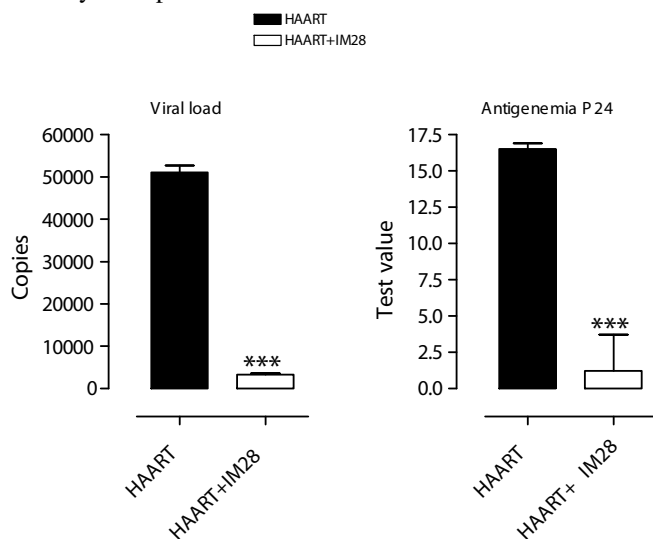Many HIV patients with both abdominal fat accumulation

Figure 2: *in vivo* antigénémie P24 and viral load following IM28 supplementation. The left panel represents viral load values and the right panel is the antigenemia P24 of 150 HIV positive (■) patients under HAART and supplemented with IM28 (?) one year later. As observed, IM28 supplementation decreased very significantly viral reservoir in patients yet receiving HAART. Values are Mean ± SEM of 150 HIV positives patients. ***, $p < 0.001$.

and osteoporosis are recognized as long-term complications of HIV infection or treatment with HAART. Although we did not measure osteoporosis, we found that both IM28 and DHEA normalized obesity and diabetes in treated HIV patients. But IM28 alone was able to significantly reduce the percentage of opportunistic affections, such as tuberculosis, malaria, skin rash, digestive rash, urinal rash, stroke, facial paralysis, language and memory troubles, dementia and anxiety (see Table 3). Remarkably, the body temperature, always higher in HIV1 patients or persisting under HAART treatment, was reduced and normalized in patients under IM28. Moreover, while in normotensive, IM28 did not affect cardiovascular values, IM28 rescued and normalized the blood pressure in patient developing hypertension under HAART treatment and (Figure 3).

Discussion

The striking findings in our study are (1) IM28, the analog of DHEA is well tolerated and safety for patients; (2) IM28 affects the size of HIV reservoir *in vivo;* (3) IM28 affects opportunistic cardiovascular diseases-induced HAART therapy and finally (4) IM28 ameliorates mood and quality of life in HAART-treated patients like it analog DHEA as previously described (Ferrando and Freyberg, 2008b; Carrico and Antoni, 2008; Poretsky et al., 2009).

Yet, IM28 that showed *in vitro* capacity to inhibit HIV-1 reverse transcriptase and to restrain cell-cell fusion mediated by HIV envelope glycoprotein with a selectivity index of 3.4 (Mavoungou et al., 2005) was well tolerated by our patients and showed real ability to low the virus reservoir *in vivo* ac-
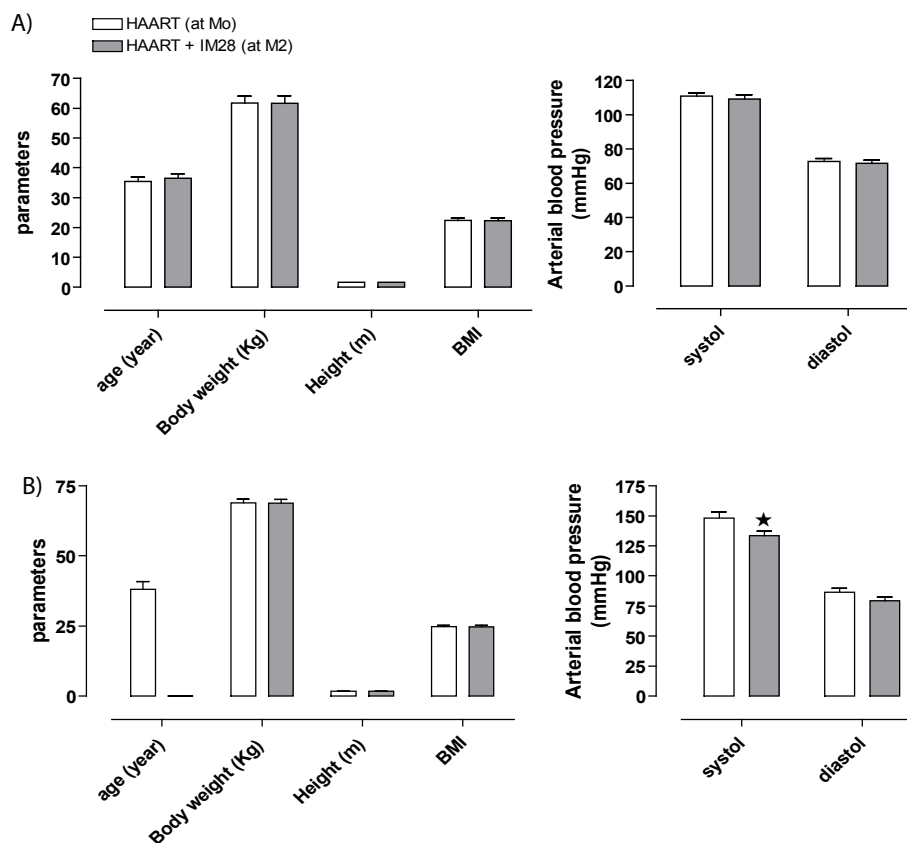
Figure 3: Effects of IM28 on the arterial pressure in HIV positive patients developing hypertension under HAART treatment. Age, Body weight and arterial pressure in normotensive patients (A), and patients developing hypertension under HAART treatment at M0 (under HAART only, ?) and at M2 (HAART + IM28, ■). IM28 clearly regulated the arterial pressure of hypertensive HIV positive patients.

cording to concomitant significant increase in CD4+, decrease in platelets, antigenemia p24 (p<0.001) and viral load (p<0.01) were observed (see Figure 2).

However, before the introduction of HAART, HIV infection was already associated to endothelial dysfunction, hypercoagulability, hypertriglyceridemia and abnormal coronary artery pathology (Assmann et al., 1998). These were ascribed to the involvement of cytokines or inflammation as endothelial dysfunction was related to chemokine receptors (Berger et al., 1999) or cytokines secreted in response to mononuclear or adventitial cell activation by the virus or directly by the secreted HIV-associated protein gp120 (Twu et al., 2002). Thus, the fact that recent introduction of HAART have conducted to the development of cardiovascular and metabolic diseases (Manfredi and Chiodo, 2001; Geraix et al., 2006; Sattler et al., 2001; Cattelan et al., 2001; Chow et al., 2003) suggest the limitation of HAART to counter the effects of cytokine and inflammation which can be responsive of opportunistic diseases. Such limitations of HAART are clearly overcome by IM28 (see Table 3), suggesting that IM28 can affect inflammatory cytokines more to reduce the size of HIV reservoir *in vivo* (see Figure 2) or to limit the inflammatory processes by its direct effect on the HIV-associated protein gp120 as demonstrated with *in vitro* studies (Diallo et al., 2000; Mavoungou et al., 2005). In addition, the fact that chronic treatment with Linoleic acid, one of the main components of IM28 can inhibit NF-kappaB activation (Shah et al., 2006) could account for the potential capacity of IM28 to inhibit NF-kappaB or its effects on cytokines.

Moreover, hemoglobin refers to one of the major biological reservoir of nitric oxide (NO) (Gladwin and Shiva, 2009). Also, the fact that IM28 can normalize hemoglobin may refer to possible effects of IM28 on NO release. Indeed, its component linoleic acid is known to induce the expression of inducible nitric oxide (iNOS) and cyclooxigenase 2 (COX-2) as well as PGE2 and NO release through activation of p42/p44, MAPK, and NF-kappaB that in turn regulate PGE2 and NO as documented in retinal pigment of epithelial cells (Jariwalla et al., 2008). These hypothetic effects on NO release, PGE regulation or MAPK activation should also explain the ability of IM28 to decrease higher temperatures found in HIV positive patients treated with HAART or not. This is relevant as IM28 reduced depression in HIV treated patients like DHEA which have been demonstrated to reduce depressive symptoms in HIV patients with subsyndromal major depression (Rabkin et al., 2006).

Taken altogether, these data suggest that, the substitution of DHEA which is already used adjunctively or as supplement in HIV-1 treatment by IM28 should represent a better therapeutic avenue for the prevention or the cure of opportunistic metabolic or cardiovascular diseases induced by HAART therapies. But additional studies are needed to fully address speculative suggestions made above.

Conclusion

DHEA is in general, widely used as an adjunctive or complementary therapy because of its capacity to enhance well-being. Our data suggest that, more to impact on the quality of life benefits, IM28 confirmed its antiviral, immune-modulating, or androgenic properties and appear as innovative insight for improving HIV patient outcomes.

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