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Endocrine effects of oral dehydroepiandrosterone in men with HIV infection: a prospective, randomized, double-blind, placebo-controlled trial

Leonid Poretsky[a,c,f,*], David J. Brillon[a,c], Stephen Ferrando[b], Judy Chiu[d], Martin McElhiney[d], Andrea Ferenczi[f], Maria Cristina Irene P. Sison[g], Ivan Haller[c], Judith Rabkin[b,d,e]

[a]*Division of Endocrinology, Department of Medicine, Weill Medical College of Cornell University, The New York Presbyterian Hospital, New York, NY 10021, USA*

[b]*Department of Psychiatry, Weill Medical College of Cornell University, The New York Presbyterian Hospital, New York, NY 10021, USA*

[c]*General Clinical Research Center, Weill Medical College of Cornell University, The New York Presbyterian Hospital, New York, NY 10021, USA*

[d]*New York State Psychiatric Institute, Columbia University College of Physicians and Surgeons, New York, NY 10032, USA*

[e]*Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY 10032, USA*

[f]*Division of Endocrinology and Metabolism, Department of Medicine, Beth Israel Medical Center and Albert Einstein College of Medicine, New York, NY 10003, USA*

[g]*North Shore-Long Island Jewish Institute for Medical Research, Biostatistics Unit, Manhasset, NY 11030, USA*

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Abstract

Dehydroepiandrosterone (DHEA) is commonly used by HIV-infected men, but its endocrine effects in this population are not well defined. We conducted an 8-week randomized, placebo-controlled trial to determine the effects of escalating doses (100-400 mg/d) of DHEA on the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axes, and on a number of metabolic parameters in 69 HIV-positive men (31 in DHEA-treated group, 38 in placebo group). High-dose (250 μg) corticotropin and luteinizing hormone–releasing hormone stimulation tests were carried out in all subjects. Fifty-four subjects (26 in the DHEA-treated group and 28 in the placebo group) also underwent optional corticotropin-releasing hormone test, and 67 subjects (31 in DHEA-treated group and 36 in placebo group) underwent optional low-dose (1 μg) corticotropin stimulation test. All tests were performed at baseline and at the end of week 8. Repeated-measures analysis of variance was used to analyze the data. We observed significant increases in circulating levels of DHEA, DHEA-sulfate, free testosterone, dihydrotestosterone, androstenedione, and estrone, and a decline in the serum concentration of sex hormone–binding globulin in the DHEA-treated group but not in the placebo group ($P < .001$). There were no differences between the groups in other endocrine or metabolic parameters or in the results of the stimulation tests. In conclusion, oral DHEA therapy in HIV-positive men significantly increases circulating levels of DHEA and DHEA-sulfate, free testosterone, dihydrotestosterone, androstenedione, and estrone and suppresses circulating concentration of sex hormone–binding globulin. Long-term studies are needed to assess the clinical significance of these hormonal changes in subjects with HIV infection receiving oral DHEA therapy.

1. Introduction

Dehydroepiandrosterone (DHEA) and its sulfated stable form, DHEA-sulfate (DHEAS), are adrenal hormones that serve as substrates for peripheral androgen and estrogen synthesis [1]. Serum concentrations of DHEAS decline with age [2] and are low in numerous disease states, including HIV infection [3] and depression [4].

In vitro, DHEA has been shown to inhibit glucose production by hepatic cells [5], increase insulin secretion by beta cells [6], enhance natural killer cell cytotoxicity [7], increase endothelial cell proliferation [8], and improve immune and endothelial cell function [8,9].

In animal studies, DHEA increased rodent life span [10], enhanced indices of immune function [11], reduced

* Corresponding author. Division of Endocrinology and Metabolism, Beth Israel Medical Center, New York, NY 10003, USA. Fax: +1 212 420 2224.

E-mail address: lporetsk@bethisraelny.org (L. Poretsky).

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carcinogenesis [12], reduced weight [13], and improved pancreatic beta-cell function [6,13].

In human subjects, treatment with DHEA allowed the reduction of concurrent glucocorticoid dosage in patients with systemic lupus erythematosus [14,15]; improved the sense of well-being, mood, energy, and activity levels [16]; increased natural killer cell cytotoxicity in postmenopausal women [17]; produced reductions in abdominal fat and indices of insulin resistance in elderly individuals [18,19]; increased muscle mass and reduced serum low-density lipoprotein and total cholesterol [20,21]; potentiated corticotropin response to stress [22]; and increased circulating levels of insulin-like growth factor I (IGF-I), possibly by inhibiting circulating levels of insulin-like growth factor binding proteins (IGFBP-1 and IGFBP-3) [18,23,24].

In patients with HIV infection, reduced circulating DHEA and DHEAS levels are associated with disease progression [25]. Compared with HIV-negative individuals, HIV-infected patients have significantly lower plasma DHEAS levels, which, before the advent of antiretroviral therapy, were reported to correlate with CD4 count [26]. Serum DHEAS concentrations decline with progression of disease and, after antiretroviral therapy, increase in association with the improvement in CD4 cell count [27].

We conducted a double-blind, placebo-controlled, randomized trial to assess primarily the antidepressant effects of DHEA in HIV-positive patients with mild depression and fatigue. The results of the psychiatric study, demonstrating the antidepressant efficacy as well as safety of DHEA, are reported separately [28] and are briefly summarized in the Discussion. A secondary objective of the trial, reported here, was to assess a number of hormonal and metabolic parameters that could be affected by oral administration of DHEA based on the animal and human studies reviewed above.

In this report we describe the effects of oral DHEA administration on the circulating levels of DHEA, DHEAS, their precursors (pregnenolone and 17-hydroxypregnenolone) and metabolites (free and total testosterone, dihydrotestosterone [DHT], androstenedione, estradiol, estrone, cortisol), growth hormone, insulin, IGF-I, IGFBP-1, IGFBP-3, lipid profile, adiponectin (an adipokine whose circulating concentrations correlate with insulin sensitivity [29], body mass index (BMI) and body cell mass, and on the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal (HPG) axes.

2. Human subjects, materials, and methods

2.1. Dehydroepiandrosterone preparation

Study subjects received micronized oral DHEA in 100-mg tablets or matching placebo (Belmar Pharmacy, Lakewood, CO). Food and Drug Administration authorization was obtained for the use of DHEA as an investigational drug.

2.2. Study participants

We included HIV-positive, medically stable individuals with mild depression defined by at least 3 but less than 5 of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for major depressive disorder [30].

We excluded individuals with a new-onset opportunistic infection in the past month, substance use disorder in the past 6 months, use of antidepressant medications within 21 days, or any steroid hormones within the 3 months before enrollment.

The antiretroviral therapy received by patients included the following agents: zidovudine (AZT), abacavir (ABC), dideoxyinosine (DDI), zalcitabine (DDC), D4t, lamividine (3TC), Combivir (AZT + 3TC; GlaxoSmithKline, Philadelphia, PA), Trizivir (AZT, 3TC, ABC; Glaxo Operations, Hertfordshire, UK), ritonavir, indinavir, nelfinavir, saquinavir, amprenavir, lopinavir/ritonavir combination, nevirapine, efavirenz, and tenofovir disoproxil. Seven individuals (3 in DHEA-treated group and 4 in the placebo group) received no antiretroviral therapy.

Of 145 patients who were initially enrolled in the psychiatric study, 12 (8%) dropped out; 4 of these were in the placebo group and 8 were in the DHEA group. The reasons for dropping out of the study included moving away, failure to appear for follow-up, starting testosterone supplementation, worsening of depression, development of an intermittent illness, relapse of drug use, and possible side effects (headaches, fatigue, and stomach pains). Of 133 patients who completed the psychiatric clinical trial, 69 men had agreed to participate in and completed the endocrine study.

Subjects were randomized to receive either oral DHEA (31 subjects) or placebo (38 subjects). The initial dose of DHEA or placebo was 100 mg/d. In the absence of clinical improvement (defined as “much” or “very much” improved mood), the daily dose of DHEA or placebo was increased to 200 mg/d in week 2, 300 mg/d in week 3, and 400 mg/d after week 4. Of 31 patients in the DHEA group, 29 reached the daily dose of 400 mg DHEA. One patient remained on 100 mg DHEA per day and 1 patient remained on 300 mg DHEA per day because their mood improved significantly at these doses. The dose of DHEA or placebo was maintained to the end of week 8 at the highest achieved level.

The study was approved by the institutional review board of each institution, and patients provided written informed consent before enrollment. In addition, consent of the patient’s primary care physician for study participation was obtained as well.

Patients were given $30 compensation and carfare for each visit at the General Clinical Research Center of the Weill Medical College of Cornell University where the endocrine testing was performed at baseline and at the end of week 8.

2.3. Mandatory studies

At baseline and at the end of week 8, morning blood samples were drawn for the following measurements: DHEA, DHEAS, pregnenolone, 17-α-hydroxypregnenolone, testosterone (free and total), DHT, androstenedione, estrone, estradiol, corticotropin, cortisol, sex hormone–binding globulin (SHBG), total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, glucose, insulin, adiponectin, growth hormone, IGF-I, IGFBP-1 and IGFBP-3, liver function tests (aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase), white and red blood cell indices, serum urea nitrogen, and creatinine.

At baseline and at the end of week 8, each patient underwent 2 stimulation tests, which were performed simultaneously. One hundred micrograms of synthetic luteinizing hormone–releasing hormone (LHRH, Factrel,

Table 1
Study parameters that did not change with the oral DHEA therapy (mean ± SEM)*

	DHEA group (n = 31)		Placebo group (n = 38)	
	Week 1	Week 8	Week 1	Week 8
Body composition				
BMI (kg/m^2)	24 ± 0.5	24 ± 0.5	25 ± 0.6	25 ± 0.6
Body cell mass index (lb/in)	0.95 ± 0.02	0.96 ± 0.02	1.01 ± 0.02	1.02 ± 0.02
Immune function				
Viral load (copies/mL)	2.6 ± 0.2	2.6 ± 0.2	2.6 ± 0.2	2.7 ± 0.2
Steroid hormones				
AM cortisol (μg/dL)	14 ± 1	13 ± 1	11 ± 1	11 ± 1
Total testosterone (ng/mL)	6 ± 0.5	6 ± 0.4	6 ± 0.5	6 ± 0.4
Estradiol (pg/mL)	37 ± 4	35 ± 2	35 ± 3	36 ± 2
Pregnenolone (ng/dL)	20 ± 3	17 ± 4	18 ± 3	14 ± 2
17-hydroxypregnenolone (ng/dL)	105 ± 25	66 ± 20	64 ± 14	59 ± 9
Insulin sensitivity				
Glucose	107 ± 5	105 ± 6	103 ± 5	104 ± 4
Insulin (uIU/mL)	33 ± 7	43 ± 11	33 ± 6	35 ± 6
Homeostatic model assessment	0.47 ± 0.09	0.51 ± 0.13	0.56 ± 0.12	0.40 ± 0.08
Adiponectin (μg/mL)	8 ± 1	8 ± 1	9 ± 1	9 ± 1
Growth hormone/IGF				
Growth hormone (ng/mL)	1 ± 0.2	1 ± 0.4	0.5 ± 0.2	1 ± 0.4
IGF-I (ng/mL)	126 ± 8	118 ± 11	129 ± 12	116 ± 12
IGFBP-1 (ng/mL)	24 ± 4	23 ± 4	16 ± 2	18 ± 3
IGFBP-3 (ng/mL)	2515 ± 221	2074 ± 170	2366 ± 190	2102 ± 161
Lipid parameters				
Cholesterol (mg/dL)	196 ± 12	188 ± 11	187 ± 11	184 ± 9
HDL (mg/dL)	39 ± 2	36 ± 2	40 ± 2	39 ± 2
LDL (mg/dL)	110 ± 9	106 ± 10	102 ± 6	100 ± 7
Triglycerides (mg/dL)	248 ± 44	242 ± 42	227 ± 37	226 ± 25
Safety parameters				
AST (U/L)	34 ± 4	35 ± 4	33 ± 3	36 ± 4
ALT (U/L)	33 ± 4	33 ± 5	36 ± 4	51 ± 12
GGT (U/L)	86 ± 20	72 ± 13	60 ± 8	59 ± 10
Serum urea nitrogen (mg/dL)	18 ± 1	17 ± 1	15 ± 1	14 ± 1
Creatinine (mg/dL)	1 ± 0.04	1 ± 0.05	1 ± 0.04	1 ± 0.1
White blood cell count (×10^3/mm^3)	5 ± 0.3	5 ± 0.2	5 ± 0.3	5 ± 0.2
Red blood cell count (×10^6/mm^3)	4 ± 0.1	4 ± 0.1	4 ± 0.1	4 ± 0.1
Hematocrit (%)	41 ± 1	41 ± 1	40 ± 1	41 ± 1

To convert the values for body cell mass index to kg/m multiply by 18. To convert the values for cortisol to nanomoles per liter, multiply by 27. 59. To convert the values for total testosterone to nanomoles per liter, multiply by 3.47. To convert the values for estradiol to picomoles per liter, multiply by 3.67. To convert the values for growth hormone to miU/L, multiply by 2.6. Insulin concentration is reported in microinternational unit/mL. To convert the values for pregnonolone to nanolones/liter, multiply by 0.0355. To convert the values for 17-OH pregnenolone to nanomoles per liter, multiply by 0.030. To convert values for total cholesterol, HDL cholesterol and LDL cholesterol to millimoles per liter, multiply by 0.025. To convert values for triglycerides to millimoles per liter, multiply by 0.011. AST, ALT, GCT are in international units. To convert the values for serum urea nitrogen to mmoles per liter, multiply by 0.355. To convert the values for creatinine to micromoles per liter, multiply by 88.67. HDL indicates high-density lipoprotein, LDL low-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, *gamma*-glutamyltransferase.

* $P > .05$ (not significant) for comparison between the groups for all parameters.

Wyeth-Ayerst, Philadelphia, PA) was injected intravenously, and serum concentrations of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were measured at 0, 15, 30, and 60 minutes. Corticotropin analog (250 μg) (cosyntropin, Cortrosyn, Organon, West Orange, NJ) was administered intravenously, and serum concentrations of cortisol were determined at 0, 30, and 60 minutes.

2.4. Optional studies

Two optional tests were performed on 2 separate days at baseline and at the end of the eighth week.

During the corticotropin-releasing hormone (CRH) stimulation test (26 subjects in the DHEA-treated group and 28 subjects in the placebo group), 1 μg/kg of corticorelin ovine triflutate (ACTHTREL, Ferring Pharmaceutical, Suffern, NY) was administered intravenously, and concentrations of plasma corticotropin and serum cortisol were determined at 0, 15, 30, and 60 minutes.

During the low-dose (1 μg) corticotropin stimulation test (31 subjects in the DHEA-treated group, 36 subjects in the placebo group), 1μg of corticotropin was injected intravenously, and samples for serum cortisol measurements were obtained at 0, 30, and 60 minutes.

2.5. Body cell mass

We determined body cell mass by bioelectric impedance analysis (RJL Systems, Clinton Township, MI). Body cell mass index was calculated by dividing body cell mass (pounds) by height (inches) (to convert to kilograms per meter, multiply by 18).

2.6. Laboratory assays

Assays for red and white blood cell counts, liver function tests, serum urea nitrogen, and creatinine as well as CD4 count were performed at Quest Diagnostics (Teterboro, NJ). HIV RNA viral load was measured at the virology laboratory of the New York Presbyterian Hospital using polymerase chain reaction (Amplicor, Roche Pharmaceuticals, Nutley, NJ).

Assays for pregnenolone and 17-hydroxypregnenolone were carried out at Quest Diagnostics using extraction radioimmunoassay. For all other endocrine measures, except for corticotropin, serum from blood drawn in the General Clinical Research Center Outpatient Unit was centrifuged in a refrigerated centrifuge, aliquoted, and stored frozen in polypropylene vials at −20°C. Blood for corticotropin assays was drawn into chilled tubes containing EDTA anticoagulant, the plasma was separated by centrifugation at 5°C, aliquoted, and stored frozen in polypropylene vials at −20°C. All assays were performed in duplicate.

Serum DHEA and DHEAS concentrations were measured by enzyme immunoassay with kits from Diagnostic Systems Laboratories (Webster, TX). Androstenedione, estrone, insulin, IGF-I, IGFBP-1, and IGFBP-3 were also assayed by enzyme immunoassay with kits from DSL. Enzyme immunoassay for DHT and for adiponectin was carried out with kits from Immuno-Biological Laboratories (Hamburg, Germany) and from Linco Research (St Charles, MO), respectively. Cortisol, testosterone, free testosterone, and corticotropin were assayed by ^{125}I-based radioimmunoassays, with kits obtained from Diagnostic Products (Los Angeles, CA) for the first 2 analytes and from Diagnostic Systems Laboratories for the other 2 analytes. Estradiol, LH, FSH, SHBG, and growth hormone were assayed by europium-based, time-resolved delayed fluorescence immunoassays, with kits from Wallac Division, PerkinElmer Life and Analytical Sciences Corporation (Shelton, CT).

2.7. Statistical analysis

Repeated-measures analysis of variance was used to analyze the data. Bonferroni-like adjustments were applied for multiple comparisons. It was determined that a log transformation of the data conformed to the standard analysis of variance assumptions. Accordingly, all analyses were conducted using the log-transformed data, but were reported in their original untransformed units to facilitate interpretation.

All of the laboratory data were analyzed in such a way that extremely small and large values were censored (values

Table 2
Study parameters that changed with DHEA administration (mean ± SEM)

	DHEA group		Placebo group		P^a
	Week 1	Week 8	Week 1	Week 8	
DHEA (ng/mL)	7 ± 2	75 ± 24**	3 ± 0.5	4 ± 0.5	.0001
DHEAS (ng/mL)	875 ± 108	17775 ± 2912**	944 ± 88	1065 ± 143	.0001
Free testosterone (pg/mL)	17 ± 2	29 ± 2**	17 ± 2	15 ± 2	.0001
DHT (pg/mL)	640 ± 65	3392 ± 772**	631 ± 67	798 ± 220	.0001
Androstenedione (ng/mL)	2 ± 0.2	13 ± 3**	2 ± 0.2	2 ± 0.2	.0001
Estrone (pg/mL)	163 ± 15	498 ± 63**	277 ± 55	272 ± 71	.0001
SHBG (nmol/L)	55 ± 8	49 ± 10*	46 ± 5	50 ± 6	.0009

To convert the values for DHEA to nanomoles per liter, multiply by 3.47. To convert the values for DHEA-S to nanomoles per liter, multiply by 2.714. To convert the values for free testosterone to picomoles/per liter, multiply by 3.467. To convert the values for DHT to picomoles per liter, multiply by 3.448. To convert the values for androstenedione to nmol/liter, multiply by 3.49. To convert the values for estrone to picomoles per liter, multiply by 3.692. SHBG is reported in SI units.

[a] P values for comparison between the DHEA-treated and placebo groups.

* $P < .001$ (from week 1 to week 8 within the DHEA-treated group).

** $P < .0001$ (from week 1 to week 8 within the DHEA-treated group).

below or above detectable limits were assigned the minimum and maximum detectable value, respectively). Of 15 525 data points, 99.54% were valid (required no lower or upper limit censoring).

3. Results

3.1. Patient characteristics

The mean patient age at baseline was 44.4 ± 1.5 years in the DHEA-treated group and 44.9 ± 1.2 years in the placebo group. There were no differences in BMI, body cell mass, CD4 count, or HIV viral load between the 2 groups either at baseline or at week 8 (Table 1).

3.2. Endocrine and metabolic parameters

The patterns of change from week 1 to week 8 for both DHEA and DHEAS significantly differed between the DHEA-treated group and the placebo group ($P < .0001$). Serum DHEA and DHEAS concentrations increased significantly from week 1 to week 8 in the DHEA-treated group ($P < .0001$ for both), but remained essentially unchanged in the placebo group (Table 2).

In the DHEA-treated group, but not in the placebo group, serum concentrations of free testosterone, DHT, androstenedione, and estrone increased significantly from week 1 to week 8 ($P < .0001$) (Table 2). The patterns of change from week 1 to week 8 for each of these variables significantly differed between groups ($P < .0001$ for all). Circulating concentrations of SHBG significantly declined in the DHEA-treated group ($P < .002$), but not in the placebo group (Table 2). The patterns of change from week 1 to week 8 for SHBG levels differed significantly between the groups ($P < .0009$).

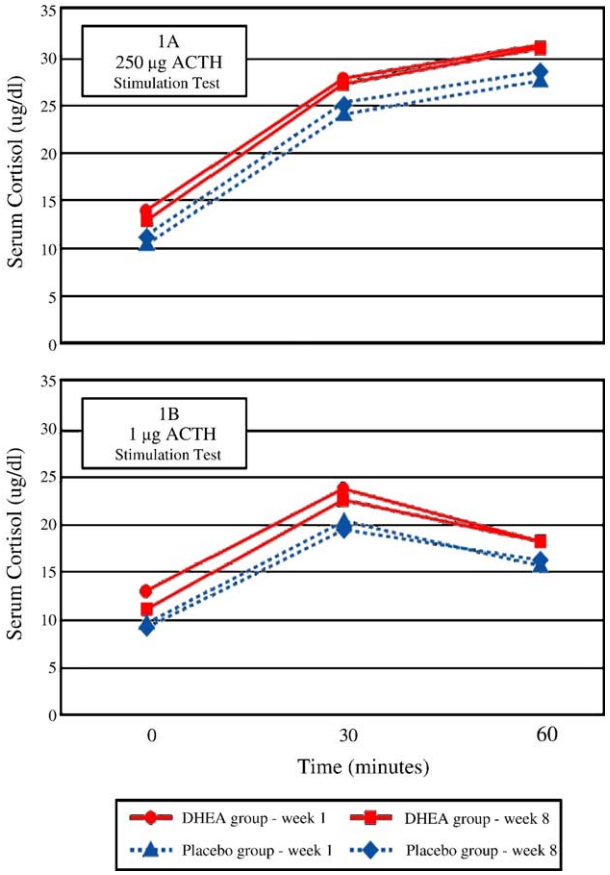

Fig. 1. Serum cortisol concentrations during 250 µg (A) or 1 µg (B) corticotropin stimulation tests.

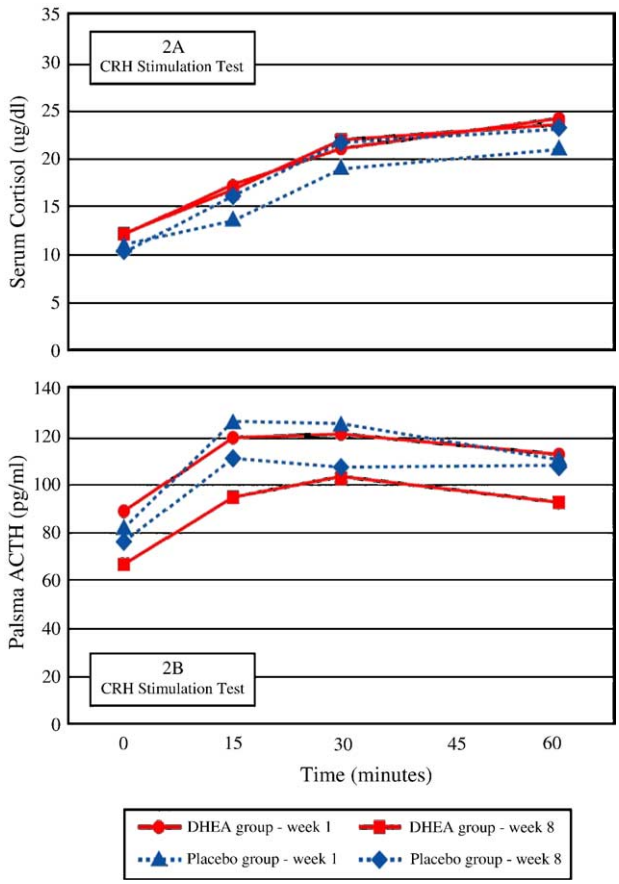

Fig. 2. Serum cortisol (A) and plasma corticotropin (B) concentrations during CRH stimulation test.

There were no significant changes in the circulating levels of morning cortisol, estradiol, total testosterone, pregnenolone, or 17-hydroxypregenenolone in any of the 2 groups from baseline to week 8 (Table 1) or between the groups. Circulating concentrations of fasting glucose, insulin, homeostatic model assessment (25 × 18/fasting insulin × fasting glucose) [31,32], IGF-I, IGFBP-1, IGFBP-3, adiponectin, and growth hormone, as well as the lipid parameters, red or white blood cell count, liver function tests, serum urea nitrogen, and creatinine were also unaltered in both groups without any difference between the groups (Table 1).

3.3. Corticotropin stimulation tests

There were no differences in unstimulated or stimulated cortisol levels between the DHEA-treated and placebo groups during either high-dose (Fig. 1A) or low-dose (Fig. 1B) corticotropin stimulation tests.

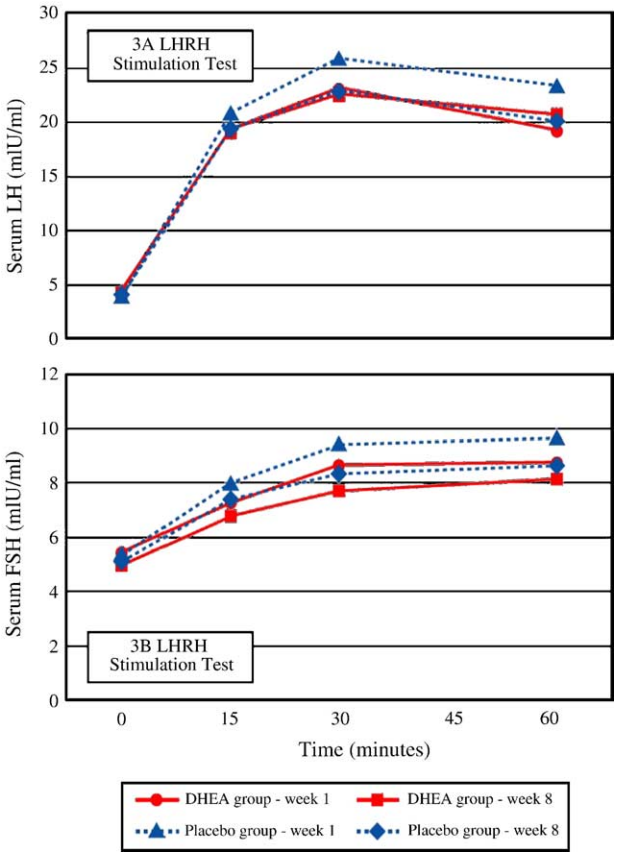

Fig. 3. Serum LH (A) and FSH (B) concentrations during LHRH stimulation test.

Four patients (1 in the DHEA-treated group and 3 in the placebo group) were found to have adrenal insufficiency (highest stimulated cortisol value <18 μg/dL) on concordantly abnormal high- and low-dose corticotropin stimulation tests. In 30 patients (16 in the DHEA group and 14 in the placebo group), the results of the low-dose corticotropin stimulation test were consistent with adrenal insufficiency, whereas the high-dose corticotropin stimulation test results were normal.

3.4. Corticotropin-releasing hormone stimulation test

The patterns of change in serum cortisol (Fig. 2A) or plasma corticotropin concentrations (Fig. 2B) after CRH stimulation were similar between the 2 treatment groups.

3.5. Luteinizing hormone–releasing hormone stimulation test

Baseline and LHRH-stimulated serum concentrations of LH (Fig. 3A) or FSH (Fig. 3B) were similar in the DHEA-treated and placebo groups.

4. Discussion

Because of its wide over-the-counter availability and claims of antiaging and other beneficial properties, DHEA is commonly used by the general population in spite of the uncertainty of its effects [33,34]. Among HIV-infected men, DHEA is used to increase energy and stamina, increase muscle mass, and even to improve the outcome of HIV infection [35]. Indeed, endogenous levels of DHEA appear to correlate with prognosis in a number of illnesses, including HIV infection [3,25], and intake of DHEA reduces manifestations of depression and improves the sense of well-being [16,28,36].

Indirect evidence suggests that DHEA may have a protective effect on immune markers. Declining DHEA levels have been associated with progression to AIDS in both cross-sectional comparisons of HIV-positive adults at different stages of HIV illness [37] and in longitudinal studies [27]. Some investigators have reported that DHEA has immunostimulating properties [16,38]. To our knowledge, however, there have been no controlled studies examining in detail endocrinologic effects of oral DHEA in men with HIV infection.

This study reports a secondary analysis of the endocrine effects of oral DHEA in a group of HIV-positive men with mild depression who received DHEA to assess primarily the DHEA effects on their mood. The analysis of the primary outcome, reported separately [28], revealed that DHEA was superior to placebo in its ability to improve patient's mood: DHEA-response rate was 62%, whereas it was 35% for placebo ($P = .003$).

The present report, to our knowledge, is the first detailed placebo-controlled, double-blind, randomized study of the endocrine and metabolic effects of DHEA in HIV-infected men. This population of patients needs to be examined on its own not only because of a relatively widespread use of DHEA among HIV-infected men, but also because a variety

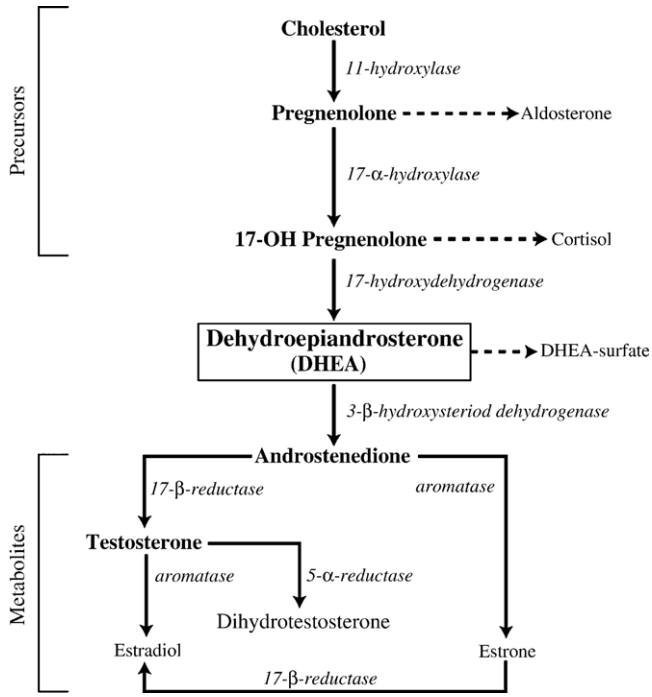

Fig. 4. Metabolism of DHEA.

Table 3
Selected published trials of oral DHEA

First author	Reference	Year published	Population studied/type of trial	Duration of trial	DHEA dose	Observed hormonal changes
Nestler	[20]	1988	5 Healthy men (age, 22-25 y)	28 d	1600 mg/d	↑ DHEAS, A ↓Percentage of body fat, T chol, LDL ↔Weight change, ↔E_1, E_2, free T↔T, SHBG, ↔fasting glu, ↔fasting insulin, tissue sensitivity to insulin
Mortola	[21]	1990	6 Postmenopausal women (age, 46-61 y); double-blind, placebo-controlled, crossover	28 d	400 mg QID	↑ DHEA, DHEAS, A, ↑ T, DHT, E_1, E_2 ↓SHBG, chol, HDL ↔Fasting glu, ↔insulin, G6PD, ↔weight
Casson	[17]	1993	11 Postmenopausal women; 3-wk double-blind, randomized, crossover	3 wk	50 mg	↑ DHEA, DHEAS, T ↔24 H UFC, IL-6 ↑ $CD8^+/CD56^+$, natural killer cell–mediated cytotoxicity ↓$CD4^+$ T cells
Morales	[24]	1994	13 Men/17 women; age, 40-70 y; double- blind, placebo- controlled, crossover	6 mo	50 mg/d	Men: ↑ DHEA, ↑ DHEAS, A, IGF-1 ↓IGFBP-1 Women: ↑ DHEA, ↑ DHEAS, A, T, ↑ DHT, IGF-I, ↓IGFBP-1, HDL ↔E_1, E_2
Beer	[56]	1996	34 Men; age, 47-75 y; double- blind, placebo-controlled	12 d	50 mg TID	↑ DHEAS ↑ E_1 ↓PAI-1, t-PA ↔Weight, BP
Khoram	[9]	1997	90 Men; average age, 63 y; single-blind, placebo-controlled	22 wk	50 mg/d	↑ Interleukin 2 ↑ Natural killer activity ↑ IGF-1
Labrie	[60]	1997	14 Women (age, 60-70 y)	12 mo	10% DHEA cream	↑ Hip BMD, ↑ osteocalcin, ↓BSAP, urine ↓Hydroxyproline/Cr, ↓serum Alk phos, ↓SHBG
Kudielka	[22]	1998	75 Men (age, 67 ± 0.9 y) and women (age, 67.6 ± 0.8 y); double-blind, placebo-controlled	2 wk	50 mg/d	Men: ↑ DHEAS, A, E_2 ↔Free T, T, BMI Women: ↑ Corticotropin, salivary free cortisol, ↑ norepinephrine ↑ Stress response, ↑ DHEAS, A, ↑ free T ↔Total cortisol, ↔Epinephrine ↔BMI
Morales	[23]	1998	9 Men, 10 women; age, 50-65 y; double- blind, placebo-controlled, crossover	6 mo	100 mg/d	Men: ↑ DHEA, ↑ DHEAS, ↑ IGF-I Women: ↑ DHEA, ↑ DHEAS, T, ↑ A, ↑ DHT, ↓SHBG, ↓GHBP
Arlt	[52]	1999	24 Women (age, 42 ± 9 y) with adrenal insufficiency; double- blind, placebo-controlled, crossover	4 mo	50 mg/d	↑ DHEA, DHEAS, ↑ A, T, DHT, ↑ androstanediol glucuronide, ↑ IGF-I (only in primary adrenal insufficiency), ↓SHBG ↔E_1, E_2, IGFBP-3
Barnhart	[61]	1999	60 Perimenopausal women (age, 45-55 y); double-blind, placebo- controlled	3 mo	50 mg/d	↑ DHEA, DHEAS, ↑ T ↓Cortisol, HDL, Lp(a) ↔E_1, SHBG, ↔cholesterol

Table 3 (*continued*)

First author	Reference	Year published	Population studied/type of trial	Duration of trial	DHEA dose	Observed hormonal changes
Rabkin	[16]	2000	30 Men; 2 women with major depression and HIV infection; open label (age?)	8 wk	100 mg/d × 2 wk; 200 mg/d × 2 wk; 300, 400, or 500 mg/d if no response detected	↑ DHEAS ↑ T (women only) ↔CD4 ↔T (men) ↔BIA
Wolkowitz	[36]	1999	22 Men and women with major depression; double-blind, placebo-controlled, randomized.	6 wk	30 mg × 2wk, then 30 mg BID × 2 wk, then 30 mg TID × 2 wk	↑ Hamilton score, improvement of depression
Baulieu	[58]	2000	280 Women and men; age, 60-79 years; randomized, double-blind, placebo-controlled	12 mo	50 mg/d	Men: ↑ DHEAS, ADG, ↑ E_2 ↔T, LH, FSH, ↔IGF-I Women: ↑ DHEAS, T, ADG, ↑ E_2 ↔IGF-I, LH, FSH
Legrain	[49]	2000	24 Healthy men and women; mean age, 67 y; double-blind, placebo-controlled, crossover	8 d	25 and 50 mg/d	Men: ↑ DHEAS, DHEA, ↑ E_1 ↔T, ADG, E_2 Women: ↑ DHEA, DHEAS, ↑ T, ↑ ADG, E_2, E_1
Hunt	[53]	2000	39 Patients with Addison's disease; double-blind, placebo-controlled, crossover	12 wk	50 mg/d	Men: ↑ DHEA, A, DHEAS ↔T,↔SHBG Women: ↑ DHEA, DHEAS, ↑ A, T, ↓SHBG ↔Salivary cortisol,↔body composition ↔Bone density, IGF-I, ↔IGFBP-3
Arlt	[50]	2001	22 Healthy men; age, 50-89 y; double- blind, placebo-controlled, crossover	4 mo	50 mg/d	↑ DHEA, DHEAS, ↑ A, ADG, E_1 ↔E_2, T, IGF-I,↔IGFBP-3,↔osteocalcin, BMI,↔WHR, lean body mass by BIA
Callies	[55]	2001	24 Women with adrenal insufficiency; double-blind, placebo-controlled, crossover	4 mo	50 mg/d	↓Leptin, ↔BMI, lean body mass by BIA, ↔fasting glu,↔osteocalcin
Chang	[15]	2002	120 Women with active systemic lupus erythematosus; randomized, double- blind, placebo- controlled	24 wk	200 mg/d	↑ T ↓E_2
Gordon	[63]	2002	61 Women with anorexia nervosa; age, 14-28 y	12 mo	50 mg/d	↑ E_2, T, IGF-I, ↑ osteocalcin ↓SHBG
Johannsson	[59]	2002	38 Women with hypopituitarism; randomized, placebo-controlled; age, 25-65 y	12 mo	20-30 mg/d	↑ DHEAS, A, T ↔IGF-I, SHBG ↓HDL, ↓apoA-I (transient) ↔PAI-1,↔fibrinogen, t-PA, ↔fasting glu,↔HbA1c,↔Insulin, ↔Osteocalcin, PICP, ↔ICTP, bone density ↑ Lean body mass
Kahn	[57]	2002	43 Healthy men; age 56-80 y; double- blind, placebo-controlled, crossover	6 mo	90 mg/d	↑ DHEA, DHEAS, ↑ E_2, ↓Osteocalcin ↔T, cortisol, PCP,↔BSAP, ↔Urine DPD
Kawano	[19]	2003	24 Men with hypercholesterolemia, mean age, 54 y; randomized, double-blind	12 wk	25 mg/d	↑ DHEAS ↓PAI-1, steady-state plasma glucose, ↔Steady-state plasma insulin

(*continued on next page*)

Table 3 (*continued*)

First author	Reference	Year published	Population studied/type of trial	Duration of trial	DHEA dose	Observed hormonal changes
Løvås	[54]	2003	39 Women (age, 18-70 y) with adrenal insufficiency; randomized, placebo-controlled	9 mo	25 mg/d	↑ DHEAS, T, A, ↓SHBG ↔Osteocalcin, ↔IGF-I, cortisol, ↔corticotropin, ↔aldosterone, ↔PRA
Villareal	[18]	2004	56 Men and women; age, 65-78 y; double-blind, placebo-controlled	6 mo	50 mg/d	Men: ↑ DHEAS, E_2, IGF-I ↓Weight, and fat, AUC for OGTT ↔SHBG, glu, IGFBP-3 Women: ↑ DHEAS, T, E_2, ↑ IGF-I ↓Weight, and fat, ↓AUC for OGTT ↔SHBG, IGFBP-3, ↔Glu

T chol indicates total cholesterol; E_1, estrone; E_2, estradiol; T, total testosterone; free T, free testosterone; Glu, glucose level; A, androstenedione; H UFC, hour urinary free cortisol; G6PD, glucose-6-phosphate dehydrogenase; apoA-I, apolipoprotein A-I; PAI-1, plasminogen activator inhibitor 1; t-PA, tissue plasminogen activator; BMD, bone mineral density; BSAP, bone-specific alkaline phosphatase; Cr, creatinine; Alk phos, alkaline phosphatase; GHBP, growth hormone–binding protein; Lp(a), lipoprotein (a); BIA, bioelectric impedance analysis; ADG, 5α-androstan-3α; WHR, waist-to-hip ratio; PICP, carboxyl-terminal propeptide of type I procollagen; ICTP, carboxyl-terminal cross-linked telopeptide of type I collagen; PCP, procollagen peptide; DPD, deoxypyridinoline; PRA, plasma rennin activity; OGTT, oral glucose tolerance test; AUC, area under the curve.

of endocrine parameters in this group of individuals differ from those in HIV-negative men [39-42]. For example, as will be discussed in more detail below, baseline serum estrone concentrations in our study subjects were higher than in HIV-negative men [43]. However, our baseline estrone data are in agreement with elevated serum estrone concentrations in men with HIV infection reported by other investigators [44,45]. Similarly, specific abnormalities of gonadal and adrenal function have been reported in men with HIV infection [39-42]. These include both primary and secondary hypogonadism [42], primary and secondary adrenal insufficiency [46,47] as well as resistance to the peripheral action of cortisol [48].

Because of these known abnormalities of endocrine function in HIV-positive men as well as because of potential effects of oral DHEA intake on serum concentrations of its precursors and metabolites (Fig. 4), we examined indices of HPA and HPG axes. We observed a significant increase in the circulating levels of DHEA, DHEAS, free testosterone, DHT, androstenedione, and estrone in the DHEA-treated group, but not in the placebo group. These changes were accompanied by a decline in the circulating SHBG concentration in the DHEA-treated group. This combination of findings appears unique to our population of patients when it is compared with DHEA trials in other groups of individuals (Table 3).

These trials uniformly demonstrated increases in calculating concentration of DHEA and DHEAS. However, the effects of oral DHEA on other indices of gonadal and adrenal function, as well as on insulin sensitivity, body composition, and immune parameters, varied widely (Table 3). One important difference in the design of the previously reported trials and our study involves study populations [18,49-61]. Previous studies focused, for example, on patients with primary adrenal insufficiency [52-55], older healthy individuals with an age-related decline in circulating DHEAS levels [18,23,56-58], healthy elderly men [9], or postmenopausal women [16,58-61]. Our study, instead, examined the effects of oral DHEA in HIV-infected men. Furthermore, in our study, the duration of treatment was shorter (8 weeks compared with 3-4 months in many previously published studies), whereas the doses of DHEA were much higher (400 vs 50-100 mg/d) than in other published studies (Table 3). Thus, the differences in patient populations and in the dose and duration of DHEA therapy may account for the differences between the results of our study and those published previously.

Most of the parameters that we examined did not change in the course of treatment with DHEA. These, in addition to the safety parameters (blood count, liver and kidney function) and indicators of the immune function (HIV viral load and CD4 count), included indices of insulin sensitivity and the functional status of HPA and HPG axes.

We had hypothesized that insulin sensitivity may improve with DHEA treatment because a number of previously published animal and human studies described such an improvement ([18,19], Table 3). Individuals with HIV infection have been reported to develop insulin resistance with consequent hyperinsulimenia, both independently and in association with the HIV-related lipodystrophy [62]. Because, in some studies, intake of DHEA was associated with improved insulin sensitivity and an increase in free circulating IGF-I [18,23,50], we examined fasting serum concentrations of insulin and adiponectin (an adipocyte-derived hormone whose circulating concentrations are closely related to insulin sensitivity) [29] as well as circulating concentrations of IGF-I, IGFBP-1, IGFBP-3,

major lipids, and body cell mass. We observed no effect of oral DHEA intake on these parameters. Once again, potential explanations for the differences between our results and those reported previously [18,23,52] include differences in patient populations and in the dose and duration of DHEA therapy.

Furthermore, the mechanisms of changes in insulin sensitivity during DHEA treatment, reported by the studies discussed above [18,19], remain unclear. It is possible that the improvement in insulin sensitivity observed in these studies was due to the increase in the lean body mass that may occur with DHEA administration because of its androgenic properties and because of DHEA-induced rise in circulating IGF-I levels [18,23,24,55,60,63]. In our study, however, neither the lean body mass measures nor the indices of IGF/growth hormone axis changed with DHEA administration. The lack of these changes may be due to the inability of DHEA to overcome a reduction of insulin sensitivity induced by HIV infection [62] and the lack of significant adiposity in our subjects (BMI of 24-25 kg/m^2) (Table 1). It is possible that parameters of insulin sensitivity remained unchanged in this group of lean individuals because their body composition did not change with administration of DHEA. Similarly, because of the lack of change in adiposity in our subjects in the course of treatment with DHEA, circulating levels of adiponectin were not altered.

We examined indices of HPA axis in our subjects because DHEA is a precursor of cortisol (Fig. 4). If a high pharmacologic dose of DHEA, which we used, were to result in excessive conversion to cortisol, the HPA axis could become suppressed. Such a finding would impact the assessment of the safety of DHEA in HIV-infected individuals because they are at risk for the development of adrenal insufficiency [46]. This safety concern, however, proved to be unfounded because the metabolism of DHEA in our subjects favored conversion to sex steroids rather than to cortisol, as will be discussed below. As a result, the HPA axis, assessed in 3 different ways (CRH testing, high-dose corticotropin testing, and low-dose corticotropin testing) remained unaffected.

Low-dose (1 μg) corticotropin stimulation test has been proposed as a more accurate alternative to the high-dose corticotropin stimulation test (250 μg) for diagnosis of adrenal insufficiency. We found 30 individuals (16 in the DHEA group and 14 in the placebo group) who exhibited discrepant cortisol response to the low-dose vs high-dose corticotropin stimulation. All of these individuals had a suboptimal response to the low-dose corticotropin stimulation test and a normal response to the high-dose corticotropin stimulation test. Discordant cortisol responses to low- and high-dose corticotropin stimulation in HIV-positive patients have been previously reported [64]. The causes of this discrepancy remain unclear, but may include technical difficulties in administering effectively extremely small (1 μg) amount of corticotropin and changes in sensitivity to corticotropin in HIV-infected individuals [46,64].

Four individuals (1 in DHEA-treated group and 3 in the placebo group) had adrenal insufficiency established by the inadequate response to the 250 μg of corticotropin (stimulated serum cortisol concentration <18 μg/mL). Prevalence of adrenal insufficiency in individuals with HIV infection ranges between 0% and 25% [39,46,64]. Its pathogenesis remains unclear, but potential causes include adrenal gland and hypothalamic/pituitary infection by HIV or opportunistic organisms [47] and possible resistance to the effects of cortisol [48]. There appears to be no effect of oral DHEA administration on the rate of adrenal insufficiency in HIV-infected individuals in our study.

Similarly to the HPA axis, HPG axis in our individuals was not affected by administration of DHEA. We hypothesized that DHEA may suppress the HPG axis because of the conversion of DHEA to testosterone and, through aromatization of testosterone, to estradiol (Fig. 4). However, our LHRH studies demonstrated that suppression of gonadal axis did not occur with administration of DHEA probably because of the lack of an increase in serum concentrations of either total testosterone or estradiol. The changes of circulating steroid hormone concentrations that did occur with administration of DHEA included, instead, increases in free testosterone, DHT, androstenedione, and estrone.

The increase in the circulating concentration of free testosterone, without significant change in total testosterone, is best explained by a decline in circulating SHBG levels, which occurred with administration of DHEA. A priori, it was difficult to predict in which direction a change of SHBG levels would occur. On one hand, a suppression of SHBG production in the liver could have been expected because of the androgenic properties of DHEA. On the other hand, had DHEA produced an improvement in insulin sensitivity and, consequently, a reduction of circulating insulin levels as reported in some studies [18], a rise in serum SHBG concentration could be expected because SHBG production in the liver is under inhibitory control of insulin [65-67]. Because, as discussed above, no change of insulin sensitivity was observed with the administration of DHEA, the androgenic effects of DHEA on SHBG production in the liver predominated, serum SHBG concentration declined, and a rise of free testosterone followed.

The preferential conversion of DHEA in our study occurred in the direction of androstenedione and, through aromatization, to estrone, rather than in the direction of testosterone and, through aromatization, to estradiol. The reasons for the predominance of this conversion route of DHEA in our population remain unclear, but may involve either the effects of HIV infection itself or those of the antiretroviral therapy on the sterodogenic enzymes (viz, inhibition of 17β-reductase) (Fig. 4). Alternatively, total testosterone concentration may not have changed because of its rapid conversion to the free hormone due to the decline of SHBG, as discussed above. The observed increase in DHT likely occurred due to the action of 5-α-reductase on the increased amounts of free testosterone (Fig. 4).

The clinical significance of the effects of oral DHEA administration in individuals with HIV infection, which we

observed, is relevant for the assessment of both safety and efficacy of DHEA therapy in this population. The negative studies with LHRH, CRH, and corticotropin establish the safety of this therapy because neither HPA nor HPG axis appears to be inhibited with DHEA administration. Although, as discussed above, previous studies reported improvement of some indices of immune functions in individuals without HIV infection, the indicators of the immune function that we measured (quantitative HIV viral load and CD4 count) did not change, presumably because the suppression of immune function in HIV-infected individuals is too profound to be measurably affected by DHEA. The clinically significant outcome of DHEA administration in our study, namely, the improvement in the mood of DHEA treated HIV-positive men with mild depression, previously reported as a primary outcome of the study [28], may have occurred because of an increase in the circulating levels of several androgens, including DHEA, DHEAS, free testosterone, androstenedione, and DHT.

We conclude that oral DHEA supplementation (up to 400 mg/d) in HIV-positive men results in significant increases in circulating levels of DHEA and DHEAS, free testosterone, DHT, androstenedione, and estrone, and a decline in circulating concentration of SHBG. Dehydroepiandrosterone therapy does not alter the overall function of the gonadal or hypothalamic-pituitary-adrenal axes and has no effect on the circulating levels of major lipids, insulin, adiponectin, growth hormone, IGF-I, IGFBP-1, or IGFBP-3. Oral DHEA therapy with up to 400 mg DHEA/d in HIV-infected men appears to be safe, with no effects on red or white blood cell count, liver function tests, or indices of kidney function. The previously reported primary outcome data from this trial clearly demonstrated that administration of DHEA can improve the mood of HIV-infected men with HIV infection and mild depression [28].

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