

# Effect of UV-B Phototherapy on Plasma HIV Type 1 RNA Viral Level: A Self-controlled Prospective Study

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**Objective:** To study the plasma human immunodeficiency virus type 1 (HIV-1) RNA levels of 12 patients seropositive for HIV who were undergoing UV-B phototherapy to determine if UV-B phototherapy up-regulates HIV activity in humans.

**Design:** A self-controlled prospective cohort of HIV-infected patients seen for the treatment of a skin disorder responsive to UV-B phototherapy. Viral levels were measured weekly for 8 weeks of phototherapy. Follow-up viral levels were measured for patients who continued phototherapy beyond 8 weeks, those who had a significant change in their viral level, or both.

**Setting:** Outpatient clinic of an academic hospital.

**Patients:** Patients with HIV disease and a skin disorder responsive to UV-B phototherapy. Inclusion criteria for patients in this study were those receiving a stable antiviral regimen for at least 6 weeks and who had no major illness or immunization in the 2 months before starting phototherapy. Of 72 patient volunteers screened, 15 met the criteria, 2 declined to participate, and 13 en-

tered the study. One patient was dropped from the study because an accurate baseline measurement could not be obtained. Twelve patients were analyzed, 2 of whom left the study early, 1 at 6 weeks and 1 at 7 weeks.

**Interventions:** Ultraviolet-B phototherapy.

**Main Outcome Measure:** Plasma HIV-1 RNA viral level.

**Results:** Plasma HIV-1 RNA levels showed no significant increase or decrease in most of the patients, defined as a 3-fold change from baseline (mean fold change from baseline after 8 weeks of phototherapy,  $-1.1$ ; 95% confidence interval,  $2.9$  to  $-5.0$ ). Trend analysis indicated no significant pattern of change in viral levels (slope,  $-0.013$  log;  $P > .25$ ). The CD4<sup>+</sup> cell counts also remained unchanged (mean before therapy,  $277 \times 10^9/L$ ; mean after therapy,  $285 \times 10^9/L$ ;  $P = .67$ ).

**Conclusion:** No significant effect of UV-B exposure was seen on plasma HIV-1 levels.

*Arch Dermatol.* 1998;134:940-945

**T**HE SAFETY of UV-B phototherapy in patients infected with the human immunodeficiency virus (HIV) remains controversial.<sup>1-6</sup> Ultraviolet-B light from artificial and natural sources was first shown to enhance HIV growth in experiments using cell culture systems.<sup>7,8</sup> In vivo studies using transgenic mice that express the HIV long-terminal-repeat promoter linked to reporter genes further indicated that sunlight and artificial UV-B in doses as low as 9 mJ/cm<sup>2</sup> can potentially stimulate viral replication in the skin.<sup>9-12</sup> In these experimental systems, ultraviolet radiation was thought to activate viral replication, either directly or through a nonspecific cellular stress response.<sup>13</sup>

Although laboratory experiments have suggested that UV-B exposure can contribute to the progression of HIV disease by directly stimulating viral replication, the results of these experiments are not readily generalized to humans. Many viruses exhibit in vitro activation by ultraviolet light, but the

same phenomenon does not occur in humans (herpes simplex virus is a notable exception).<sup>14,15</sup> Furthermore, in humans, the epidermis is a limited reservoir of HIV, with the polymerase chain reaction assay detecting the presence of HIV RNA and DNA predominantly in the dermis.<sup>16</sup> Upon UV-B exposure, the epidermis thickens and melanin deposition increases, both of which protect against UV-B penetration to anatomical areas where HIV may be present.<sup>17</sup> If UV-B penetrates to HIV-infected dendritic cells, it may increase viral levels by directly enhancing viral replication, or it may lower viral levels by being directly toxic to HIV-infected dendrocytes.<sup>18-20</sup>

*For editorial comment  
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Although the laboratory evidence that UV-B directly activates HIV may not readily translate to humans, there remains a theoretical concern that UV-B may indirectly activate HIV and therefore promote disease progression. Ultraviolet-B ex-

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## PATIENTS AND METHODS

### PATIENT SELECTION

Patients infected with HIV who have a dermatosis responsive to UV-B phototherapy were eligible for the study. The diagnosis was confirmed with a biopsy when indicated. Patients had to be 18 years or older and receiving a stable antiviral regimen (or no antiviral drugs) for at least 6 weeks to allow for the reestablishment of baseline plasma RNA levels.<sup>43</sup> Patient 4 discontinued zidovudine and lamivudine immediately before starting phototherapy and is included in the study in an intention-to-treat analysis because he initially met the inclusion criteria. Patient 5 had his dose of nevirapine increased 4 weeks before study entry. This patient had 3 baseline plasma viral RNA measurements that indicated a stable pattern with no further reduction in the plasma viral RNA level and was therefore allowed to enter the study because he was anxious, due to intense pruritus, to start phototherapy. Patients were excluded from the study if they had received phototherapy or had a clinically apparent infection or immunization in the 8 weeks before beginning the study. Informed consent was obtained from all participants.

### PHOTOTHERAPY PROTOCOL

Patients received UV-B phototherapy with the Elder I (model 57000, Psoralite Corp, Columbia, SC) phototherapy unit using 8 UV-B lamps (model 72-50R, FS72T12EREHO, Light-source Inc, Milford, Conn) that emit primarily in the UV-B spectrum. Patients received treatments at the same time of day, 3 times per week, for as long as 8 weeks. The starting dose was determined by estimating the minimal erythema dose from a patient's history of response to ultraviolet light and the degree of skin pigmentation. Patients were started at one third the estimated minimal erythema dose, and the dose was increased by approximately one third each subsequent treatment as tolerated until a maximal tolerated dose was reached. The clinical response to treatment was monitored monthly, and symptoms of pruritus were evaluated before starting treatment and at the completion of the study. Pruritus was measured by self-report using an instrument that combines methods previously described by Duo<sup>44</sup> and Pardo et al.<sup>45</sup> Patients described their pruritus on a scale of 0 to 10 (0 indicates no itching; 1-3, mild [a few brief episodes of scratching per day]; 4-6, moderate [several brief or 1 long episode of scratching per day]; 7-9, severe [scratching without relief and producing excoriations]; and 10, intolerable).

### DETERMINATION OF MARKERS OF HIV ACTIVITY

The CD4<sup>+</sup> cell counts were determined by standard flow cytometry in the clinical laboratory before starting

phototherapy and after up to 8 weeks of phototherapy. Patients had 2 baseline viral level measurements 5 to 10 days apart immediately before beginning phototherapy. Viral levels were then measured weekly, 2 hours and 48 hours after the first treatment of the week, for as long as 8 weeks. Specimens were collected with EDTA, and plasma was separated and frozen (-80°C) within 4 hours of collection. Viral levels were measured by polymerase chain reaction assay (Amplicor HIV-1 Monitor, Roche Molecular Systems, Branchburg, NJ) (sensitivity, 100 copies per milliliter). To minimize variation, all of a patient's specimens were analyzed together in the same run using the same kit.

### DATA ANALYSIS

Pruritus scores were analyzed using the Wilcoxon signed rank test. The CD4<sup>+</sup> data were normally distributed (based on an omnibus test of normality) and were analyzed using a paired *t* test. Plasma viral RNA data were transformed to a log scale. The baseline viral level was determined for each patient by averaging the log-transformed value of the patient's 2 viral levels before starting phototherapy. The patient's baseline plasma viral RNA level was then compared with the respective individual's subsequent weekly plasma viral RNA levels. Preliminary data (n = 7) indicated that during phototherapy, there was no difference between the viral levels 2 hours and 48 hours after phototherapy. To simplify the analysis, when available, the 2- and 48-hour measurements were averaged and reported as a single value for that week. Statistical modeling indicates that this simplification does not alter the interpretation of the results.

In light of the laboratory and steady-state variability of the plasma viral RNA assays, a 3-fold change (0.5 log) from baseline was defined as significant.<sup>42</sup> Assuming the detection of a minimum-effect size of a 0.5-log change in viral level and a 0.5-log variation in the plasma viral RNA assay, it was estimated that a sample size of 10 patients would achieve a statistical power of .80 when using a 2-tailed test, for an  $\alpha$  of .05.<sup>46</sup> Fold change analysis was also performed for the 9 patients with detectable plasma viral RNA levels by averaging the weekly fold change values, plus or minus 95% confidence intervals.

An analysis for trend was performed on log-transformed data using a computer-generated linear regression line for each patient, and by using a linear model based on the 9 patients with detectable viral levels to determine the overall trend. Patients with undetectable viral levels throughout the study were considered to have no significant change in viral level and were not included in the trend analysis. Patients with viral levels below the linear range of the assay (ie, detectable but <400 copies per milliliter) were arbitrarily assigned a value of 400.

posure stimulates the epidermis to release several cytokines into the circulation.<sup>21</sup> Ultraviolet-B has been shown to increase systemic levels of cytokines known to enhance viral replication, such as interleukin 1 and 6, and to increase HIV inhibitory cytokines such as interleukin 10.<sup>22-24</sup> In addition, UV-B exposure transiently lowers circulating T-cell levels.<sup>25,26</sup> This transient systemic immunosuppression may facilitate increased viral replication.

Despite the concern that UV-B irradiation may cause HIV disease progression, patients infected with HIV routinely receive phototherapy for skin disorders such as eosinophilic folliculitis, idiopathic pruritus, psoriasis, and eczema.<sup>27</sup> A recent multicenter study<sup>28</sup> found that among patients receiving phototherapy, a substantial percentage (8.4%) are known to be seropositive for HIV, 80% of whom receive phototherapy with UV-B. The studies evaluating the safety of UV-B pho-

**Characteristics and Treatment of 12 HIV-Infected Patients Undergoing UV-B Phototherapy\***

Patient No.	Diagnosis/ CDC Stage†	Age, y/ Sex	Phototype/ Cumulative Dose, mJ/cm <sup>2</sup>	Antiviral Agents	Copies per Milliliter			Viral Level Trend (P), Slope	CD4 <sup>+</sup> Before/After Therapy, ×10 <sup>9</sup> /L
					Baseline Viral RNA Level	Final Viral RNA Level	>3-Fold Change at Any Week?		
1	RPC/A	45/M	V/3667	None	75 076	43 291	No	↓ (.05), -0.031	510/640
2	Prurigo/B	35/F	VI/3780	Zidovudine, 3TC	380 627	875 387	No	↑ (.03), 0.08	330/240
3	Atopic dermatitis/C	36/M	II/2918	Nevirapine, indinivir sulfate	<100	<100	No	NA	500/480
4	Pruritus/C	49/M	IV/4974	Ritonavir, saquinivir mesylate‡	<100	<100	No	NA	310/340
5	Pruritus/B	37/M	III/3536	Zidovudine, 3TC, nevirapine§	1257	4101	Yes, ↑	Not significant (.25), 0.044	200/250
6	Prurigo/C	46/M	IV/2967	Stavudine, 3TC, indinivir	3048	400	Yes, ↓	↓ (.001), -0.16	160/120
7	Atopic dermatitis/C	39/M	V/5053	Nevirapine, saquinivir	358 757	432 558	No	Not significant (1.0), 0	70/40
8	Pruritus/A	48/M	IV/4547	None	431 072	782 612	No	Not significant (.29), 0.021	720/850
9	EF/C	40/M	VI/3066	3TC, saquinivir	1 138 544	861 291	No	Not significant (.87), -0.005	30/20
10	Prurigo/C	28/M	VI/5328	Zidovudine, 3TC	211 179	99 873	Yes, ↓ wk 3 only	Not significant (.86), 0.006	60/60
11	EF/C	33/M	V/3864	3TC, stavudine, indinivir	<100	<100	No	NA	320/310
12	EF/C	40/F	III/2209	Stavudine, 3TC, indinivir	201 767	86 567	No	↓ (.004), -0.046	110/70

\*CDC indicates Centers for Disease Control and Prevention; RPC, reactive perforating collagenosis; 3TC, lamivudine; NA, not applicable; and EF, eosinophilic folliculitis. †1993 CDC classification system (MMWR Morb Mortal Wkly Rep. 1992;42[RR-17]). A indicates asymptomatic; B, symptomatic; and C, acquired immunodeficiency syndrome.

‡Patient discontinued zidovudine therapy and 3TC immediately before beginning phototherapy.

§Patient started taking nevirapine as a single additional agent to his existing antiviral therapy 6 weeks before beginning phototherapy and increased the nevirapine dose 4 weeks before phototherapy.

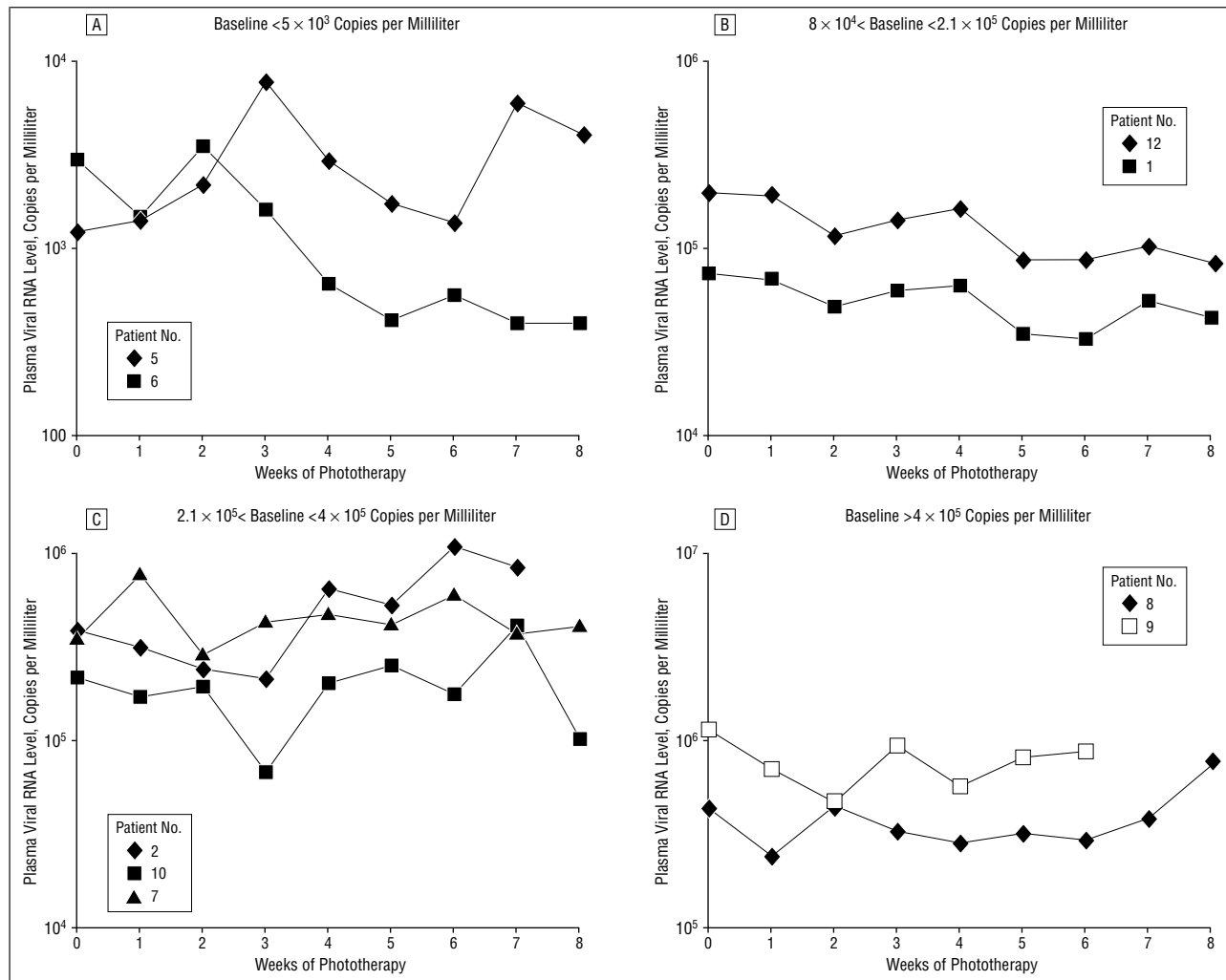
totherapy in HIV-infected patients to date have been limited by small sample sizes and the use of insensitive or nonspecific markers of HIV activity. Meola et al<sup>29</sup> studied 6 patients undergoing UV-B phototherapy and found no significant change in CD4<sup>+</sup> cell counts or β<sub>2</sub>-microglobulin or p24 antigen levels. Other investigators, however, have noted increasing p24 antigen levels<sup>30</sup> and increasing serum HIV RNA levels in HIV-infected patients treated with UV-B phototherapy.<sup>24</sup> The laboratory evidence and reports<sup>30</sup> of patient deterioration while receiving UV-B treatment have prompted several investigators<sup>2-4,15</sup> to question the safety of UV-B phototherapy and excessive sunlight exposure in HIV-infected patients.

To determine if UV-B exposure affects HIV activity in humans, we prospectively studied the plasma viral levels before and after UV-B phototherapy in 12 HIV-infected patients undergoing treatment of a variety of dermatoses. The plasma viral level is the most sensitive marker of HIV activity and is now widely used to monitor HIV-infected patients. The plasma viral level represents ongoing viral replication and rapidly reflects changes in a patient's steady state because the viral life cycle is only 2.6 days.<sup>31</sup> The consequence of a high viral level is an increased risk of progression to the acquired immunodeficiency syndrome or death.<sup>32,33</sup> Each 3-fold increase in plasma viral RNA levels is associated with a 1.55-fold increase in the relative risk of death.<sup>34</sup> Further consequences of an increasing viral level include an increased likelihood of developing resistance to antiviral therapy.<sup>35</sup> In addition, HIV plasma levels are stable over time, allowing patients to serve as their own control.<sup>36</sup> Factors that transiently affect the viral level, such as antiviral agents, infections,<sup>37</sup> or immunizations,<sup>38-41</sup> can be readily monitored.<sup>42</sup>

**RESULTS**

The 12 patients studied represented a wide range of baseline CD4<sup>+</sup> cell counts and baseline plasma viral levels (**Table**). As reported by other investigators, CD4<sup>+</sup> cell counts did not change significantly from baseline (mean count before treatment, 277 × 10<sup>9</sup>/L; mean count after treatment, 285 × 10<sup>9</sup>/L; P = .67).<sup>29,47</sup> Of note, 3 of the 12 patients had undetectable baseline viral levels, and all 3 maintained undetectable plasma viral levels throughout the study. **Figure 1** and **Figure 2** show viral RNA levels and the fold change from baseline viral levels throughout the study for each of the 9 patients with detectable viremia. Most patients showed no significant increase or decrease in viral RNA levels (defined as a 3-fold change from baseline) at early stages of treatment when low doses are used or at later stages when higher doses are given. Two patients (patients 1 and 8) were taking no antiviral medications and had no significant change in viral level. Patient 8 continued phototherapy for an additional 8 weeks (3230 mJ/cm<sup>2</sup>), and follow-up viral level testing showed that his levels remained near the pretreatment baseline (600 000 copies per milliliter).

Group analysis showed that the mean fold change in viral levels from baseline did not vary significantly from 0 and that the upper-limit 95% confidence interval did not include a 3-fold increase at any of the time points examined (Figure 2, B). The exceptions to the stable viral level pattern occurred in patient 5, who had a greater than 3-fold increase, and patients 6 and 10, who had a greater than 3-fold decrease, in viral levels. Patient 5 continued receiving phototherapy and, despite an addi-



**Figure 1.** Effect of UV-B phototherapy on plasma viral RNA levels (data for patients with undetectable viral RNA levels not shown). Most patients (11 of 12) showed no significant increase ( $>3$ -fold).

tional month ( $1402 \text{ mJ/cm}^2$ ) of treatment, showed no further significant increase in viral levels (5516 copies per milliliter).

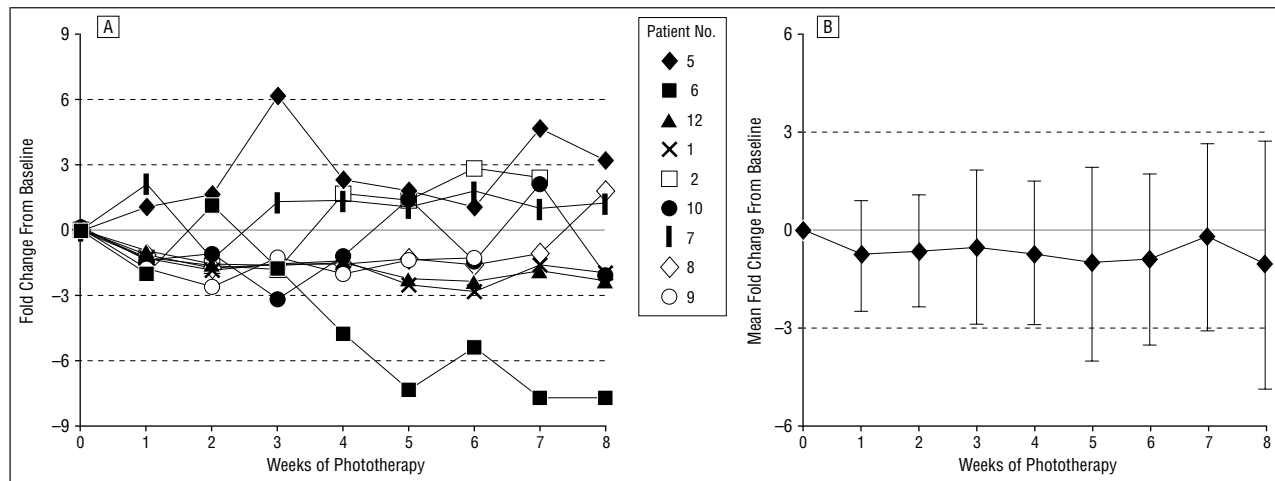
**Figure 3** shows trends in viral levels during the 8 weeks of phototherapy. The overall trend for the 9 patients with detectable viral levels indicated no significant pattern of change (slope,  $-0.013 \text{ log}$ ;  $P > .25$ ). On an individual basis, most patients had no statistically significant trend for viral levels to change, but 1 (patient 2) showed a trend for viral levels to increase. Patients 1, 6, and 12 had a trend for viral levels to decrease statistically, but in only 1 (patient 6) was the trend substantial.

All patients experienced an improvement in their skin disease. Most patients ( $n = 9$ ) had disabling pruritus before beginning phototherapy. The mean pretreatment pruritus scores were in the severe range (8.3), whereas posttreatment scores were in the mild range (2.2) ( $P = .007$ ) (data not shown). All patients tolerated phototherapy well, and all achieved high cumulative UV-B doses. Two of the 12 patients left the study early (patient 9 at 6 weeks and patient 2 at 7 weeks) because they were symptomatically improved and had high baseline viral levels requiring new antiviral medications.

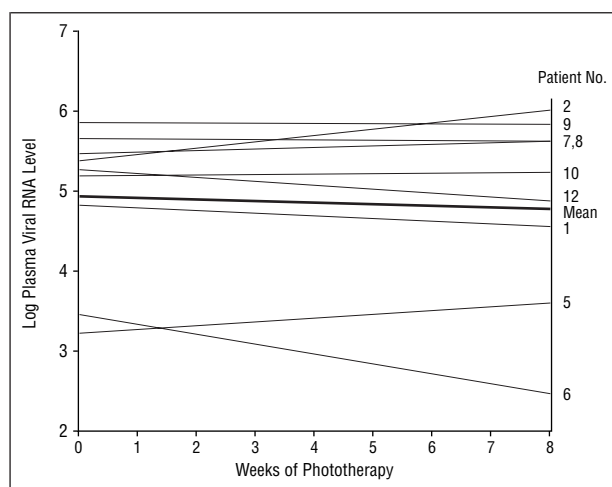
## COMMENT

The 12 HIV-infected patients in this study maintained remarkably stable plasma viral RNA levels while undergoing UV-B phototherapy. Most patients showed no significant change or trend for viral levels to change throughout the study. Our findings are in strong contrast to those of studies investigating other manipulations of HIV activity, such as immunizations and infections, in which most patients responded with significant short-term elevations of viral levels.<sup>37-41</sup>

Patient 5 was the only one whose viral level increased significantly ( $>3$ -fold) during treatment. This increase may be due to the predictable development of antiviral resistance and not a UV-B-induced activation of HIV as the patient started taking nevirapine as a single additional antiviral agent 6 weeks before starting the study. When used as monotherapy, nevirapine is known to decrease viral levels for approximately 6 weeks, with a return to pretreatment levels in the ensuing weeks as the virus develops resistance.<sup>48</sup> This patient's viral levels never increased significantly above his prenevirapine set point of 4000 copies per milliliter during 3 months of phototherapy, and 2 months after completing phototherapy,



**Figure 2.** A, The weekly fold change from baseline plasma viral RNA levels in each of the 9 patients with detectable plasma viral RNA. Significant (>3-fold) changes occurred in patients 5, 6, and 10. B, Mean fold changes in plasma viral RNA level from baseline during the 8-week study for the 9 patients with detectable viremia (week 7, n = 8; week 8, n = 7). The 95% confidence intervals remain below a 3-fold increase from baseline at all time points.



**Figure 3.** The effect of phototherapy on trends in plasma viral RNA levels. The mean trend indicated no significant pattern of change (slope,  $-0.013$  log;  $P > .25$ ). On an individual basis, statistically significant changes in trends occurred in patient 2 (increase) and patients 1, 6, and 12 (decrease).

his levels remained close (3858 copies per milliliter) to the levels before he began taking nevirapine.

Patient 2 was the only other patient whose viral level appeared to increase during UV-B phototherapy. Coincidentally, patient 2 underwent an elective repair of an umbilical hernia during week 3 of the study. Although this patient's viral RNA levels never increased significantly, she demonstrated a trend toward increasing levels that could represent natural disease progression, an effect of a subclinical infection or the surgical procedure, or possibly an effect of UV-B phototherapy. This patient left the study at 7 weeks to start a new antiviral medication regimen, which resulted in a dramatic decrease in viral levels (to 700 copies per milliliter) and an increase in her CD4<sup>+</sup> cell count to  $350 \times 10^9/L$ .

The most convincing change in viral levels during our study occurred in patient 6. His viral level decreased more than 8-fold from a baseline of 3347 copies per milliliter to less than 400 copies per milliliter after completing 8 weeks of phototherapy. One month after completing phototherapy, his viral level returned to baseline (2974 cop-

ies per milliliter). The patient's antiviral regimen was stable for 4 months before he started our study, and he complies fully with his medications. It remains possible that UV-B treatment decreased his viral burden because the effect was lost when phototherapy was discontinued.

Of particular note, 3 patients had undetectable viral levels while undergoing UV-B phototherapy. Despite exposure to high doses of UV-B, these patients continued to have undetectable plasma viral RNA levels. This finding is particularly important because it suggests that patients who achieve a complete antiviral response do not have breakthrough viral replication with the subsequent development of antiviral resistance when exposed to UV-B. Furthermore, most patients in this study (n = 10) were receiving combination antiviral therapy, often including protease inhibitors (n = 7), and all tolerated UV-B phototherapy without an adverse (ie, photosensitivity) reaction. Also, 2 asymptomatic patients at early stages of HIV disease underwent UV-B phototherapy while receiving no antiviral medication. Neither of these asymptomatic, antiviral-naïve patients had a significant change in viral levels despite exposure to high levels of UV-B for up to 16 weeks.

Our findings support the observations<sup>14,29,47,49</sup> of a number of investigators who have found no adverse effect of UV-B exposure on immunological markers of HIV progression. This study adds to previous reports by examining quantitative plasma viral RNA levels with a standardized assay, which represents the most sensitive and reliable method of detecting in vivo HIV replication. Most patients in this study required phototherapy for only 8 weeks, whereas the 2 patients in the study who required further treatment also maintained stable viral RNA levels during the extended period. Nevertheless, it remains possible that long-term phototherapy may affect the viral burden in an as-yet-unidentified patient subset. Therefore, it is important that primary care providers responsible for routinely (ie, every 3-4 months)<sup>50</sup> monitoring plasma viral levels be informed of ongoing phototherapy, although other common clinical events such as immunizations or infections may confound the interpretation of results.

Most published reports have shown no adverse effect of UV-B on HIV in humans. The consistency of these di-

verse studies supports the safety of UV-B phototherapy in HIV-infected persons. Ultraviolet-B phototherapy is highly efficacious in treating many of the skin disorders that dramatically impair the quality of life of HIV-infected patients and should not be withheld from this population.

Accepted for publication December 23, 1997.

This study was supported by a grant from the New York Community Trust, New York, NY; in part by research grant NIH 5 M01 RR00071 from the Mount Sinai General Clinical Research Center, New York, NY; and in part by a Carl W. Walter Research Award from Harvard Medical School, Boston, Mass (Dr Gelfand).

Prepared for presentation at the 56th annual meeting of the American Academy of Dermatology, Orlando, Fla, March 2, 1998.

We thank the patients who volunteered their time and considerable effort. We also thank the following people for their assistance in carrying out this protocol: Linda Pizana, RN, and the nurses at the Mount Sinai General Clinical Research Center for their nursing support; Susan DeGeorge and John Quijije for assisting in performing phototherapy; Laura Pustilnik, Inna Fuksina, and Barbara Blosswick for their technical support in performing viral levels; Nancy Margeson for her patient outreach efforts; Beverly Dale, PhD, and Richard Manners for helping to support the study with plasma viral RNA assay kits; Sylvan Wallenstein, PhD, for assistance with statistical analysis; Chiara F. Baxt, MA, for technical assistance in preparing the manuscript; and Charles Taylor, MD, for his valuable advice regarding the manuscript.

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