Paronychia in Association with Indinavir Treatment

Amy E. Colson,[1] Paul E. Sax,[1] Marla J. Keller,[1] Barbara K. Turk,[2] Parker T. Pettus,[1] Richard Platt,[1,2] and Peter W. Choo[1,2]

[1]Channing Laboratory and Department of Medicine, Brigham and Women's Hospital, and [2]Department of Ambulatory Care and Prevention, Harvard Pilgrim Health Care, Harvard Medical School, Boston

To assess a possible association between antiretroviral treatment and paronychia, we conducted a retrospective cohort study of 288 human immunodeficiency virus–positive protease inhibitor recipients. Indinavir treatment—adjusted for age, sex, CD4 count, diabetes status and other antiretroviral drug exposures—was significantly associated with paronychia of the great toe (hazard ratio 4.7; 95% confidence interval 1.6–13.9).

An ingrown toenail occurs when the nail plate pierces the lateral nail fold; this is often associated with marked inflammation of the nail fold, a condition known as "paronychia" [1]. Recent reports have noted an association between paronychia and potent combination antiretroviral therapy among patients infected with human immunodeficiency virus type 1 (HIV-1). Zerboni et al. [2] reported a case series of 12 HIV-1–positive patients with paronychia who had all taken lamivudine during the 3 months preceding the onset of paronychia. Bouscarat et al. [3] subsequently described 42 recipients of indinavir who presented with great-toe paronychia secondary to ingrown nails. Recently, Bourezane et al. [4] reported a case-control study in which patients were matched on the basis of CD4 cell counts, which suggested a strong association between indinavir therapy and ingrown toenails (OR, 10.9; 95% CI, 1.6–∞). No additional predictors of ingrown toenails, including other antiretroviral drugs and plasma HIV virus load, were identified. To determine which antiretroviral agents are independently associated with paronychia, we conducted a retrospective cohort study in a well-defined population of managed-care patients who received protease inhibitor (PI)–based antiretroviral therapy from 1996 through 1998.

Harvard Vanguard Medical Associates (HVMA), a multispecialty group practice affiliated with Harvard Pilgrim Heath Care, a large New England health maintenance organization, was the source of patients for this study. All outpatient encounters at HVMA are recorded in a computerized medical record system that includes vital signs, providers' notes in their entirety, and laboratory test results. All diagnoses, prescribed treatments, and laboratory tests ordered are also stored by use of COSTAR codes [5]. Approximately 90% of HVMA members have prescription drug coverage that provides medications for a nominal copayment at on-site HVMA pharmacies. All prescriptions filled at HVMA pharmacies are captured in a computerized pharmacy record that is fully linkable to the computerized medical record.

PI recipients who did not meet the following inclusion criteria were subsequently excluded from the cohort: confirmed diagnosis of HIV infection: age >18 years on 1 January 1990; continuous medical care at HVMA during observation period; acquisition of all noninvestigational antiretroviral medications through an HVMA pharmacy during observation period. Patients were observed from 1 January 1990, or, if later, from the date of their enrollment in the health plan or the date of their presumed infection with HIV. Observation ceased with the first presentation with a great-toe paronychia, or, if earlier, termination of health plan membership, or 1 November 1998.

Exposure to noninvestigational antiretroviral drugs was determined by use of the HVMA computerized pharmacy database. Specifically, the "days-supply field" (which specifies the number of days the dispensed prescription covers; e.g., 30 days' worth of indinavir dispensed) in each dispensing record was used to construct exposure windows for the 4 US Food and Drug Administration–approved PI agents as well as for nucleoside reverse transcriptase inhibitors (NRTIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs). Exposure to experimental antiretroviral drugs was ascertained only for patients with paronychia by reading their full-text medical records, but this information was not used to establish their exposure status, because it was not always possible to determine when and if the patient was receiving active therapy. Presentations with paronychia were identified by a search of the full-text electronic medical record by use of a list of screening terms (e.g., "par-

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Reprints or correspondence: Dr. Amy E. Colson, Channing Laboratory, 181 Longwood Ave., Boston, MA 02115.

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onychia" and "nail"). All paronychial events were considered to be confirmed by medical-record review if there was a description of pain, swelling, erythema, or other evidence of inflammation in the affected nail fold. A paronychia was considered to be a distinct event if there was no history of a paronychia at the affected nail border or if there was clear documentation of complete resolution of previous paronychia at the affected nail border.

$CD4^+$ lymphocyte counts and serum HIV-1 RNA levels were obtained from the HVMA computerized laboratory database. Given the evolution in the sensitivity of serum HIV-1 RNA assays that occurred during our observation period, we chose to treat virus load as a dichotomous variable with 10,000 copies/mL as the breakpoint. Finally, information on diabetes mellitus was ascertained by a search of the ambulatory medical record for corresponding COSTAR-coded diagnoses. Diabetes diagnoses were considered to be confirmed if the full-text medical record documented 2 fasting blood glucose measurements >140 mg/dL, a diagnostic oral glucose tolerance test, or use of insulin or oral hypoglycemic therapy.

Extended Cox models were used to identify unadjusted associations with first presentations of great-toe paronychia [6]. Exposure to antiretroviral drugs, the $CD4^+$ lymphocyte count, and the serum HIV-1 RNA level were treated as time-dependent variables. Age, sex, and diabetes status were not considered to vary by time. Terms for each PI were initially used in the regression models. Because none of the PIs (with the exception of indinavir) was associated with paronychia in the unadjusted analyses, nonindinavir PI agents were subsequently collapsed into a single exposure category. Given that a previous case series had suggested that lamivudine might be a risk factor for paronychia [2], nucleoside analogs were divided into lamivudine and nonlamivudine agents for the purposes of this analysis. NNRTIs were modeled as a single drug class rather than at the level of individual agents because there was no previous suspicion of an association with paronychia. All covariates were also included in a common model to determine their independent contribution to great-toe paronychia. Because virus load was not associated with paronychia, did not change the other point estimates, and was missing for 39% of the cohort, we present only the results of models that do not adjust for virus load. Only descriptive data on paronychia of sites other than the great toe are presented because the small number of events precluded a full analysis of risk factors for paronychia involving sites other than the great toe.

We identified a total of 288 adults who had a confirmed diagnosis of HIV-1 infection, who received a noninvestigational PI before 1 March 1998, and who received continuous medical care and acquired noninvestigational antiretroviral drugs through HVMA during our observation period. As displayed in table 1, the median observation time was 6.0 years (interquartile range, 3.4–8.2 years); 90% of the cohort were men, and the median age at the start of observation was 35 years (range, 21–67 years). Overall, the cohort had advanced HIV disease; 81% of individuals had a $CD4^+$ lymphocyte count of <200 cells/mm^3 at the start of observation, and 82% had a serum HIV-1 RNA level >10,000 copies/mL at the start of PI therapy. Indinavir was the most frequently prescribed PI agent (63%), followed by nelfinavir (48%), ritonavir (46%), and saquinavir (39%). More than 92% of the study population received lamivudine at some time during follow-up.

Table 1. Characteristics of 288 patients with human immunodeficiency virus type 1 (HIV-1) who received protease inhibitor (PI)–based antiretroviral therapy from 1996 through 1998.

Variable	Value
Total no. of patients	288
Male, *n* (%)	259 (90)
Age at start of observation, median y (range)	35 (21–67)
Observation time, median y (interquartile range)	6.0 (3.4–8.2)
Diagnosis of diabetes during observation, *n* (%)	15 (5)
CD4 count	
At start of observation, *n* (%)[a]	
<50 cells/mm^3	70 (25)
50–199 cells/mm^3	166 (60)
200–499 cells/mm^3	20 (7)
⩾500 cells/mm^3	16 (6)
At start of PI therapy, *n* (%)[b]	
<50 cells/mm^3	84 (29)
50–199 cells/mm^3	151 (52)
200–499 cells/mm^3	25 (9)
⩾500 cells/mm^3	11 (4)
HIV-1 RNA level, <10,000 copies/mL at start of PI therapy, *n* (%)	51 (18)
Exposure to antiretroviral agent, *n* (%)	
Indinavir	181 (63)
Nelfinavir	137 (48)
Ritonavir	132 (46)
Saquinavir (hard gel cap and soft gel cap)	112 (39)
Lamivudine	264 (92)
Duration of exposure to antiretroviral agents, median d (interquartile range)	
Indinavir	366 (187–1044)
Nelfinavir	333 (150–509)
Ritonavir	178 (81–405)
Saquinavir	172 (62–346)
Lamivudine	569 (311–837)

NOTE. Data are no. (%) of patients, unless otherwise indicated. cap, capsule.

[a] Percentages do not total 100% because data were not available for 2% of patients.

[b] Percentages do not total 100% because data were not available for 6% of patients.

A total of 30 patients had at least one documented paronychia of the great toe during our observation period. In unadjusted analyses, the rate of first great-toe paronychia was elevated during treatment with indinavir (hazard ratio, 10.7; 95% CI, 4.6–24.4) and lamivudine (hazard ratio, 3.9; 95% CI, 1.3–11.2). Nonindinavir PIs, NRTIs other than lamivudine, NNRTIs, age, sex, $CD4^+$ lymphocyte count, and serum HIV-1 RNA level were not associated with an increased risk of paronychia (table 2).

When all antiretroviral agents and classes as well as age, sex, diabetes status, and CD4 cell count were included in a multivariate model, indinavir treatment alone remained significantly associated with a 4.7-fold increased risk of great-toe paronychia (95% CI, 1.6–13.9) (table 2). Lamivudine was no longer significantly associated ($\alpha \leq .05$) with great-toe paronychia in the multivariate model (hazard ratio, 2.3; 95% CI, 0.7–7.5). The decline in the indinavir point estimate from 10.7 to 4.7 was largely due to adjustment for lamivudine exposure. Similarly, the attenuation of the crude association with lamivudine exposure was mostly attributable to adjustment for indinavir use. Therefore, the unadjusted risk associated with lamivudine therapy was likely a result of confounding that resulted from use of indinavir.

The clinical characteristics of the 30 patients with ⩾1 great-toe paronychia are presented in table 3. Twelve of these patients experienced ⩾1 subsequent occurrences of great-toe paronychia during our observation period, and the majority of the recurrences occurred while the patients were receiving regimens containing indinavir (90%). Overall, a total of 64 procedures on the great toe were performed, including incision and drainage, simple avulsion of the nail plate, and resection or phenol destruction of the nail germinal matrix. Eleven patients also experienced paronychia of their fingernails (11 events—none of which coincided with indinavir therapy).

Previous reports have suggested an association between paronychia and both indinavir [3, 4] and lamivudine [2] among patients with HIV infection. In our retrospective cohort study, indinavir, but not lamivudine, was strongly associated with great-toe paronychia. Ingrown nails and paronychia have been seen with only a small number of other medications, including synthetic derivatives of vitamin A (retinoids), methotrexate, and sulfonamides [7, 8]. It is believed that the association between ingrown nails and retinoids relates to retinoic acid's function as a regulator of epithelial cell proliferation and differentiation. Bouscarat et al. [3] and Bourezane et al. [4] have suggested that disturbances of retinoic acid metabolism may underlie the nail changes seen in indinavir recipients as well. Of interest, alterations in retinoic acid metabolism also have

Table 2. Unadjusted and adjusted associations with presentation of great-toe paronychia.

Variable	Unadjusted hazard ratio (95% CI)	Fully adjusted[a] hazard ratio (95% CI)
Age at start of observation, y	1.0 (0.9–1.0)	1.0 (0.9–1.0)
Male sex	0.9 (0.3–3.0)	0.8 (0.2–2.7)
Diabetes	1.5 (0.7–3.1)	1.8 (0.8–3.9)
CD4 count		
<200 cells/mm^3	1.2 (0.6–2.7)	1.3 (0.6–2.8)
200–500 cells/mm^3	0.4 (0.0–2.9)	0.4 (0.0–3.3)
>500 cells/mm^3	1.00	1.00
HIV-1 RNA level, >10,000 copies/mL	0.7 (0.2–2.7)	—
Exposure to		
PI		
Indinavir	10.7 (4.6–26.4)	4.7 (1.6–13.9)
Nonindinavir PI	2.0 (0.6–6.3)	1.2 (0.3–4.5)
None	1.00	1.00
NRTI		
Lamivudine	3.9 (1.3–11.2)	2.3 (0.7–7.5)
Nonlamivudine NRTI	2.2 (0.7–6.8)	1.9 (0.6–5.9)
None	1.00	1.00
NNRTI	0.7 (0.1–5.9)	0.8 (0.1–6.3)

NOTE. HIV-1, HIV type 1; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

[a] All variables listed, with the exception of virus load, were inserted into a common model. Virus load was not included in the model presented here because measurements were not available for 39% of the cohort.

Table 3. Characteristics of 30 patients with great-toe paronychia.

Characteristic	Value
Location of first paronychia	
Great toe	25 (83)
Both great toes	5 (17)
Indinavir exposure status at first presentation	
Receiving noninvestigational indinavir	16 (53)
Receiving definite or possible investigational indinavir[a]	4 (13)
Not receiving indinavir	10 (33)
Patients who experienced subsequent great-toe paronychia	12 (40)
Total subsequent cases of great-toe paronychia	31
Indinavir exposure status at subsequent presentation, *n*	
Receiving noninvestigational indinavir	28
Receiving definite or possible investigational indinavir	0
Not receiving indinavir	3
Great-toe nail procedures performed[b]	64

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] "Definite investigational indinavir" was defined as indinavir given to patients as part of an expanded-access program or an open-label trial; "possible investigational indinavir" was defined as a closed-label trial of indinavir.

[b] Procedures that were performed included incision and drainage, simple avulsion of the nail plate, and resection or phenol destruction of the nail germinal matrix.

been postulated to play a role in the syndrome of peripheral fat lipoatrophy seen in PI recipients [9].

Indinavir has been associated with other epidermal side effects in addition to paronychia [10, 11]. In a randomized study comparing the safety and efficacy of amprenavir and indinavir, hair loss was seen in <1% of amprenavir recipients compared with 7% of indinavir recipients ($P < .001$), and dry skin was observed in 3% of amprenavir recipients compared with 14% of indinavir recipients ($P < .001$). These observations suggest that indinavir may have unique effects on the epidermis and its appendages and that these effects may not be shared by other members of the PI drug class. The mechanism for this unique profile of possible side effects remains to be elucidated.

We were unable to confirm an elevated risk of paronychia with the use of lamivudine. In the cohort we studied, the unadjusted association of paronychia with lamivudine appeared to be a result of concomitant use of indinavir, which highlighted the complicated nature of the identification of possible causes of outcomes of combination antiretroviral therapy. Concurrent use of various antiretroviral agents may introduce confounding effects such as those that we observed when indinavir and lamivudine were used concurrently.

Our findings indicate that individuals have a considerably increased risk of paronychia while they are receiving indinavir. This complication of indinavir-based therapy can cause discomfort and increased utilization of medical resources. Furthermore, individuals who continue receiving indinavir after developing a paronychia may be at even higher risk of developing later paronychial infections; this may justify heightened monitoring for this possibility, if not a change in PI agent. Whether dysmorphic body changes or other dermatological abnormalities, such as alopecia or xerosis, may mark recipients of indinavir who are at higher risk of developing paronychia remains to be determined.

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