Safe Interruption of Maintenance Therapy against Previous Infection with Four Common HIV-Associated Opportunistic Pathogens during Potent Antiretroviral Therapy

Ole Kirk, MD; Peter Reiss, MD; Caterina Uberti-Foppa, MD; Markus Bickel, MD; Jan Gerstoft, MD; Christian Pradier, MD; Ferdinand W. Wit, MD; Bruno Ledergerber, PhD; Jens D. Lundgren, MD; and Hansjakob Furrer, MD, for Seven European HIV Cohorts*

Background: **The safety of interrupting maintenance therapy for previous opportunistic infections other than *Pneumocystis carinii* pneumonia among patients with HIV infection who respond to potent antiretroviral therapy has not been well documented.**

Objective: **To assess the safety of interrupting maintenance therapy for cytomegalovirus (CMV) end-organ disease, disseminated *Mycobacterium avium* complex (MAC) infection, cerebral toxoplasmosis, and extrapulmonary cryptococcosis in patients receiving antiretroviral therapy.**

Design: **Observational study.**

Setting: **Seven European HIV cohorts.**

Patients: **358 patients taking potent antiretroviral therapy (≥3 drugs) who interrupted maintenance therapy at a CD4 lymphocyte count greater than 50 × 10^6 cells/L.**

Measurements: **Recurrence of opportunistic infection after interruption of maintenance therapy.**

Results: **379 interruptions of maintenance therapy were identified: 162 for CMV disease, 103 for MAC infection, 75 for toxoplasmosis, and 39 for cryptococcosis. During 781 person-years of follow-up, five patients had relapse. Two relapses (one of CMV disease and one of MAC infection) were diagnosed after maintenance therapy was interrupted when the CD4 lymphocyte count was less than 100 × 10^6 cells/L or when only one recent measurement exceeded this value. Two relapses (one of CMV disease and one of MAC infection) were diagnosed after maintenance therapy was interrupted once CD4 counts were greater than 100 × 10^6 cells/L for 10 and 8 months, respectively. One relapse (toxoplasmosis) was diagnosed after maintenance therapy interruption at a CD4 lymphocyte count greater than 200 × 10^6 cells/L for 15 months. The overall incidences of recurrent CMV disease, MAC infection, toxoplasmosis, and cryptococcosis were 0.54 per 100 person-years (95% CI, 0.07 to 1.95 per 100 person-years), 0.90 per 100 person-years (CI, 0.11 to 3.25 per 100 person-years), 0.84 per 100 person-years (CI, 0.02 to 4.68 per 100 person-years), and 0.00 per 100 person-years (CI, 0.00 to 5.27 per 100 person-years), respectively.**

Conclusion: **Maintenance therapy against previous infection with CMV, MAC, *Toxoplasma gondii*, or *Cryptococcus neoformans* in patients with HIV infection can be interrupted after sustained CD4 count increases to greater than 200 (or possibly 100 to 200) × 10^6 cells/L for at least 6 months after the start of potent antiretroviral therapy.**

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For author affiliations, see end of text.

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*For members of the participating European HIV cohorts, see the Appendix.

Immune restoration has been demonstrated among HIV-infected patients who respond to potent antiretroviral therapy. Increasing memory and naive CD4 lymphocyte counts and recovery of CD4 lymphocyte reactivity against opportunistic pathogens have been documented (1–3). Resolution of active ongoing opportunistic infections after initiation of antiretroviral therapy has also been reported (4–8). As a result, the question arose whether chemoprophylaxis against opportunistic infections could be interrupted after CD4 lymphocyte counts had increased to levels at which the risk for opportunistic infections is limited (9).

Solid evidence from randomized trials and observational cohort studies indicates that primary chemoprophylaxis against common opportunistic pathogens, such as *Pneumocystis carinii*, *Mycobacterium avium* complex (MAC), and *Toxoplasma gondii,* may be safely interrupted (10–20). However, given the high risk for recurrence after a first episode of an opportunistic infection among patients who did not receive potent antiretroviral therapy (21–26), extrapolation from the safety of interrupting primary chemoprophylaxis to that of interrupting maintenance therapy should be done with caution. A collaboration between eight European cohorts recently documented the safety of interrupting maintenance therapy for *P. carinii* pneumonia (27). For other opportunistic infections, only limited documentation exists; consequently, the formal recommendations on interruption of maintenance therapy for these opportunistic infections have thus far remained conservative (9, 28).

We examined the safety of interrupting maintenance therapy for infection with cytomegalovirus (CMV), MAC, *T. gondii*, and *Cryptococcus neoformans*.

Methods

Cohorts

Seven cohorts from Europe participated in our joint analysis: AIDS Therapy Evaluation Project Netherlands; Danish Cohort of Patients Discontinuing Chemoprophylaxis; EuroSIDA; Frankfurt HIV Cohort; Hospedale San Raffaele Cohort, Milan; Dossier Médico-économique de l'Immunodeficience Humaine-2 Cohort, Nice University Hospital; and Swiss HIV Cohort Study (14, 27, 29–34). All of the study groups obtained ethical approval by their

Context

Primary chemoprophylaxis against opportunistic infections in HIV-infected patients can be safely interrupted after immune reconstitution by antiretroviral therapy. Data are not as clear on interruption of maintenance therapy after treatment of active opportunistic infection.

Contribution

Seven observational cohorts were used to evaluate interruption of maintenance therapy for cytomegalovirus end-organ disease, cryptococcosis, *Mycobacterium avium* complex disease, and cerebral toxoplasmosis after antiretroviral therapy increased CD4 cell counts to stable levels. Among 358 patients (379 events) whose maintenance therapy was interrupted, there were only 5 recurrences.

Implications

Interruption of maintenance therapy for opportunistic infections in patients taking potent antiretroviral therapy carries low risk for recurrence and decreases both cost and complexity of management.

–The Editors

local governing bodies to collect observational data. Data from the cohorts were obtained by using standardized data collection forms that were administered at regular intervals.

Patients

Patients included in the analysis interrupted maintenance therapy for infection with CMV, MAC, *T. gondii*, or *C. neoformans* while taking potent antiretroviral therapy (≥3 antiretroviral drugs of any type). To avoid including patients who discontinued maintenance therapy but had terminal disease with severe immune deficiency, we restricted the analysis to patients with a CD4 lymphocyte count of at least 50×10^6 cells/L at the time of interruption of maintenance therapy.

We studied four opportunistic infections. For CMV chorioretinitis, we accepted a presumptive diagnosis, defined as visual disorder with characteristic appearance on serial ophthalmoscopy; for extraocular CMV end-organ disease, we required definitive diagnosis by biopsy (histologic or cytologic findings). Cryptococcosis was defined as extrapulmonary infection with definitive diagnosis by microscopy, culture, or antigen detection in affected tissue or normally sterile body fluid. Infection with MAC or *Mycobacterium kansasii* was defined as extrapulmonary infection definitively diagnosed by culture. Finally, cerebral toxoplasmosis was cerebral infection definitively diagnosed by histologic or cytologic examination of brain tissue or presumptively diagnosed by response to appropriate therapy, recent onset of focal neurologic abnormalities, and reduced level of consciousness in combination with characteristic lesions that produced a mass effect on computed tomography or magnetic resonance imaging.

The analysis was restricted to patients who had received maintenance therapy that fulfilled the recommendations in the 1999 U.S. Public Health Service and Infectious Diseases Society of America guidelines. This criterion included the following treatments: ganciclovir (intravenous or oral), foscarnet, ganciclovir implant plus oral ganciclovir, cidofovir, or fomivirsen injected into the vitreous to treat CMV end-organ disease; fluconazole, amphotericin B, or itraconazole to treat cryptococcosis; clarithromycin or azithromycin plus ethambutol, with or without rifabutin, to treat MAC or *M. kansasii* infection; and sulfadiazine or clindamycin plus pyrimethamine, and atovaquone with or without pyrimethamine, to treat toxoplasmosis (9).

Other regimens may also protect against recurrent MAC infection or toxoplasmosis. To avoid including patients who were at least partially protected against recurrent disease, the time point of interruption was defined as the date of complete interruption of any potentially protective

Table 1. **Data Collection***

Characteristic	Data Collected
Demographic information	Year of birth, sex, HIV transmission category, lowest CD4 lymphocyte count before stopping maintenance therapy (value and date)
Previous opportunistic infection	Type of opportunistic infection for which maintenance therapy was interrupted, method of diagnosis, location of opportunistic infection for which maintenance therapy was interrupted (MAC and CMV only), date of initial diagnosis of relevant opportunistic infection, date of starting maintenance therapy, last drugs used for maintenance therapy before stopping, dates of stopping the individual drugs, CD4 lymphocyte count at time of initial episode of the relevant opportunistic infection (until 6 months before), HIV RNA level at time of stopping maintenance therapy (including detection limit, whether undetectable, and RNA detection method)
Anti-HIV therapy	Date of starting initial regimen of potent antiretroviral therapy, drugs used for initial regimen of potent antiretroviral therapy, and regimens at stopping maintenance therapy
Follow-up data	Date of stopping potent antiretroviral therapy, if any (last regimen), censoring date: last follow-up, date of and reason for restarting maintenance therapy, date of recurrence of opportunistic infection after stopping maintenance therapy, type of diagnosis of recurrent opportunistic infection, CD4 count at time of recurrent opportunistic infection, HIV RNA level at time of recurrent opportunistic infection (including detection limit, if undetectable), date and type of new AIDS-defining events after stopping maintenance therapy (including relapse of previously diagnosed events), date and cause of death, CD4 lymphocyte count immediately before/at date of starting potent antiretroviral therapy and all subsequent values

*CMV = cytomegalovirus end-organ disease; MAC = *Mycobacterium avium* complex infection.

Table 2. **Distribution of Patients in the Seven Participating Cohorts***

Cohort (Reference)	CMV End-Organ Disease	Cryptococcosis	Disseminated MAC Infection	Toxoplasmosis	Total
	←		*n (person-years of follow-up)*		→
AIDS Therapy Evaluation Project Netherlands (34)	27 (59)	5 (11)	13 (27)	23 (32)	68 (129)
Danish Cohort of Patients Discontinuing Chemoprophylaxis (14)	11 (24)	0 (0)	9 (23)	5 (13)	25 (60)
EuroSIDA (29)	63 (147)	16 (28)	26 (60)	17 (34)	122 (269)
Frankfurt HIV Cohort (30)	11 (28)	2 (5)	10 (23)	2 (6)	25 (63)
Hospedale San Raffaele Cohort, Milan (31)	14 (37)	6 (10)	9 (19)	8 (13)	37 (78)
Dossier Médico-économique dé l'Immunodeficience Humaine-2 Cohort, Nice University Hospital (32)	8 (22)	5 (8)	4 (12)	3 (4)	20 (46)
Swiss HIV Cohort Study (33)	28 (52)	5 (9)	32 (58)	17 (17)	82 (135)
Total	162 (370)	39 (70)	103 (222)	75 (119)	379 (781)

*CMV = cytomegalovirus; MAC = *Mycobacterium avium* complex.

drugs. Therefore, the date of interruption was the date of interruption of the last regimen, whether it was the recommended regimen or a partially protective regimen. Partially protective regimens were defined before eligible patients were identified. For MAC and *M. kansasii* infection, such regimens were azithromycin, clarithromycin, or rifabutin alone, and azithromycin, clarithromycin, or ethambutol combined with rifabutin. For toxoplasmosis, the regimens were co-trimoxazole; dapsone with or without pyrimethamine; and monotherapy with clindamycin, sulfadiazine, or pyrimethamine.

Patients were excluded from analysis if no CD4 lymphocyte count was available in the 6 months before interruption of maintenance therapy or no follow-up was done thereafter. The EuroSIDA is a multinational study and may include patients who are also participants of the other cohorts. Therefore, each of the other cohort studies verified that none of the patients that they included were simultaneously enrolled in EuroSIDA.

Data Collection

Standardized data for analysis were derived from the databases at each of the cohort coordinating centers (**Table 1**). All data on relapses of opportunistic infections, deaths, and reinitiation of maintenance therapy were validated and supplemented by chart review by using a standardized data collection form.

Outcome Measures

The primary outcome measure was recurrence of any of the four opportunistic infections after interruption of maintenance therapy. The secondary outcome measure was diagnosis of other AIDS-defining events, with the intent to analyze whether interruption of maintenance therapy could have facilitated these events.

Statistical Analysis

In addition to overall incidences in the sample, incidences were calculated for strata of CD4 lymphocyte counts at which maintenance therapy was interrupted (50 to 99 $\times 10^6$ cells/L, 100 to 199 $\times 10^6$ cells/L, and $\geq 200 \times 10^6$ cells/L). Three strategies were used to assess the CD4 lymphocyte count at interruption of maintenance therapy, based on 1) the last available value before interruption, 2) the smallest of the two last values before interruption, and 3) the highest value above which the patient's CD4 lymphocyte count had remained for at least 6 months before interruption of maintenance therapy. The CD4 lymphocyte count was assessed according to plan (1), unless other timings of measurement are explicitly mentioned. Patients with fewer than two CD4 lymphocyte measurements or less than 6 months between starting the potent antiretroviral therapy regimen and interruption of maintenance therapy were excluded from the latter two analyses.

We performed additional calculations of incidences. First, we censored patients at the time of interruption of potent antiretroviral therapy or reinitiation of maintenance therapy, or when CD4 lymphocyte counts decreased to less than the lower limit of the CD4 lymphocyte stratum into which the patient was classified at interruption of maintenance therapy. For example, after interruption of maintenance therapy at a CD4 lymphocyte count of 50 to 99 $\times 10^6$ cells/L, follow-up was censored when the CD4 lymphocyte count first became less than 50 $\times 10^6$ cells/L. Second, we calculated incidences according to the latest CD4 lymphocyte count, allowing patients to move among strata, because their CD4 lymphocyte count may have increased or decreased during follow-up after interruption of maintenance therapy. Finally, we performed a subgroup analysis in which we classified patients according to a plasma HIV RNA level less than or equal to 500 copies/mL or at least 500 copies/mL at interruption of maintenance therapy. The closing date for the analysis was 15 April 2001.

Confidence intervals were calculated by assuming a Poisson distribution of events. All statistical analyses were performed by using SAS version 6.12 (SAS, Inc., Cary, North Carolina) or Stata software, version 7.0 (Stata Corp., College Station, Texas).

Results

Patients

Of more than 19 000 patients in the seven participating cohorts who were taking potent antiretroviral therapy, 358 interrupted maintenance therapy for at least one of the

Table 3. **Characteristics of All Patients***

Characteristic	CMV End-Organ Disease (*n* = 162)	Cryptococcosis (*n* = 39)	Disseminated MAC Infection (*n* = 103)	Toxoplasmosis (*n* = 75)
Definitive/presumptive diagnosis, %/%	0.0/100.0, 100.0/0.0†	100.0/0.0	100.0/0.0	16.0/84.0
Age, *y*‡	38 (34–47)	36 (35–40)	37 (33–43)	37 (32–43)
Women, %	20.4	5.1	28.2	29.3
Nadir CD4 lymphocyte count, × 10^6 *cells/L*‡	10 (3–40)	12 (5–46)	8 (3–19)	30 (10–64)
CD4 lymphocyte count at diagnosis, × 10^6 *cells/L*‡	25 (8–96)	48 (11–94)	16 (7–50)	44 (20–97)
CD4 count at interruption of maintenance therapy, × 10^6 *cells/L*‡	231 (150–386)	297 (180–392)	190 (129–290)	320 (233–474)
CD4 lymphocyte count at interruption, %				
50–99 × 10^6 cells/L	10.5	7.7	13.6	6.7
100–199 × 10^6 cells/L	30.9	20.5	39.8	13.3
≥200 × 10^6 cells/L	58.6	71.8	46.6	80.0
Plasma HIV RNA level at interruption, *copies/mL*‡	<500 (<500–1000)	<500 (<500–1200)	<500 (<500–1183)	<500 (<500–4388)
HIV RNA level ≤500 copies/mL, %§	65.1 (129)	73.5 (34)	66.3 (80)	60.3 (68)
Most recent CD4 count, × 10^6 *cells/L*‡	381 (265–560)	369 (220–522)	350 (215–530)	407 (304–650)
Time after initial opportunistic infection, *mo*‡	24 (16–34)	29 (20–42)	23 (12–31)	24 (15–43)
Duration of potent antiretroviral therapy, *mo*‡	19 (11–27)	25 (17–32)	19 (11–26)	23 (14–30)
Number of antiretroviral drugs at interruption of maintenance therapy, %				
3	75.3	69.2	76.7	76.0
4	16.0	28.2	16.5	18.7
≥5	8.6	2.6	6.8	5.3
Regimen including protease inhibitor, %	98.8	79.5	95.2	88.0
Regimen including NNRTI, %	13.0	25.6	16.5	16.0
Prophylactic regimen, *n*	Intravenous ganciclovir: 112 Foscarnet: 15 Cidofovir: 20 Oral ganciclovir: 13 Combinations of the above: 2	Fluconazole: 34 Itraconazole: 4 Amphotericin B: 1	Ethambutol + clarithromycin/azithromycin: 81 Ethambutol + clarithromycin/azithromycin + rifabutin: 22	Clindamycin + pyrimethamine: 33 Sulfadiazine + pyrimethamine: 30 Atovaquone: 8 Atovaquone + pyrimethamine: 4
Duration of abstinence from maintenance therapy, *mo*‡	29 (19–37)	20 (12–29)	26 (15–36)	18 (9–27)

* CMV = cytomegalovirus; MAC = *Mycobacterium avium* complex; NNRTI = nonnucleoside reverse transcriptase inhibitor.
† CMV chorioretinitis and extraocular CMV end-organ disease, respectively.
‡ Data are presented as the median (interquartile range).
§ Numbers in parentheses are the numbers of patients for whom plasma HIV RNA values were available.

four opportunistic infections studied. Of these 358 patients, 21 interrupted maintenance therapy against two of the infections, resulting in 379 interruptions (**Table 2**). The interruptions included 162 events in patients with previous CMV disease (140 with CMV chorioretinitis, 10 with gastrointestinal CMV disease, and 12 with CMV disease at other anatomic sites), 39 with previous cryptococcosis, 103 with previous MAC infection, and 75 with previous cerebral toxoplasmosis.

Patients interrupted maintenance therapy at a wide range of CD4 lymphocyte counts, and the duration of potent antiretroviral therapy before interruption ranged from less than 1 month to more than 5 years. At the time of interruption of maintenance therapy, approximately one fourth of the patients received four or more antiretroviral drugs, and almost all patients received a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor (**Table 3**).

Eight patients (four with previous CMV, one each with cryptococcosis or MAC infection, and two with toxoplasmosis) restarted maintenance therapy without confirmed relapse of opportunistic infection. Five of these eight patients restarted maintenance therapy at a CD4 lymphocyte count greater than 200 × 10^6 cells/L, one at a count of 177 × 10^6 cells/L, and two at a count less than 50 × 10^6 cells/L. Of the eight patients, one restarted maintenance therapy because of suspected recurrent cerebral toxoplasmosis that could not subsequently be confirmed, and two patients (one with toxoplasmosis and one with CMV infection) restarted maintenance therapy as a result of the treating physician's decision, without suspicion of relapse. Three patients (two with CMV disease and one with MAC infection) restarted maintenance therapy because of immunologic deterioration. Finally, the treating physician restarted maintenance therapy on the basis of patient concern in one patient with cryptococcosis and request in one patient with CMV disease. Seven patients interrupted potent antiretroviral therapy after interruption of maintenance therapy (CMV, one patient; MAC, four patients; and toxoplasmosis, two patients), but none restarted maintenance therapy. Twenty-two patients, two of whom restarted maintenance therapy, had a CD4 lymphocyte count less 50×10^6 cells/L during follow-up after interruption of maintenance therapy.

Outcome

Tables 4 and **5** show relapses of the four opportunistic infections and other new or recurrent AIDS-defining events.

The initial search of the seven databases identified nine patients with possible relapses: six with previous CMV end-organ disease, two with previous MAC infection, and one with previous cerebral toxoplasmosis. Subsequent chart review documented that four of the possible CMV events could not be classified as relapses according to our definitions. Two of these four patients were considered to have relapse of CMV disease on the basis of one positive measurement of CMV DNA in the blood or a urine or throat swab, without clinical evidence of end-organ involvement. One patient with previous CMV chorioretinitis was given maintenance therapy after admission to hospital for other reasons until an ophthalmologist later ruled out recurrence of CMV chorioretinitis. One patient had relapse of CMV disease, but at chart review, this incident was found to have occurred before potent antiretroviral therapy was started. As a result, this patient was considered in violation of protocol and was excluded from the analysis.

Five patients thus experienced a validated relapse of the relevant opportunistic infection after interruption of maintenance therapy: two with CMV chorioretinitis, two with MAC infection, and one with cerebral toxoplasmosis. None of these patients had signs or symptoms of CMV disease, MAC infection, or toxoplasmosis at the time of interruption of maintenance therapy. All had been closely monitored after interruption of maintenance therapy, and four of the five relapses occurred within 6 months of interruption (**Table 4**).

The two relapses of CMV disease occurred at CD4 lymphocyte counts of 91 and 221×10^6 cells/L, respectively. The patient with the lower count had no value greater than 100×10^6 cells/L in the 6 months before interruption of maintenance therapy, whereas the other patient had had CD4 lymphocyte counts continuously greater than 100×10^6 cells/L for 8 months before interruption. The two recurrences of MAC infection were diagnosed at CD4 lymphocyte counts of 129 and 270×10^6 cells/L; these counts had been greater than 100×10^6 cells/L for less than 1 month and for 10 months, respectively, before interruption of maintenance therapy. Finally, the CD4 lymphocyte count was 316×10^6 cells/L in the patient with recurrent cerebral toxoplasmosis; it had remained greater than 200×10^6 cells/L for more than 1 year before interruption of maintenance therapy (**Table 4**).

During follow-up for which information was available, 11 patients developed other new or recurrent AIDS-defining events (**Table 5**). Two of these 11 patients had interrupted therapy against both CMV disease and MAC infection. Ten patients died; a new AIDS-defining event was diagnosed in 1 of those patients (**Table 5**). In 1 patient with previous CMV chorioretinitis, severe *Herpes simplex* virus infection was diagnosed 1 month after interruption of ganciclovir maintenance therapy at a CD4 lymphocyte count of 450×10^6 cells/L. No other patients developed AIDS-defining events against which the interrupted maintenance therapy may have offered at least partial protection. No patient with a new AIDS-defining event and none of those who died had recurrence of opportunistic infection after interruption of specific maintenance therapy.

Incidence Data

The patients were followed for 781 person-years. The incidences of relapse were 0.54, 0.00, 0.90, and 0.84 per 100 person-years of follow-up for CMV disease, cryptococcosis, MAC infection, and toxoplasmosis, respectively (**Table 6**). The incidences tended to be highest at a lower CD4 lymphocyte count, both when the value obtained at interruption of maintenance therapy or the most recent value during follow-up was used. The incidence of relapse did not significantly differ between patients with or without plasma HIV RNA levels less than 500 copies/mL at interruption of maintenance therapy (**Table 6**).

Restricting the analysis to the 337 patients who stopped only one type of maintenance therapy did not markedly change the overall results. On the basis of 688 person-years of follow-up, incidences of relapse were 0.62, 0.00, 1.06 and 0.88 per 100 person-years of follow-up for CMV disease, cryptococcosis, MAC infection, and toxoplasmosis, respectively. Of note, the upper limit of the CIs increased less than 1 per 100 person-years of follow-up for each of the opportunistic infections. None of the 21 patients who interrupted two types of maintenance therapy experienced relapse.

When follow-up was censored at interruption of potent antiretroviral therapy, reinitiation of maintenance therapy, or the first CD4 lymphocyte count below the lower limit of the specific CD4 stratum used for the analysis, the incidences remained similar. One relapse (patient 4 in **Table 4**) occurred after the CD4 lymphocyte count had decreased to less than 100×10^6 cells/L.

Patients were then stratified according to the lowest of the two most recent CD4 lymphocyte counts before interruption of maintenance therapy. This process generally resulted in reclassification of many patients to a lower CD4 lymphocyte count category, as indicated by events and person-years of follow-up moving from a higher to a lower CD4 lymphocyte count stratum. As a consequence, incidences were higher in the stratum of 50 to 99×10^6 cells/L and lower in the stratum of 200×10^6 cells/L or greater.

To further reflect the current guidelines, incidences were assessed according to the highest value above which the patient's CD4 lymphocyte count had remained for at

Table 4. **Characteristics of Five Patients Who Experienced Relapse of Opportunistic Infection after Interruption of Maintenance Therapy***

Characteristic	Relapse of CMV Disease	
	Patient 1	Patient 2
Age, *y*	48	46
HIV risk group	Homosexual	Homosexual
Sex	Male	Male
CD4 lymphocyte count at first diagnosis of the opportunistic infection, $\times 10^6$ *cells/L*	53	12
CD4 lymphocyte count at interruption of maintenance therapy (second to last measurement), $\times 10^6$ *cells/L*	91 (75)	221 (162)
Plasma HIV RNA level at interruption of maintenance therapy, *copies/mL*	234 800	197
CD4 lymphocyte count at relapse, $\times 10^6$ *cells/L*	91	247
Plasma HIV RNA level at relapse, *copies/mL*	140 840	705
Duration of potent antiretroviral therapy at interruption of maintenance therapy, *mo*	18	28
Duration of sustained CD4 lymphocyte count before interruption of maintenance therapy, *mo*‡		
$>50 \times 10^6$ cells/L	8	21
$>100 \times 10^6$ cells/L	–	8
$>200 \times 10^6$ cells/L	–	0
Duration of maintenance therapy before interruption, *mo*	16	26
Duration of abstinence from maintenance therapy after interruption, *mo*	2	2
Assessment at time of interruption	Fundoscopy; no activity of CMV	Fundoscopy: no activity of CMV, macular edema (judged to be saquinavir associated)
Follow-up after interruption (including examination at relapse)	3 ophthalmologic examinations	3 ophthalmologic examinations
Objective findings at relapse	Fundoscopy: CMV chorioretinitis	Fundoscopy: CMV chorioretinitis, macular cystoiditis/edema
Clinical symptoms at relapse	Black spots	Decreased visual acuity
Effect of specific therapy after relapse of opportunistic infection	Positive	Positive, later relapsed

* CMV = cytomegalovirus; MAC = *Mycobacterium avium* complex.
† This patient had three CD4 lymphocyte counts $<100 \times 10^6$ cells/L between interruption of maintenance therapy and diagnosis of relapse.
‡ Includes only duration after start of potent antiretroviral therapy.

least 6 months before interruption of maintenance therapy (9, 28). When maintenance therapy was interrupted in a patient whose CD4 lymphocyte level had been sustained at greater than 100×10^6 cells/L for at least 6 months, the incidence of relapse during follow-up was low (one relapse of CMV disease and one of MAC infection); when sustained at greater than 200×10^6 cells/L, only one relapse (toxoplasmosis) was diagnosed (**Table** 4).

Table 5. **Characteristics of Patients Who Experienced a New or Recurrent AIDS-Defining Event or Died after Interruption of Maintenance Therapy***

Characteristic	CMV End-Organ Disease	Cryptococcosis	Disseminated MAC Infection	Toxoplasmosis
New or recurrent AIDS-defining events, *n*	8†	0	5†	0
Type of new or recurrent AIDS-defining event	Severe *Herpes simplex* virus infection, AIDS-related dementia, cerebral toxoplasmosis (× 2), *Pneumocystis carinii* pneumonia, progressive multifocal leukoencephalopathy, cryptosporidiosis (× 2)		Toxoplasmosis (× 2), AIDS-related dementia, CMV chorioretinitis and Kaposi sarcoma‡, esophageal candidiasis and CMV	
Deaths, *n*	2	1	3	4
Cause of death	Non-Hodgkin lymphoma, acute myeloblastic leukemia	Cardiac failure	Anal cancer, staphylococcal septicemia, Kaposi sarcoma	Epileptic seizures§, CMV encephalopathy, suicide, pneumonia

* CMV = cytomegalovirus; MAC = *Mycobacterium avium* complex.
† Two patients stopped both CMV and MAC maintenance therapy; one developed cerebral toxoplasmosis, and one developed AIDS-related dementia.
‡ The patient subsequently died.
§ Known epilepsy due to cerebral calcifications after previous cerebral toxoplasmosis.

Table 4—**Continued**

Relapse of MAC Infection		Relapse of Toxoplasmosis
Patient 3	**Patient 4†**	**Patient 5**
32	31	45
Intravenous drug use	Homosexual	Heterosexual
Male	Male	Male
1	6	7
270 (107)	129 (99)	316 (362)
<7	1220	<20
270	129	316
<7	3000	<20
21	18	27
14	16	22
10	0	19
0	–	15
20	28	31
3	15	1
Negative blood culture, no clinical symptoms	No clinical symptoms	No clinical symptoms
1 blood culture and clinical examination	8 clinical examinations	1 clinical examination
Positive blood culture	No blood culture performed	Magnetic resonance imaging: inflammatory lesion in globus pallidus irradiating into internal capsule and cerebral peduncle, no mass effect
None	Weight loss, diarrhea	Weakness, paresthesia in legs
Positive, later relapsed	Positive	Positive

DISCUSSION

Our results provide substantial evidence that sustained increases of CD4 lymphocyte counts to greater than 100 to 200×10^6 cells/L are associated with a sufficient degree of immune recovery to safely interrupt maintenance therapy against recurrent CMV end-organ disease, disseminated MAC infection, toxoplasmosis, and cryptococcosis. This conclusion was also suggested by published case series (5, 14, 35–45) and is consistent with the proven safety of discontinuation of maintenance therapy against *P. carinii* (17, 27).

Five patients taking potent antiretroviral therapy experienced relapse of their opportunistic infection at a CD4 lymphocyte count greater than 50×10^6 cells/L. Two of these patients interrupted maintenance therapy when their CD4 lymphocyte count was less than or only a recent value was greater than 100×10^6 cells/L—not a level considered appropriate according to the current U.S. guidelines (28). The other three patients had relapse of CMV disease, MAC infection, and toxoplasmosis, respectively, shortly after interruption of maintenance therapy, despite CD4 lymphocyte counts that remained continuously greater than 100×10^6 cells/L for more than 6 months. The patients had no signs or symptoms of ongoing opportunistic infection when maintenance therapy was interrupted, and at the time of relapse, the CD4 lymphocyte count was greater than 200×10^6 cells/L and the plasma HIV RNA level was less than 500 copies/mL. The two patients with recurrent CMV and MAC each experienced a second relapse, and all three patients may have had persistent deficits in CMV-specific, MAC-specific, and *T. gondii*–specific immune responses, as recently reported in two patients with multiple relapses of CMV chorioretinitis (46).

The overall incidences of relapse after interruption of maintenance therapy were 0 to 1 per 100 person-years of follow-up, with an upper 95% confidence limit of 5 or fewer relapses per 100 person-years of follow-up. These incidences are low compared with relapse rates when no maintenance therapy was instituted and with breakthrough rates among patients receiving maintenance therapy before the availability of potent antiretroviral therapy (21–26, 47).

Undesirable effects of maintenance therapy, such as adverse drug reactions; possible impairment of quality of life; cost; and, from a public health perspective, the potential contribution to emergence of resistance in the population, seem to well outweigh the low risk for relapse after interruption that we observed (21, 48).

Our prospective observational cohort study has limitations and biases, and the safety of interrupting maintenance therapy should ideally be addressed in randomized,

Table 6. **Incidence of Recurrent Opportunistic Infections among Patients Who Interrupted Maintenance Therapy While Taking Potent Antiretroviral Therapy***

Characteristic	CMV End-Organ Disease		Cryptococcosis	
	Events/Person-Years of Follow-up, *n/n*	Incidence (95% CI)	Events/Person-Years of Follow-up, *n/n*	Incidence (95% CI)
All interruptions of maintenance therapy (n = 379)	2/370	0.54 (0.07–1.95)	0/70	0.00 (0.00–5.27)
CD4 lymphocyte count at interruption				
50–99 × 10^6 cells/L (n = 39)	1/34	2.9 (0.1–16.4)	0/5	0.0 (0.0–73.8)
100–199 × 10^6 cells/L (n = 109)	0/134	0.0 (0.0–2.8)	0/16	0.0 (0.0–23.1)
≥200 × 10^6 cells/L (n = 231)	1/202	0.5 (0.0–2.8)	0/49	0.0 (0.0–7.5)
Plasma HIV RNA level at interruption				
≤500 copies/mL (n = 204)	1/185	0.5 (0.0–3.0)	0/40	0.0 (0.0–9.2)
>500 copies/mL (n = 108)	1/103	1.0 (0.0–5.4)	0/17	0.0 (0.0–21.7)

* CMV = cytomegalovirus; MAC = *Mycobacterium avium* complex.

controlled trials (49, 50). However, given the low incidence of relapse in our study, such trials would have to enroll a large sample to be followed for a prolonged period. It is therefore unlikely that a randomized trial would be able to definitively answer the question of whether it is safe to interrupt maintenance therapy within an acceptable time frame. In the absence of results from randomized trials or prospectively designed systematic observational studies with clear entry criteria and standardized follow-up, analyses from observational cohorts such as ours are useful. In contrast to studies with clear entry criteria, incidences of recurrent opportunistic infections after interruption of maintenance therapy can be calculated for strata of CD4 lymphocyte counts and HIV RNA levels obtained from observational studies (13).

We included all patients who interrupted maintenance therapy at a CD4 lymphocyte count greater than 50 × 10^6 cells/L if they had received maintenance therapy as recommended in U.S. guidelines (9, 28). The relatively broad inclusion criteria probably better reflect current clinical practice than do the smaller groups of highly selected patients reported in many other studies. In addition, only patients with previous opportunistic infections that fulfilled well-defined diagnostic criteria were included, and formalized quality assurance procedures in the participating cohorts ensured appropriate identification of patients. Finally, a standardized chart review of all possible relapses was performed to confirm that the events fulfilled the diagnostic criteria.

The absence of consistent prospectively mandated follow-up for early signs of relapse, such as brain imaging for toxoplasmosis, blood cultures for MAC infection, or scheduled ophthalmologic examinations for CMV chorioretinitis, is a limitation. However, the median follow-up of more than 18 months makes it unlikely that clinically meaningful relapses would have gone unnoticed.

Loss to follow-up may lead to bias potentially working in both directions in the assessment of the safety of interrupting maintenance therapy, depending on the reason for loss to follow-up. In our study, the loss to follow-up was less than 5%. Few patients were excluded due to lack of follow-up after interruption of maintenance therapy.

Our study is based on data in patients and physicians from Europe, who do not necessarily adhere to the current U.S. guidelines; extrapolation to other groups should therefore be done with caution (9, 28). Many clinics across Europe have already adopted the practice of interrupting primary prophylaxis and maintenance therapy. We speculate that this practice stems in part from the impression that it is safe; however, we have no specific data on the reason for interruption of maintenance therapy to support this idea (10, 11, 13, 14).

Before interruption, the patients had taken maintenance therapy for a prolonged time after the CD4 lymphocyte count had increased to greater than 200 × 10^6 cells/L. Therefore, our findings should be extrapolated with caution to patients in whom CD4 lymphocyte counts have been above 200 × 10^6 cells/L for a shorter time and in those with less pronounced increases in CD4 lymphocyte count. We believe that our findings permit extrapolation to groups with similar characteristics and similar responses to potent antiretroviral therapy as those of our patients.

Detectable plasma HIV RNA at interruption of maintenance therapy did not seem to influence the incidence of recurrence of opportunistic infections. However, less than half of the patients had detectable HIV RNA and CD4 lymphocyte counts above threshold values, and less than one quarter of patients had HIV RNA levels greater than 5000 copies/mL at the time of discontinuation. Therefore, we could not substantiate the safety of interruption in this group. However, a recent study showed that discontinuation of primary prophylaxis against *P. carinii* infection is safe even in patients with discordant virologic and immunologic responses (51).

Careful clinical monitoring of patients in whom maintenance therapy is interrupted remains important, as shown by the three patients in our study who had relapse of opportunistic infection despite CD4 lymphocyte counts greater than 200 × 10^6 cells/L during potent antiretroviral therapy. However, even HIV-infected patients with no

Table 6—**Continued**

Disseminated MAC Infection		Toxoplasmosis	
Events/Person-Years of Follow-up, *n/n*	Incidence (95% CI)	Events/Person-Years of Follow-up, *n/n*	Incidence (95% CI)
2/222	0.90 (0.11–3.25)	1/119	0.84 (0.02–4.68)
0/37	0.0 (0.0–10.0)	0/11	0.0 (0.0–33.5)
1/92	1.1 (0.0–6.1)	0/17	0.0 (0.0–21.7)
1/93	1.1 (0.0–6.0)	1/92	1.1 (0.0–6.1)
1/109	0.9 (0.0–5.1)	1/60	1.7 (0.0–9.3)
1/66	1.5 (0.0–8.4)	0/52	0.0 (0.0–7.1)

previous opportunistic infections remain at risk for opportunistic infections at a CD4 lymphocyte count greater than 200×100^6 cells/L, although the risk is substantially lower than that in patients with lower CD4 lymphocyte counts.

In the absence of results from specific studies, maintenance therapy should probably be reinitiated once the CD4 lymphocyte count falls below the threshold levels above which it seems safe to interrupt maintenance therapy, or if potent antiretroviral therapy must be interrupted. In most patients, interruption of maintenance therapy was not associated with an increased risk for other new or recurrent AIDS-defining events against which it may have offered at least partial protection. The exception was one patient who acquired severe *H. simplex* infection shortly after interruption of intravenous ganciclovir therapy. No cases of recurrent bacterial pneumonia were detected among patients who interrupted macrolide therapy, but this finding does not definitively rule out an increased risk for non–AIDS-defining events, such as isolated episodes of bacterial pneumonia or other bacterial infections, after interruption of maintenance therapy. It is reassuring, however, that only a few cases of bacterial pneumonia were observed in a recent study of interruption of maintenance therapy against *P. carinii* infection (27).

In conclusion, our study provides substantial evidence that interruption of maintenance therapy for previous infection with CMV, MAC, *T. gondii*, or *C. neoformans* in HIV-infected patients is safe after CD4 lymphocyte counts are sustained at greater than 200×10^6 cells/L (or, possibly, 100 to 200×10^6 cells/L) for at least 6 months after starting potent antiretroviral therapy.

APPENDIX

The members of the seven study groups that contributed patient data, and the cities in which they are located, are as follows.

AIDS Therapy Evaluation Project Netherlands

W. Bronsveld, Alkmaar; H. Weigel, K. Brinkman, P. Frissen, J. ten Veen, M. Hillebrand, S. Schieveld, J. Mulder, E. van Gorp, P. Meenhorst, A. van Eeden, F. Claessen, R. Perenboom, S. Danner, J.K. Eeftinck Schattenkerk, E. Gisolf, M. Godfried, M. Jambroes, J. Lange (*Study Coordinator*), J. van der Meer, J. Nellen, D. Notermans, T. van der Poll, M. van Praag, J. Prins, P. Reiss, M. Reijers, T. Ruys, M. van der Valk, E. van der Ven, A. Verbon, G.J. Weverling, F. Wit, F. de Wolf (*Study Coordinator*), J Wubbels, Amsterdam; C. Richter, Arnhem; R. Vriesendorp, R. Kauffmann, E. Kogger, The Hague; B. Bravenboer, Eindhoven; C. ten Napel, K. Pogany, Enschede; H.G. Sprenger, G. Law, Groningen; R.W. ten Kate, Haarlem; M. Leemhuis, Leeuwarden; F. Kroon, G. Schrey, S. van der Geest, A. van der Ven, Maastricht; P. Koopmans, M. Keuter, D. Telgt, Nijmegen; M. van der Ende, I. Gyssens, S. de Marie, Rotterdam; J. Juttmann, C. van der Heul, Tilburg; M. Schneider, J. Borleffs, I. Hoepelman, C. Jaspers, K. Schurink, Utrecht; W. Blok, Vlissingen.

Danish Cohort of Patients Discontinuing Chemoprophylaxis

J. Gerstoft, Copenhagen; C. Pedersen, Odense; N. Obel, S. Jensen-Fangel, Aarhus; H. Nielsen, Aalborg; J.D. Lundgren, O. Kirk, Hvidovre.

EuroSIDA

Austria: N. Vetter (*National Coordinator*), Vienna.

Belgium: N. Clumeck (*National Coordinator*), P. Hermans, B. Sommereijns, Brussels; R. Colebunders, Antwerp.

Czech Republic: L. Machala (*National Coordinator*), H. Rozsypal, Prague.

Denmark: J. Nielsen (*National Coordinator*), J. Lundgren, T. Benfield, O. Kirk, J. Gerstoft, T. Katzenstein, B. Røge, P. Skinhøj, Copenhagen; C. Pedersen, Odense.

France: C. Katlama (*National Coordinator*), C. Rivière, J.-P. Viard, Paris; T. Saint-Marc, P. Vanhems, Lyon; C. Pradier, Nice.

Germany: M. Dietrich (*National Coordinator*), C. Manegold, J. van Lunzen, Hamburg; V. Miller, S. Staszewski, Frankfurt; F.-D. Goebel, Munich; B. Salzberger, Cologne; J. Rockstroh, Bonn.

Greece: J. Kosmidis (*National Coordinator*), P. Gargalianos, H. Sambatakou, J. Perdios, G. Panos, M. Astriti, Athens.

Hungary: D. Banhegyi (*National Coordinator*), Budapest.

Ireland: F. Mulcahy (*National Coordinator*), Dublin.

Israel: I. Yust (*National Coordinator*), D. Turner, Tel Aviv; S. Pollack, Z. Ben-Ishai, Haifa: Z. Bentwich, Rehovot; S. Maayan, Jerusalem.

Italy: S. Vella (*National Coordinator*), A Chiesi (*National Coordinator*), V. Vullo, P. Santopadre, P. Narciso, A. Antinori, P. Franci, M. Zaccarelli, Rome; C. Arici, Bergamo; R. Pristerá, Bolzano; F. Mazzotta, A. Gabbuti, Florence; R. Esposito, A. Bedini, Modena; A. Chirianni, E. Montesarchio, Naples; A. Lazzarin, R. Finazzi, A. D'Arminio Monforte, Milan.

Luxembourg: R. Hemmer (*National Coordinator*), T. Staub, Luxembourg.

The Netherlands: P. Reiss (*National Coordinator*), Amsterdam.

Norway: J. Bruun (*National Coordinator*), A. Maeland, V. Ormaasen, Oslo.

Poland: B Knysz (*National Coordinator*), J. Gasiorowski, Wroclaw; A. Horban, Warsaw; D. Prokopowicz, A. Wiercinska-

Drapalo, Bialystok; A. Boron-Kaczmarska, M. Pynka, Szczecin; M. Beniowski, Chorzow; H. Trocha, Gdansk.

Portugal: F Antunes (*National Coordinator*), K Mansinho, R Proenca, Lisbon.

Spain: J. González-Lahoz (*National Coordinator*), R. Polo, V. Soriano, Madrid; B. Clotet, A. Jou, J. Conejero, C. Tural, Badalona; J.M. Gatell, J.M. Miró, Barcelona.

Sweden: A Blaxhult (*National Coordinator*), B. Heidemann, P. Pehrson, Stockholm.

Switzerland: B. Ledergerber (*National Coordinator*), R. Weber, Zürich; P. Francioli, A. Telenti, Lausanne; B. Hirschel, V. Soravia-Dunand, Geneva.

United Kingdom: S. Barton (*National Coordinator*), A.M. Johnson, D. Mercey, A. Phillips, C. Loveday, M.A. Johnson, A. Mocroft, A. Pinching, J. Parkin, J. Weber, London; M. Fisher, Brighton; R. Brettle, Edinburgh.

Frankfurt HIV Cohort

S. Staszewski, V. Miller, E.B. Helm, M. Bickel, Frankfurt.

Hospedale San Raffaele Cohort, Milan

A. Lazzarin, C. Uberti-Foppa, Milan.

Dossier Médico-économique de l'Immunodeficience Humaine-2 Cohort, Nice University Hospital

J.P. Cassuto, J. Cortalorda, P. Dellamonica, J. Durant, J.G. Fuzibet, C. Gisbert, Y. Le Fichoux, J.F. Michiels, N. Oran, A. Pesce, C. Pradier, P.M. Roger, E. Rosenthal, F. Sanderson, Nice.

The Swiss HIV Cohort Study

M. Battegay (*Chairman of the Scientific Board*), M.C. Bernard, E. Bernasconi, H. Bucher, P. Bürgisser, M. Egger, P. Erb, W. Fierz, M. Flepp (*Chairman of the Clinical and Laboratory Committee*), P. Francioli (*President of the Swiss HIV Cohort Study, Centre Hospitalier Universitaire Vaudois, Lausanne*), H.J. Furrer, M. Gorgievski, H. Günthard, P. Grob, B. Hirschel, C. Kind, T. Klimkait, B. Ledergerber, U. Lauper, M. Opravil, F. Paccaud, G. Pantaleo, L. Perrin, J.C. Piffaretti, M. Rickenbach (*Head of Data Center*), C. Rudin (*Chairman of the Mother and Child Substudy*), J. Schupbach, A. Telenti, P. Vernazza, T. Wagels, R. Weber.

From Hvidovre Hospital, University of Copenhagen, Hvidovre, and Rigshospitalet, Copenhagen, Denmark; Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; San Raffaele Hospital, Milan, Italy; J.W. Goethe University Clinic, Frankfurt, Germany; Hôpital l'Archet, Nice, France; University Hospital Zurich, Zurich, Switzerland; and University Hospital Bern, Bern, Switzerland.

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Requests for Single Reprints: Ole Kirk, MD, Coordinating Centre of EuroSIDA, Department of Infectious Diseases, Hvidovre University Hospital, Kettegaard Alle, 2650 Hvidovre, Denmark; e-mail, oki@cphiv.dk.

Current author addresses and author contributions are available at www.annals.org.

Current Author Addresses: Drs. Kirk and Lundgren: Coordinating Centre of EuroSIDA, Department of Infectious Diseases, Hvidovre University Hospital, Kettegaard Alle, 2650 Hvidovre, Denmark.
Drs. Reiss and Wit: Academic Medical Center, University of Amsterdam, Division of Infectious Diseases, Tropical Medicine, and AIDS, and National AIDS Therapy Evaluation Center, Amsterdam, The Netherlands.
Dr. Uberti-Foppa: San Raffaele Hospital, Infectious Diseases Department, Milan, Italy.
Dr. Bickel: J.W. Goethe University Clinic, Department of Infectious Diseases, Frankfurt, Germany.
Dr. Gerstoft: Rigshospitalet, Department of Infectious Diseases, Copenhagen, Denmark.
Dr. Pradier: Hopital l'Archet, Tropical and Infectious Diseases Department, Nice, France.
Dr. Ledergerber: University Hospital Zürich, Division of Infectious Diseases and Hospital Epidemiology, Zürich, Switzerland.
Dr. Furrer: University Hospital Bern, Division of Infectious Diseases, Bern, Switzerland.

Author Contributions: Conception and design: O. Kirk, P. Reiss, B. Ledergerber, J.D. Lundgren, H. Furrer.
Analysis and interpretation of the data: O. Kirk, B. Ledergerber, J.D. Lundgren, H. Furrer.
Drafting of the article: O. Kirk, B. Ledergerber, J.D. Lundgren, H. Furrer.
Critical revision of the article for important intellectual content: O. Kirk, P. Reiss, J.D. Lundgren, H. Furrer.
Final approval of the article: O. Kirk, P. Reiss, C. Uberti-Foppa, M. Bickel, J. Gerstoft, C. Pradier, F.W. Wit, B. Ledergerber, J.D. Lundgren, H. Furrer.
Provision of study materials or patients: O. Kirk, P. Reiss, C. Uberti-Foppa, M. Bickel, J. Gerstoft, C. Pradier, F.W. Wit, H. Furrer.
Statistical expertise: O. Kirk, B. Ledergerber.
Obtaining of funding: O. Kirk, J.D. Lundgren, H. Furrer.
Administrative, technical, or logistic support: O. Kirk, B. Ledergerber, H. Furrer.
Collection and assembly of data: O. Kirk, C. Uberti-Foppa, M. Bickel, C. Pradier, F.W. Wit, H. Furrer.

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At ninety, bed-bound
in the facility, my mother gasped
as she sucked oxygen
through cannulae. Shyly she confessed
her tormenting obsession
to eat a piece of apple pie.
We watched her chew
the slice from Letha's Family Restaurant,
smiling as she paused
to breathe, her face gorgeous with happiness.

I sat at her bedside
every afternoon for half an hour,
dwelling in the luminous
air of her pride and affection.
She died quietly
and quickly on a morning in late March
before I could reach her,
while a tender woman held her hand.
I sat with her white body
half an hour and kissed her forehead,
and at night the telephone
rang although no one was calling.

Donald Hall
The Old Life
Boston: Houghton Mifflin; 1996:119

Submitted by:
James J. Castles, MD
University of California, Davis
Davis, CA 95616

Submissions from readers are welcomed. If the quotation is published, the sender's name will be acknowledged. Please include a complete citation (along with page number on which the quotation was found), as done for any reference.–*The Editor*