Treatment of Acute C Hepatitis in HIV-Infected Patients

To the Editor:

Since the introduction of highly active antiretroviral therapy, hepatitis C virus (HCV) infection has emerged as a major cause of morbidity and mortality in patients with HIV infection.[1]

Although treatment with pegylated interferon (pegIFN) and ribavirin has significantly improved the therapeutic outcome of chronic HCV hepatitis, 30% to 50% of such patients do not achieve a sustained virologic response (SVR), and lower response rates are recorded in HCV/HIV-coinfected patients for several reasons, including a poorer treatment tolerance.[2] Recent studies evidenced that IFN α-2b is highly effective in patients with acute HCV hepatitis (ACH), with rates of SVR higher than those achievable with pegIFN and ribavirin in chronic C hepatitis.[3] There are no data on the effectiveness of pegIFN in HIV-positive patients with ACH.

Based on the favorable results obtained in the treatment of acute HCV infection in non-HIV–infected subjects,[4] we administered pegIFN α-2b on a open-label basis to 4 consecutive HIV-infected patients who developed ACH.

Diagnosis of ACH was made with positive HCV RNA and elevated serum alanine aminotransferase (ALT) levels with documented seroconversion for anti-HCV antibodies or the presence of a known risk factor in the preceding 6 months.

Patients received supervised treatment with pegIFN α-2b at a dosage ranging between 1.1 and 1.5 μg/kg once weekly for 12 weeks. ALT level, CD4 cell count, HCV RNA, and HIV RNA measurements were made at baseline and at weeks 1, 2, 3, 4, 8, 12, 24, and 36. The HCV RNA measurements were analyzed by a quantitative branched DNA assay (bDNA, version 3.0 Assay, Versant, Bayer, Tarritown, NY), with a lower detection limit of 3.2×10^3 copies/mL and by a qualitative reverse transcriptase polymerase chain reaction (RT-PCR; Cobas Amplicor HCV test version 2.0, Roche, Branchburg, NJ) with a lower detection limit of 125 copies/mL. The primary endpoint was the SVR, defined as a negative RT-PCR result 24 weeks after the end of treatment.

Two patients were women. The median age was 32.5 years (range, 23–62 years), and the median time from HIV infection was 30 months (range, 4–96 months). HCV genotype 1 was found in 2 patients and genotype 2 in the other 2 patients. All patients were naive for antiretroviral therapy. Risk factors for HCV transmission were intravenous drug use (50%) and sexual exposure (50%). Only one patient had constitutional symptoms attributable to acute HCV infection. At baseline, the median HCV RNA level was 7.5×10^6 copies/mL (range, 3.2×10^3–39.5×10^6); the median HIV RNA level was 5×10^4 copies/mL (range, 2×10^4–26×10^5) and the median CD4 cell count was 431/mm^3 (range, 404–567). Treatment was given within 120 days (range, 30–120) since the peak level of ALT.

All patients completed the supervised 12-week course of pegIFN without significant side effects or dose reduction. As shown in Table 1, the SVR was achieved in 3 patients (75%); the patient in whom treatment failed had a negative bDNA at week 8 and negative RT-PCR results only at week 12 but subsequently relapsed. It is noteworthy that all 3 responders had negative RT-PCR findings as early as week 4, with ALT normalization at week 3. The patient who did not respond had the highest baseline HCV RNA load, the oldest age, and had received the lowest IFN dose (1.1 μg/kg).

At the 1st week, a mean decrease of HIV RNA of 0.6 $\log_{10}$ was recorded, with no further changes until the end of therapy. At week 12 the HIV RNA increased and returned to values comparable to baseline. No significant changes in CD4 cell count were observed throughout the study period.

The treatment outcome of acute HCV infection has been repeatedly shown to be far more favorable than that achievable in chronic HCV hepatitis. According to the data reported here, the same seems to apply to HIV/HCV-coinfected subjects. A short treatment course with pegIFN provided an SVR of 75%, was well tolerated, and did not interfere with any significant HIV-related parameter. Furthermore, as also seen in HCV-monoinfected patients with acute infection, the therapeutic response was not influenced by the HCV genotype.[4]

Although no definite conclusion can be drawn from this small study, our findings suggest that the treatment of ACH in HIV-infected patients deserves to be further explored to better define the time of intervention and the most

TABLE 1. Branched DNA (bDNA) and RT-PCR Results at Baseline (BL)

		BL	W1	W2	W3	W4	W8	W12	W24	W36
Patient 1	RT-PCR	Pos	Pos	Pos	Pos	Neg	Neg	Neg	Neg	Neg
	bDNA	78×10^3	12×10^3	Neg	Neg	Neg	Neg	Neg	Neg	Neg
Patient 2	RT-PCR	Pos	Pos	Pos	Pos	Neg	Neg	Neg	Neg	Neg
	bDNA	3.2×10^3	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg
Patient 3	RT-PCR	Pos	Pos	Pos	Pos	Neg	Neg	Neg	Neg	Neg
	bDNA	14.9×10^6	1.2×10^6	Neg	Neg	Neg	Neg	Neg	Neg	Neg
Patient 4	RT-PCR	Pos	Pos	Pos	Pos	Pos	Pos	Neg	Pos	Pos
	bDNA	39.5×10^6	27.5×10^6	12.3×10^6	4.2×10^6	3.2×10^6	Neg	Neg	33.2×10^6	33.8×10^6

During treatment W1 = first week; W2 = second week; W3 = third week; W4 = fourth week; W8 = eighth week; W12 = twelth week, and after treatment W24 = 12 weeks after the end treatment; W36 = 24 weeks after the end of treatment.

Pos = positive; Neg = negative.

appropriate dosage and treatment duration with pegIFN.

As opposed to what is usually seen in intravenous drug users, in subjects at risk for sexual exposure transmission of HCV infection may take place after HIV infection. Although intravenous drug use remains the major risk factor for HCV infection, an increased sexual transmission of HCV has recently been reported, especially in the presence of other sexually cotransmitted diseases (eg, syphilis).[5] Currently, sexual activity ranks as the 2nd risk factor for HCV infection in patients with acute hepatitis, suggesting that sexual transmission may contribute significantly to the total burden of HCV infection.[6] Because a sizeable proportion of patients who acquired HIV through the sexual route are still free of HCV infection, attention should be paid to the serologic screening for acute C hepatitis in any subject with persistent risk factors, or when ALT levels increase during antiretroviral treatment. Should these results be further validated in larger clinical studies, the early detection and treatment of HCV infection might provide a unique opportunity for reducing its relevant morbidity and mortality burden in subjects with HIV infection.

Sabrina Audagnotto, MD, DTM&H
Francesco Giuseppe De Rosa, MD
Olivia Bargiacchi, MD
Silvia Garazzino, MD
Lorenzo Veronese, MD
Giuseppe Cariti, MD
Giovanni Di Perri, MD, PhD, DTM&H
Department of Infectious Diseases
University of Turin
Turin, Italy

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Utility of Interrupting Antiretroviral Treatment Before HIV Drug Resistance Testing in Patients With Persistently Detectable Low-Level Viremia

To the Editor:

Recent studies have not detected accumulation of resistance mutations in highly active antiretroviral therapy (HAART)–treated patients whose plasma viral load (VL) persists at less than 50 copies/mL.[1] In contrast, at viremia levels of 50 to 1000 copies/mL, low-grade viral replication may lead to an accumulation of resistance mutations that endanger the effectiveness of current and even posterior treatments.[2,3] Although these patients ideally should undergo resistance testing before deciding on treatment change or intensification, current clinical assays for resistance often fail to yield results when VL is lower than 1000 copies/mL.

Treatment interruption (TI) is usually followed by VL rebound within days or weeks.[4,5] Therefore, TI followed by resistance testing when VL reaches 1000 copies/mL, in theory, may be used to advantage to perform conventional resistance tests in these patients. The problem is that some of these mutations may go undetected in the resistance test a few days after TI due to replacement of the mutating virus by wild-type virus,[6–8] which could reduce the utility of this strategy.

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We performed TI in 9 clinically and immunologically stable patients with persistent viremia of 50 to 1000 copies/mL (using Amplicor HIV-1 Monitor test, version 1.5, Roche Molecular System, Branchburg, NJ; lower limit of detection = 50 copies/mL) on at least 3 consecutive occasions separated by intervals of at least 1 month.

All were on continuous HAART for at least 1 year, with good compliance. None had previously undergone resistance testing.

One week after total TI, blood samples were obtained to determine VL, and 4 mL was frozen for later use in the resistance test. When VL was less than 1000 copies/mL, the frozen sample was discarded; this process was repeated weekly until a VL of at least 1000 copies/mL was detected. Then the corresponding frozen sample was thawed and used to perform the genotypic resistance test (Trugene, Bayer HealthCare LLC, Tarrytown, NY). Patients received no antiretroviral treatment until the results of the test were obtained and evaluated to guide the new treatment regimen. Informed consent was obtained from all patients.

All patients were male with a mean age of 46 years (range, 39–61 years). By Centers for Disease Control classification (1993), 1 patient was at stage A-1, 3 at A-2, 3 at B-2, 1 at B-3, and 1 at stage C-2.

Mean time receiving continuous HAART before TI was 57 months (range, 31–84 months); 5 patients had changed their HAART plan at least once due to adverse effects (1 patient) or previous virologic failure (4 patients). Thus when low-level viremia was detected, mean time on the last HAART regimen was 22.7 months (range, 3–60 months).

Only 2 patients had started antiretroviral treatment with a HAART-type regimen, whereas the remaining 7 had started with non-HAART regimens.

Table 1 shows all the antiretroviral drugs that each patient had received previously, those being taken at the time this study began, and the mutations found in each patient.

All patients had stable viremia of 50 to 1000 copies/mL, with a mean 6.5 determinations of VL (range, 3–14) as from the 1st determination of more than 50 copies/mL, and a median time of 11 months (interquartile range [IQR] 5–20).

TABLE 1. Antiretroviral Drugs That Each Patient Had Received Previously, Those Being Taken at the Time This Study Began, and Mutations Found in Each Patient

Patient	Previous Drug Exposure	Current HAART Regimen as at TI	Retrotranscriptase Gene Mutations	Protease Gene Mutations
1		AZT + 3TC + IND	M184V	L10R, M46L, I54V, L63P, V82A
2	AZT, 3TC, ddC, ddI, d4T, ABC, IND	D4T + DDI + EFV	K103N, M184V	L63P
3	AZT	AZT + 3TC + NVP	M184V, G190A	L63P
4	AZT, 3TC, ddC, d4T, IND	d4T + 3TC + IND/RTV (800/100)	M41L, E44D, M184V, L210W, T215Y	A71V
5	AZT, 3TC, ddI, d4T, IND, NFV	AZT + 3TC + ABC	M41L, D67N, K70R, M184V, T215Y, K219E	L63P
6	AZT, 3TC, ddC, ddI, ABC, EFV, IND	d4T + TEN + EFV	M41L, K103N, T215Y	L63P, A71T
7	AZT, ddC	d4T + 3TC + NFV	M184V	D30N, L63P, N88D
8	AZT, 3TC, ddI, d4T, NVP, SQV	d4T + TEN + NVP	D67N, K70R, Y188H, G190A, K219Q	K20R, M36I
9	AZT, 3TC, NFV	d4T + ddI + NVP + SQV/RTV (400/400)	L74V, K103N, Y181C	M36I, L63P, A71T, L90M

ABC, abacavir; AZT, zidovudine; ddC, zalcitabine; ddI, didanosine; d4T, stavudine; EFV, efavirenz; IND, indinavir; NFV, nelfinavir; NVP, nevirapine; RTV, ritonavir; SQV, saquinavir; 3TC, lamivudine; TEN, tenofovir.

At the time of initiating TI, median VL was 428 copies/mL (IQR 162–727) and median CD4 lymphocytes was 598/mm^3 (IQR 383–740).

Mean time between TI and resistance testing was 2.4 weeks (median 2, IQR 1–3.5). Median VL at the time of resistance testing was 8105 copies/mL (IQR 2132–23,275). Two patients presented significant decline of 115 and 228 lymphocytes CD4/mm^3, respectively, during TI, whereas the other patients' CD4 values remained stable. No clinical events were recorded during TI.

We found a mean of 5.3 resistance mutations per patient (range 3–7), and in all patients we detected resistance mutations that compromised the effectiveness of at least 1 of the drugs used in their current treatment (range, 1–4). Furthermore, 3 patients presented with resistance mutations related to drugs previously taken.

In 8 patients, salvage therapy began 2 to 8 weeks after TI, except in 1 patient in whom this was 32 weeks by personal decision.

After evaluating resistance test results, treatment changes were as follows: 1 patient, 1 drug; 5 patients, 2 drugs; 2 patients, 3 drugs; and 1 patient, 4 drugs. In only 4 patients, all the drugs were changed.

On initiating the new regimen, median VL was 48,200 copies/mL (IQR 2135–84,800) and median CD4 count was 487/mm^3 (IQR 201–761).

After treatment change, mean follow-up was 13 months (range 3–21 months). All patients presented with a VL of less than 50 copies/mL as from 3 months until the last follow-up analysis.

CD4 lymphocyte evolution after treatment change was: no change in 4 patients, significant increase (mean 276/mm^3; range, 93–364) in 4 patients, and decrease (−292/mm^3) in 1 patient.

No HIV-related clinical event was recorded during follow-up.

The strategy we employed to be able to perform conventional resistance testing in our 9 patients with persistently detectable low-level viremia proved safe and effective. After treatment changes based on this procedure, all patients achieved a VL of less than 50 copies/mL. Despite the small sample size, our results suggest that this strategy merits further study and meanwhile should be considered when planning changes in antiretroviral therapy for such patients.

In this series we found what we consider a high number of resistance mutations, probably attributable to the fact that 7 of the 9 patients had started with non-HAART therapy. All patients presented with resistance mutations compromising the effectiveness of at least 1 of the drugs in their current treatment, and 7 of the 9 patients presented mutations compromising the effectiveness of at least 2 of these drugs. This highlights the need for resistance testing in this type of patient and justifies the strategy of TI used in this study. Had we waited for the VL to reach 1000 copies/mL without TI, the risk of further mutation accumulation would have increased and could have complicated the new salvage antiretroviral regimen.

Reversibility of resistance mutations has been demonstrated as soon as 15 days after TI in some patients, whereas in others these persisted for years.[7–9] An important aspect of our strategy was performing the resistance test as soon as the viremia rose over 1000 copies/mL, which makes it theoretically improbable that current treatment-related mutations reverted after TI, because viral replication at that time was still low and thus extensive replacement of mutant virus by wild-type virus was improbable.

In our study, resistance mutations were found to drugs taken in the past, but not currently, in 3 patients. The possibility of our not having detected other such mutations exists, but the favorable response of all our patients to the new regimen indicates that, had they existed, they were not determinant.

All drugs were withdrawn simultaneously, which could favor the appearance of resistance mutations to nevirapine or efavirenz as from TI in those patients taking them, due to their long half-life and low genetic threshold. In fact, we detected resistance mutations to nonnucleoside reverse transcriptase inhibitors in all patients

taking them. Although it would seem more logical that these mutations developed during the months when viremia was detectable, we cannot rule out the possibility that they were produced by TI in some cases. Currently, there is controversy as to the frequency and clinical significance of this occurring after TI, and about the most appropriate strategy to prevent it.[10–13]

In our study, because all our patients presented with sufficiently high CD4 values, treatment was suspended until the results of resistance testing became available. Two patients presented with significant decline in CD4 values during the period of no treatment. One made a clear recovery after salvage therapy was initiated; at 6-months follow-up, he had gained 304 CD4 cells with respect to his immediate post-TI values. In contrast, the other patient presented with a continual decline in CD4 values, from 1102/mm^3 before TI to 469/mm^3 at 17 months on the new salvage treatment with VL of less than 50 copies/mL. It is noteworthy that his salvage treatment included tenofovir–didanosine, and this particular combination has recently been associated with a decline in CD4 lymphocytes despite viremia control.[14]

To minimize the decline in CD4 lymphocytes during TI, current antiretroviral treatment could be resumed while waiting for resistance test results, thus reducing nontreatment time (<15 days for 50% of our study patients); this would keep basal VL low at initiation of salvage treatment, thus favoring the virologic success of the new therapy[15] as well as minimizing the decline in CD4 lymphocyte count—which is especially important in heavily immunosuppressed patients.

Determining weekly VL is costly and time-consuming for both patients and staff. In our experience, the cost and effort was acceptable because TI was soon followed by VL greater than 1000 copies/mL in all patients (mean number of 2 determinations before resistance testing). It remains to be established whether a greater interval between VL determinations (2–3 weeks perhaps) is equally effective. However, important interpatient variations in progression of VL after TI have been reported[4,5] and a greater interval might increase the risk of not detecting reverting resistance mutations.

In conclusion, in this small series, the strategy of interrupting antiretroviral therapy until patients reach a VL of 1000 copies/mL followed by conventional resistance testing proved safe and useful to establish more effective antiretroviral salvage therapy in patients with persistently detectable low-level viremia despite HAART.

Juan Luis Gomez Sirvent, MD, PhD
Maria Mar Alonso Socas, MD, PhD
Carlos Hernandez Calzadilla, MD, PhD*
Ana M. Lopez Lirola, MD, PhD
Maria Remedios Aleman Valls, MD, PhD
Infectious Diseases Section
*Laboratory Service
Hospital Universitario de Canarias
Tenerife, Spain

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Adherence to First-Line Antiretroviral Regimens in Rwanda

To the Editor:

We report our experience in the Ensemble de Solidarité Thérapeutique Hospitalière En Réseau (ESTHER) antiretroviral treatment program at the Center Hospitalier de Kigali in Kigali, Rwanda. The adherence to highly active antiretroviral therapy (HAART) has been assessed in the 95 patients first started on antiretroviral therapy; group 1 (n = 27) in May 2003 (zidovudine [ZDV] and lamivudine [3TC] sold as Avocomb [Ranbaxy, Gurgaon, India] and efavirenz [EFV] sold as Stocrin [Merck, Whitehouse Station, NJ]) and group 2 (n = 68) from September to December (stavudine [d4T], 3TC, and nevirapine [NVP] in fixed-dose combinations sold as Triomune or Triviro [depending on dosage of d4T] [Cipla, Mumbai, India]). We used a standardized questionnaire and performed therapeutic drug monitoring (TDM) for the nonnucleoside component of the regimen. Eighty percent of the patients were from a low socioeconomic status, and 98% of them were at an advanced stage of the HIV infection (World Health Organization [WHO] stage III or IV). More than 90% of the

patients reported adverse effects. Five percent (5 of 95 patients) admitted to having forgotten 1 to 4 doses during the last 3 days. On a visual scale, 87% (83 of 95 patients) reported no missed dose during the last month, whereas 13% (12 of 95 patients) reported having taken "most" or "nearly all" the doses. TDM for group 1 showed detectable levels of EFV in 100% of the patients: 85% (23 of 27 patients) in the therapeutic range (1–4 μg/mL) and 15% (4 of 27 patients) slightly below (0.83–0.97 μg/mL). In the second group of patients who were taking Triomune or Triviro, blood samples were obtained from 41 persons; TDM showed that 93% (38 of 41 patients) were within the therapeutic range for NVP (>3 μg/mL), whereas 5% (2 of 41 patients) had an undetectable level. We concluded that a high level of treatment adherence, confirmed by TDM, was achieved despite the poverty, the adverse effects, and the advanced clinical stage of these patients. We have noticed that counseling and family support were essential to this success. From these results as well as from those obtained by Oyugi et al,[1] we conclude that adherence rates equal to those in industrialized countries may be obtained in resource-limited settings. Meanwhile the scale-up ensures that more than 150 new patients are starting antiretroviral therapy each month at the main treatment clinic, and the challenge is to maintain similar levels of adherence with large numbers of patients followed.

Rémy Demeester, MD*
Christine Omes*
Jean Claude Karasi, MD†
Serge Schneider, MD‡
Jules Mugabo, MD*
Marie Josée Maliboli*
Vic Arendt, MD§
*Lux Development Centre Hospitalier de Kigali
Kigali, Rwanda
†Treatment and Research AIDS Center
Kigali, Rwanda
‡Division de Toxicologie
Laboratoire National de Santé
Luxembourg, Grand-Duché de Luxembourg
§Laboratoire de Rétrovirologie
CRP-Santé
Luxembourg, Grand-Duché de Luxembourg

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Efficacy of Highly Active Antiretroviral Therapy in Nonclinical Trial Setting of a Developing Caribbean Country

To the Editor:

Highly active antiretroviral therapy (HAART) is used with increasing frequency in the Caribbean, which has the second highest prevalence of HIV infection in the world.[1] There are no published data on the virologic or immunologic response to HAART in HIV-infected individuals from the English-speaking Caribbean. Barbados is a middle-income, developing, English-speaking Caribbean country, with a population of 260,000 and an estimated overall prevalence of HIV infection of 1.75%.[2] Since 2002, HAART has been available to all HIV-infected individuals in Barbados free of cost, provided by the government through its health care delivery system. All HIV-infected adults in Barbados are followed up at a centralized HIV/AIDS care and treatment facility, the Ladymeade Reference Unit (LRU). We studied the virologic and immunologic response to HAART after 12 months of therapy in a population-based cohort of treatment-naive HIV-infected adults attending the LRU.

This is a prospective observational study. All treatment-naive HIV-positive adults in Barbados who attended the LRU clinic and were started on HAART between January 2002 and March 2003 were included in this study. All 3 classes of antiretroviral agents, including nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), and nonnucleoside reverse transcriptase inhibitors (NNRTIs), were available at the LRU throughout the study. Patients started on HAART had baseline (measured less than 4 weeks before starting therapy) CD4 cell counts and viral load estimation. For all patients in the study, a complete profile of antiretroviral therapy was maintained prospectively, including the medications prescribed, the amount dispensed, the dose, and the prescription fill dates, along with other information on sociodemographic characteristics and clinical and health status elicited at the time of initial enrollment. After initiation of therapy, patients were scheduled for a follow-up visit at the LRU at 1 month, 2 months, and every 3 months thereafter for clinical and adherence assessment and for determination of CD4 cell count and viral load to assess the response to HAART. Participants' deaths were ascertained continuously using a combination of active surveillance methods and recorded during this 12-month study period. The virologic and immunologic responses to antiretroviral therapy in HIV-1–infected antiretroviral drug-naive adults were estimated by use of as-treated analyses. Data were analyzed using SPSS statistical software (SAS Institute, Cary, NC). Associations between categoric variables were assessed for statistical significance by the χ^2 test. $P \leq 0.05$ was considered to be statistically significant.

A total of 158 adults (median age = 39 years, 42.4% women) were started on HAART. Of the 92 male participants, 74 (80.4%) were heterosexual, 16 (17.4%) were homosexual, and 2 (2.2%) were bisexual. Among the 66 female participants, 1 was bisexual. None of these patients gave any history of intravenous illicit drug use; however, 19 (12%) patients gave a history of having smoked marijuana. Eighty-seven (53.2%) had an AIDS-defining illness at the time of starting HAART. Of these, most (73 patients) had presented with opportunistic infections, including oropharyngeal and esophageal candidiasis (33 patients) and *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonia (16 patients). Most (82.1%) of the patients were at an advanced stage of immunodeficiency at the start of therapy (CD4 <200 cells/μL). The median CD4 cell count at baseline (n = 156) was 74 cells/μL (interquartile range [IQR]: 22.2–176.7 cells/μL), and the viral load (n = 94) was 122,500 HIV copies/mL (IQR: 54,125–350,000 copies/mL). Most patients (n = 131 [82.9%]) were started on 2 NRTIs and 1 NNRTI, whereas a smaller proportion were administered 2 NRTIs and 1 PI (n = 25 [15.8%]). Two patients (1.4%)

received a triple-NRTI regimen. The specific treatment regimens by drug class are summarized as follows: among the 131 patients on triple-NNRTI regimens, 129 received efavirenz (EFV) and only 2 received nevirapine (NVP); among the 25 patients on PI regimens, 13 received indinavir (IDV), 7 were on NFV, and 5 were on lopinavir/ritonavir (LPV/r); and both patients on triple-NRTI regimens were administered a combination of ZDV plus lamivudine (3TC) plus abacavir (ABC). The distribution of the nucleoside backbone across the 158 patients was: zidovudine (ZDV) plus 3TC (n = 132), stavudine (d4T) plus 3TC (n = 24), and d4T plus didanosine (ddI) (n = 2). The most frequently represented treatment regimen was ZDV plus 3TC plus EFV (n = 104). Overall, 110 (69.6%) persons had an adherence level greater than 90% throughout the study period.

The overall retention rate for the cohort at 12 months was 148 (93.7%). There were 2 deaths, 2 persons discontinued follow-up, and 6 persons did not have a viral load or CD4 cell count measured at baseline and/or at 12 months. One hundred forty-eight persons who completed 12 months of HAART were analyzed for the virologic and immunologic outcome using as-treated analysis. After 12 months of HAART, 79.7% (118 of 148 patients) had virologic success (viral load <50 copies/mL). Table 1 describes the univariate analysis of factors associated with virologic success (posttreatment viral load <50 copies/mL). Persons aged 40 years or older (85.9%), those on an NNRTI-based regimen (85.1%), and those with greater than 90% adherence to HAART (92.3%) were significantly more likely to achieve virologic success. One hundred thirty-eight patients had CD4 cell counts measured at baseline and at 12 months of HAART. Ninety-nine (71.7%) persons had an increase of at least 100 cells/μL over baseline value (immunologic success). The median increase in the CD4 cell count after 12 months of HAART was 165 cells/μL (IQR: 94–264 cells/μL). Female gender (80.3%) and greater than 90% adherence to HAART (70.4%) were statistically significantly associated with achieving immunologic success (Table 2).

This study of the Barbados cohort of HIV-infected persons is the first such report of the efficacy of HAART in a community-based setting from the English-speaking Caribbean. HIV-infected persons in Barbados who started HAART did so at an advanced stage of their illness. Although published data are scarce, late presentation is common in Barbados and in the wider Caribbean region, probably because of widespread stigmatization of People Living with HIV/AIDS (PLWHAs), leading to nondisclosure of their HIV status.[3] Clinical trials have shown that HAART is able to reduce HIV plasma viral loads to undetectable levels in 70% to 90% of patients and to increase CD4 cell counts.[4,5] Studies of HAART in community settings (ie, nonclinical trial situations) in developed and developing countries have been reported to be much less effective.[6–8] The high rates

TABLE 1. Factors Associated With Virologic Success* Among 148 Men and Women Who Initiated HAART Between March 2001 And June 2003 and Completed 12 Months of Treatment

Variables	Virological Success N (%)	95% Confidence Interval for % Success	*P*†
Gender			
Male (n = 84)	63 (75.0)	64.1, 83.5	0.075
Female (n = 64)	55 (85.9)	74.5, 93.0	
Age (y)			
<40 (n = 74)	57 (77.0)	65.5, 85.7	0.011
≥40 (n = 74)	61 (82.4)	71.5, 89.9	
Baseline CD4 cell count			
<50 cells/μL (n = 57)	51 (89.5)	77.8, 95.6	0.114
50–199 cells/μL (n = 58)	36 (62.1)	48.3, 74.1	
≥200 cells/μL (n = 23)	13 (56.5)	34.8, 76.1	
Antiretroviral regimen			
1 NNRTI + 2 NRTIs (n = 121)	103 (85.1)	77.2, 90.7	0.002
1 PI + 2 NRTIs (n = 24)	13 (54.2)	33.2, 73.8	
3 NRTIs (n = 3)	2 (66.7)	12.5, 98.2	
Adherence			
90%–100% (n = 109)	101 (92.7%)	85.6, 96.5	0.000
<90% (n = 39)	17 (43.6%)	28.2, 60.2	

*Assessed as viral load reduced to <50 copies/mL.
†*P* determined by χ^2 test.

TABLE 2. Factors Associated With Immunological Success* Among 138 Men and Women Who Initiated HAART Between March 2001 and June 2003 and Completed 6 Months of Treatment and Follow-Up

Variables	Immunological Success N (%)	95% Confidence Interval for % Success	*P*†
Gender			
Male (n = 77)	51 (66.3)	54.5, 76.4	0.000
Female (n = 61)	49 (80.3)	67.8, 89.0	
Age (y)			
<40 (n = 69)	49 (71.0)	58.7, 81.0	0.182
≥40 (n = 69)	51 (73.9)	61.7, 83.4	
Baseline CD4 cell count			
<50 cells/μL (n = 57)	51 (89.5)	77.8, 95.6	0.161
50–199 cells/μL (n = 58)	36 (62.1)	48.3, 73.4	
≥200 cells/μL (n = 23)	13 (56.5)	34.9, 76.1	
Antiretroviral regimen			
1 NNRTI + 2 NRTIs (n = 112)	79 (70.5)	61.1, 78.6	0.838
1 PI + 2 NRTIs (n = 23)	17 (73.9)	51.3, 88.9	
3 NRTIs (n = 3)	3 (100.0)	0.3, 1.0	
Adherence			
90%–100% (n = 102)	79 (77.4%)	67.9, 84.9	0.041
<90% (n = 36)	21 (58.3%)	40.9, 74.0	

*Assessed as an increase in the CD4 cell counts of at least 50 cells/μL over the baseline values.
†*P* determined by χ^2 test.

of virologic and immunologic success with predominantly NNRTI-based regimens in this cohort are notable. Farmer et al[9] demonstrated that community-based approaches to HIV treatment were successful in rural Haiti, with 86% of patients having undetectable viral loads after at least 6 months of therapy. In addition, several recent studies have shown a good response to HAART despite advanced disease status with low CD4 cell counts and a high viral load.[10,11]

Further follow-up of the cohort in this ongoing study should be useful in assessing the durability of the excellent response at 12 months into therapy and long-term efficacy of HAART in adults with advanced HIV disease in a Caribbean population. Findings from this study should be taken into consideration when scaling up antiretroviral therapy for HIV-infected adults in the Caribbean countries, where people often present late in the course of their illness.

Alok Kumar, MD*
Krishna R. Kilaru, MD†
Namrata Sippy, MSc†
Anne O. Carter, MD*
Timothy C. Roach, FRCP†
*School of Clinical Medicine and Research
University of West Indies (Cave Hill)
and Queen Elizabeth Hospital
Martindales Road
St. Michael, Barbados
†Ladymeade Reference Unit
Ministry of Health
Barbados

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Does Highly Active Antiretroviral Therapy Increase the Risk of Congenital Abnormalities in HIV-Infected Women?

To the Editor:

With increasing numbers of HIV-infected pregnant women receiving highly active antiretroviral therapy (HAART),[1] concerns have been raised over the possible teratogenic effects related to exposure in early pregnancy. We have previously reported a 1.4% prevalence of congenital abnormalities in uninfected infants exposed to antiretroviral therapy (ART; mainly monotherapy and/or dual therapy), which is similar to that seen in those not exposed.[2] It is unclear whether risk of congenital abnormalities is increased by first-trimester exposure or by use of HAART, however. In this analysis, we further assess the additional risk of antenatal use of HAART during pregnancy by investigating the prevalence of congenital abnormalities by earliest exposure to and type of treatment regimen.

The European Collaborative Study (ECS) is an ongoing cohort study in which infants of HIV-infected women identified during pregnancy are followed according to standard clinical and laboratory protocols.[2,3] Information collected at enrollment and during pregnancy includes maternal ART use and timing of initiation, laboratory tests, illicit injecting drug use, and other sociodemographic characteristics. Gestational age was assessed by ultrasound and reported to the nearest completed week. Information on the child's health and development was collected according to standard laboratory and clinical protocols.[2,3] Infants were assessed at birth by a senior obstetrician and/or senior pediatrician; additional perinatal assessments were made by experienced pediatricians, who were also responsible for reports on further pediatric follow-up visits.

To assess the outcome of pregnancies by type of treatment regimen, ART exposures were grouped into 4 categories: nucleoside analogue reverse transcriptase inhibitor(s) (NRTI) only; combinations of NRTI and protease inhibitor (PI); NRTI and nonnucleoside reverse transcriptase inhibitor (NNRTI); or a combination of NRTI, NNRTI, and PI. HAART was defined here as regimens including 3 or more drugs. Because organogenesis occurs in the first trimester, rates of congenital abnormalities among infants with second- and/or third-trimester exposures to ART were grouped together and compared with those among infants with first-trimester exposures. The first trimester of pregnancy was defined as up to and including 12 gestational weeks. Data entry was carried out using MS Access 2000, and analyses were performed using R 1.9.0 statistical software (R Foundation for Statistical Computing, Vienna, Austria, 2003) and SAS statistical software (version 8.02; SAS Institute, Cary, NC).

This analysis included data on 3740 mother-child pairs enrolled between 1986 and December 2003, of whom 1973 infants were exposed to ART in utero, including 602 exposed to HAART. Of the 1973 women who received antenatal ART, 789 (40%) received ART in the first trimester of pregnancy and had all initiated treatment before conception. Median

maternal age at delivery was 28 years (range: 10–45 years). Most women were white (72%, 2700 of 3740 women), 21% (781 of 3740 women) were black (mainly from sub-Saharan Africa), and 7% (256 of 3740 women) were from other ethnic groups. Thirteen percent (493 of 3740 women) used illicit drugs during pregnancy. CD4 cell counts were routinely assessed since 1992 and were available for 2042 (55%) women, with a median CD4 count at delivery of 420 cells/mL (range: 0–2350 cells/mL). Median gestational age at delivery was 38 weeks (range: 22–43 weeks), and median birth weight was 2940 g (range: 500–5190 g).

Congenital abnormalities were recorded in 1.5% (55 of 3740 children), 31 of whom had been exposed to ART in utero and 14 in the first trimester of pregnancy. The abnormalities included ear malformations (2 children), cleft palate (2 children), ventricular septal defect (6 children), atrial septal defect (2 children), blood-clotting disorder (1 child), hydrocele in both testes (1 child), polydactyly (3 children), Down syndrome (3 children), polycystic kidney (3 children), hydronephrosis (2 children), esophageal atresia (2 children), ileostoma and enteritis (1 child), gastric perforation (1 child), hydrocephalus (1 child, who died 4 days after birth), cataract (1 child), and situs inversus transposition of arteries (1 child). Congenital abnormalities in the 24 unexposed children included cleft palate (1 child), ventricular septal defect (4 children), cardiac rhabdomyoma (1 child), tetralogy of Fallot (1 child), polydactyly (2 children), syndactyly (1 child), polycystic kidney (2 children), hydronephrosis (2 children), esophageal atresia (3 children), microcephalus (1 child), hydrocephalus (1 child), hip dysplasia (2 children), cataract (1 child), situs inversus transposition of arteries (1 child), and diaphragmatic hernia (1 child) (Table 1).

No increase in any particular abnormality with the use of ART or HAART during pregnancy was apparent. Among all 3740 infants, 1.4% of those not exposed to antenatal ART (24 of 1767 children) had a congenital abnormality versus 1.6% of those exposed (31 of 1973 children; $\chi^2 = 0.16$; Yates corrected, $P = 0.69$). There was also no discernible pattern between the type and timing of ART during pregnancy (see Table 1). The prevalence of congenital abnormalities in children exposed to any antenatal ART in the first trimester (14 of 789 children [1.8%], 95% confidence interval [CI]: 0.97–3.0) was similar to that of children exposed in the second or third trimester (17 of 1184 children [1.4%], 95% CI: 0.84–2.3) ($\chi^2 = 0.17$; $P = 0.68$). Among the 789 infants with first-trimester exposure, there was no difference in prevalence of congenital abnormalities among infants exposed to HAART (11 of 546 children [2.0%], 95% CI: 1.0–3.6) compared with those exposed to monotherapy and/or dual therapy (3 of 243 children [1.2%], 95% CI: 0.26–3.6) (Fisher exact test, $P = 0.57$).

In multi-variable logistic regression analysis involving 3471 mother-child pairs with information on all variables included, the presence of congenital abnormalities was not associated with the use of monotherapy or dual therapy or HAART during pregnancy after adjusting for maternal age at delivery and injecting drug use during pregnancy (adjusted odds ratios [AORs] = 1.05 [95% CI: 0.49–2.2; $P = 0.91$] and 1.22 [95% CI: 0.57–2.6; $P = 0.61$] for monotherapy or dual therapy and HAART, respectively, with "no antenatal ART" as the reference category). Rerunning the logistic regression, with time period instead of ART exposure (grouped as <1994 [pre-ART prophylaxis era], 1994–1996 [monotherapy or dual therapy era], and >1996 [HAART era]) similarly showed a lack of association with the prevalence of congenital abnormalities (data not shown). These findings confirm the lack of evidence for an increase in the prevalence of congenital abnormalities as a result of HAART in this population. In a subanalysis among 1810 mother-child pairs with antenatal ART use adjusting for maternal age at delivery, there was no

TABLE 1. Summary of Congenital Abnormalities by Exposure to ART

		Earliest ART Exposure in First Trimester					
	No Antenatal Exposure to ART	NRTI(s) Only	PI(s) + NRTI(s)	NRTI(s) + NNRTI(s)	PI(s) + NRTI(s) + NNRTI(s)	Overall First-Trimester Exposure	Earliest ART Exposure in Second and/or Third Trimester
Mother-child pairs (n)	1767	280	273	195	41	789	1184
Children with congenital abnormalities (n)	24	1	7	6	0	14	17
Number of abnormalities							
Ear, face and neck	0	0	0	0	0	0	2
Cleft palate	1	0	0	0	0	0	2
Ventricular septal defect	4	1	1	1	0	3	3
Other heart defects	2	0	1	1*	0	2	0
Other circulatory system defects	0	0	1	0	0	1	0
Male genitalia defects	0	0	0	1*	0	1	0
Limb reduction/addition	3	0	0	0	0	0	3
Down syndrome	0	0	0	0	0	0	3
Renal and kidney defects	4	0	1	2	0	3	2
Gastrointestinal defects	3	0	2	2	0	4	0
Neurologic defects	2	0	0	0	0	0	1
Hip dysplasia	2	0	0	0	0	0	0
Cataract	1	0	0	0	0	0	1
Other	2	0	1	0	0	1	0

*One child with 2 defects: hydrocele in both testes and atrial septal defect.

increased risk of congenital abnormalities associated with first-trimester exposure to ART compared with later exposures (AOR = 1.33, [95% CI: 0.64–2.8; P = 0.44]). None of the mothers of children with congenital abnormalities used injecting drugs during pregnancy, precluding adjustment for this variable here.

Although efavirenz should be avoided in pregnant women and in women planning a pregnancy because of potential teratogenicity,[4,5] 19 women in this cohort received efavirenz-containing HAART regimens at the time they became pregnant and continued taking the drug for a median of 40 days into their pregnancy (range: 24–106 days). No congenital abnormalities (0%, 95% CI: 0–17.6) were reported in this group.

In our study we found a similar pattern and prevalence of congenital abnormalities among infants exposed to antenatal ART and those who were not, and this was also true for exposure to HAART. Furthermore, there was no evidence to suggest that exposure to first-trimester ART increases the risk of congenital abnormalities. As such, our findings are consistent with those of the Antiretroviral Pregnancy Registry.[5,6] As a long-running birth-cohort study, however, we benefit from a large number of mother-child pairs (exposed and nonexposed) and are not subject to the potential for ascertainment and reporting bias that may limit interpretation of registry data. Although a small risk cannot be excluded, such data should reassure the increasing number of HIV-infected women becoming pregnant while taking HAART. Further monitoring and research are necessary, however, particularly to assess the teratogenic risk of use of combinations of antiretroviral and other drugs at the time of conception or in early pregnancy.

European Collaborative Study, prepared by
Deven Patel, MSc
Claire Thorne, PhD
Simona Fiore, MSc
Marie-Louise Newell, PhD

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APPENDIX

ECS collaborators include the following individuals: C. Giaquinto, E. Ruga, and A. De Rossi (Universita degli Studi di Padova, Padua, Italy); I. Grosch-Wörner (Charite Virchow-Klinikum, Berlin, Germany); J. Mok (Royal Hospital for Sick Children, Edinburgh, United Kingdom), F. Johnstone (Department of Obstetrics, University of Edinburgh, United Kingdom); I. de José, I. Bates, F. Hawkins, C. Ladròn de Guevara, J. Mª. Peña, J. Gonzalez Garcia, J. R. Arribas Lopez, and M. C. Garcia-Rodriguez (Hospital Infantil La Paz, Madrid, Spain); F. Asensi-Botet, M. C. Otero, D. Pérez-Tamarit, and G. Suarez (Hospital La Fe, Valencia, Spain); H. Scherpbier, M. Kreyenbroek, and K. Boer (Academisch Medisch Centrum, Amsterdam, The Netherlands); A. B. Bohlin, S. Lindgren, E. Belfrage, L. Navér, B. Anzén, and K. Lidman (Karolinska University Hospital, Huddinge and Solna, Sweden); J. Levy, P. Barlow, M. Hainaut, A. Peltier, and T. Goetghebuer (Hospital St. Pierre, Brussels, Belgium); A. Ferrazin and D. Bassetti (Department of Infectious Diseases, University of Genoa, Genoa, Italy); A. De Maria (Department of Internal Medicine, University of Genoa, Genoa, Italy); C. Gotta (Department of Obstetrics and Gynecology–Neonatology Unit, University of Genoa, Genoa, Italy); A. Mûr, A. Payà, M. A. Lòpez-Vilchez, and R. Carreras (Hospital del Mar, Universidad Autonoma, Barcelona, Spain); N. H. Valerius (Hvidovre Hospital, Hvidovre, Denmark); J. Jimenez (Hospital 12 De Octubre, Madrid, Spain); O. Coll, A. Suy, and J. M. Perez (Hospital Clínic, Barcelona, Spain); C. Fortuny and J. Boguña (Hospital Sant Joan de Deu, Barcelona, Spain); M. Casellas Caro (Hospital Vall D'Hebron, Barcelona, Spain); Y. Canet (Hospital Parc Tauli de Sabadell, Barcelona, Spain); G. Pardi and M. Ravizza (Ospedale San Paolo, Milan, Italy); B. Guerra, M. Lanari, S. Bianchi, and L. Bovicelli (Policlinico S. Orsola, Bologna, Italy); E. Prati and M. Duse (Universita di Brescia, Brescia, Italy); G. Scaravelli and M. Stegagno (Universita La Sapienza, Rome, Italy); M. De Santis (Universita Cattolica, Rome, Italy); A. E. Semprini, V. Savasi, and A. Viganò (Ospedale L. Sacco, Milan, Italy); F. Ravagni Probizer and A. Maccabruni (Policlinico S. Matteo, Pavia, Italy); A. Bucceri and L. Rancilio (Clinica Mangiagalli and Clinica De Marchi, Milan, Italy); S. Alberico, M. Rabusin, and M. Bernardon (IRCCS Burlo Garofolo, Trieste, Italy); G. P. Taylor and E. G. H. Lyall (St. Mary's Hospital, London, United Kingdom); Z. Penn (Chelsea and Westminster Hospital, London, United Kingdom); W. Buffolano and R. Tiseo (Pediatric Department, Federico II University, Naples, Italy); P. Martinelli, M. Sansone, and A. Agangi (Obstetric Department, Federico II University, Naples, Italy); C. Tibaldi, S. Marini, G. Masuelli, and C. Benedetto (University di Torino, Torino, Italy); T. Niemieç (National Research Institute of Mother and Child, Warsaw, Poland); and M. Marczynska and A. Horban (Medical University of Warsaw, Warsaw, Poland).