tein of VLDL) and plasma apo CIII is elevated in HTG (*19, 20*). It had been thought that the elevation in plasma apo CIII concentration that occurs in HTG was a secondary effect due to a combination of increased production or decreased catabolism of VLDL particles. Using transgenic animals, we have shown that a primary overproduction of apo CIII can result in HTG with a highly significant linear relation between plasma apo CIII and plasma triglyceride concentrations (Fig. 4). Our results suggest that the apo CIII concentration may regulate the metabolism of triglyceride-rich lipoproteins. Indirect evidence from a number of sources is compatible with our observation. In vitro apo CIII can inhibit the lipolysis of triglyceride-rich lipoproteins by lipoprotein lipase (*21, 22*). In hypertriglyceridemic patients, a plasma inhibitor of lipoprotein lipase copurifies with apo CIII (*23*), and some studies have shown that hypertriglyceridemics have an elevated apo CIII/apo CII ratio (*24, 25*). Turnover studies in hypertriglyceridemic subjects indicate oversynthesis of apo CIII (*26*). Finally, fasting triglycerides were reduced in two sisters with genetic apo A-I and apo CIII deficiency, and hydrolysis of their VLDL by lipoprotein lipase in vitro was inhibited by exogenous apo CIII (*27, 28*).

Primary or secondary apo *CIII* overexpression may underlie many of the hypertriglyceridemic states in humans. A Sac I restriction fragment length polymorphism (RFLP) in the 3′ untranslated region of the apo *CIII* is associated with severe HTG in Caucasians (*29–31*). When considered together with our work, these results suggest that a common mutation may exist in linkage disequilibrium with this RFLP that can cause apo *CIII* overexpression and HTG, which could occur by transcriptional or posttranscriptional mechanisms. Studies on the transcriptional regulation of apo *CIII* have identified distal and proximal positive elements and a negative element that control liver-specific gene expression (*32*). Mutations in regulatory elements could lead to increased apo *CIII* expression. The apo *CIII* negative regulatory element is homologous to the interferon regulatory element (*32*). This element binds the transcription factor NF-κB, which mediates cytokine effects on gene expression (*33*). If NF-κB regulates expression of apo *CIII*, the HTG of infection or other altered physiological states might be explained by this mechanism.


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# AIDS—The Leading Cause of Adult Death in the West African City of Abidjan, Ivory Coast


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**In 1988 to 1989, 698 adult cadavers in Abidjan's two largest morgues were studied, representing 38 to 43% of all adult deaths in the city over the study period, and 6 to 7% of annual deaths. Forty-one percent of male and 32% of female cadavers were infected with human immunodeficiency virus (HIV). Fifteen percent of adult male and 13% of adult female annual deaths are due to acquired immunodeficiency syndrome (AIDS). In Abidjan, AIDS is the leading cause of death and years of potential life lost in adult men, followed by unintentional injuries and tuberculosis. In women, AIDS is the second leading cause of death and premature mortality, after deaths related to pregnancy and abortion. AIDS-specific and AIDS-proportional mortality rates may be higher in other African cities where AIDS has been found for a longer time than in Abidjan.**


ALTHOUGH THE PREVALENCE OF INfection with HIV, the causative agent of AIDS, is high in many countries of sub-Saharan Africa (*1*), data concerning mortality due to AIDS are scarce. In Kinshasa, Zaire, the annual incidence of AIDS in adults was reported to be 500 to 1000 cases per million in 1985 (*2*), with an annual AIDS-specific adult mortality rate of at least 1 per 1000 (*1*). In Abidjan, Ivory Coast, where infection with both HIV-1 and HIV-2 occurs (*3*), the epidemic of AIDS has developed rapidly since recognition of the first AIDS cases in 1985. A recent study in this West African city documented a minimum annual incidence of AIDS of 1447 cases per million in adult men and 340 per million in adult women (*4*).

In African cities that have high rates of HIV infection, AIDS is having important, but little assessed, effects on patterns of

mortality. We undertook the present study to determine the proportion of adult deaths due to AIDS, to estimate minimum rates of population-based AIDS-specific mortality, and, by estimating cause-specific years of potential life lost (YPLL), to assess the importance of AIDS as a cause of premature mortality.

Our study was based on examination and HIV testing of adult (aged >14 years) cadavers admitted consecutively to the morgues associated with Abidjan's two largest hospitals, in December to January 1988–1989 and April to May 1989 for periods of 62 days (Mortuary A) and 43 days (Mortuary B), respectively. Together, these mortuaries receive about 60% of all deaths officially reported in the city. All patients dying in the two hospitals and all fatalities outside of hospital that require an autopsy for forensic reasons are brought to these mortuaries.

Demographic data were recorded on all cadavers studied, and all corpses were examined within 24 hours of admission to the morgue for the physical signs listed in the World Health Organization (WHO) clinical case definition for AIDS (*5*). Hospital charts and death certificates were reviewed to assess the cause of death in each case, and to see whether features of the WHO AIDS case definition had been recorded.

Blood was drawn from each cadaver by intracardiac or central venous puncture. Serum specimens were tested for antibodies to HIV-1 and HIV-2 by whole virus enzyme-linked immunosorbent assay (ELISA) (Genetic Systems). Repeatedly reactive specimens were further tested by the appropriate virus-specific immunoblot (Du Pont de Nemours for HIV-1; Diagnostics Pasteur for HIV-2) and by synthetic peptide ELISA tests (Diagnostics Pasteur) recognizing antibodies to the transmembrane glycoproteins of HIV-1 and HIV-2, as previously described (*6*).

Deaths were considered due to AIDS if all the following criteria were met: (i) the cadaver was HIV antibody–positive; (ii) no other specific, non-AIDS–related cause of death (for example, hypertension) was listed; and (iii) at least two major WHO clinical case definition criteria, or one major and one minor criteria, or Kaposi's sarcoma were present, or one of the following was listed as the cause of death: AIDS, retroviral disease, wasting, pneumonia, chronic diarrhea, extrapulmonary tuberculosis. For adult cadavers with pulmonary tuberculosis as the listed cause of death, cough and fever were not counted as criteria for the diagnosis of AIDS (*7*). For other specific diseases, the cause of death was taken from the death certificate or from the clinical records.

To determine the minimum annual number of cause-specific as well as total deaths, we adjusted the numbers of observed cause-specific and total deaths during the study period in each mortuary to deaths expected over 1 year, corrected for seasonal variations observed for total mortality in Abidjan. Adult AIDS-proportional mortality (proportion of adult deaths due to AIDS) was calculated by dividing the estimate of minimum annual adult deaths due to AIDS by the total number of adult cadavers expected in the mortuaries over 1 year.

Minimum adult AIDS-specific mortality rates (number of adult deaths due to AIDS per 100,000 population per year) were calculated by dividing the annual number of AIDS deaths, derived from the observed cases, by the estimated total population of Abidjan on 1 January 1989 (*8*).

To assess the impact of specific diseases on adult premature mortality, we made calculations of disease-specific YPLL for persons aged 15 years and older (*9*). Calculation of annual YPLL for a specific disease was performed by multiplying expected annual numbers of cases of that disease by the difference between the ages at death of cases and an arbitrary expected age of 55 years (*10*).

To assess the representativeness of deaths studied, and to assess the extent to which deaths are reported, we compared official city death registers in each of Abidjan's ten districts, where by law all deaths should be reported, with a sample of deaths studied in the mortuaries. In addition, we analyzed deaths reported to the official city registers over the past year by age and sex, so as to know official mortality statistics. We also compared our number of studied deaths with an independent estimate by a demographer (B.B.) of the true number of deaths (reported to the city death registers and unreported) expected over a year in Abidjan.

We studied 698 adult cadavers: 181 (26%) represented deaths in the community (almost all received in Mortuary A) and 517 (74%) represented deaths in the hospitals. Overall rates of reactivity to HIV (HIV-1 and HIV-2 combined) were 43 and 34% in men and women, respectively, in Mortuary A, and 35 and 27%, respectively, in Mortuary B. Table 1 shows the age-specific rates for HIV infection in all cadavers studied. The highest rates were found in men and women aged 30 to 39 years. Serologic reactivity to HIV-1 alone (24% in males, 21% in females) was more frequent than reactiv-

**Table 1.** Prevalence of HIV infection in cadavers and AIDS-specific and AIDS-proportional mortality in Abidjan, 1988 to 1989.

| Age (years) | Observed HIV-positive cadavers/ total cadavers tested (%) | Observed AIDS deaths/ total deaths of known cause (%) | Expected annual AIDS deaths/ total deaths of known cause (%) | Population* | Expected annual minimum AIDS-specific deaths per 100,000 population per year |
|---|---|---|---|---|---|
| | | | *Males* | | |
| 15–19 | 1/10 (10%) | 0/10 | 0/56 | 103,425 | |
| 20–29 | 46/110 (42%) | 18/95 (19%) | 97/542 (18%) | 227,535 | 43 |
| 30–39 | 88/165 (53%) | 32/150 (21%) | 182/886 (21%) | 147,553 | 123 |
| 40–49 | 35/93 (38%) | 12/84 (14%) | 62/502 (12%) | 71,314 | 87 |
| 50+ | 27/102 (26%) | 8/97 (8%) | 46/590 (8%) | 37,627 | 122 |
| Total | 197/480 (41%) | 70/436 (16%) | 388/2,576 (15%) | 587,454 | 66 |
| | | | *Females* | | |
| 15–19 | 4/18 (22%) | 2/12 (17%) | 10/75 (13%) | 123,125 | 8 |
| 20–29 | 22/57 (39%) | 6/51 (12%) | 35/335 (10%) | 205,865 | 17 |
| 30–39 | 25/63 (40%) | 10/58 (17%) | 52/363 (14%) | 108,547 | 48 |
| 40–49 | 10/34 (29%) | 3/28 (11%) | 16/162 (10%) | 46,886 | 34 |
| 50+ | 8/46 (17%) | 7/44 (16%) | 45/270 (17%) | 31,323 | 144 |
| Total | 69/218 (32%) | 28/193 (15%) | 158/1,204 (13%) | 515,746 | 31 |

*Population is estimated for 1 January 1989.

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ity to both viruses (11% in males, 7% in females), which in turn exceeded reactivity to HIV-2 alone (6% in males, 4% in females) (*6*).

Overall HIV reactivity rates in cadavers brought to the mortuaries from the community, 50/134 (37%) in males and 13/47 (28%) in females, were not significantly different from rates in cadavers derived from in-hospital deaths studied in Mortuary A, 116/257 (45%) for males and 40/111 (36%) for females.

Inadequate information existed to determine the cause of death in 69 (10%) of the 698 adult deaths studied, and these were excluded from further analysis. Table 1 also shows the distribution by age and sex of observed AIDS deaths and total deaths; the minimum AIDS deaths and total deaths expected over the course of 1 year, weighted to correct for the different time periods worked in the two mortuaries and for seasonal variations; and minimum annual AIDS-specific mortality rates. These annual rates are considered minimum estimates in the sense that they are based on observed cases only.

Sixty-four (65%) cadavers with AIDS were reactive to HIV-1 and 10 (10%) to HIV-2, and 24 (24%) showed reactivity to both HIV-1 and HIV-2. AIDS was the cause of death in 16% of the male adult cadavers that we studied, and in 15% of female adult cadavers. The weighted data suggest that 15% of the annual male deaths in Abidjan and 13% of the annual female deaths are due to AIDS. The minimum AIDS-specific mortality rate (AIDS-specific deaths per 100,000 population per year) was 66/100,000 for men, 31/100,000 for women, and 49/100,000 for both sexes combined. The high mortality rate from AIDS in women aged 50 years and older reflects the fact that seven of the eight seropositive cadavers examined met the AIDS case definition, as well as the small population denominator in this group.

Table 2 shows minimum cause-specific annual deaths, cause-specific proportional mortality (proportions of annual deaths expected from specific causes), and annual cause-specific and proportional YPLL. AIDS is the leading cause of death in men, and the leading cause of YPLL, accounting for 17% of premature mortality measured in this way. In women, AIDS is the second most common cause of death and YPLL, after conditions related to pregnancy, including deaths from induced abortion. Pregnancy-related deaths are responsible for 15% of female mortality and 22% of YPLL. When data for male and female adults are combined, AIDS accounts for 14% of deaths and 16% of YPLL, more than any other specific disease. Compared with AIDS, maternal mortality accounts for a disproportionate number of YPLL in women because pregnancy-related deaths tend to occur at a younger age than deaths from AIDS.

Official city death registers were examined to see what proportion of 498 mortuary cadavers, 71% of all those studied, that were identifiable by name had been reported as deaths to the authorities. Seventy percent of these adult cadavers were registered in the official city death registers.

The number of officially reported adult deaths in Abidjan in 1988 was 6,192 (4,700 men and 1,492 women), corresponding to a crude mortality rate of 448/100,000 per year in persons aged 15 years and older (*11*). Assuming that 70% of all 629 studied cadavers were officially reported, the study captured 7% of all deaths officially reported in Abidjan in 1988, or approximately 43% of deaths reported over the study period.

A demographer (B.B.) estimated the true mortality rate in adults in Abidjan in 1988 to be 879/100,000 per year, giving a total of 9,826 deaths (*12*). Total adult deaths studied in the morgues (reported and unreported) represented 629/9,826 (6%) of the estimated true deaths in Abidjan during 1988, or approximately 38% of true deaths citywide over the study period.

Caution is needed in interpreting hospital and autopsy data, since hospital deaths may differ substantially from deaths in the community. The present study assessed 6 to 7% of all officially reported or estimated true deaths in Abidjan in 1988. Twenty-six percent of the cadavers we studied were from outside the hospital, and no significant difference in levels of HIV infection was found between hospital and community-derived cadavers. Therefore, despite the potential for selection bias, we believe the data are representative.

AIDS is now the leading cause of death in Abidjan for adult men and the second most common cause of death for women. Fifteen percent of adult male deaths and 17% of male YPLL resulted from AIDS. In women, AIDS accounted for 13% of deaths and 12% of YPLL, second only to deaths and YPLL from maternal mortality. The higher incidence (and hence associated mortality) of AIDS in men than women in Abidjan has been previously discussed (*4*). The observed deaths in women related to pregnancy indicate a minimum maternal mortality rate of the order of 200 per 100,000 live births, a serious cause for concern.

These figures probably underestimate the true mortality due to HIV infection. Factors

**Table 2.** Cause-specific and proportional mortality, and cause-specific and proportional YPLL in Abidjan, 1988 to 1989. Percentages in parentheses indicate percent of annual deaths or YPLL due to a specific cause. NA, not applicable.

| Condition (*n*) | Males | | Females | |
|---|---|---|---|---|
| | Cause-specific annual deaths (%) | Cause-specific YPLL (%) | Cause-specific annual deaths (%) | Cause-specific YPLL (%) |
| AIDS (98) | 388 (15%) | 7,532 ( 17%) | 158 (13%) | 2,793 (12%) |
| Maternal mortality (25) | NA | NA | 180 (15%) | 5,015 (22%) |
| Unintentional injury (74) | 351 (14%) | 7,181 (17%) | 87 (7%) | 2,000 (9%) |
| Tuberculosis* (64) | 290 (11%) | 3,695 (9%) | 66 (6%) | 1,129 (5%) |
| Gastrointestinal diseases† (41) | 183 (7%) | 2,511 (6%) | 97 (8%) | 1,750 (8%) |
| Cancer (41) | 142 (6%) | 1,689 (4%) | 124 (10%) | 1,544 (7%) |
| Cardiovascular diseases (28) | 142 (6%) | 1,694 (4%) | 20 (2%) | 418 (2%) |
| Chronic liver diseases‡ (26) | 125 (5%) | 1,883 (4%) | 30 (3%) | 565 (3%) |
| Cerebrovascular diseases (28) | 121 (5%) | 922 (2%) | 74 (6%) | 1,221 (5%) |
| Meningitis (32) | 119 (5%) | 2,279 (5%) | 47 (4%) | 1,062 (5%) |
| Diarrheal diseases (non-AIDS) (26) | 103 (4%) | 1,786 (4%) | 40 (3%) | 451 (2%) |
| Homicide and suicide (15) | 67 (4%) | 1,694 (4%) | 10 (1%) | 181 (1%) |
| Viral hepatitis (11) | 40 (2%) | 985 (2%) | 21 (2%) | 249 (1%) |
| Malaria (3) | 20 (1%) | 586 (1%) | 0 | 0 |
| Infectious diseases, misc.§ (58) | 233 (9%) | 4,626 (11%) | 113 (9%) | 2,222 (10%) |
| Other, noninfectious‖ (59) | 251 (10%) | 4,227 (10%) | 138 (12%) | 2,213 (10%) |
| Total (629) | 2,575 (100%) | 43,290 (100%) | 1,204 (100%) | 22,813 (100%) |

*Excludes HIV-positive extraprapulmonary tuberculosis, which has been classified as AIDS; includes HIV-positive pulmonary tuberculosis without other evidence of AIDS (see text). †Noninfectious causes only. ‡Hepatocellular carcinoma is included under cancer. §Includes all other infectious diseases not listed and not meeting AIDS case definition. ‖Includes all other noninfectous diseases not listed.

leading to underassessment of AIDS-related deaths include exclusion of pediatric patients from the estimates, the rigidity of the case definition used, lack of clinical information concerning a number of deaths, the unknown proportion of AIDS deaths not brought to the study mortuaries, and the cultural practice of seriously ill persons leaving Abidjan to die in their home area. Deaths due to pulmonary tuberculosis, the third-ranking cause of male adult death, were specifically not counted as AIDS cases, although with 50% of such cadavers testing HIV-positive, an important fraction of such deaths were probably attributable to HIV infection. Since our study assessed less than half of all Abidjan deaths over the study period, but used the whole population as denominator, true AIDS-specific mortality rates must be considerably higher than the minimum estimates quoted.

The disparity between rates of AIDS-specific mortality in Abidjan and in the industrialized world is extreme. Minimum AIDS-specific mortality rates in both men and women in Abidjan are higher than those in New York City (*13*). Maternal mortality is also strikingly more frequent than in the developed world. Twenty-eight percent of adult female deaths, and 34% of adult female YPLL, were due to AIDS, pregnancy-related conditions, or induced abortions, illustrating how reproductive health dominates the lives and deaths of women in this city (*14*).

Calculation of YPLL offers a useful way of estimating premature mortality (*9*) and of assessing the broader social impact of specific diseases. A number of other cities in Africa have been affected by AIDS for a longer period of time or have higher levels of HIV infection in their populations, or both. Although data concerning mortality due to AIDS are scarce, AIDS is likely to be the leading cause of adult death in a number of other African cities also, and the disease may already be affecting certain standard demographic parameters (*14*).


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15. Review of records in the hospitals associated with the study mortuaries showed that death rates (deaths per 1000 admissions) in medical patients increased by 54% between 1983 and 1988, with increases of 106 and 98% in men aged 20 to 29 and 30 to 39 years, respectively, and 199 and 42% in women of the same age ranges. Over the same period, official Abidjan mortality statistics showed an increase in mortality rates (deaths per 100,000 per year) of 54% in men aged 20 years and older and of 28% in women aged 30 years and older. For discussion of possible demographic consequences of AIDS in developing countries, see R. M. Anderson, R. M. May, A. R. McLean, *Nature* **332**, 228 (1988).


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# Expression of Gene *rrg* Is Associated with Reversion of NIH 3T3 Transformed by LTR–c-H-*ras*


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**A partial complementary DNA was isolated for a gene (*rrg*) that is normally expressed in mouse NIH 3T3 cells, but is down-regulated after cellular transformation by long terminal repeat (LTR)–activated c-H-*ras* (LTR–c-H-*ras*). This gene was reexpressed in a nontumorigenic persistent revertant cell line created by prolonged treatment of the transformed cells with mouse interferon α/β. Persistent revertants stably transfected with *rrg* complementary DNA antisense expression vectors appeared transformed, had decreased amounts of *rrg* messenger RNA, and were tumorigenic in nude mice. Stable transfection with sense constructs did not alter the normal morphology, message level, or nontumorigenicity of the persistent revertant cell line.**


BOTH ACTIVATED *ras* ONCOGENES and elevated levels of normal *ras* product p21 have been found in a variety of human tumors (*1–4*). The inappropriate expression of the human cellular *ras* also leads to a transformed state in cultured mouse cells (*5*). Although there is a definite correlation between *ras* gene expression and cellular transformation, it is not yet clear by what means this oncogene exerts an effect on a cell's growth control system.

Samid *et al.* (*6–8*) examined the effect of interferon treatment on cell line RS485, a mouse NIH 3T3 cell line transformed by LTR–activated human c-H-*ras* (*5*). This treatment yielded persistently reverted cell lines, including PR4, that were phenotypically nontransformed and nontumorigenic, but maintained pre-reversion levels of *ras* mRNA and p21. It is possible that reversion by interferon involved either the activation or the deactivation of one or more genes that affect the transforming activity of *ras*. To identify such genes, we screened the transformed and persistent revertant cell lines for messages that were differentially expressed.

A cDNA phage library was prepared from the persistent revertant cell line PR4. Duplicate plaque lifts were hybridized with $^{32}$P-labeled cDNA from PR4 and from the *ras*-transformed RS485. Plaques that exhibited differential hybridization signals were selected and rescreened until pure phage populations were obtained. The insert cDNAs of 14 recombinant phage were isolated, subcloned into the Eco RI site of plasmid vector pSP72, and used to probe RNA blots of NIH 3T3, RS485, and PR4. The expression of the "*ras* recision gene" (*rrg*, cDNA rrg-1) was dramatically reduced upon transformation of NIH 3T3 with LTR–c-H-*ras*, and was restored in the persistent revertant cell line (Fig. 1) to levels that varied among RNA preparations from 35 to 200% of


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