Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies

*The Antiretroviral Therapy Cohort Collaboration**

Summary

Background Combination antiretroviral therapy has led to significant increases in survival and quality of life, but at a population-level the effect on life expectancy is not well understood. Our objective was to compare changes in mortality and life expectancy among HIV-positive individuals on combination antiretroviral therapy.

Methods The Antiretroviral Therapy Cohort Collaboration is a multinational collaboration of HIV cohort studies in Europe and North America. Patients were included in this analysis if they were aged 16 years or over and antiretroviral-naive when initiating combination therapy. We constructed abridged life tables to estimate life expectancies for individuals on combination antiretroviral therapy in 1996–99, 2000–02, and 2003–05, and stratified by sex, baseline CD4 cell count, and history of injecting drug use. The average number of years remaining to be lived by those treated with combination antiretroviral therapy at 20 and 35 years of age was estimated. Potential years of life lost from 20 to 64 years of age and crude mortality rates were also calculated.

Findings 18 587, 13 914, and 10 854 eligible patients initiated combination antiretroviral therapy in 1996–99, 2000–02, and 2003–05, respectively. 2056 (4·7%) deaths were observed during the study period, with crude mortality rates decreasing from 16·3 deaths per 1000 person-years in 1996–99 to 10·0 deaths per 1000 person-years in 2003–05. Potential years of life lost per 1000 person-years also decreased over the same time, from 366 to 189 years. Life expectancy at age 20 years increased from 36·1 (SE 0·6) years to 49·4 (0·5) years. Women had higher life expectancies than did men. Patients with presumed transmission via injecting drug use had lower life expectancies than did those from other transmission groups (32·6 [1·1] years *vs* 44·7 [0·3] years in 2003–05). Life expectancy was lower in patients with lower baseline CD4 cell counts than in those with higher baseline counts (32·4 [1·1] years for CD4 cell counts below 100 cells per µL *vs* 50·4 [0·4] years for counts of 200 cells per µL or more).

Interpretation Life expectancy in HIV-infected patients treated with combination antiretroviral therapy increased between 1996 and 2005, although there is considerable variability between subgroups of patients. The average number of years remaining to be lived at age 20 years was about two-thirds of that in the general population in these countries.

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*Members listed at end of paper and contributors to each cohort are listed in webappendix 1

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Introduction

Treatment with antiretroviral drugs of people infected with HIV-1 has improved significantly since the introduction of combination antiretroviral therapy in 1996. In treatment-naive patients, first-line combination therapy selection is generally derived from two different forms of regimen, which contains either non-nucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors (PIs).[1] Both regimens function by suppressing viral replication and rapidly increasing CD4 cell counts.[2]

Over the past decade, combination therapy regimens have become more effective, better tolerated, and have been simplified in terms of dosing.[3–8] Clinical trials and observational studies have shown profound reductions in mortality and morbidity in patients infected with HIV as a result of combination antiretroviral therapy.[9–18] This decrease in mortality is particularly apparent in industrialised, high-income countries where access to health care and antiretroviral treatments is more readily available.[19]

Life expectancy and mortality are universally viewed as important population health indicators. As such, several studies have displayed the negative relation between HIV prevalence and life expectancy at a population level.[20] However, the effect of HIV on life expectancy in the era of combination therapy is not well understood because of the relative novelty of this treatment. The objective of this study was to compare changes in mortality rates and life expectancy among HIV-positive individuals on combination therapy in high-income countries over three separate periods (1996–99, 2000–02, and 2003–05) and in subgroups defined by patient characteristics at initiation of such treatment.

Methods

Participants

The Antiretroviral Therapy Cohort Collaboration (ART-CC) is a multinational cohort study of antiretroviral-naive HIV-positive patients initiating combination antiretroviral therapy.[21–23] The collaboration was estab-

	1996–99 (N=18 587)	2000–02 (N=13 914)	2003–05 (N=10 854)
Age (years)			
Median	36 (31–43)	37 (31–44)	38 (32–45)
16–29 years	3106 (16·7%)	2481 (17·8%)	1935 (17·8%)
30–39 years	9039 (48·6%)	5916 (42·5%)	4181 (38·5%)
40–49 years	4248 (22·9%)	3614 (26·0%)	3123 (28·8%)
50+ years	2194 (11·8%)	1903 (13·7%)	1615 (14·9%)
Sex			
Female	4045 (21·8%)	4133 (29·7%)	3572 (32·9%)
Male	14 542 (78·2%)	9781 (70·3%)	7282 (67·1%)
Risk factor for transmission			
Injecting drug use	3495 (18·8%)	1836 (13·2%)	910 (8·4%)
Other	15 092 (81·2%)	12 078 (86·8%)	9944 (91·6%)
CD4 cell count (cells per μL)			
<100	4848 (26·1%)	4104 (29·5%)	2769 (25·5%)
100–199	3165 (17·0%)	2943 (21·2%)	2395 (22·1%)
≥200	10 574 (56·9%)	6867 (49·3%)	5690 (52·4%)
Clinical CDC stage			
A/B	14 258 (76·7%)	10 467 (75·2%)	8576 (79·0%)
C	4329 (23·3%)	3447 (24·8%)	2278 (21·0%)
Plasma HIV RNA level (log_{10} copies per mL)			
<4·00	2533 (13·6%)	1798 (12·9%)	1439 (13·3%)
4·00–4·99	7543 (40·6%)	5403 (38·8%)	4260 (39·3%)
≥5·00	8511 (45·8%)	6713 (48·3%)	5155 (47·5%)
Initial drug regimen			
PI-based	14 530 (78·2%)	5977 (43·0%)	5375 (49·5%)
NNRTI-based	3072 (16·5%)	5547 (39·9%)	4248 (39·1%)
Three NRTIs	620 (3·3%)	1994 (14·3%)	969 (8·9%)
Other	365 (2·0%)	396 (2·8%)	262 (2·4%)

Data are median (IQR) or n (%). NNRTI=non-nucleoside reverse transcriptase inhibitor. NRTI=nucleoside reverse transcriptase inhibitor. PI=protease inhibitor.

Table 1: **Baseline characteristics of patients initiating combination antiretroviral therapy by period of initiation**

lished in 2001, with datasets updated in 2004 and 2007, and includes cohort studies in Canada, Europe, and the USA.

Cohort studies were eligible to join if they had enrolled at least 100 HIV-1-infected antiretroviral-naive patients aged 16 years or older who initiated potent combination therapy with at least three antiretrovirals and had been followed up for median duration of at least 1 year. All prospective studies that joined the collaboration have been approved by their local ethics committees or institutional review boards, use standardised methods of data collection, and schedule follow-up visits at least once every 6 months.

Data collection

Patient selection and data extraction were done at the data centres of the participating cohort studies. Non-nominal data from each cohort on a predefined set of demographic, laboratory, and clinical variables were then pooled and analysed centrally. Cohort data managers from EuroSIDA were asked to provide a unique study identification for each record, since EuroSIDA patients could also be members of other cohort studies and therefore could potentially be included in the dataset twice. 14 cohorts were included in the analysis: the 1917 Clinic Cohort (USA; n=646), Aquitaine Cohort (France; 950), AIDS Therapy Evaluation project Netherlands (ATHENA; Netherlands; 5661), British Columbia Centre for Excellence in HIV/AIDS (BCCfE-HIV; Canada; 1363), Köln/Bonn Cohort (Germany, 627), Collaborations in HIV Outcomes Research US (CHORUS; USA; 1596), the Multicenter Study Group on EuroSIDA (Europe and Argentina; 1658), French Hospital Database on HIV (FHDH; France; 19 095), Frankfurt HIV Cohort (Germany; 1965), Italian Cohort of Antiretroviral-Naive Patients (ICONA; Italy; 3003), Proyecto para la Informatización del Seguimiento Clínico-epidemiológico de la Infección por HIV y SIDA (PISCIS; Spain; 2511), Royal Free Hospital Cohort (UK; 867), South Alberta Clinic (Canada; 407), and the Swiss HIV Cohort Study (SHCS; Switzerland; 3006). Some cohorts participating in the collaboration were excluded from this study because their data were not available at the time of these analyses.

Information on all cause mortality was obtained either through linkages with Vital Statistics agencies or through active follow-up of cohort participants. Patients

	1996–99	2000–02	2003–05	1996–2005
Mortality rates (per 1000 person-years)				
Overall	16·3 (14·9–17·8)	12·4 (11·5–13·2)	10·0 (9·3–10·8)	12·0 (11·5–12·5)
Between the ages 20 and 44 years	13·1 (11·7–14·7)	10·3 (9·4–11·2)	7·5 (6·8–8·3)	9·7 (9·1–10·2)
Potential years of life lost before age 65 years (per 1000 person-years)				
20–64 years	365·9	260·4	189·4	247·0
Life expectancy (years; adjusted)				
At exact age 20 years	36·1 (SE 0·60)	41·2 (SE 0·52)	49·4 (SE 0·54)	43·1 (SE 0·33)
At exact age 35 years	25·0 (SE 0·42)	30·1 (SE 0·31)	37·3 (SE 0·37)	31·7 (SE 0·21)
Percent surviving from 20 to 44 years	75·5%	79·5%	85·7%	81·1%

Mortality rates are deaths per 1000 person-years (95% CI).

Table 2: **Health indicators for overall (20 years or older) population by period of follow-up**

were included in this analysis if they were aged 16 years or older, were antiretroviral naive when initiating combination therapy, and did not receive fusion inhibitors in their initial regimen. Patients' analysis time started on the date they started combination therapy (after Jan 1, 1996); follow-up was censored at Dec 31, 2005.

Statistical analysis

Crude (all ages) and age-specific mortality rates for individuals with age between 20 and 44 years were calculated. Mortality rates (per 1000 person-years) were calculated by dividing the total number of deaths by the total number of person-years of follow-up. Mortality rates were stratified by sex, transmission group (injecting drug use *vs* other), and baseline CD4 cell count (<100, 100–199, ≥200 cells per μL). Rates in periods defined by period of initiation of combination therapy and period of follow-up were internally standardised by including centred values of prognostic variables (values with mean zero) in Poisson regression models.

Potential years of life lost (PYLL) were calculated as the sum of years that HIV-positive participants in our analyses lost because of premature death.[24,25] PYLL is calculated with death before the age of 65 years being considered premature, since this is deemed to be the age at which most people retire. PYLL were expressed as per 1000 person-years from age 20 to 64 years. Values were stratified by sex, transmission group, and baseline CD4 cell count.

Abridged life tables were constructed from age-specific mortality rates to compare life expectancies at the age of 20 years in 1996–99, 2000–02, and 2003–05. Large populations are needed to overcome systematic and random variations in mortality when building complete life tables, therefore abridged life tables were used in this study. These tables describe the mortality experience that hypothetical cohorts of HIV-positive individuals would have had if they were subjected to the mortality rates in the observed calendar periods. The life expectancy at an exact age is a demographic indicator that measures the average number of additional years that will be lived by a person after that age, according to the cross-sectional age-specific mortality rates for all causes of death during the study period. Life expectancy values at exact ages 20 and 35 years were reported for the total cohort as well as stratified by sex, transmission group, and baseline CD4 cell count. Detailed information on the calculations of life tables, potential years of life lost, crude and age-specific mortality rates can be found in webappendices 2 and 3.

Analyses were done with Stata version 10.0 and Microsoft Excel 2008.

Role of the funding source

The study sponsors had no role in the design or conduct of this study, or in the collection, analysis, or interpretation of the data. The corresponding author, Margaret May, and Jonathan Sterne had full access to all the data. The corresponding author had the final responsibility for the decision to submit for publication.

	1996–99	2000–02	2003–05
Crude mortality rates			
Initiated 1996–99	16·3 (14·9–17·8)*	11·4 (10·4–12·4)	9·9 (8·9–11·0)
Initiated 2000–02	..	14·7 (13·2–16·5)*	8·7 (7·7–9·8)
Initiated 2003–05	..	..	13·3 (11·5–15·4)*
Standardised mortality rates†			
Initiated 1996–99	12·9 (11·8–14·2)*	9·2 (8·4–10·0)	8·1 (7·2–9·1)
Initiated 2000–02	..	11·1 (9·9–12·5)*	6·7 (5·9–7·6)
Initiated 2003–05	..	..	10·3 (8·9–12·0)*

Data are deaths per 1000 person-years (95% CI). *Follow-up restricted to the same period during which combination therapy was initiated. †Standardised rates were internally standardised by sex, age at initiation of combination therapy, presumed mode of transmission (injecting drug use *vs* other), and CD4 cell count.

Table 3: **Crude and standardised rates of mortality by period of initiation and period of follow-up**

Results

Our analyses were based on 43 355 eligible patients and 2050 (4·7%) deaths from the 14 participating cohorts. Table 1 shows the distribution of baseline variables of interest according to calendar period of initiation of combination antiretroviral therapy. Because of the large sample size, there were statistically significant differences in the distribution of all variables over the three periods studied, although the magnitudes of some differences were small. Over time, there were increases in median age, and in the proportion of participants who were women, who did not have a history of injecting drug use, who had CDC clinical stage A/B disease (ie, no pre-antiretroviral therapy AIDS-defining event), and were on non-PI-based regimens.

Table 2 shows mortality rates, PYLLs, and life expectancy at ages 20 and 35 years for the entire cohort. Overall mortality rates (20 years and above), mortality rates between the ages of 20 and 44 years, and PYLLs declined between 1996–99 and 2003–05. Between 1996–99 and 2003–05, there was a gain in life expectancy for those at age 20 years of about 13 years; similar gains in life expectancy in those aged 35 years were also seen. Table 3 reports crude and internally standardised mortality rates by period of initiation and period of follow-up of combination therapy. There were declines in mortality rates by both period of initiation and period of follow-up.

Table 4 shows the same health indicators as in table 2 stratified by sex and transmission group (ie, injecting drug use *vs* non-injecting drug use). Women had lower mortality rates and PYLLs and somewhat higher life expectancies than did men. Individuals with a history of injecting drug use also had higher rates of mortality and lower life expectancy than did non-injecting drug users. Life expectancy at age 20 years and at age 35 years was

See Online for webappendices 2 and 3

	Men	Women	Injecting drug users	Non-injecting drug users
Mortality rates (per 1000 person-years)				
Overall	12·9 (12·3–13·6)	9·1 (8·2 – 10·1)	20·7 (19·0–22·5)	10·5 (10·0–11·0)
Between the ages 20 and 44 years	10·3 (9·7 –11·0)	7·9 (7 – 8·9)	18·6 (16·9–20·6)	7·8 (7·2–8·3)
Potential years of life lost before age 65 years (per 1000 person-years)				
20–64 years	257·8	214·4	505·5	202·5
Life expectancy (years; adjusted)				
Exact age 20 years	42·8 (SE 0·45)	44·2 (SE 0·55)	32·6 (SE 1·06)	44·7 (SE 0·34)
Exact age 35 years	31·7 (SE 0·24)	32·5 (SE 0·44)	23·4 (SE 0·60)	33·0 (SE 0·22)
Percent surviving from 20 to 44 years	80·2%	83·1%	66·5%	84·1%

Mortality rates are deaths per 1000 person-years (95% CI).

Table 4: **Health indicators stratified by sex and injecting drug use**

	<100 cells per µL	100–199 cells per µL	≥200 cells per µL
Mortality rates (per 1000 person-years)			
Overall	21·4(20·1–22·8)	13·4 (12·2–14·8)	7·0 (6·4–7·5)
Between the ages 20 and 44 years	19·7 (18·1–21·3)	10·7 (9·4–12·2)	5·0 (4·5–5·6)
Potential years of life lost before age 65 years (per 1000 person-years)			
20–64 years	460·9	264·9	138·3
Life expectancy (years; adjusted)			
Exact age 20 years	32·4 (SE 1·09)	42·0 (SE 0·62)	50·4 (SE 0·41)
Exact age 35 years	27·0 (SE 0·37)	30·4 (SE 0·45)	37·2 (SE 0·33)
Percent surviving from 20 to 44 years	59·8%	80·6%	89·9%

Mortality rates are deaths per 1000 person-years (95% CI).

Table 5: **Health indicators stratified by baseline CD4 cell count**

lower in injecting drug users than in non-injecting drug users.

Table 5 displays mortality rates, PYLLs, and life expectancy stratified by baseline CD4 cell count. Overall mortality rates, mortality rates between the ages of 20 and 44 years, and PYLLs decreased substantially with increasing CD4 cell count at baseline, as did life expectancy at age 20 years and at age 35 years.

Sensitivity analyses were done to examine the effect of cohorts from France on our estimates of life expectancy in the main analyses, since the two French cohorts (n=20 695) represent nearly half our study population and the majority of people who initiated combination therapy in France since 1996. The overall mortality rates in the French cohorts were very similar to those reported in cohorts from other countries (webtable). Life expectancy at 20 years was 43·6 years in the French cohorts and 43·0 years in non-French cohorts, and 32·5 years in French cohorts and 31·5 years in non-French cohorts at 35 years.

See Online for webtable

Discussion

Our analysis of 14 cohort studies and 43 355 HIV-infected patients indicate that there has been an improvement of outcomes with combination antiretroviral therapy between 1996 and 2005, characterised by a marked decrease in mortality rates and potential years of life lost, and by corresponding increases in life expectancy and the proportion of patients surviving from age 20 to age 44 years. Life expectancy differs markedly between subgroups defined by patient characteristics at initiation of combination therapy, and is notably lower in patients with presumed transmission via injecting drug use and who initiated treatment at lower CD4 cell counts.

Previous studies have shown similar decreases in mortality rates and increases in life expectancy as a result of combination therapy.[26–33] However, such findings have been restricted to countrywide analyses, and have often been localised at the provincial or state level.[30,31] Additionally, all previous studies have been based on substantially smaller samples. One of the larger studies, which took place in the USA, analysed a cohort of nearly 5000 HIV-infected patients and exhibited similar survival benefits for individuals being treated with combination antiretroviral therapy.[29] However, the study did not take into account previous exposure to antiretroviral therapy before initiation of combination treatment, which may be a confounding factor. By contrast, all patients in our analysis were treatment naive at initiation of combination therapy.

The progressive reductions in mortality and gains in life expectancy over the three periods studied here are probably the result of both improvements in therapy during the first decade of combination therapy and continuing declines in mortality rates among individuals on such treatment for long periods. These results lend further credence to earlier reports. In a recent study by Lima and colleagues,[31] 2238 HIV-infected antiretroviral-naive patients initiating therapy in British Columbia, Canada, were surveyed over several periods between 1993 and 2004. The authors noted the vast improvements in drug regimens since the pre-combination antiretroviral therapy era as well as over the course of development of combination treatment. In the early era of antiretroviral therapy, monotherapies were the main form of treatment. Since the advent of combination antiretroviral therapy, triple antiretroviral combinations have become the standard of care for HIV-infected patients in high-income countries and have improved substantially as treatments

developed. These advances in treatment have transformed HIV from being a fatal disease, which was the reality for patients before the advent of combination treatment, into a long-term chronic condition. In fact, a number of studies have found that AIDS-defining illnesses as the cause of death are declining dramatically:[27,34,35] Because of improvements in treatment, fewer HIV-infected patients are dying of characteristic HIV-related illnesses, such as non-Hodgkin lymphoma.[36]

Despite these reassuring results, there is still a large discrepancy between the life expectancy of the general population and the life expectancy of an HIV-infected individual. A person starting combination therapy can expect to live about 43 years at 20 years of age, about two-thirds as long as the general population in these countries. This discrepancy in life expectancy could be attributed to active HIV infection or to other underlying lifestyle, socioeconomic, and health issues. Further research must be devoted to the ongoing improvement of antiretroviral therapy to lessen the gap between the life expectancy of HIV-infected patients and the general population, as well as to improve the quality of life of individuals living with HIV.

There is also considerable heterogeneity between subgroups in life expectancy. For example, the disparity in life expectancy between HIV-infected injecting drug users and non-injecting drug users is very large. This finding is consistent with previous findings.[32,37] There may be several reasons for this discrepancy, such as issues of adherence, inadequate or unequal access to treatment, active illicit drug use, hepatitis C co-infection, higher rates of smoking and alcohol use, and socioeconomic status.[38] The increasing proportion of women starting combination therapy could be the result of migration of women infected through heterosexual sex in sub-Saharan Africa: a number of settings have reported higher numbers of sub-Saharan African women accessing therapy in the past few years.[39] Higher life expectancy in women could be due to the higher median baseline CD4 cell count in women, because women tend to be diagnosed earlier in the course of their infection, in antenatal settings.

Our life expectancy results are representative of all individuals who started combination therapy, including those who did not remain on such treatment throughout follow-up. Therefore, the changes in mortality and life expectancy over time might reflect not only the long-term tolerability and diminishing side-effects of antiretroviral drugs, but also reductions in rates of treatment discontinuation and non-adherence. A previous article[40] found little evidence that short-term (1 year) survival had improved between 1996 and 2003, despite an improvement in virological response after initiation of combination therapy. The reductions in mortality rates and corresponding improvements in life expectancy seen here probably reflect both improvements in 3 year survival apparent in the extended and updated dataset analysed here, and the continuing declines in mortality rates among patients on combination therapy for extended periods.

Our study is potentially limited by the under-reporting of deaths by some cohorts that do not actively link to administrative records. Such under-reporting could imply that the mortality rates reported here are underestimates. The reporting methods among the cohorts participating in this study were not the same; some cohorts used record linkages done with vital statistics, while others used self-reporting systems to monitor mortality rates. We were reassured by the lack of difference in mortality rates between the French and non-French cohorts. Furthermore, we were not able to distinguish between active and a history of injecting drug use or the effect of subsequent changes in antiretroviral therapy over the period of observation. We do not have detailed data on causes of death, although we are currently collecting available information for all patients and, where possible, using this to categorise causes of death. Preliminary data suggest that 85% of patients who died had some information on cause of death. Of these, about 50% died of an AIDS-defining condition. Other major causes of death included non-AIDS malignancy, heart disease, infection, violent causes (including suicide and substance abuse), and liver-related causes. Lastly, the estimation of mortality in the last open interval (65 years and more) is difficult because the person-years of follow-up in this interval is limited—few patients in our study are over the age of 65 years and those patients who are enrolled tend to be younger (within this age-group) than those in the general population. Therefore, mortality rates were adjusted in this open interval to limit the effect of the under ascertainment of deaths (webappendix 2). Our results are similar to those reported from Denmark for people on treatment since the mid-1990s.[41] However, extended follow-up of older HIV-infected patients treated with combination antiretroviral therapy will be needed to produce reliable estimates of mortality rates in these groups, and improved estimates of life expectancy for all patients.

In summary, the results of this study indicate that people living with HIV in high-income countries can expect increasing positive health outcomes on combination antiretroviral therapy. The marked increase in life expectancy since 1996 is a testament to the gradual improvement and overall success of such treatment. Because there is still a large discrepancy in life expectancy between the general population and HIV-infected individuals, we encourage health planners to use these data to improve health services and living conditions for such people. Cohort studies must continue to observe and monitor individuals initiating combination antiretroviral therapy to monitor long-term effects and toxicities.

Contributors

RHo, VL, SG, MM, JACS, and ME conceived and designed the study. VL, RHo, MM, and RHa analysed the data. SG, AvS, AJ, ME, MBa, Ad'AM, AE, SS, AM, RHo, AH, MBo, FL, J-CW, MJG, MJM, MM, RHa, and JACS acquired data and/or interpreted the data. RHo, AH, VL, MM, and JACS drafted the manuscript. RHa, SG, ME, AM, MBa, MBo, MJM, AvS, J-CW, MJG, AJ, Ad'AM, FL, AE, SS, JG, AH, and MK critically revised the manuscript for important intellectual content. All authors saw and approved the final manuscript.

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Conflict of interest statement

RHo has received travel grants and grant support from Abbott, Boehringer Ingelheim, GlaxoSmithKline, and Merck. MBa has received research grants from Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Hoffmann-La-Roche-Trimeris, and Merck Sharp & Dohme-Chibret and consultancy fees from Boehringer-Ingelheim and Hoffmann-La-Roche. JG has received investigator initiated grants from Abbott Laboratories. MM has received travel grants from GlaxoSmithKline. MJM has received grant support from Tibotec Therapeutics and Bristol-Myers Squibb. JACS has received travel grants from GlaxoSmithKline and honoraria from Gilead Sciences. J-CW has received travel grants and honoraria for lectures and participation in advisory boards from Abbott Laboratories, Boehringer Ingelheim, GlaxoSmithKline, Pfizer, and Tibotec. SS has received honoraria for attending a symposium, speaking, research, participation in the advisory boards, or lectures at satellite symposia from GlaxoSmithKline, Abbott, Gilead, Boehringer-Ingelheim, Bristol-Meyers Squibb, Tibotec, and Roche. MBo, AE, FL, AJ, AH, VL, RHa, AM, ME, Ad'AM, AvS, and MJG declare that they have no conflict of interest.

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