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Is the virulence of HIV changing? A meta-analysis of trends in prognostic markers of HIV disease progression and transmission

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Abstract

Objective—The potential for changing HIV-1 virulence has significant implications for the AIDS epidemic, including changing HIV transmission rates, rapidity of disease progression, and timing of ART. Published data to date have provided conflicting results.

Design—We conducted a meta-analysis of changes in baseline $CD4^+$ T-cell counts and set point plasma viral RNA load over time in order to establish whether summary trends are consistent with changing HIV-1 virulence.

Methods—We searched *PubMed* for studies of trends in HIV-1 prognostic markers of disease progression and supplemented findings with publications referenced in epidemiological or virulence studies. We identified 12 studies of trends in baseline $CD4^+$ T-cell counts (21 052 total individuals), and eight studies of trends in set point viral loads (10 785 total individuals), spanning the years 1984–2010. Using random-effects meta-analysis, we estimated summary effect sizes for trends in HIV-1 plasma viral loads and $CD4^+$ T-cell counts.

Results—Baseline $CD4^+$ T-cell counts showed a summary trend of decreasing cell counts [effect=−4.93 cells/μl per year, 95% confidence interval (CI) −6.53 to −3.3]. Set point viral loads showed a summary trend of increasing plasma viral RNA loads (effect=0.013 $\log_{10}$ copies/ml per year, 95% CI −0.001 to 0.03). The trend rates decelerated in recent years for both prognostic markers.

Conclusion—Our results are consistent with increased virulence of HIV-1 over the course of the epidemic. Extrapolating over the 30 years since the first description of AIDS, this represents a $CD4^+$ T cells loss of approximately 148 cells/μl and a gain of 0.39 $\log_{10}$ copies/ml of viral RNA

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Conflicts of interest
None declared.

measured during early infection. These effect sizes would predict increasing rates of disease progression, and need for ART as well as increasing transmission risk.

Keywords

CD4 lymphocyte count; disease progression; HIV infections/epidemiology; HIV infections/virology; HIV pathogenicity; viral load/trends; virulence

Introduction

Changing HIV-1 virulence over the course of the AIDS epidemic carries implications for the future treatment and prevention of HIV/AIDS. Virulence is defined as the severity of a disease; for HIV, virulence is defined as the rate of progression to AIDS in untreated infections. Multiple studies have examined trends in HIV-1 virulence, yet no consensus exists; there have been reports of stable [1–12], increasing [13–23], and decreasing virulence [24–32] (see Table, Supplemental Document 1, http://links.lww.com/QAD/A190).

The first studies took place prior to the availability of potent antiretroviral therapy (ART) and, thus, were able to use direct measures of virulence, such as the number of HIV-infected individuals that progressed to a clinical AIDS [25,26] or the rate of disease progression (the time to AIDS or AIDS-related death after infection [1,2,8,13,14,27–31]). With the advent of ART and prophylaxis against opportunistic infections, direct measures of virulence no longer reflected the natural course of HIV-1 infection. Instead, prognostic markers of HIV-1 disease progression, such as the baseline $CD4^+$ T-cell count [3,7,11,12,16,18–20], the set point plasma viral RNA load [10–12,18,20,33], or the rate of $CD4^+$ T-cell decline within an individual [3,5,6,9–11,15,22,30,33], were used as virulence proxies. Most commonly, multiple linear regression analysis of prognostic marker measurements versus calendar time of measurement was performed, with covariates including transmission risk group, sex, age at infection, clinic site, sampling lag-time and seroconversion lag-time (Tables 1 and 2). Regression slopes reflected trends in marker values over time and were interpreted as possible changes in HIV-1 virulence; increasing set point viral loads or decreasing baseline $CD4^+$ T-cell counts were interpreted as increasing virulence, whereas decreasing viral loads or increasing $CD4^+$ T-cell counts were interpreted as decreasing virulence.

We sought to attain robust estimates of temporal trends in HIV-1 prognostic markers. To that end, we summarize the published trends in prognostic markers of HIV-1 infection over time; conduct meta-analyses of select trends; and examine variation in the magnitude of study trends (effect sizes) and possible sources for that variation.

Methods

Study selection

Studies were identified by a *PubMed* search (MeSH terms are as follows: HIV and viral load, CD4 count, virulence, evolution, attenuation, trends; last accessed on 15 January 2011) and by scanning reference lists and related citations. We first identified all studies that assessed virulence changes, and then selected for the meta-analysis only those studies that assessed trends in either set point plasma viral RNA loads or baseline $CD4^+$ T-cell counts, controlled for ART use, and either reported linear regression slopes, reported data with which we could estimate regression slopes, or the authors of the study shared data for this purpose (see Figure, Supplemental Document 2, http://links.lww.com/QAD/A190).

We focused on trends in set point viral loads and CD4 cell counts because these are prognostic markers for clinical AIDS endpoints, including time from seroconversion to

AIDS or AIDS-related death [34–37], and thus are proxies for HIV-1 virulence. Most studies defined baseline CD4 cell count and set point viral load as the first measurement taken after seroconversion but prior to onset of clinical AIDS, approximately 1 year after seroconversion. HIV-1 viral load at the time of transmission risk activity is also a robust predictor of HIV transmission [38–41] and, thus, could also be associated with virulence trends.

Data extraction

Effect sizes—When possible, we extracted multivariate regression slopes for untransformed baseline CD4 cell counts or $\log_{10}$-transformed viral loads, standard errors of the regression slopes, and study sample sizes. If a study did not report these particular regression slopes, we extracted the mean and/or median annual untransformed baseline CD4 cell counts or mean $\log_{10}$ virus loads from the manuscripts, and with this data we estimated weighted and unweighted univariate linear regression slopes of annual median CD4 cell counts (weights determined by individuals per year), and quantile regression slopes of annual median cell counts (Table 3). The choice of medians for the CD4 cell counts and means for the $\log_{10}$-transformed viral loads was driven by data availability. For three studies [10,20,21], additional raw data were kindly shared by the authors and cohorts, including patient data up to the present time for two studies [the Swiss HIV Cohort (SHCS) [10,42] and the Italian MASTER cohort [21]]. The effect sizes reported for the SHCS [10] and the MASTER cohort [21] reflect results from the updated analyses; multivariate regression design included sex, risk group, age at diagnosis, and calendar date of diagnosis as covariates.

Study covariates—The covariates used by most studies included sex, age at seroconversion, seroconversion lag-time (period between last negative and first positive HIV-1 antibody test), sampling lag-time, and transmission risk group [heterosexual sex (HET); IDU; MSM; and other risk group) (Tables 1 and 2). Although ancestry (race or ethnicity) was not addressed or known in all of the studies, it is likely that most individuals were of European ancestry. Although HIV-1 subtype was not explicitly addressed (or known) in all of the studies, it is likely that all studies reflect mostly HIV-1 subtype B infections, as the cohorts are located in North America, Australia, and Europe, where subtype B is by far the most prevalent. If individuals of non-European ancestry or HIV-1 non-B subtypes were included, these were included as covariates [11,12,19,20] or excluded from the analyses [10,21] due to the demonstrated effect of ancestry [33,43–45].

Seroincident and seroprevalent cohorts—Critically, seroincident and seroprevalent cohorts were included in our meta-analyses. Seroincident cohorts comprised only individuals with known HIV seroconversion or infection dates; seroprevalent cohorts comprised individuals without established seroconversion dates. Seroincident cohorts are longitudinal prospective cohorts in which seronegative individuals are enrolled and screened regularly for HIV infection. These cohorts should not experience changes over time in the diagnosis or recruitment of newly infected individuals and, thus, biases due to cohort sampling procedures should not have undue influence on trends in prognostic markers.

Statistical analysis

Meta-analysis—We calculated summary regression slopes (summary effect sizes) in the metafor package [46] of the R statistical software [47], using a weighted least-squares approach under both fixed-effects and random-effects models. Weights were determined by the reciprocals of the variances: for fixed-effects analyses, the variances were the squares of the individual study standard errors; for random-effects analyses, the variances were the sum of individual study variances and the study heterogeneity variance [48]. Cochran's *Q*-test of

heterogeneity was used to identify differences among study effect sizes. We tested the influence of single studies on the summary effect with a 'leave one out' analysis. Possible publication bias was assessed using funnel plots.

Association between trends in CD4 cell counts and set point viral loads— Trends in baseline CD4 cell counts and set point viral loads may reflect the same underlying biological process, resulting in an inverse relationship between the magnitudes of trends. For studies that reported CD4 and viral load trends from the same cohort, we used linear regression and the Spearman's rank correlation test to examine their relationship.

Sources of heterogeneity—We tested for correlations between study-level covariates and effect sizes using univariate linear regression with a mixed-effects model (a random effects model that additionally includes study-level covariates as sources of study heterogeneity) [49]. Inferences from meta-regression analyses should be treated with caution; meta-regression can be error-prone due to the generally small number of studies available for analysis, the post-hoc selection of study covariates, and the potential differing relationships seen among covariates across studies and among covariates across patients within individual studies [49]. With these limitations in mind, covariates tested were population frequencies of transmission risk groups HET, IDU, and MSM; study sample size; sampling lag-time; seroconversion lag-time; the number of years included in the study; and the median of the years included.

Results

Studies of HIV virulence trends

We identified 32 publications in which potential changes in HIV-1 virulence were addressed (see Table, Supplemental Document 1, http://links.lww.com/QAD/A190). Relatively equal numbers of (statistically significant) trend directions have been reported: nine with decreasing, 11 with increasing, and 12 with stable virulence. Reported virulence trends shifted over time and in association with the measurement of virulence. The majority of studies that inferred decreasing HIV-1 virulence were published in the 1990s and used direct measures of virulence: the number of clinical AIDS diagnoses per year [25,26] or the rate of progression to AIDS or AIDS death [27–31]. These early studies were primarily concerned with the potential effects of therapy and opportunistic infection prophylaxis on the HIV-1 epidemic; ART use was generally not excluded, and ART was often identified as the likely cause of observed decreasing virulence. Although containing important epidemiological and clinical findings, these studies are not directly comparable with later studies of HIV-1 virulence that use prognostic markers measured prior to ART initiation. Prognostic markers used to assess HIV-1 virulence trends included the baseline $CD4^+$ T-cell count, the rate of $CD4^+$ T-cell decline within an individual, the rate of decline of the CD4:CD8 ratio within an individual, the timing of p24 antigenemia, and the set point plasma viral RNA load.

From the 32 publications, we selected 12 studies of trends in baseline $CD4^+$ T-cell counts (Table 1), and eight studies of trends in set point viral RNA loads (Table 2) that fit the criteria described in the Methods section. Each study examined an HIV-1-infected population with majority European ancestry infected primarily with HIV-1 subtype B; when other ancestries or subtypes were present, these were included as covariates. The mean study period was 17 years (range 8–26) for CD4 cell count studies, and 17.25 years (range 9–24) for viral load studies. The majority of studies (nine of 12 CD4 cell count studies, six of eight viral load studies) included only seroincident individuals (individuals with established HIV infection dates); the remaining studies included seroprevalents with undocumented dates of infection.

Meta-analysis of CD4 cell count trends

Meta-analysis of 12 studies of CD4 cell count trends showed a statistically significant decreasing overall trend [summary effect=−4.93 cells/μl per year, 95% confidence interval (CI) −6.53 to −3.34, $P<1\times10^{-4}$) (Fig. 1a). The summary estimate from only the nine seroincident cohorts showed a larger decreasing trend ($CD4^+$ T-cell count=−6.01 cells/μl per year, 95% CI −7.37 to −4.65, $P<1\times10^{-4}$). Among all studies, Cochran's *Q*-test revealed significant heterogeneity in effect sizes (Q=22.88, P=0.02); among only studies of seroincident cohorts, the heterogeneity was no longer significant (Q=4.93, P=0.76). A fixed-effects model fitted to all 12 studies revealed equivalent results (summary effect=−4.87, 95% CI −5.79 to −3.96, $P<1\times10^{-4}$).

Meta-analysis of set point viral load trends

Meta-analysis of eight studies of viral load trends revealed a borderline significant increasing overall trend (summary effect=0.013 $\log_{10}$ copies/ml per year, CI −0.001 to 0.027, P=0.07) (Fig. 1b). The summary estimate from only the six seroincident cohorts showed a larger increasing trend and was statistically significant (viral RNA=0.018 $\log_{10}$ copies/ml per year, 95% CI 0.002–0.034, P=0.03). Among all studies, there was significant heterogeneity in effect sizes (Q=49.12, $P<1\times10^{-4}$), although substantially less heterogeneity was found among only studies of seroincident cohorts (Q=24.05, P=0.002) A fixed-effects model fitted to all eight cohorts provided similar results (summary effect=0.009, 95% CI 0.004–0.014, $P=4\times10^{-4}$). No apparent publication bias was observed; funnel plots revealed no significant asymmetry for CD4 or viral load studies (P=0.74, P=0.16, respectively). In leave-one-out sensitivity analyses, summary effect sizes were robust for both CD4 cell count and viral load trends (CD4: mean summary effect size=−4.95, range −5.81 to −4.6; viral load: mean summary effect size=0.013, range 0.009–0.017).

Association between trends in CD4 cell counts and set point viral loads

Ten of 12 studies reported decreasing trends in CD4 cell counts and six of eight studies reported stable or increasing trends in viral loads, consistent with the prediction that these trends reflect the same biological process. Trends of CD4 cell counts and viral loads for the same cohort were estimated for eight studies (five studies covered the exact same period): analysis of these paired studies revealed a nonsignificant relationship between the two measures (linear regression R^2=0.02, P=0.71; Spearman's rho=0.36, P=0.39).

Sources of heterogeneity

We attempted to identify relationships between study covariates and the magnitude of the trends in baseline CD4 cell counts or set point viral loads. No covariate showed significant association with CD4 effect size (see Figure, Supplemental Document 3, http://links.lww.com/QAD/A190). In viral load analyses, only seroconversion lag showed a significant association with effect size ($P=4.3\times10^{-4}$, remaining significant after Bonferroni correction for multiple comparisons) (see Figure, Supplemental Document 4, http://links.lww.com/QAD/A190): shorter periods between last negative and first positive HIV-1 antibody tests correlated with increased trends in set point viral loads.

Changing trends over time

In order to assess whether trends in these markers have changed over time, for each year from 1984 to 2010, we estimated summary effect sizes for each year, using only those studies that included that year (Fig. 2). Over time, the summary effect sizes for CD4 cell counts and viral loads decreased in magnitude. Trends for the two markers were strongly correlated across years (Spearman's rho=−0.79, $P=1.05\times10^{-6}$) (Fig. 2).

Discussion

Over the course of the HIV-1 subtype B epidemic in North America and Europe, there are overall trends of decreasing baseline $CD4^+$ T-cell counts and increasing set point viral loads. The $CD4^+$ T-cell trends of −4.93 cells/μl per year and viral RNA of 0.013 $\log_{10}$ copies/ml per year would reflect a loss of $CD4^+$ T-cells of 148 cells/μl and an increase of 0.39 $\log_{10}$ copies/ml RNA over a 30-year period (from the first CDC report of the epidemic in 1981). More accurate estimates from a meta-analysis of only the seroincident cohorts are of greater magnitude: $CD4^+$ T-cell count −6.01 cells/μl per year and HIV viral RNA of 0.018 $\log_{10}$ copies/ml per year, reflecting a loss of approximately $CD4^+$ T-cells of 180 cells/μl and an increase of 0.54 $\log_{10}$ copies/ml HIV viral load over 30 years. Changes of this magnitude may reflect major changes in the AIDS epidemic: a 0.3 $\log_{10}$ copies/ml change is a clinically significant change in viral load [35,50]. Additionally, the relationship between set point and disease progression predicts that an increase in set point of 0.5 $\log_{10}$ decreases the median time to AIDS by 3 years [51], and similar increases or decreases in viral load (at any time point) will modify the per year transmission rate by up to 37% [38–41]. Similarly, a decrease in baseline CD4 cell count of approximately 150 cells/μl over the last 30 years of the epidemic could impact the timing of ART initiation (i.e. the time from infection to a CD4 cell count below 500, 350, or 200 cells/μl, depending on the cut-off used for ART initiation; see http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf).

These trends are consistent with increased virulence of HIV-1 due to viral evolution in the human population. However, it is also possible for these trends to be the result of unmeasured confounders or biases in the individual studies assessed. The limitations may include the following:

Measurement or cohort sampling biases

Numerous HIV-1 viral load and CD4 cell count assays and platforms with varying ranges of quantification have been used over the course of the epidemic. Unfortunately, biases potentially introduced by changes in the assay type cannot be corrected for in trend analysis, because they correlate completely with calendar year. However, viral load and CD4 cell count assays used in the various studies often differed during any single calendar period and, thus, are unlikely to introduce a consistent directional bias. Additionally, it is unlikely that increasing precision and lower limits of detection of HIV viral load tests could result in the observed increased viral loads, as improved tests generally allowed for the detection of lower viral loads. Similarly, improved assays and platforms for CD4 cell counting over time are unlikely to have systematically undercounted CD4 cells in the later years of the epidemic.

A longitudinal trend in set points may be a consequence of improvements over time in referral or cohort recruitment practices [52], or of improvements in diagnostic techniques and identification of new HIV infections [53]. Such changes have the potential to produce cohort sampling biases, because HIV viral loads in primary infection are higher in symptomatic individuals [54,55]. For example, if rapid progressors are more readily identified later in the epidemic and these individuals initiate ART before set point is measured, then fewer high set point viruses will be sampled as the epidemic ages, leading to inferred trends of decreasing virulence; alternatively, if increased diagnosis and recruitment of newly infected individuals results in the sampling of more symptomatic individuals, then trends of increasing virulence may be reported (as relatively fewer asymptomatic individuals, with lower viral loads, are sampled). Although these issues are of significant concern in seroprevalent cohorts, the majority of studies included in the meta-analyses were based on seroincident cohorts, which include only individuals with documented HIV infection, making a bias for or against the biased sampling of rapid progressors as the

epidemic progresses very unlikely. If, however, fewer rapid progressors were available for sampling at set point later in the epidemic, due to earlier diagnosis and ART initiation, the summary trends we observed would be conservative estimates. Indeed, the summary estimates for only the seroincident cohorts are of greater magnitude (for viral load trends, 0.018 and 0.013 $\log_{10}$ copies/ml per year viral RNA; for CD4 cell count trends, −6.01 and −4.93 cells/μl $CD4^+$ T cells, for only seroincident and for all cohorts, respectively).

Changing epidemiology of HIV-1

It is possible that trends in prognostic markers reflect HIV-1 epidemiology, including changes in the behavior or characteristics of individuals at risk for infection [56–58]. The HIV-1 epidemic in Europe and North America is increasingly populated by individuals of non-European ancestry and nonsubtype B viruses [59], and ancestry has been shown to affect prognostic marker levels [33,43–45]. However, within our meta-analysis the studies that included individuals of non-European descent controlled for ancestry; thus, it is unlikely that shifts in HIV-1-infected cohorts toward increasing frequencies of non-European individuals have resulted in the observed trends in prognostic markers. In addition, although the HIV-1 epidemic in Europe and North America is increasingly populated by individuals of different transmission risk group, we found no evidence that changes in the frequencies of transmission risk group explained our results.

Viral evolution and adaptation to humans

The observed temporal trends in CD4 cell counts and viral loads may reflect adaptive evolution of HIV-1 virulence. There are well documented associations between plasma viral load and probability of successful viral transmission [39,40,60,61], and between set point viral load and progression rate to AIDS or AIDS-related death [34–37]. As well, recent studies have reported heritability in viral load set point across transmitting partners, with heritability estimates ranging from 0.23 to 0.59 [62–65]. Thus, the essential components of adaptive evolution of HIV-1 set point (as a proxy for virulence) are present: there is phenotypic variation among individuals in viral loads; the variation is associated with differential transmission; and the variation is heritable (the viral load phenotype is at least partially linked to the virus genotype). As proposed by Fraser *et al.* [41], this may result in an evolutionarily optimal set point, defined as the viral load that balances transmission probability with virulence. For example, low viral loads will result in low probabilities of transmission but longer durations of infection, whereas high viral loads will result in high probabilities of transmission but shorter lifespans. Fraser *et al.* estimate this optimal viral load as 4.52 $\log_{10}$ copies/ml. Indeed, we found evidence for convergence toward a virulence optimum: the summary trends in CD4 cell counts and viral loads decreased in magnitude over time when calculated separately for each year (Fig. 2). This suggests that the rate of virulence evolution has slowed, perhaps approaching an optimum and stable virulence.

Is there evidence that HIV-1 is indeed evolving in the human population?

Increased virulence of HIV-1 may result from viral evolution away from human cytotoxic T lymphocyte (CTL) and humoral immune responses. It is known that CTL are the major force acting on the viral population at the intrahost [66,67] and interhost population level [68,69]. Whether HLA alleles such as B*57, B*51, or B*27 that associated with viral control [69–71] will maintain their protectiveness over the course of the epidemic is unclear. There is evidence that viral escape mutations associated with HLA B*51 alleles have increased in the Japanese population in the last 25 years, resulting in a reduced protective effect of these alleles [69]. There is also evidence for HIV-1 interhost adaptation to the humoral response over the course of the epidemic, with increases in the length of variable loops in envelope gp120 [72,73], the number of potential N-linked glycosylation sites [72], and viral resistance

to antibody neutralization [72]. Questions remain about whether such interhost adaptation will have clinical impacts or will affect overall virulence levels.

Overall, our meta-analysis of trends in prognostic markers of HIV-1 disease progression suggests that HIV-1 has become virulent over the more than 30-year history of the global HIV/AIDS epidemic. Further studies in other populations and locales, especially in sub-Saharan Africa, are needed to further assess our finding and its potential future impact.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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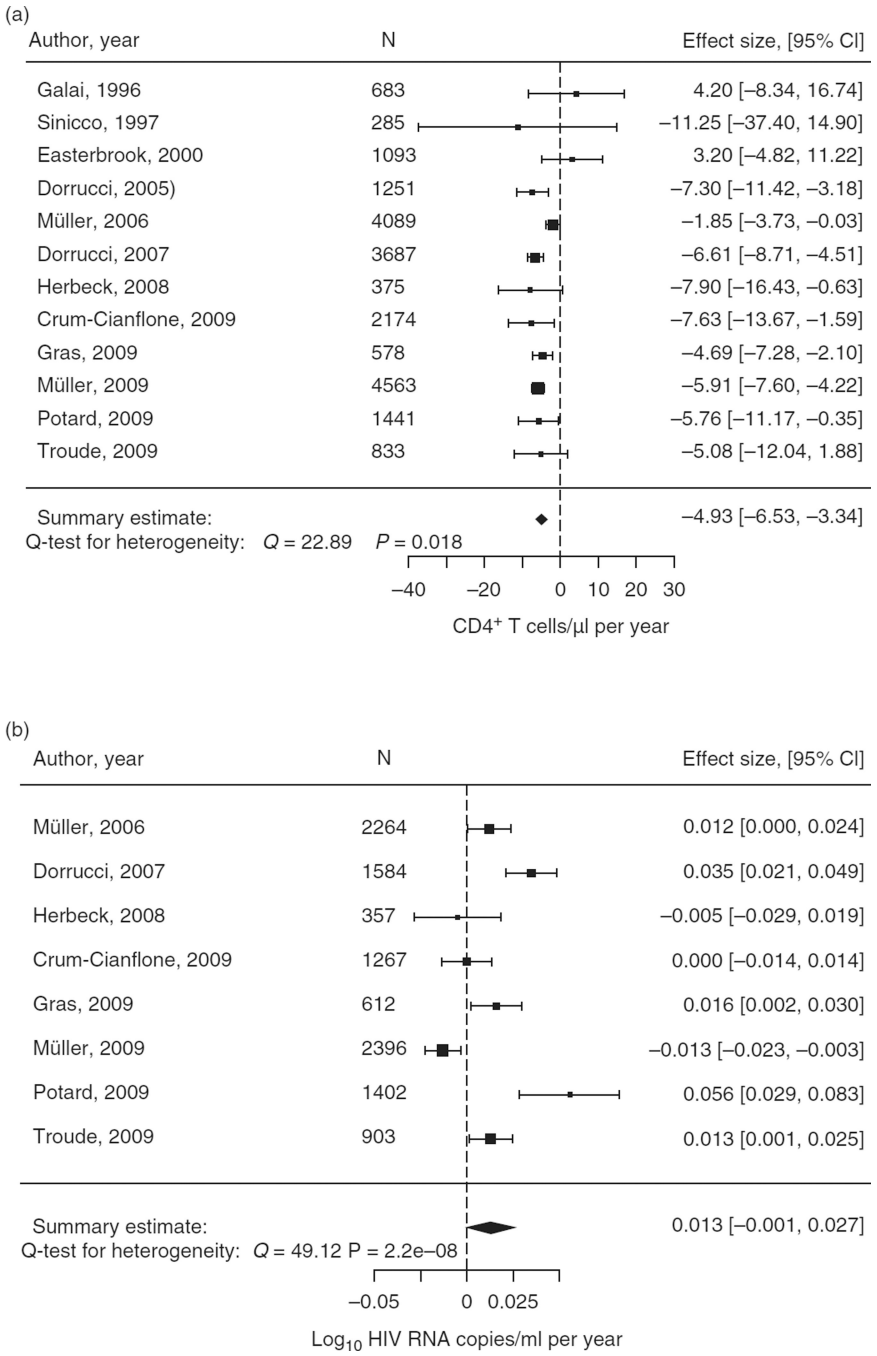

Fig. 1. Forest plots of trends in prognostic markers of HIV disease progression

Forest plot for (a) trends in baseline $CD4^+$ T-cell count; and (b) trends in set point plasma HIV-1 RNA loads (log_{10}-transformed). The 95% confidence intervals for each study are represented by horizontal lines, and the effect sizes (regression slopes) are represented by squares, with the squares area equal to the weight of the study (with the weight calculated as the inverse of the variance). Confidence interval for summary effect size is represented by the width of the diamond shape.

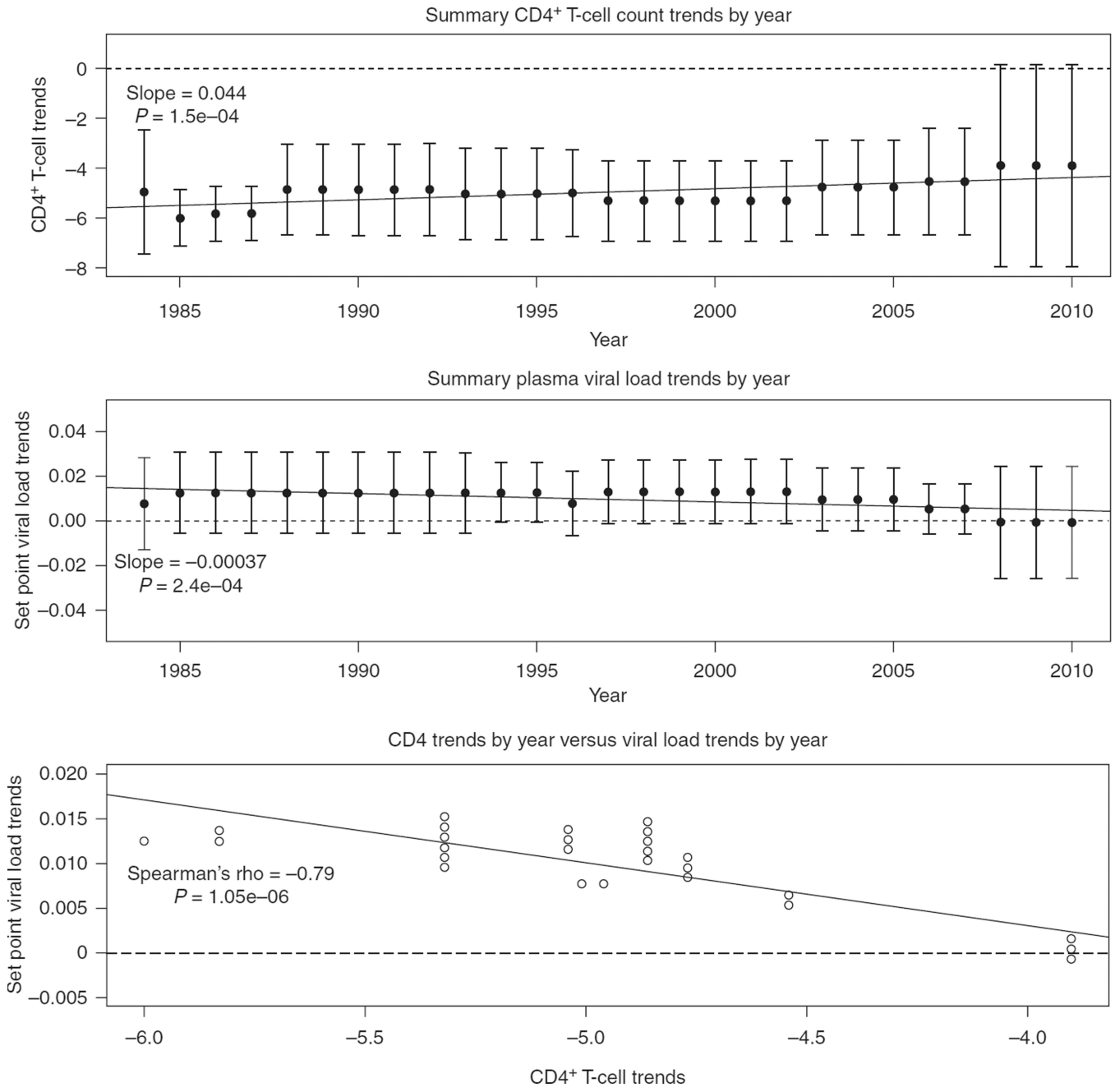

Fig. 2. Plot of summary trends by year

Random-effects meta-analyses for each year from 1984 to 2010 for $CD4^+$ T-cell counts and set point viral loads. Summary trends were estimated using effect sizes from those studies that spanned each specific year. The 95% confidence intervals are shown for summary trends in the top two panels. Bottom panel shows correlation between magnitude of CD4 cell counts and viral load trend sizes per year tested by linear regression. Identical data points are jittered vertically.

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Table 1

Studies of trends in baseline $CD4^+$ T-cell counts after HIV-1 infection used in this meta-analysis.

Study	Years (*N*)	Site	Cohort	*N*	Risk groups	Statistical method	Covariates	Sampling lag[a]	SC lag[b]
Galai *et al.* [7]	1985–1992 (8)	IT	NA	683	HET, IDU, MSM	Linear regression	Sampling lag, SC lag, age at SC, risk group, clinic site	4.6 months (range 0.5–24.0)	7.1 months (range 0.5–12.0)
Sinicco *et al.* [15]	1985–1995 (11)	IT	NA	285	HET, IDU, MSM, other	Survival analysis	Age at SC, sex, education, job, risk group, laboratory measurements, lifestyle, smoking, drinking, drug use, annual income, STD history, acute HIV Infection	3.0 months (range 0.03–5.6)	6.0 months (range 0.7–11.2)
Easterbrook *et al.* [4]	1986–1996 (11)	UK	NA	1093	HET, IDU, MSM	Linear regression	Age at diagnosis, risk group, clinic site, sex	NA[c]	NA
Dorrucci *et al.* [16]	1985–2002 (18)	IT	ISS	1251	HET, IDU, MSM, other	Linear regression	Sampling lag, SC lag, age at SC, risk group, clinic site	4.0 months (range 0.1–24.0)	6.0 months (range 0.2–12.0)
Müller *et al* [d] [10]	1988–2010 (23)	CH	SHCS	4089	HET, IDU, MSM, other	Linear regression	Age at diagnosis, risk group, sex	NA	NA
Dorrucci *et al.* [18]	1985–2002 (18)	EU, AU, CA	CASCADE	3687	HET, IDU, MSM, other	Linear regression	Sampling lag, SC lag, age at SC, risk group, clinic site, sex, AIDS within 2 years	4.4 months (range 1.7–8.0)	5.8 months (range 1.0–8.5)
Herbeck *et al.* [11]	1984–2005 (21)	US	MACS	375	MSM	Linear regression	Age at SC, clinic site, race, CCR5delta32	9 and 15 months	<1 year
Crum-Cianflone *et al.* [22]	1985–2007 (23)	US	TriService	2174	HET, other	Linear regression	Sampling lag, SC lag, age at SC, risk group, clinic site, sex, race, BMI, HIV load	1.4 months (range 1.0–2.4)	1.45 years (24% >2 years)
Gras *et al.*[e] [20]	1984–2007 (24)	NL	ACS and ATHENA	811	HET, IDU, MSM, other	Linear regression	Sampling lag, age at SC, risk group, sex, region of origin (race), HIV-1 subtype, HBV or HCV co-infection, drug resistance mutations	10.5 months	<1 year
Müller *et al.* [f] [21]	1985–2010 (26)	IT	MASTER	4563	HET, IDU, MSM	Linear regression	Age at diagnosis, risk group, sex	NA	NA
Potard *et al.* [23]	1997–2005 (9)	FR	FHDH	1441	HET, MSM	Linear regression	Sampling lag, age at diagnosis, risk group, sex, AIDS within 1 year, known SC date	4.3 months (range 2.5–6.2)	<1 year
Troude *et al.* [12]	1996–2007 (12)	FR	ANRS PRIMO	833	MSM	Linear regression	Sampling lag, age, sex, place of birth (race),	1.5 months	<1 year

Study	Years (*N*)	Site	Cohort	*N*	Risk groups	Statistical method	Covariates	Sampling lag[a]	SC lag[b]
							symptomatic HIV infection, smoking, HIV-1 subtype		

ACS, Amsterdam Cohort Studies on HIV Infection and AIDS; ANRS PRIMO, French National Agency for Research on AIDS, PRIMO cohort; ATHENA, AIDS Therapy Evaluation in the Netherlands Cohort; AU, Australia; CA, Canada; CASCADE, Concerted Action on Seconversion to AIDS and Death in Europe; CH, Switzerland; EU, Europe; FHDH, French Hospital Database on HIV Infection; FR, France; HBV, hepatitis B virus; HCV, hepatitis C virus; HET: heterosexual; ISS, Italian Seroconversion Study; IT, Italy; MACS, Multicenter AIDS Cohort Study; MASTER, Italian MASTER Cohort; NA, not applicable; NL, The Netherlands; SC, seroconversion; SHCS, Swiss HIV Cohort Study; STD, sexual transmitted disease; US, United States.

[a] Sampling lag: time from estimated date of seroconversion to first CD4 cell count measurement. A 'NA' denotes seroprevalent studies that did not limit inclusion to individuals with estimated dates of seroconversion (individuals with a documented HIV-seronegative followed by a seropositive test).

[b] SC lag: seroconversion lag, the time between last HIV seronegative test and first positive test. NA: see note under sampling lag.

[c] Easterbrook *et al.* [4], criteria do not include estimated dates of seroconversion, only HIV diagnosis.

[d] Müller *et al.* [10] examined the slope of CD4 cell count decline; additional and updated baseline CD4 cell count data were extracted *post hoc*; sample size refers to the multivariate analysis.

[e] Data from the ATHENA and ACS cohorts was used to estimate a linear trend; for the current meta-analysis this included 578 individuals of the MSM risk group.

[f] Müller (2009) examined the slope of CD4 cell count decline; additional and updated baseline CD4 cell count data were extracted *post hoc*; sample size refers to the multivariate analysis.

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Table 2

Studies of trends in plasma HIV-1 viral RNA set point used in this meta-analysis.

Study	Years (*N*)	Location	Cohort	*N*	Risk groups	Statistical method	Covariates	Sampling lag[a]	SC lag[b]
Müller *et al.* [c][10]	1995–2010 (16)	CH	SHCS	2264	HET, IDU, MSM	Linear regression	Age at diagnosis, risk group, sex	NA	NA
Dorrucci *et al.* [18]	1985–2002 (18)	EU, AU, CA	CASCADE	1584	HET, IDU, MSM, other	Linear regression	Sampling lag, SC lag, age at SC, risk group, clinic site, sex, AIDS within 2 years	4.4 months (range 1.7–8.0)	5.8 months (range 1.0–8.5)
Herbeck *et al.* [11]	1984–2005 (21)	US	MACS	357	MSM	Linear regression	Age at SC, clinic site, race, CCR5delta32	9 and 15 months	<1 year
Crum-Cianflone *et al.* [22]	1985–2007 (23)	US	TriService	1267	HET, other	Linear regression	Sampling lag, SC lag, age at SC, risk group, clinic site, sex, race, BMI, HIV load	1.4 months (range 1.0–2.4)	1.5 years (24% >2 years)
Gras *et al.*[d][20]	1984–2007 (24)	NL	ACS and ATHENA	906	MSM	Regression	Sampling lag, age at SC, risk group, sex, region of origin, HIV-1 subtype, HBV or HCV co-infection, drug resistance mutations	10.5 months	<1 year
Müller *et al.* [e][21]	1996–2010 (15)	IT	MASTER	2396	HET, IDU, MSM	Linear regression	Age at diagnosis, risk group, sex	NA	NA
Potard *et al.* [23]	1997–2005 (9)	FR	FHDH	1402	HET, MSM	Linear regression	Sampling lag, age at diagnosis, risk group, sex, AIDS within 1 year, known SC date	4.4 months (range 2.6–6.3)	<1 year
Troude *et al.* [12]	1996–2007 (12)	FR	ANRS PRIMO	903	MSM	Linear regression	Sampling lag, age, sex, place of birth, symptomatic HIV infection, smoking, HIV-1 subtype	1.5 months	<1 year

ACS, Amsterdam Cohort Studies on HIV Infection and AIDS; ANRS PRIMO, French National Agency for Research on AIDS, PRIMO cohort; ATHENA, AIDS Therapy Evaluation in the Netherlands Cohort; AU, Australia; CA, Canada; CASCADE, Concerted Action on Seconversion to AIDS and Death in Europe; CH, Switzerland; EU, Europe; FHDH, French Hospital Database on HIV Infection; FR, France; HBV, hepatitis B virus; HCV, hepatitis C virus; HET: heterosexual; ISS, Italian Seroconversion Study; IT, Italy; MACS, Multicenter AIDS Cohort Study; MASTER, Italian MASTER Cohort; NA, not applicable; NL, The Netherlands; SC, seroconversion; SHCS, Swiss HIV Cohort Study; STD, sexual transmitted disease; US, United States.

[a]Sampling lag: time from estimated date of seroconversion to first viral load measurement. A 'NA' denotes seroprevalent studies that did not limit inclusion to individuals with estimated dates of seroconversion (individuals with a documented HIV-seronegative followed by a seropositive test).

[b]SC lag: seroconversion lag, the time between last HIV seronegative test and first positive test. NA: see note under sampling lag.

[c]Additional and updated plasma viral load data from the SHCS were extracted *post hoc*; sample size refers to the multivariate analysis.

[d]Data from the ATHENA and ACS cohorts was used to estimate a linear trend; for the current meta-analysis this included 612 individuals of the MSM risk group.

[e]Additional and updated plasma viral load data from the MASTER cohort were extracted *post hoc*; sample size refers to the multivariate analysis.

Table 3

Reported and reconstructed effect sizes for trends in prognostic markers of HIV-1 infection.

	Linear regression reported adjusted (unadjusted)		Linear regression on medians unadjusted weighted by *n*		Linear regression on medians unadjusted not weighted		Quantile regression on medians unadjusted not weighted		Linear regression reported adjusted (unadjusted)	
$CD4^+$ T-cell counts	**cells/μl per year**	**s.e.**	**cells/μl per year**	**s.e.**	**cells/μl per year**	**s.e**	**cells/μl per year**	**s.e.**	**Transformed CD4**	**s.e.**
Galai[a][7]	4.20 (4.30)	6.40 (6.30)	3.75	8.66	0.45	7.39	−1.67	11.94	NA	
Sinicco *et al.*[b][15]			−11.25	13.34	−10.23	14.29	−15.96	22.34	NA	
Easterbrook *et al.*[b][4]			3.2	4.09	4.14	3.93	3.33	6.37	log; 0.01 (0.001)	0.01 (0.01)
Dorrucci *et al.* [16]	−7.3 (−8.60)	2.1 (2.0)	−13.71	1.37	−13.3	1.34	−13.85	2.8	NA	
Müller *et al.*[c][10]	−1.85 (−2.22)	0.96 (0.56)	−1.11	1.9	−0.13	1.6	0.93	3.89	Slope;−0.66 (NA)	0.84 (NA)
Dorrucci *et al.* [18]	−6.61 (−6.33)	1.07 (1.06)	−5.8	0.79	−5.43	0.74	−6.11	1.55	NA	
Herbeck *et al.* [11]	−7.9 (−7.7)	4.35 (3.48)	−7.12	2.2	−5.41	3.86	−2	6.8	sqrt;−0.15 (−0.14)	0.07 (0.08)
Crum-Cianflone *et al.*[b,d][22]			−7.63	3.08	−7.24	3.01	NA		ref; −101.5 (−118)	20.7 (15.6)
Gras *et al.* [20]			−4.69	1.32	−4.67	2.34	−5.63	3.1	cbrt;−0.03 (−0.03)	0.01 (0.01)
Müller *et al.*[e][21]	−5.91 (−11.9)	0.86 (0.57)	−11.07	2.63	−14.3	2.44	−9.5	6.17	Slope;−1.69 (−2.0)	0.30 (0.35)
Potard *et al.* [23]	−5.76 (−6.28)	2.76 (2.72)	−6.71	0.89	−6.88	0.87	−6.83	2.61	NA	NA
Troude *et al.*[b][12]			−5.08	3.55	−6.69	3.39	−5.5	6.13	sqrt;−0.01 (−0.07)	NA

	Linear regression reported adjusted (unadjusted)		Linear regression on means unadjusted weighted by *n*		Linear regression on means unadjusted not weighted	
Set point viral loads	**log_{10} copies/ml per year**	**s.e.**	**log_{10} copies/ml per year**	**s.e.**	**log_{10} copies/ml per year**	**s.e.**
Müller *et al.*[c][10]	0.012 (0.016)	0.006 (0.004)	0.016	0.007	0.016	0.007
Dorrucci *et al.* [18]	0.035 (0.044)	0.007 (0.005)	0.045	0.011	0.044	0.01
Herbeck *et al.* [11]	−0.005	0.012	0.015	0.01	0.018	0.019
Crum-Cianflone *et al.*[b][22]			0.000	0.007	1.60E-03	0.005
Gras *et al.*[a][20]			0.016	0.007	0.023	0.01
Müller *et al.*[e][21]	−0.013 (−0.006)	0.005 (0.004)	−0.006	0.005	0.003	0.008
Potard *et al.* [23]	NA (0.056)	NA (0.014)	0.03[f]	0.02	0.033[f]	0.019

	Linear regression reported adjusted (unadjusted)		Linear regression on means unadjusted weighted by *n*		Linear regression on means unadjusted not weighted	
Set point viral loads	**log_{10} copies/ml per year**	**s.e.**	**log_{10} copies/ml per year**	**s.e.**	**log_{10} copies/ml per year**	**s.e.**
Troude *et al.* [12]	0.01 (0.015)	NA	0.013[f]	0.006	0.014[f]	0.007

Effect sizes and standard errors in grey boxes were used for meta-analysis. ACS, Amsterdam Cohort Studies on HIV Infection and AIDS; ATHENA, AIDS Therapy Evaluation in the Netherlands Cohort; cbrt, cube root; MASTER, Italian MASTER Cohort; ref, reference; s.e., standard error; SHCS, Swiss HIV Cohort Study; sqrt, square root.

[a] Data shared by ATHENA and ACS for calculation of linear regression slope (effect size).

[b] Data extracted from published manuscript for calculation of linear regression slope (effect size).

[c] pdated estimate from analysis of additional unpublished data from the SHCS.

[d] Mean values used.

[e] Updated estimate from analysis of additional unpublished data from the MASTER cohort.

[f] Median values used.