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The role of co-infections in HIV epidemic trajectory and positive prevention: a systematic review and meta-analysis

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Abstract

Objectives—Recurrent or persistent co-infections may increase HIV viral load (VL) and, consequently, risk of HIV transmission, thus increasing HIV incidence. We evaluated the association between malaria, HSV-2 and TB co-infections and their treatment on HIV VL.

Design—Systematic review and meta-analysis of the association of malaria, HSV-2 and tuberculosis co-infections and their treatment on HIV VL.

Methods—PunMed and Embase databases were searched to February 10th 2010 for studies in adults that reported HIV plasma and/or genital VL by co-infection status or treatment. Meta-analyses were conducted using random-effects models.

Results—Forty-five eligible articles were identified (6 malaria, 20 HSV-2 and 19 tuberculosis). There was strong evidence of increased HIV VL with acute malaria (0.67 $\log_{10}$ copies/mL, 95% CI: 0.15, 1.19) and decreased VL following treatment (−0.37 $\log_{10}$ copies/mL, 95% CI: −0.70, −0.04). Similarly, HSV-2 infection was associated with increased HIV VL (0.18 $\log_{10}$ copies/mL, 95% CI: 0.01, 0.34), which decreased with HSV suppressive therapy (−0.28 $\log_{10}$ copies/mL, 95% CI: −0.36, − 0.19). Active tuberculosis was associated with increased HIV VL ($\log_{10}$ copies/mL 0.40, 95% CI: 0.13–0.67), but there was no association between tuberculosis treatment and VL reduction ($\log_{10}$ copies/mL −0.02, 95% CI −0.19, 0.15).

Conclusions—Co-infections may increase HIV VL in populations where they are prevalent, thereby facilitating HIV transmission. These effects may be reversed with treatment. However, to limit HIV trajectory and optimize positive prevention for HIV-infected individuals pre-ART, we must better understand the mechanisms responsible for augmented VL and the magnitude of VL reduction required, and retune treatment regimens accordingly

Keywords

HIV; HIV Co-infections; HSV-2; malaria; tuberculosis; viral load; viral load

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Conflicts of interest: We declare we have no conflicts of interest.

Background

The HIV pandemic has carved starkly different trajectories around the globe in the past three decades. In 2009, 33.3 million people were living with HIV and approximately 2.6 million people were newly infected [1]. Sub-Saharan Africa is the most severely affected region, home to two-thirds of those living with HIV (an estimated HIV prevalence in adults of 5%) and almost 70% of new infections. In contrast, about 12% of HIV-infected people live in South and South East Asia, while just less than half this number live in North America (5%) and Latin America (4%), with smaller proportions in Western and Central Europe (2%), representing estimated HIV prevalences in adults of 0.3% to 0.6%. [1].

The differential spread of HIV between populations results from multiple factors which drive transmission [2]. One key determinant of HIV transmission is HIV viral load (VL) [3,4]. A growing body of evidence suggests that recurrent or persistent co-infections, such as malaria, tuberculosis, herpes simplex virus type 2 (HSV-2) infection and helminths, may increase HIV VL and thus facilitate HIV transmission at both individual and population levels by increasing the person-time at VL levels associated with risk of ongoing spread. In areas where these co-infections are common, they may increase VL during the protracted interval between acute HIV infection and AIDS or initiation of antiretroviral therapy (ART), and the duration at this elevated level, driving HIV transmission. Infections may also increase susceptibility to HIV, as seen with the association between HSV-2 infection, and HIV acquisition [5].

While HIV prevention strategies initially focused primarily on HIV-negative individuals, the advent of ART has radically reframed the opportunities for and potential efficiencies of prevention in HIV positives [6]. The growing emphasis on “positive prevention” recognizes that combinations of interventions targeted at HIV-infected people could simultaneously improve survival and reduce transmission. Indeed, interventions such as ART that reduce HIV viral load are likely not only to delay HIV progression, but also to limit secondary infections. In individuals diagnosed with HIV who are not yet eligible for ART, treatment of co-infections may offer an important alternative approach to reducing HIV viral load and thereby slow disease progress, delay ART initiation and decrease HIV transmission.

We, therefore, explore the potential role of three persistent or recurrent infections (malaria, HSV-2 and tuberculosis (TB)) on HIV transmission and acquisition by systematically reviewing the literature. These three co-infections were selected because they are common among HIV infected persons in sub-Saharan Africa (co-infection rates for TB and HSV-2 are ~33% [7] and 85% [8], respectively, and HIV increases the frequency and severity of acute malaria [9,10]). Further, effective treatment options are available. The impact of helminth co-infections on HIV VL was recently reviewed elsewhere [11]. Finally, we discuss opportunities to enhance HIV prevention and care by treatment of these co-infections.

Methods

We followed Cochrane Collaboration guidelines in conducting our review [12], and PRISMA guidelines in reporting results [13].

Criteria for considering studies for this review

The *a priori* criteria for considering studies for the review are tabulated in the Appendix (Table S1). Both observational studies and randomized controlled trials (RCT) were eligible. To ensure comparability between groups in observational studies, we searched for studies which controlled for key confounders of viral load, including time from infection or CD4

count. We excluded the following from analyses: studies in which all participants were on ART, were pregnant women, children or HIV-2 infected individuals; studies in which the intervention modified HIV viral load with and without co-infection; and studies in which the control group was not proven negative for the co-infection. For studies in which a subgroup of participants was on ART, pregnant, aged <16 or HIV-2 positive, results were extracted excluding these participants. The only exception was episodic HSV-2 therapy for which three of the four trials had small numbers on ART (<4% of all participants) and it was not possible to extract data on ART naïve participants only.

Search strategy for identification of studies

Electronic searches of PubMed and Embase databases were conducted on January 31st 2009 and updated on February 10th 2010. In PubMed the following MeSH search terms were used: “HIV Infections” AND “Malaria/Herpesvirus 2/Tuberculosis” AND “Adult”. In Embase the following search terms were used: (human immunodeficiency virus infection and malaria/herpes simplex virus 2/tuberculosis and adult). The searches were done separately for each co-infection, included all languages, and were limited to human studies. Because the search for TB yielded over 6000 abstracts, many of which reported on clinical management, the following additional filters were used independently: 1) clinical trial, 2) viral load or viral shedding, and 3) disease susceptibility. Reference lists in articles were hand searched, as were infectious disease conference abstract books. Finally, correspondence with authors yielded one PhD thesis [14] and two in press articles [15,16].

Selection of studies, data extraction and synthesis

Abstracts were reviewed and full-text articles of potentially relevant studies were examined independently by two authors (RVB and JNW for the initial search; ELW and HAW for the updated search) against pre-specified selection criteria (Table S1, Appendix). Data were extracted independently by RVB, JNW and ELW for the original search, and by ELW and HAW for the updated search, using a data extraction form. Discrepancies were discussed and consensus reached.

When data from the same individuals were reported in multiple publications, we used the more informative publication. When multiple timepoints were reported, we extracted results based on all time-points provided; results based on repeated measures analyses were used only if the authors reported no evidence of a change in treatment effect over time, otherwise we report data for the timepoint most compatible with other studies for that disease. For TB, this was the earliest timepoint after conclusion of treatment or the latest timepoint during treatment (if no data were collected post-treatment). For four studies [17–20], we calculated mean differences directly from the raw data provided. Unpublished data were requested from authors of eight articles [17,21–27], primarily to obtain 95% confidence intervals (CI) for the mean difference. Three provided the requested data [17,24,25]. We estimated CIs based on standard deviations reported or displayed in the articles for the remainder.

The methodological quality of included studies was reviewed by RVB and ELW based on the selection criteria listed above. Studies were rated at low (A); moderate (B); or high (C) risk of bias. A key factor in this assessment was how studies attempted to account for time since HIV seroconversion, because viral load is dynamic and changes over time. Studies that reported HIV viral load stratified by CD4 count and, in addition, adjusted for other viral load cofactors such as gender were generally rated as “A.” In contrast studies that reported and compared the mean CD4 counts of each group and did not adjust for other co-factors were rated as “B.” Studies that did not adjust for CD4 count were rated as “C.”

Statistical methods

Plasma and genital VL were considered as separate outcomes. HIV plasma viral load (PVL) is reported as $\log_{10}$ copies/ml and HIV genital viral load (GVL) as $\log_{10}$ copies/ml or/swab. The measure of effect was the mean difference (and 95% CI) by co-infection or treatment status respectively, adjusted for potential confounders.

Random-effects meta-analyses were performed separately for each co-infection and for each co-infection treatment. Heterogeneity was quantified using the I^2 statistic [28], defined as the percentage of total variation in the study estimates that is due to between-study heterogeneity. For example an I^2 value of 50% would mean that half of the total variability among effect sizes is cause not by sampling error, but by true heterogeneity between studies. Funnel plots [29] were visually examined and Egger tests [30] were conducted to assess the possibility of publication bias. All statistical analyses were conducted in STATA version 11 (StataCorp, College Station, TX, USA).

Results

We identified 351 potentially relevant abstracts for malaria, 380 for HSV-2 and 812 for tuberculosis (Fig. 1). Of these, 45 studies met the pre-specified selection criteria for the systematic review (6 malaria, 20 HSV-2 and 19 tuberculosis). Forty of these studies were included in the meta-analysis (6 malaria, 19 HSV-2 and 15 tuberculosis). Of the 5 studies not included in the meta-analysis, the results of 3 are reported in the tables: 1 HSV-2 study reported only genital VL [31] and 2 studies of latent TB [18,32]. For the remaining 2 studies it was not possible to distinguish between the effects of TB infection and treatment [22,33] and therefore these studies were not included in the tables.

We identified no studies of the impact of HSV-2 on HIV acquisition that were published since the last systematic review of this topic [5]. No studies were identified examining the effect of malaria or TB on HIVacquisition.

Malaria

All six eligible malaria studies were observational. Four were prospective cohort studies [25,34–36], one was a nested case control study [37] and one was a challenge study with P. vivax [20]. The sample sizes ranged from 10 to 89 (Table 1). All studies except one from Guangzhou, China, were conducted in Africa. Recruitment in each study was facility-based, through hospitals, clinics, HIV screening or AIDS support organizations. All participants were HIV infected adults with or without malaria, followed through the course of malaria infection and subsequent treatment. Malaria was diagnosed through standard tests and treated appropriately. One study [28] used four definitions of malaria, and in this study we analyzed data for those with parasitaemia and fever to be consistent with the other studies.

All four studies that assessed the association between malaria co-infection and HIV VL (Table 1a) found increased PVL in the presence of acute malaria [20,34–36,38], with a summary estimate of the PVL increase of 0.67 $\log_{10}$ copies/mL (95% CI: 0.15, 1.19) (Fig. 2a). All estimates showed an increase in PVL, but there was substantial heterogeneity in the magnitude of effect (I^2=94.7%), with estimates from 0.13 $\log_{10}$ copies/mL (95% CI: −0.06, 0.32) to 1.23 $\log_{10}$ copies/mL (95%CI: 1.01, 1.45).

Six studies assessed the impact of malaria treatment on PVL (Table 1b). The impact of malaria treatment was measured as the mean difference in PVL before and after malaria treatment. Of these, five found that malaria treatment was associated with decreased PVL [20,34–37], with estimates from −0.89 $\log_{10}$ copies/mL (95% CI: −1.03, −0.75) to −0.10 (95% CI: −0.31, 0.11). The remaining study, which showed an increase in PVL, [25] had a

follow-up period of 9 days compared with a minimum of 28 days for the other studies. The summary estimate showed a trend towards decrease in PVL of −0.25 $\log_{10}$ copies/mL (95% CI: −0.59, 0.10) associated with treatment (Fig. 2b), although there was substantial heterogeneity between studies (I^2 =92.3%). Excluding the study with short follow-up [25] the summary estimate was a mean decrease of −0.37 $\log_{10}$ copies/mL (95% CI: −0.70, −0.04) with I^2 =92.5%. Further, when the challenge study was excluded [20] there was little evidence of heterogeneity in the malaria treatment studies; I2 =20.3%. This decrease in heterogeneity may be explained by differences between the challenge study design compared to naturally acquired malaria in the other studies, including number of bites, inoculum size and protection offered by malaria prevention interventions.

HSV-2

We identified 20 studies of the effect of HSV-2 infection and treatment and HIV VL. Of these, eight assessed the association between HSV-2 infection and PVL (Table 2a); three were cohort studies [21,39,40], four were cross-sectional [41–44] and one was a nested case-control study [45]. Cross-sectional and case-control studies compared PVL among participants with or without HSV-2, and cohort studies measured PVL through the course of a HSV-2 clinical episode. Three articles reported results from separate sub-studies according to stage of HSV-2 and HIV-1 infections [21,44] or gender [43] (Table 2a). One of the two cohorts analysed in Gray et al. [41] was reported on more fully in another article [45]; only the latter, more informative data were included in the meta-analysis. The effect of incident HSV-2 infection (i.e. recent seroconversion) on PVL was reported in two articles, neither of which found any association [21,39]. Eight studies examined the association between prevalent HSV-2 infection and HIV PVL. The summary estimate revealed a mean increase in PVL of 0.20 $\log_{10}$ copies/mL (95% CI: 0.00, 0.41). Pooling studies of HSV-2 prevalence and incidence, the summary estimate showed a mean PVL increase of 0.18 $\log_{10}$ copies/mL (95% CI: 0.01, 0.34), with substantial heterogeneity (I^2 =60.3%; Fig. 2c).

Eight studies assessed the impact of HSV-2 suppressive therapy on PVL (Table 2b). Of these, half evaluated regimens using acyclovir 400 mg twice daily, while the remainder tested higher dose acyclovir or valacyclovir regimens. Seven studies were RCTs [46–52] and one was an observational cohort study [53]. Sample sizes ranged between 12 and 3302 participants and trials were conducted in the United States, Thailand, Burkina Faso, South Africa, Uganda, Tanzania, Botswana, Zambia, Kenya, Rwanda and Peru. Seven of these studies found decreases in PVL associated with suppressive therapy, with effect estimates from −0.53 $\log_{10}$ copies/mL (95% CI: −0.72, −0.35) to −0.25 $\log_{10}$ copies/mL (95% CI: −0.29, −0.22). The remaining suppressive treatment study [16] found no evidence of an effect possibly due to the comparatively low adherence (123/232 participants [16] compared to 2363/2924 participants [54] with >90% adherence) and relatively low dose of acyclovir (400 mg twice daily by mouth). Overall, the summary estimate of the decrease in PVL was −0.28 (95% CI: −0.36, −0.19), with I^2 =83.1% (Fig. 2d).

Four studies (three RCTs and one cohort study) assessed the relationship between episodic therapy (5–10 days of acyclovir treatment at a range of doses) and PVL up to 45 days after treatment initiation [15,40,55,56]. Sample sizes ranged from 8 to 422 participants, and studies included participants in the United States, Malawi, South Africa, Ghana and the Central African Republic. Three of the four trials [15,55,56] had small numbers on ART (<4% of all participants), and it was not possible to extract data on ART naïve participants only. Two of the studies using higher dose acyclovir regimens reported a significant decrease in PVL associated with episodic therapy, while the other two studies found no evidence of an association (summary estimate of decrease −0.08 $\log_{10}$ copies/mL, 95% CI: −0.28, 0.11).

Eleven studies measured genital VL (GVL) [15,16,31,43,46,50,52,55–58]. There was wide variation in treatment regimens and in both the site and method of collection of samples for this outcome. Collection methods included cervicovaginal lavage, semen samples and endocervical and rectal swabs. Ten of the 11 studies were RCTs of the effect of HSV-2 treatment (7 suppressive; 3 episodic). The remaining was a cross-sectional study [43] that found no difference in GVL by HSV-2 infection status. Six of the RCTs found that treatment significantly decreased GVL (5 suppressive, 1 episodic) [31,46,50,52,55,58]. All of these evaluated valacyclovir or high dose acyclovir regimens. The remaining studies found no significant effects. A formal meta-analysis was not undertaken for this outcome, due to numerous sources of heterogeneity, including the range of treatment regimens, the variety of techniques used for sample collection, the variable lower limits of detection in the GVL assays used and day-to-day variations in detectable levels of VL present in genital samples. Individual study results for the RCTs are summarized in Table 2c.

Tuberculosis

Eight articles (one containing results from two studies, of which one study was divided into particiapants with CD4 count ≤500 and >500 [26]) reported on the effect of TB infection on PVL (Table 3a), and 12 examined the association of TB treatment and PVL (Table 3b). Sample sizes varied from 7 participants to 276 (median 20). All studies were facility-based (hospital, clinic or TB treatment center) and located in urban or peri-urban settings. The majority were conducted in Africa.

The infection studies were all observational, with three cohort [19,26,59], three nested case-control [18,32,60], and three cross-sectional studies [26,61,62]. Two of these reported on the association of latent TB with VL, one finding a significant decrease [32] and the other finding no effect [18]. Of the six papers on active TB, three were pulmonary [26,60,61], two were both pulmonary and extra-pulmonary TB [59,62] and the sixth paper did not specify site of infection [19]. Overall, active TB was associated with a mean increase in VL of 0.40 $\log_{10}$ copies/mL (95% CI: 0.13, 0.67) (Fig. 2e), although there was again substantial heterogeneity between studies (I^2 =78.8%).

Of the 12 studies that investigated associations between treatment of active TB and PVL, ten were cohort studies and two were RCTs of non-TB treatment (immune modulators pentoxifylline and Immunoxel) plus standard TB treatment versus standard TB treatment alone [17,63]. In both trials, the intervention arm showed a significantly greater reduction in PVL than controls. We, therefore, used data only from the standard TB treatment arms of these RCTs. Duration of treatment and study follow-up varied considerably (2–8 months; and 2–12 months post treatment initiation, respectively). The summary estimate of the mean difference in PVL was a decrease of −0.03 $\log_{10}$ copies/mL (95% CI: −0.19, 0.13) (Fig. 2f), which did not change significantly when studies with less than 6 months of follow-up were excluded.

Two additional studies [22,33] reported change in PVL from before active TB onset compared to post TB treatment, so that it was not possible to distinguish between the effects of infection and treatment. However, both showed a significant increase in VL associated with infection/treatment (results not shown).

Risks of bias within and across studies

The methodological quality of studies varied. For malaria, the majority of studies were cohort studies which reported viral load before, during and after acute malaria infection and were therefore rated A or B, depending on whether there was an external control group. One cross-sectional study was rated C for methodological quality because associations between

treatment and PVL did not adjust for difference in CD4 count between the comparison groups. Studies of HSV-2 treatment were of high methodological quality, the majority being RCTs. However, studies examining HSV-2 infection were of variable methodological quality. Two did not adjust for potential confounders [41,43] and were, therefore, rated C. For TB, three cross-sectional studies were rated C due to extremely small sample size or failure to adjust for time since infection. For each co-infection, removal of studies rated C from the meta-analysis did not significantly change results.

Funnel plots and the Egger test for each outcome did not indicate any evidence of publication bias (results not shown).

Discussion

Malaria, HSV-2 and TB contribute significantly to the global burden of infectious disease, with high prevalence areas geographically overlapping with HIV endemic regions. Here, dual infection occurs commonly, making the role of co-infections and their treatment in HIV transmission salient questions. We identified 45 studies of the effect of these co-infections on HIV viral load (6 for malaria, 20 for HSV-2 and 19 for TB). We found significant increases in HIV PVL associated with acute malaria (0.67 $\log_{10}$ copies/mL; 95% CI: 0.15, 1.19), HSV-2 (0.18 $\log_{10}$ copies/mL; 95% CI: 0.01, 0.34) and active TB (0.40 $\log_{10}$ copies/mL; 95% CI: 0.13, 0.67). Overall treatment for malaria appeared to have limited impact on viral load (−0.25 $\log_{10}$ copies/mL, 95% CI: −0.59, 0.10), however when the study with less than 10 days of follow-up was excluded, viral load decreased significantly with malaria treatment (−0.37 $\log_{10}$ copies/mL; 95% CI: −0.70, −0.04). These results are consistent with an earlier study suggesting that the full impact of malaria treatment on HIV VL does not occur within 4 weeks post treatment [35], Kublin and colleagues chose 8 weeks after malaria treatment as the follow-up time necessary to see a return of HIV viral load to baseline [36], suggesting that a 9 day follow-up period would be too short. Suppressive treatment for HSV-2 produced significant decreases in HIV viral load (−0.28 $\log_{10}$ copies/mL, 95% CI: −0.36, −0.19), however there was no significant impact of either episodic HSV-2 treatment (−0.08 $\log_{10}$ copies/mL, 95% CI: −0.28, 0.11) or TB therapy (−0.03 $\log_{10}$ copies/mL, 95% CI: −0.19, 0.13) on HIV viral load. Collectively these studies suggest that co-infections increase HIV viral load, and that some of these effects may be reversed by treatment using current treatment regimen.

We found that TB treatment did not significantly reduce viral load, an unexpected finding because active TB was associated with a 0.40 log10 copies/mL increase in VL. There are at least two possible reasons for this finding. First, the long course of TB treatment (6 to 9 months) and variable follow-up times make comparisons challenging since both the outcome of interest (VL) and its main modifier (CD4) may change over the course of treatment. However, excluding studies with less than 6 months of follow-up did not change our results. Second, standard TB treatment regimens may not address the underlying mechanisms that trigger increased PVL. Assessing the impact of treatment on chronic co-infection will require careful study designs to account for modifiers of effect that change over time.

Our results add to those in a recent review of the impact of co-infection treatment [64]. Our findings for impact of malaria and HSV-2 treatment support those of the review, but our TB results do not. The Modjarrad review included two studies of malaria treatment, two of TB treatment and 6 of HSV-2 treatment. In contrast, we identified 6 studies of malaria treatment, 12 of TB treatment and 8 of HSV-2 suppressive treatment, as well as studies of co-infection prior to treatment. There are several differences between the reviews, including the inclusions/exclusion criteria, methods of analysis, and data extracted. For example, the Modjarrad review required studies to include a control group to adjust for natural history

changes in VL over time, but most of the additional studies included in our review were cohort studies conducted over relatively short periods during which VL would not be expected to change substantially in the absence of co-infection or intervention. We therefore included pre-post studies without control groups. Further, the Modjarrad review used the standardized mean difference (SMD) as the measure of effect, rather than the actual viral load, which tends to exaggerate differences between studies because the dimensionless scale of the SMD is not directly interpretable. Finally, for the two TB studies that were included in both this and the Modjarrad review [19,61], the data extracted in the Modjarrad review used a subgroup of patients, while we included data from all patients.

Impact on HIV transmission

Although our review found only modest changes in PVL associated with co-infections and their treatment (0.2 $\log_{10}$ to 0.7 $\log_{10}$ for co-infections and −0.3 $\log_{10}$ to −0.4 $\log_{10}$ for treatment), modeling studies have reported that small changes in mean viral load at population level could translate to significant reductions in HIV incidence – a decrease in PVL of 0.3 $\log_{10}$ was estimated to decrease HIV transmission by 20% and HIV progression by 25% [65]. Lingappa and colleagues produced similar estimates in their analysis of PVL among 108 genetically linked HIV transmission events, suggesting that a 0.3 $\log_{10}$ reduction in PVL would reduce HIV transmission risk by 25% [66].

Fraser and colleagues proposed that HIVevolves to reach a balance between sufficiently high viral load for successful transmission with each exposure and sufficiently low viral load for a protracted asymptomatic period to maximize transmission opportunities [67]. We posit that co-infections help HIV achieve that “sweet spot” viral load through immune activation [68,69], increasing the cumulative time spent at the optimum viral load for both asymptomatic disease and HIV transmission. From a population perspective, this may accelerate HIVepidemic trajectory by increasing the aggregate person-time at viral loads at which the risk for transmission is sufficient to maintain the reproductive rate above 1 in the population. ART may be able to supersede other factors in forcing VL back below these levels. However, for the vast number of HIV-infected individuals who are in the pre-ART window or who do not have access to ART despite being eligible, interventions to prevent and treat co-infections may be an important strategy to tip the balance in favor of the host not only by limiting progression and delaying ART initiation, but also by maintaining community viral load at levels that limit transmission and help curb epidemic trajectory. It is noteworthy that the potential impact of co-infections on total community viral load over time is a function not only of the magnitude of the increase in HIV VL observed in co-infected individuals, but also of the prevalence of the infection among HIV-positives and the average duration or proportion of time during an interval such as one year that co-infection is likely to exist. When the results of our meta-analysis are examined from this perspective, the potential impact of HSV-2 co-infection on total community viral load over a year is likely to markedly outstrip that of malaria and TB, even though the increase in HIV VL in co-infected individuals with malaria is more than three times that observed with HSV-2, and the increase with TB is more than twice that with HSV-2.

Although treatment of co-infections has been demonstrated to delay HIV disease progression and ART initiation, it has yet to be shown to reduce HIV transmission in intervention trials. While an RCT of HSV-2 suppressive therapy found a 16% reduction in HIV progression as measured by CD4<200, ART initiation or death (HR 0.83 (0.71–0.98)), there was no effect on HIV transmission [47,70]. This may be due to persistent immune activation, including HIV target cells in the genital tract as much as two months after ulcer healing on standard HSV suppressive therapy [71]. Hence, while HSV-2 suppressive therapy decreases PVL sufficiently to help reduce the impact of HIV disease on infected individuals, further work is needed to fully understand the mechanisms by which HSV boosts HIV VL,

better define the VL reductions needed to curb transmission, and design HSV treatment regimens that reliably achieve these targets. One recent model indicates that at least a 0.75 $\log_{10}$ reduction in HIV VL is needed to decrease transmission by 50% [66]. Trials are needed to evaluate the impact of carefully redesigned treatment regimens for HSVand other co-infections on HIV transmission, as well as on the surrogate of HIV viral load. Evidence of an impact of TB and malaria on HIV progression is limited, with mixed findings for TB [72,73] and no effect for malaria [74,75]. In evaluating non-ART regimens to reduce HIV disease progression we suggest using outcomes as defined by Lingappa and colleagues: ART initiation, CD4<200 and HIV related death [70].

Study limitations

Methodological quality of individual studies was variable. Several studies (especially of malaria and TB) were cross-sectional and thus particularly susceptible to bias. However, nearly all controlled for potential confounders such as CD4 and gender, and results were similar when restricted to these studies. Although we found no evidence of publication bias, we may not have had sufficient power to detect this. Studies included used different diagnostic methods and definitions for acute/active infection, which could affect our findings (although when examined explicitly for malaria [36], no material difference was found in the results. Further, assays for measuring viral load and CD4 count also varied between studies and standardization of tests would likely narrow the confidence intervals.

We used a random effects model and found that heterogeneity was significant, which we would expect given variability in study design, populations, sample sizes and follow-up times. Follow-up times varied from 9 to 65 days post malaria treatment, 28 days to 24 months for HSV-2 therapy and 2 to 12 months for TB treatment. In addition, differences in treatment regimens contributed to the observed heterogeneity. Thus, our results are interpreted with caution, but provide strong stimulus for further research on the impact of co-infections on HIV viral load and transmission.

Our study focused on plasma viral load, a reproducible quantitative measure of HIV infectiousness. However, because HIV is sexually transmitted in regions bearing the greatest burden of the epidemic, it would be most relevant to determine the impact of co-infections on genital viral load. In a study among 2 521 African HIV serodiscordant couples, Baeten and colleagues demonstrated that higher GVL was associated with greater risk of HIV transmission – they found that a 1 $\log_{10}$ increase in GVL was associated with roughly a two-fold increased risk of HIV transmission (2.2 fold, 95% CI 1.60–3.04 for endocervi-cal swabs and 1.8, 95% CI 1.30–2.47 for semen) [76]. To date, data on GVL are limited in studies of the effect of co-infections and their treatment on HIV viral load. Indeed, GVL was not measured in any of the malaria or TB studies that we reviewed. However, it is plausible that compared to systemic infections, sexually transmitted infections increase GVL more than PVL due to local inflammatory factors in the genital tract. A key area for future research is elucidating the HIV viral load dynamics between plasma and the genital compartment for both systemic and sexually transmitted infections that modulate viral load. Improved approaches to accurately and reproducibly measure GVL will help answer these questions.

Conclusions

In combination with other interventions, prevention and treatment of some frequently recurrent or persistent HIV co-infections may offer important opportunities to reduce viral load, and thereby both curb HIV transmission and extend the period before ART is required. Our results suggest that malaria prevention and treatment should be evaluated as part of multi-component HIV prevention packages in appropriate epidemiologic contexts. While HSV-2 infection and active TB increase viral load, we do not yet have HSV-2 treatment

regimens with demonstrated efficacy in reducing HIV transmission, or TB treatment regimens capable of reducing HIV PVL. However, due to their prevalence and persistence, HSV-2 co-infections may be particularly important drivers of total community viral load over time. For HSV-2 infection, we have assumed that regimens with well-documented efficacy in reducing clinical symptoms and HSV-2 genital shedding would perform equally well in reducing HIV viral load and transmission. It is now clear that we must better understand the mechanisms responsible for augmented plasma and genital viral load, and retune HSV-2 treatment regimens accordingly. Similar approaches may well be key to development of strategies to reduce the impact of malaria or TB on HIV transmission. We must also better define the level of viral load reduction that we must achieve with these treatment regimens to limit HIV transmission.

Understanding the role of co-infection in the trajectory of HIVepidemics and in positive prevention is critical to the development of evidence-based HIV prevention and care policies and programs, and to the rational allocation of resources to implement them with the requisite quality and scale. As we develop multi-component combination packages of HIV prevention interventions tailored to people across the full range of HIV status and risk, prevention and treatment of co-infections may be particularly relevant for HIV-infected individuals who are not on ART, and may offer an important entry point for broader HIV prevention and care services in communities with high burdens of these intertwined diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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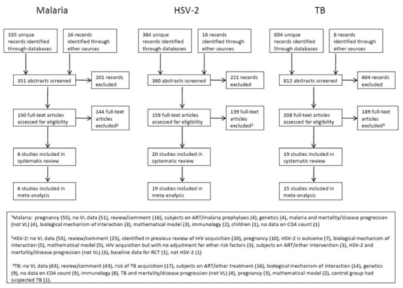

Fig. 1. Systematic review flowhart

[1]Malaria: pregnancy [55], no VL data [51], review/comment [16], subjects on ART/malaria prophylaxis [4], malaria and mortality/disease progression (not VL) [4], biological mechanism of interaction [3], mathematical model [3], Immunilogy [2], children [1], no data on CD4 count [1]. [2]HSV-2: no VL data [55], review/comment [25], identified in previous reivew of HIV acquisition [20], pregnancy [10], HSV-2 is outcome [7], biological mechanism of interaction [5], mathematical model [5], HIV acquisition but with no adjustment for other risk factors [3], subjects on ART/other intervention [3], HSV-2 and mortality/disease progression (not VL) [3], baseline data of RCT [1], not HSV-2 [1]. [3]TB: not VL data [63], review/comment [43], risk of TB acquisition [17], subjects on ART/other treatment [16], biological mechniasm of interaction [14], genetics [9], no data on CD4 count [9], Immunology [8], TB and mortaligy/disease progression (not VL) [4], pregnancy [3], mathematical model [2], control group hadsuspected TB [1].

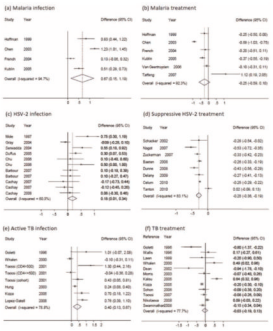

Fig. 2.

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Table 1

Association between malaria and HIV-1 viral load.

a) Malaria infection and HIV-1 plasma viral load

Study	Location	Period	Study Design	Endpoint/follow-up	Population	Malaria Diagnosis	Study Size	Mean difference (95% CI)	Viral load assay
Chen[1]	Guangzhou, China	no details	Challenge	Acute malaria (10 febrile episodes)	HIV-1 positive individuals infected with malaria	P. vivax + 10 febrile episodes	10	1.23 (1.01, 1.45)	bDNA
Hoffman[2]	Malawi	1997	Cross-sectional[a]	n/a	Hospital-based HIV-1 positive individuals with or without malaria	P. falciparum + malaria symptoms	89	0.83 (0.44, 1.22)	MASBA
Kublin[3]	Malawi	2000-1	Cohort	Acute malaria after median of 112 malaria-free days	HIV-1/malaria co-infected individuals recruited through HIV screening	P. falciparum + fever	36	0.42 (0.24, 0.60)	RT-PCR
French[4]	Uganda		Cohort	no details	Hospital-based HIV-1/malaria coinfected individuals	P. falciparum + fever	10	0.13 (−0.06, 0.32)	RT-PCR

b) Malaria treatment and HIV-1 plasma viral load

Study	Location	Period	Study Design	Endpoint/follow-up	Population	Malaria Diagnosis	Treatment	Study Size	Mean difference (95% CI)	Viral load assay
Chen[1]	Guangzhou, China	no details	Challenge	1 month post-treatment	HIV-1 positive individuals infected with malaria	P. vivax + 10 febrile episodes	Chloroquine	10	−0.89 (−1.03, −0.75)	bDNA
Hoffman[2]	Malawi	1997	Cohort	28 days post-treatment	Hospital-based HIV-1/malaria coinfected individuals	P. falciparum + malaria symptoms	SP	27	−0.25 (−0.50, 0.00)	MASBA
Kublin[3]	Malawi	2000–1	Cohort	mean 65 days post-treatment	HIV-1/malaria co-infected individuals recruited through HIV screening	P. falciparum + fever	SP	36	−0.37 (−0.55, −0.19)	RT-PCR
Tatfeng[5]	Benin City, Nigeria	2004–5	Cohort	9 days post-treatment	HIV-1/malaria co-infected individuals, recruited from clinics	P. falciparum + fever	Dihydroartemisinin	144	1.12 (0.19, 2.05)	RT-PCR
Van Geertruyden[6]	Ndola, Zambia	2004–5	Nested case-control	28 days post-treatment	HIV-1/malaria co-infected individuals, recruited from clinics	P. falciparum >1000 parasites/μl + fever	SP or AL	68	−0.10 (−0.31, 0.11)	RT-PCR
French[4]	Uganda		Cohort	no details	Hospital-based HIV-1/malaria coinfected individuals	P. falciparum + fever	SP	10	−0.20 (−0.51, 0.11)	RT-PCR

[a]Baseline measurements from cohort study

Table 2

Association between HSV-2 and HIV-1 viral load.

a) HSV-2 infection and HIV-1plasma viral load

Study	Location	Period	Study design	Endpoint/follow-up	Population	Study Size	Mean difference (95% CI)	Viral load assay
Barbour[7]	Sao Paulo, Brazil	no details	Cohort	Quarterly visits, median follow-up 381 days	HSV-2/HIV-1 coinfected adults	186	0.10 (−0.27, 0.47)	no details
					HIV-1 infected adults with acute HSV-2 infection	47	0.10 (−0.19, 0.39)	no details
Cachay[8]	San Diego, USA	1996-2005	Cross-sectional [1]	NA	HSV-2 seropositive men with incident HIV-1 infection	85	−0.17 (−0.73, 0.44)	RT-PCR
					HSV-2 seropositive men with early HIV-1 infection	209	−0.12 (−0.45, 0.20)	RT-PCR
Cachay[9]	San Diego, USA	1996-2005	Cohort	Median follow-up 779 days	HIV-1 infected men with acute HSV-2 infection	9	0.08 (−0.30, 0.46)	RT-PCR
Chu[10]	Bangkok, Thailand	2000–1	Cross-sectional [2]	NA	HIV-1/HSV-2 coinfected men	69	0.10 (−0.39, 0.59)	NASBA
					HIV-1/HSV-2 coinfected women	71	0.50 (0.03, 0.97)	NASBA
Duffus[11]	2 sites, Uganda	1997–9	Cross-sectional	NA	HIV-1/HSV-2 coinfected individuals	339	0.30 (0.07, 0.53)	no details
Gray[12]	Rakai, Uganda	1994–8	Cross-sectional	NA	HIV-1/HSV-2 coinfected individuals	345	−0.09 (−0.28, 0.10)	RT-PCR
Mole[13]	Palo Alto, USA	1991–4	Cohort	Single endpoint, 30–45 days	HIV infected males, with acute or reactive HSV-2 infection	8	0.75 (0.30, 1.19)	bDNA
Serwadda[14]	Rakai, Uganda	1994–8	Nested case-control	NA	Acute HIV-1 infected individuals, from a CRT of STI control	219	0.55 (0.16, 0.94)	RT-PCR

b) HSV-2 treatment and HIV-1 plasma viral load

Study	Location	Period	Study Design	Population	Therapy	Endpoint/follow-up	Study Size	Mean difference (95% CI)	VL assay
Suppressive therapy trials									
Baeten[15]	Lima, Peru	2005	RCT	HIV-1/HSV-2 seropositive women	Suppressive (valacyclovir 500 mg twice daily for 8 weeks)	Weekly visits, 18 weeks (cross-over)	20	−0.26 (−0.33, −0.19)	RT-PCR
Celum[16]	14 sites in 7 countries in Africa	2004–7	RCT	Heterosexual HIV discordant couples	Suppressive (acyclovir 400 mg twice daily for 24 months)	Quarterly visits, 24 months	3302	−0.25 (−0.29, −0.22)	RT-PCR
Delany[17]	Johannesburg, South Africa	2005–6	RCT	HIV-1/HSV-2 seropositive women	Suppressive (acyclovir 400 mg twice daily for 3 months)	Monthly visits, 3 months	288	−0.27 (−0.41, −0.13)	RT-PCR
Dunne[18]	Chiang Rai, Thailand	no details	RCT	HIV-1/HSV-2 coinfected women	Suppressive (acyclovir 800 mg twice daily for 1 month)	Monthly visits, 3 months (cross-over)	128	−0.43 (−0.56, −0.29)	RT-PCR
Nagot[19]	Burkino Faso	2004–5	RCT	HIV-1/HSV-2 coinfected women,	Suppressive (valacyclovir twice daily for 3 months)	Thrice weekly visits, 3 months	136	−0.53 (−0.72, −0.35)	RT-PCR
Schacker[20]	Seattle, USA	1994–6	Cohort	Facility-recruited HIV/HSV-2 coinfected individuals	Suppressive (acyclovir 800 mg thrice daily for 8 weeks)	Weekly visits, 8 weeks	12	−0.28 (−0.54, −0.02)	bDNA
Tanton[21]	Tanzania	2004, 2006	RCT	HIV-1/HSV-2 coinfected women attending mobile clinic	Suppressive (acyclovir 400 mg twice daily until censoring)	6, 12 and 24 month visits, 24 months	419	0.02 (−0.09, 0.13)	RT-PCR
Zuckerman[22]	Lima, Peru	2003–4	RCT	HIV-1/HSV-2 coinfected MSM	Suppressive (valacyclovir 500 mg twice daily for 8 weeks)	Weekly visits, 18 weeks (cross-over)	20	−0.33 (−0.42, −0.23)	RT-PCR

b) HSV-2 treatment and HIV-1 plasma viral load

Study	Location	Period	Study Design	Population	Therapy	Endpoint/follow-up	Study Size	Mean difference (95% CI)	VL assay
Episodic therapy trials									
Mayaud[23]	3 sites in Ghana/CAR	2003–7	RCT	HIV-1 infected women with HSV-2 ulcers	Episodic (acyclovir 400 mg thrice daily for 5 days)	Single endpoint, 28 days	93	0.09 (−0.10, 0.30)	RT-PCR
Mole[13]	Palo Alto, USA	1991–4	Cohort	HIV infected males, with HSV-2 ulcers	Episodic (acyclovir 200 mg 5 times a day for 10 days)	Single endpoint, 30–45 days	8	−0.48 (−0.77, −0.20)	bDNA
Paz-Bailey[24]	Gauteng, South Africa	2005–6	RCT	HIV-infected males with HSV ulcers	Episodic (acyclovir 400 mg thrice daily for 5 days)	Single endpoint, 28 days	295	−0.12 (−0.23, −0.01)	RT-PCR
Phiri[25]	Lilongwe, Malawi	2004–6	RCT	HIV-1 infected individuals with HSV-2 ulcers	Episodic (acyclovir 800 mg twice daily for 5 days)	Single endpoint, 28 days	244	0.09 (−0.08, 0.26)	RT-PCR

c) HSV-2 treatment and HIV-1 genital viral load

Study	Location	Period	Population	Therapy	Endpoint/Follow-up	Specimen	Study Size	Mean difference (95% CI)	VL assay
Suppressive therapy trials									
Baeten[15]	Lima, Peru	2005	HIV-1/HSV-2 seropositive women	Suppressive (valacyclovir 500 mg twice daily for 8 weeks)	Weekly visits, 18 weeks (cross-over)	Self-collected genital swab	20	−0.67 (−1.08, −0.26)	RT-PCR
						Endocervical swab specimen	20	−0.35 (−0.46, −0.25)	RT-PCR
Delany[17]	Johannesburg, South Africa	2005–6	HIV-1/HSV-2 seropositive women	Suppressive (acyclovir 400 mg twice daily for 3 months)	Monthly visits, 3 months	Cervicovaginal lavage	288	−0.13 (−0.28, 0.03)	RT-PCR
Dunne[18]	Chiang Rai, Thailand	no details	HIV-1/HSV-2 coinfected women	Suppressive (acyclovir 800 mg twice daily for 1 month)	Monthly visits, 3 months (cross-over)	Cervicovaginal lavage	128	−0.32 (−0.48, −0.19)	RT-PCR
Nagot[26]	Burkino Faso	2004–5	HIV-1/HSV-2 coinfected women	Suppressive (valacyclovir twice daily for 3 months)	Thrice weekly visits, 3 months	Cervicovaginal lavage	136	−0.29 (−0.44, −0.15)	RT-PCR
Tanton[21]	Tanzania	2004, 2006	HIV-1/HSV-2 seropositive women	Suppressive (acyclovir 400 mg twice daily until censoring)	6, 12 and 24 month visits, 24 months	Cervicovaginal lavage	425	0.03 (−0.11, 0.16)	RT-PCR
Zuckerman[22]	Lima, Peru	2003–4	HIV-1/HSV-2 coinfected men	Suppressive (valacyclovir 500 mg twice daily for 8 weeks)	Thrice weekly visits, 18 weeks (cross-over)	Anoscopy with Snostrips	20	−0.16 (−0.25, −0.07)	RT-PCR
Zuckerman[27]	Lima, Peru	no details	HIV-1/HSV-2 coinfected men	Suppressive (valacyclovir 500 mg twice daily for 8 weeks)	Weekly visits, 18 weeks (cross-over)	Semen	19	−0.29 (−0.48, −0.11)	RT-PCR
Episodic therapy trials									
Mayaud[23]	3 sites in Ghana/CAR	2003–5	HIV-1 infected women with HSV-2 ulcers	Episodic (acyclovir 400 mg thrice daily for 5 days)	Day 7, 28 days	Cervicovaginal lavage	89	−0.06 (−0.40, 0.30)	RT-PCR
Paz-Bailey[24]	Gauteng, South Africa	2005–6	HIV-1 infected men with HSV-2 ulcers	Episodic (acyclovir 400 mg thrice daily for 5 days)	Day 7, 28 days	Ulcer lavage	193	−0.82 (−1.45, −0.18)	RT-PCR
Phiri[25]	Lilongwe, Malawi	2004–6	HIV-1 infected men with HSV-2 ulcers	Episodic (acyclovir 800 mg twice daily for 5 days)	Day 14, 28 days	Semen	62	−0.14 (−0.72, 0.44)	RT-PCR
			HIV-1 infected women with genital ulcers			Cervical swab	41	−0.08 (−0.66, 0.50)	

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Table 3

Association between TB and HIV-1 viral load.

a) TB infection and HIV-1 plasma viral load

Study	Location	Period	Study design	Population	Follow-up	TB	Study Size	Mean difference (95% CI)	VL assay	TB diagnosis
Goletti[28]	3 sites in USA and Italy	no details	Cohort	HIV-1/TB co-infected patients	6–10 months	Active	2	1.01 (−0.07, 2.08)	bDNA	Culture positive for MTB
Hung[29]	Taiwan	1994-2002	Cross-sectional[2]	HIV infected individuals		Active	276	0.24 (0.08, 0.40)	RT-PCR	Culture positive for MTB
Kizza[30]	Kampala, Uganda	2000–1	Cross-sectional[2]	HIV-1/TB-coinfected subjects		Active	40	0.70 (0.18, 1.22)	RT-PCR	Culture positive for MTB
Lopez-Gatell[31]	USA	1984-2005	Cohort	HIV-1/TB-coinfected men	Median 5.4 years	Active	15	0.76 (0.39, 1.10)	RT-PCR	Culture, cytology, clinical or radiology confirmed
Manoff[32]	Baltimore, USA	1990–4	Nested case-control	HIV-1 infected subjects		Latent	6	−0.14 (−0.94, 0.66)	bDNA	TST >5mm
Mawa[33]	Entebbe, Uganda	2000	Nested case-control	HIV-1 infected subjects		Latent	29	−0.5 (−0.99, −0.01)	RT-PCR	TST >5mm
Toossi[34]	Kampala, Uganda	1993–5	Cross-sectional	HIV-1/TB coinfected subjects with CD4<500		Active	51	−0.04 (−0.36, 0.28)	RT-PCR	Culture positive for MTB
			Cross-sectional	HIV-1/TB coinfected subjects with CD4>500		Active	23	1.30 (0.44, 2.16)	RT-PCR	Culture positive for MTB
			Cohort	HIV-1 infected subjects who developed pulmonary TB	6 months	Active	10	0.43 (0.05, 0.81)	RT-PCR	Culture positive for MTB
Whalen[35]	Kampala, Uganda	1993–4	Nested case-control	HIV infected individuals with and without tuberculosis		Active	40	−0.10 (−0.31, 0.11)	RT-PCR	Culture positive for MTB

b) TB treatment and HIV-1 plasma viral load[a]

Study	Location	Period	Population	Therapy	Follow-up[b]	TB	Study Size	Mean difference (95% CI)	VL assay	TB diagnosis
Dean[36]	South-East UK	1996–9	HIV-1/TB co-infected patients	Multiple	12 months	Active	20	−0.94 (−1.78, −0.10)	Multiple	Culture positive for MTB

b) TB treatment and HIV-1 plasma viral load[a]

Study	Location	Period	Population	Therapy	Follow-up[b]	TB	Study Size	Mean difference (95% CI)	VL assay	TB diagnosis
Goletti[28]	3 sites in US and Italy	no details	HIV-1/TB co-infected patients		3–10 months	Active	5	−0.80 (−1.37, −0.22)	bDNA	Culture positive for MTB
Kalou[37]	Abidjan, Ivory Coast	1995–8	HIV-1 infected patients with newly diagnosed TB	2HRZ/4HR	12 months	Active	44	0.64 (0.32, 0.96)	RT-PCR	2 positive sputum smears
Kizza[30]	Kampala, Uganda	2000–1	HIV-1/TB-coinfected subjects	2HRZE/4HR	6 months	Active	27	−0.20 (−0.30, −0.10)	RT-PCR	Culture positive for MTB
Lawn[38]	Ghana	no details	HIV-1/TB coinfected subjects	2SHRZ/6HE	3 months	Active	20	−0.20 (−0.90, 0.50)	RT-PCR	At least 2 out of 3 positive sputum smears
Morris[39]	South Africa	1997–8	HIV-1/TB-coinfected subjects	2HRZE/4HR	6 months	Active	57	−0.07 (−0.40, 0.26)	RT-PCR	Sputum positive for AFB and radiology
Nikolaeva[40]	Ukraine	no details	HIV-1/TB-coinfected subjects	2HRZSE	2 months	Active	20	0.09 (−0.03, 0.22)	RT-PCR	Culture positive for MTB, or positive sputum smear and radiology
Swaminathan[41]	Chennai, India	1999-2000	HIV/TB coinfected subjects	$2EHRZ_3/4RH_3$	6 months	Active	14	−0.15 (−1.03, 0.72)	RT-PCR	Sputum smear positive for AFB, or radiology/ histopathology
Schon[42]	Gondor, Ethiopia	no details	HIV-1/TB-coinfected subjects	2HZES/6HE	2 months	Active	20	−0.09 (−0.38, 0.20)	RT-PCR	Sputum smear positive for AFB
Toossi[43]	Kampala, Uganda	no details	HIV-1/TB-coinfected subjects		6 months	Active	15	−0.08 (−0.26, 0.09)	RT-PCR	Culture positive for MTB
Wallis[44]	Kampala, Uganda	up to 1995	HIV-1/TB-coninfected subjects	2HZER/6HR	12 months	Active	20	0.17 (−0.27, 0.61)	RT-PCR	Culture positive for MTB
Whalen[35]	Kampala, Uganda	1993–4	HIV infected individuals with and without tuberculosis	2HRZE/6HR	12 months	Active	20	0.49 (0.02, 0.96)	RT-PCR	Culture positive for MTB

[a] All are cohort studies.

[b] Time since diagnosis.

Details about these studies in column 1 (study column) can be found in SDC