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Modelling the impact of early antiretroviral therapy for adults coinfected with HIV and hepatitis B or C in South Africa

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Abbreviations: HIV: human immunodeficiency virus, HBV: hepatitis B virus, HCV: hepatitis C virus, ART: antiretroviral therapy, TDF: tenofovir, 3TC: lamivudine, FTC: emitricitabine, DALY: disability-adjusted life-year, CC: compensated cirrhosis, DC: decompensated cirrhosis, HCC: hepatocellular carcinoma, PMTCT: prevention of mother-to-child transmission of HIV, HBIG: hepatitis B immune globulin, HBsAg: hepatitis B virus surface antigen, HBeAg: hepatitis B virus e antigen

Key words: human immunodeficiency virus, antiretroviral therapy, coinfection, hepatitis B virus, hepatitis C virus

ABSTRACT

Objective There has been discussion over whether individuals coinfected with HIV and hepatitis C virus (HCV) or hepatitis B virus (HBV) (<30% of all people living with HIV) should be provided early HIV antiretroviral therapy (ART). We assess the relative benefits of providing early (CD4 count <500 cells/mm^3) or immediate ART to adults coinfected with HCV and HIV or HBV and HIV compared with HIV-monoinfected adults. We evaluate individual outcomes

(HIV disease and liver disease progression) and preventive benefits in a generalized HIV epidemic setting.

Methods We modelled disease progression for HIV-monoinfected, HBV- and HIV-coinfected and HCV- and HIV-coinfected adults for differing ART eligibility thresholds (CD4 count <350 cells/mm^3, "early ART" at CD4 count <500 cells/mm^3 and immediate ART when infected). We report disability-adjusted life-years averted per 100 person-years on ART as a measure of the health benefits generated from ART. Sensitivity analysis explored the impact on sexual HIV and vertical HIV, HCV and HBV transmission.

Results For HBV- and HIV-coinfected adults, early ART generates 9% greater health benefits per year on ART (48 DALYs averted per 100 person-years on ART) than for HIV-monoinfected adults (44 DALYs averted per 100 person-years on ART). In addition, early ART could prevent 25% of HIV vertical transmission, 47% of HIV sexual transmission and 32% of HBV vertical transmission. Early ART for HCV and HIV coinfection generates 10% fewer health benefits (40 DALYs averted per 100 person-years on ART) than for HIV monoinfection, unless ART reduces progression to cirrhosis by >70% (33% in the base case).

Conclusions The additional therapeutic benefits of ART for HBV-related liver disease results in ART generating more health benefits among HBV- and HIV-coinfected adults than HIV-monoinfected individuals, whereas less health benefits are generated among HCV and HIV coinfection in a generalized HIV epidemic setting.

Introduction

Worldwide, an estimated 30% of people living with HIV are coinfected with either hepatitis C virus (HCV) or hepatitis B virus (HBV), with 4–5 million people living with HIV coinfected with HCV and 2–4 million coinfected with HBV (1,2). Adults living with HIV who are coinfected with HBV (HBV- and HIV-coinfected) or HCV (HCV- and HIV-coinfected) experience increased liver disease progression *(3–5)* and mortality *(6)*. However, access to HBV or HCV testing and treatment remains very limited in low- and middle-income countries, so few are diagnosed and treated for their hepatitis infection *(7)*. There has been debate as to the optimal timing of antiretroviral therapy (ART) initiation among coinfected adults because of additional harms due to HIV infection and the potential benefits of ART on liver disease progression. However, the benefit of providing ART to coinfected adults compared with HIV-monoinfected adults has not been quantified, which is necessary to inform rational use of resources and good clinical practice.

In the past decade, policy changes and substantial increases in funding have resulted in widespread scale-up of ART for people living with HIV in low- and middle-income countries. At the end of 2011, approximately 8 million people in low- and middle-income countries were receiving ART – a 25-fold increase since 2002 *(8)*. In 2010, the World Health Organization (WHO) guidelines recommended ART initiation for HIV-monoinfected adults at CD4 counts <350 cells/mm^3 or with WHO clinical stage 3 or 4 disease *(9)*. Recent data have shown that early ART initiation (CD4 counts above 350 cells/mm^3) in HIV-monoinfected individuals can reduce onwards HIV transmission and may have individual therapeutic benefits *(10,11)*. As a result, the

2013 WHO guidelines now recommend ART initiation for adults living with HIV with a CD4 count <500 cells/mm^3. However, despite continued expansion of ART eligibility, uptake remains relatively low in many settings. As of 2011, only 54% of those eligible for ART with a CD4 count <350 cells/mm^3 were receiving it worldwide *(12)*.

For HBV- and HIV-coinfected adults, the 2010 and 2013 WHO guidelines recommend immediate ART initiation regardless of CD4 count among those with severe chronic liver disease due to accelerated liver disease progression and the dual HIV and HBV benefits of the ART regimens that contain anti-HBV treatment *(9)*. The guidelines recommend ART containing a combination of tenofovir (TDF) and either lamivudine (3TC) or emtricitabine (FTC). By contrast, HCV- and HIV-coinfected adults have not historically been given priority for immediate ART but are being considered because of increasing evidence that ART slows liver-disease progression in HCV and HIV coinfection *(4,13)*, even though ART does not contain anti-HCV active agents. Nevertheless, uncertainty exists as to the magnitude of the impact of ART on HCV disease progression, and it was decided there was insufficient evidence for a benefit of ART at higher CD4 counts to recommend immediate ART initiation for the 2013 WHO guidelines.

We aim to use a mathematical model to evaluate the relative benefits of early ART (at CD4 <500 cells/mm^3) and immediate ART regardless of CD4 count among adults with HCV and HIV coinfection or HBV and HIV coinfection compared with HIV monoinfection in a generalized HIV epidemic setting. We evaluate individual outcomes (HIV and liver disease progression and mortality) and additional preventive benefits on vertical and horizontal transmission.

Methods

Mathematical models and parameterization

A deterministic, compartmental model was developed to simulate disease progression of HIV-monoinfected, HBV- and HIV-coinfected and HCV- and HIV-coinfected adults with differing CD4 eligibility thresholds for ART initiation (schematics in Fig. 1). We aimed to compare the full potential health benefits of ART between cohorts and therefore considered an idealized scenario in which all individuals are diagnosed and promptly initiate ART when eligible. The model simulated a cohort of coinfected adults followed until death. The model was parameterized to South Africa (background and HIV mortality, fertility, and estimated serodiscordancy rates, Annex Table 1). Individuals were assumed to become HIV infected at age 25 years. Due to a lack of data surrounding the age of acquiring HCV in generalized HIV epidemics driven by sexual transmission (in which HCV transmission routes are unknown but include iatrogenic transmission *(14)*), it was assumed that individuals are infected with HIV and HCV at a similar time. Individuals in this setting will likely have acquired HBV at birth or early childhood, but childhood liver disease progression rates are very slow, and few will have progressed to cirrhosis by 25 years *(15,16)*. Accordingly, both coinfection models assumed that adults are in the mildest hepatitis stage (chronic HBV and mild HCV) when they acquire HIV. We assumed that individuals would not be treated for their hepatitis infection specifically. For the sensitivity analysis, the model included HIV transmission to serodiscordant stable sexual partners and vertical transmission of HIV and HBV or HCV (see Annex).

HIV monoinfection model

For HIV monoinfection, individuals progress through HIV disease stages (CD4 >500, 350–500, 200–350 and <200 cells/mm^3) to HIV-related death and experience background mortality from each stage. All individuals start in the highest CD4 stage; ART was assumed to slow HIV progression rates by four-fold for each disease stage at the base case *(17–21)*. We assumed that everyone continues receiving ART after initiation to compare the potential full benefits of ART.

HCV and HIV coinfection model

For HCV and HIV coinfection, we simulated coinfection progression among adults with chronic HCV (HCV RNA+), where liver disease stages (mild HCV, moderate HCV, compensated cirrhosis, decompensated cirrhosis and hepatocellular carcinoma) were stratified by HIV stage. Age-stratified HCV monoinfection progressing to cirrhosis rates *(22,23)* were accelerated in HCV and HIV coinfection by 2.5-fold, 95% confidence interval (95% CI) 1.8–3.4) *(4)*. Death rates from decompensated cirrhosis were also elevated in coinfection (by 2.3-fold, 95% CI 1.5–3.4) *(24)*. ART was assumed to reduce progression to cirrhosis by 33% (from a recent meta-analysis *(4)*) at the base case. For the base case, we assumed that HCV does not affect HIV progression *(6)* or response to ART *(6,25–29)* but explored this in the sensitivity analysis.

HBV and HIV coinfection model

The HBV and HIV model simulated progression through liver disease stages (chronic HBV (defined as HBV surface antigen positive, HBsAg+), compensated cirrhosis, decompensated cirrhosis and hepatocellular carcinoma), each stratified by HIV stage. Given that the impact of

HBV in immune-compromised individuals is driven by the level of HBV viraemia and oral antiviral agents are highly effective in both HBV e antigen (HBeAg)-positive and -negative individuals, we used a simplified model of HBV and HIV coinfection progression in which HBV viraemia was the dominant influence on disease. We modelled a homogeneous population with transition rates weighted by progression for high and low HBV viraemia. We recognize that this ignores subtle differences in outcomes between HBeAg+ and HBeAg– active disease, but given the uncertainty and overlap surrounding coinfection transition rates in these two different disease states, we believe our model uses the most appropriate approach with available data.

We assumed coinfection accelerates progression to cirrhosis by 4.6-fold (95% CI 1.5–13.7) for those with high HBV viraemia and CD4 <200 cells/mm^3 *(5,30)*; for CD4 >200 cells/mm^3, progression was equal to monoinfection *(30,31)*. It was assumed that, in accordance with current WHO guidelines, HBV- and HIV-coinfected individuals would receive ART containing TDF and 3TC or FTC. These regimens were assumed to reduce all liver-disease progression rates (by 63–90% depending on disease transition) except from hepatocellular carcinoma to death *(32–34)*. Although some data indicate that tenofovir may reverse fibrosis *(32,35)*, we conservatively assumed that this does not occur. We reduced the impact of tenofovir on progression to cirrhosis among coinfected individuals with CD4 <200 cells/mm^3 (elevating progression in this group by 2.3-fold (95% CI 1.5–5.3)) *(36)*. It was assumed that individuals would be switched to second-line ART regimens containing anti-HBV treatment if necessary. For the base case, we assumed no discontinuation of therapy because no evidence indicates that discontinuation rates differ by coinfection status and reported discontinuation rates are negligible *(32,37)*. We assumed that HBV does not affect HIV progression or response to ART *(31,38,39)*.

Individual health impact evaluation

We evaluated the individual impact of "early ART" initiation at CD4 <500 cells/mm^3 (intervention) compared with ART initiation at CD4 <350 cells/mm^3 (baseline) for each cohort (first excluding transmission benefits). Additionally, we evaluated the impact of immediate ART regardless of CD4 count (intervention) compared with early ART initiation at CD4 <500 cells/mm^3 (baseline). To consider the impact of uncertainty in underlying parameters, we performed multivariate probabilistic uncertainty analysis, in which 1000 parameter sets were randomly sampled from the parameter distributions in Annex Tables 1 and 2. All parameters were sampled except background mortality rates, the impact of ART on HIV disease progression and the impact of ART on progression to cirrhosis for HCV- and HIV-coinfected individuals (a conservative point estimate was used for the base case and increased in the univariate sensitivity analysis). For each of the 1000 parameter sets, the model was run for the baseline and intervention analysis, with a lifetime time horizon. The model tracked life expectancy, health benefits measured in averted disability-adjusted life-years (DALYs) and person-years on ART. Disability weights were taken from the 2010 Global Burden of Disease estimates *(40)* (Annex Table 2). For coinfected individuals, disability weights were compounded multiplicatively: disability weight=1– ((1 – HIV disability weight) × (1 – hepatitis disability weight)). For all outputs, the median and 95% interval values (taken from outputs generating the 2.5% and 97.5% values) were generated from the distribution in outputs from the multivariate uncertainty sampling runs.

We report DALYs averted per 100 person-years on ART as a measure of the incremental health benefits of a given ART provision strategy; both DALYs and person-years of ART were discounted at 3% per year at baseline *(41)*. We also report the ratio of DALYs averted per 100 person-years on ART for HCV and HIV or HBV and HIV coinfection over HIV monoinfection, in which a ratio of >1 indicates that ART for HCV and HIV or HBV and HIV coinfection generates more health benefits (DALYs averted) per 100 person-years on ART than in HIV monoinfection. Linear regression analysis of covariance (ANCOVA) was performed on the DALYs averted per 100 person-years on ART, and the proportion of the sum-of-squares contributed by each parameter was calculated to estimate the importance of individual parameters to the overall uncertainty. The model was coded and solved in MATLAB (version R2010a).

Sensitivity analysis on individual impact

For all 1000 parameter sets, we reran the simulations varying a single parameter to explore the impact of: discount rate (0% or 6% per year, compared with 3% at base case), discontinuation from ART for coinfected individuals only (1% or 3% annually, compared with 0% at base case) and a 20-year time horizon (lifetime at base case). Due to uncertainty in a number of parameters, we also explored hypothesized associations found in the literature: impact of ART on reducing HCV liver disease progression by up to 80% (33% at base case but evidence of up to 67% *(13)*); impaired ART impact on HIV by 25% for coinfected individuals (three-fold reduction in progression compared with four-fold at base case) *(42–44)*, or 5% if started in the progressed liver-disease stage (moderate HCV- or HBV-compensated cirrhosis). Finally, we explore the

impact if all the HBV- and HIV-coinfected individuals have high levels of viraemia (33% at base case).

Analysis of impact on transmission

We explored how ART affects the sexual transmission of HIV to long-term serodiscordant partners. ART was assumed to reduce heterosexual transmission rates by 96% *(10)* at base case (lowered to 70% as a sensitivity analysis). No data were available to inform HIV transmission rates from coinfected individuals in serodiscordant partnerships; we assumed that transmission rates are equal to monoinfection, since no evidence indicates that HIV viral loads are elevated in HBV or HCV coinfection *(45,46)*.

We also evaluated the impact on vertical transmission of HIV, HCV and HBV in a cohort of women (full details in Annex). We assumed that all mothers receive initiatives for preventing mother-to-child transmission (PMTCT) *(47)*. All HBV- and HIV-coinfected mothers were assumed to receive vaccination and hepatitis B immunoglobulin (HBIG). South Africa's 2010 guidelines do not recommend TDF-containing PMTCT *(47)*, but TDF-PMTCT became available in South Africa in April 2013 *(48)*, so we performed two analyses exploring the impact of PMTCT containing or not containing TDF. We assumed no vertical transmission of HBV from HBeAg-seroconverted mothers, 23% HBV transmission from mothers with high HBV viraemia where PMTCT regimens do not include TDF *(49)* and a 0.31 relative risk of transmitting HBV (95% CI 0.15–0.63) with TDF-PMTCT or lifelong ART compared with PMTCT without TDF *(50)*. HCV vertical transmission from coinfected mothers was assumed to be 1.9-fold (95% CI 1.4–2.7) *(51)* higher than in HCV monoinfection. The impact of ART on HCV vertical

transmission is unclear; ART is known to increase HCV viral loads *(52–54)*, but one study reported a reduction in transmission on ART *(55)*, so we assumed no ART impact at base case.

Results

Life expectancy gains

In South Africa, HBV and HIV or HCV and HIV coinfection marginally reduces life expectancy at age 25 years compared with HIV monoinfection both in the absence of ART and under all ART eligibility scenarios (by <3 years per individual, Table 1). A change from ART at a CD4 count of <350 cells/mm^3 to early ART (CD4 <500 cells/mm^3) results in slightly more impact on life expectancy in HBV and HIV coinfection as compared with HIV monoinfection (0.4 years (8%) greater), whereas the impact is 0.7 years less (14% lower) in HCV and HIV coinfection compared with HIV monoinfection.

Impact of ART on individual benefits

Table 2 and Fig. 2 summarize the individual impact of incremental eligibility changes (early ART at CD4 <500 cells/mm^3 versus CD4 <350 cells/mm^3 or immediate ART regardless of CD4 count compared with CD4 <500 cells/mm^3). For both coinfection cohorts, most deaths (>46%) are due to HIV under all ART eligibility thresholds; expanding ART eligibility progressively averts HIV deaths (by a relative 21% or 15% with early ART for HCV and HIV or HBV and HIV coinfection, respectively, and a further 11% or 7% with immediate ART, respectively). Because the direct effect of ART on HBV progression is strong, early or immediate ART for HBV- and HIV-coinfected people decreases HBV-related mortality (by a relative 28% with early ART and a further 17% with immediate ART). However, ART for HCV- and HIV-coinfected

individuals increases liver-related deaths (by a relative 34% or 10% with early or immediate ART, respectively), since individuals survive longer and succumb to liver-related mortality because ART impact on liver progression is weaker.

Early ART for HBV- and HIV-coinfected individuals averts more lifetime DALYs than for HIV monoinfection (5.1 and 4.8 DALYs averted per HBV- and HIV-coinfected and HIV monoinfected adult, respectively (Fig. 2a)). Treatment of HBV and HIV coinfection provides 9% greater health benefit in DALYs averted per 100 person-years on ART than for HIV monoinfection (48 and 44 DALYs averted per 100 person-years on ART for HBV and HIV coinfection and HIV monoinfection, respectively (Fig. 2b)). By contrast, early ART for HCV- and HIV-coinfected individuals averts fewer DALYs overall (3.9 per HCV- and HIV-coinfected adult) and provides less health benefit per year on ART (40 DALYs averted per 100 person-years on ART). For each sampled projection, Fig. 3c shows the ratio of the DALYs averted per 100 person-years on ART of coinfection over monoinfection; in 94% of the simulations, early treatment for HBV and HIV coinfection provided more DALYs averted per 100 person-years on ART than for HIV monoinfection, whereas early ART for HCV and HIV coinfection never provided more DALYs averted per 100 person-years on ART. Similar relative efficiency holds for immediate ART. Immediate ART (compared with earlier ART) provides slightly more DALYs averted per 100 person-years on ART (by 13–14%) than early ART (compared with CD4 <350 cells/mm^3) for all cohorts.

In the ANCOVA analysis for HCV and HIV coinfection, the variability in DALYs averted per 100 person-years on ART was primarily due to uncertainty in progression rates to cirrhosis

(contributing 42% of variability) and disutility weights for ART and compensated cirrhosis (48%). For HBV and HIV coinfection, variability was primarily due to uncertainty in disutility weights for ART and chronic HBV (contributing 72%) the rate of chronic HBV to compensated cirrhosis with CD4 >200 cells/mm^3 (16%).

Sensitivity analysis

Univariate sensitivity analysis on the health benefit per 100 person-years on ART (DALYs averted per 100 person-years on ART) with early ART at CD4 <500 cells/mm^3 indicates that variations in assumptions regarding discount rate (0% or 6% compared with 3% at base case), and 1% annual discontinuation from ART among coinfected individuals (0% at base case) changed the absolute efficiency but not the relative efficiency of treating coinfected or monoinfected individuals (Fig. 3a). However, at a 3% annual discontinuation rate among HBV- and HIV-coinfected individuals, ART became slightly less beneficial than for HIV monoinfection (where no discontinuation was assumed). At a 20-year time horizon, ART for HBV- and HIV-coinfected individuals was still more beneficial, but benefit was equal between HCV- and HIV-coinfected individuals and HIV monoinfected individuals. If ART impact on HIV is impaired in coinfection (3-fold increase of HIV-survival, base-case 4-fold), then ART became less beneficial for both coinfected cohorts and roughly equal between HBV and HIV coinfection and HIV monoinfection. For HCV- and HIV-coinfected individuals, ART at CD4 <500 cells/mm^3 (compared with CD4 <350 cells/mm^3) only becomes more beneficial for than for HIV monoinfection if ART reduces the progression to cirrhosis by >70% (Fig. 3b). Negligible (<1%) impact change was seen if 5% of the cohort started in a more progressed liver-disease

stage; if all HBV- and HIV-coinfected individuals have high HBV viraemia, benefit was marginally increased (by <4%) compared with baseline (not shown).

Impact of ART on HIV sexual transmission

Changing ART eligibility from CD4 <350 cells/mm^3 to early ART at CD4 <500 cells/mm^3 was estimated to avert 47–48% of HIV infections among stable partners (35–36 people acquiring HIV out of a cohort of 1000 coinfected people). Including the DALYs averted from these prevented transmissions increased the benefit of ART by 19–24%, with ART for HBV- and HIV-coinfected adults still resulting in greater benefit than for HIV monoinfection (Fig. 3a). Further increasing the eligibility from early ART to immediate ART averts 49–50% of the remaining HIV transmission among partners (20 people acquiring HIV infection). Reducing the impact of ART on HIV transmission (to 70%) lowered impact for all cohorts but did not change relative impact (not shown).

Impact of ART on vertical transmission

Early or immediate ART for a cohort of women living with HIV is projected to increase the total number of babies due to increased life expectancy but reduces the proportion of infants infected with HIV (2.0%, 1.5% and 1.3% with CD4 <350 or <500 cells/mm^3 or immediate ART guidelines in all cohorts (Fig. 3c)). Additionally, if PMTCT does not contain TDF (South Africa's 2010 guidelines *(47)*), then expanding ART eligibility for HBV- and HIV-coinfected mothers reduces the relative proportion of HBV vertical transmissions by 32% with early ART (from 4.4% with ART at CD4 <350 cells/mm^3 to 3.0% with ART at CD4 <500 cells/mm^3) and a further 20% (to 2.4%) with immediate ART (Fig. 3d). However, if PMTCT contains TDF

(available in South Africa from April 2013), no additional impact is achieved with lifelong ART. ART was not assumed to reduce HCV transmission from coinfected mothers, so no impact was seen on HCV vertical transmissions (Fig. 3d, 11.8% of infants HCV infected for all scenarios).

Discussion

Main findings

Our comparative modelling analysis shows, for the first time, that in a generalized HIV epidemic setting such as South Africa, early ART at CD4 <500 cells/mm^3 has greater health benefits per year on ART (by 9%) for HBV- and HIV-coinfected adults than for HIV monoinfected individuals, in addition to preventing vertical HBV transmission when PMTCT does not contain TDF. By contrast, early ART for HCV- and HIV-coinfected people has fewer health benefits compared with early ART for HIV monoinfection, unless ART reduces liver-disease progression by >70%.

Comparison with other studies and limitations

Although modelling studies have explored the impact of HCV antiviral therapy for HCV and HIV coinfection *(56–58)* and HBV treatment among HBV monoinfection *(59–61)*, to our knowledge our study is the first analysis to compare how ART affects liver-disease progression among HBV and HIV or HCV- and HIV-coinfected individuals.

These projections are based on a theoretical model and subject to several limitations. First, several parameters are uncertain. Liver-disease progression rates were unavailable for coinfected

African populations and may differ from the estimates used from primarily Asian populations. Among HBV- and HIV-coinfected individuals, there is uncertainty in outcomes and transition rates between HBeAg-negative and -positive disease. We used wide sampling bounds to account for this uncertainty, and our analysis indicated that projections were sensitive to cirrhosis progression rates; future research should target this area of uncertainty as a priority. For HCV and HIV coinfection, evidence on ART impact is variable, with studies reporting point estimates of 33–67% reduction in progression to cirrhosis *(4,13)*. Our results indicate an impact of >70% could make treating HCV and HIV coinfection more beneficial than HIV monoinfection. For HBV and HIV coinfection, the impact of combination TDF therapy was taken from small-scale studies or estimated from monoinfection studies. A small, non-randomized study has shown improvement in fibrosis among coinfected individuals *(35)*, which we did not model; including this benefit would increase treatment benefits.

Further, evidence is mixed in HCV and HIV coinfection regarding the impact of HCV on HIV *(6,42,62)* and CD4 response to ART, with some studies reporting delayed CD4 recovery *(42–44)* and others reporting little to no impairment *(25–29)* or suggesting that delayed responses could be due to injecting drug use cofactors *(63,64)*. Our results indicate that impaired recovery would further reduce impact among HCV- and HIV-coinfected individuals. Additionally, we assume that ART does not affectHCV vertical transmission, based on a lack of strong data and increased HCV viral loads when ART *(29,52–54)*. However, one study suggests that ART may reduce HCV vertical transmission *(55)*, so if this is true, then treatment could provide more benefit than we project.

Second, we model prompt initiation of ART at eligibility to compare the optimal health impact of ART and because no data suggest that linkage to ART is related to coinfection status. Therefore, projections do not include "real world" programmatic issues such as HIV testing and linkage to care, which would likely make provision of ART less beneficial for all the cohorts. Further data are needed to inform more detailed models of ART provision in South Africa.

Third, we do not include costs in this analysis, as uncertainties surround the costs associated with case-finding, linkage to care and treatment of coinfection. Consequently, we were not able to determine cost–effectiveness. Importantly, in areas where HBV or HCV testing among people living with HIV is not recommended, guidelines changes among this population could have limited impact without a corresponding scale-up of screening. However, if a programme were to give priority to treating individuals with coinfection (or giving priority to TDF treatment for HBV- and HIV-coinfected adults if the supply is limited), screening costs could be substantial in generalized HIV epidemics, where prevalence is low. However, in concentrated epidemics (such as in epidemics driven by injecting drug use, where HCV seroprevalence among adults living with HIV can reach 95% *(65)*), screening costs could be much lower.

Finally, our analysis was based on a generalized HIV epidemic setting (South Africa), and we neglect any potential additional benefits of ART on preventing the transmission of HIV, HCV or HBV among populations at higher risk such as people who inject drugs. In particular, the benefits of ART for people coinfected with HIV and HCV may be much higher in concentrated epidemics, where HIV is spread through injecting drug use, where ART for HCV- and HIV-

coinfected individuals could have a substantial impact on preventing injecting-related HIV transmission *(66,67)*.

Conclusions

Our findings underscore the individual and prevention benefits of early ART for all adults living with HIV and especially HBV- and HIV-coinfected adults. In generalized HIV epidemics, ART for HCV- and HIV-coinfected adults is unlikely to be more beneficial than for HIV monoinfection, but further studies quantifying the impact of ART on HCV-related liver disease progression or HCV vertical transmission would reduce uncertainty surrounding this estimate. Further modelling work should evaluate the cost–effectiveness of HBV screening and immediate ART among HBV- and HIV-infected adults.

Table 1. Comparisons of model projections of life expectancy for the cohorts with different ART eligibility criteria. We assumed prompt initiation of ART when eligible and neglect loss to follow-up to evaluate the full potential health benefits of ART

	Life expectancy from age 25 years in South Africa, median (95% interval)			
	No ART	**ART at CD4 <350 cells/mm^3**	**ART at CD4 <500 cells/mm^3**	**Immediate ART**
Uninfected	42.6	N/A	N/A	N/A
HCV monoinfection	39.5 (38.7–40.3)	N/A	N/A	N/A
HBV monoinfection	32.3 (26.8–36.5)	N/A	N/A	N/A
HIV monoinfection	9.8 (9.6–10.1)	24.5 (24.0–25.1)	29.7 (29.2–30.1)	31.6 (31.2–32.0)
HCV and HIV coinfection	9.7 (9.5–9.9)	22.7 (21.7–23.6)	27.1 (25.7–28.1)	28.7 (27.3–29.8)
HBV and HIV coinfection	9.2 (8.7–9.6)	23.0 (21.9–23.9)	28.5 (27.5–29.2)	30.6 (29.6–31.3)

Table 2. Summary of the individual benefits that accrue to HBV- and HIV-coinfected, HCV- and HIV-coinfected, and HIV monoinfected adults (excluding sexual or vertical transmission) with early (CD4 <500 cells/mm^3) or immediate ART regardless of CD4 count in South Africa. Median values are presented, with the 95% interval values shown in parentheses. We assume prompt initiation of ART when eligible and neglect loss to follow-up to evaluate full potential health benefits of ART. It was assumed that ART slows the rate of HIV-progression by four-fold regardless of CD4 compartment. ART=antiretroviral therapy, DALY=disability-adjusted life-year, NA=not applicable.

	HIV-monoinfected adults		**HBV- and HIV-coinfected adults**		**HCV- and HIV-coinfected adults**	
	Baseline	**Intervention**	**Baseline**	**Intervention**	**Baseline**	**Intervention**
ART at CD4 <500 cells/mm^3 (compared with baseline of CD4 <350 cells/mm^3)						
DALYs averted per person, undiscounted	–	4.8 (4.6–5.0)	–	5.1 (4.6–5.6)	–	3.9 (3.5–4.2)
Additional person–years of ART per person, undiscounted	–	8.0 (7.8–8.1)	–	8.3 (7.9–8.7)	–	7.2 (6.8–7.5)
No. of HIV deaths per 1000 people	738 (726–751)	610 (597–623)	677 (636–707)	574 (538–597)	646 (597–684)	511 (463–550)
% of HIV deaths averted	–	*17% (17–18%)*	–	*15% (13–17%)*	–	*21% (19–23%)*
No. of hepatitis deaths per 1000 people	NA	NA	90 (50–145)	65 (31–118)	153 (97–2213	205 (133–286)
% hepatitis deaths averted	–	*NA*	–	*28% (7–49%)*	–	*–34% (–28 to –40%)*
DALYs averted per 100 person–years on ART, 3% discounted	–	44 (43–46)	–	48 (43–52)	–	40 (38–42)
Immediate ART regardless of CD4 count (compared with baseline of CD4 <500 cells/mm^3)						
DALYs averted per person, undiscounted	–	1.8 (1.7–2.0)	–	2.0 (1.7–2.4)	–	1.5 (1.3–1.6)
Additional person–years of ART per person, undiscounted	–	2.7 (2.5–2.9)	–	2.9 (2.6–3.3)	–	2.4 (2.2–2.6)
No. of HIV deaths per 1000 people	610 (597–623)	559 (546–573)	574 (538–597)	531 (497–555)	511 (463–550)	456 (410–497)
% of HIV deaths averted	–	*8% (7–9%)*	–	*7% (6–9%)*	–	*11% (9–12%)*
No. of hepatitis deaths per 1000 people	NA	NA	65 (31–118)	54 (19–109)	205 (133–286)	225 (146–310)
% of hepatitis deaths averted	–	*NA*	–	*17% (3–42%)*	–	*–10% (–8% to –11%)*
DALYs averted per 100 person-years on ART, 3% discounted	–	51 (49–53)	–	55 (50–61)	–	47 (44–49)

FIGURE LEGENDS

Fig. 1. **Model schematics of disease progression.** A. HIV monoinfection progression. B. HCV and HIV coinfection progression. Background mortality occurs from all stages. C. HBV and HIV coinfection progression. Background mortality occurs from all stages. For the HBV and HIV coinfection model, transitions from HBsAg+ (chronic HBV) to other states are weighted by progression rates for high or low HBV viraemia (where low HBV viraemia is defined as HBeAg seroconverted).

Fig. 2. Individual health impact of early ART at CD4 <500 cells/mm^3 compared with CD4 <350 cells/mm^3. A. Undiscounted lifetime DALYs averted per adult. B. DALYs averted per additional 100 person-years on ART, with DALYs and person-years on ART each discounted at 3% annually. C. The ratio of the DALYs averted per 100 person-years on antiretroviral therapy for coinfection over HIV monoinfection (with a ratio of >1 indicating more benefit for treating coinfected adults than HIV monoinfection).

Fig. 3. Model sensitivity analysis. A. Median DALYs averted per 100 person-years on ART under different assumptions for with early ART at CD4 <500 cells/mm^3 compared with CD4 <350 cells/mm^3. B. Effect of varying the impact of ART on cirrhosis progression in HCV- and HIV-coinfected individuals on median DALYs averted per 100 person-years on ART, with early ART compared with CD4 <350 cells/mm^3. C. The impact of different ART eligibility thresholds on HBV or HCV vertical transmission, showing the predicted proportion of hepatitis-infected children, assuming that PMTCT does not contain TDF. The bars show the median values, with whiskers showing the 95% interval. ART=antiretroviral therapy.

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