Modeling the impact of whole blood pathogen inactivation on risk of transfusion-related adverse events and healthcare spending in Ghana

W. Alton Russell1,2, Shirley Owusu-Ofori3, Alex Owusu-Ofori3,4, Eileen Micah3, Betty Norman3,4, Brian Custer3,4

1Department of Management Science and Engineering, Stanford University Stanford, CA

2Blood Systems Research Institute, San Francisco, CA

3Department of Medicine, Komfo-Anokye Teaching Hospital, Kumasi, Ghana

4Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

5Department of Laboratory Medicine, University of California, San Francisco, CA

**Corresponding author:** W. Alton Russell, Management Science and Engineering, Stanford University, Stanford CA 94305. email: [altonr@stanford.edu](mailto:altonr@stanford.edu).

**Alt. author contact:** Brian Custer, [bcuster@vitalant.org](mailto:bcuster@vitalant.org)

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# Abstract [241/250 words]

**Background:** Despite the promise of pathogen inactivation for reducing transfusion-related adverse events in sub-Saharan Africa, no health-economic assessment is publicly available.

**Methods:** We estimated the annual rate of six infectious and one non-infectious transfusion-related adverse events in Ghana with and without whole blood pathogen inactivation using a mathematical risk reduction model. We used detail micro-costing to estimate the net present cost for each adverse event. For HIV, HCV, and HBV, we simulated disease progression using Markov models, accounting for the likelihood and timing of clinical detection and treatment. We performed probabilistic and univariate sensitivity analysis.

**Results:** The addition of whole blood pathogen inactivation would reduce the number of adverse events by 19,626 (13,077 – 27,723) annually, primarily by averting bacterial sepsis (51%) and malaria (32%) infections. One year of whole blood pathogen inactivation would cost $8,037,191 ($6,377,146 – $9,816,742) and reduce net present healthcare spending by $9,287,311 ($5,580,062 – $13,669,226) due to averted adverse events, resulting in an annual net savings of $1,250,120 (-$2,588,103 – $5,457,009). Pathogen inactivation reduced overall healthcare spending in 66% of probabilistic sensitivity analysis iterations. Findings were sensitive to uncertainty in the baseline risk and probability of clinical disease due to sepsis infection and the cost of pathogen inactivation.

**Conclusions:** Whole blood pathogen inactivation would substantially reduce the burden of infectious and non-infectious adverse events in Ghana and may reduce overall healthcare spending. Additional benefits may include averting secondary transmission of infectious diseases, reducing non-medical costs, and preventing other adverse events.

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# Introduction

Pathogen inactivation (PI) has been described as a promising new technology for reducing transfusion-transmitted (TT-) infections (TTIs) and non-infectious transfusion-related adverse events in Sub-Saharan Africa [1]. PI uses UV light, often in combination with an additive, to inactivate pathogens in blood components or whole blood [2]. The health-economic consequences of PI of plasma and platelet components have been estimated for different health systems, including Poland and Canada [3,4]. Compared to the European and North American settings where prior analyses of PI have focused, health systems in sub-Saharan Africa often experience greater resource constraints, greater baseline rates of certain transfusion-related adverse events, and more frequent blood shortages [5,6]. Furthermore, the common practice of transfusion whole blood rather than derived products limits the applicability of platelet and plasma PI [7]. Whole blood PI may be a more appropriate technology for this region, and a recent randomized trial has analyzed the effectiveness of whole blood PI for averting TT-malaria in Ghana [8]. However, no health-economic assessment has been published for whole blood PI. We developed a decision-analytic model to estimate how the addition of whole blood PI to the existing blood safety program in Ghana would impact the number of transfusion-related adverse events and total healthcare expenditures.

# Methods

We developed a decision analytic model to estimate the health-economic consequences of whole blood pathogen inactivation in Ghana from a healthcare payer perspective. We considered seven adverse events, including viral TTIs (HIV, HCV, HBV), bacterial TTIs (syphilis, bacterial sepsis), malaria, and febrile non-hemolytic transfusion reactions (FNHTRs), a non-infectious adverse event. We estimated the cost per adverse event averted and the budget impact of whole blood PI, and we assessed uncertainty through deterministic and probabilistic sensitivity analysis. The model was programmed in R. All data and code are available in a public repository [I will do this before submitting].

## Risk reduction model structure

Our two-armed decision tree compared the costs and consequences of status quo blood safety interventions to those of the status quo plus whole blood PI. The status quo was to test all donations using HIV-Ab, HIV-Ag, HBsAg, Anti-HCV Ab, and syphilis serologic tests [9]. All parameters values for the risk reduction model are shown in Table 1 [8–17], and mathematical calculations are provided in the online supplement section A. For each input parameter, we estimated a range of likely values for deterministic sensitivity analysis and assigned a distribution for probabilistic sensitivity analysis. We used beta distributions when estimates were based on counts for a binary outcome or when the parameter source used a beta distribution. Otherwise we sampled from a PERT distribution. For all outcomes, we reported the expected value from the base case scenario and a 95% uncertainty interval based on the 2.5th and 97.5th quantiles of results from 10,000 iterations of probabilistic sensitivity analysis.

We assumed that each whole blood donation would be transfused to a single recipient, and we assumed that if one recipient experienced multiple adverse events from a single transfusion then any adverse event costs would be additive. For each of the six TTIs, the baseline (without PI) number of clinically meaningful adverse events was calculated from the annual number of whole blood donations collected nationally, the percent of collected donations not transfused (wastage), the estimated residual risk among donors after TTI screening, and the risk of symptomatic outcome (i.e., likelihood that transfusion of an infectious unit results in a clinically relevant case). For FNHTR, a non-infectious adverse event, the baseline rate of clinically meaningful adverse events per recipient was extrapolated from local data and prior studies, and the per-donation risk of FNHTR was derived by multiplying the per-recipient rate by the estimated average number of whole blood units transfused per recipient. We assumed some recipients were not at risk of symptomatic outcomes due to factors such as prior malaria infection, HBV vaccination, and existing HIV infection. For each adverse event, we divided by a fold risk-reduction factor to estimate the number of adverse events when using whole blood PI. These factors were based on clinical trials where available (malaria, FNHTR) and otherwise sourced from prior modeling studies.

## Cost of adverse events

We estimated the average health care spending associated with each transfusion-related adverse using a micro-costing approach. For most adverse events, authors with relevant clinical experience at the Komfo Anokye Teaching Hospital (KATH) in Kumasi, Ghana, estimated the costs and utilization patterns for resources used to treat each adverse event. For HIV, we used cost estimates from a recent study of healthcare spending for HIV treatment with and without antiviral therapy (AVT) [18]. We treated FNHTR, malaria, syphilis, and sepsis as acute infections and assumed all costs were incurred within a year of transfusion. We treated HIV, HBV, and HCV as chronic viral infections and used Markov models to estimate lifetime healthcare costs. Supplemental Table S1 contains estimates and uncertainty ranges for all micro-costing parameters, and Supplemental Table S2 contains the calculations used for the four acute adverse events and for each disease state of the chronic viral infections.

For each chronic viral infection, we modeled a pediatric cohort (age 5 at transfusion) and an adult cohort (age 40 at transfusion). Models captured the natural history, treatment uptake, and treatment effectiveness. We used a one-year timestep, discounted future costs at 3% annually, and used the cycle tree method to correct for discretization error [19]. The probability of dying from another cause in all disease states was based on the 2016 age-specific death rate indicator in the World Health Organization Global Health Observatory data repository [20]. All other transition probabilities and their sources are listed in Supplemental Table S3. The supplement also contains schematics for the transition matrix for each chronic adverse event (Supplementary Figures S1 – S3) and Markov trace plots of the proportion of transfusion recipients in each disease state over time (Supplementary Figures S4 – S6).

For HCV, our natural history model and treatment efficacy estimates were based on a health economic model developed for The Gambia [21], and transitions into treatment were estimated based on the authors’ clinical experience. We assumed a small portion of infections would be detected during the acute phase in the first year and receive antiviral therapy (AVT); otherwise, recipients would have subclinical acute infections. We assumed a portion of subclinical infections in the chronic, compensated cirrhosis, and decompensated cirrhosis would be detected each year, and those patients would receive AVT. We assumed AVT would clear most HCV infections, but some patients would experience treatment failure and be subject to disease progression while receiving monitoring and care.

For HBV, our natural history model and treatment efficacy estimates were based on a health economic model developed for South Africa [22]. We assumed a small fraction of acute infections would be detected and receive monitoring and care during the first year, but most infectious would start as subclinical. Subclinical infections in the immune reactive, compensated cirrhosis, or decompensated cirrhosis states had an annual probability of clinical detection, at which point AVT would be begun. subclinical patients in the chronic HBeAg- phase also had an annual probability of detection. Those patients would transition to receiving monitoring and care without AVT but could be started on AVT due to clnical indications such as a spike in viral load. We assumed patients on AVT would not progress to later disease states and would continue with AVT and monitoring for their lifetimes. For those on AVT with cirrhosis, a small annual risk of developing hepatocellular carcinoma remained.

For HIV, we constructed a natural history model and calibrated the annual probability of progression to AIDS, death from HIV, and death from AIDS to a longitudinal study of HIV progression from Uganda (Figure S7) [23]. We assumed patients on AVT would not progress to AIDS and would continue with treatment for the remainder of their lives. Costs on AVT were based on an empirical study from ART clinics in Ghana that found that on average, medical expenses were highest in the year of ART initaition and tapered off over three years [18]. We estimated the annual probability of initiating AVT based on the authors’ clinical experience.

## Scenario analysis

In a scenario analysis, we approximated secondary infections by assuming each recipient infected with HIV, HBV, or HCV infects one other person during the first year.

# Results

The estimated number of adverse events in a year without PI was 24,844 (21,204 – 37,983). PI reduced the number of adverse events by 19,626 (13,077 – 27,723) to 5,218 (5,215 – 14,397) per year. Most of the averted adverse events were sepsis (51%) and malaria (32%) infections (Table 2).

The estimated net present cost per adverse event ranged from $2.70 ($1.37 – $4.73) for syphilis to $1,617.45 ($871.22 – $2,677.92) for HBV. Because most HIV, HCV and HBV infections would be subclinical for the first year, over 90% of healthcare spending associated with these three adverse events is estimated to occur in later years (Supplementary Table S4). The total net present healthcare costs due to adverse events was $10,123,723 ($6,454,403 – $15,097,085) without PI and $836,411 ($710,412 – $1,733,060) with PI. Of the adverse events evaluated, sepsis infection had only the third highest per-case cost at $694.80 ($547.06 – $877.09) but represented the majority of healthcare spending due to adverse events without PI (72%) and the majority of net present healthcare savings due to PI (75%).

One year of whole blood PI in Ghana would cost an estimated $8,037,191 ($6,377,146 – $9,816,742) and reduce net present healthcare spending by $9,287,311 ($5,580,062 – $13,669,226) due to averted adverse events, resulting in an annual net savings of $1,250,120 (-$2,588,103 – $5,457,009) (Figure 2). Whole blood PI led to an overall reduction in net present healthcare spending in 66% of probabilistic sensitivity analysis iterations. For 15 uncertain input parameters, varying the parameter along their uncertainty ranges led to a variation in the annual net savings of PI of $500,000 or more. Our finding that whole blood PI would lead to an overall reduction in net present healthcare spending did not hold when the baseline risk or probability of symptomatic outcome for sepsis infections were lower than our base case estimates or when the per-donation cost of pathogen inactivation was higher than our base case estimate (Figure 3).

In the scenario analysis where all HBV, HCV, and HIV-infected recipients infect one other person, the net present health savings from PI increased from $9,287,311 to $11,304,511 ($6,919,082 – $16,201,910) annually. In this scenario, the net impact of PI was an overall reduction in healthcare spending in 90% of iterations.

# Discussion

Adding whole blood PI to the existing blood safety portfolio in Ghana would prevent many transfusion-related adverse events and may decrease overall healthcare spending. We estimated a 66% probability that whole blood PI would lead to a net reduction in healthcare costs, but this increased to 90% when factoring in healthcare costs for one secondary case for each HIV, HBV, and HCV infection. Our analysis did not consider non-healthcare costs such as family caregiver time, productivity loss, or transportation costs. We also did not evaluate all types of adverse events for which pathogen inactivation may reduce risk, which could include emerging infectious diseases not yet identified as blood safety threats, and we did not quantify the associated reductions in death and disability. Due to these factors, the total societal benefit of pathogen inactivation likely exceeds the impact on direct healthcare spending as estimated here.

We employed a detailed approach to estimating the costs of adverse events that accounted for subclinical disease. This approach, combined with price reductions for some resources such as HIV antiviral therapy drugs [24], led to lower estimates of the per-infection costs for HBV, HCV, and HIV events as compared to past analyses of blood safety interventions in sub-Saharan Africa [25–27]. Our analysis also suggested that bacterial sepsis is an underappreciated blood safety threat in sub-Saharan Africa, accounting for large percentage of transfusion-related adverse events cases and the majority of associated healthcare spending.

This study has several limitations. Data on the rate of transfusion-related adverse events in Ghana, and in sub-Saharan Africa generally, are limited. The benefit of pathogen inactivation also depends on the baseline residual risk of each adverse event, and updated risk estimates from recent hemovigilance data could reduce uncertainty. While our detailed micro-costing approach to estimating the disease trajectories and associated healthcare costs for adverse events was based on clinical expertise, a rigorous empirical study may increase accuracy. For most diseases, the modeled risk reduction due to PI was based on estimates from prior modeling study because the low baseline rate of these adverse outcomes makes empirical estimation difficult. Our findings were sensitive to parameter values regarding the baseline rate of bacterial sepsis and the cost of pathogen inactivation. We also assumed the per-treatment costs of pathogen inactivation incorporated all capital costs and equipment maintenance.

Our analysis provides further evidence that pathogen inactivation is a promising technology for sub-Saharan Africa. Future research could further elucidate the societal impact of pathogen inactivation and other blood safety technologies by improving estimation of the burden of illness from transfusion-related adverse events, estimating other impacts beyond direct healthcare spending, and considering other settings in sub-Saharan Africa.

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# Declarations

**Funding:** This work was supported by Terumo BCT, Inc.

**Conflicts:** WAR received consulting fees from Terumo BCT, Inc. related to this analysis. BC … .

**Ethics/Consent:** This analysis was based on public data and was exempt from institutional ethics review.

**Data and materials:** All data and materials have been uploaded to a public repository.

**Code availability:** All code has been uploaded to a public repository.

**Authors’ contributions:** [To do]

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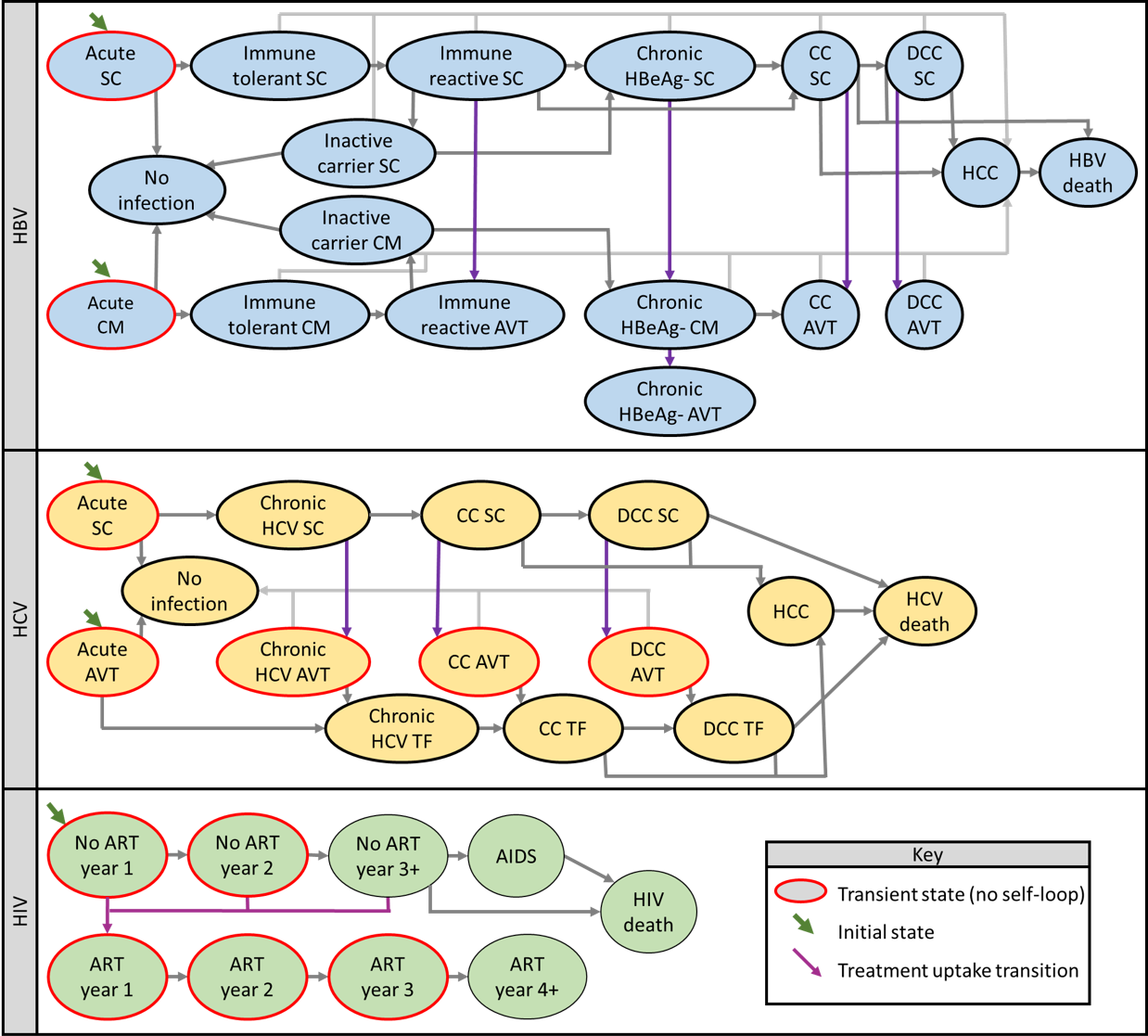
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**Table 1** Parameters for modeling the risk of adverse events with and without whole blood pathogen inactivation

| **Risk model parameters** | **Value (range); distribution** | **Source** |
| --- | --- | --- |
| System parameters | | |
| Percent recipients who are pediatric | 19% (15%–25%); PERT | # |
| Number of components transfused | 160000 (128000–192000); PERT | # |
| Percent of donations not transfused | 9% (1%–17%); PERT | A |
| Cost of PI per treatment (in $) | $46 ($37–$55); PERT | B |
| Baseline risk | | |
| HIV | 0.112% (0.036%–0.324%); PERT | # |
| Sepsis | 13% (7.56%–18.6%); Beta(24, 168) | # |
| HCV | 0.54% (0.135%–1.22%); PERT | # |
| HBV | 0.94% (0.235%–2.12%); PERT | # |
| Syphilis | 0.064% (0.034%–0.092%); PERT | C |
| Malaria | 25% (19.8%–30.2%); Beta(91, 276) | # |
| FNHTR | 3.17% (1.6%–5.98%); Beta(26, 406) | # |
| Symptomatic outcome risk | | |
| HIV | 98.3% (50%–100%); PERT | # |
| Sepsis | 50% (30%–70%); PERT | # |
| HCV | 100% (50%–100%); PERT | # |
| HBV | 55.2% (40%–70%); PERT | # |
| Syphilis | 57% (0%–100%); PERT | D |
| Malaria | 18.5% (8.4%–33.7%); PERT | # |
| FNHTR | 100% | # |
| Fold reduction of PI | | |
| HIV | 10 (5–20); PERT | # |
| Sepsis | 25 (10–40); PERT | # |
| HCV | 10 (5–20); PERT | # |
| HBV | 10 (5–20); PERT | # |
| Syphilis | 20 (10–40); PERT | # |
| Malaria | 6.05 (1–20); PERT | # |
| FNHTR | 1.5 (1–3); PERT | # |

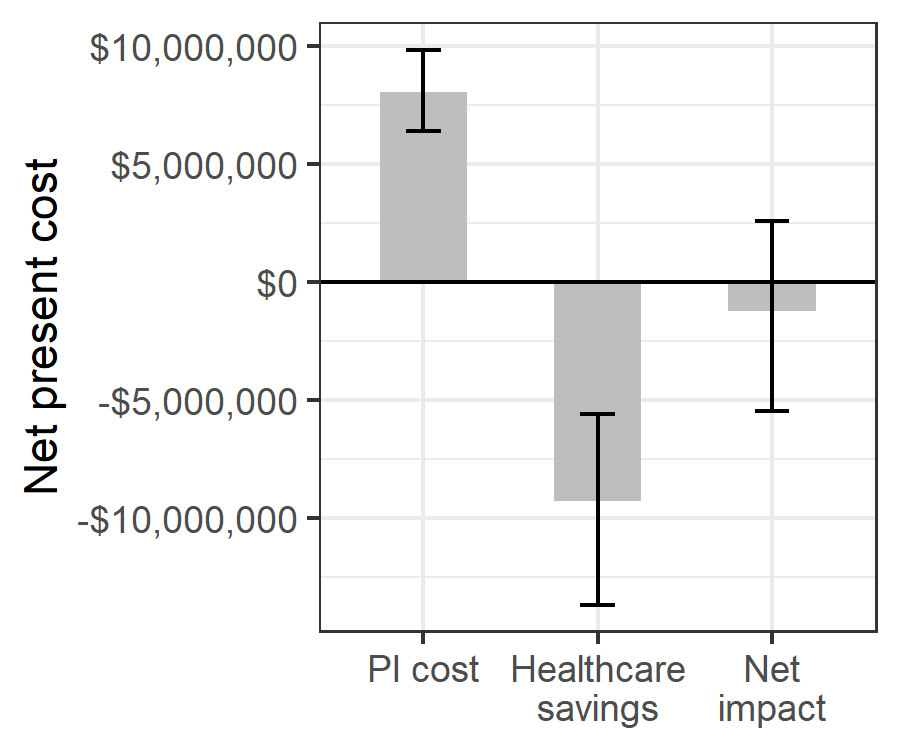
**Table 2** Estimated cases and healthcare spending incurred for each adverse event with and without whole blood pathogen inactivation for one year.

| **Outcome** | **Sepsis** | **Malaria** | **FNHTR** | **Syphilis** | **HBV** | **HCV** | **HIV** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Cases without PI | 10,419 (5,774 – 15,908) | 7,414 (3,916 – 11,859) | 5,079 (6,205 – 13,893) | 58 (19 – 104) | 832 (318 – 1,530) | 866 (300 – 1,443) | 176 (62 – 334) |
| Cases with PI | 417 (205 – 820) | 1,225 (431 – 5,171) | 3,386 (3,538 – 11,102) | 3 (1 – 7) | 83 (29 – 195) | 87 (27 – 186) | 18 (6 – 41) |
| Cases reduced by PI | 10,002 (5,545 – 15,250) | 6,189 (2,102 – 9,878) | 1,693 (429 – 6,120) | 56 (18 – 99) | 749 (285 – 1,362) | 779 (268 – 1,292) | 159 (55 – 301) |
| Net present cost per case | $694.80 ($547.06 – $877.09) | $28.50 ($21.12 – $36.17) | $85 ($59.57 – $116.35) | $2.70 ($1.37 – $4.73) | $1,617.45 ($871.22 – $2,677.92) | $835.82 ($623.84 – $1,069.45) | $977.76 ($893.84 – $1,113.51) |
| Total net present cost without PI | $7,239,243 ($3,747,412 – $11,657,983) | $211,289 ($104,349 – $356,502) | $431,700 ($464,091 – $1,312,077) | $157.88 ($40.57 – $359.18) | $1,345,297 ($423,084 – $2,978,779) | $723,483 ($236,176 – $1,252,948) | $172,553 ($61,611.95 – $338,480) |
| Total net present cost with PI | $289,570 ($135,411 – $584,612) | $34,900.70 ($11,778.51 – $151,526) | $287,800 ($271,090 – $1,022,943) | $7.89 ($1.94 – $21.34) | $134,530 ($37,967.60 – $360,678) | $72,348.34 ($21,165.68 – $157,729) | $17,255.34 ($5,492.08 – $41,691.34) |
| Total net present cost reduced by PI | $6,949,673 ($3,589,032 – $11,189,109) | $176,388 ($57,606.56 – $295,713) | $143,900 ($35,147.67 – $560,368) | $149.99 ($38.16 – $339.94) | $1,210,767 ($379,852 – $2,657,250) | $651,135 ($208,463 – $1,121,205) | $155,298 ($54,350.25 – $303,366) |



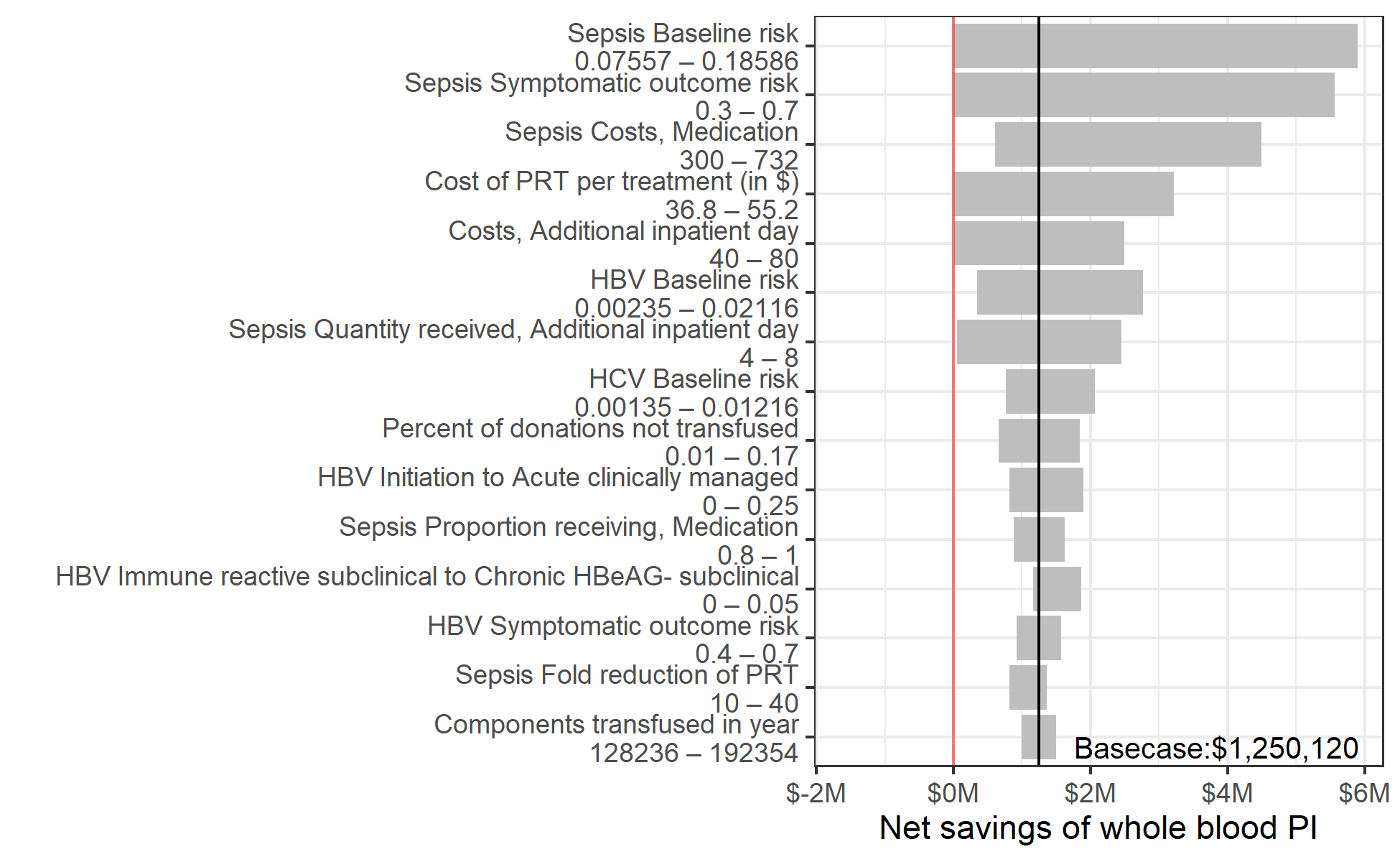
**Fig. 1.** Schematics for Markov models used to estimate net-present lifetime costs for chronic viral infections. Death from other causes possible from any disease state (not shown). Abbreviations AVT, antiviral therapy, CC, compensated cirrhosis, CM, clinical monitored, DCC, decompensated cirrhosis, HCC, hepatocellular carcinoma, HBV, hepatitis B, HCV, hepatitis C, HIV, human immunodeficiency virus, TF, treatment failure, SC, subclinical

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**Fig. 2.** Estimated net impact on healthcare spending of whole blood pathogen inactivation. Net impact is the cost of pathogen inactivation minus the net present healthcare savings from avert transfusion-related adverse events.

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**Fig. 3.** Sensitivity of the net savings of pathogen inactivation to changes in the value of individual input parameters within prespecified uncertainty ranges. Y-axis shows all model parameters for which varying the value along the indicated range while keeping other parameters at their base case value led to a variation of more than $500,000 in the estimated net savings of whole blood pathogen inactivation.

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# Supplemental materials

# A. Calculations for estimating the outcomes of pathogen inactivation

[I still need to write this!]

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**Table S1** Parameters for the micro-costing calculations

| **Micro-costing parameters** | **Value (range); distribution** | **Source** |
| --- | --- | --- |
| Costs | | |
| Additional inpatient day | 60 (40–80); PERT | E |
| Liver function test | 13 (11–15); PERT | E |
| International normalized ratio test | 7.7 (6.3–9); PERT | E |
| Full blood count | 6.4 (5.5–7.3); PERT | E |
| Blood urea nitrogen, creatinine, & electrolytes | 11.5 (10–13); PERT | E |
| Alpha fetoprotein | 11.5 (11–12); PERT | E |
| Brief outpatient visit | 6 (4–8); PERT | E |
| Extensive outpatient visit | 12 (8–16); PERT | E |
| Abdominal ultrasonography | 10 (8–12); PERT | E |
| Endoscopy with band ligation | 272 (245–350); PERT | E |
| Spironolactone | 350 (182–782); PERT | E |
| Furosemide | 60.8 (55–66); PERT | E |
| Transarterial chemoembolization | 1810 (1400–2200); PERT | E |
| Triphasic CT scan | 173 (150–196); PERT | E |
| Sorafenib (9-12 tablets) | 1920 (1640–2190); PERT | E |
| Medication, Sepsis | 372 (300–732); PERT | E |
| Outpatient clinic visit, Malaria | 15 (10–20); PERT | E |
| RDT + Microscopy, Malaria | 3 (1–5); PERT | E |
| Medication, Malaria | 12 (4–20); PERT | E |
| Diagnosis, Syphilis | 15 (10–40); PERT | E |
| Treatment, Syphilis | 12 (5–20); PERT | E |
| Consultation and medication, FNHTR | 25 (20–30); PERT | E |
| HBsAg test, HBV | 3.78 (2.16–5.4); PERT | E |
| HBV profile test, HBV | 35.1 (21.6–48.6); PERT | E |
| HBV DNA test, HBV | 73.8 (72–75.6); PERT | E |
| ART for non-cirrhotic patients, HBV | 326 (261–391); PERT | E |
| ART with cirrhosis, HBV | 869 (326–3590); PERT | E |
| Ab screen and confirmation, HCV | 9 (7–13); PERT | E |
| RNA test, HCV | 145 (120–170); PERT | E |
| Genotyping, HCV | 163 (140–186); PERT | E |
| Antiviral medication, HCV | 650 (548–1090); PERT | E |
| ART for decompensated cirrhosis, HCV | 1630 (1100–2170); PERT | E |
| HIV care no ART year 1, HIV | 0 | # |
| HIV care no ART year 2, HIV | 0 | # |
| HIV care no ART year 3, HIV | 0 | # |
| AIDS care, HIV | 150 (600–50); PERT | # |
| HIV care first year on ART, HIV | 187 (149–224); PERT | # |
| HIV care second year on ART, HIV | 64.5 (51.6–77.4); PERT | # |
| HIV care third year on ART, HIV | 57 (45.6–68.4); PERT | # |
| HIV care annual cost after third year on ART, HIV | 46.4 (37.1–55.6); PERT | # |
| Proportion receiving | | |
| Medication, Sepsis | 90% (80%–100%); PERT | E |
| Additional inpatient day, Malaria | 5% (1%–9%); PERT | E |
| Outpatient clinic visit, Malaria | 50% (40%–60%); PERT | E |
| Diagnosis & treatment, Syphilis | 10% (5%–20%); PERT | E |
| Additional inpatient day, FNHTR | 50% (40%–60%); PERT | E |
| Quantity received | | |
| Additional inpatient day, Sepsis | 6 (4–8); PERT | E |
| Additional inpatient day, Malaria | 1.5 (1–2); PERT | E |
| Outpatient clinic visit, Malaria | 1.2 (1–2); PERT | E |
| Additional inpatient day, FNHTR | 2 (1–3); PERT | E |
| Annual brief outpatient visits for chronic HBeAg-negative infection no ART, HBV | 3 (2–4); PERT | E |
| Annual brief outpatient visits for chronic HBeAg-negative infection with ART, HBV | 1 (0–2); PERT | E |
| Annual brief outpatient visits for compensated cirrhosis no ART, HBV | 3 (2–4); PERT | E |
| Annual brief outpatient visits for compensated cirrhosis with ART, HBV | 3 (2–4); PERT | E |
| Annual brief outpatient visits for decompensated cirrhosis no ART, HBV | 4 (2–6); PERT | E |
| Annual brief outpatient visits for decompensated cirrhosis with ART, HBV | 4 (2–6); PERT | E |
| Annual brief outpatient visits for acute infection with ART, HCV | 3 (2–4); PERT | E |
| Annual brief outpatient visits for chronic HCV without cirrhosis no ART, HCV | 3 (2–4); PERT | E |
| Annual brief outpatient visits for compensated cirrhosis no ART, HCV | 4 (2–6); PERT | E |
| Annual brief outpatient visits with decompensated cirrhosis no ART, HCV | 4 (2–6); PERT | E |

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**Table S2** Annual transition probabilities used in the Markov models of chronic HIV, HBV, and HCV infections. Transitions indicated by `#` are calculated as one minus the probability of transitioning to any other state.

| **Annual transition probability** | | **Value (range); distribution** | **Source** |
| --- | --- | --- | --- |
| **From** | **To** |
| HBV natural history | | | |
| Initiation | Acute clinically managed | 10% (0%–25%); PERT | # |
| Acute subclinical | # | # |
| Acute subclinical | Immune tolerant subclinical | 95% (90%–99%); PERT | # |
| No infection | # | # |
| Acute clinically managed | Immune tolerant clinically managed | 95% (90%–99%); PERT | # |
| No infection | # | # |
| No infection | No infection | 100% | # |
| Immune tolerant subclinical | Immune reactive subclinical | 10% (3%–20%); β(5.063, 45.57) | # |
| Hepatocellular carcinoma | 0.3% (0%–0.6%); β(3.985, 1324.35) | # |
| Immune tolerant subclinical | # | # |
| Immune tolerant clinically managed | Immune reactive on AVT | 10% (3%–20%); β(5.063, 45.57) | # |
| Immune tolerant clinically managed | # | # |
| Carrier subclinical | Chronic HBeAG- subclinical | 2.68% (1.55%–4.71%); β(11.173, 405.74) | # |
| Hepatocellular carcinoma | 0.065% (0%–0.1%); β(0.057, 94.89) | # |
| No infection | 1% (0.97%–2.26%); β(17.146, 1257.65) | # |
| Carrier subclinical | # | # |
| Carrier clinically managed | Chronic HBeAG- clinically managed | 2.68% (1.55%–4.71%); β(11.173, 405.74) | # |
| No infection | 1% (0.97%–2.26%); β(17.146, 1257.65) | # |
| Carrier clinically managed | # | # |
| Immune reactive subclinical | Chronic HBeAG- subclinical | 0.5% (0%–5%); β(0.154, 30.69) | # |
| Carrier subclinical | 5.74% (4.58%–6.88%); β(11.971, 196.76) | # |
| Hepatocellular carcinoma | 0.65% (0.27%–1%); β(12.596, 1925.3) | # |
| Immune reactive subclinical | # | # |
| Chronic HBeAG- subclinical | Compensated cirrhosis subclinical | 4% (1%–5.2%); β(11.173, 300.92) | # |
| Hepatocellular carcinoma | 0.616% (0.27%–1%); β(11.3, 1824.5) | # |
| Chronic HBeAG- subclinical | # | # |
| Chronic HBeAG- clinically managed | Compensated cirrhosis on AVT | 4% (1%–5.2%); β(11.173, 300.92) | # |
| Hepatocellular carcinoma | 0.616% (0.27%–1%); β(11.3, 1824.5) | # |
| Chronic HBeAG- clinically managed | # | # |
| Compensated cirrhosis subclinical | Decompensated cirrhosis subclinical | 3.9% (3.2%–4.6%); β(2.848, 70.18) | # |
| Hepatocellular carcinoma | 3.66% (0.8%–8%); β(3.947, 103.88) | # |
| HBV-related death | 3.9% (3.9%–50.7%); β(0.27, 6.66) | # |
| Compensated cirrhosis subclinical | # | # |
| Decompensated cirrhosis subclinical | Hepatocellular carcinoma | 3.76% (2.3%–7.1%); β(9.411, 240.88) | # |
| HBV-related death | 31.4% (4.3%–57%); β(3.583, 7.83) | # |
| Decompensated cirrhosis subclinical | # | # |
| Hepatocellular carcinoma | HBV-related death | 50% (40%–100%); β(5.056, 5.06) | # |
| Hepatocellular carcinoma | # | # |
| HBV-related death | HBV-related death | 100% | # |
| HBV treatment effectiveness | | | |
| Immune reactive on AVT | Immune reactive on AVT | 100% | # |
| Chronic HBeAG- on AVT | Chronic HBeAG- on AVT | 100% | # |
| Compensated cirrhosis on AVT | Hepatocellular carcinoma | 0.5% (0%–1%); β(0.747, 149) | # |
| Compensated cirrhosis on AVT | # | # |
| Decompensated cirrhosis on AVT | Hepatocellular carcinoma | 1% (0%–4.4%); β(0.808, 80) | # |
| Decompensated cirrhosis on AVT | # | # |
| HBV treatment uptake | | | |
| Chronic HBeAG- subclinical | Chronic HBeAG- clinically managed | 5% (10%–20%); PERT | # |
| Chronic HBeAG- clinically managed | Chronic HBeAG- on AVT | 9% (4%–18%); PERT | # |
| Compensated cirrhosis subclinical | Compensated cirrhosis on AVT | 30% (10%–40%); PERT | # |
| Decompensated cirrhosis subclinical | Decompensated cirrhosis on AVT | 70% (50%–90%); PERT | # |
| HCV natural history | | | |
| Initiation | Acute on AVT | 10% (0%–25%); PERT | # |
| Acute subclinical | # | # |
| Acute subclinical | No infection | 32% (15%–40%); PERT | # |
| Chronic HCV subclinical | # | # |
| No infection | No infection | 100% | # |
| Chronic HCV subclinical | Compensated cirrhosis subclinical | 1.1% (0.5%–1.8%); PERT | # |
| Chronic HCV subclinical | # | # |
| Chronic HCV treatment failure | Compensated cirrhosis treatment failure | 1.1% (0.5%–1.8%); PERT | # |
| Chronic HCV treatment failure | # | # |
| Compensated cirrhosis subclinical | Decompensated cirrhosis subclinical | 6.4% (3%–7%); PERT | # |
| Hepatocellular carcinoma | 3.6% (1.5%–4%); PERT | # |
| Compensated cirrhosis subclinical | # | # |
| Compensated cirrhosis treatment failure | Decompensated cirrhosis treatment failure | 6.4% (3%–7%); PERT | # |
| Hepatocellular carcinoma | 3.6% (1.5%–4%); PERT | # |
| Compensated cirrhosis treatment failure | # | # |
| Decompensated cirrhosis subclinical | Hepatocellular carcinoma | 6.8% (4.1%–9.9%); PERT | # |
| HCV-related death | 16.8% (12%–40%); PERT | # |
| Decompensated cirrhosis subclinical | # | # |
| Decompensated cirrhosis treatment failure | Hepatocellular carcinoma | 6.8% (4.1%–9.9%); PERT | # |
| HCV-related death | 16.8% (12%–40%); PERT | # |
| Decompensated cirrhosis treatment failure | # | # |
| Hepatocellular carcinoma | HCV-related death | 60.5% (30%–80%); PERT | # |
| Hepatocellular carcinoma | # | # |
| HCV-related death | HCV-related death | 100% | # |
| HCV treatment effectiveness | | | |
| Acute on AVT | No infection\* | 95% (90%–99%); PERT | # |
| Chronic HCV treatment failure | #; PERT | # |
| Chronic HCV on AVT | No infection | 95% (90%–99%); PERT | # |
| Chronic HCV treatment failure | #; PERT | # |
| Compensated cirrhosis on AVT | No infection | 95% (90%–99%); PERT | # |
| Compensated cirrhosis treatment failure | #; PERT | # |
| Decompensated cirrhosis on AVT | No infection | 95% (90%–99%); PERT | # |
| Decompensated cirrhosis treatment failure | #; PERT | # |
| HCV treatment uptake | | | |
| Chronic HCV subclinical | Chronic HCV on AVT | 10% (5%–30%); PERT | # |
| Compensated cirrhosis subclinical | Compensated cirrhosis on AVT | 30% (10%–40%); PERT | # |
| Decompensated cirrhosis subclinical | Decompensated cirrhosis on AVT | 70% (50%–90%); PERT | # |
| HIV natural history | | | |
| No ART, 1st year | No ART, 2nd year | 100% | # |
| No ART, 2nd year | No ART, 3+ years | 100% | # |
| No ART, 3+ years | AIDS (pediatric) | 4.21% (3.07%–5.62%); PERT | # |
| AIDS (adult) | 15% (10.1%–22.6%); PERT | # |
| HIV-related death (pediatric) | 1.5% (0%–6.9%); PERT | # |
| HIV-related death (adult) | 0% (0%–5.5%); PERT | # |
| No ART, 3+ years | # | # |
| AIDS | HIV-related death (pediatric) | 60.2% (32.4%–60.2%); PERT | # |
| HIV-related death (adult) | 61.5% (28.6%–64.9%); PERT | # |
| AIDS | # | # |
| HIV-related death | HIV-related death | 100% | # |
| HIV treatment uptake | | | |
| No ART, 1st year | ART year 1 | 15% (5%–40%); PERT | # |
| No ART, 2nd year | ART year 2 | 20% (10%–50%); PERT | # |
| No ART, 3+ years | ART year 3 | 60% (30%–90%); PERT | # |
| HIV treatment effectiveness | | | |
| ART year 1 | ART year 2 | 100% | # |
| ART year 2 | ART year 3 | 100% | # |
| ART year 3 | ART year 4+ | 100% | # |
| ART year 4+ | ART year 4+ | 100% | # |

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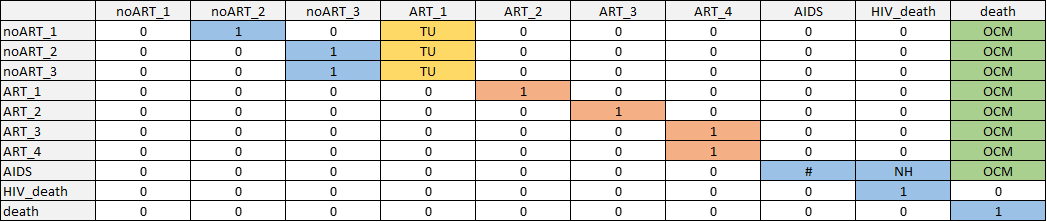
**Table S3** Calculations used for each disease state (acute illness for sepsis, malaria, febrile non-hemolytic transfusion reactions, and syphilis; annual costs for each disease state in the HBV and HIV Markov models)

| **Disease state** | **Microcosting calculation** |
| --- | --- |
| Sepsis | (cost × quantity) additional inpatient days +  (proportion × cost) medication |
| Malaria | (cost × quantity × proportion) additional inpatient days +  (cost × quantity × proportion) outpatient clinic visits +  (cost) diagnosis +  (cost) medication |
| FNHTR | (cost) medication and consult +  (cost × quantity × proportion) additional inpatient days |
| Syphilis | (cost × proportion) diagnosis +  (cost × proportion) medications |
| HBV acute clinically managed | (2 × cost) HBsAg test +  (cost) HBV profile +  (cost) HBV DNA test +  (cost) extensive outpatient clinic visit +  (cost) brief outpatient clinic visit |
| HBV acute subclinical | 0 |
| HBV no infection | 0 |
| HBV immune tolerant clinically managed | (cost) extensive outpatient clinic visit +  (cost) HBsAg test +  (cost) HBV profile +  (cost) HBV DNA test +  (cost) liver function test |
| HBV immune tolerant subclinical | 0 |
| HBV carrier subclinical | 0 |
| HBV carrier clinically managed | 0 |
| HBV immune reactive on AVT | cost) extensive outpatient clinic visit +  (cost) HBsAg test +  (cost) HBV profile +  (cost) HBV DNA test +  (cost) liver function test +  (cost) HBV antivirals for non-cirrhotic patients |
| HBV immune reactive subclinical | 0 |
| HBV chronic HBeAg- on AVT | (cost) liver function test +  (cost) HBV profile +  (cost) HBV DNA test +  (cost) blood urea nitrogen, creatinine, & electrolytes +  (cost) full blood count +  (cost) alpha fetoprotein test +  (cost) abdominal ultrasonography +  (cost × quantity) brief outpatient visit +  (cost) HBV antivirals for non-cirrhotic patients |
| HBV chronic HBeAg- clinically managed | (cost) liver function test +  (cost) HBV profile +  (cost) HBV DNA test +  (cost) blood urea nitrogen, creatinine, & electrolytes +  (cost) full blood count +  (cost) alpha fetoprotein test +  (cost) abdominal ultrasonography +  (cost × quantity) brief outpatient visit |
| HBV chronic HBeAg- subclinical | 0 |
| HBV compensated cirrhosis on AVT | (cost) liver function test +  (cost) international normalized ratio test +  (2 × cost) HBV DNA test +  (cost) blood urea nitrogen, creatinine, & electrolytes +  (cost) full blood count +  (2 × cost) alpha fetoprotein test +  (2 × cost) abdominal ultrasonography +  (cost × quantity) brief outpatient visit |
| HBV compensated cirrhosis subclinical | 0 |
| HBV decompensated cirrhosis on AVT | (cost) liver function test +  (cost) international normalized ratio test +  (2 × cost) HBV DNA test +  (cost) blood urea nitrogen, creatinine, & electrolytes +  (cost) full blood count +  (2 × cost) alpha fetoprotein test +  (2 × cost) abdominal ultrasonography +  (cost × quantity) brief outpatient visit +  (cost) HBV antivirals for patients with cirrhosis |
| HBV decompensated cirrhosis subclinical | 0 |
| HBV hepatocellular carcinoma | (cost) liver function test +  (cost) international normalized ratio test +  (cost) Full blood count +  (cost) alpha fetoprotein test +  (cost) triphasic CT scan +  (cost) endoscopy with band ligation +  (cost) sorafenib +  (cost) transarterial chemoembolization |
| HBV related death or other-cause death | 0 |
| HCV acute subclinical | 0 |
| HCV acute with AVT | (cost) Ab screen and confirmation +  (2 × cost) HCV RNA test +  (cost) HCV genotyping +  (cost) liver function test +  (cost) Blood urea nitrogen, creatinine, & electrolytes +  (cost × quantity) brief outpatient visit +  (cost) HCV antivirals |
| HCV no infection | 0 |
| HCV chronic subclinical | 0 |
| HCV chronic with AVT | (cost) liver function test +  (cost) Blood urea nitrogen, creatinine, & electrolytes +  (cost) Full blood count +  (cost) alpha fetoprotein test +  (cost) abdominal ultrasonography +  (cost) HCV genotyping +  (2 × cost) HCV RNA test +  (cost × quantity) brief outpatient visit  (cost) HCV antivirals |
| HCV chronic treatment failure | (cost) liver function test +  (cost) Blood urea nitrogen, creatinine, & electrolytes +  (cost) Full blood count +  (cost) alpha fetoprotein test +  (cost) abdominal ultrasonography +  (cost) HCV genotyping +  (2 × cost) HCV RNA test +  (cost × quantity) brief outpatient visit |
| HCV compensated cirrhosis subclinical | 0 |
| HCV compensated cirrhosis with AVT | (cost) liver function test +  (cost) international normalized ratio test +  (cost) Blood urea nitrogen, creatinine, & electrolytes +  (cost) Full blood count +  (2 × cost) alpha fetoprotein test +  (2 × cost) abdominal ultrasonography +  (cost) HCV genotyping +  (2 × cost) HCV RNA test +  (cost × quantity) brief outpatient visit  (cost) HCV antivirals |
| HCV compensated cirrhosis treatment failure | (cost) liver function test +  (cost) international normalized ratio test +  (cost) Blood urea nitrogen, creatinine, & electrolytes +  (cost) Full blood count +  (2 × cost) alpha fetoprotein test +  (2 × cost) abdominal ultrasonography +  (cost) HCV genotyping +  (2 × cost) HCV RNA test +  (cost × quantity) brief outpatient visit |
| HCV decompensated cirrhosis subclinical | 0 |
| HCV decompensated cirrhosis with AVT | (cost) liver function test +  (cost) international normalized ratio test +  (cost) Blood urea nitrogen, creatinine, & electrolytes +  (cost) Full blood count +  (2 × cost) alpha fetoprotein test +  (2 × cost) abdominal ultrasonography +  (cost) HCV genotyping +  (3 × cost) HCV RNA test +  (2 × cost) endoscopy with band ligation +  (cost) spironolactone +  (cost) furosemide +  (cost × quantity) brief outpatient visit  (cost) HCV antivirals |
| HCV decompensated cirrhosis treatment failure | (cost) liver function test +  (cost) international normalized ratio test +  (cost) Blood urea nitrogen, creatinine, & electrolytes +  (cost) Full blood count +  (2 × cost) alpha fetoprotein test +  (2 × cost) abdominal ultrasonography +  (cost) HCV genotyping +  (3 × cost) HCV RNA test +  (2 × cost) endoscopy with band ligation +  (cost) spironolactone +  (cost) furosemide +  (cost × quantity) brief outpatient visit |
| HCV hepatocellular carcinoma | (cost) liver function test +  (cost) international normalized ratio test +  (cost) Full blood count +  (cost) alpha fetoprotein test +  (cost) triphasic CT scan +  (cost) endoscopy with band ligation +  (cost) sorafenib +  (cost) transarterial chemoembolization |
| HCV related death or other-cause death | 0 |

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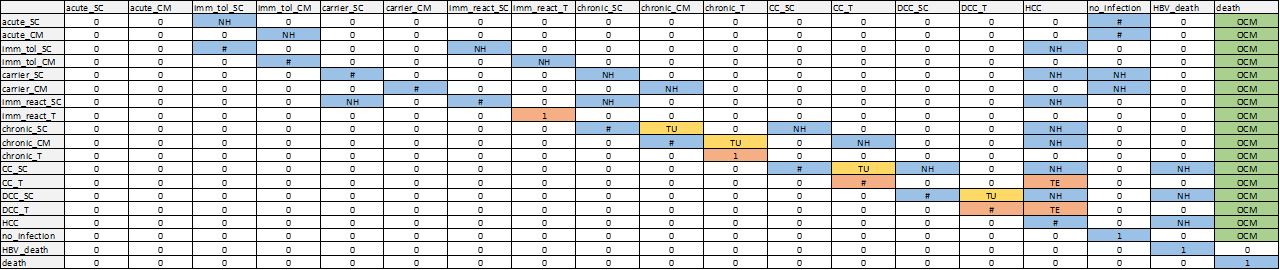
**Table S4** Calculated annual costs for each disease state in the HIV, HBV, and HCV disease progression Markov models

| **Disease state** | **Annual cost** | **Undiscounted Lifetime cost, Adult** | **Undiscounted Lifetime cost, Pediatric** | **Net present lifetime cost, Adult** | **Net present lifetime cost, Pediatric** |
| --- | --- | --- | --- | --- | --- |
| HBV | | | | | |
| Acute clinically managed | $134.46 | $6.72 | $6.72 | $6.72 | $6.72 |
| Acute subclinical | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 |
| Carrier clinically managed | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 |
| Carrier subclinical | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 |
| Chronic HBeAG- clinically managed | $179.30 | $56.01 | $256.13 | $24.21 | $72.03 |
| Chronic HBeAG- on AVT | $493.23 | $124.31 | $1,394.15 | $47.94 | $299.43 |
| Chronic HBeAG- subclinical | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 |
| Compensated cirrhosis on AVT | $1,116.34 | $199.99 | $1,970.19 | $78.30 | $436.89 |
| Compensated cirrhosis subclinical | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 |
| Decompensated cirrhosis on AVT | $2,076.14 | $11.35 | $94.40 | $4.48 | $21.98 |
| Decompensated cirrhosis subclinical | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 |
| HBV-related death | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 |
| Hepatocellular carcinoma | $4,210.60 | $590.69 | $1,064.21 | $360.08 | $501.91 |
| Immune reactive on AVT | $463.61 | $832.44 | $2,123.99 | $459.05 | $794.61 |
| Immune reactive subclinical | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 |
| Immune tolerant clinically managed | $137.68 | $143.35 | $162.57 | $111.65 | $120.85 |
| Immune tolerant subclinical | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 |
| No infection | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 |
| Other-cause death | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 |
| HCV | | | | | |
| Acute on AVT | $1,154.50 | $57.72 | $57.72 | $57.72 | $57.72 |
| Acute subclinical | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 |
| Chronic HCV on AVT | $1,173.40 | $638.34 | $673.03 | $529.72 | $552.87 |
| Chronic HCV subclinical | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 |
| Chronic HCV treatment failure | $523.40 | $245.67 | $473.53 | $146.08 | $212.30 |
| Compensated cirrhosis on AVT | $1,208.60 | $31.67 | $34.25 | $24.32 | $25.95 |
| Compensated cirrhosis subclinical | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 |
| Compensated cirrhosis treatment failure | $558.60 | $26.70 | $61.02 | $14.40 | $23.95 |
| Decompensated cirrhosis on AVT | $3,291.40 | $12.70 | $13.93 | $9.35 | $10.11 |
| Decompensated cirrhosis subclinical | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 |
| Decompensated cirrhosis treatment failure | $1,657.40 | $21.43 | $53.16 | $11.10 | $19.76 |
| HCV-related death | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 |
| Hepatocellular carcinoma | $4,210.60 | $40.23 | $68.46 | $25.99 | $34.42 |
| No infection | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 |
| Other-cause death | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 |
| HIV | | | | | |
| AIDS | $150.00 | $5.40 | $2.22 | $4.91 | $1.99 |
| ART year 1 | $186.70 | $178.93 | $184.14 | $168.24 | $172.96 |
| ART year 2 | $64.52 | $61.42 | $63.52 | $56.07 | $57.92 |
| ART year 3 | $57.02 | $53.87 | $56.05 | $47.75 | $49.62 |
| ART year 4+ | $46.35 | $1,138.88 | $2,562.77 | $662.24 | $1,050.48 |
| HIV-related death | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 |
| No ART, 1st year | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 |
| No ART, 2nd year | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 |
| No ART, 3+ years | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 |
| Other-cause death | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 |



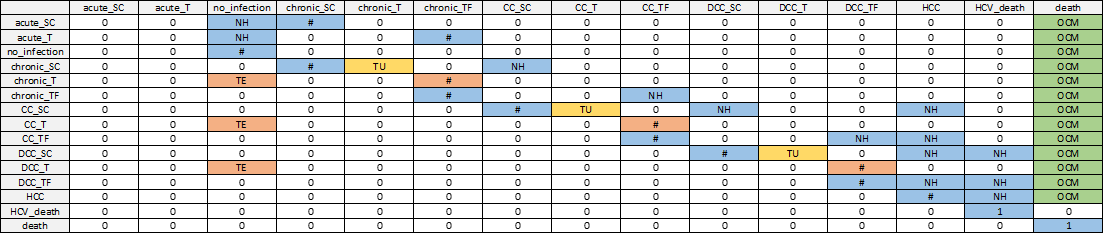
**Fig. S1.** Transition matrix schematic for HIV. Non-zero transition probabilities are indicated in blue for natural history transitions, yellow for treatment uptake transitions, orange for treatment effectiveness transitions, and green for other-cause mortality. Markov model constructed by first creating a transition matrix without treatment uptake or other-cause death; then adding in treatment uptake transitions while scaling other transitions such that each row still sums to 1; then adding in transitions to other-cause mortality with the same approach. Disease state names: AIDS, AIDS; ART\_1, ART year 1; ART\_2, ART year 2; ART\_3, ART year 3; ART\_4, ART year 4+; HIV\_death, HIV-related death; noART\_1, No ART, 1st year; noART\_2, No ART, 2nd year; noART\_3, No ART, 3+ years; death, Other-cause death. Abbreviations: NH, natural history (blue); TU, treatment uptake (marigold); TE, treatment effectiveness (orange); OCM, other cause mortality (green)

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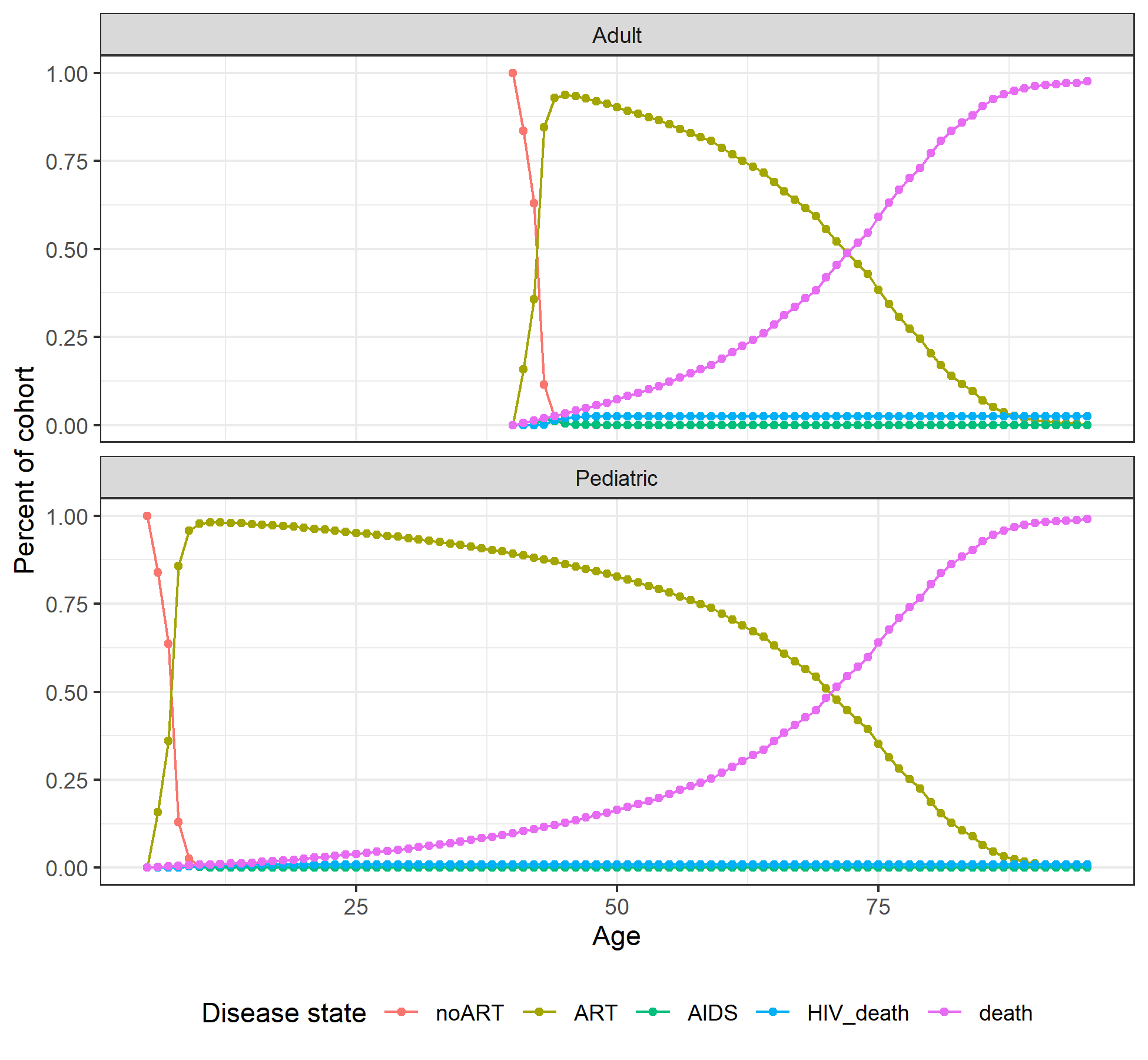


**Fig. S2.** Transition matrix schematic for HBV. Non-zero transition probabilities are indicated in blue for natural history transitions, yellow for treatment uptake transitions, orange for treatment effectiveness transitions, and green for other-cause mortality. Markov model constructed by first creating a transition matrix without treatment uptake or other-cause death; then adding in treatment uptake transitions while scaling other transitions such that each row still sums to 1; then adding in transitions to other-cause mortality with the same approach. Disease state names: acute\_CM, Acute clinically managed; acute\_SC, Acute subclinical; carrier\_CM, Carrier clinically managed; carrier\_SC, Carrier subclinical; CC\_SC, Compensated cirrhosis subclinical; CC\_T, Compensated cirrhosis on AVT; chronic\_CM, Chronic HBeAG- clinically managed; chronic\_SC, Chronic HBeAG- subclinical; chronic\_T, Chronic HBeAG- on AVT; DCC\_SC, Decompensated cirrhosis subclinical; DCC\_T, Decompensated cirrhosis on AVT; HBV\_death, HBV-related death; HCC, Hepatocellular carcinoma; imm\_react\_SC, Immune reactive subclinical; imm\_react\_T, Immune reactive on AVT; imm\_tol\_CM, Immune tolerant clinically managed; imm\_tol\_SC, Immune tolerant subclinical; init, Initiation; no\_infection, No infection; death, Other-cause death. Abbreviations: NH, natural history (blue); TU, treatment uptake (marigold); TE, treatment effectiveness (orange); OCM, other cause mortality (green)

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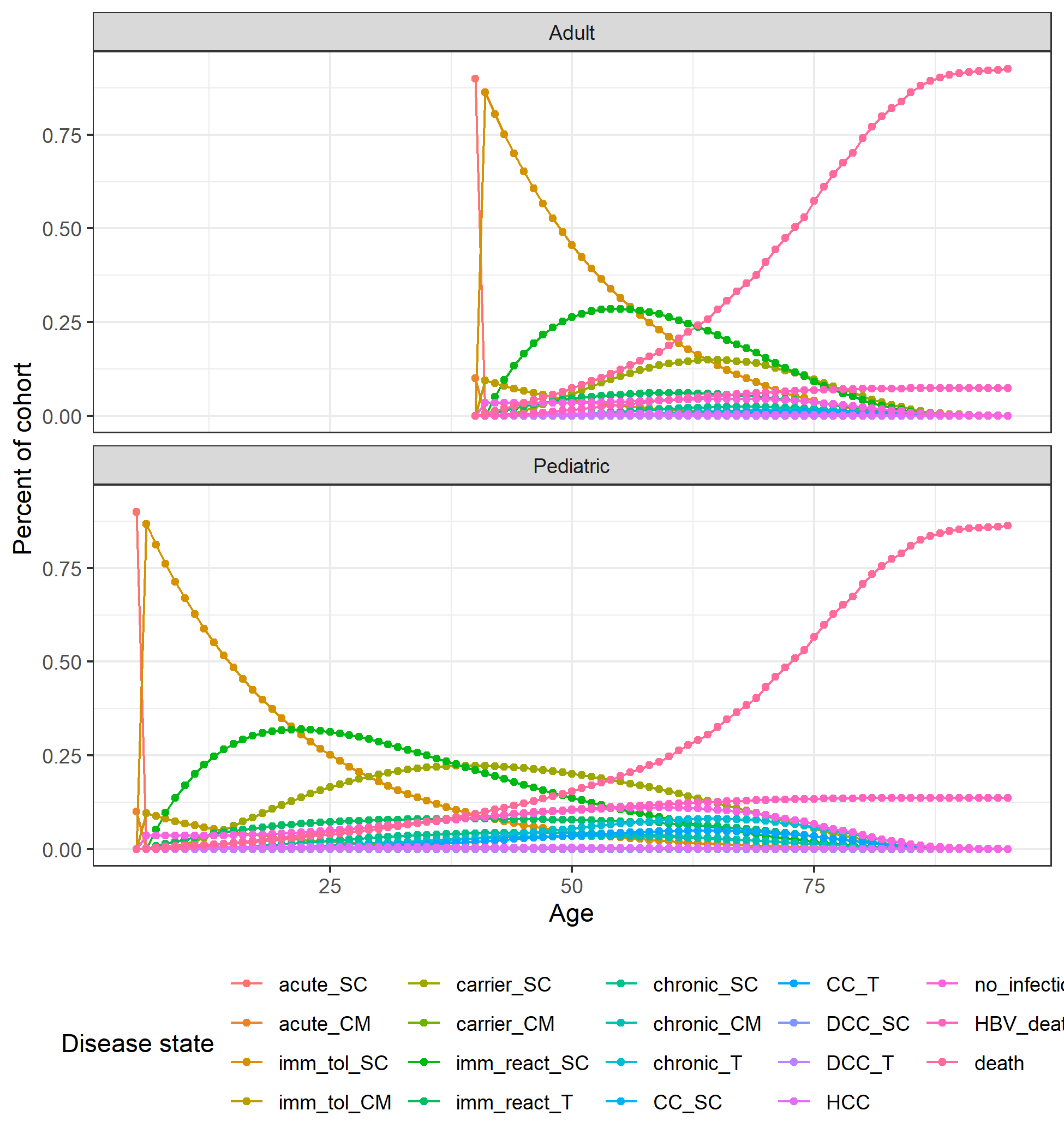


**Fig. S3.** Transition matrix schematic for HCV. Non-zero transition probabilities are indicated in blue for natural history transitions, yellow for treatment uptake transitions, orange for treatment effectiveness transitions, and green for other-cause mortality. Markov model constructed by first creating a transition matrix without treatment uptake or other-cause death; then adding in treatment uptake transitions while scaling other transitions such that each row still sums to 1; then adding in transitions to other-cause mortality with the same approach. Disease state names: acute\_SC, Acute subclinical; acute\_T, Acute on AVT; CC\_SC, Compensated cirrhosis subclinical; CC\_T, Compensated cirrhosis on AVT; CC\_TF, Compensated cirrhosis treatment failure; chronic\_SC, Chronic HCV subclinical; chronic\_T, Chronic HCV on AVT; chronic\_TF, Chronic HCV treatment failure; DCC\_SC, Decompensated cirrhosis subclinical; DCC\_T, Decompensated cirrhosis on AVT; DCC\_TF, Decompensated cirrhosis treatment failure; HCC, Hepatocellular carcinoma; HCV\_death, HCV-related death; init, Initiation; no\_infection, No infection; death, Other-cause death. Abbreviations: NH, natural history (blue); TU, treatment uptake (marigold); TE, treatment effectiveness (orange); OCM, other cause mortality (green)



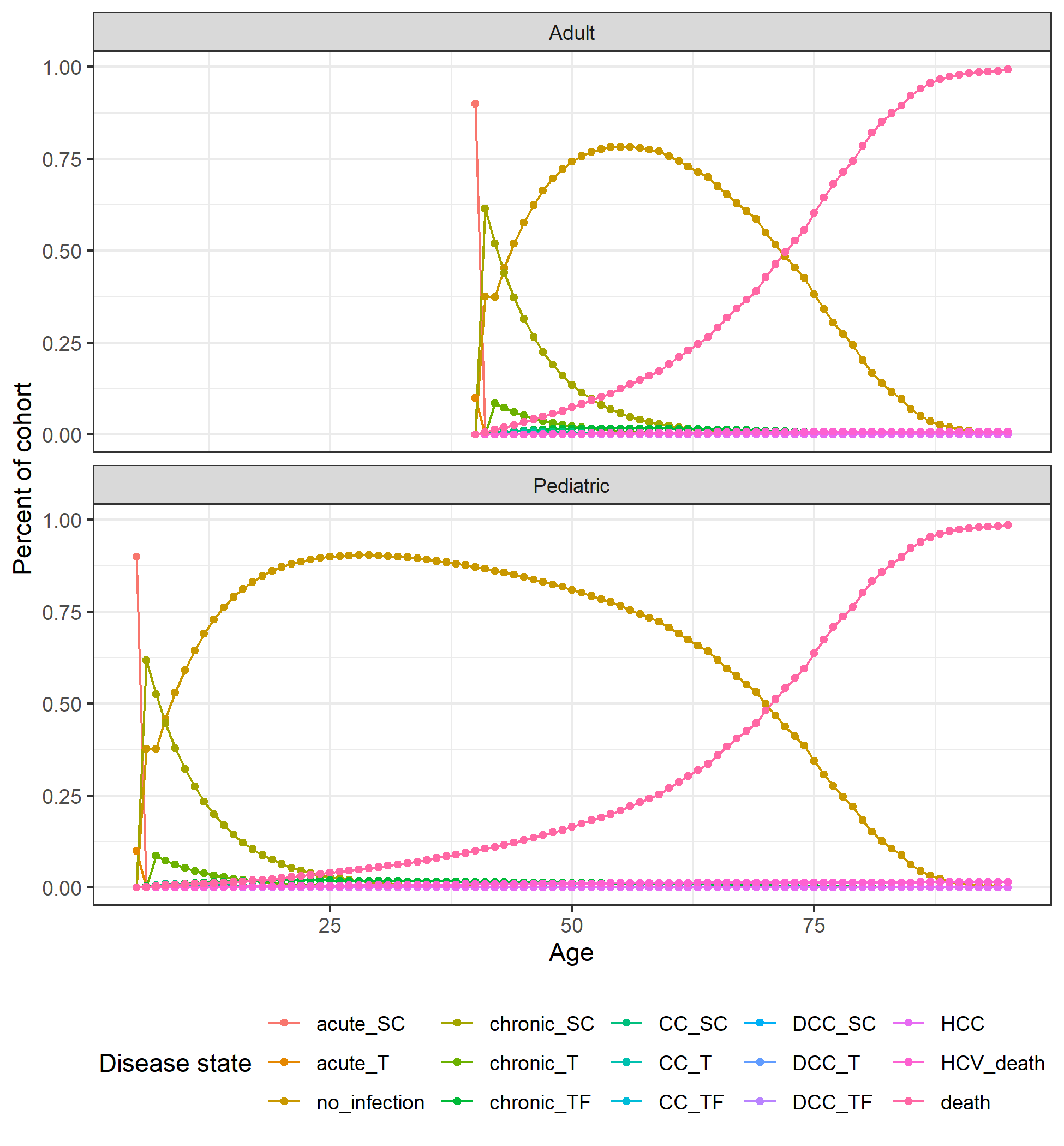
**Fig. S4.** Markov trace plot for HIV pediatric and adult cohorts. Disease state names: AIDS, AIDS; ART\_1, ART year 1; ART\_2, ART year 2; ART\_3, ART year 3; ART\_4, ART year 4+; HIV\_death, HIV-related death; noART\_1, No ART, 1st year; noART\_2, No ART, 2nd year; noART\_3, No ART, 3+ years; death, Other-cause death.

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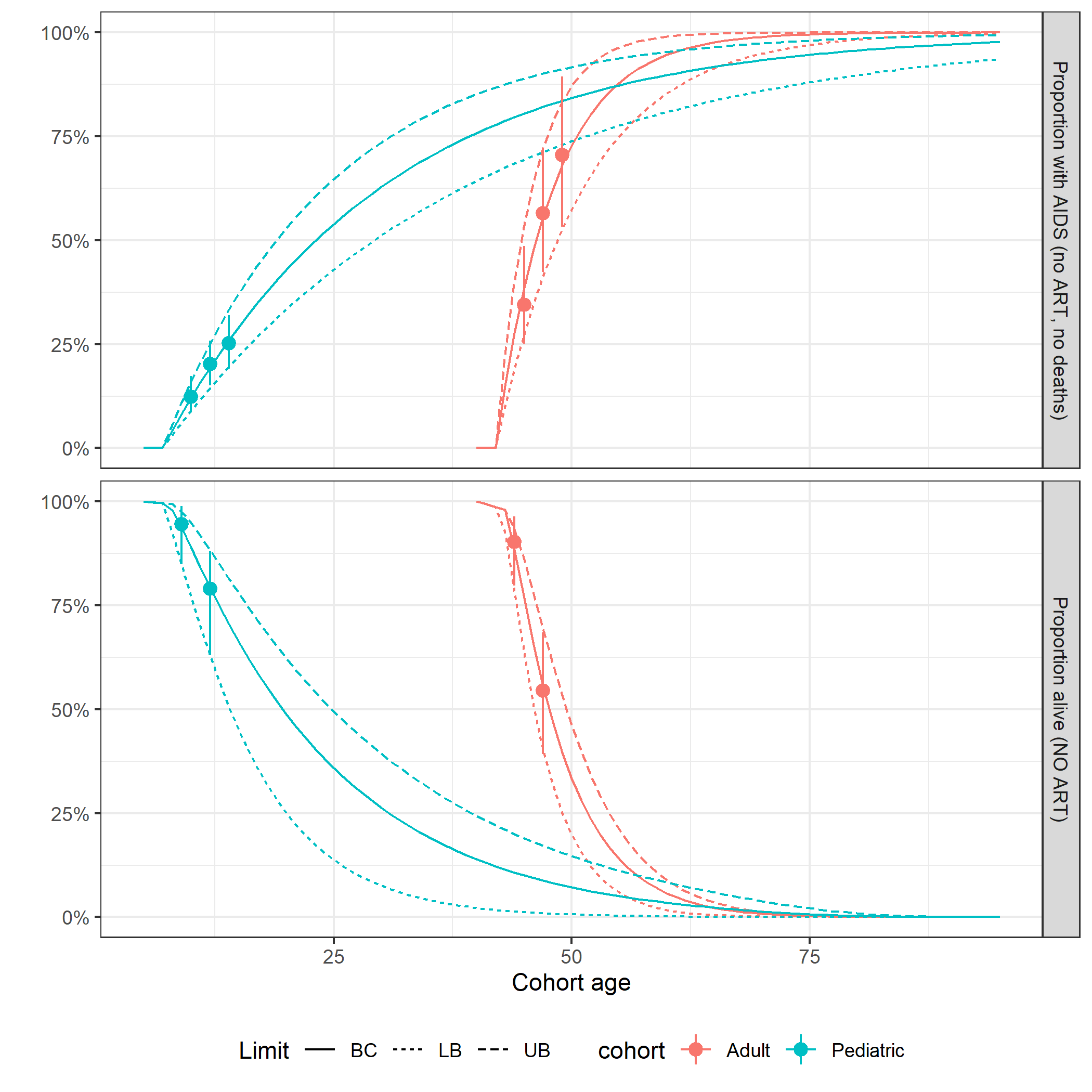
**Fig. S5.** Markov trace plot for HBV pediatric and adult cohorts. Disease state names: acute\_CM, Acute clinically managed; acute\_SC, Acute subclinical; carrier\_CM, Carrier clinically managed; carrier\_SC, Carrier subclinical; CC\_SC, Compensated cirrhosis subclinical; CC\_T, Compensated cirrhosis on AVT; chronic\_CM, Chronic HBeAG- clinically managed; chronic\_SC, Chronic HBeAG- subclinical; chronic\_T, Chronic HBeAG- on AVT; DCC\_SC, Decompensated cirrhosis subclinical; DCC\_T, Decompensated cirrhosis on AVT; HBV\_death, HBV-related death; HCC, Hepatocellular carcinoma; imm\_react\_SC, Immune reactive subclinical; imm\_react\_T, Immune reactive on AVT; imm\_tol\_CM, Immune tolerant clinically managed; imm\_tol\_SC, Immune tolerant subclinical; init, Initiation; no\_infection, No infection; death, Other-cause death.

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**Fig. S6.** Markov trace plot for HCV pediatric and adult cohorts. Disease state names: acute\_SC, Acute subclinical; acute\_T, Acute on AVT; CC\_SC, Compensated cirrhosis subclinical; CC\_T, Compensated cirrhosis on AVT; CC\_TF, Compensated cirrhosis treatment failure; chronic\_SC, Chronic HCV subclinical; chronic\_T, Chronic HCV on AVT; chronic\_TF, Chronic HCV treatment failure; DCC\_SC, Decompensated cirrhosis subclinical; DCC\_T, Decompensated cirrhosis on AVT; DCC\_TF, Decompensated cirrhosis treatment failure; HCC, Hepatocellular carcinoma; HCV\_death, HCV-related death; init, Initiation; no\_infection, No infection; death, Other-cause death.

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**Fig. S7.** Calibration plots for HIV transition probabilities.