Estimating HIV Management and Comorbidity Costs Among Aging HIV Patients in the United States: A Systematic Review

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ABSTRACT

BACKGROUND: As life expectancy of patients infected with human immunodeficiency virus (HIV) approaches that of the general population, the composition of HIV management costs is likely to change.

OBJECTIVES: To (a) review treatment and disease management costs in HIV, including costs of adverse events (AEs) related to antiretroviral therapy (ART) and long-term toxicities, and (b) explore the evolving cost drivers.

METHODS: A targeted literature review between January 2012 and November 2017 was conducted using PubMed and major conferences. Articles reporting U.S. costs of HIV management, acquired immunodeficiency syndrome (AIDS)-defining events, end of life care, and ART-associated comorbidities such as cardiovascular disease (CVD), chronic kidney disease (CKD), and osteoporosis were included. All costs were inflated to 2017 U.S. dollars. A Markov model-based analysis was conducted to estimate the effect of increased life expectancy on costs associated with HIV treatment and management.

RESULTS: 22 studies describing HIV costs in the United States were identified, comprising 16 cost-effectiveness analysis studies, 5 retrospective analyses of health care utilization, and 1 cost analysis in a resource-limited setting. Management costs per patient per month, including routine care costs (on/off ART), non-HIV medication, opportunistic infection prophylaxis, inpatient utilization, outpatient utilization, and emergency department utilization were reported as CD4+ cell-based health state costs ranging from \$1,192 for patients with CD4 > 500 cells/mm³ to \$2,873 for patients with CD4 < 50 cells/mm³. Event costs for AEs ranged from \$0 for headache, pain, vomiting, and lipodystrophy to \$31,545 for myocardial infarction. The mean monthly per-patient costs for CVD management, CKD management, and osteoporosis were \$5,898, \$6,108, and \$4,365, respectively. Improvements in life expectancy, approaching that of the general population in 2018, are projected to increase ART-related and AE costs by 35.4% and comorbidity costs by 175.8% compared with estimated costs with HIV life expectancy observed in 1996.

CONCLUSIONS: This study identified and summarized holistic cost estimates appropriate for use within U.S. HIV cost-effectiveness analyses and demonstrates an increasing contribution of comorbidity outcomes, primarily associated with aging in addition to long-term treatment with ART, not typically evaluated in contemporary HIV cost-effectiveness analyses.

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What is already known about this subject

- Improvements in antiretroviral therapy (ART) have steadily increased the life expectancy of human immunodeficiency virus (HIV) patients, which is now approaching that of the general population.
- Limited data are available on the effect of long-term toxicities and age-related comorbidities on health care costs for patients with HIV in the United States.
- As HIV treatment efficacy has improved over the years, more patients are becoming virally suppressed; consequently, HIV patients are estimated to incur lower costs due to HIV management, which includes costs for treatment of acquired immunodeficiency syndrome-defining events.

What this study adds

- The proportion of HIV management costs attributable to ART-associated long-term toxicities such as cardiovascular disease, chronic kidney disease, and osteoporosis was estimated to increase as patients living with HIV approach life expectancy of the general population.
- The overall cost of HIV management has increased over the last few years and is projected to increase further as patients live longer and experience more ART-related comorbidities.
- The composition of these costs is also changing, with the cost of ART-related comorbidities, treatment, and adverse events playing a much greater role than before.

Human immunodeficiency virus (HIV) causes the progressive deterioration of the immune system through impairment of immune cells such as CD4 lymphocytes, thus making the host more susceptible to infections and other adverse outcomes.¹ Treatment for HIV infections using antiretroviral therapy (ART) has improved steadily since the advent of potent combination therapy in 1996. With successful treatment, patients can have a life expectancy nearly equivalent to that of the general population.^{2,3} Over the past 2 decades, this has resulted in significant reductions in acquired immunodeficiency syndrome (AIDS)-related deaths, thereby transforming HIV infection to a chronic condition.⁴

HIV prevalence in the United States was estimated to include 1.1 million people aged 13 years or over living with

TABLE 1 Costs Used in Model Inputs

Variable		Mean Value (USD)	Standard Error (USD)	Source
Outpatient care	CD4 < 50	67	6.72	Farnham et al. ²³
	CD4 50-200	73	7	
	CD4 200-350	71	7	
	CD4 350-500	68	7	
	CD4 > 500	66	7	
ED visits	CD4 < 50	117	12	
	CD4 50-200	53	5	
	CD4 200-350	30	3	
	CD4 350-500	23	2	
	CD4 > 500	16	2	
Inpatient days	CD4 < 50	2,162	216	
	CD4 50-200	892	89	
	CD4 200-350	389	39	
	CD4 350-500	243	24	
	CD4 > 500	191	19	
CD4+ cell count test	CD4 < 50	18	2	
	CD4 50-200	18	2	
	CD4 200-350	18	2	
	CD4 350-500	18	2	
	CD4 > 500	18	2	
HIV-1 RNA test	CD4 < 50	42	4	
	CD4 50-200	42	4	
	CD4 200-350	42	4	
	CD4 350-500	42	4	
	CD4 > 500	42	4	
OI prophylaxis	CD4 < 50	107	11	
	CD4 50-200	68	7	
	CD4 200-350	28	3	
	CD4 350-500	17	2	
	CD4 > 500	11	1	
Non-HIV medication	CD4 < 50	238	24	
	CD4 50-200	230	23	
	CD4 200-350	213	21	
	CD4 350-500	217	22	
	CD4 > 500	242	24	

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HIV (PLHIV) in 2015, of whom 162,500 were undiagnosed patients.⁵ The incidence of new HIV diagnoses in the United States is steady, with 38,739 new patients diagnosed in 2017.⁵ With the advent of newer, more potent ARTs, the life expectancy of patients living with HIV has substantially improved, and by 2020, an estimated 70% of PLHIV in the United States are projected to be aged 50 years and above.^{6,7} HIV requires life-long treatment, and chronic use of ART has been shown to significantly increase the risk of fractures and osteoporosis, renal and metabolic disorders, central nervous system (CNS) disorders, cardiovascular disease (CVD), and liver disease.⁸ These long-term ART toxicities, coupled with comorbidities, which are more prevalent in PLHIV, have the potential to substantially increase health care resource utilization and costs associated with HIV management.

Historically, U.S. health economic analyses in HIV have focused on the costs associated with HIV treatment and management, costs of AIDS-defining events, and to a lesser extent, HIV prevention costs.⁹⁻¹⁶ However, considering the increasing prevalence of ART-related long-term toxicities and age-related HIV comorbidities, an assessment of their impact on health care costs is warranted. The objective of this study was to review costs associated with HIV management, with particular focus on ART-related long-term toxicities, including CVD, chronic kidney disease (CKD), and osteoporosis. A secondary objective was to subsequently highlight and quantify the evolving cost drivers associated with HIV management through an economic modeling analysis.

TABLE 1 Costs Used in Model Inputs (*continued*)

Variable		Mean Value (USD)	Standard Error (USD)	Source
AE treatment costs	Diarrhea (grade 3/4)	204	20	Simpson et al. ³⁴
	Nausea (grade 3/4)	264	26	
	Vomiting (grade 3/4)	0	0	
	Rash/injection site reaction (grade 3)	97	10	
	Nightmares/abnormal dreams (grade 3/4)	1,426	143	Dekoven et al. ⁴⁸
	Dizziness (grade 3/4)	1,457	146	
	Depression (grade 3/4)	2,590	259	
	Insomnia (grade 3/4)	1,426	142.58	
CVD costs	Initial cost associated with CVD event	3,890	389	Smit et al. ²⁶
	Additional monthly costs applied in each subsequent month	3,890	389	
Costs of death: End of life care cost (last 3 months)		75,397	7,540	Morris et al. ³⁵
Individual AIDS-defining event costs	Acute viral OI-related costs	6,868	687	Farnham et al. ²³
	Acute bacterial OI-related costs	4,412	441	
	Acute fungal OI-related costs	7,519	752	
	Acute protozoal OI-related costs	25,957	2,596	
	Other OI-related costs	5,036	504	
Long-term toxicity: Cost associated with fracture	Forearm	1,979	198	Burge et al. ²⁴
	Shoulder	1,979	198	Assumption
	Hip	59,702	5,970	Burge et al. ²⁴
	Spine	2,889	289	
Long-term toxicity: Cost associated with CKD	Stage 1	0	0	Assumption
	Stage 2	0	0	Assumption
	Stage 3	3,056	306	Smit et al. ²⁶
	Stage 4	3,056	306	Smit et al. ²⁶
	Stage 5	3,056	306	Smit et al. ²⁶

AE=adverse event; AIDS=acquired immunodeficiency syndrome; CKD=chronic kidney disease; CVD=cardiovascular disease; ED=emergency department; HIV=human immunodeficiency syndrome; OI=opportunistic infection; USD=U.S. dollars.

Methods

Literature Review

A targeted literature review was conducted to identify estimates of U.S. costs of HIV management. The review was designed according to the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) checklist.¹⁷ The search strategy used to identify articles is displayed in Appendix A (available in online article). PubMed searches were conducted from January 2012 to November 2017. In addition, 4 conference abstract databases comprising the International Society for Pharmacoeconomics and Outcomes Research (U.S. and European), ID Week contributors (Infectious Diseases Society of America, Society for Healthcare Epidemiology of America, HIV Medicine Association, and Pediatric Infectious Disease Society), and International Aids Society were searched for studies published over the last 5 years.

Titles and abstracts identified by the search strategy were selected based on eligibility criteria. Studies in adult PLHIV reporting costs of HIV management, in particular CD4+ or viral load-based health states, adverse events (AEs), AIDS-defining events, and end of life care, were included. Studies reporting costs of common long-term ART toxicities such as

CVD, CKD, and osteoporosis, including fractures, were also included. The inclusion criteria restricted studies to cost of illness studies or economic evaluations published in the English language. The costs associated with HIV testing, AEs, comorbidities, and HIV management were extracted and inflated to 2017 U.S. dollars using the U.S. Bureau of Labor Statistics Consumer Price Index before reporting in this study.¹⁸ Where mean costs are presented, a simple mean across endpoints was utilized (i.e., means were not weighted).

Modeling

A modeling analysis was undertaken to estimate the impact of increased life expectancy among PLHIV on costs associated with HIV treatment and management. A previously presented and validated economic model was used.¹⁹⁻²² Model inputs were derived from U.S.-focused publications where possible, and U.S.-specific costs identified by the literature review were used (Table 1). Our model used published values of CD4 health state costs and AIDS-defining events estimated using simulation techniques by Farnham et al. (2013) to predict HIV-related events and associated costs over patient lifetimes.²³ Costs related to fractures were estimated from a study by Burge et al.

TABLE 2 Summary of Modeling Studies for CEAs or Economic Evaluations

Author	Cost/Resource Description	Cost/Resource Source and Description
Modeling studies		
Bayoumi et al. ³⁶	<ul style="list-style-type: none"> Monthly HIV-related treatment costs, excluding drugs, by CD4 cell count category; and monthly drug costs, excluding ART, by CD4 cell count category Serious AE (per event) costs for first and second events Monthly HIV-related treatment costs, excluding drugs, by AIDS event incidence Monthly drug costs, excluding ART, by AIDS event incidence 	<p>The majority of parameters were estimated from the OPTIMA trial (Holodniy et al.)⁵³ and the Department of Veterans Affairs; Barnett et al. (Department of Veterans Affairs)⁶¹</p> <p>Unit costs: U.S. Veterans Health Administration</p> <p>Inpatient costs: Regression method</p> <p>Outpatient costs: Medicare</p>
Borre et al. ³⁸	<ul style="list-style-type: none"> Routine care cost by CD4 cell count category, monthly, off/on ART costs Monitoring costs per test: HIV RNA and CD4 cell count 	<p>Gebo et al.⁶² and Bozzette et al.⁶³</p> <p>Monitoring costs: CMS⁶⁷</p> <p>Costs estimated based on average price for monthly supply of medication and dosage with dispensing/administration fees from a national retail pharmacy, a university-based hospital participating in a buying consortium, and a federal distributor (Bozzette et al.)</p>
Cragin et al. ³⁹	<ul style="list-style-type: none"> Monthly costs: Post-diagnosis, pre-HAART (physician counseling, CD4 count test, and viral load test every 3 months) Pre-AIDS on HAART cost AIDS cost 	<p>Schackman et al.¹⁵</p> <p>Average cost per inpatient day: Derived from the University Health System Consortium database of costs for academic medical centers and affiliated community hospitals in the U.S. (Schackman et al.¹⁵)</p>
Farnham et al. ²³	<ul style="list-style-type: none"> Health care utilization costs by CD4 cell count category (quarterly): Non-HIV medication, OI prophylaxis, inpatient utilization, outpatient utilization, ED utilization Cost of AIDS-defining event (per event): PCP, MAC, toxoplasmosis, CMV, fungal infection, other Disease monitoring costs: CD4 count test (applied quarterly), HIV RNA viral load testing (applied quarterly), HIV genotype testing (applied at initiation of each ART) Other: Non-HIV medication costs only (applied to individuals not in care; mean for all CD4 cell counts), program cost per positive HIV test (ED scenario) 	<p>Gebo et al.⁶⁴</p> <p>Cost calculations were performed from the perspective of a large-scale purchaser of services. Expenditures were estimated by multiplying utilization data for inpatient days, outpatient visits, ED visits, and lab tests by a unit cost. Data on charges and cost-to-charge ratios for HIV-related inpatient admissions from the Healthcare Expenditure and Utilization Project State Input Databases were used to estimate unit cost/inpatient day (Gebo et al.⁵⁴)</p> <p>Estimated unit cost for outpatient visit: 2006 Medicare payment for outpatient visit involving complex evaluation and management</p>
Girouard et al. ³⁷	<ul style="list-style-type: none"> Routine care by CD4 category (annual cost) Disease monitoring costs (assumed per event): CD4 cell test, HIV RNA test 	<p>Walensky et al.⁴⁶ who, in turn, sourced costs from Gebo et al.⁶⁴</p> <p>Costs from CMS, Clinical Diagnostic Laboratory Fee Schedule</p>
Hutchinson et al. ⁴⁰	<ul style="list-style-type: none"> HIV testing costs (annual, per patient), fourth generation: Assay, test kit costs, labor costs, specimen collection, pretest information, Western blot, labor, controls, total test cost HIV testing costs (annual, per patient), rapid: Assay, test kit costs HIV testing-related labor costs: Specimen collection, pretest information, Western blot, labor, controls, total test cost Tests: CD4 count, viral load test, resistance testing, outpatient costs 	<p>The HIV Detection and Transmission mathematical model⁴⁶</p> <p>Lifetime costs based on Farnham et al.²³ and Schackman et al.⁴² which sourced costs from Gebo et al.⁶⁴</p>
Juusola et al. ⁴⁷	<ul style="list-style-type: none"> Annual HIV-related health care costs, mean (range): Acute HIV, asymptomatic HIV (untreated), symptomatic HIV (untreated), symptomatic HIV (treated with ART) (excludes ART costs) Cost of AIDS: Untreated, treated with ART (excludes ART costs) Annual non-HIV-related health care costs for uninfected and infected individuals Cost of HIV antibody testing: Uninfected, HIV-infected 	<p>Dynamic compartmental model of HIV transmission and progression⁴⁷ utilizing HIV cost study values: Long et al.⁶⁵ and Bozzette et al.⁶³</p> <p>Annual HIV-related costs: Juusola et al.,⁴⁷ Vergis et al.,⁶⁸ Schacker et al.,⁶⁹ Daar et al.,⁷⁰ Long et al.,⁷¹ Bozzette et al.,¹⁴ Schackman et al.,¹⁵ Barnett et al.⁶¹</p> <p>Cost of AIDS: Long et al.,⁷¹ Bozzette et al.,¹⁴ Schackman et al.,¹⁵ Barnett et al.,⁶¹ Gebo et al.,¹² Hutchinson et al.,⁷² Sanders et al.⁷³</p> <p>HIV testing: CMS⁶⁷</p>
Morris et al. ³⁵	<ul style="list-style-type: none"> Routine care (by CD4, monthly) on ART AIDS-defining events (cost per infection): Pneumocystis jirovecii pneumonia, MAC, toxoplasmosis, CMV, fungal infections, other OIs End of life care: Chronic AIDS, any other event Other costs: CD4 test, HIV RNA test 	<p>Routine care, acute OI events, end of life care: Gebo et al.⁶², Schackman et al.¹⁵, University Health System Consortium⁷⁴</p> <p>Other costs: CMS⁶⁷</p>

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TABLE 2 Summary of Modeling Studies for CEAs or Economic Evaluations (continued)

Author	Cost/Resource Description	Cost/Resource Source and Description
Peng et al. ⁴¹	<ul style="list-style-type: none"> AIDS-defining events, acute AIDS-related events (per event): Cervical cancer, cryptosporidiosis, coccidiosis, oral esophageal candidiasis, histoplasmosis, PCP, pneumonia, salmonella sepsis, tuberculosis Chronic AIDS-related events (annual): AIDS dementia, CMV retinitis, CMV colitis/other, cryptococcal meningitis, Kaposi's sarcoma cutaneous, Kaposi's sarcoma visceral, lymphoma (central nervous system), lymphoma (other), MAC, PML, toxoplasmic encephalitis, wasting syndrome CVD cost per episode Other costs: Disease monitoring long-term follow-up costs (incurred every 3 months), non-AIDS-related cancer (annual), non-AIDS-related infection (per episode) 	<p>Disease monitoring, AIDS-defining events, chronic AIDS-related events, other costs: Simpson et al.³⁴ who derived AIDS-defining events from event data for South Carolina Medicaid patients from 2002-2003⁷⁵</p> <p>CVD: 2007 and 2008 HCUP state inpatient data from State Inpatient Databases⁷⁶</p>
Schackman et al. ⁴³	<ul style="list-style-type: none"> Cost of genotyping for resistance 	Schackman et al., ⁷⁷ which sourced costs from the Clinical Laboratory Fee Schedule 2009 ⁷⁸
Schackman et al. ⁴²	<ul style="list-style-type: none"> All-cause health care cost by CD4 for different age groups (estimated mean monthly costs): 18-29 years old, 30-39 years old, 40-49 years old, 50+ years old Other costs: Inpatient visit, outpatient visit, ED visit, CD4 test, HIV RNA test 	<p>Gebo et al.⁶⁴</p> <p>All-cause health care cost, ED visits: Medical expenditure panel survey⁷⁹ and Medicare data; HIVRN</p> <p>Inpatient cost: HCUP SID^{80,81}</p> <p>Outpatient: Medicare National Physician Fee Schedule 2009</p> <p>HIV/CD4 test: Medicare and Medicaid⁸²</p>
Simpson et al. ³⁴	<ul style="list-style-type: none"> AEs; non-serious side effects (per episode): Diarrhea, headache, nausea, pain, rash, vomiting Serious side effects (per episode): Acute hepatitis/liver failure, acute renal failure, cholelithiasis, intracranial hemorrhage, nephrolithiasis, pancreatitis, severe rash/toxic epidermal necrolysis, MI, stroke, lipoatrophy, lipodystrophy AIDS-defining events; acute OIs (per episode): Cervical cancer, cryptosporidiosis, coccidiosis, oral esophageal candidiasis, histoplasmosis, PCP, pneumonia, salmonella sepsis, tuberculosis Chronic AIDS-related events (per month): AIDS dementia, CMV retinitis, CMV colitis/other, cryptococcal meningitis, Kaposi's sarcoma cutaneous, Kaposi's sarcoma visceral, lymphoma (central nervous system), lymphoma (other), MAC, PML, toxoplasmic encephalitis, wasting syndrome 	AEs, serious and non-serious side effects, AIDS-defining events, chronic AIDS-related events: South Carolina Medicaid data 2002 and 2003 ⁸³
Smit et al. ²⁶	<ul style="list-style-type: none"> CVD: Inpatient admissions, outpatient services, prescription medication (non-ART), total cost (annual) CKD: Inpatient admissions, outpatient services, prescription medication (non-ART), total cost (annual) Other HIV costs: Inpatient admissions, outpatient services, prescription medication (non-ART), ART Diabetes: Inpatient admissions, outpatient services, prescription medication (non-ART), total costs 	<p>Adaptation of a Dutch patient-level simulation model to the U.S. setting⁵⁰</p> <p>Annual per-capita costs estimated by calculating incremental costs in HIV-positive patients with the NCDs to costs for matched HIV-positive patients without the NCD</p>
Song et al. ⁴⁴	<ul style="list-style-type: none"> Annual HIV-related health care costs: Acute HIV, asymptomatic HIV (untreated), symptomatic HIV (untreated), symptomatic HIV (treated with ART; excludes ART cost) 	<p>All costs from Gebo et al.⁶⁴ and Krentz et al.⁶⁶</p> <p>Gebo et al.⁶⁴: Expenditures estimated by multiplying utilization data for inpatient days, outpatient visits, ED visits, and lab tests by a unit cost</p> <p>Krentz et al.⁶⁶: ARV and non-ARV drug costs, lab utilization, and outpatient care costs were derived directly from the SAC pharmacy, Calgary Laboratory Services, and the SAC costing database. Inpatient costs (i.e., unit service costs) were supplied by the regional health service providers. The unit costs used are market values charged to the regional payer (Calgary Health Region). All costs were obtained directly from the costing agencies, reported in Canadian dollars, and adjusted for inflation to 2006</p>

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TABLE 2 Summary of Modeling Studies for CEAs or Economic Evaluations (*continued*)

Author	Cost/Resource Description	Cost/Resource Source and Description
Sweet et al. ⁴⁵	<ul style="list-style-type: none"> All-cause health care costs by CD4 (ART not included, annual): Inpatient costs/other medical costs Other: <ul style="list-style-type: none"> o STR: Total costs, medication costs, inpatient costs, other costs o MTR: Total costs, medication costs, inpatient costs, other costs 	All costs from Gebo et al. ⁶⁴
Walensky et al. ⁴⁶	<ul style="list-style-type: none"> Routine care by CD4 count, annual (excluding ART) Per-person costs by CD4: No ART, 3-pill generic ART, branded ART 	Routine care by CD4 count: Gebo et al., ⁸⁴ Bamezai et al., ⁸⁵ University Health System Consortium Gebo et al. ⁸⁴ : Expenditures estimated by multiplying utilization data for inpatient days, outpatient visits, ED visits, and lab tests by a unit cost ⁸⁴
Retrospective review of claims data		
Ritchwood et al. ⁵⁰	<ul style="list-style-type: none"> Unadjusted means of total costs and breakdown of health care expenditures: Total, inpatient, office-based, medications, outpatient, ED, home health, dental 	All costs from Medical Expenditure Panel Survey-Household Component for the years 2002-2011
Dekoven et al. ⁴⁸	AEs: <ul style="list-style-type: none"> • Depression (all-cause health care costs) • Diabetes/insulin resistance (all-cause health care costs) • Diarrhea (all-cause health care costs) • Dizziness (all-cause health care costs) • Hepatic disorders (all-cause health care costs) • Lipid disorders (all-cause health care costs) • Nausea/vomiting (all-cause health care costs) • Rash (all-cause health care costs) • Renal disorders (all-cause health care costs) • Somnolence/sleep effects (all-cause health care costs) 	Data derived from IMS Health's PharMetrics Plus Health Plan Claims Database Inpatient costs based on hospitalizations, with ICD-9 diagnosis code reported ICD-9 codes were used to calculate outpatient costs (ED visits, GP visits, lab and pathology claims, radiology, surgery, and ancillary services)

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(2007) (the underlying study utilized by Gallant et al. [2018]), while CKD and CVD costs were informed by Smit et al. (2017).²⁴⁻²⁶ Costs and benefits were discounted at a rate of 3% annually.

The model has been described in detail elsewhere.¹⁹⁻²² In brief, modeled health states included CD4 cell count-based health states nested within 3 strata of viral load and death. Patients initiated their first treatment (ART 1) in one of the CD4 and viral load states based on their baseline parameters. During each monthly cycle, patients' viral status can improve, decline, or remain constant, driven by treatment-specific efficacy estimates. Four treatment lines are incorporated: 3 defined ART regimens and 1 unspecified salvage therapy line composed of pooled ART regimens. Patients are assumed to be at risk of experiencing treatment failure due to AEs, virologic failure (inability to achieve HIV RNA level <50 copies/mL), and viral rebound (HIV RNA ≥ 50 copies/mL after virologic suppression). Upon discontinuation, patients moved to the next treatment line. In a typical cycle length of 1 month, patients were exposed to risks of treatment-related AEs, AIDS-defining events, CVD events, CKD progression, bone fractures, and death.

Analyses

The current analysis focused on the potential impact of improving HIV survival on the incidence and costs of CVD, end-stage renal disease (ESRD), and fracture incidence. Utilizing published estimates, the model was calibrated to HIV-specific life expectancy predicted at different time points between 1996 and 2008.²⁷ Mortality in the cost-effectiveness model is estimated based on country-specific life table estimates adjusted based on relative risks stratified by CD4 cell counts; calibration was undertaken through adjustment of virologic suppression rates for PLHIV, with historic cohorts less likely to remain suppressed. The incidence of CVD was estimated using Framingham risk equations and the incidence of fractures was estimated by the Sheffield FRAX tool.^{28,29} The incidence of CKD stage 5 was defined as an estimated glomerular filtration rate (eGFR) of <15 mL/min/1.73 m². An annual decline in eGFR (mean annual decline: -1.23 mL/min/1.73 m²) and bone mineral density (mean annual decline: -0.0029 g/cm³) was applied based on published literature.^{30,31} With the exception of age, all prognostic factors utilized by the Framingham risk equations remained constant over the modeled horizon.

TABLE 2 Summary of Modeling Studies for CEAs or Economic Evaluations (*continued*)

Author	Cost/Resource Description	Cost/Resource Source and Description
Gallant et al. ²⁵	<p>CVD, CKD, and fracture per-patient per-month costs:</p> <ul style="list-style-type: none"> • Commercial (private payer) (CVD, CKD, and fracture), Medicare (public payer) (CVD and CKD): • Inpatient admissions • Outpatient services • ED visits (outpatient subset) • Prescriptions total • Prescription HIV medications • Prescription non-HIV medications • Total health care expenditures • Incremental health care expenditures <p>Other costs; CKD + CVD event population, per-patient per-month costs (case):</p> <ul style="list-style-type: none"> • Commercial (private payer) and Medicare (public payer) • Inpatient admissions • Outpatient services • Prescriptions total • Prescription HIV medications • Prescription non-HIV medications • Total health care expenditures 	U.S. administrative claims data representing private (commercial) and public (Medicaid) payer segments from the MarketScan Commercial Claims and Encounters database (commercial) and the MarketScan Multi-State Medicaid (Medicaid) database
Korsnes et al. ⁴⁹	<p>Other costs:</p> <ul style="list-style-type: none"> • Mean cost per patient: Inpatient cost, ED cost, prescription cost, non-pharmacy service 	All costs from the MarketScan family of databases: MarketScan Commercial Claims and Encounters Database and the Medicare Supplemental and Coordination of Benefits database (commercial) and state Medicaid programs (MarketScan's Medicaid Multi-State Database)
Solem et al. ⁵¹	<ul style="list-style-type: none"> • Other costs by CD4 (unadjusted total costs per patients per month) 	All costs from the MarketScan Commercial Claims and Encounters Database (2007-2011) and the MarketScan Lab Database (2007-2010)

AE = adverse event; AIDS = acquired immunodeficiency syndrome; ART = antiretroviral therapy; CEA = cost-effectiveness analysis; CKD = chronic kidney disease; CMS = Centers for Medicare & Medicaid Services; CMV = cytomegalovirus; CVD = cardiovascular disease; ED = emergency department; HAART = highly active antiretroviral therapy; HCUP = Healthcare Cost and Utilization Project; HIV = human immunodeficiency virus; HIVRN = HIV Research Network; ICD-9 = International Classification of Diseases, Ninth Revision; MAC = mycobacterium avium complex; MI = myocardial infarction; MTR = multi-tablet regimen; NCD = noncommunicable disease; OI = opportunistic infection; PCP = pneumocystis pneumonia; PML = progressive multifocal leukoencephalopathy; SAC = Southern Alberta Cohort; SID = state inpatient database; STR = single-tablet regimen.

A comparative analysis was performed utilizing 6 hypothetical cohorts, representing the life expectancy of PLHIV at different periods in time, with a baseline age of 20 years modeled over a lifetime. These included patients that do not achieve viral suppression (assumed equivalent to survival prior to the introduction of multiclass combination ART [approved by the U.S Food and Drug Administration in 1997]; cohort 1); patients with survival rates observed in years 1996, 2000, 2004, and 2008 (cohorts 2-5); and patients achieving a life expectancy equivalent to the general population in the United States in 2018 (cohort 6).^{32,33} The predicted cumulative incidence of CVD; CKD stage 5; and hip, spine, shoulder, and arm fractures and total lifetime HIV-related costs were compared. Analyses were varied probabilistically to reflect the heterogeneity of the population by varying clinical inputs related to CVD, ESRD,

and fracture incidence, with all other parameters remaining unchanged.

Results

The index searches identified 1,347 references resulting in 59 full-text articles. In total, 33 publications that described costs or resource use in the U.S. setting were included in the qualitative synthesis of this study (Appendix B, available in online article). Of these, 5 conference proceedings that did not present the costing year were excluded from the final selection.

Of the 22 full-text publications that fully described costs, 16 studies used an economic model to conduct cost-effectiveness analyses (CEAs) or economic evaluations, 5 were retrospective analyses of health care utilization, and 1 study undertook a cost analysis in a resource-limited setting (Table 2).^{23,25,26,34-52}

FIGURE 1 Overview of Mean Monthly Costs Identified in the Review and Stratified by CD4 Cell Count Category

USD = U.S. dollars.

Costs by CD4 Cell Count Categories

A total of 6 studies reported HIV treatment and disease management costs associated with CD4 cell-based health states. They were presented as annual, quarterly, or monthly costs.^{23,37,38,42,45,46} The total costs ranged from \$254 to \$6,608 per month, with lower CD4 cell counts associated with higher costs (Figure 1, presenting CD4 categories used in the model). The mean monthly costs ranged from \$2,873 for patients with CD4 counts <50 cells/mm³ to \$1,192 for patients with CD4 counts >500 cells/mm³. Across the most commonly identified CD4 cell categories, and those that were utilized in the model, the average monthly costs were \$2,873 (range = \$1,136-\$4,596), \$2,546 (range = \$1,317-\$3,509), \$1,531 (range = \$536-\$2,983), \$1,357 (range = \$385-\$2,721), and \$1,192 (range = \$254-\$2,565) for the <50 cells/mm³, 50-200 cells/mm³, 201-350 cells/mm³, 351-500 cells/mm³, and >500 cells/mm³ CD4 cell count categories, respectively. Six studies reported costs of tests to estimate CD4+ counts (mean cost = \$70.07; range = \$53.36-\$126.48) and HIV RNA (mean cost = \$104.10; range = \$69.78-\$151.63).^{23,37,38,42,45,46} Further, 3 studies estimated costs of HIV genotype testing (mean cost = \$315.59; range = \$40.03-\$535.98) to assess resistance profiles of patients.^{23,40,42}

AE and AIDS-Defining Event Costs

Three studies estimated costs of AEs, reporting them as per-event costs or annual event-related costs (Table 1).^{34,36,48} Bayoumi et al. (2013) estimated the cost of first and subsequent serious AEs to be \$12,412 and \$15,930 using data from the OPTIMA trial in 2017.^{36,53} Studies by Simpson et al. (2013) and Dekoven et al. (2016) using U.S. claims databases calculated costs for several AEs ranging from \$0 for AEs such as headache, pain, vomiting, and lipodystrophy to \$23,964 for intracranial hemorrhage, \$25,912 for stroke, and \$31,545 for myocardial infarction.^{34,48} Costs for the majority of AEs were less than \$5,000 per event. Four studies estimated costs stratified by types of opportunistic infections (OIs) into bacterial OIs, viral OIs, fungal OIs, protozoal OIs, cancer, and others (Table 1).^{23,34,35,41} The mean per-event costs for OIs ranged from \$8,495 for viral OIs to \$13,036 for protozoal OIs. The overall mean cost per event across all AIDS-defining events was \$10,465 and the corresponding monthly mean cost was \$4,464.

Long-Term Toxicity Costs

Outcomes associated with CVD, CKD, and fractures/osteoporosis were explored as long-term toxicities in HIV-infected patients. Three studies reported the cost of CVD, 2 studies reported the cost of CKD, and a single study reported the cost

FIGURE 2 Estimated Survival of HIV Patients, Stratified by Year, Compared to the Cumulative Incidence of CVD, CKD Stage 5, and Bone Fractures Among the Total Cohort

CKD=chronic kidney disease; CVD=cardiovascular disease; HIV=human immunodeficiency virus.

of fracture/osteoporosis.^{25,26,41} The study by Peng et al. (2015) reported the total per-event cost of CVD to be \$28,728, while studies by Smit et al. and Gallant et al. (2018) reported further cost breakdowns with inpatient, outpatient, emergency care, and prescription costs for non-HIV prescriptions (Table 1).^{25,41} The mean monthly cost of CVD management across all studies was estimated to be \$5,898 per patient. The costs of CKD and osteoporosis were also further divided into cost components, with average monthly costs of \$6,108 and \$4,365, respectively.

Modeling Analyses

Predicted survival for each of the modeled patient cohorts is presented in Figure 2. In line with published estimates, the model assumed improved survival between 1996 and 2008. Patients failing to achieve viral suppression (cohort 1), who were assumed representative of patients before the widespread use of highly active ART, were estimated to be associated with a life expectancy of 22.4 years. The model estimated life expectancies of 36.2, 37.9, 40.5, and 45.1 years for a typical 20-year-old patient at the time of diagnosis for cohorts 2-5, respectively.

The incidence of bone fractures remained relatively constant over the modeled horizon, while there was a gradual increase

in CVD incidence between 40 and 80 years, after which it plateaued. The incidence of CKD stage 5 remained relatively low until patients reached the age of 75 and increased significantly thereafter. Analysis showed a 33.4% increase in life expectancy in cohort 6 compared to cohort 5. Such an improvement in survival represented an increase of 71.3%, 58.3%, and >1,000% in the incidence of bone fractures, CVD, and CKD stage 5, respectively.

The economic impact associated with the increased incidence of CVD, CKD stage 5, and bone fractures was reflected in the total lifetime cost outcomes predicted by the model (Figure 3). The total HIV lifetime cost per patient was estimated to be \$1,246,810, \$1,420,869, and \$1,673,510 for cohorts 2, 5, and 6, respectively. The cost increases were driven by treatment and AE costs (35.4% increase between cohort 2 and cohort 6) but also by costs of treatment for comorbidities such as CVD (179.9% increase) and CKD (174.3% increase). HIV management costs, including costs of inpatient care, emergency department and outpatient visits, OI prophylaxis, HIV testing, and non-HIV medication, however, decreased as HIV patients approached general population survival rates due to improvements in CD4 cell counts and viral loads.

FIGURE 3 Estimated Total Lifetime Costs per Patient

^aTreatment and AEs: treatment costs and treatment of AEs.

^bDisease management: outpatient care, emergency department visits, inpatient day, HIV testing, OI prophylaxis, and non-HIV medication.

^cComorbidities: CVD, CKD, and fracture risk.

AE = adverse event; CKD = chronic kidney disease; CVD = cardiovascular disease; HIV = human immunodeficiency virus; OI = opportunistic infection.

Discussion

With the advent of newer, more efficacious ARTs, HIV patients are expected to live longer, with a mean life expectancy approaching that of the general population.^{6,7} This aging population requires chronic care to manage HIV disease progression, and with extension of life comes the likelihood of additional resource-intensive age-related comorbidities, which are not currently a focus of contemporary HIV CEAs.⁵⁴ Long-term ART exposure has the potential to lead to the early onset of such comorbidities due to the impact of certain HIV therapies on long-term toxicity risk factors.⁵⁵⁻⁵⁷ As a result, the composition of care needed for HIV patients has evolved over the last 2 decades and is expected to change further in the future.

Our study reviewed published literature on costs of HIV management in the United States and modeled the potential future costs of aging HIV patients. Modeled results estimated that, as the survival of HIV patients approached that of the general population, lifetime HIV costs increased, with the distribution of costs across different contributors varying significantly. HIV treatment and related AE and toxicity costs were estimated to increase as patients received treatment for a longer duration, while HIV management costs showed an estimated decrease, as improved survival is inherently associated with improved viral load and CD4 cell count profiles and associated reductions

in AIDS-defining event incidence and virological failure. The most significant estimated changes were the rapid increase in costs of comorbidities associated with aging and long-term use of ART, such as CVD, CKD stage 5, and osteoporosis. As life expectancy improved beyond 50 years, the estimated incidence of these ART- and age-associated comorbidities significantly increased, resulting in their increased contribution to total HIV costs.

This study focused on 3 of the most common ART-specific comorbidities. However, there is evidence to suggest that several other chronic conditions such as depression, diabetes, and respiratory diseases are more prevalent in HIV patients, and their contribution to lifetime HIV costs is likely to increase in aging patients.⁵⁴ Interventions that improve communication and potentially regular contact between patients and health care professionals are likely to lead to early detection and better management of these comorbidities. There is a large amount of literature relating ART to long-term toxicities, some of which are highly prevalent in aging HIV patients. Interventions that reduce the cumulative exposure of antiretrovirals may also help in reducing prevalence of these toxicities. Future research should focus on assessing the impact of reduced antiretroviral exposure on lifetime HIV costs.

The costs of specific comorbidities identified in our review for HIV patients were higher than those reported in the literature for non-HIV patients. The mean annual cost of CKD stage 5 in our study was \$73,296. A study by Ozieh et al. (2017) estimated the annual cost of CKD in the U.S. general population to be \$37,649 in 2010/2011 (inflated to \$44,644 in 2017), while another study by Honeycutt et al. (2013) estimated the annual cost of stage 4 CKD to be \$12,700 in 2010 (inflated to \$15,518 in 2017).^{58,59} Similarly, Weaver et al. (2017) estimated the annual medical and pharmacy costs following an incident fracture to be \$27,844.⁶⁰ The corresponding annual costs in our study, which included medical and prescription costs, were \$52,380. This suggests an additional cost burden among HIV patients for these comorbidities, which may be due to the effect of long-term treatment with ART. Given the substantial costs associated with such comorbidities, there is real potential for the incidence of such events to significantly affect cost-effectiveness outcomes and, subsequently, reimbursement decisions.

Limitations

This study has some limitations. First, all HIV- and ART-associated potential comorbidities were not considered. Second, although systematic literature reviews are the preferred method for sourcing parameters for cost-effectiveness models, our approach was limited to a targeted literature review. We would not anticipate a systematic review to identify much or any additional relevant sources, however, since the evidence base in this specific area is not extensive. Third, those studies captured by this review commonly obtained cost data from one of a number of key cost studies, due to the limited evidence base, which represents a key limitation of this study.

Conclusions

This study demonstrated that as life expectancy of HIV patients improved, a significantly increased contribution of ART-associated comorbidities, including CKD, CVD, and osteoporosis, is observed. This contrasts with the overall estimated decrease in HIV management costs, likely due to improvements in patients' viral load and CD4 cell counts and subsequent reduced likelihood of experiencing AIDS-defining event incidence and virological failure. Future CEAs should consider the complete range of clinical outcomes for which HIV treatments may have an impact, rather than relying on historical precedent when informing modeled endpoints. Future research should also focus on assessing the effect of reduced antiretroviral exposure on lifetime HIV costs, in addition to how the resultant costs compare to that of a general population.

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DISCLOSURES

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APPENDIX A Search Strategy

#	Terms	Items Found
1	HIV[MeSH Terms]	90,546
2	HIV Infections[MeSH Terms]	256,012
3	(HIV Infections[Title/Abstract] OR HIV?1*[Title/Abstract] OR HIV?2*[Title/Abstract] OR HIV infect*[Title/Abstract] OR human immuno?deficiency virus[Title/Abstract] OR human immune?deficiency virus[Title/Abstract])	159,768
4	(human immun*[Title/Abstract]) AND deficiency virus[Title/Abstract]	573
5	(acquired immuno?deficiency syndrome[Title/Abstract] OR AIDS[Title/Abstract] OR acquired immunodeficiency syndrome[Title/Abstract] OR acquired immune deficiency[Title/Abstract])	138,790
6	(acquired immun*[Title/Abstract]) AND deficiency syndrome[Title/Abstract]	5,611
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	360,958
8	"economics, medical"[MeSH Terms]	13,981
9	(economics) OR economics[MeSH Terms]	702,821
10	"economic evaluation"	7,820
11	((health care cost[MeSH Terms]) OR health care costs[MeSH Terms]) OR (costs and cost analysis[MeSH Terms]) OR costs[MeSH Terms]	209,467
12	"health care utilization"	5,644
13	"drug costs"[MeSH Terms]	14,208
14	(resource*[Title/Abstract] OR healthcare[Title/Abstract] OR service*[Title/Abstract])	766,056
15	(use*[Title/Abstract] OR utilis*[Title/Abstract] OR utilize*[Title/Abstract] OR consume*[Title/Abstract] OR consuming[Title/Abstract] OR consumption*[Title/Abstract])	1,650,819
16	((("cost-benefit analysis"[MeSH Terms] OR cost effectiveness[Text Word]) OR cost-effectiveness[Title/Abstract] OR CEA[Title/Abstract]))	113,410
17	Cost[Title/Abstract] or costs[Title/Abstract] or costing[Title/Abstract]	440,869
18	cost utility*[Title/Abstract] OR cost benefit*[Title/Abstract] OR cost minimi*[Title/Abstract]	14,507
19	economic*[Title/Abstract] OR pharmacoeconomic*[Title/Abstract]	232,353
20	expenditure*[Title/Abstract] NOT energy[Title/Abstract]	24,556
21	value[Title/Abstract] AND money[Title/Abstract]	2,478
22	Budget*[Title/Abstract]	24,899
23	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22	3,145,374
24	((energy cost[Title/Abstract] OR oxygen cost[Title/Abstract]))	3,577
25	metabolic cost[Title/Abstract]	1,176
26	((energy expenditure[Title/Abstract] OR oxygen expenditure[Title/Abstract]))	21,616
27	#24 OR #25 OR #26	25,463
28	#23 NOT #27	3,135,155
29	#7 AND #28	74,419
30	(((((case report) OR case study) OR letter) OR editorial) OR case reports[Publication Type]) OR letter[Publication Type] OR editorial[Publication Type])	3,258,037
31	#29 NOT #30	70,484
32	"United States"[Title/Abstract] OR America[Title/Abstract] OR USA[Title/Abstract]	340,947
33	#31 AND #32	5,031
34	#33 Date: 2012-01-01 to present	1,365
35	#34 Language: English	1,351

APPENDIX B PRISMA Diagram