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Twenty Years Of Antiretroviral Therapy For People Living With HIV: Global Costs, Health Achievements, Economic Benefits

ABSTRACT Since the introduction of azidothymidine in 1987, significant improvements in treatment for people living with HIV have yielded substantial improvements in global health as a result of the unique benefits of antiretroviral therapy (ART). ART averted 9.5 million deaths worldwide in 1995–2015, with global economic benefits of $1.05 trillion. For every $1 spent on ART, $3.50 in benefits accrued globally. If treatment scale-up achieves the global 90-90-90 targets of the Joint United Nations Programme on HIV/AIDS, a total of 34.9 million deaths are projected to be averted between 1995 and 2030. Approximately 40.2 million new HIV infections could also be averted by ART, and economic gains could reach $4.02 trillion in 2030. Having provided ART to 19.5 million people represents a major human achievement. However, 15.2 million infected people are currently not receiving treatment, which represents a significant lost opportunity. Further treatment scale-up could yield even greater health and economic benefits.

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In 1987 the US Food and Drug Administration approved the use of azidothymidine (AZT), the first antiretroviral drug for treatment of HIV/AIDS. AZT monotherapy slowed viral replication and disease progression but added only months to life and had severe side effects. HIV rapidly developed resistance to this single drug.[1]

In the period 1988–95, four additional reverse transcriptase inhibitors and the first protease inhibitors were approved by the Food and Drug Administration. Scientists recognized that a combination of antiretrovirals could greatly improve treatment outcomes. In 1995 Merck and the National Institute of Allergy and Infectious Diseases began a trial of a three-drug combination. The success of this was announced at the 1996 International AIDS Conference and in the *New England Journal of Medicine*.[2]

Antiretroviral therapy (ART) using three-drug combinations remained complex, with multiple tablets, complicated schedules, and the need for extensive monitoring. Poor funding and infrastructure, and sometimes political opposition, challenged many countries that considered expanded provision of ART. Treatment was expensive, at $10,000–$15,000 per patient per year.

Brazil introduced local production of antiretrovirals in 1995 and in 1996 established a right of access to free antiretrovirals.[3] In December 1997 the Joint United Nations Programme on HIV/AIDS (UNAIDS) launched the HIV Drug Access Initiative in Uganda and Côte d'Ivoire. In 2000 the Accelerating Access Initiative of the World Health Organization (WHO) significantly reduced antiretroviral prices for thirty-nine countries, and the WHO also launched prequalification for generic antiretrovirals. The Global Fund to Fight AIDS, Tuberculosis, and Malaria was established in 2002, followed in 2003 by President George W. Bush's $15 billion US President's Emergency Plan for AIDS Relief

(PEPFAR).

Moves to reduce prices resulted in the World Trade Organization's Doha Declarations, which allowed countries to manufacture generic medications to address public health crises.[4] Starting in 2006, some major originator companies for antiretrovirals signed voluntary licenses, enabling generic companies to sell antiretrovirals at greatly reduced prices in developing countries. In addition, patent pools, through which drug manufacturers can obtain the rights to manufacture needed formulations, gave countries access to various combinations of antiretrovirals with reduced royalties to manufacturers.[5]

Access to and the effectiveness of ART evolved dramatically worldwide. Single-tablet regimens, led by Atripla in 2006, replaced multiple daily doses. Side effects of treatment were reduced dramatically, limiting regimen changes and drug resistance while increasing the quality and length of life for people living with HIV.[6]

Various researchers have attempted to quantify the change in life expectancy attributable to the evolution in the effectiveness of ART.[7–9] The most comprehensive data on changes come from Brazil, which was an early adopter of ART and has been able to monitor changes in life expectancy over time.[10] The gains in life expectancy for people initiating ART rose dramatically in Brazil, from 3.3 years in 1997 to 25.7 years in 2014.

To realize the potential offered by advances in treatment effectiveness, UNAIDS established the 90-90-90 treatment targets in 2014. These targets aim to "end AIDS" by ensuring that 90 percent of people living with HIV know their HIV status, 90 percent of those who are diagnosed (81 percent of all people with HIV) receive treatment, and 90 percent of those (73 percent of all people with HIV) have viral suppression by 2020.[11]

Despite the successes, significant challenges lie ahead. In 2017 there were 1.8 million new HIV infections and 36.9 million people living with HIV worldwide.[11] There were still 1 million AIDS-related deaths[11]—over twice the estimated 435,000 global malaria deaths per year.[12] Of people living with HIV, 41 percent (15.2 million people) were not receiving treatment.[11]

Goals And Objectives

The overall goal of this study was to quantify the societal benefits and costs of improvements in HIV treatment coverage and effectiveness from its inception in 1995 through 2030. The intention was to estimate the benefits and costs of investments in HIV treatment to date, as well as the impact of moving toward the 90-90-90 targets, when compared to scenarios in which treatment had not been developed, improved, or scaled up as quickly. For this reason, the following analysis will assess both a counterfactual in which ART had never been developed and a counterfactual in which current levels of treatment coverage are not further scaled up in the future.

The study objectives were as follows: (1) to model the demographic, economic, and epidemiologic impact of treatment by comparing a retrospective scenario in which ART had never been available to one that represents the actual improvements in both the coverage and the effectiveness of ART in 1995–2015; (2) to assess the impact of historical changes in treatment effectiveness (measured by the years of additional life expectancy of people on treatment); and (3) to assess the demographic, economic, and epidemiologic impact of future scenarios (2016–30) by modeling the scale-up of ART to achieve 90 percent access to treatment.

Study Data And Methods

MODELING APPROACH Demographic and epidemiological impacts were calculated using the Spectrum package of models.[14] Spectrum includes the AIDS Impact Model (AIM), which projects variables such as the number of HIV infections and AIDS deaths given assumptions about HIV prevalence.[13] AIM country files are regularly used and validated by UNAIDS and represent the most robust, contemporary estimates of demographic, epidemiological, and programmatic data. For this study 161 AIM files were available, representing 44 high-income and 117 low- or middle-income countries. The AIM country files were used to produce the three retrospective and three prospective scenarios described below. Improved effectiveness of treatment was modeled by varying the life expectancy for people on treatment in AIM and calculating the effects on projected numbers of AIDS deaths.

The impact of treatment on new HIV infections was quantified using the Goals model in Spectrum, which can reflect the reduced infectiousness of people receiving ART. Goals files that modeled these secondary benefits of treatment were available for forty-nine countries, which accounted for an estimated 87 percent of new global infections. For the other countries, proxy country data were used.

DEFINING SCENARIOS The demographic, epidemiologic, and economic modeling defined several scenarios for retrospective (1995–2015) and prospective (2016–30) assessments. In all retrospective scenarios, HIV prevention strategies (for example, condoms and male circumcision) remained unchanged from observed historical coverage. Prospective scenarios assumed con-

When costs of treatment are compared to full income benefits, the benefits in all regions substantially exceed the costs.

stant coverage of HIV prevention strategies at 2015 levels.

RETROSPECTIVE SCENARIOS (1995–2015)

▶ **ACTUAL SCALE-UP AND TREATMENT EFFECTIVENESS OF ANTIRETROVIRAL THERAPY:** This scenario followed the evolution of coverage of ART from 1995 to 2015, based on the AIM country files. Many developed countries initiated ART in 1996, but most developing countries began providing it around 2003.

▶ **NO SCALE-UP OF ANTIRETROVIRAL THERAPY:** This is a counterfactual scenario in which ART was not available for either treatment or preventing mother-to-child transmission.

▶ **ACTUAL SCALE-UP OF ANTIRETROVIRAL THERAPY COVERAGE BUT NO IMPROVEMENT IN TREATMENT EFFECTIVENESS:** This counterfactual scenario increased coverage as in the first scenario, but it removed the improvement in treatment effectiveness (years of additional life) for 1995–2015 based on the estimates for Brazil.[10] The scenario therefore distinguished the benefits of increased coverage from those due to more effective treatment.

PROSPECTIVE SCENARIOS (2016–30) Three scenarios assessed the potential effects of further treatment scale-up. They focused exclusively on treatment scale-up and therefore did not assume any increase in prevention coverage.

▶ **AGGRESSIVE TREATMENT SCALE-UP:** This scenario estimated the benefits of scaling up to 81 percent treatment coverage in each country, consistent with the 90-90-90 targets. However, it assumed that certain regions would achieve this target later than envisaged by UNAIDS (UNAIDS assumed that there would be 81 percent coverage in every region and country by 2020). Treatment effectiveness was assumed to remain at 2015 levels.

▶ **NO SCALE-UP OF ANTIRETROVIRAL THERAPY:** This scenario continued the retrospective "no scale-up of ART" counterfactual from 1995 through 2030. This scenario clarified the full past and future benefits of ART when compared to the retrospective "actual scale-up" and the prospective "aggressive treatment scale-up" scenarios, and it allowed us to analyze the economic benefits of ART over the entire thirty-five-year study period.

▶ **AGGRESSIVE SCALE-UP OF TREATMENT COVERAGE BUT NO EVOLUTION IN TREATMENT EFFECTIVENESS FROM 1995:** This scenario modeled further aggressive scale-up of treatment coverage, but without any increase in treatment effectiveness after 1995, when ART first became available. This counterfactual helped illustrate how benefits arise from improvements in both treatment effectiveness and treatment coverage.

ECONOMIC ASSESSMENT The economic benefits of treatment were assessed using the full income approach. This approach reflects the concern that other benefit measures now in broad use (for example, the cost of illness approach) fail to include key factors that contribute to well-being: namely, better health and longer life expectancy.[15–18] The full income approach, adopted in 2013 by a *Lancet* Commission in "Global Health 2035,"[19] goes beyond simple measures of health as a percentage of per capita gross domestic product (GDP) or earnings forgone and includes the wider benefits associated with better health. The method has subsequently been used for assessing the benefits of maternal and child health and surgical programs.[20–22]

To assess the costs and economic benefits of treatment, the demographic and epidemiologic estimates were run through an Excel model. The full income benefit calculations used methods based on those developed for the *Lancet* Commission[19] and more recent work.[23] Benefits of the reduced mortality each year due to treatment were assigned a monetary value linked to multipliers of per capita GDP, which enabled the models to estimate benefit-to-cost ratios.

We calculated other costs and benefits of treatment based on the number of people in various states of treatment each year (for example, on ART or end-of-life care). Treatment costs included the health-sector costs of antiretrovirals, laboratory monitoring, and service delivery. Costs are reported net of the estimated health service costs of non-ART HIV/AIDS end-of-life care that were avoided. The online appendix gives further details on costing methods and sources.[24]

For developing countries, costs of antiretrovirals, ART service delivery, and non-ART care were derived from historical costs collated for previous global resource needs estimates, as well as studies that explored trends and variations in

costs.[25] Unit costs for developed countries were derived from published estimates of antiretrovirals, as well as of ART and non-ART care costs and trends, and they considered differences between countries and public- and private-sector prices wherever data allowed.

The results are presented in 2016 US dollars and assume a discount rate of 3 percent. Where uncertainty existed, conservative estimates of parameters were selected for baseline costs or benefit projections, to avoid inflated benefit-to-cost ratios.

LIMITATIONS The study had several main limitations. First, the responses of national governments, populations, and international organizations are uncertain under a counterfactual with no treatment. All that is known for certain is how the pandemic progressed in the presence of ART. There may have been larger, more sustained reductions in risk behavior in response to the impact of so many people dying of HIV/AIDS. Conversely, without ART, there could have been less prevention spending, since programs such as PEPFAR might not have existed. While prevention interventions are likely to have changed in the absence of treatment, it was not practical to model counterfactual scenarios that attempted to reflect the many permutations of what would have occurred without resources being spent on ART.

Second, the achievement of the 90-90-90 targets does not rely solely on the introduction of treatment. The targets can be achieved only if sufficient resources are available and sufficient demand exists. Thus, the attribution of achieving 90-90-90 treatment targets solely to ART might not adequately reflect the importance of scaling up testing services.

Third, the measure of treatment effectiveness was derived from data in Brazil, which suggest that life expectancy rose by 22.4 years from the earliest time when ART was available. We used Brazil because it provided the most complete estimates of life expectancy changes with ART over time. However, it should be noted that service quality, treatment adherence, and the types of regimens available could all result in different estimates of how treatment effectiveness has affected life expectancy. Countries with lower adherence than exists in Brazil, for example, might expect less of an impact associated with improvements in treatment effectiveness.

Fourth, in none of the prospective scenarios were there improvements in treatment effectiveness. However, historically there have been substantial improvements in treatment effectiveness, which are not likely to stop in the future. Treatment effectiveness will likely continue to evolve in the future, leading to greater retention and further improvements in life expectancy. However, uncertainty about these improvements prevented the study from producing reasonable estimates of the possible outcomes.

Fifth, the full income approach provides a unique ability to quantify the value of improved health and life expectancy. However, the approach has yet to be applied to a broader range of health and other interventions, and its full value will emerge only when a broader set of comparators (which compete for limited health funding) become available. A further discussion of the full income approach is in the appendix.[24]

Sixth, representative, rigorous data on the costs of ART and non-ART care for people living with HIV are scarce. However, this seems unlikely to have substantively affected the main conclusions of this analysis.

Finally, this analysis examined only the benefits of treatment, prevention of mother-to-child transmission (PMTCT), and treatment as prevention. Other uses of antiretrovirals, such as pre-exposure prophylaxis (PrEP), were not included.

Study Results

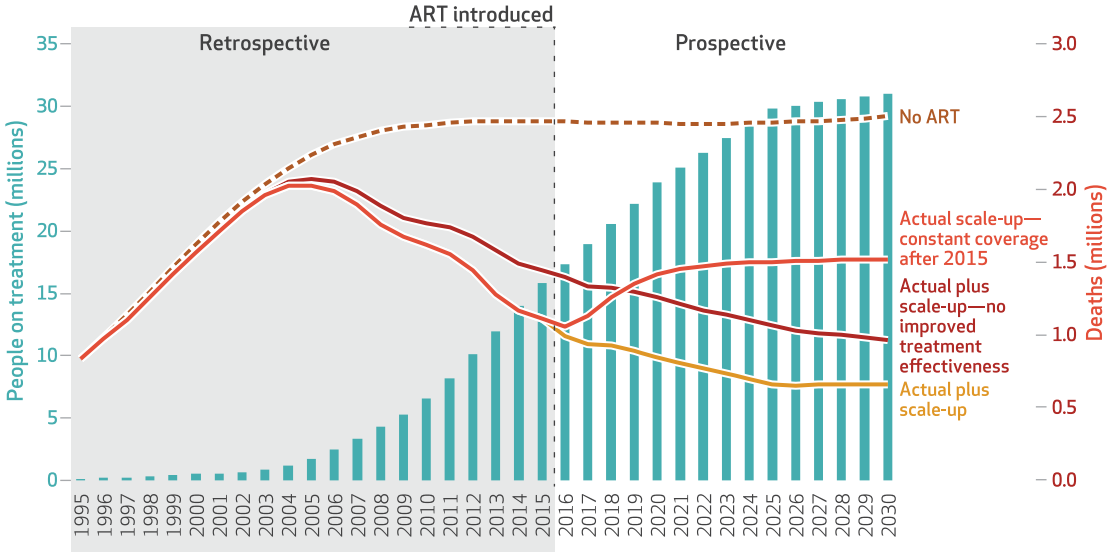
DEMOGRAPHIC IMPACT OF TREATMENT In the absence of treatment, the estimated global number of AIDS deaths each year would have reached a plateau at about 2.5 million in 2013 (exhibit 1). This plateau represents an equilibrium of new AIDS deaths and new HIV infections, occurring about ten years after the period when new HIV infections peaked.

However, the scale-up of treatment, along with its improved effectiveness, produced a dramatic decline in the global number of AIDS deaths. The projections drop to about 1.12 million annual AIDS deaths in 2015 (consistent with UNAIDS estimates of 1.1 million AIDS deaths in 2015).[26] Cumulatively, the introduction and actual scale-up of treatment is estimated to have averted 9.5 million AIDS deaths from the introduction of ART in 1995 through 2015 (exhibit 2).

As noted, annual AIDS deaths fell to 1.12 million in 2015, rather than the expected 1.45 million without improvements in treatment effectiveness (as shown by the "Actual plus scale-up—no improved treatment effectiveness" scenario in exhibit 1). Treatment coverage thus accounted for around 75 percent of the reduction in mortality, while increases in treatment effectiveness accounted for the remaining 25 percent. By combining the actual historical scale-up of treatment with the projected future ambitious scale-up of ART, it is possible to estimate that treatment could avert 34.9 million deaths during 1995–2030.

EXHIBIT 1

Annual AIDS deaths and numbers of people on treatment, by scenario, 1996–2030



SOURCE Authors' analysis of Spectrum projections. **NOTES** The numbers of people on treatment are actual until 2015 and then assume that antiretroviral therapy (ART) is scaled up according to future projections (discussed in the text). "No ART" is the scenario in which combination ART was never introduced. "Actual scale-up—constant coverage after 2015" is the scenario in which ART coverage is not increased after 2015. "Actual plus scale-up—no improved treatment effectiveness" is the scenario in which ART effectiveness is not improved from 1995 levels. "Actual plus scale-up" is the scenario in which ART is scaled up after 2015 according to future targets and projections.

EXHIBIT 2

Full income benefits of and costs avoided by HIV treatment, benefit-to-cost ratios, and deaths avoided in 1995–2015 and 2016–30

	Billions of 2016 US dollars			Benefit-to-cost ratio		
Region	Full income benefit	Net cost of ART	Net benefit	Actual 1995–2015; scale-up 2016–30	Constant ART effectiveness	Deaths avoided (millions)[a]
1995–2015						
Asia-Pacific	71	11.2	59.8	6.36	4.96	1.15
Eastern Europe and Central Asia	75	36.3	38.3	2.06	1.87	0.21
East and Southern Africa	367	18.0	349.0	20.38	13.79	5.55
Latin America and Caribbean	66	17.6	48.5	3.76	2.93	0.61
Middle East and North Africa	2.6	0.7	1.9	3.52	2.40	0.03
North America	233	127.4	105.2	1.83	1.74	0.33
West and Central Africa	36	4.3	32.0	8.45	6.26	1.18
Western and Central Europe	203	85.6	117.3	2.37	2.17	0.45
Total	1,053	301.0	752.0	3.50	2.88	9.51
2016–30						
Asia-Pacific	377	41.0	336.0	9.22	6.57	3.24
Eastern Europe and Central Asia	351	71.0	280.0	4.96	4.37	1.42
East and Southern Africa	704	51.0	653.0	13.80	10.06	14.01
Latin America and Caribbean	191	29.0	162.0	6.69	5.06	1.35
Middle East and North Africa	21	5.0	16.0	4.05	3.09	0.28
North America	801	455.0	346.0	1.76	1.64	0.67
West and Central Africa	208	14.0	194.0	14.36	10.64	3.88
Western and Central Europe	315	214.0	101.0	1.47	1.27	0.54
Total	2,967	880.0	2,087.0	3.37	2.73	25.40

SOURCE Authors' analysis of Spectrum and economic data. **NOTES** The dollar values were discounted to reflect the effects of the different dates when antiretroviral therapy (ART) was rolled out in different regions. The dollar values for 1995–2015 are actual. The dollar values for 2016–30 assume that ART is scaled up according to future projections (discussed in the text). The "Constant effectiveness" scenario is the same as "Actual" and "Scale-up," but with no improvement of ART effectiveness after 1995. [a]For 1995–2015, the numbers are those of deaths actually avoided by the introduction of ART. For 2016–30, the numbers assume that ART is scaled up according to future projections (discussed in the text).

More than half of the needed scale-up of treatment has already occurred: Our modeling estimates indicate that in 2017, treatment coverage was estimated at 59 percent. However, increasing global coverage will have important implications for reducing AIDS deaths. For each 1 percent increase in global coverage, an estimated 275,000 global AIDS deaths would be averted through 2030.

Assessment of the impact by region shows that most deaths already averted by treatment would have occurred in Eastern and Southern Africa (5.6 million) and West and Central Africa (1.2 million) (exhibit 2). This improvement occurred even though most African countries only began to scale up ART in about 2003.

In addition to deaths averted, there are also prevention benefits of ART, as people with lower viral loads are less likely to infect their sexual partners. Globally the number of new HIV infections peaked at about 3.5 million per year in 1997 and declined to under 2.0 million in 2016 (exhibit 3). In the absence of treatment, the number of new HIV infections was projected to remain at 3.5–4.0 million per year. In 1995–2015, treatment averted 7.9 million HIV infections.

The number of new HIV infections is expected to continue to decline as 90-90-90 targets are achieved. The Goals model projects that treatment will have averted 40.2 million HIV infections in 1995–2030. In 2030 alone, instead of 3.8 million new HIV infections, treatment could limit the number to 1.3 million (exhibit 3).

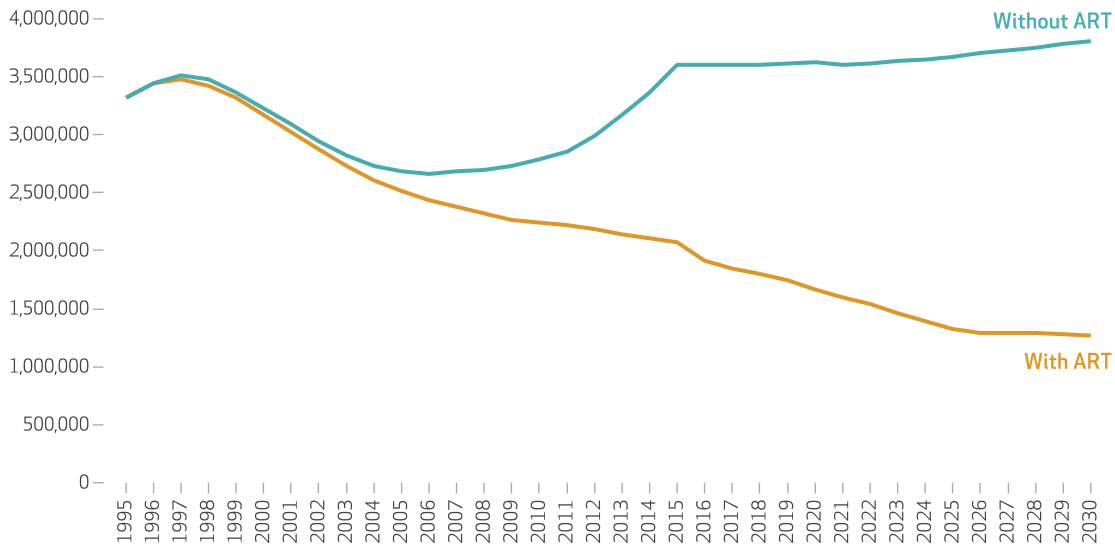
Another secondary benefit of treatment is a reduction in the numbers of children who lose one or both of their parents to HIV/AIDS. There are fewer double orphans (children younger than age eighteen who lose both parents to HIV/AIDS) as a result of treatment scale-up. The number of double orphans peaked in 2010 at approximately 4.5 million and then declined to 4.0 million in 2015 as a result of death and aging out of the population at age eighteen (exhibit 4). In the absence of treatment, the modeling projects that the number of double orphans globally would have continued to rise, reaching nearly 5.8 million in 2015. Thus, the modeling projects that the number of double orphans was reduced by 1.8 million in 2015.

The number of double orphans globally will continue to decline to 1.6 million by 2030, with the projected growth in treatment coverage (data not shown). In the absence of treatment, the number of double orphans is estimated to remain at over 4.9 million in 2030. Thus, further treatment scale-up would cut the number of double orphans by two-thirds by 2030.

ECONOMIC COSTS AND BENEFITS OF TREATMENT The scale-up of treatment cost $301 billion globally in 1995–2015 (exhibit 2). With the continued rollout of treatment, a further $880 billion will be expended on drugs and service delivery to achieve the 90-90-90 targets by 2030 (exhibit 2). About 7–10 percent of treatment costs are conservatively estimated to be offset by savings of non-ART care, particularly hospi-

EXHIBIT 3

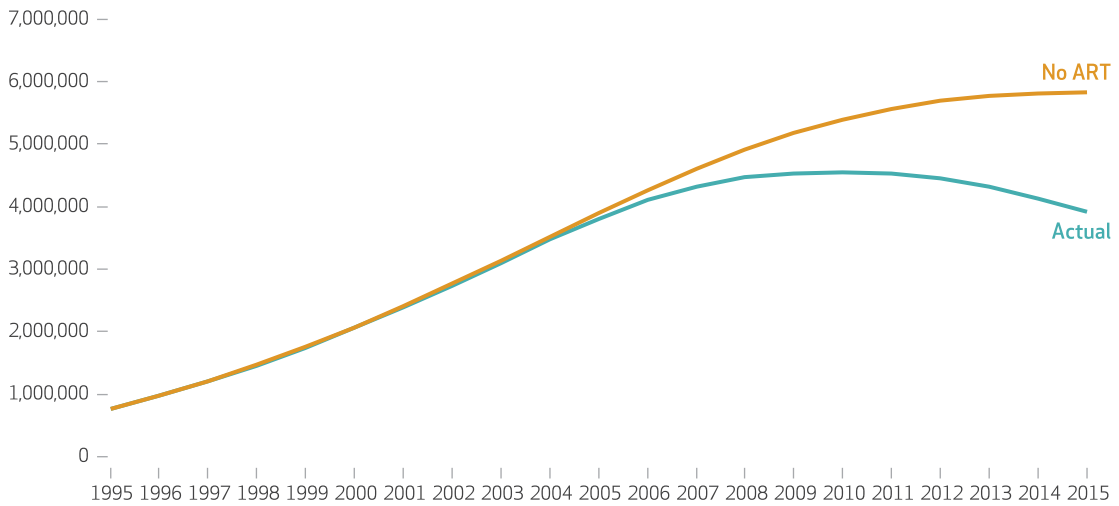
Annual new HIV infections globally in 1995–2030, with and without antiretroviral therapy (ART)



SOURCE Authors' analysis of Spectrum projections. **NOTES** "Without ART" is the scenario in which combination ART was not introduced in 1995. "With ART" shows actual numbers for 1995–2015 and numbers for 2016–30 that assume ART is scaled up after 2015 according to future targets and projections (discussed in the text).

EXHIBIT 4

Numbers of children losing both parents to HIV in 1995–2015



SOURCE Authors' analysis of Spectrum projections. **NOTES** "Actual" shows estimates of the real numbers of "double orphans" (defined as children under age eighteen who lost both parents). "No ART" shows the projected numbers of double orphans if antiretroviral therapy (ART) had not been introduced. In most countries, the benefits of ART in terms of reducing the number of children orphaned didn't occur until after 2002, when ART first began to become widely available in Sub-Saharan Africa.

talization, of around $33.3 billion in 1995–2015 and $70.8 billion in 2016–30 (data not shown).

For the period 1995–2015 the 9.5 million deaths averted globally by treatment were calculated to represent an economic gain of $1.05 trillion. The full income economic benefits of treatment, as well as related treatment costs, for actual rollout in that period appear in exhibit 2. The total economic benefits of treatment are largest in sub-Saharan Africa, North America, and Western and Central Europe, followed by Eastern Europe and Central Asia and then the Asia-Pacific region. Regions and countries that have relatively large epidemics (in East and Southern Africa) or higher GDP per capita (North America and Western and Central Europe) tend to derive the largest absolute benefit from treatment.

The projections for 2016–30 indicate that the absolute economic benefits of treatment over future years will be markedly higher than what has been achieved already. This is due to a combination of higher numbers of people on treatment and deaths avoided, as well as trends in treatment costs and per capita GDP, which differ by region. The 25.4 million fewer AIDS deaths across all regions in 2016–30 due to treatment scale-up represent a global economic benefit of $2.97 trillion in 2016 US dollars (exhibit 2).

As shown in exhibit 2, the largest corresponding regional economic gains are projected to be in North America ($801 billion), East and Southern Africa ($704 billion), Asia-Pacific ($377 billion), and Eastern Europe and Central Asia ($351 billion). In prospective projections (2016–30), the overall benefit-to-cost ratio in the actual and scale-up scenarios remains 3.37:1, a level similar to that of the period ending in 2015. North America is at 1.76:1, and middle- and lower-income regions are substantially above that level. Certain countries with high HIV burdens continue to have net benefits substantially above the average. For example, South Africa's projected benefit-to-cost ratio is 27:1 (data not shown). France, with Western Europe's largest number of people living with HIV, is estimated to have a ratio of 1.63:1.

The future benefits of the scale-up scenario (2016–30) can be compared to an estimated $1.6 trillion benefit in the scenario with no further scale-up, where coverage is maintained at 2015 levels. Thus, around 55 percent of the 2016–30 benefit accrues from just maintaining the levels of coverage already achieved by the recent rapid scale-up. However, the benefits of further accelerated scale-up are substantial, and they are particularly high in regions where current coverage is relatively low—for example, North America, the Middle East and North Africa, West and Central Africa, and the Asia-Pacific region.

If we examine benefit-to-cost ratios by country income categories, we see that the ratio averaged 3.5:1 globally in 1995–2015, which indicates that investments in treatment have been a positive use of global resources (exhibit 5). Regions

EXHIBIT 5

Full income benefit-to-cost ratio of HIV treatment, by country income category, 1995–2015 and 2016–30

	Billions of 2016 US dollars			Benefit-to-cost ratio	
Income category	Full income benefit	Net cost of ART	Net benefit	1995–2015	2016–30
High	526	256	270	2.1	1.9
Upper middle	415	28	387	15.1	19.9
Lower middle	68	8	60	8.6	13.0
Low	44	10	34	4.6	5.0
All	1,053	301	752	3.5	3.4

SOURCE Authors' analysis of Spectrum and economic data. **NOTES** The dollar values above are for 1995–2015 and were discounted to reflect the effects of the different dates when antiretroviral therapy (ART) was rolled out in different regions. The benefit-to-cost ratios for 1995–2015 are actual. The ratios for 2016–30 assume that ART is scaled up according to future scale-up projections (discussed in the text). The income categories are those of the World Bank, using 2016 incomes.

where per capita GDP is low tend to have higher returns on investment. African regions have both the highest HIV burden (East and Southern Africa and West and Central Africa) and the greatest fiscal challenges of providing treatment at scale, even though they can access antiretrovirals at low prices. In wealthier countries, the benefit-to-cost ratio ranges from 1.9:1 to 2.1:1 for the two periods, representing smaller but still substantially positive benefits. Future trends in regional benefit-to-cost ratios are produced by a complex interplay of factors that are discussed further in the appendix.[24]

Of note, in the scenario in which treatment remained at 1995 effectiveness levels, there were smaller total benefits and smaller benefit-to-cost ratios. This is due to the fact that although expenditures were similar, fewer deaths were avoided, and a smaller proportion of people with HIV have survived into an era of less expensive treatment.

Analyses of our key results' sensitivity to uncertainty about input parameters are presented in the appendix.[24] In general, our conclusions and results were robust to changes, within reasonable ranges, in assumptions about discount rates; ART costs, coverage, and effectiveness; end-of-life costs; and GDP growth.

Discussion

The achievements made to date with the extension of ART coverage and effectiveness are impressive: Between 1995 and 2015 over 9.5 million deaths and 7.9 million HIV infections were averted. Treatment has produced substantial benefits in all regions of the world and in countries at all levels of income, as a result of large-scale reductions in mortality. The successful scale-up of treatment in 1995–2030 will avert 34.9 million deaths and 40.2 million HIV infections. In that period, treatment will have reduced AIDS deaths by twice the number of people killed in World War I (17 million).

When costs of treatment are compared to full income benefits, the benefits in all regions substantially exceed the costs, which indicates that treatment has been and continues to be a significantly positive investment.

The full income approach illustrates how treatment has produced substantial development benefits. The value placed on life-years saved shows individual and social benefits of health gains that are seldom quantified. Saved life-years capture some of the dramatic benefits of treatment for survival and quality of life. Patients and clinicians witness these advantages, which amount to substantially more than just the sum of a patient's future remuneration.

How ART prices compare to per capita GDP is a critical determinant of the full income benefit-to-cost ratio, as well as of ART cost-effectiveness and sustainability. Rapid progress in making less expensive antiretrovirals available at scale has played a key role in reducing the cost and huge fiscal burden of treatment in many low- and middle-income countries. An important challenge for further research is to find appropriate balances for human and economic development, while ensuring the ongoing availability of new lines of treatment to tackle emerging resistance or side effects that will affect vast numbers of people globally.

A comparison with the scale of benefits of other major initiatives is also of interest. A recent study of ten routine and newly introduced vaccines estimated that they would avert 20 million deaths and 500 million cases of illness in the period 2001–20.[27] Associated benefits were estimated as $350 billion using the cost of illness approach, or economic and social benefits of $820 billion and $600 billion, respectively, if full economic and welfare benefits were considered. Cancer prevention, early detection, and treatment strategies save an estimated 2.4–3.7 million lives per year, at an economic benefit of $331–$451 billion.[28]

More than thirty years after the approval of AZT and more than twenty years after the introduction of combination ART, the overall scale of treatment costs and benefits indicates the magnitude of what has been achieved in combating HIV/AIDS. However, the large disease burden globally emphasizes the importance of reinforcing both treatment and prevention.

Our projections of impact and resource requirements seem broadly consistent with the results of other recent studies, although comparisons are made difficult by the larger scope and

Saved life-years capture some of the dramatic benefits of treatment for survival and quality of life.

somewhat different focus and methods used here.[29]

Policy Implications

Further expansion of treatment access to reach the 90-90-90 targets clearly represents good value for money for countries in every region and income category. However, countries must overcome numerous barriers to realize these gains. Denmark appears to have been the first country to have achieved all three 90-90-90 targets.[30] For selected countries in the Organization for Economic Cooperation and Development, the percentage of HIV-infected people who have viral suppression is 52 percent in France, 61 percent in the UK, and only 30 percent in the US. Brazil has attained a composite score of 40 percent, but Georgia has achieved one of only 20 percent, and Russia lags behind at around 9 percent.[31]

Reasons for these shortfalls in achieving treatment goals vary. Among European countries, the main limitation is getting people with HIV to be tested, so more active outreach and case finding are likely priorities. In the US, the problem is linkage with and retention in care: A high proportion of people living with HIV know their status but do not start or stay on treatment.[32]

Health budgets are constrained globally. Mobilizing, allocating, and absorbing the costs of expanded treatment will not be simple.[33] Donor aid for HIV has plateaued and remains under pressure. This modeling suggests that caps on coverage and investment could lead to substantial residual impact in many countries, and even to rebounding epidemics. Furthermore, the scale of treatment funding required in many high-burden countries means that treatment may end up competing with very cost-effective core services or interventions for limited health budgets. The high full income returns of ART in many such countries therefore become an important justification for allocating larger budgets to health sectors, to accommodate treatment without compromising other core services.

Coverage alone is unlikely to maximize treatment benefits and value for money. Viral suppression among the large numbers of people on treatment is also critical for prevention.[34,35] The study results therefore also challenge clinicians, policy makers, and the pharmaceutical industry to develop innovative, high-quality services and drugs that maximize access to and retention in care and limit the human and economic risks of ART resistance.

In each region and country, careful analyses of national treatment program performance in the three dimensions of 90-90-90 will need to be carried out to enhance benefits and efficiency. ■

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