Annex 1

Methodology for estimating the resource needs for HIV, TB and malaria

As most of the funds raised for the Eighth Replenishment of the Global Fund, 2026-2028, will be implemented in grants over the years 2027-2029, the total resource need has been defined as the amount of funding that would be required over the 2027-2029 period for every country in the Global Fund portfolio to achieve the intervention coverage and impact levels expected in the respective global plans for each disease for 2029.

The resource needs over 2027-2029 are taken from the respective global plans, which are described below. The global resource needs were adjusted to reflect the portfolio of countries eligible for Global Fund support. The disease-specific global plan costing estimates factor in health systems costs differently, and as such are not directly comparable.

A short description of the global plans

For **HIV** the estimate of resources needed for 2027-2029 is based on the latest targets and modeling approach set out in *The Urgency of Now: AIDS at a Crossroads* analysis and *End Inequalities. End AIDS. Global AIDS Strategy 2021-2026.* [1,2,3] The framework for the 2025 targets places people living with HIV and communities at risk at the center of the response and emphasizes that comprehensive and evidence-based HIV services must be tailored to individual subpopulations based on their particular needs. It also recognizes that societal, service and system enablers are needed to reach high levels of service coverage and impact. The HIV response is situated within a multisectoral framework for global health and sustainable development. In the Global AIDS Strategy, coverage scales up from 2020 levels to targets in 2025 and remains constant after 2025. For most interventions this means a linear increase in costs

[1] End Inequalities. End AIDS. Global AIDS Strategy 2021-2026. UNAIDS. Geneva, 2021. https://www.unaids.org/sites/default/files/PCBSS_Global_AIDS_Strategy_2021--2026_EN.pdf.

[2]The Urgency of Now: AIDS at a Crossroads. UNAIDS. Geneva, 2024. https://www.unaids.org/sites/default/files/media_asset/2024-unaids-global-aids-update_en.pdf.

[3] Modelling the epidemiological impact of the UNAIDS 2025 targets to end AIDS as a public health threat by 2030. Stover J, Glaubius R, Teng Y, Kelly S, Brown T, Hallett TB, et al. PLoS Med 18(10): e1003831. https://doi.org/10.1371/journal.pmed.1003831.

through 2025 and then smaller increases after 2025. For treatment, the increases in the number of people on treatment are partially offset by the assumptions of declining cost per person treated.

The Global AIDS Strategy includes accelerated scale-up of HIV prevention and treatment tools over the first few years of the strategy. Specific elements include the rapid scale-up of antiretroviral therapy, significantly higher coverage of prevention interventions for key populations, economic empowerment activities for girls in countries with very high HIV prevalence, voluntary medical male circumcision in priority countries and pre-exposure prophylaxis. The 2030 global target is a 90% reduction in new HIV infections and AIDS-related deaths from 2010 levels.

The Global AIDS Strategy costing estimate also builds in assumptions of shifting more care from facility- to community-based delivery, recognizing the importance of strengthening community systems and improved viral suppression. This will deliver cost savings and improve the uptake of services and bring them closer to the people who need them. It also assumes continued reductions in the average cost of treatment due to continued reductions in drug costs, and reduced visit and testing schedules for those maintaining viral suppression.

The Global AIDS Strategy also includes costs for scaling up societal enablers to address social barriers.

Above site-level costs and resources for procurement and supply chain strengthening, health management information systems, human resource capacity building, and management and administration are included as a fixed mark-up on the direct costs for the interventions, based on their use in the fully costed plan. The strategy emphasizes the importance of addressing inequalities supported by investments in data systems and analysis throughout the planning cycle.

During the period of the Replenishment, mitigating steps needed to tackle resistance are assumed to be taken, with the net result being that the overall effectiveness and costs of the intervention types used are not diminished. That is, new drugs are phased in to maintain the same, or higher, level of effectiveness as assumed now.

For **TB**, the estimate of resources needed for 2027-2029 is based on the Global Plan To End TB 2023-2030[4] and The UN General Assembly (UNGA) High-level Meeting on the Fight Against Tuberculosis 2023.[5] The new strategy is based on a more comprehensive normative approach to estimating costs from approximately 70 TB services and unit costs that are arranged into screening and care algorithms. The algorithms in turn are designed to meet patient needs, while conforming to current World Health Organization (WHO) guidelines. The strategy also includes new service elements such as new diagnostic methods. These include a new point-of-care rapid molecular test, a non-sputum-based test, improved drug sensitivity testing, next-generation sequencing and AI-based ultramobile X-ray screening. Drug regimens included in the costing include four-month or less TB treatment, six-month or less drug-resistant TB treatment and more options for the shorter TB preventive treatment regimens. Health and community systems, private sector engagement, enablers, equity and stigma are also given prominence in the coming strategy period.

Resource needs for TB include the expansion of preventive therapy for child and adult contacts and HIV patients and other populations at high risk of TB infection, implementation of new treatment guidelines and regimens, as well as the implementation of modern diagnostic tools such as X-ray and GeneXpert. In addition, the plan includes laboratory costs, procurement and distribution of commodities, health care utilization and program management costs. Costs related to enabling activities including advocacy and communication, direct patient support, mobile technology, public-private mix activities and community engagement are included. As far as possible, the costing model for TB explicitly accounts for necessary investments in health systems for the provision of the set of TB services included in the global plans, and this is done by making use of WHO's financing database.

Costs for this period include new tools and treatment regimens; it is noted that reaching the 2030 and 2035 milestones of the End TB Strategy continue to require additional new tools not currently available, including improved point-of-care tests and effective TB vaccines.

Estimated resource needs have increased compared to previous TB global plan estimates. Reasons for this include the increasing use of relatively more screening in provider-initiated programs, relatively more costly treatments for drug-resistant TB; scaling up of preventive therapy; modernized diagnostics and enabling activities that

[4] The Global Plan To End TB 2023-2030. The Stop TB Partnership. Geneva, 2022. https://www.stoptb.org/what-we-do/advocate-endtb/global-plan-end-tb/global-plan-end-tb-2023-2030.

[5] Political declaration of the high-level meeting on the fight against tuberculosis. UN General Assembly. 2023. www.stoptb.org/sites/default/files/imported/page/file/16959/file_16959.pdf.

support greater impact, and a significant portion of the planned scale-up occurring during the 2024-2026 period by when several systematic screening programs are assumed to be fully implemented. The eventual reduction in costs that is projected to result from a decrease in the TB burden is partially offset by an increase in costs linked to a drop in overall prevalence and resulting yield.[6] As a result, resources to meet coverage targets of the various screening programs remain substantial post 2027.

For the resource need estimate to roll out the TB vaccine,[7] based on discussions with TB technical partners, the TB resource needs for the 2027-2029 assume that a new TB vaccine will be rolled out in 2029, with a volume of US$2 billion.

The spread of drug-resistant TB, of all types, is modeled, and the cost and effectiveness of treatment is assumed to be modified in future years accordingly. It is assumed that treatment success rates will increase to 90%, reflecting an expansion of treatment options for patients with drug-resistant TB and new drugs (including bedaquiline) and increased patient support and in-patient care.

For **malaria** the estimate of resources needed for 2027-2029 are from the Global Technical Strategy 2016-2030, 2021 Update (GTS).[8] Based on the GTS update, to reach over 80% coverage of currently available interventions, malaria investments, including both international and domestic contributions, need to increase substantially above the current annual spending of US$3 billion. The annual investment will need to increase to an estimated total of US$9.3 billion per year by 2025 and US$10.3 billion by 2030. The cost of implementation has been estimated from the quantities of goods required for expanding interventions, multiplied by the estimated unit cost for the provider to deliver each intervention, and an analysis of the surveillance and financing data available in national strategic plans. It is important to note that the malaria costing does not include the essential health system costs required to deliver case management through the public sector.

Key increases in the resources needed for malaria over the 2027-2029 period are driven by the scale-up of mosquito nets. In addition to increasing insecticide-treated net coverage during this period, there is also a switch to using more costly, new technology nets (pyrethroid-PBO or pyrethroid-chlorfenapyr) to combat pyrethroid insecticide resistance. There are relatively small increases in resources needed as a result of increasing coverage of other interventions during this period (seasonal malaria

[6] An assumed expansion of eligibility criteria for entering clinical evaluation (e.g., patients without clear symptoms of TB are also screened) also leads to a decrease in prevalence among those accessing care.

[7] The analysis uses the Stop TB Partnership's assumptions regarding vaccine unit costs and coverage by 2035.

[8] Global Technical Strategy for Malaria 2016-2030, 2021 update. WHO. Geneva, 2021. https://www.who.int/publications/i/item/9789240031357.

chemoprevention, perennial malaria chemoprevention, malaria vaccine, indoor residual spraying (IRS)), and the costs associated with increasing the coverage of diagnosis and treatment are largely offset by reductions in burden. Costs include scale-up of the following interventions: vector control with long-lasting insecticidal nets or IRS, chemoprevention in children, diagnostic testing of fevers for malaria, malaria case treatment and surveillance. Other program elements were included as fixed costs (following the GTS methodology): program management, surveillance (including routine epidemiological and entomological components, malaria indicator surveys and enhanced surveillance in countries with low levels of transmission) and rapid diagnostic tests for non-malaria fever. The 2021 update emphasizes improvements to efficiency, equity and impact through the use of data to stratify and tailor malaria interventions to the local context, and that a resilient health system underpins the overall success of the malaria response. The projected cost of introducing the malaria vaccine is aligned with projections provided by Gavi, the Vaccine Alliance (Gavi) and funded through Gavi's Investment Opportunity 2026-2030.[9]

[9] Gavi's Investment Opportunity 2026-2030. Gavi, the Vaccine Alliance. 2025. https://www.gavi.org/sites/default/files/investing/funding/resource-mobilisation/Gavi-Investment-Opportunity-2026-2030.pdf.

Annex 2

Methodology for the projection of available resources for HIV, TB and malaria

A methodology and a model were developed to project the levels of funding likely to be available for HIV, TB and malaria from domestic and other external (development assistance for health, or DAH) sources in Global Fund-eligible countries over 2027-2029.

The projection was carried out for all countries eligible for Global Fund financing according to the 2024 eligibility list, except for countries that were not historically provided with an individual country allocation, and those countries eligible under paragraph 9B of the Eligibility Policy.

The resulting projections were used as inputs to the disease transmission models, which project impact from all domestic and international financing, including the Global Fund, to generate the results presented in this Investment Case.

Domestic financing

National responses to HIV, TB and malaria are increasingly financed by domestic resources, albeit at very different levels across different countries and diseases, meaning that robust projections of domestic financing are critical for predicting impact accurately.

The domestic financing projection approach estimated baseline domestic financing of HIV, TB and malaria in 2023 for each country in the set of countries described above. Plausible growth scenarios for future financing were then applied to this 2023 baseline to generate estimates for each year/country/disease between 2024 and 2029.

In previous Investment Cases, domestic funding commitments to the Global Fund were taken as the starting point for constructing the baseline. For this Investment Case, the baseline was estimated using at least five years of historic annual expenditure data supplied by Global Fund technical partners (WHO and UNAIDS), which collect reports of disease-specific domestic expenditure from countries annually.

For most countries, the most recently reported historical expenditures were for 2022. Gaps in the historic data for some countries in some or all years meant that it was necessary to impute missing values using a Bayesian mixed effects regression model using gross domestic product (GDP) per capita and disease burden as predictors. As a result of this imputation, there was a complete data set of expenditures by country, disease and year for the time period 2018-2022. From this point, the method proceeded through three more steps to arrive at a 2023 domestic expenditure baseline.

First, a 2023 estimate of public expenditure was derived from the historical data in the following way. First, the direction of the five-year growth trend was observed using ordinary least-squares regression with annual spend as the dependent variable and year as the only predictor variable. For countries with a positive trend, the 75th percentile of historic estimates was used. For countries with a negative trend, the median value of historic estimates was used. This approach was taken to deal with year-to-year variability in reported spending within countries that resulted in imprecise estimates of annual growth rate. The method mitigates the influence of both low and high outlier values by using median instead of mean spending level. Moreover, for countries with positive growth, it is conservative, because a country's 2023 estimate could not exceed its highest observed amount of annual spending during the historical period.

Second, a projection of private domestic spending was generated in addition to public domestic spending. Private spending on health is significant in many countries, and makes an important contribution to impact, and therefore needs to be modelled, even though some forms of private expenditure may be regressive. For TB and malaria, private spending was estimated by applying a multiplier to 2023 public spending. Country-specific and disease-specific multipliers were derived from country-specific estimates of public and private spending made by the Institute for Health Metrics and Evaluation for TB[1] and malaria.[2] For HIV, estimates of private spending by country income group were provided by UNAIDS, and private spending within the income group was allocated to countries according to their share of total people living with HIV (PLHIV) in the group.

[1] Tracking total spending on tuberculosis by source and function in 135 low-income and middle-income countries, 2000-17: a financial modelling study. Su Y, Garcia Baena I, Harle AC, Crosby SW, Micah AE, Siroka A, Sahu M, Tsakalos G, Murray CJL, Floyd K, Dieleman JL. Lancet Infect Dis. 2020 Aug;20(8):929-942. doi: 10.1016/S1473-3099(20)30124-9. Epub 2020 Apr 23. PMID: 32334658; PMCID: PMC7649746.

[2] Tracking spending on malaria by source in 106 countries, 2000-16: an economic modelling study. Haakenstad A, Harle AC, Tsakalos G, Micah AE, Tao T, Anjomshoa M, Cohen J, Fullman N, Hay SI, Mestrovic T, Mohammed S, Mousavi SM, Nixon MR, Pigott D, Tran K, Murray CJL, Dieleman JL. Lancet Infect Dis. 2019 Jul;19(7):703-716. doi: 10.1016/S1473-3099(19)30165-3. Epub 2019 Apr 26. PMID: 31036511; PMCID: PMC6595179.

Third, an adjustment was made to align historic data on TB disease program spending with modeled estimates of the cost of the TB response. This adjustment for TB introduces the health systems costs incurred in detecting, diagnosing and treating TB that are not included in TB disease program expenditure reported to WHO by countries. Reported expenditures normally include the costs of commodities, technical staff and diagnostics equipment purchased for TB, but may not account for, amongst others, health worker time, facilities or inpatient costs. In addition, reported expenditures may not include sub-national spending or spending through health insurance schemes. To make this adjustment, we compared estimates of cost for historical TB programs modeled using the TIME (TB Impact Model and Estimates) suite of models[3] for 29 countries with reported external and domestic spending for the same period. Any gap was attributed to under-reported domestic spending, and domestic spending was adjusted (upwards) accordingly. No adjustment to reported domestic spending was made for countries in which reported spending exceeded modeled costs. The ratio of adjusted to unadjusted TB spending was calculated for the modeled countries and the median value of this ratio was used to adjust TB spending in non-modeled countries.

We performed exploratory analysis of four ways to model the future of domestic disease financing and two were shortlisted – one conservative and one optimistic. The conservative "Economic Growth" scenario assumes that domestic financing will grow from its 2023 baseline in each country in proportion to the growth in non-debt service government expenditure forecast for that country in the International Monetary Fund's October 2024 World Economic Outlook.[4]

[3] TIME Impact – a new user-friendly tuberculosis (TB) model to inform TB policy decisions. Houben, R.M.G.J., Lalli, M., Sumner, T. et al. BMC Med 14, 56 (2016).

[4] World Economic Outlook Database. International Monetary Fund. October 2024. https://www.imf.org/en/Publications/WEO/weo-database/2024/October.

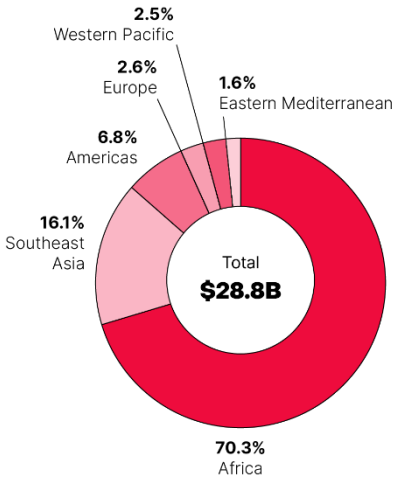
The more optimistic “Closing the Prioritization Gap” scenario builds on the Economic Growth scenario by assuming that countries that are lagging behind in their prioritization of domestic disease spending will catch up to their peers over the period 2024-2029. Specifically, lagging countries are defined as those spending relatively less on a disease, after adjusting for their economic capacity (government health spending) and their disease burden (disease-specific disability-adjusted life years (DALYs)), than the median of their income-level peer group. These countries catch up by closing an additional 20% per year of the gap between their economic growth forecasted spending and the spending that would be considered median level of prioritization, between 2024 and 2029, thereby reaching the median level of disease spending priority by 2029. Those that spend more than their peers remain on the Economic Growth path described above. In some cases, domestic financing forecasts for future years exceed estimates of total resources required to fully fund robust national disease responses. It would not be logical to use these estimates as inputs to the modeling exercise planned for the Investment Case. Therefore, we capped the domestic expenditure projection for each country within each three-year grant cycle period such that they do not exceed the resource need estimate values for that country.

For our projections for the Investment Case, we used the more conservative Economic Growth scenario for all countries and diseases, except for projected domestic spending for TB in India, where recent strong political will has been demonstrated to end TB and the fiscal space exists in the country to do so. For TB in India, the “Closing the Prioritization Gap” scenario was therefore used.

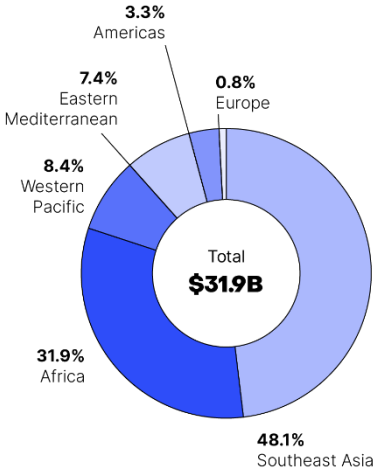
Finally, we considered the cost implications of malaria and possible TB vaccines through the Eighth Replenishment period. Using the co-financing assumptions set out in our partner Gavi’s Investment Opportunity (2026-2030), we attributed additional domestic financing of US$173 million across three years for malaria vaccine rollout. We assumed US$2 billion of costs in 2029 for TB vaccine rollout and assumed that the same proportion would be funded domestically as the wider global TB response, resulting in an additional US$1.287 billion in domestic funding for TB.

The figures below show the total forecast and breakdown for HIV, TB and malaria domestic financing by region, excluding vaccines. The total projection of US$69.7 billion (2022 US$) including vaccines represents an increase from the US$56.8 billion (2022 US$) that the model projects for the period of the Seventh Replenishment.

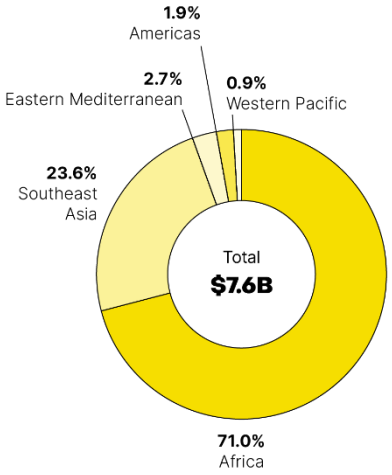
HIV domestic financing in 2027-2029



TB domestic financing in 2027-2029



Malaria domestic financing in 2027-2029



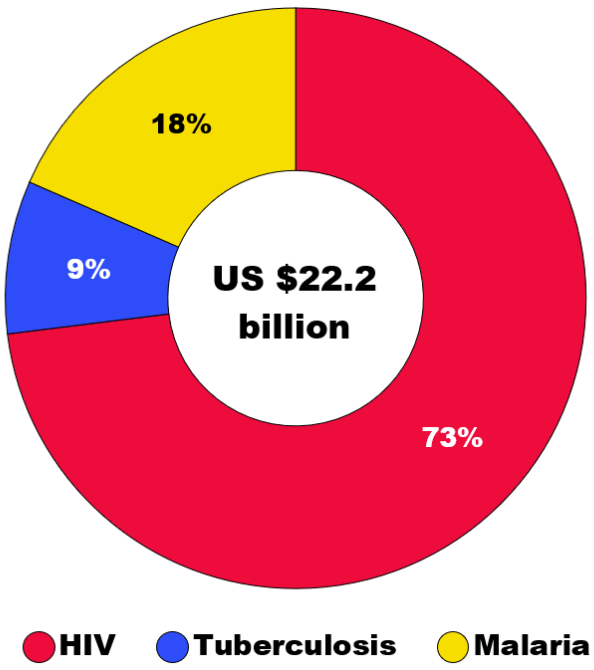
Regional charts exclude vaccine-related financing and are grouped by WHO regions.

Regional charts exclude vaccine-related financing and are grouped by WHO regions.

Non-Global Fund external financing

DAH from other sources, excluding Global Fund financing, was assumed constant in real terms at the same levels as the average of 2020-2022 disease-specific DAH through non-Global Fund channels, as modeled by the Institute for Health Metrics and Evaluation (IHME). This goes some way to smoothing out the spike in DAH created by the COVID-19 pandemic, and represents a relatively conservative assumption given that overall DAH has grown in real terms over the past decade. In-kind DAH reported in the IHME analysis was excluded, and disease spending not allocated to specific countries was included in aggregate results, but not in specific countries. Some of the costs of malaria and TB vaccines are introduced in line with the description above, adding US$1.4 billion across both malaria and TB vaccines in GC8. The figure below shows the breakdown between HIV, TB and malaria. In real terms, this represents a 12% reduction from the GC7 Investment Case forecast of non-Global Fund DAH for HIV, TB and malaria.

Projected non-Global Fund development assistance for HIV, TB and malaria over 2027-2029 (in 2022 US$)



Note: Excludes projected vaccine costs.
Source: Institute for Health Metrics and Evaluation.

Global Fund financing

The Investment Case assumes that Global Fund financing for the three diseases for the 2027-2029 period is US$18 billion. Based on actual expenditures of the last six years, US$1 billion is assumed for operational expenditure. The remaining US$17 billion is distributed across the three diseases according to the Board-approved global disease split for the 2026-2028 allocation methodology approved by the Global Fund Board (GF/B52/08B, 21 November 2024).[5]

Changes to methodology

The Global Fund commissioned a health decision scientist[6] on the faculty of the Department of Health Policy and Management at the Harvard T.H. Chan School of Public Health to develop the methodology and model used. A number of enhancements were made to the methodology previously applied in the Investment Case for the Seventh Replenishment, including:

- Using historic annual expenditure data provided by countries to Global Fund technical partners (UNAIDS and WHO), rather than domestic financing commitments to the Global Fund for constructing the baseline.
- Removing the "scaling" approach that aligned domestic co-financing commitments to Global Plan needs estimates by using National Strategic Plan cost estimates, unnecessary given the use of actual expenditure data.
- Applying an adjustment to the TB expenditure baseline to encompass health system costs, as described more fully above.
- Including private sector expenditures in the baseline calculation, as described above.

[5] Allocation Methodology for Grant Cyle 8: 52nd Board Meeting. The Global Fund, 2024. https://archive.theglobalfund.org/media/15310/archive_bm52-08b-allocation-methodology-gc8_report_en.pdf.

[6] Stephen C. Resch. Lecturer on Health Decision Science, Health Policy and Management, Harvard T.H. Chan School of Public Health. https://hsph.harvard.edu/profile/stephen-c-resch/.

Annex 3
Methodology for impact modeling

The modeling for this Investment Case aims to quantify the *minimum* funding necessary to generate health impacts and epidemiological trajectories over the Global Fund's implementation period 2027-2029 that are consistent with the long-term targets (2030) described in the global plans for HIV, TB and malaria. The required funding is made up of different funding sources, including the Global Fund Replenishment amount, domestic funding, and non-Global Fund international funding to Global Fund-eligible countries.

The modeling groups undertaking these analyses and the models used are those that were responsible for the modeling of the respective disease global plans.[1] The three disease models are population-scale dynamic transmission models, providing country-level projections that are then aggregated to the Global Fund portfolio. The models for HIV/AIDS and malaria have, over several years, been reviewed and developed in collaboration with international modeling consortia. The model for TB is a new release of the well-established TIME model, the development of which has been guided by the TB Modelling and Analysis Consortium (TB MAC) and experts and academics linked to TB MAC, including the Stop TB Partnership. The scope and application of the models is described in Section 1.

The model projections were generated in three steps. First, the disease transmission models are calibrated with the aim to recreate historic trajectories in each country for each disease up to the year of most recent data that is consistent with latest official estimates published by WHO and UNAIDS. The official estimates are informed by epidemiological data, program data and modeling assumptions.[2] Second, the models were used to project impact up to 2026 based on assumptions about the programs' configurations, as set out in the Global Fund Performance Frameworks. Third, the models made projections over the 2027-2029 Replenishment period, based on assumptions around available funding and the level of service coverage that could be achieved with that funding (Section 3).

[1] UNAIDS, "Global AIDS Strategy 2021-2026" (Geneva, 2021), https://www.unaids.org/en/Global-AIDS-Strategy-2021-2026; Stop TB Partnership, "Global Plan to End TB 2023-2030" (Geneva, 2022), https://www.stoptb.org/what-we-do/advocate-endtb/global-plan-end-tb; World Health Organization, "Global Technical Strategy for Malaria 2016-2030, 2021 Update" (Geneva, 2021), https://www.who.int/publications/i/item/9789240031357; See Annex 8 for further details of technical partners and strategies.

[2] See accounts provided in the Global Tuberculosis Report 2024, World Malaria Report 2024, and UNAIDS Global AIDS Update 2024.

Section 1: Description and application of models

HIV: Impact modeling was performed by Avenir Health using the Goals model,[3] which was set up for 95 countries. Costs included in the Global AIDS Strategy estimates, in addition to the direct cost of interventions (including community mobilization, testing, enabling environment and program support), are accounted for by applying a proportional mark-up to the intervention costs, following UNAIDS methods.

TB: Impact modeling was performed by Avenir Health applying a new version of the TIME model. The earlier version of the same model was used in supplementary modeling work for the Global Plan to End TB, 2023-2030 and has since been developed further to fully replicate the main results of the Global Plan to End TB, 2023-2030.[4] The new model was applied in 29 Global Fund-eligible countries with the greatest TB burden. Unit cost estimates for diagnostics, drugs and other supplies were obtained from four sources (Value TB study database, WHO Global TB Program's CHOICE Health service delivery costs, the Global Health Costing Consortium, and the Global Drug Facility product catalogue) following a methodology developed by a Stop TB Partnership-led technical working group convened to inform the resource needs estimates for the TB Global Plan (2022). Program support costs were obtained from expenditure reports that countries submit each year to WHO.

Malaria: Impact modeling was performed using the *malariasimulation* malaria transmission model developed at Imperial College London,[5] which contributed to the development of the WHO Global Technical Strategy for Malaria. It represents 51 Global Fund-eligible countries that have stable Plasmodium falciparum transmission and includes geographic specificity to the first administrative level. Those countries with unstable transmission or that were in prevention of reintroduction stages were not modeled.

For each disease area, therefore, models are produced for a subset of countries in the Global Fund portfolio that account for the vast majority of the burden of disease in

[3] "Modeling the Epidemiological Impact of the UNAIDS 2025 Targets to End AIDS as a Public Health Threat by 2030". John Stover et al. *PLOS Medicine* 18, no. 10 (October 18, 2021): e1003831, doi:10.1371/journal.pmed.1003831.

[4] The main results of the global plan 2023-2030 were developed with the TB Impact Model and Estimates (TIME). The model structure of TIME is detailed in the publication: TIME Impact – a New User-Friendly Tuberculosis (TB) Model to Inform TB Policy Decisions, Hoeben et al, BMC Medicine 2016 14:56. The new global and portfolio-level model, which builds on and aligns with TIME modeling structures, was used in validation work. It was also used in supplementary modeling work, such as modeling vaccine impact, which the current version of TIME cannot do.

[5] Jamie T. Griffin et al., "Potential for Reduction of Burden and Local Elimination of Malaria by Reducing Plasmodium Falciparum Malaria Transmission: A Mathematical Modelling Study," *The Lancet Infectious Diseases* 16, no. 4 (April 1, 2016): 465–72, doi:10.1016/S1473-3099(15)00423-5; Michael T. White et al., "Modelling the Impact of Vector Control Interventions on Anopheles Gambiae Population Dynamics," *Parasites & Vectors* 4, no. 1 (July 28, 2011): 153, doi:10.1186/1756-3305-4-153; Jamie T. Griffin, Neil M. Ferguson, and Azra C. Ghani, "Estimates of the Changing Age-Burden of Plasmodium Falciparum Malaria Disease in Sub-Saharan Africa," *Nature Communications* 5 (2014): 3136, doi:10.1038/ncomms4136; Jamie T. Griffin et al., "Gradual Acquisition of Immunity to Severe Malaria with Increasing Exposure," *Proceedings. Biological Sciences* 282, no. 1801 (February 22, 2015): 20142657, doi:10.1098/rspb.2014.2657; Griffin et al., "Potential for Reduction of Burden and Local Elimination of Malaria by Reducing Plasmodium Falciparum Malaria Transmission."

Global Fund-eligible countries (99% for HIV, 90% for TB, 99% for malaria of the estimated burden of the three diseases).[6] Extrapolations are made to the full portfolio by assuming that the trajectory of the "unmodeled" countries is the same as in "modeled" countries.

Section 2: Projecting impact up to the beginning of the Replenishment period (2024-2026)

The projections for the period from the start of 2024 to the end of 2026 are constructed assuming that country programs over that period fully achieve the targets agreed in the Global Fund Performance Frameworks. The Global Fund Performance Framework contains country-specific indicators and targets the programs need to achieve, which are submitted by grant implementers when applying for Global Fund funding.

In some cases, the Performance Framework does not include national targets for all indicators or all years for a given country. In these cases, targets were taken from a similar modeling exercise, the Global Fund 2021-2028 Strategy impact target setting exercise, which used the same disease transmission models to project programmatic targets that would be consistent with the funding projected to be available for the 2024-2026 period.

Section 3: Projecting service delivery and impact over the Replenishment period (2027-2029)

To estimate the epidemiological impact over the period 2027-2029, assumptions for available funding were handled as described below, with available funding made up of different funding sources: the Global Fund Replenishment amount, domestic funding, and non-Global Fund international funding to Global Fund-eligible countries. First, available resources were allocated between countries and across intervention elements (and also across sub-national units for malaria). Second, the impact on the epidemic was projected as a result of the configuration of interventions, as outlined above. The starting point for these projections is the epidemic status and intervention configurations achieved at the end of 2026 (see Section 2).

[6] Sum of new HIV infections and AIDS-related deaths, sum of new TB cases and TB deaths (excluding HIV+), sum of malaria cases and malaria deaths in modeled countries in 2023 compared to the Global Fund-eligible countries for which estimation of burden was available from WHO and UNAIDS.

Stage 1: Determining the allocation of resources between countries, sub-national units and across intervention elements

For each country and disease, the models are used to find the program configuration that would allow for the greatest impact. That "impact" is defined as achieving the lowest number for deaths and new infections (for HIV) or cases (for malaria and TB) [7] given a cap on the total cost of the program. The program configuration in the model can vary in the extent to which different services are scaled up, nationally or in particular regions, but prioritizes maintaining existing levels of treatment coverage. This is repeated for a wide range of values for the cap.

Two types of program funding are projected for each disease for the Replenishment period (see Annex 2: Methodology for projection of available resources for HIV, TB and malaria): (i) non-Global Fund resources (comprising domestic and external sources other than the Global Fund); (ii) funds from a successful Global Fund Replenishment.

The Global Fund budget that would become available for use in each disease area consists of the Replenishment amount (excluding the overhead cost) split between the three diseases, in accordance with the Global Fund's global disease split formula.[8] Then, for each disease, the share of funds available to each country is determined to be the amount that maximizes the overall impact across the Global Fund portfolio of countries.[9] The same applies to non-Global Fund external funding amounts within each disease that have not been earmarked to specific countries (see Annex 2: Methodology for projection of available resources).

Stage 2: Projecting impact and service delivery over 2027-2029 and later

The models are used to project the impact on the epidemic that would result from the program configurations that are specified by the approach outlined above. Projected impact after the Replenishment period (from the start of 2030 to the end of 2030 for HIV/AIDS and malaria and to the end of 2035 for TB) assume that this program configuration achieved by the start of 2030 is maintained for all interventions, except for a TB vaccine, which is assumed to increase to coverages outlined in the TB Global Plan by 2035. Intervals for the projections represent the uncertainty that arises as a result of the uncertainty in the overall disease burden, intervention effectiveness, and costs of the proposed interventions.

[7] Equal weighting is given to the proportionate reduction in total deaths and infections/cases in the period 2027-2030, relative to the respective value achieved in the global plans, under the assumption that the program can be continued in the years following the Replenishment.

[8] Allocation Methodology GC8. The Global Fund. https://archive.theglobalfund.org/media/15310/archive_bm52-08b-allocation-methodology-gc8_report_en.pdf.

[9] Using the same approach to defining maximal impact as done for each country.

The impact on the program scale-up in terms of lives saved over 2027-2029 is computed by comparing the modeled trajectories of deaths under the Replenishment scenario to a counterfactual scenario, which is defined as follows:

- For HIV/AIDS, there is an assumption of no antiretroviral therapy (ART) from the beginning of 2024 onwards. All other interventions and risk behavior are assumed to remain at the same level as the beginning of 2023.
- For TB, there is an assumption of no prevention or treatment for TB from the beginning of 2024, applying the case fatality rate of untreated cases to the estimate of incidence.
- For malaria, the counterfactual scenario is constructed by applying the 2000 mortality rates to the projected population at risk from the beginning of 2024, i.e., returning to the levels they were at without intervention.

The impact in terms of infections (for HIV) or cases averted (for TB and malaria) is estimated by comparing model-based trajectories of infections or cases based on the Replenishment scenario compared to a counterfactual scenario, as follows:

- For HIV/AIDS and TB the counterfactual assumes service coverage of disease programs are maintained at 2023 service levels.
- For malaria, the counterfactual scenario is constructed by applying the 2023 incidence rate to the projected population at risk.

The choice of counterfactuals reflects the recommendations of a Global Fund health impact experts meeting held in July 2014 and is aligned with the counterfactual used in other Global Fund exercises.

The models make epidemiological projections at the country level for countries that are in the Global Fund portfolio. Funding for the programs, which are driving this epidemiological impact, comes from various sources (see Annex 2: Methodology for projection of available resources). As a result, the impact that is ascribed to the set of countries in the Global Fund portfolio has been *contributed* to by the Global Fund. No estimate of what fraction of that impact could be *attributed* to the Global Fund is offered because the overall impact is a result of the entirety of a country's response. It would not be meaningful, for instance, to try to estimate the impact of diagnostics alone (which one funder might cover), or the impact of health care workers alone (which another funder might cover), as the value of such components is only realized in combination with one another, and with other factors, such as treatment availability, prevention programs, etc.

The assumptions that are made in the disease models regarding how interventions develop during the Replenishment period, including new interventions becoming available, are the same as those made in the respective disease global plans:

- For HIV/AIDS, the model incorporates improvements in the proportion of patients being tested and being virally suppressed through new approaches (e.g., community-based testing, adherence support groups, etc.), improvements in diagnostics (e.g., self-tests, point-of-care viral load testing, and early infant diagnosis, etc.) and availability of new treatments.
- For TB, several programmatic changes are incorporated into algorithms that implement screening, diagnosis and first- and second-line treatment (including multidrug-resistant TB (MDR-TB) according to prevailing guidelines for both adults and children. In addition, the TB global plan calls for more active screening for TB, including screening for subclinical TB, using X-rays for screening and rapid molecular tests (GeneXpert and other molecular WHO-recommended rapid diagnostic tests) for diagnosis. It further calls for universal access to the latest short, safe and effective treatment regimens, routine drug susceptibility testing with GeneXpert to inform correct treatment approaches and patient support (including psychosocial and nutritional support) as a routine part of care. According to the global plan, prevention, based on the latest preventive treatment regimens, should be provided to all eligible contacts, ART patients and other persons at high risk of TB infection. Further, it was agreed with partners that for the purpose of this Investment Case, the rollout of a vaccine is assumed, starting in 2029.
- For malaria, it is assumed that there is a rollout of a vaccine consistent with projections that Gavi, the Vaccine Alliance (Gavi) has formulated as part of their Investment Opportunity 2026-2030. To achieve high target usage rates, we assumed that net mass distribution frequency could increase from every 3 years to every 2 years; and that next generation indoor residual spraying, rectal artesunate, and next generation long-lasting insecticidal nets are all introduced. The model incorporates the increasing risk of insecticide resistance, but otherwise assumes that changing epidemiological circumstances do not have a material impact on the cost or effectiveness of the program. The potential impact of the emergence and spread of artemisinin and partner drug resistance in sub-Saharan Africa is not modeled.

The Global Fund commissioned the Vice President of Avenir Health,[10] a senior analyst at Avenir Health[11] and research fellow from Imperial College London[12] to perform the modeling work. There are the same individuals who conducted modeling work for the three global plans.

[10] "Avenir Health," accessed January 23, 2025, https://www.avenirhealth.org/our-team.php.

[11] "Avenir Health," accessed January 23, 2025, https://www.avenirhealth.org/our-team.php.

[12] Peter Winskill, Advanced Research Fellow, School of Public Health – Faculty of Medicine, Imperial College London. https://profiles.imperial.ac.uk/p.winskill.

Annex 4

Methodology for return on investment (ROI) calculations

The economic return on investment (ROI) projected to be made during the Global Fund Seventh Replenishment period was estimated for each country and disease via two methods: "intrinsic" and "instrumental" valuation of the averted burden of the three diseases over the period 2024-2030. Estimates of the "intrinsic" value of health are based on what individuals are willing to pay for improvements in their own health (Section 1), whereas the "instrumental" valuation considers the extent to which reductions in sickness and premature deaths increase productive work (Section 2).

The Investment Case scenario was compared to a "constant coverage" counterfactual scenario in which the coverages of key interventions were assumed to be maintained at 2023 levels. For the investment and counterfactual scenarios, the modeling that has been conducted as part of this Investment Case (see Annex 3: Methodology for impact modeling) has estimated the annual number of cases, deaths, disability-adjusted life years (DALYs) and cost. The cost of the investment compared to the counterfactual scenario is a net cost that includes both the cost of the interventions, i.e., those that prevent cases of disease or improve treatment, as well as health sector cost savings from not having to treat as many cases. For both valuations, and following standard approaches,[1,2] the present value of the projected stream of future costs and benefits was calculated by applying a discount rate of 3% per year. As Global Fund investment in countries varies as a proportion of the total cost of the investment scenario, a Global Fund-specific ROI ratio was derived by weighting the disease-specific costs and benefits according to the countries' share of Global Fund allocations during 2027-2029.

Section 1: Intrinsic valuation

Following the methodology of recent Benefit Cost Analysis (BCA) guidelines[1,2] an adjusted Value of a Statistical Life-year (VSLY) calculation was used to calculate country- and year-specific VSLYs that anticipate economic growth in Global Fund-supported countries:

[1] Departmental Guidance on Valuation of a Statistical Life in Economic Analysis. U.S. Department of Transportation, 2022 [cited 2022 January 15]. https://www.transportation.gov/office-policy/ transportation-policy/revised-departmental-guidance-on-valuation-of-astatistical-life-in-economic-analysis.

[2] Valuing nonfatal health risk reductions in global benefit-cost analysis. Robinson LA, Hammitt JK, O'Keefe LO. Journal of Benefit-Cost Analysis 2019;10(Suppl 1):1-36.

$$VSLY_{it} = \frac{VSL_{USA}\left(\frac{GDP_{it}}{GDP_{USA}}\right)^{e}}{\frac{1-(1+r)^{-0.5*LEB_i}}{r}}$$

Value of Statistical Life in the United States, VSL_{USA}
Per capita Gross Domestic Product, purchasing power parity adjusted, GDP_{it}
Income Elasticity, e
Life Expectancy at Birth, LEB_i
discount rate, r
year index, t
country index, i

Where *VSLYit* is calculated using the 2019 estimate of the Value of a Statistical Life (VSL) for the USA of US$12.31M[3], and transferring it to Global Fund-supported countries based on the difference in income between the USA (GDP_{USA}) and the country (GDP_{it}), where GDP_{it} is purchasing power parity (PPP)-adjusted gross domestic product (GDP) per capita of country *i* in year *t* in international dollars, which was obtained from the October 2024 World Economic Outlook;[4] GDP_{USA} is the PPP-adjusted GDP per capita of the USA (estimated at US$82,715 for 2023); *e* is a conservative estimate of income elasticity of 1.5, reflecting that poorer individuals are willing to pay a lower portion of their income for a given incremental of health risk reduction, compared to higher income individuals; and the term in the denominator is the present value of remaining life expectancy for a person in middle-age. As a proxy (recommended in BCA guidelines),[5] we used one-half of life expectancy at birth of country *i* in the year 2023 obtained from the World Bank.[6] We deviated from the BCA guidelines by discounting the remaining life expectancy at 3% per year when converting VSL to VSLY, but this was necessary in order to be consistent in discounting all health benefits and costs, accounting for the year in which they occur. To calculate the ROI, the total number of discounted DALYs averted in each country and year as predicted by the modeling underlying the Investment Case was multiplied by the country/year-specific VSLYs. In this way, we made a choice to value deaths proportionally to the remaining life expectancy associated with the counterfactual of

[3] Productivity Costs: Principles and Practice in Economic Evaluation. Pritchard C, Sculpher M. London: Office of Health Economics, 2000.

[4] World Economic Outlook, April 2024 update. International Monetary Fund, 2024.

[5] Valuing nonfatal health risk reductions in global benefit-cost analysis. Robinson LA, Hammitt JK, O'Keefe LO. Journal of Benefit-Cost Analysis 2019;10(Suppl 1): 1-36.

[6] World Development Indicators Databank. World Bank. https://data.worldbank.org/indicator/SP.DYN.LE00.IN [cited 2018 Dec 4].

that death (how long they would live if they had not died), and we are also valuing the reductions in non-fatal morbidity associated with these diseases.

Section 2: Instrumental valuation

When cases are prevented or effectively treated, household members can continue or return to productive work. Following a standard human capital approach for calculating "indirect cost" in cost-of-illness studies,[7] the productivity loss per case was calculated by multiplying an average duration of temporary disability by a wage rate for both investment and counterfactual scenarios. The duration represented the average days of lost work by the patient (or the patient's parent for childhood malaria cases).

For both TB and malaria, the episode duration was not affected by treatment access, but for malaria, the episode duration depended on whether the case was severe or not. The episode duration for HIV cases was assumed to be the period of symptomatic untreated disease, which include untreated adult patients (>15 years old) with CD4 count below 200 in any one year.[8] During this period, we assumed a 15% reduction in productivity.[9] Wage rate was derived from GDP per capita after subtracting natural resource rents obtained from the World Bank and a further downward adjustment to account for the disproportionate concentration of disease burden in groups of lower socioeconomic status.

Productivity loss due to premature death (i.e., remaining lifetime earnings had the death not occurred prematurely) was calculated by multiplying remaining working years at age of death by a wage rate, assuming that people work until age 65. For persons dying from malaria under 5 years old, we assumed a lag of 10 years before the working age period would begin.

Over 90% of the productivity-based ROI is due to averting productivity losses due to death. Our approach does not account for the potential societal-level impacts on other households not experiencing the disease-related death. It is possible, in settings where much labor is unskilled and unemployment levels are high, that when workers leave the workforce due to death or disease, they are replaced quickly by another – previously unemployed – person, so the net loss at the society level may be reduced. In addition, our analysis does not consider the future consumption (costs) associated with avoiding a premature disease-related death. Finally, we do not consider other macrolevel economic changes that may occur, such as a shift toward lower fertility and

[7] Productivity Costs: Principles and Practice in Economic Evaluation. Pritchard C, Sculpher M. London: Office of Health Economics; 2000.

[8] Data from nine country Population based HIV Impact Assessment (PHIA) surveys, showing the unweighted average proportion of patients not on antiretroviral therapy (ART) who had CD4<200 was 17.5%, which is taken as a proxy for "symptomatic." Personal communication with John Stover, Avenir Health.

[9] Work and home productivity of people living with HIV in Zambia and South Africa: Evidence from the HPTN 071 (PopART) trial. Thomas R, Friebel R, Barker K, Mwenge L, Kanema S, 2019.

greater per-child investment as child survival increases, and the resulting increase in education levels and economic productivity.

To see the method to estimate historical ROI, see https://www.theglobalfund.org/en/results/methodology/.

The Global Fund commissioned a health decision scientist[10] on the faculty of the Health Policy and Management Department at the Harvard T.H. Chan School of Public Health to conduct this study.

[10] Stephen C. Resch, lecturer on Health Decision Science. Health Policy and Management, Harvard T.H. Chan School of Public Health. https://hsph.harvard.edu/profile/stephen-c-resch/.

Annex 5

Methodology for calculations on health inequality across countries

The impact of Global Fund investments during 2023-2029 on inequality in global life expectancy across countries were obtained in two steps: Life expectancy was calculated for each country and year, and investment scenario (Section 1); estimates of life expectancy across countries were transformed into indicators on health inequality across countries (Section 2).

The basic methods for this forward-looking analysis of how Global Fund investments will impact global inequality in life expectancy (LE) between 2023-2029 is adapted from the original retrospective analysis covering 2002 to 2019[1] that was updated to 2021 for this Investment Case. The main data source for the retrospective analysis is the Institute for Health Metrics and Evaluation (IHME) estimates of all-cause and disease-specific mortality by country, age, sex and year in the 2021 Global Burden of Disease (GBD) study.[2]

In contrast to the retrospective analysis, forward analysis is based on mortality rates estimated directly from a simulation of the policy impact in disease-specific epidemiological models. These models generate estimates of the number of deaths by age group for the Investment Case and Constant Coverage at 2023 levels. But they do not make an estimate of future rates of deaths from causes other than HIV, TB and malaria. Therefore, we used all-cause mortality rates from the 2021 GBD study, and assumed the mortality rates from other causes would not change in the period extending to 2029.

[1] Contributions of Declining Mortality, Overall and from HIV, TB and Malaria, to Reduced Health Inequality and Inequity Across Countries. Haacker, Markus. 2023. *Health Policy Plan* 38 (8): 939–48.

[2] Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2021 (GBD 2021) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2022. Available from https://vizhub.healthdata.org/gbd-results/.

Section 1: Estimating life expectancy

Baseline life expectancy used output data from IHME models from the 2021 GBD study on country-, age-, sex- and cause-specific probability of death for the year 2021. In this data, probability of death is available in five-year age intervals, which were converted to single-age annual mortality rates that were assumed to remain constant through 2029. Life expectancy was calculated as the expected duration of life (equivalent to the area underneath the survival curve), applying established methods for this purpose.[3] First, for each country and year, we constructed a survival curve which, for each age, shows the probability of surviving to that age, applying the mortality rate for the respective age bracket for age-specific attrition. The probability of surviving to age *t+1*, P_{t+1} is calculated from the probability of surviving to age t as $P_{t+1} = P_t e^{-m_{S_t}}$ where m_{S_t} is the mortality for age bracket s that contains age t. Life expectancy is then obtained as the expected duration of life for this survival curve, by a procedure that is equivalent to calculating the area under the survival curve.

For the Investment Case and the counterfactual scenario, age-specific mortality profiles by disease were obtained from the impact modeling for HIV, TB and malaria undertaken for the Investment Case, and summed to obtain the combined contribution of HIV, TB and malaria to mortality. The year-on-year change in mortality of HIV, TB and malaria was computed for both scenarios. Then these year-on-year changes were applied to the baseline mortality obtained from the GBD study. In this way, we mapped the model-predicted reductions in mortality expected under each scenario. This allowed us to compare the gain in life expectancy between 2023 and 2029 expected under both scenarios.

Section 2: Estimating health inequality across countries

The analysis of mortality profiles from the impact modeling gives a set of annual estimates of life expectancy across countries. In addition to discussing the distribution of gains informally – e.g., looking at how the gains are distributed across groupings of countries – we estimate the impact of investments on health inequality across countries.

[3] Demography: Measuring and Modelling Population Processes. Preston SH, Heuveline P, Guillot M. 2001. Oxford and Malden MA: Blackwell Publishers.

In this analysis, health inequality is measured by the Gini index applied to life expectancy, with countries weighted by their respective population size.[4,5] The Gini index is equal to zero if life expectancy is the same across all countries; the higher the index, the more uneven life expectancy is distributed across countries. Using the country- and year-specific life expectancy obtained using the methods described in Section 1, we calculate a Gini for 2023 and for 2029 for the counterfactual scenario, as well as the Investment Case scenario. The Gini calculation included all countries for which we had data from the GBD study, but the modeled changes in mortality of HIV, TB and malaria were only in countries supported by the Global Fund. For countries not supported by the Global Fund, we assumed no change in mortality rates of HIV, TB and malaria. We were then able to compare the magnitude of global inequality reduction due to investments in interventions related to HIV, TB and malaria in Global Fund-supported countries under both scenarios.

It should be noted that the Gini index is more commonly applied to income and takes much larger values for comparisons by income levels. This reflects that income differs much more across countries than life expectancy, e.g., gross domestic product (GDP) per capita in 2021 ranged from US$230 (South Sudan) to US$131,000 (Luxembourg) (differing by a factor of 571), while life expectancy ranged from 52.9 years (Central African Republic) to 84.3 years (Japan). However, a poor health outlook and low incomes affect well-being in very different ways, so health inequality and income inequality should not be compared as equal in kind. Depending on the context, we also describe this health inequality as an inequity, to emphasize inequalities across countries that are avoidable and can be mitigated by global action, as evident from the gains achieved in reducing mortality from HIV, TB and malaria over the last two decades.

The Global Fund commissioned a health decision scientist[6] on the faculty of the Health Policy and Management Department at the Harvard T.H. Chan School of Public Health to do this work.

[4] Atkinson, AB. 2013. “Health Inequality, Health Inequity, and Health Spending,” in: Eyal, Nir, Samia A Hurst, Ole F Norheim, Dan Wikler (eds.), 2013, *Inequalities in Health: Concepts, Measures, and Ethics* (Oxford and New York: Oxford University Press).

[5] Wagstaff A, Paci P, van Doorslaer E. 1991. “On the Measurement of Inequalities in Health,” Social Science and Medicine, Vol. 33, No. 5, pp. 545 557.

[6] Stephen C. Resch, Lecturer on Health Decision Science, Health Policy and Management, Harvard T.H. Chan School of Public Health. https://hsph.harvard.edu/profile/stephen-c-resch/.

Annex 6

Methodology to estimate impact of HIV, TB and malaria investments on utilization of primary health care

Providing effective care for HIV, TB, and malaria can reduce the need for primary health care, by preventing individuals with one of these conditions from becoming ill and seeking care, and by preventing disease transmission that would lead to ill health and treatment-seeking in the future. These analyses estimated how investments in HIV, TB and malaria have reduced the need for primary care in Global Fund-supported countries, over two periods: a historical analysis that covers the period from the inception of the Global Fund in 2002 until 2023, and a forward-looking analysis that forecasts results for the period 2023-2029. For the historical analysis we compared two scenarios – one scenario representing the actual scale-up of care for each of the three diseases over 2002-2023, and a hypothetical counterfactual scenario in which care for each disease was limited to services levels in the year 2000 (representing what might have happened with no additional investments from government, Global Fund and other sources over the following decades). The forward-looking analysis takes a similar approach, comparing a scenario representing the possible scale-up of care for each of the three diseases over 2023-2029, and a hypothetical counterfactual scenario in which care for each disease is limited to service levels reported for the year 2023. Epidemiological projections for each disease, country and scenario were generated by the disease-specific models described in Annex 3, to maintain consistency with other analyses. Based on these modeled estimates, we calculated the number of individuals who would have symptomatic disease (from HIV, TB and malaria), and yet would fail to receive appropriate care. We applied rates of treatment-seeking from the literature for these individuals with unmet health care needs to derive rates of health care utilization (outpatient clinic visits, inpatient bed days) within the routine health system. We estimated the impact of disease-specific investments by computing the difference in utilization between scenarios and summed these results across countries and over time to compute the total reduction in routine utilization produced by disease-specific investments. In addition, we applied standardized country-specific unit costs (as reported by WHO CHOICE) to the estimated number of outpatient clinic visits and inpatient bed days, in order to estimate the total cost-savings due to reduced utilization resulting from disease-specific investments. For countries that have received Global Fund support for each of the three diseases over the 2002-2023 period, we compared estimates of averted inpatient bed days to data

on total hospital capacity in each country (reported number of available hospital beds each year, multiplied by 365), to calculate averted hospitalization as a percentage of actual capacity. Similarly, for each country we divided total averted costs by reported government health care spending over the period, to calculate averted costs as a percentage of total government health spending.

This analysis did not consider any additional supply constraints, beyond those that impact current levels of health care access and utilization within each country. It is possible that access to routine health care would be lower if demand surged as a result of uncontrolled HIV, TB and malaria in the counterfactual scenarios. In addition, this analysis did not take into account reductions in utilization that would result from early death due to HIV, TB or malaria.

The Global Fund commissioned an associate professor of global health[1] on the faculty of the department of epidemiology at the Harvard T.H. Chan School of Public Health to conduct this study.

[1] Nicolas Alan Menzies, Associate Professor of Global Health, Global Health and Population, Harvard T.H. Chan School of Public Health. https://hsph.harvard.edu/profile/nicolas-alan-menzies.

Annex 7

Methodology to estimate the benefits of investing in health systems to reduce the burden of HIV, TB and malaria as well as other conditions

A modeling analysis was conducted using the Thanzi La Onse (TLO Model)[1] to estimate the health impact of recent investments on human resources for health (HRH), consumables and disease-specific programs for HIV, TB and malaria in Malawi. The TLO model is an individual-based simulation of the interactions between individuals and the health system. It includes representations of a wide range of disease and conditions, including malaria, HIV, TB, measles, childhood infections (e.g., acute lower respiratory infections, diarrhea), non-communicable diseases (including diabetes, hypertension, heart disease, cancers, stroke), and reproductive, maternal and newborn health.

This analysis evaluated the health and economic impacts of three investment approaches in Malawi over the period 2023-2029: (i) investments in broader health systems strengthening, (ii) scale-up of HIV, TB and malaria programs; and (iii) a combined approach integrating both (i) and (ii). For (i), the health system investments were: scale-up (6% per year) of primary health care workforce, scale-up (6% per year) in number of health care workers (matching recent scale-up rates), reductions in stock-outs of consumables so that every facility has the same performance of that of the facility currently at the 75th percentile for fewest stock-outs. For (ii), the HIV, TB and malaria program scale-up involved expanding the scale, scope and coverage of interventions for these diseases within the constraints of existing health system resources. Specifically:

- **HIV**: Increasing access to preventive treatment for HIV (for female sex workers and adolescent girls); increased retention on preventive or antiretroviral therapy; increased uptake of medical male circumcision; increased HIV testing during pregnancy, childbirth, or for newborns; increased annual testing rates for adults;

[1] Estimates of resource use in the public-sector health-care system and the effect of strengthening health-care services in Malawi during 2015–19: a modelling study (Thanzi La Onse). Hallett, T. B. et al. The Lancet Global Health 13, e28–e37, 2025.

and increased likelihood of viral suppression on treatment (through adherence support and longer-acting formulations).

- **Tuberculosis**: Expanded first-line GeneXpert testing; increased treatment success rates for drug-sensitive and drug-resistant infections (through earlier and more accurate diagnosis, faster referral and patient adherence); and expanded access to preventive therapy for people living with HIV and child contacts of active cases.

- **Malaria**: Increased uptake of testing; improved treatment success (through increased access to treatment and timely initiation); expanded coverage of indoor residual spraying in high-risk districts; and higher coverage of insecticide-treated mosquito nets across all districts.

Health outcomes were summarized using disability-adjusted life years (DALYs), total deaths and life expectancy, with DALYs providing a comprehensive measure of disease burden by combining years of life lost due to premature death with years lived with disability. Cost estimates incorporated standardized inputs for human resources, medical consumables and infrastructure. The return on investment (ROI) was based on the magnitude of incremental health benefits monetized using a value of a statistical life year (VSLY) of US$834 for Malawi. The cost of implementing these changes, over and above the cost of incremental health system inputs, was unknown. Therefore, the computation was repeated for a range of hypothetical implementation costs.

Further details on the model, including source code and documentation, can be found at www.tlomodel.org.

The Global Fund commissioned the TLO modeling team[2] to conduct this study, which was undertaken by a professor of global health[3] and a research fellow[4] in the faculty of medicine at Imperial College London, and a research fellow[5] at the University of York.

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[2] The Thanzi La Onse (TLO) Model. https://www.tlomodel.org.

[3] Timothy Hallett, Professor of Global Health School of Public Health, Faculty of Medicine, Imperial College London. https://profiles.imperial.ac.uk/timothy.hallett.

[4] Tara Mangal, Research Fellow, School of Public Health - Faculty of Medicine, Imperial College London. https://profiles.imperial.ac.uk/t.mangal.

[5] Sakshi Mohan, Research Fellow in Global Health at the Centre for Health Economics, University of York. https://www.york.ac.uk/che/people/sakshi-mohan/.

Annex 8

Global plan milestones and targets

Global AIDS Strategy 2021-2026 End Inequalities. End AIDS. UNAIDS, Geneva, 2021. 2024 Global AIDS Report – The Urgency of Now: AIDS at a Crossroads. UNAIDS, Geneva, 2024.	Target	2023 status
By 2025		
Combination HIV prevention for all		
Reduce new HIV infections to under 370,000	370,000	1,300,000
Reduce new HIV infections among adolescent girls and young women to below 50,000	50,000	210,000
95% of people at risk of HIV access effective combination prevention	95%	50%/40%/39%/39% (medians) (sex workers/gay men and other men who have sex with men/people who inject drugs/transgender people)
Pre-exposure prophylaxis (PrEP) for 10 million people at substantial risk of HIV infection (or 21.2 million who used PrEP at least once during the year)	21.2 million	3.5 million
50% opioid agonist maintenance therapy coverage among people who are opioid-dependent	50%	0 of 8 regions
90% sterile injecting equipment at last injection	90%	11 of 27 countries
90% of men aged 15 years and over in 15 priority countries have access to voluntary medical male circumcision	90%	67%

Global AIDS Strategy 2021-2026 End Inequalities. End AIDS. UNAIDS, Geneva, 2021. 2024 Global AIDS Report – The Urgency of Now: AIDS at a Crossroads. UNAIDS, Geneva, 2024.	Target	2023 status
95–95–95 for HIV testing and treatment		
Reduce annual AIDS-related deaths to under 250,000	250,000	630,000
34 million people are on HIV treatment by 2025	34 million	30.7 million
95–95–95 testing, treatment and viral suppression targets	95–95–95	All ages: 86–89–93 Women (aged 15+ years): 91–91–94 Men (aged 15+ years): 83–86–94 Children (aged 0–14 years): 66–86–84 Key populations: unknown
90% of people living with HIV receive preventive treatment for tuberculosis (TB) by 2025	90%	17 million people living with HIV initiated on TB preventive treatment between 2005 and 2022
Reduce numbers of TB-related deaths among people living with HIV by 80%	80%	71%
Pediatric HIV		
75% of children living with HIV have suppressed viral loads by 2023	75%	48%
100% of pregnant and breastfeeding women with HIV receive antiretroviral therapy and 95% achieving viral suppression	100%	84%

Global AIDS Strategy 2021-2026 End Inequalities. End AIDS. UNAIDS, Geneva, 2021. 2024 Global AIDS Report – The Urgency of Now: AIDS at a Crossroads. UNAIDS, Geneva, 2024.	Target	2023 status
Gender equality and empowerment of women and girls		
<10% of women and girls experienced physical or sexual violence from a male intimate partner in the past 12 months	10%	13% [10–16%]
<10% of people from key populations experienced physical and/or sexual violence in the past 12 months	10%	21%/8%/28%/24% (medians) (sex workers/gay men and other men who have sex with men/people who inject drugs/transgender people)
<10% people support inequitable gender norms by 2025	10%	24.2% (median)
95% of women and girls aged 15-49 years have their sexual and reproductive health care service needs met	95%	Median of 50.8% of women currently married or in union make their own decisions regarding sexual relations, contraceptive use and their own health care (data from 16 countries)

Global AIDS Strategy 2021-2026 End Inequalities. End AIDS. UNAIDS, Geneva, 2021. 2024 Global AIDS Report – The Urgency of Now: AIDS at a Crossroads. UNAIDS, Geneva, 2024.	Target	2023 status
Realize human rights and eliminate stigma and discrimination		
<10% of countries criminalize: • Sex work • Possession of small amounts of drugs • Same-sex sexual behavior • HIV transmission, exposure or nondisclosure	10%	169 countries 152 countries 63 countries 156 countries
<10% of countries lack mechanisms for people living with HIV and people from key populations to report abuse and discrimination and seek redress		52% of countries have mechanisms established by the government, 66% of countries have mechanisms established by communities
<10% of people living with HIV and people from key populations lack access to legal services	10%	39% of countries
>90% of people living with HIV who experienced rights abuses have sought redress	90%	31% of people sought redress
<10% of people in the general population report discriminatory attitudes towards people living with HIV	10%	47% (median)
<10% of people living with HIV report internalized stigma	10%	38%
<10% of people from key populations report experiencing stigma and discrimination	10%	26%/16%/40%/49% (medians) (sex workers/gay men and other men who have sex with men/people who inject drugs/transgender people)
<10% of people living with HIV report experiencing stigma and discrimination in health care and community settings	10%	13% (HIV care) 25% (non-HIV care) 24% (community settings)

Global AIDS Strategy 2021-2026 End Inequalities. End AIDS. UNAIDS, Geneva, 2021. 2024 Global AIDS Report – The Urgency of Now: AIDS at a Crossroads. UNAIDS, Geneva, 2024.	Target	2023 status
Community leadership		
Community-led organizations deliver 30% of testing and treatment services	30%	As existing monitoring systems generally do not track the proportion of services and programs delivered by community-led organizations, UNAIDS is currently examining options for developing metrics to track progress towards the 30–80–60 targets
Community-led organizations deliver 80% of HIV prevention services for women and populations at high risk of HIV infection	80%	
Community-led organizations deliver 60% of programs to support societal enablers	60%	
Universal health coverage and integration		
Systems for health and social protection that provide 90% of people living with, at risk of, or affected by HIV with integrated HIV services	90%	
90% of people in humanitarian settings access integrated HIV services	90%	
45% of people living with, at risk of, or affected by HIV have access to social protection benefits	90%	
Investments and resources		
Fully fund the HIV response by increasing annual HIV investments in low- and middle-income countries to US$29 billion	US$29.3 billion	US$19.8 billion

Global AIDS Strategy 2021-2026 End Inequalities. End AIDS. UNAIDS, Geneva, 2021. 2024 Global AIDS Report – The Urgency of Now: AIDS at a Crossroads. UNAIDS, Geneva, 2024.	Target	2023 status
By 2030		
Population viral load suppression of 90% among all people living with HIV (to be approved)	90%	
PrEP to 50% of people at very high risk of HIV infection (to be approved)	50%	
Continued push for community-led services (30-80-60 targets) that will ensure the quality and reach of services (to be approved)	30-80-60 targets	
90% reduction in the number of new HIV infections from the 2010 baseline	90%	
90% reduction in the number of AIDS deaths from the 2010 baseline	90%	

Global Health Sector Strategies on HIV, Viral Hepatitis and STIs for the Period 2022-2030. WHO, Geneva, 2022.	Target	2023 status
By 2030		
End epidemics and advance universal health coverage, primary health care and health security		
End AIDS and the epidemics of viral hepatitis and sexually transmitted infections by 2030		
1. Deliver high-quality, evidence-based, people-centered services		
2. Optimize systems, sectors and partnerships for impact		
3. Generate and use data to drive decisions for action		
4. Engage empowered communities and civil society		
5. Foster innovations for impact		

The End TB Strategy/Global Plan to End TB/Second UN high-level meeting. The United Nations General Assembly, New York, 2023.	Target	2023 status
By 2025		
Percentage reduction in the absolute number of TB deaths (compared with 2015 baseline)	75%	23% reduction in absolute number of TB deaths, compared with 2015
Percentage reduction in the TB incidence rate (compared with 2015 baseline)	50%	8.3% decline in TB incidence rate, compared with 2015
0% of TB-affected households facing catastrophic total costs due to TB (level in 2015 unknown)	0%	49% of TB-affected families facing catastrophic costs due to TB
By 2027		
90% TB treatment coverage (percentage of the estimated number of people who develop TB disease each year who are provided with quality-assured diagnosis and treatment) (equivalent to up to 45 million people globally in the 5-year period 2023–2027, including up to 4.5 million children and up to 1.5 million people with drug-resistant TB)	90%	75% of all people with TB diagnosed and placed on appropriate treatment
90% coverage of TB preventive treatment (percentage of people at high risk of developing TB disease who are provided with TB preventive treatment) (equivalent to up to 45 million people globally in the 5-year period 2023–2027, including 30 million household contacts of people with TB and 15 million people living with HIV)	90%	Coverage of TB preventive treatment (TPT) 56% among people living with HIV who were newly enrolled on antiretroviral therapy (ART), and 21% among household contacts of people diagnosed with TB
100% coverage of rapid diagnostic testing for TB (percentage of those diagnosed with TB who were initially tested with a WHO-recommended rapid molecular test)	100%	49% of people diagnosed with TB initially tested with a rapid diagnostic test
100% coverage of health and social benefits package for people with TB so they do not have to endure financial hardship because of their illness	100%	
Annual funding for universal access to quality prevention, diagnosis, treatment and care for TB: US$22 billion	US$22 billion	
Annual funding for TB research: US$5 billion	US$5 billion	

The End TB Strategy/Global Plan to End TB/Second UN high-level meeting. The United Nations General Assembly, New York, 2023.	Target	2023 status
By 2030		
90% reduction in the absolute number of TB deaths (compared with 2015 baseline)	90%	23% reduction in absolute number of TB deaths, compared with 2015
80% reduction in the TB incidence rate (compared with 2015 baseline)	80%	8.3% decline in TB incidence rate, compared with 2015
0% of TB-affected households facing catastrophic total costs due to TB (level in 2015 unknown)	0%	
Annual funding for universal access to quality prevention, diagnosis, treatment and care for TB: US$35 billion	US$35 billion	
Availability of new TB vaccines that are safe and effective – rollout initiated, preferably from 2028		Six vaccine candidates in Phase III trials as of August 2024
By 2035		
95% reduction in the absolute number of TB deaths (compared with 2015 baseline)	95%	
90% reduction in the TB incidence rate (compared with 2015 baseline)	90%	
0% of TB-affected households facing catastrophic total costs due to TB (level in 2015 unknown)	0%	

Global Technical Strategy for Malaria 2021-2030, 2021 Update. WHO, Geneva, 2021.	Target	2023 status
By 2025		
Reduction in malaria case incidence and mortality rate of at least 75%, compared with 2015	75%	4.1% increase in malaria case incidence, compared with 2015; and 8.1% increase in malaria mortality rate, compared with 2015
Eliminate malaria from countries in which malaria was transmitted in 2015 – at least 20 countries	20 countries	Elimination in 26 countries (18 certified malaria-free by WHO) since 2000
Prevent re-establishment of malaria in all countries that are malaria-free		100% of malaria-free countries have prevented re-establishment
By 2030		
Reduction in malaria case incidence and mortality rate of at least 90%, compared with 2015	90%	
Eliminate malaria from countries in which malaria was transmitted in 2015 – at least 35 countries – re-establishment prevented	35 countries	
Prevent re-establishment of malaria in all countries that are malaria-free – re-establishment prevented		
Optimize the use of currently available interventions at levels above 80% coverage of at-risk populations and by improving the quality of services	80%	

Source documents

HIV and AIDS

- Global AIDS Strategy 2021-2026: End Inequalities. End AIDS. (https://www.unaids.org/sites/default/files/PCBSS_Global_AIDS_Strategy_2021--2026_EN.pdf)
- The Urgency of Now: AIDS at a Crossroads. Geneva: Joint United Nations Programme on HIV/AIDS, 2024. (https://www.unaids.org/sites/default/files/media_asset/2024-unaids-global-aids-update_en.pdf)
- Global Health Sector Strategies on, Respectively, HIV, Viral Hepatitis and STIs, 2022–2030 (GHSS). Geneva: WHO, 2022.(Global health sector strategies on HIV, viral hepatitis and sexually transmitted infections for the period 2022-2030)
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Tuberculosis

- Global Tuberculosis Report 2024, WHO. (https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2024)
- Tuberculosis Research Funding Trends, 2005-2023, Treatment Action Group. (https://www.treatmentactiongroup.org/resources/tbrd-report/tbrd-report-2024/#:~:text=December%2013%2C%202024%20%E2%80%93%20A%20new,High%2DLevel%20Meeting%20(HLM))
- Political Declaration of the High-level Meeting on the Fight Against Tuberculosis, 2023. (https://digitallibrary.un.org/record/4025280?ln=en&v=pdf)
- The Global Plan to End TB 2023-2030. (https://www.stoptb.org/what-we-do/advocate-endtb/global-plan-end-tb/global-plan-end-tb-2023-2030)
- The End TB Strategy. WHO, 2015. (https://iris.who.int/bitstream/handle/10665/331326/WHO-HTM-TB-2015.19-eng.pdf?sequence=1&isAllowed=y)

Malaria

- Global Technical Strategy for Malaria 2016-2030, 2021 update. WHO, Geneva, 2021. (https://iris.who.int/bitstream/handle/10665/342995/9789240031357-eng.pdf)

Annex 9

Upcoming market-shaping efforts for the introduction of new health products

The Global Fund partnership routinely maps out the health product pipeline to gain visibility into upcoming products and those already on the market that may require market-shaping interventions. This process is essential to ensuring the availability of improved and innovative tools that can effectively address evolving challenges and gaps in the fight against HIV, TB and malaria. The pipeline focuses on tools developed to combat these diseases categorized into prevention, diagnostics and therapeutics.

For HIV, the pipeline includes long-lasting preventive medications, improved testing methods and extended-duration treatments like injections. TB efforts concentrate on shorter treatment courses, enhanced local testing and the detection of TB infections before symptoms appear. Malaria initiatives feature new antimalarial drugs, better diagnostics, vaccines to prevent transmission and antibody-based treatments.

Timeline	HIV and related conditions	Tuberculosis (TB)	Malaria
2024-2026 (GC7)	• Making prevention easier with long-lasting medications that require less regular dosing. • Improved testing options, including self-testing kits.	• Shorter treatment courses and fixed-dose combinations for easier treatment. • Tests that can be done closer to patients' homes. • Better ways to detect TB early, including ultraportable chest X-rays with computer-aided design.	• New combination treatments to reduce chances of drug resistance. • Improved mosquito control tools. • Better diagnostic tests to detect gene mutations, ensuring improved diagnostic accuracy.
2027-2029 (GC8)	• Combined tests that can check for multiple infections at once. • More HIV prevention health product offerings, whether long-acting or multi-purpose technologies. • Treatments that last longer, like injections that replace daily pills. • Improved diagnostics and more effective treatments for opportunistic infections.	• Artificial intelligence (AI) technologies. • First TB vaccine. • Universal treatments that work for all forms of TB. • Alternative sampling types, such as tongue swabs and urine and near-point-of-care tests.	• Novel mosquito control methods. • More effective treatments. • New types of preventive tools.
2030-2032 (GC9)	• Further long-acting HIV prevention and treatment innovations that greatly simplify product use. • Potential cure developments.	• Next-generation testing methods • More effective vaccines. • Simpler treatment approaches.	• More effective vaccines that provide longer-lasting immunity and greater protection. • Innovative diagnostic approaches. • New types of antimalarial medications.