HIV/AIDS research insights: impacts, trends, opportunities
Executive summary

An estimated 38 million people worldwide are living with HIV, and while a decline in research output reflects success in tackling the disease, research into new drug targets continues.

Human Immunodeficiency Virus (HIV) is still a major public health problem globally, and particularly in sub-Saharan Africa, despite a steady decline in incidence rates. In 2018, there were 1.7 million new cases compared to 1.9 million in 2017. Research output has tracked the incidence rates, with the greatest output seen between 1995 and 2000, which coincides with the height of the pandemic, when there were 52 new cases per 100,000 people — or about double the current rate.

As the research output has steadily declined, so too has its focus. HIV protein targets have been a major source of focus in the published scientific literature over the past 20 years. In that time, an increasing body of published data has also begun to look at the potential of a patient’s own intrinsic immune defense system to reduce viral replication. The last 10 years have seen research into novel host targets, with emerging targets including SAMHD1.

The United States is the top producer of HIV/AIDS related research, followed by the UK, South Africa and China. In terms of the relative activity in HIV/AIDS research, output is highest in Uganda, Kenya, South Africa and Nigeria, reflecting the high priority of this research in countries where the disability-adjusted life years lost due to HIV/AIDS per 100,000 individuals is high, along with the strong research culture in these countries.

International collaboration is a key feature: of the top 10 institutions that produce the most research on HIV/AIDS, more than half of the output involves international collaboration. This is particularly the case for South African institutions: research from the University of Cape Town and the University of the Witwatersrand involves 73.9% and 74.1% international collaboration respectively.
Key findings

Global burden of disease per 100,000 individuals

- 712.6 disability-adjusted life years lost
- 660.9 years life lost

Top 10 countries based on publication count

1. United States
2. United Kingdom
3. South Africa
4. China
5. Canada
6. France
7. India
8. Italy
9. Australia
10. Spain

Top 10 institutions based on publication count

- Harvard University
- Johns Hopkins University
- University of California at San Francisco
- Centers for Disease Control and Prevention
- National Institutes of Health
- University of Washington
- Institut National de la Santé et de la Recherche Médicale
- University of Cape Town
- University of the Witwatersrand
- University of North Carolina
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Chapter 1

Global impact of HIV
Global impact of HIV

Human immunodeficiency virus (HIV) is a transmissible virus. Globally, nearly 38 million people are currently living with HIV.12

HIV attacks the immune system by infecting CD4 lymphocytes and causes progressive immune deficiency if untreated. In 2017, there were 1.9 million new cases globally, representing 25 new cases per 100,000 people.2 At the peak of the pandemic’s acceleration, in 1997 there were 52 new cases per 100,000 people – more than double the current rate. The greatest decline has been in children under the age of one, reflecting the positive impact of efforts to prevent mother to child transmission of the virus.

HIV is transmitted via certain bodily fluids – including blood, semen and breast milk – so sexual contact and needle sharing are two major causes of its spread. In children infected with HIV, transmission usually occurs from mother to baby in utero, during birth or through breastfeeding.

Mild symptoms may occur at the time of infection but many, including newborns, may be symptom-free in the weeks after infection. The stage of infection can be defined by its duration or degree of immunodeficiency. The most advanced stage of infection is acquired immunodeficiency syndrome (AIDS), which is characterized by an abnormally low CD4 count or opportunistic infections. People with AIDS often have comorbidities, most commonly hepatitis B virus, hepatitis C virus and tuberculosis. While some patients with AIDS can be asymptomatic, others may have dermatologic symptoms, weight loss, diarrhea, muscle wasting and cognitive dysfunction, as well as opportunistic infections.

Diagnosis and treatment

HIV infection is diagnosed via a blood test to detect HIV proteins, RNA or DNA. CD4 lymphocyte testing is used to confirm AIDS, which is indicated by a count of less than 200 CD4 cells/µL. This is supported by clinical measures of immunodeficiency – the presence and severity of opportunistic infections.

People with HIV/AIDS can be treated with antiretroviral therapy, and treatment should be started as soon as possible to reduce HIV viral load; all patients with AIDS should receive antiretroviral therapy. Treatment can be expensive, and resource limitations remain a frequent barrier to management, especially in Africa. During treatment, patients should be monitored for their viral load and adverse events, so that therapy can be adjusted to account for drug resistance, comorbidities and interactions with existing medications.

Unless otherwise indicated, this section on disease risks, prevention and treatment comes from Elsevier’s ClinicalKey®

There are some challenges with treatment. Adverse effects are common with antiretroviral therapy, including liver and kidney problems, osteoporosis and cardiac events. Antiretroviral drugs also frequently interact with other medications, which can interfere with their efficacy or lead to adverse effects. In children, the improvement of immune function after antiretroviral therapy is started may result in an intense inflammatory reaction to opportunistic infections, causing symptoms to worsen temporarily, which could be life-threatening. While long-term treatment can keep the infection at low levels, there are uncertainties about the long-term metabolic effects of antiretrovirals, so prognosis in later decades of adulthood is unknown for children undergoing treatment.

Patients must be willing and able to adhere to a regimen – inconsistency in taking medication leads to drug resistance, but adverse effects are a common reason for people discontinuing therapy. For children in particular, intensive preparatory education and counseling should be provided before the start of therapy and should be reinforced at every visit. When designing a treatment regimen, convenience and palatability should be considered, keeping the child’s age in mind.

However, treatment is critical for survival: untreated infection in babies usually results in death before they reach the age of five. Combination antiretroviral therapy improves the prognosis dramatically in children, and if the infection is managed well, they have a promising life expectancy. Most adult patients with AIDS who receive treatment are still alive three years after their AIDS diagnosis.
There were an estimated 38 million people infected with HIV globally in 2018, including 1.7 million children aged under 15. An estimated 1.7 million people were newly infected with HIV in 2018, down from 1.9 million in 2017.4 5

The burden of HIV and AIDS from mortality and morbidity varies from region to region. The World Health Organization (WHO) quantifies this burden using disability-adjusted life years (DALYs). One DALY is one lost year of ‘healthy’ life. DALYs reflect the gap between the population’s current health status and an ideal status, in which people lived their full lives without disease. In this case, DALYs are the sum of years of life lost and years lived with disability for people living with HIV/AIDS. The DALY rate ranges from 2 to 20,000 DALYs per 100,000 individuals, with the highest rates in countries in sub-Saharan Africa (FIGURE 1-1).

In 2017, the highest incidence of infection was seen in children aged under one, with 36 deaths and 101 new cases per 100,000 children under the age of one globally, resulting in 3,154 DALYs lost per 100,000 individuals. The highest prevalence was seen among people aged 25-60.

Chapter 2

HIV/AIDS research: progression and trends
HIV/AIDS research: progression and trends

HIV research tracked global output until tailing off a few years ago. Trends in protein research reflect developments in drug targets.

HIV/AIDS research output

To understand the landscape of HIV/AIDS related research, we queried Scopus, the largest abstract and citation database of peer-reviewed literature. A source-neutral database curated by independent subject matter experts, Scopus includes all publication types, such as articles, reviews, conference papers, book chapters, editorials and abstract reports.

For this report, HIV/AIDS-related research was identified by querying publication titles, abstracts and keywords for the presence of any of the following terms: “acquired immune deficiency syndrome”, “acquired immunodeficiency syndrome”, “human immunodeficiency virus” or “HIV”. The acronym “AIDS” was omitted from the query to avoid the retrieval of research related to hearing aids and other aids.

In addition to this, there are a number of indexed keywords associated with a publication, which are derived from several thesauri, one of which is Elsevier’s life science thesaurus Emtree. A hierarchically structured, controlled vocabulary for biomedicine and the related life sciences, Emtree is used for deep, full-text indexing of journal articles, maximizing their discoverability. The Scopus search automatically groups together different forms of the search term – it lemmatizes terms – so using the search term “human immunodeficiency virus” retrieves a broad set of HIV and AIDS-related publications.

Although the Centers for Disease Control and Prevention (CDC) was aware of the disease long before it was named, the term acquired immunodeficiency syndrome was only coined in July 1982. The following year, two different research groups published their findings showing a virus was causing AIDS but each naming it differently, settling on the name HIV in 1986. Since HIV and AIDS were named, research related to this field rose to represent nearly 1.2% of all Scopus-indexed research publications (from 1992-1995). Subsequent to 1995, HIV and AIDS related publications have declined relative to all Scopus-indexed publications, now representing 0.6% of all Scopus-indexed research output (in 2018) with a total of 79,643 publications from 2014-2018 (FIGURE 2-1 and FIGURE 2-2).

Looking at the change in percentage of HIV/AIDS publications over time together with trends in incidence, these data suggest the successful outcome that can result from focused research. This is illustrated in FIGURE 2-3, which shows that HIV/AIDS publications came to represent an increasing percentage of all research between 1990 and 1995, when the incidence rate was also on the rise. This was followed by a period during which the incidence rate was stable (from 1995 to 2000), which was accompanied by a slight decline in the publication share represented by HIV/AIDS research. Finally,
between 2000 and 2018, the incidence rate declined along with the publication share represented by HIV/AIDS research.

**FIGURE 2-1**
Number of publications related to HIV/AIDS from 1982 to 2018.
Source: Scopus

**FIGURE 2-2**
Percent of all Scopus-indexed research publications mentioning HIV or AIDS.
Source: Scopus
FIGURE 2-3
Percent of all Scopus-indexed research publications mentioning HIV or AIDS versus HIV/AIDS incidence rate (per 100,000 individuals) shown for every year from 1990 to 2017.
Source: Scopus and Global Health Data Exchange (http://ghdx.healthdata.org/)
HIV drug targets

To provide insight on HIV drug target research and identify the most studied and trending viral and host targets, we used an Elsevier text mining solution covering over 12 million full-text publications, 29 million abstracts and 521,000 grant applications. To find proteins suggested as drug targets, we searched for abstracts with semantic relationships between host and viral proteins and concepts describing the disease (HIV, HIV infection and AIDS) and drug targets (e.g. “treatment”, “therapy” or “drug target”) with their synonyms and child concepts. A custom vocabulary of HIV genes and gene products was created to find information about viral proteins. Examples of sentences matching the criteria include: “CCR5 is a key target in the human immunodeficiency virus infection”, “integrase strand transfer inhibitors are recommended for first-line HIV therapy” and “inhibitors of the HIV aspartyl protease are the cornerstone of treatment for HIV”.

Our findings reveal that HIV protein targets have been a major source of focus in the published scientific literature over the past 20 years (FIGURE 2-4). Through this research, the Food and Drug Administration (FDA) approved therapeutics have been designed to target viral proteins (specifically, viral protease, reverse transcriptase, integrase and gp41) with an aim to suppress viral replication to undetectable levels in a patient. Over the two decades, an increasing body of published data has begun to look at the potential of a patient’s own intrinsic immune defense system to reduce viral replication (FIGURE 2-5). Host proteins are becoming a powerful source of study for the development of complementary therapeutics to supplement anti-retroviral drugs. Among the host protein targets shown in FIGURE 2-5, drugs specific to CCR5 and CD4 have been approved by the FDA.
Studying new targets is important to maintain the tremendous progress in HIV treatment as this can broaden the spectrum of available treatments, thereby reducing the impact of HIV drug resistance. In the last decade, there has been increased research into other novel host targets (FIGURE 2-6) to suppress viral replication in host cells, to increase the immune response and to find alternative therapeutics to prevent the emergence of drug-resistant HIV. We identified these emerging targets by looking at the ratio of the number of publications mentioning a semantic relationship between a host protein target and concepts describing the disease (HIV, HIV infection and AIDS) in their abstract in 2018 compared to 2008. The protein SAMHD1 stands apart among these emerging targets with a relatively high count of publications studying its potential as a target. SAMHD1 is an enzyme that blocks HIV replication in certain types of immune cells by depleting the pool of dNTPs required for viral DNA synthesis.
FIGURE 2-6
Proteins trending, 2008-2018
Source: PathwayStudio
Chapter 3

Countries and institutions leading the charge
Countries and institutions leading the charge

The United States is the top producer of HIV/AIDS related research, followed by the UK, South Africa and China.

Publication output is an indicator of a country’s contribution to HIV/AIDS research. We assessed output by country using Scopus and SciVal, revealing that the United States is by far the biggest producer in terms of output, with 35,493 publications related to HIV/AIDS between 2014 and 2018. This surpasses the second-highest contributor, the UK, by over 27,000 publications.
Our data for the 10 countries publishing the highest number of HIV/AIDS publications includes publication count, outputs in top citation percentiles, percentage of international collaborations, field-weighted citation impact (FWCI) and percentage of academic-corporate collaborations. Top citation percentile refers to the percentage of the country’s publications on HIV/AIDS that are among the top 10 percent most cited publications compared to all Scopus-indexed publications worldwide.

Table 3-1 shows that countries with higher levels of collaboration tend to have higher FWCI scores. The high percentages of publications resulting from academic-corporate collaboration are also of interest: 3.4% (2,713) of all HIV research publications in 2014-2018 were the result of collaboration between academic and corporate institutions. The top three corporate institutions involved in this research are Leidos (290 publications), Gilead Sciences (178 publications) and GlaxoSmithKline (153 publications).

<table>
<thead>
<tr>
<th>Country</th>
<th>Scholarly output</th>
<th>Outputs in top 10 citation percentiles (%)</th>
<th>Field-Weighted Citation Impact (FWCI)</th>
<th>International collaboration (%)</th>
<th>Academic-corporate collaboration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>35,493</td>
<td>20.6</td>
<td>1.5</td>
<td>44.2</td>
<td>6.5</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>7,879</td>
<td>24.7</td>
<td>2.2</td>
<td>73.5</td>
<td>6.5</td>
</tr>
<tr>
<td>South Africa</td>
<td>6,823</td>
<td>18.3</td>
<td>1.9</td>
<td>66.6</td>
<td>3.5</td>
</tr>
<tr>
<td>China</td>
<td>5,382</td>
<td>9.6</td>
<td>1.6</td>
<td>30.3</td>
<td>1.8</td>
</tr>
<tr>
<td>Canada</td>
<td>4,338</td>
<td>22.7</td>
<td>2.4</td>
<td>59.9</td>
<td>5.2</td>
</tr>
<tr>
<td>France</td>
<td>3,923</td>
<td>21.6</td>
<td>2.4</td>
<td>58.6</td>
<td>6.0</td>
</tr>
<tr>
<td>India</td>
<td>3,842</td>
<td>9.6</td>
<td>1.6</td>
<td>30.3</td>
<td>1.8</td>
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<tr>
<td>Italy</td>
<td>2,983</td>
<td>22.1</td>
<td>2.5</td>
<td>49.5</td>
<td>5.0</td>
</tr>
<tr>
<td>Australia</td>
<td>2,963</td>
<td>23.2</td>
<td>2.8</td>
<td>67.5</td>
<td>5.8</td>
</tr>
<tr>
<td>Spain</td>
<td>2,960</td>
<td>18.6</td>
<td>2.5</td>
<td>44.2</td>
<td>6.1</td>
</tr>
</tbody>
</table>

Table 3-1: Top 10 countries based on publication count (HIV/AIDS, 2014-2018).

Source: Scopus and SciVal

Figure 3-1 and Table 3-1 provide a global view of country level research output on HIV/AIDS based on absolute publication count. For context, we looked at the relative level of focus on HIV/AIDS research in each country. To do this, we used the relative activity index (RAI), which is a measure of the proportion of the country’s research output in the subject (HIV/AIDS in this case) relative to the proportion seen globally.
When a country’s RAI for a particular subject is above 1.0, it indicates that the country’s research in that subject exceeds the proportion seen on average globally. When a country’s RAI is below 1.0, its research is below the proportion seen globally.

We looked at the relative activity in HIV/AIDS research in countries that produced at least 1,000 publications between 2014 and 2018. The RAI for HIV/AIDS research is highest in Uganda, Kenya, South Africa and Nigeria – four sub-Saharan African countries of differing World Bank Classification income groups (FIGURE 3-2). This may reflect, to some extent, the combination of the high priority this research has taken in countries where the disability-adjusted life years lost due to HIV/AIDS is high and research culture (i.e., infrastructure and workforce) are strong.
FIGURE 3-2
Relative activity index (RAI) in HIV/AIDS research in each country for countries with 1,000 or more publications in 2014-2018 shown at top. RAI compared to DALY rate per 100,000 individuals is shown at bottom (log scale displayed).
Source: Scopus and SciVal
International collaboration is a feature of research coming from the top institutions: among the top 10 institutions that produce the most research on HIV/AIDS, more than half of the output involves international collaboration (TABLE 3-2). The highest percentage of collaboration can be seen in research by the University of Cape Town and the University of the Witwatersrand, with approximately 74% involving collaborators overseas. Academic-corporate collaborations are also prominent among the top institutions, with one in five publications from the National Institutes of Health and one in 10 publications from Harvard University produced this way.

### Table 3-2
Top 10 institutions based on publication count (HIV/AIDS, 2014-2018), listed from highest to lowest field-weighted citation impact

<table>
<thead>
<tr>
<th>Institution</th>
<th>Country</th>
<th>Scholarly Output</th>
<th>Outputs in Top Citation Percentiles (%)</th>
<th>Field-Weighted Citation Impact (FWCI)</th>
<th>International Collaboration (%)</th>
<th>Academic-Corporate Collaboration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Cape Town</td>
<td>South Africa</td>
<td>1,873</td>
<td>26.6</td>
<td>3.8</td>
<td>73.9</td>
<td>4.0</td>
</tr>
<tr>
<td>National Institutes of Health</td>
<td>United States</td>
<td>2,307</td>
<td>35.1</td>
<td>3.6</td>
<td>47.5</td>
<td>18.3</td>
</tr>
<tr>
<td>University of Washington</td>
<td>United States</td>
<td>2,085</td>
<td>26.7</td>
<td>3.4</td>
<td>57.3</td>
<td>7.6</td>
</tr>
<tr>
<td>University of North Carolina</td>
<td>United States</td>
<td>1,826</td>
<td>22.8</td>
<td>3.1</td>
<td>54.7</td>
<td>9.0</td>
</tr>
<tr>
<td>Harvard University</td>
<td>United States</td>
<td>3,538</td>
<td>31.7</td>
<td>3.0</td>
<td>57.1</td>
<td>12.2</td>
</tr>
<tr>
<td>University of the Witwatersrand</td>
<td>South Africa</td>
<td>1,868</td>
<td>21.0</td>
<td>2.9</td>
<td>74.1</td>
<td>4.9</td>
</tr>
<tr>
<td>University of California at San Francisco</td>
<td>United States</td>
<td>2,785</td>
<td>28.3</td>
<td>2.9</td>
<td>53.5</td>
<td>8.5</td>
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<tr>
<td>Johns Hopkins University</td>
<td>United States</td>
<td>3,308</td>
<td>25.6</td>
<td>2.8</td>
<td>49.7</td>
<td>7.2</td>
</tr>
<tr>
<td>Centers for Disease Control and Prevention</td>
<td>United States</td>
<td>2,343</td>
<td>23.1</td>
<td>2.7</td>
<td>51.1</td>
<td>5.3</td>
</tr>
<tr>
<td>Institut National de la Santé et de la Recherche Médicale (INSERM)</td>
<td>France</td>
<td>1,884</td>
<td>22.2</td>
<td>1.9</td>
<td>53.1</td>
<td>4.2</td>
</tr>
</tbody>
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*Source: SciVal*
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