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Research-targeting, spillovers, and the direction of science: Evidence from HIV research-funding

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ABSTRACT

HIV/AIDS has been a major focus for research funders. The US National Institutes of Health (NIH) alone has spent over $70bn on HIV/AIDS. Such investments ushered in antiviral drugs, helping to reverse a rapidly growing HIV/AIDS pandemic. However, the idea that research can deliver unexpected benefits beyond its targeted field, in fact, predates HIV/AIDS to at least Vannevar Bush's influential 1945 report. Cross-disease spillovers – research investments that yield benefits beyond the target disease – remains unexplored, even though it could inform both priority-setting and calculations of returns on research investments. To this end, we took a sample of NIH's HIV grants and examined their publications. We analyzed 118,493 publications and found that 62 % of these were spillovers. We used Medical Subject Headings (MeSH) terms assigned to publications to explore the content of these spillovers, as well as to corroborate non-spillovers. We located spillovers on a network of MeSH co-occurrence, drawn from the broader universe of biomedical publications, for comparison. We found that HIV spillovers were unevenly distributed across disease-space, and often in close proximity to HIV (60 % local; 40 % remote). We further reviewed 1000 grant–publication pairs from a local sample and 1000 pairs from a remote sample. For local spillovers, a quarter seemed to be unexpected, on the basis of their grant description; for remote spillovers, that proportion increased to one third. We also found that the NIH funding institutes whose remits were most closely related to HIV/AIDS were less likely to produce spillovers than others. We discuss implications for theory and policy.

1. The arrow of funds and research

In 1984, the US health secretary announced the discovery of HIV: "The arrow of funds, medical personnel, research and experimentation [we] aimed and fired at the disease AIDS has hit the target. First, the probable cause of AIDS has been found… Second, a new process has been developed to mass produce this virus… Third, we now have a blood test for AIDS… Finally, we hope to have a vaccine ready for testing in two years" (quoted in Panem, 1988 p25).

Since then, the HIV/AIDS "target" has grown to be a major locus of social, economic and political activity. For >20 years, over half a per cent of the entire US federal budget has been allocated to HIV/AIDS (KFF, 2019). Globally, over half a trillion USD has been spent on HIV/AIDS since 2000 (Dieleman et al., 2018). The Joint United Nations Programme on HIV/AIDS (UNAIDS), the International AIDS Vaccine Initiative, and a plethora of other HIV/AIDS organizations have emerged. And the largest ever global health program focused on a single disease target, the US President's Emergency Plan for AIDS Relief (PEPFAR), was launched (Fauci and Eisinger, 2018).

HIV/AIDS has been the focus of one of the biggest research efforts of the last 40 years.[1] The US National Institutes of Health (NIH) alone has spent over $70bn on HIV research (Schwetz and Fauci, 2018). The effort included a new Office of AIDS Research within NIH, Congress mandating that 10 % of NIH research funds be set aside specifically for HIV, and the Presidential appointment of an AIDS co-ordinator. The research effort helped to deliver antiretroviral drugs capable of reducing viral loads to undetectable and non-transmissible levels. From peaks of 3 million new cases in 1997 and 2 million deaths in 2004, infections and deaths decreased sharply to around half of those extremes by 2020 (UNAIDS, 2021).

As resources were being mobilized for HIV/AIDS, policymakers highlighted that some of the outputs of the research effort could end up going beyond what was targeted. Senator Kennedy (D-MA) remarked in a Congressional hearing (US Congress, 1997a) that "AIDS research…

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[1] Until the COVID-19 pandemic, it may well have been the biggest ever research effort against an infectious disease.

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enhances our ability to fight not just AIDS, but all diseases." Similarly, Senator Frist (R-TN) asserted that "Scientific research holds the potential for discoveries that are applicable to many different diseases" (US Congress, 1997b). An influential report (IoM, 1991) claimed, somewhat presciently, that the research would "provide a base of knowledge that will be useful in dealing with epidemics of the future."

Such claims were becoming a staple feature in policy debates, as advocates lobbied for research to target specific diseases (Dresser, 1999). In response to concerns about the allocation of research funds across diseases, NIH Director Harold Varmus argued in his testimony to Congress (Varmus, 1997): "There are legitimate limits to our ability to plan science. Because science attempts to discover what is unknown, it is inherently unpredictable… Research aimed in one direction frequently provides benefits in an unexpected direction." This raises the question, *How frequently?*

NIH is an ideal setting to explore HIV/AIDS research spillovers. Globally, it is the largest biomedical research funder and, within the US, it is the largest funder of research excluding development, with 70 % of all federally funded academic science coming from NIH (Mowery, 2009; Sampat, 2009). The agency has been a dominant feature of the HIV research system and offers a plausible environment in which HIV research spillovers might transpire.

Initially, HIV/AIDS was slow to gain recognition as a priority.[2] A concerted advocacy effort, perhaps the largest ever in history to have been sustained on a single disease, would serve to broaden its appeal (Epstein, 1996). Moreover, there was growing hope and optimism that research would be able to help address HIV/AIDS because it was the first major epidemic since the advent of molecular biology, modern biotechnology, and the emergence of a large biomedical research system. By the mid-1980s, NIH saw rapid budget growth for its HIV/AIDS research.

NIH's annual budget for HIV/AIDS grew from $60 m in 1985 to $600 m in 1989; by 1990, at $740 m, HIV/AIDS commanded around one tenth of the entire NIH budget (IoM, 1991). HIV/AIDS research funding continued to grow thereafter, largely in lockstep with NIH-wide increases, to around $2bn by 2000; and, from 2005 onwards, it remained at around $3bn per year (NIH, 2021). Cumulatively, by 2018, NIH had spent $70bn on HIV/AIDS (Schwetz and Fauci, 2018).

If HIV research had been organized as an NIH institute in its own right, it would likely have been one of the top three largest institutes in terms of staff and budget. However, NIH administrators resisted calls for an HIV-specific institute amidst concerns about the proliferation of institutes (Varmus, 2001; IoM, 2003). So instead, within NIH, the Office of AIDS Research was established in 1988. It was authorized by Congress to plan, co-ordinate and budget HIV/AIDS research. The HIV/AIDS research program was to be an NIH-wide endeavor, "an institute without walls" (IoM, 1991 p2). This was in part motivated by explicit assumptions that spillovers would cut across institutes and that the benefits of HIV/AIDS research would "often go well beyond those applicable strictly to HIV/AIDS" (IoM, 1991, p.15). The outputs of the HIV research effort may well have ended up being different to what was targeted – but if so, how *often* was it different, and *how* was it different?

Here, we explore the frequency and magnitude of spillover and non-spillover outputs for research on a given disease. We develop methodological approaches for offering some empirical estimates, and we undertake an extensive manual review. Our findings suggest that spillovers are far from rare. We also find that there are likely social, organizational and political influences that affect the frequency and magnitude of spillovers. Lastly, we discuss implications for theory and policy.

2. Frequency, magnitude and unexpectedness of research spillovers

2.1. A high frequency of spillover could affect rate-of-return estimates

Long before HIV/AIDS emerged, Vannevar Bush's (1945) centerpiece of post-war science policy claimed that spillovers were not only "certain", but also likely to occur "often":

> "Discoveries pertinent to medical progress have often come from remote and unexpected sources, and it is certain that this will be true in the future. It is wholly probable that progress in the treatment of cardiovascular disease, renal disease, cancer, and similar refractory diseases will be made as the result of fundamental discoveries in subjects unrelated to those diseases, and perhaps entirely unexpected by the investigator. Progress in the war against disease results from discoveries in remote and unexpected fields of medicine and the underlying sciences."

Understanding the frequency at which research spills over into other fields would inform both priority-setting and calculations of returns on research investments. Spillovers have been examined as research crossing between public and private organizations, or from one firm to another, or from one region to another (Teece, 1986; Jaffe, 1989; Audretsch and Feldman, 1996; Audretsch and Stephan, 1999; Breschi and Lissoni, 2001; Cohen et al., 2002; Mowery and Ziedonis, 2015). However, few studies have examined the tendency of biomedical research funding in one disease area to then later yield outputs in other disease areas. One notable exception for the study of cross-disease spillovers – defined here as research investments that yield benefits beyond the target disease – is provided by Azoulay et al. (2019), who examined patenting by disease area. They showed that over half of the patents resulting from NIH funding are for disease areas distinct from the one that funded the initial research (Azoulay et al., 2019 p149). This underscores the importance of including the scale of spillovers when evaluating returns to research.

When moving further upstream from patents into the domain of publications, it remains unclear whether spillovers would feature as prominently. On the one hand, the patent-based evidence above includes greater involvement of industry and relates largely to inventive activity, which may encourage higher spillovers. Conversely, it may be that research activity in less applied contexts entails uncertainties that encourage higher spillovers. Our understanding of how often cross-disease spillovers occur in this domain, and how we might make sense of spillovers that do occur, has remained limited. One reason may be that the multiplicity of conceivable spillover areas is so large that it is far from obvious to know where to begin looking for them. A systematic view of plausible spillover destinations is needed.

The paucity of empirical evidence on cross-disease spillovers is especially notable given the increasingly prominent roles played by diagnosis into disease categories throughout medical research and practice (C. Rosenberg, 1988, 2002, 2003; Jutel and Nettleton, 2011; Sturmberg and Martin, 2016). Although there is a stream of rich empirical studies emphasizing the uncertainties and contingencies of medical innovation, there is less work on how medical innovation might contribute to the reification of disease entities (Nelson et al., 2011; Sampat et al., 2013; Consoli et al., 2015).

Such work could inform the growing interest in: targeting research toward particular diseases, technologies, missions and transformations (Mowery, 2009; Sampat, 2012; Schot and Steinmueller, 2018; Coburn

[2] HIV/AIDS has not always been a major priority. Groups at risk from AIDS were subject to social exclusion (Fox and Fee, 1992; Fee and Krieger, 1993). Calls for an HIV/AIDS effort were widely met with active opposition or, at best, indifference (Shilts, 1987; Oppenheimer, 1998). The transformation of HIV/AIDS is reminiscent of Charles Rosenberg's (1962 p5–7) observation that: "Cholera, a scourge of the sinful to many in 1832, had, by 1836, become the consequence of remedial faults in sanitation… Filthy illiterate peasants could expect no greater exemption from cholera in Boston than that which they had received in Ireland."

et al., 2023); the alignment of research effort with societal needs (Ciarli and Ràfols, 2019; Confraria et al., 2024; Kumar et al., 2024); and, priority-setting in research more generally (Brooks, 1978; Sarewitz, 1996; Wallace and Ràfols, 2015).

The frequency of research spillovers may be affected by the organization of research (Murayama et al., 2015; Shibayama et al., 2015; Walsh and Lee, 2015). The 27 institutes comprising NIH have varying missions and disease orientations, so some institutes will be more prone to spillover than others. For example, a higher frequency of spillovers may emerge from the National Institute of General Medical Sciences (NIGMS), whose remit is not oriented to any specific disease and is colloquially known as NIH's basic research institute. In contrast, fewer spillover outputs from HIV research may emerge from the National Institute of Allergy and Infectious Diseases (NIAID), whose remit accommodates HIV research perhaps more than any other institute.

2.2. *Magnitude and unexpectedness of spillover could affect how we value it*

In addition to whether HIV research funding has generated benefits in other disease areas, our concern also extends to how often it may have done so relative to outputs that remained on target. If HIV spillovers turn out to be frequent – say, if there are as many spillover outputs as there are on-target outputs – then one can no longer assume as easily that such spillovers are all of the same kind.

Because diseases are not mutually exclusive, research output can relate to more than one disease. Some spillover areas will overlap with HIV and be only slightly off-target, whereas others will be exclusive of HIV and distinctly more off-target. This will further affect how spillovers are perceived and valued (Pontikes, 2012; Trapido, 2015; Leahey et al., 2017). The aggregate frequency of spillovers might overlook variation in the way spillovers are distributed. This raises the need to be able to examine not just the frequency of spillovers, but also their composition and magnitude.

One way to understand the magnitude of spillovers is to locate them on a network that reflects disease relationships. Fortunately, there have been studies offering "global maps of science" on which to locate spillovers, which can help us draw inferences about their distance and direction from HIV (Ràfols et al., 2010; Ràfols et al., 2012; Carley et al., 2017). These networks offer a view of underlying cognitive and social structures in research, reflecting how various pathogens and symptoms are understood to be related to each other, as co-infections, co-morbidities, secondary complications and so forth. Spillovers can be viewed not only in terms of high or low frequency in a given category but also in terms of their location across disease-space.

In addition to visualization, these network relationships invite us to consider HIV spillovers in terms of their distance from on-target outputs. Measuring the proximity of HIV spillovers allows us to distinguish local and remote spillovers, and further investigate their varying nature. We can explore spillovers without assuming their magnitude is random.

It is conceivable that some HIV spillovers will be highly localized because they cross into neighboring disease areas exhibiting "related variety" (Frenken et al., 2007); for example, those that also feature viral infections, such as papillomavirus infections; or those carrying social stigma, such as opioid-related disorders (Bayer, 1991; Farmer, 2001; Parker and Aggleton, 2003; Castro and Farmer, 2005). If certain aspects of HIV/AIDS cannot be readily targeted and funded, this might drive local spillovers into sexually transmitted infections, drug abuse, and other stigmatized realms that are related to HIV.

Whether spillovers are generated in addition to, or instead of, the target may also affect how HIV spillovers are perceived. For HIV research investments, spillover to other areas beyond HIV could be considered an additionality. Conversely, it is possible that such efforts may yield spillovers without having "hit the target" (to use the 1984 US health secretary's terminology).

One prima facie example of failure seems potentially helpful here: namely, the absence of an HIV vaccine. This could provide some insight into spillovers emerging from challenging research conditions and the particular problems posed by the target. Some scholars have suggested that constraints could even enable creativity in certain settings (Simonton, 2003; Stokes, 2005; Rosso, 2014). Research that targets difficult and perhaps even intractable problems may present distinct opportunities for creativity and offer fertile ground for more far-reaching spillovers.[3] It is in this contrasting context of nominal failure that identifying, understanding and interpreting spillovers becomes even more pertinent in valorizing returns on research investments.

Remote spillovers could be indicative of unexpected findings or surprise discoveries (Brooks, 1986; Yaqub, 2018a; Wuestman et al., 2020), or may feature influential research techniques that can diffuse far and wide (Hacking, 1983; Price, 1984). Conversely, a scarcity of unexpectedness could reflect researchers eschewing opportunities to pursue more risk-averse outputs (Veugelers et al., 2022; Azoulay, 2023; Carson et al., 2023; Franzoni and Stephan, 2023).

Remote spillovers could also be indicative of new tools and techniques, forged in the HIV context and then applied elsewhere (Hacking, 1983; Consoli et al., 2015; Koppman and Leahey, 2019; Zyontz, 2019; Baruffaldi and Gaessler, 2021). A great deal of laboratory work involves "instrumentalities… the discovery of new techniques for doing something or producing some new effect, then perfecting and extending the technique and using it on everything in sight" (Price, 1984 p12) or the reorientation of existing datasets (Leahey, 2005; Hine, 2006; Nagaraj et al., 2020). These tools and techniques might then spill over in forms that others have referred to as "research technologies", "standardized packages", "epistemic machinery", and "thing knowledge" (Fujimura, 1992; N. Rosenberg, 1992; Joerges and Shinn, 2001; Baird, 2004; Knorr-Cetina, 2013).

One concern with studying spillover outputs in this way that we shall address directly is that they could be related to wide-remit research programs, where HIV is only one of several non-exclusive research targets (Wallace and Ràfols, 2015; Rushforth et al., 2019). Our empirical setting is ideal, not only because it comprises a set of research outputs but also because it includes a description of research projects at their outset, with an indication of the techniques and approaches to be deployed in the research. From this, we will be able to separately identify (1) spillovers that could be expected as part of the initial research endeavor; (2) spillovers that could be expected from the tools, techniques and datasets involved; and (3) spillovers that seem more unexpected.

3. Data and methods

We began by identifying a sample of HIV research grants in NIH RePORTER using a set of selected search terms.[4] We retrieved grants and their publication outputs, along with their titles and abstracts. After removing duplicates, our final dataset comprised 118,493 publications.

[3] Much of the prestige accorded to HIV research comes from the recognition of the immense challenges posed by the characteristics of the virus: the virus is difficult to explore in humans safely, viral infection is not simulated easily in animal models, the infection targets the very immune system responsible for clearing it, and the virus mutates rapidly (Yaqub, 2018b).

[4] Search terms used: HIV, Human Immuno Deficiency Virus, Human Immune Deficiency Virus, Human Immuno-deficiency Virus, Human Immune-deficiency Virus, Human Immunodeficiency Virus, Human Immunedeficiency Virus, Acquired Immuno Deficiency Syndrome, Acquired Immune Deficiency Syndrome, Acquired Immunodeficiency Syndrome, Acquired Immunedeficiency Syndrome, Acquired Immuno-deficiency Syndrome, Acquired Immune-deficiency Syndrome, HIV/AIDS, anti*retroviral, HAART, PEPFAR, President's Emergency Plan for AIDS Relief in Africa, NeuroAIDS, AIDS*dementia, Efavirenz, Ritonavir, Emtricitabine, Abacavir, Atazanavir, Zidovudine, Nevirapine, Dolutegravir, Lopinavir, Stavudine, Raltegravir, Indinavir. See Appendix 1 for alternative search terms.

Next, we disaggregated the publications into two sets: (1) cases where any of the HIV search terms used to retrieve the sample of grants were also present in the publication title and/or abstract, and (2) others.[5] In this way, we report publications as either "on-target" or "spillover", respectively.

We validated whether the on-target set relates mostly to HIV. For this, we exploited Medical Subject Headings (MeSH) assigned to the publication outputs of our HIV grants sample (Leydesdorff et al., 2012; Petersen et al., 2016). MeSH categories are expert-assigned from a controlled vocabulary managed by the US National Library of Medicine (NLM). The MeSH tree has been curated by indexers for over 50 years, at substantial cost, to offer a degree of consistency in the way it is applied to publications (Lipscomb, 2000). In this study, we focused on the C-branch of the MeSH tree, which provides an indication of disease orientation (C01–C20, and C25, and their sub-branches).

If the most frequent MeSH term in the on-target set of publications is, for example, "HIV infections", this offers reassurance that the on-target set does indeed relate substantively to HIV. Furthermore, comparing the MeSH terms of the on-target set and the spillover set offers an indication of whether the two sets are substantively different to each other.

Besides identifying whether publication outputs from HIV grants were on-target or spillovers, we also used MeSH to examine all disease areas for the presence of spillover outputs. We examined how the spillovers are distributed, in terms of how often HIV research outputs fall into a given MeSH category.

To distinguish spillover categories that overlap with HIV from those that are more distinct from HIV, we compared MeSH categories by their output proportion as well as their spillover frequency. We observed not only how often HIV research outputs fall into a given MeSH category, but also the proportion of those outputs that are spillovers relative to on-target outputs for that respective MeSH category. This provides an indication of the degree to which the MeSH categories overlap with HIV.

So far, these methods allow us to report the proportion of publications that represent spillovers, validate the spillover publications as distinct from on-target publications, and identify the disease areas in which spillovers are frequently present. They also offer an indication on whether the disease areas with spillovers overlap with HIV. However, MeSH categories are not mutually exclusive; a publication can be assigned more than one MeSH category. To better understand where these spillovers occur in terms of disease-space, we located spillovers in a network of MeSH relationships.

The network of relationships in which we located our spillovers is drawn from the broader universe of MeSH data assigned to all publications in PubMed (6,522,491 articles and reviews, published 2000–2019). Fig. 1 offers a view of underlying cognitive and social structures in biomedical research. It reflects how various pathogens and symptoms are understood to be related to each other, in a network of co-occurrences. In the resulting visualization, the location of a node is determined by a visualization-of-similarities algorithm (van Eck and Waltman, 2007).[6] The algorithm places the MeSH terms in such a way that the distance between them reflects their similarity.

Over this network, we then examined the spillover set, in terms of both frequency and proportion (Ràfols et al., 2010; Carley et al., 2017). The locations of the nodes remain identical across these visualizations because these are determined by the underlying network; however, their size and color depend on whether a node receives either a high frequency or a high proportion of spillovers, respectively. To aid the interpretation of Fig. 1, we have labeled clusters of nodes by disease group, whereas spillovers located on this network are presented later, in the Results section.

Similarly, we examined the grant set over this network to see how focused on HIV the grants were. Grants were assigned MeSH categories by passing their project description texts through the NLM Medical Text Indexer algorithm. Separately, we explored the feasibility of using this algorithm for this purpose and found it to be sufficiently reliable in terms of recall and precision (Moore et al., 2024). Locating grants on this network allows us to visualize their HIV focus and any other areas with which they might overlap.

Another way to explore spillovers is to categorize them as local or remote, by assigning each spillover output a distance from the on-target set. We determined distance by expressing each spillover output as a vector of the MeSH categories assigned to it, and calculating its cosine similarity with a reference vector of MeSH categories contained in the on-target set (top 50 terms by frequency). We used a cosine similarity threshold of $\leq$0.01 to indicate a greater distance from HIV (Leydesdorff et al., 2012).

We then sampled 2000 remote and local spillovers in order to identify their origins and understand what might affect their distance from HIV. For this, we focused our analysis on the links between grants and publications. We randomly drew a sample of 1000 grant–publication pairs from spillovers with cosine similarity >0.01 (the local spillover sample); and, we randomly drew a sample of 1000 grant–publication pairs from spillovers with cosine similarity of 0.01 or less (the remote spillover sample).

We examined these 2000 grant–publication pairs on both sides of the dyad, reviewing the grant title and abstract on the one hand, and reviewing the publication title and abstract on the other hand. We also reviewed the full text of the publication where available. The pairs were categorized by two independent reviewers as being one of the following: expected, as part of the remit of the grant; expected, from the tools and techniques involved; expected, from reorienting datasets; or unexpected.[7] However, it should be noted that our judgment of expectedness, on a case-by-case basis, may not necessarily be in agreement with that of other researchers, funding agencies, or advocacy organizations. Further details and the categorization manual are available in Appendix 1.

Lastly, an overview of our data and methods is shown in Appendix 1 (Fig. 4). Two additional checks using textual analysis are described in Appendix 2. First, we identified frequently occurring text, vectorized these, and calculated cosine similarity scores to see whether grant, on-target, and spillover texts are different. Second, we used Latent Dirichlet Allocation (LDA) topic modelling (Blei et al., 2003; Hackett et al., 2021) into two topics to see whether this yields similar results (see Appendix 2).

4. Results

4.1. Frequency

We found that 73,730 (62 %) of the 118,493 retrieved publications from our sample of HIV research grants were spillovers (i.e., they did not include any of the HIV search terms used to retrieve the grants sample), and the remaining publications were on-target (i.e., at least one search term used to retrieve the grants sample was also present in the output publications).

To confirm that the on-target publications related mostly to HIV and the spillover publications related mostly to other diseases, we examined

[5] This approach means that search terms may be present across the grant–publication pair, but they may not necessarily be exactly the same. For example, the grant may feature "HIV" only, and the publication may feature "anti-retroviral" only. In such cases, we still categorized the grant–publication pair as being on-target.

[6] We checked the network by reviewing 100 publications taken from the 10 largest clusters in terms of MeSH co-occurrence, to confirm that publications in those clusters do indeed pertain to those MeSH categories in terms of relevance.

[7] Coding reliability was assessed in 200 pairs selected at random. Intercoder reliability was sufficient for our purposes, with Kappa coefficients of $\geq$0.89 for each category (at the 95 % confidence level range of $\pm$0.05) (Landis and Koch, 1977).

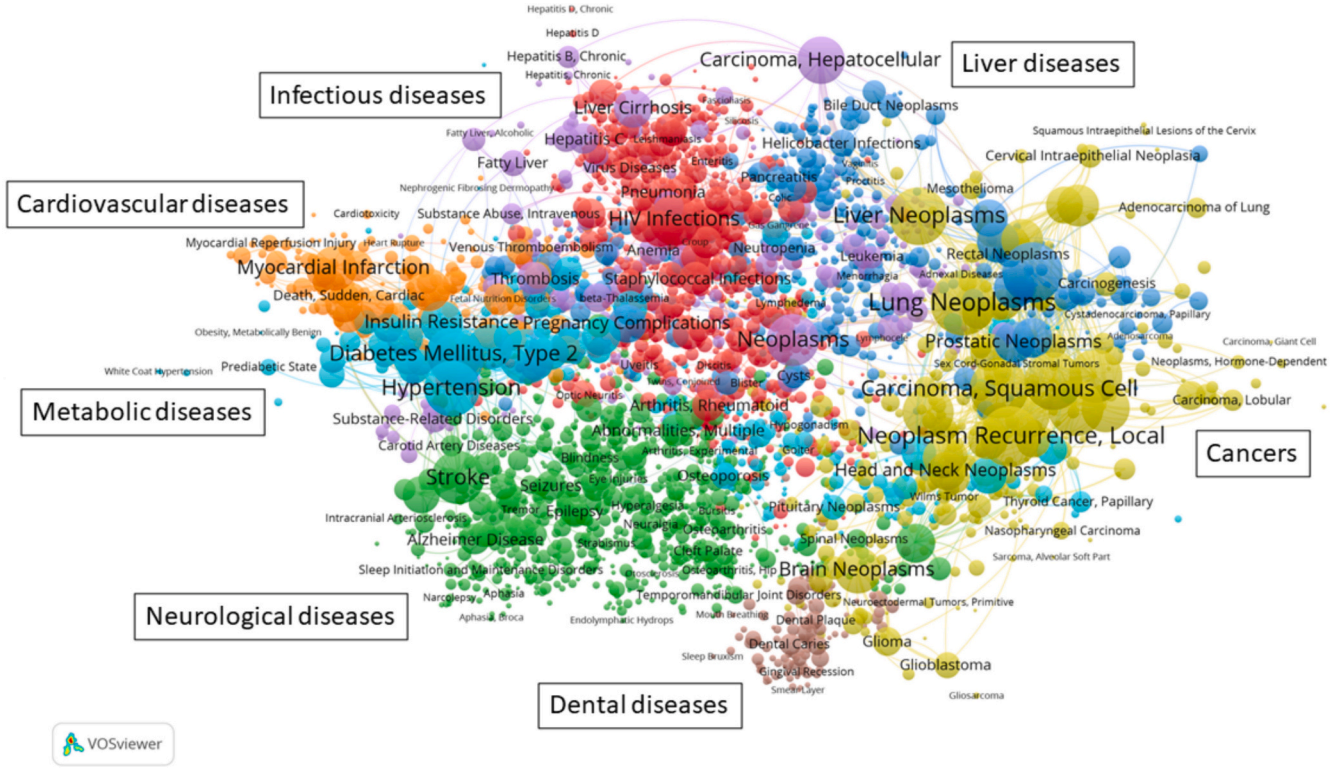

Fig. 1. A network of disease relationships on which to locate spillovers. The network is drawn from over 6 million publications. Each publication can have more than one MeSH assigned to it, and the visualization below displays similar MeSH categories in proximity with each other depending on how often they co-occur in publications. The network offers a view of underlying cognitive and social structures in research, reflecting how various pathogens and symptoms are understood to be related to each other. Different disease areas are visible in different parts of the network. In the Results section, we will return to this network and locate spillovers within this disease-space.

how the MeSH terms were assigned to both of these sets.

We found that the on-target set was much more heavily skewed toward a small handful of HIV-related MeSH categories, and that the modal category (HIV Infections) was at least 20 times larger than other MeSH categories. In contrast, the spillover set was almost entirely devoid of these HIV-related categories and was, in fact, distributed across a much larger number of MeSH categories.

Overall, the on-target set was distinct from the spillover set in terms of its distribution across MeSH categories (see Fig. 2 and Appendix 3).

In addition to identifying whether publications from HIV grants were on-target or spillovers, we also used MeSH to examine all disease areas for the presence of spillover publications. We found that the aggregate 62 % spillover output rate was not evenly distributed across MeSH categories. The top five MeSH categories with the most spillover publications were: Substance-Related Disorders (2554), Neoplasms (1283), Opioid-Related Disorders (961), Tuberculosis (910), and Obesity (857).

We then compared MeSH categories by their spillovers as a proportion of all outputs in that category. This helped to distinguish spillover categories that overlap with HIV. For example, the MeSH category Tuberculosis has a large absolute number of spillover publications, making it a high-frequency spillover category; however, tuberculosis is a common coinfection with HIV, so the term also yields a large number of on-target publications. Thus, the proportion of publications in the Tuberculosis category that are spillovers is lower than might be suggested by frequency alone. In this high-frequency and low-proportion example, Tuberculosis might be considered to be a spillover category that overlaps with HIV. The converse is also possible; for example, Obesity is a spillover category that is low-frequency and high-proportion.[8] This suggests that the Obesity category is more distinct from HIV than is the Tuberculosis category.

The top five MeSH categories, by spillover proportion, were: Breast Neoplasms (90 %), Prostatic Neoplasms (90 %), Alzheimer's disease (90 %), Diabetes Mellitus Type 2 (90 %), and Obesity (90 %). Spillovers in these categories can be interpreted as having less overlap with, and being more exclusive of, HIV.

Table 1 shows the top 10 MeSH categories with the most spillover publications. These spillovers were accompanied by differing proportions of on-target publications in their respective MeSH categories. Table 2 shows the top 10 MeSH categories with the highest proportion of spillover publications (as a proportion of all output publications in that category). Spillovers beyond the top 10 MeSH categories are reported in Appendix 3.

The frequency of spillover outputs varied by NIH institute. The three institutes that produced the most HIV-related publications were NIAID, the National Institute on Drug Abuse (NIDA), and the National Institute of Mental Health (NIMH). This result indicates the most prominent and active institutes in our sample of HIV research funding.

Table 3 shows the differing spillover proportions across the 10 institutes with the most publications. NIGMS, the basic research institute, had a spillover proportion of 58 %. This contrasted with NIAID, NIMH,

[8] There were fewer spillover publications in the MeSH category Obesity than in Tuberculosis, but the proportion of spillovers relative to on-target publications was higher for Obseity than for Tuberculosis (i.e., lower frequency, higher proportion). This suggests that, of these two spillover categories, Tuberculosis overlaps more with HIV, and Obesity is more exclusive of HIV.

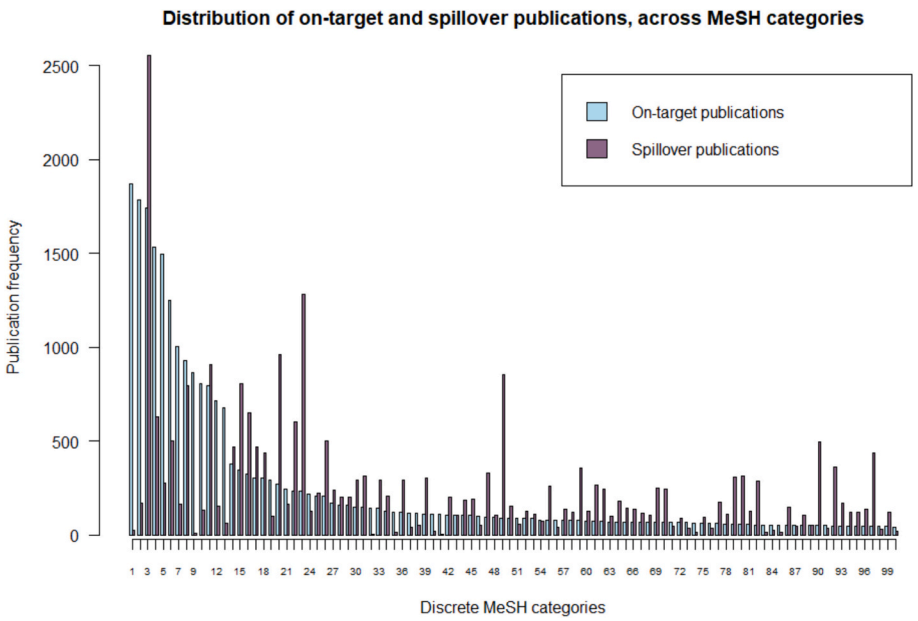

Fig. 2. On-target and spillover sets are substantively different in terms of their distinct distributions across MeSH categories. The MeSH term "HIV Infections", with over 25,000 publications, has been excluded from the Figure for clarity. MeSH categories are discussed in more detail in the main text and Appendices.

Table 1
The 10 MeSH categories with the highest number of spillover publications.

	Publication MeSH term	Number of on-target publications	Number of spillover publications	Total number of publications	Spillovers as a proportion of total publications
1	Substance-Related Disorders	1742	2554	4296	59 %
2	Neoplasms	232	1283	1515	85 %
3	Opioid-Related Disorders	274	961	1235	78 %
4	Tuberculosis	794	910	1704	53 %
5	Obesity	92	857	949	90 %
6	Breast Neoplasms	32	806	838	96 %
7	Alcoholism	344	804	1148	70 %
8	Hepatitis C	928	797	1725	46 %
9	Papillomavirus Infections	323	652	975	67 %
10	Substance Abuse, Intravenous	1535	628	2163	29 %

Table 2
The 10 MeSH categories with the highest proportion of spillover publications relative to the total number of publications.

	Publication MeSH term	Number of on-target publications	Number of spillover publications	Total number of publications	Spillovers as a proportion of total publications
1	Breast Neoplasms	32	806	838	96 %
2	Prostatic Neoplasms	21	371	392	95 %
3	Alzheimer's disease	50	496	546	91 %
4	Diabetes Mellitus, Type 2	45	435	480	91 %
5	Obesity	92	857	949	90 %
6	Marijuana Abuse	41	323	364	89 %
7	Influenza, Human	48	360	408	88 %
8	Malaria, Falciparum	56	314	370	85 %
9	Lung Neoplasms	56	311	367	85 %
10	Neoplasms	232	1283	1515	85 %

and the Office of the Director (which accommodates the Office of AIDS Research), all of which have spillover proportions of 20–30 %. Other institutes exhibited higher and lower proportions than these, although they had fewer total publications (Appendix 4).

So far in our results, we have described the proportion of publications that represent spillover, verified that the spillover set is distinct from the on-target set, and reported which MeSH categories spillover publications are frequently found in. We have also shown that some of these categories may overlap with HIV. However, MeSH categories are not mutually exclusive; a publication can be assigned more than one MeSH category. In the next section, we report the results of locating spillovers within a broader network of MeSH category relationships.

Table 3
Spillover output proportions vary by institute.

	Funding institute	Number of on-target publications	Number of spillover publications	Total number of publications	Spillovers as a proportion of total publications
1	National Institute of General Medical Sciences	6043	8308	14,351	58 %
2	National Institute of Diabetes and Digestive and Kidney Diseases	6500	4855	11,355	43 %
3	National Cancer Institute	16,602	11,766	28,368	41 %
4	National Institute on Drug Abuse	26,934	18,702	45,636	41 %
5	National Institute on Aging	7619	4301	11,920	36 %
6	National Institute of Child Health and Human Development	17,793	9041	26,834	34 %
7	Office of the Director	24,388	10,356	34,744	30 %
8	National Institute of Allergy and Infectious Diseases	69,180	28,834	98,014	29 %
9	National Heart Lung and Blood Institute	14,876	5854	20,730	28 %
10	National Institute of Mental Health	29,259	8076	37,335	22 %

4.2. Magnitude

To understand where spillovers occur in terms of disease-space, we located grants and publications from our dataset in a network of MeSH category relationships drawn from a broader dataset of MeSH co-occurrences. The underlying network was drawn from MeSH data assigned to all publications in PubMed. The co-occurrence network highlights how some combinations of MeSH categories are assigned in a given publication more often than other combinations. In this sense, MeSH categories can have differing proximity to each other, and to HIV.

When HIV grants and their publication outputs are located on the MeSH co-occurrence network, a range of clusters can be viewed. By examining these clusters, we found differences not only between the on-target set and the spillover set, but also differences within the spillover set. The grants and their on-target outputs are concentrated in, or very tightly around, the HIV Infections MeSH category (Fig. 3a and 3b), whereas spillover publications reach across disease-space (contrast Fig. 3b with 3c). The tighter focus of the inputs can be seen, relative to the dispersion of outputs.

The distribution of spillovers is uneven (Fig. 3c). Relative to the HIV Infections MeSH category, some clusters are local, whereas others appear further away and less connected. There are some areas that see particularly high levels of traffic, with a high number of spillover publications, while others are left empty or with very few spillover publications. Many of the high-traffic spillover categories (e.g. Hepatitis C), visible as large clusters, are local to HIV, suggesting that, although they are spillovers, they overlap with HIV. The spillover publications that are distributed even more widely come into view when we focus on spillovers as proportions, visible as deep blue in color. These more remote clusters include disease areas such as Alzheimer's disease, suggesting that as spillovers, they are more distinct from HIV.

These results show considerable variation in the locations of spillovers across an interconnected disease-space (Fig. 3c, contrast the size and color of remote clusters with the size and color of local clusters). The variation across disease-space is significant if we take the network as reflecting how various pathogens and symptoms are understood to be related to each other and to HIV.

4.3. Unexpectedness

So far, our results have shown how frequently spillovers occur, and how they are unevenly distributed across disease-space. To examine the expectedness of these spillovers and understand whether this might be related to their distance from HIV, we differentiated between local and remote spillovers by their cosine similarity to a reference vector (the on-target set's 50 most frequent MeSH categories). After randomly sampling local and remote spillovers, we found that the nature of the publications in each sample varied greatly in terms of topics. This provided reassurance that the cosine similarity approach differentiated between the two samples.[9] Assigning each spillover with a cosine similarity and removing those with cosine similarities >0.01, left 29,366 spillover publications.[10] This offers a more conservative estimate by discounting local spillovers.

Furthermore, for each spillover publication, we reviewed the aims of the study using the description of research projects at their outset. We categorized spillover publications that could be expected as part of the initial research endeavor and those that seem unexpected. We found variation between local and remote spillovers in their apparent expectedness. Table 4a shows that, compared with local spillovers, remote spillovers were more likely to seem unexpected. Taking our proportion of unexpectedness in our manually reviewed spillovers and extrapolating it to our overall sample offers an estimate of unexpected spillovers from research funding.[11]

Table 4b shows that two explanations account for almost all the expected spillovers in our samples. Over half were expected as part of their grants, and the remainder were related to the tools and techniques involved. Some further expected spillovers were found to be related to the reorientation of datasets, but this accounted for only a small number of observations. Although we anticipated there may be a difference in the nature of expected spillovers, Table 4b shows that they did not in fact differ much between the local and remote samples, with the possible exception of "reorienting datasets" featuring more in the sample of local spillovers.

5. Discussion

5.1. HIV spillovers: implications of overlooking them, challenges of incorporating them

HIV/AIDS has been a major focus of research for 40 years. We explored whether that effort contributed to disease areas beyond HIV/AIDS. Specifically, we examined the frequency and magnitude of cross-disease research spillovers, defined here as research investments that yield benefits beyond the target disease. We mapped both spillovers and non-spillovers for visualization and undertook extensive manual review.

[9] For example, the term "Drug users" appeared in 34 publications from the local sample, compared with 3 from the remote sample. "Chlamydia" appeared in 27 publications from the local sample, compared with 0 from the remote sample. In contrast, "Arthritis" appeared in 1 publication from the local sample, compared with 9 publications from the remote sample. "Stroke" appeared in 2 publications from the local sample, compared with 10 publications from the remote sample.

[10] As a proportion of spillovers, remote spillovers comprised 40 %, calculated as 29,366/73,730. As a proportion of all outputs, remote spillovers comprised 25 %, calculated as 29,366/118,493.

[11] As a proportion of all outputs, unexpected spillovers comprised 17 %, calculated as ((44,364*0.24) + (29,366*0.32))/118,493.

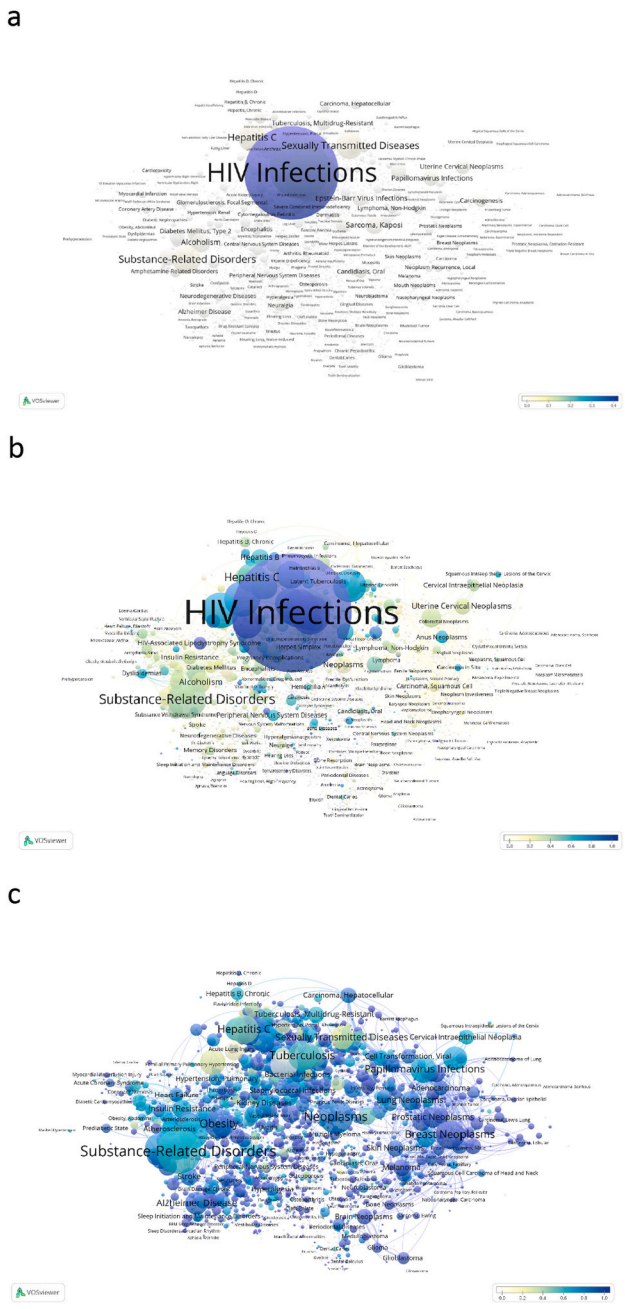

Fig. 3. a: HIV grants, located on a MeSH co-occurrence network. In addition to showing that the grants are HIV-focused, this visualization also provides a comparison point for the publication output of the grants. The size of the node indicates frequency.
b: HIV on-target publications, located on a MeSH co-occurrence network. The on-target set is concentrated tightly around the HIV Infections MeSH category. For each node, the size indicates on-target frequency, and the color indicates the proportion of on-target publications relative to all output publications. HIV Infections is both very large and deep blue, indicating a category with few spillovers despite a large number of outputs there.
c: HIV spillover publications, located on a MeSH co-occurrence network. For each node, the size indicates spillover frequency, and the color indicates the proportion of spillover publications relative to all output publications. There are large nodes in the vicinity of the HIV Infections category, and there are deep blue nodes that are more remote from HIV Infections. This shows that HIV spillovers are unevenly distributed across disease space. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 4a
Proportion of sampled spillover outputs that were expected or unexpected.

	Local spillover outputs (n = 1000)	Remote spillover outputs (*n* = 1000)
Expected	76 %	68 %
Unexpected	24 %	32 %
Total	100 %	100 %

Table 4b
Sources of expected spillovers and their cumulative proportions.

	Local spillover outputs (*n* = 759)	Remote spillover outputs (*n* = 681)
Expected, as part of wide-remit grant	60 %	64 %
Expected, from tools and techniques involved	95 %	99 %
Expected, from reorienting datasets	100 %	100 %

First, our results support the notion that cross-disease research spillovers exist. The results show that HIV research targeting delivered outputs not only in relation to HIV/AIDS but also to other disease areas beyond HIV/AIDS.[12] We found that half of publications from HIV research funding were cross-disease spillovers. If we had looked only at HIV/AIDS publications to assess the impact of HIV research, we would have missed half of its publication outputs.[13] Overlooking cross-disease research spillovers would lead to a substantial under-estimate on the returns to HIV research funding.

This finding has implications for how research investments are motivated. Whilst it may be useful for galvanizing support and mobilizing funding, we should be aware of some of the limits of a singular focus on one motivating disease for research targeting. Research efforts that can have payoffs in a wide range of areas perhaps ought not to be justified solely on the basis of any one area in particular.

Second, our results showed that spillovers were unevenly distributed across disease areas. This showed that whilst some spillovers occasionally went further afield, with their categories being more distinct from HIV, much of the HIV spillover traffic went to areas that overlap with HIV/AIDS or neighboring disease areas. The proximity of these spillovers to HIV suggests that in some cases the publications related to an antecedent disease.[14] These seem to account for half of the spillovers. We were able to visualize these differences across disease-space on a network of MeSH categories. Moreover, reviewing research projects at their outset allowed us to distinguish spillovers that were expected from spillovers that seem to be unexpected. Notably, unexpected spillovers seemed to comprise only a quarter of these local spillovers. Scarcity of unexpected spillovers could reflect researchers favoring more risk-averse publications.

Our results showed that not all spillovers are the same, at least in terms of their distance from HIV and their unexpectedness. The variety in the nature of the spillovers we observed presents challenges for valuation, and for incorporation into rate-of-return calculations. For some these spillovers ought to be discounted, for others they ought to be included.

Local and overlapping spillovers could be a by-product of a narrow

[12] By HIV research targeting, we mean research funding oriented to HIV.
[13] Azoulay et al. (2019) note that if they had restricted their analysis to outputs of the same disease area, they would have missed half of patent outputs.
[14] For example, given that intravenous drug use is a mechanism for contracting HIV, substance-related disorders leading to HIV would make HIV the spillover rather than the other way round. Often, in practice, such cases are described simply as "co-morbidities" without clear specification of direction of causality.

target category (Bowker and Star, 1999). That is, a given disease category is unable to capture the full extent of causes, symptoms, pathogens, diagnoses and the range of issues pertinent to the disease (Rosenberg, 2002). A narrow framing of the target would then contribute to spillovers into neighboring areas. However, that same narrow focus may also have served to mobilize research funding. Local and expected spillovers could then reflect a divergence between the range of possible ways of addressing disease vis-à-vis the approaches that more readily find favor in terms of research funding.

Remote spillovers can be characterized differently. When separating spillovers on the basis of their proximity to HIV, we found that remote spillovers were more likely to seem unexpected than local spillovers. Tools, techniques and datasets accounted for the expectedness of many of the spillovers in our sample, based on our categorization of project descriptions. This seems consistent with claims about HIV generating new approaches for tackling other diseases.

Third, spillovers do not seem completely random. There is notable variation across NIH institutes. NIH's basic research institute, NIGMS, had a higher spillover proportion than institutes for whom HIV is more clearly a focus (e.g. NIAID), suggesting that the research organization may play a role in the direction of research outputs. It is possible that researchers are self-selecting into the institutes with similar remits to their own work, or that certain types of work are inherently more prone to spillovers. Further research may be helpful here, in particular pursuing the identification of causal mechanisms of spillover may help to separate differences in degree from differences in kind.

Overall, our results suggest that cross-disease spillovers are a common feature of biomedical research. They reflect not only uncertainty and unexpectedness in research, but also how interconnected disease categories are in biomedicine, and the importance of tools and techniques in the diffusion of biomedical research. It seems researchers often encounter opportunities to work across diseases, or frequently find relevance and implications in their work for other diseases. As such, it is likely to be undesirable, perhaps even unfeasible, to eliminate cross-disease spillovers completely in pursuit of a research target. However, there may still be scope to shape spillover frequency and magnitude at the margins, via certain allocation choices and specific policy instruments. In summary, the main implication of overlooking cross-disease spillovers would be an underestimate of returns; whilst the main challenge of incorporating them is their wide variety – spillovers are not uniform.

5.2. Spillovers from failure (to hit the target)

Whether spillovers are generated in addition to, or instead of, the target could affect how they are viewed. The broader literature outside of our results indicates that HIV vaccine research has proved useful in responding to outbreaks of other diseases. Most recently, for COVID-19, "The decades-long effort to produce a workable HIV vaccine has hardly been a failure. To the contrary, the scientific know-how acquired along the way has served as the critical foundation for the development of vaccines against the novel, pandemic SARS-CoV-2 virus" (Harris, 2021 p1). And similarly, an analysis of the Zika vaccine literature revealed that its two most highly cited publications were authored by HIV vaccine researchers funded by HIV grants (Yaqub et al., 2022). Seen in this light, HIV research investments helped to build resilience and capabilities in the research system.

It seems that the difficulties and challenges encountered in HIV vaccine development played an active role in generating these spillovers. "HIV vaccine developers have experienced repeated failure using the standard approaches to vaccine development. This has forced them to consider immune responses in greater depth and detail." (Shapiro, 2019 p3400). For example, the rapidly mutating nature of HIV posed challenges for vaccine designers and forced a focus on specific conserved epitopes and structure-based vaccine design, whose lessons could be transferred to other pathogens. It is specifically the obstacles of HIV vaccine development that laid many of the foundations for spillovers such as covid vaccines.

For policymakers, this could be an important feature of where the spillovers might be coming from and what might drive them. In this view, the spillovers are not merely cropping up amidst repeated setbacks and failures, but perhaps *because* of them. These conditions may spur the development of research tools and techniques, and the diffusion and maintenance of research capabilities.

5.3. Future research

To classify spillovers, we used search terms, MeSH, MeSH mapping, MeSH cosine similarities, and manual review. It would be interesting to explore these results further with alternative classification systems. For example, Web of Science categories, or journal names and categories, could be used in a similar approach to designate HIV research from non-HIV research, though some may find these categories too coarse or highly aggregated to be useful. The Leiden algorithm offers a more sophisticated and granular classification at the level of individual articles and the communities that generate them, though this system may require adaptation for the context of classifying into specific diseases in biomedical research (Traag et al., 2019).

Further work into various project characteristics could also be helpful for understanding conditions for spillovers, for example whether they are affected by the cost and duration of projects, or by other additional constraints or requirements of the grant (Azoulay et al., 2011; Myers and Tham, 2023). Some conditions may allow for the possibility where "researchers use resources that were dedicated to one particular purpose for another" (Augsdorfer, 2005; Laudel, 2006; Criscuolo et al., 2014; Gläser, 2019 p439). Some project types may allow for more flexibility over the content of deliverables and more time may allow more novelty to emerge in the deliverables.

Our finding that there is variation in spillovers across NIH institutes suggests that further research on this may be useful. Further work comparing funders, funding schemes and timelines could identify more direct and measurable effects (see for example a comparison of NIH with HHMI in Azoulay et al. (2011)). Since there is a view that some funders may be more risk-averse than others (Veugelers et al., 2022; Azoulay, 2023; Carson et al., 2023; Franzoni and Stephan, 2023), it may be interesting to see whether other funders show higher spillovers than we found here alongside other measures.

The organization of research work may also have effects on spillovers, with research increasingly being undertaken in teams with highly specialized division of labor and hierarchical management lines (Murayama et al., 2015; Shibayama et al., 2015; Walsh and Lee, 2015). Disentangling some of these issues seems an important challenge for future research.

5.4. Revisiting rationales for research policy

We have known for a long time that research in general has high rates of return. HIV research seems consistent with this and, moreover, it seems that including spillovers would yield even higher returns to research in terms of aggregate social welfare gains. However, it seems that simply incorporating spillovers into the returns to research, without explicit attention to their variety, masks some possible trade-offs in research policy. Our results do not support the "myths of infinite benefit and of unfettered research" (Sarewitz, 1996 p17–50), though it does suggest some potential drawbacks to motivating public research funding with specific targets. Further study of spillovers could help to develop rationales centered on research capabilities, as well as on research relevance to social priorities. In particular, cross-case comparisons may help to inform some of these trade-offs. We hope future research along these lines will prove fruitful for further developing theory and policy implications.

CRediT authorship contribution statement

Ohid Yaqub: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Josie Coburn:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Duncan A.Q. Moore:** Conceptualization, Investigation, Methodology, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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