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A Landscape Analysis of HIV Cure-Related Clinical Trials in 2018

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INTRODUCTION

Advances in antiretroviral therapy (ART) have transformed the medical management of HIV infection, and newly diagnosed individuals who promptly initiate treatment now have a life expectancy close to that of their HIV-negative counterparts. Suppression of HIV viral load by ART can also prevent most types of HIV transmission, leading to the Undetectable=Untransmittable (U=U) public health campaign. But treatment can be imperfect because of side effects, inconvenience, cost, and inaccessibility. Additionally, HIV-positive people on treatment may still face an increased risk for some illnesses and aging-associated conditions.

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Inspiration has been drawn from the case of Timothy Ray Brown, the first individual considered cured of HIV. In 2007, Brown — who had been HIV-positive and on ART for many years —received stem cell transplants from a donor with a genetic mutation associated with resistance to HIV (the CCR5Δ32 mutation) as part of a series of treatments for a life-threatening cancer diagnosis. The transplants endowed Brown with a new, largely HIV-resistant immune system derived from the donor stem cells. Levels of HIV in his body became undetectable even by very sensitive tests, and ART was stopped without any rebound of viral load.[1] Brown has now been off ART for more than 12 years, hence the belief that his HIV infection is cured.

In early 2019, researchers presented information about two additional individuals who have possibly been cured in similar circumstances, having received stem cell transplants from donors with the CCR5Δ32 mutation as therapy for cancer diagnoses.[2,3] In these new cases, however, the time off ART is still relatively short (22 months in one case and eight in the other).[4]

Stem cell transplants are very risky and only appropriate for certain cancers, so they cannot be used as a basis for a widely applicable HIV cure. Developing a curative therapy that could be efficacious and accessible for the majority of people with HIV is a daunting challenge. At this time, the research is still at an early stage. Scientists are exploring multiple different possible approaches in hopes of generating results that can help chart the path toward a cure.

The National Institutes of Health (NIH) now considers the development of a cure to be one of three key HIV research priorities.[5] Global funding for HIV cure research has significantly increased in recent years, from US$88 million in 2012 to US$2.8 billion in 2017, with NIH by far the largest contributor.[6]

Since 2014, Treatment Action Group (TAG) has published a regularly updated listing of HIV cure-related clinical research on the organization's website (clinical research refers to studies that involve human participants).[7] The primary sources of information are online clinical trial registries, particularly the U.S.

government's clinicaltrials.gov database and the World Health Organization's International Clinical Trials Registry Platform.

There are two main types of clinical research included in TAG's listing:

- Interventional trials: as the name suggests, these involve the administration of interventions such as drugs, antibodies, or vaccines. The interventions may be experimental (not yet approved for prescription).
- Observational studies: these typically collect information and samples from participants but do not administer interventions. In some cases, participants may be receiving treatments that are part of their routine care.

TAG designates research as cure-related based on the measures and outcomes being assessed. For example, many studies evaluate the size of the latent HIV reservoir (the amount of residual, dormant HIV present in people on ART) and/or other factors linked to the persistence of the virus in the body. Immune responses potentially connected to controlling viral replication are another common subject of interest, and some trials include "analytical treatment interruptions" (ATIs) as a means to assess if an intervention has an effect on how HIV viral load rebounds when treatment is temporarily stopped.

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TAG divides cure-related interventional trials into different categories in an effort to make the listing more manageable and comprehensible, since a wide variety of approaches are currently being studied. For the purposes of the listing, "combinations" refers to trials that combine interventions from different categories. Trials involving multiples of the same type of approach (e.g., two therapeutic vaccines) are included within those categories.

In August 2018, the Bill & Melinda Gates Foundation contracted TAG to undertake a survey of investigators conducting studies included in our listing in order to obtain more detailed information about the current landscape of HIV cure-related clinical research. A scientific journal article describing the findings has been published in the open access *Journal of Virus Eradication*,[8] and this accompanying piece for the TAG website aims to provide a less technical summary of the results.

THE SURVEY

Survey questions were developed related to trial development, trial design, recruitment, enrollment, study completion, and dissemination plans. The survey was sent via Google Forms to the contact(s) in the registry listing for each study. The link was first sent at the end of August 2018, with a request for responses by October 5, 2018. Representatives for 73 studies completed the survey by the time of this analysis (a 57% response rate). Additional information was collected from clinicaltrials.gov for all 128 studies:

- Locations in which the trial is being conducted.
- Study procedures (as listed in clinicaltrials.gov).
- Demographic information (when available for completed studies).
- Study sponsors.
- Estimated study completion date.

The data from clinicaltrials.gov and survey responses were then analyzed to look for trends in development speed, enrollment speed, and participant diversity based on trial category, location, sponsor, invasive procedures, and other factors.

RESULTS

During the period of evaluation (August–November 2018), the HIV cure-related clinical research included in TAG's listing comprised 29 observational studies and 99 interventional trials grouped into 23 different categories. Combinations (17 trials) and antibodies (13 trials) were the most common categories of interventional trial (see Table 1). The diversity of categories is indicative of the early, exploratory stage of cure research.

A total of over 7,000 individuals will be recruited

into these studies based on the clinical trial registry information on enrollment targets. Numbers of participants for individual trials range from 5 to 905.* Most of the studies (118) are enrolling adults while nine include neonates, infants, or young children; one is limited to adolescents. The most common location of the research is the United States (65 of 128 studies), but there are a substantial number of trial sites across the globe, with study locations in 26 countries on six continents. (For a more recent version of the TAG listing that includes study location information, see the 2019 *Research Toward a Cure and Immune-Based Therapies Pipeline Report*.)[9].

Projected completion dates for the majority (~90%) of the currently listed trials fall between the 4th quarter of 2018 and the end of 2020. The results will inform plans for newer studies, hopefully allowing researchers to make progress toward increasingly effective interventions. For historical context, it took some time to proceed from the first studies of individual antiretroviral therapies in the 1980s to the types of effective ART combinations in use today, and there were a considerable number of failures along the way.

* Enrollment targets for two trials of HIV treatment in newborns (totaling 1505 participants) represent the number of pregnant women at risk for mother-to-child transmission due to late HIV diagnosis that will be enrolled. The primary goal of these studies is to treat the small subset of newborns diagnosed with HIV infection, which is likely to be a number in the range of 5-10% of the enrollment target total. Most newborns will be uninfected and receive standard preventive HIV treatment, exiting the trials 4-6 weeks postpartum. These two trials are included in the "Treatment Intensification/Early Treatment" category.

Table 1. Overview of Study Characteristics

Category	Number of Studies	Average Number of Participants	Range	Total Number of Participants
Adoptive immunotherapy	1	12	---	12
Anti-inflammatory	3	66 (median 60)	30-110	200
Anti-proliferative	1	5	---	5
Antibodies	13	38 (median 34)	12-68	500
Antifibrotic	2	42 (median 42)	21-63	84
Antiretroviral therapy	1	36	---	36
Cannabinoids	1	26	---	26
Combinations	17	40 (median 30)	5-192	680
Cytokines	2	15 (median 15)	10-20	30
Dual Affinity re-targeting (DART) molecules	1	26	---	26
Gene therapies	8	16 (median 12)	6-40	132
Gene therapies for HIV positive people w/ cancers	8	8 (median 7)	3-18	69
Gonadotropin-releasing hormone (GnRH) agonists	1	52	---	52
Hormones	1	22	---	22
Imaging studies	2	7 (median 7)	5-10	15
Immune checkpoint inhibitors	4	46 (median 40)	20-84	184
Latency reversing agents	3	32 (median 28)	9-60	97
mTOR inhibitors	2	16 (median 16)	10-22	32
Observational	29	88 (median 50)	10-536	2571
Proteasome inhibitors	1	17	---	17
Stem cell transplantation	4	13 (median 12)	5-25	55
Therapeutic vaccines	8	46 (median 39)	26-105	374
Toll-like receptor agonists	2	50 (median 50)	28-72	100
Treatment intensification/Early treatment	10	68 (median 65) 205 (median 72)	15-905	2054
Total				7373

The 73 studies for which completed surveys were received will enroll 3,936 of the 7,373 total participants anticipated for the entire trials listing (53%).

Study Development and Trial Design

Developing a clinical study requires multiple steps, including the drafting of a detailed research protocol, seeking community input (often via a community advisory board), securing supplies of any interventions that are involved, creating an informed consent form (which potential participants must read, agree to and sign in order to join a study), and obtaining approval from several different regulatory bodies, such as the local Institutional Review Board (IRB) and the national Food and Drug Administration (FDA) (or equivalent agency if outside the United States).

Survey respondents reported an average study development time of 20 months (range = 4–60 months). Most respondents reported that at least one challenge had arisen during the process, although 21 respondents did not cite any significant problems. Local regulatory issues (e.g., difficulties during IRB review) were the most frequently cited challenge during development (25 responses), followed by securing funding (19 responses), and research team concerns over the intensity of the demands upon participants (16 responses).

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The concerns over the intensity of HIV cure trials were primarily related to the number of invasive procedures required of participants. Of the 128 studies, at least 32 (25%) across nine categories required participants to undergo an ATI. An additional 67 studies included invasive procedures, such as biopsies from lymph nodes or gut-associated lymphoid tissue (GALT), lumbar punctures, leukapheresis (a lengthy procedure used to sample large numbers of white blood cells), and/or stem cell transplants (in studies for people with HIV who require the transplants for cancer treatment).*

In addition to ATIs and invasive sampling procedures, survey respondents expressed some apprehension over potential trial participants' ability to meet inclusion/exclusion criteria as well as the duration of study participation.

Of the 73 respondents, 38 specified that community representatives or advisory bodies were involved in protocol development and had an opportunity to provide feedback. Most of these respondents (22) noted that community comments were positive, while four respondents reported concerns that were largely related to ATIs and the risk of HIV developing drug resistance.

Participant Enrollment

A majority of respondents (51) reported encountering at least one obstacle to enrollment, while 19 cited no obstacles. The most frequently mentioned impediment to enrollment was the reluctance of potential participants to undergo invasive procedures (21 responses), followed by "study has no benefit to participants" (15 responses). The latter point relates to the exploratory nature of most current studies—participants are not expected to accrue direct benefits, but rather are being asked to altruistically contribute to scientific research in the hope of benefitting people with HIV in the future.

Additional factors cited as having a potentially negative impact on enrollment were strict inclusion/exclusion criteria (12 responses) and complicated study visit schedules/lengthy follow up periods (10 responses).

Respondents were also asked about current enrollment status, in order to gain insight into the progress of the studies. A slight majority (55%) reported having enrolled more than half of their total participant target. About a third (30%) were less than a quarter enrolled, although this proportion included a number of studies that, while entered into clinical trial registries, had not yet opened for enrollment.

* Information on study procedures was collected from trial registry entries. Some studies may involve additional invasive procedures that were not entered into the registry record.

The average anticipated time for studies to fully enroll varied substantially from less than six months (categories = imaging studies, anti-proliferative, and hormones) to longer than two years (categories = treatment intensification/early treatment, observational, immune checkpoint inhibitors, and stem cell transplantation), with an average across studies of 21.4 months (range = 3–84 months).

The potential impact of invasive procedures on pace of enrollment was analyzed, with studies involving ATIs expected to enroll in an average of 22.86 months, those with GALT biopsies estimating 24.7 months, and studies with lumbar punctures and lymph node biopsies citing average expected enrollment times of 26.68 and 28 months, respectively. These data suggest that despite the lack of benefit for trial participants and intense nature of sampling procedures, HIV cure-related trials that require invasive procedures and/or ATIs are able to enroll at speeds similar to those without such requirements.

Participant Demographics

The survey requested demographic information on participants where available, but only a small proportion of respondents were able to provide it (because it was not yet available, not yet sufficient to be meaningful, or for other reasons). For some studies that have since been completed, this information has been provided in the clinicaltrials.gov registry entry or included in published results. Combining these three sources of demographic data (survey responses, clinicaltrials.gov and publications), race or ethnicity breakdowns were identified for 34 studies and sex breakdowns for 44 studies.

Reported percentages of female participants ranged from 0% to 100%, with an average across categories of 17 percent female and 83 percent male.

Unfortunately, information on racial and ethnic diversity in trial participants was insufficient to conduct any analyses for non-U.S. or multinational studies. In U.S.-only studies, enrollment (or enrollment-to-date) was as follows: 39% Black or African American, 52% white, and 16% Hispanic. There was no significant correlation between study category and the demographic diversity of participants.

Reported percentages of female participants ranged from 0% to 100%, with an average across categories of 17 percent female and 83 percent male (see Table 2). One trial sponsored by the AIDS Clinical Trials Group (ACTG) only enrolled women (accounting for the 100 percent end of the range) because the purpose was to explore whether modulating estrogen receptor expression with the drug tamoxifen affects the efficacy of a strategy to awaken latent HIV, as laboratory studies have suggested it might.

Enrollment (or enrollment-to-date) was 100 percent male for 18 of the 44 studies where sex information was available; one of the 18 was limited to male participants, while another recruited from a predominantly male cohort. The remaining 16 studies with only male participants did not have specific criteria excluding women. In other words, there was no scientific rationale for enrolling only males.

The limited information available from studies including ATIs indicated that 89 percent of participants were male. Studies that enrolled infants and pre-adolescent children reported approximately equal sex distributions.

Enrollment of both men and women was reported by 25 of the 44 studies that included available information on participant sex. The average female enrollment in these studies was 28 percent. When studies enrolling newborns and infants are excluded, the average female enrollment drops to 16 percent.

Women's underrepresentation varied across curative strategy (Table 2), with five categories of curative strategy reporting no female participants enrolled to date. There was no apparent correlation between higher rates of female enrollment and study sponsor, study location, or category of trial.

Table 2. Sex Distribution (when reported/available)

Category	Percent Male	Percent Female	Number of Studies in Category with Sex Data Available (of Total Number of Studies in Category)
Anti-inflammatory	100%	0%	2 (of 3)
Anti-proliferative	100%	0%	1 (of 1)
Antibodies	73%	27%	7 (of 13)
Antifibrotic	100%	0%	1 (of 2)
Combinations	79%	21%	6 (of 17)
Gene therapies	77%	23%	1 (of 8)
Immune checkpoint inhibitors	73%	27%	3 (of 4)
mTOR inhibitors	100%	0%	1 (of 2)
Observational	86%	14%	7 (of 29)
Proteasome inhibitors	100%	0%	1 (of 1)
Stem cell transplantation	75%	25%	2 (of 4)
Therapeutic vaccines	96%	4%	5 (of 8)
Treatment intensification/ Early treatment	73%	27%	7 (of 10)
Total	**82.73%**	**17.27%**	

CONCLUSION

The current landscape of cure-related clinical research includes a diverse array of interventional and observational studies. In the majority of cases, trials are early stage (phase I or II) and sample sizes are small. Results are likely to become available over the next two to four years. There is no expectation of curing HIV infection, with the possible exception of efforts to recapitulate the example of Timothy Brown by providing stem cell transplants from donors homozygous for the CCR5Δ32 mutation to people with HIV requiring the procedure to treat concomitant cancers.

The hope is that current trials will provide information to assist in the iterative improvement of interventions, enhancing the prospects for achieving temporary remissions or cures in the future.

Potential obstacles to the implementation of study protocols that were identified in our survey included local regulatory review, which may suggest a need to enhance the knowledge of institutional review board members regarding HIV cure research. Securing funding was also cited, emphasizing the importance of investing in the field.

An important limitation that could have an effect on the generalizability of anticipated results is the relatively homogenous population involved in current studies. Considering previously identified sex differences in HIV reservoirs and persistence,[10,11,12] the underrepresentation of women is of particular concern. This highlights a need to try to diversify participation, while recognizing that the absence of potential benefit raises difficult questions regarding how to ethically manage risk, and places an onus on altruism as a motivation to join studies. Facilitating the informed participation of a broader spectrum of people living with HIV is likely to require increasing the availability and accessibility of educational materials on cure research.

Community support for HIV cure research remains strong, and there are ongoing efforts to diversify the participant base.[13,14] Many researchers have

recognized the importance of early and meaningful community engagement from trial development through implementation.[15] More than half of survey respondents reported community involvement during trial development, and TAG strongly encourages researchers to continue soliciting input from diverse communities. In addition to monitoring participation, further characterization of community involvement and engagement—particularly how it is understood and operationalized in different settings and by different stakeholders—will be an important area of future research.

Many researchers have recognized the importance of early and meaningful community engagement from trial development through implementation.

An overarching lesson is that clinical trial registries can provide a vital source of information on a particular research field, in addition to serving as an important resource for potential participants. TAG asks that investigators and study coordinators strive to be diligent about entering and maintaining clinical trials.gov (or other online registry) records, as this greatly enhances the ability of all stakeholders to track progress toward the ultimate goal—the development of a highly efficacious and accessible HIV cure.

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