Is it time to abandon single intervention cure trials?

Only one person in the world has been cured of HIV. The Berlin patient was transplanted with CCR5-negative and HIV-resistant stem cells for cancer that eradicated his HIV.[1] Reported in 2009, the case renewed interest in the search for a cure. But what has happened in the ensuing years? In 2013, apparent HIV remission (ie, undetectable plasma viral load in the absence of antiretroviral therapy or ART) in the two Boston patients transplanted with HIV-permissive CCR5-positive stem cells for cancer[2] and the Mississippi baby treated with ART extremely early in life[3] were met with disappointments when HIV subsequently reappeared in all three.

Studies with latency-reversing agents to reactivate hidden viruses universally failed to deplete HIV proviral DNA sufficiently and to eliminate infected cells.[4] The VISCONTI cohort of adults in HIV remission for longer than 10 years remains unique, but it has reinforced the relevance of early ART in HIV cure research.[5] No therapeutic HIV vaccine trials in human beings have produced the substantial benefits needed to eliminate HIV-infected cells, although vaccines recently studied in animals show potential.[6] Broadly neutralising antibodies can lower HIV viral load, nonetheless are not believed to target latently infected cells.[7] Gene editing and cell-based therapies that modify stem cells to become resistant to HIV or have better killing ability are promising, but have inherent risks and scalability issues.[8] Much progress has been made in understanding the mechanisms of HIV persistence, immune destruction and immune activation. These investigations highlight the extent to which HIV has mastered immune evasion to stay hidden in diverse cell types and tissues. The limits to tissue sampling and technology to assess HIV reservoirs hinder quantification of the effects of interventions on HIV persistence in people.

The key question now is how can we make significant gains in HIV cure research in the next 5 years? On the basis of experience from current studies, single therapies would be unlikely to lead to long-term HIV remission.[9] Combination therapies are far more promising, but researchers continue to struggle to identify what these combinations would be. This brings us to the vital question: what are the best pathways to combination cure? The usual approach would be to start with single therapy trials in animal models for safety and potency endpoints, and then to proceed to trials in people to determine safety before moving to efficacy trials. Each step takes years and is then repeated when compounds are put into combinations. With such a process, an HIV cure remains too far in the future.

How can we innovate our way to combination cure? We argue that now is the time to move directly from in vitro studies to combination therapy trials in animals and then people. Concerns over having less information about investigational drugs when they are not studied individually could be lessened by use of animal models to investigate the mechanisms and understand successes and failures. Animal models afford opportunities to test activity of interventions, to investigate biomarkers, and to do extensive tissue studies.

Combinations could be carefully selected on the basis of extensive in vitro and existing animal and human data and animal and human studies could run in parallel (figure). Each regimen could have two or more compounds with multimodal targeting of HIV. An example is one or more latency reversing compounds plus immunotherapeutic agents that provide passive humoral and active cellular immunity against the virally infected cells. Another includes gene-editing therapy to make cells resistant to the virus plus immunotoxins to target already infected cells in tissues and peripheral blood. Combinations that are safe are selected to proceed in animal efficacy and phase 1 human safety studies simultaneously. Once information from these

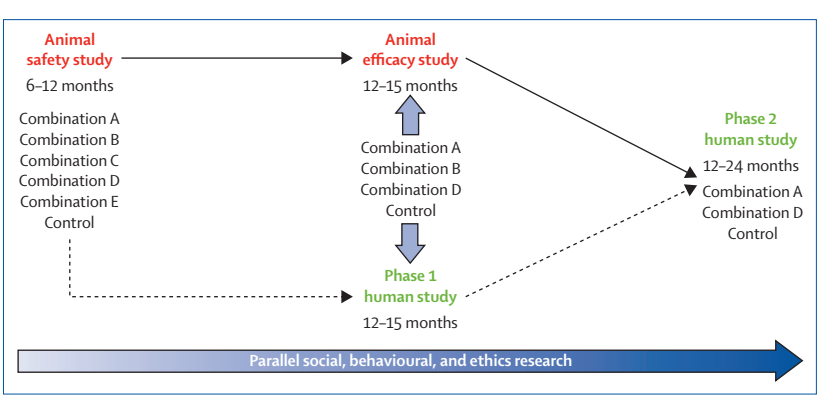

Figure: **Possible roadmap to combination cure research for HIV**
An example of a roadmap of parallel animal and human studies that begins with combination therapies in animals. Combinations are carefully selected on the basis of extensive in vitro and existing animal and human data. Each combination contains two or more compounds with multimodal targeting of HIV. Combinations safe in animals are selected to proceed, at the same time, to animal efficacy and phase 1 human safety studies. These studies are used to select combinations to proceed to a phase 2 human study. Parallel social, behavioural, and ethics research is essential.

studies is available, combinations are selected to proceed immediately to the phase 2 human study. The efficiency and feasibility of such an approach relies heavily upon streamlining regulatory review and approval processes, and engaging sponsors and industry to jointly fund and collaborate in such an effort. Engagement of patients and community is vital.

Can this type of roadmap accelerate the regulatory approval of the co-development of two or more new investigational drugs for use in combination? According to US Food and Drug Administration guidance[10] certain criteria should be fulfilled: first, the development of compounds for treating a serious disease; second, a strong biological rationale for use of the combination; third, compelling reasons why the agents would be expected to have limited activity when used as monotherapy; and finally, a full non-clinical characterisation of activity or a short-term clinical study to suggest that a combination is superior to individual agents. Although the last point suggests that human trials of single interventions would be needed, we argue that given what we have learned from single-intervention trials to date, this criterion could be met with data from animal studies. Moreover, many potential compounds for HIV cure research have been extensively used for research and treatment of autoimmunity and cancers; therefore, adequate safety data are available for other indications.

Although HIV is transitioning to become a manageable chronic disease, ART alone will not achieve cure. To balance patients' safety and potential scientific gain, the proposed roadmap calls for partnership and coordination between preclinical, clinical, bioethics, and behavioural researchers from multiple disciplines both within and outside the HIV specialty to do combination trials with the potential to move research forward. It is important to identify ethical ways to study HIV cure, particularly in these early stages when the risk-to-benefit ratio is high and there may be no individual gain.[11] Equally important is understanding how to communicate the research to trial participants and the community.[12] Single therapies are deemed to have less risk, but participating in these trials with no or little chance of success carries its own risks. Moreover, some therapies, such as broadly neutralising antibodies, are associated with resistance when only one antibody is used. Studying the social, behavioural, and ethical aspects of HIV cure research in parallel with preclinical and clinical trials is essential.

How can we make significant advancement towards cure for the 35 million people living with HIV worldwide and the 2·5 million people newly infected every year? It is time we pool our best efforts to critically interrogate the existing data and generate new in vitro data to identify the most promising combination therapies for animal studies to proceed to human trials. This proposed data driven roadmap will enable us to accelerate efforts to transform HIV from an incurable disease to a durable remission.

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