Towards a scalable HIV cure research agenda: the role of co-infections

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Abstract

The development of a cure is among the foremost contemporary priorities in the field of HIV research. The science that underpins a potential HIV cure should be generalisable to the many millions of persons globally who enter antiretroviral treatment programs with advanced immunosuppression and/or an opportunistic infection. We provide five key suggestions for incorporation into the HIV cure research agenda to maximise the generalisability and applicability of an HIV cure once developed.

Keywords: HIV, AIDS, HIV cure, opportunistic infections

Introduction

The eradication of detectable HIV infection from Mr Timothy Brown was first reported in 2009 and subsequently confirmed with detailed investigations [1–3], igniting a new effort in HIV therapeutics: the quest for HIV cure. Recently, at the International AIDS Society conference in Vancouver in July 2015, a French teenager perinatally treated with antiretroviral therapy (ART) was reported to have an unexpected functional cure with virus still detected via laboratory assays, but plasma viraemia maintained below the clinical limit of detection in the absence of ART [4]. Other reports of prolonged spontaneous remission of plasma HIV viraemia include two persons who underwent allogeneic stem cell transplantation for lymphoma [5] and two babies born to HIV-infected mothers and treated shortly after delivery with ART, which was then later discontinued [6]. All these patients subsequently had virological rebound at various times after ART discontinuation [7,8]. The HIV research field has enthusiastically embraced these cases to decipher their differences and similarities in order to comprehend the reproducible elements necessary to achieve a sterilising or functional cure, or at least long-term HIV suppression in the absence of ART.

Based on US President Barack Obama's December 2013 announcement to increase funding for HIV cure research, the US National Institutes of Health (NIH) launched a 3-year initiative beginning in fiscal year (FY) 2015 to further augment its HIV cure research budget. In this regard, the President's FY 2016 budget request includes $149 million for NIH HIV cure research (Director's office, National Institute of Allergy and Infectious Diseases, personal communication). Ten different grant programmes are tailored to match specific priority areas to answer basic scientific questions that underpin the search for a cure [9]. In addition, numerous conferences and review papers have been devoted exclusively to cure-related issues, and newer assays to better study the HIV viral reservoir are being developed [10–12]. Yet there remain knowledge gaps in understanding HIV latency, and the HIV reservoirs in cells and tissue compartments that pose significant challenges in designing successful cure strategies [13–16].

Despite these challenges, the HIV research community is committed to the goal of HIV cure. Importantly, any cure strategy should be simple, safe and scalable [17]. Genetic modification techniques have shown promise [17,18] but are expensive, complicated and possibly would not be broadly applicable. It also appears that ART commenced very early after HIV infection may favourably alter immune responses, limit HIV reservoir size and may provide the possibility of a long-term functional cure, with or without adjuvant strategies [19,20].

In a rapidly growing HIV cure literature, little discussion has focused on how the current cure agenda addresses the 15 million persons living with HIV and being treated with ART, many of whom started therapy with WHO stage 3 or 4 disease (AIDS) often having had one or more opportunistic infections prior to, or during early ART [21,22]. Due to inadequacies in healthcare services, barriers to accessing care, difficulties in retention in care prior to ART, and people not knowing their HIV status until late in disease progression, it remains commonplace in many parts of the world for patients to start ART with advanced immunosuppression. In 2013, approximately 23% of people initially diagnosed with HIV infection in the United States were simultaneously diagnosed with stage 3 disease (AIDS); an additional ~30% were diagnosed with stage 2 disease (CD4 count 200–499 cells/μL) [23]. The US Centers for Disease Control and Prevention has estimated that only 30% of all HIV-infected persons in the US have virological suppression, with an average duration of HIV infection of ~6 years before initiating ART [23–25]. In middle or low-income countries, CD4 cell counts at diagnosis are frequently lower than 200 cells/μL [21].

Despite evolving HIV treatment guidelines, CD4 cell counts at time of ART initiation are only slowly increasing [21,22,24]. Based on 2013–2014 UNAIDS data, of nearly 16 million people worldwide with CD4<350 cells/μL, 61% were receiving ART [26,27]. This leaves 6.2 million individuals urgently requiring ART, of whom ~50% have CD4 cell count <200 cells/μL including an estimated 2.2 million persons living with AIDS and not accessing ART. Among those newly initiating ART, the current incidence of those lost to follow-up coupled with virological failure is 22.4% by one year (95% confidence interval [CI] 13.9–32.4%) [28]. This leaves approximately 4 million individuals with CD4 cell counts <200 cells/μL not on effective ART, with virological failure, or who are lost to follow-up and who are also at risk for an opportunistic infection.

Among late presenters, opportunistic infections remain common. Two of the more common opportunistic infections are tuberculosis (TB) and cryptococcosis [29,30]. Approximately 1.1 million incident cases of HIV-associated TB occur annually [29]. In sub-Saharan Africa, approximately 25% or more of those with CD4 cell counts <200 cells/μL entering HIV care will be receiving TB treatment or be diagnosed with TB at entry [31]. In areas with high burdens

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of HIV and TB, such as South Africa, up to 40% of patients in some areas start ART while on TB treatment [32,33]. Cryptococcal antigen prevalence among persons with CD4 cell counts <100 cells/μL averages 7.2% (95% CI 6.8–7.6%) in 37 studies of 14,815 patients in low- and middle-income countries [34], with an estimated global incidence of ~230,000 cryptococcal infections annually in 2014 (unpublished data). Between TB and *Cryptococcus* alone, this equates to approximately 30% of persons with CD4 cell counts <200 cells/μL entering into care with an active co-infection. When considering these data and data from a systematic review of immune reconstitution inflammatory syndrome (IRIS) [35], globally, nearly 50% of persons initiating ART with CD4 cell counts <200 cells/μL may have had an opportunistic infection, with some variation by region.

In reviewing recent literature evaluating the HIV reservoir and strategies for viral eradication or interventions with curative potential, in many cases the status of participants at ART initiation was that of stable chronic infection, acute/primary infection or early infection. To ensure patient safety, studies of analytic treatment interruption usually exclude persons with lower nadir CD4 cell counts and who are likely to have larger HIV viral reservoirs [36]. This omits a substantial proportion of persons living with HIV.

In research of potential curative strategies, despite achieving remarkable granularity of specific subsets of CD4 cells harbouring virus, details of the study participants' co-infection history may not be as detailed or known. Many studies demonstrate that activated CD4+ T cells (e.g. PD-1+) are important cellular viral reservoirs [37]. Higher proportions of activated CD4 T cell subsets have also been described in many HIV co-infections like TB [38]. Similarly, pro-inflammatory cytokines can facilitate seeding of HIV reservoir and are elevated in co-infections [39,40]. One could hypothesise that active co-infections, such as TB, very common in areas in the world with high HIV prevalence, could play an important role in establishment of larger viral reservoirs both with respect to cellular subsets and tissue sanctuaries. The latter is probably even more important in central nervous system (CNS) infections such as cryptococcal or TB meningitis [41]. Therefore, it is possible that the current cure agenda and treatment strategies may not be generalisable to persons with opportunistic infections or low nadir CD4 cell counts at ART initiation, despite such patients representing a large proportion of people living with HIV worldwide on ART. The same holds true for many laboratory studies looking at reservoir measurements: in these publications, opportunistic infections are not always adequately addressed. It is unknown how infections such as TB or cryptococcosis may affect long-term viral reservoirs, compartmentalisation of virus, and as such the potential efficacy of future eradication strategies. These same opportunistic infections significantly increase CD4 T cell activation suggesting that they may facilitate further recruitment of CD4 targets for HIV entry and replication [37,42–44].

We would thus suggest that the HIV cure research agenda should continue to aim for strategies that are simple, safe and scalable, and also generalisable to the many millions of persons diagnosed late in the course of disease and/or with an opportunistic infection. Potential strategies and studies to avoid an emerging 'cure gap' could be as follows.

(1) Include detailed clinical histories of subjects participating in reservoir/latency and curative strategy studies, especially with regard to co-infections. This could also apply to participants starting ART during acute infection who may have herpesvirus disease or hepatitis C co-infection or other sexually transmitted diseases like syphilis that may influence reservoir seeding and size.

(2) Determine whether and how persons starting ART in the presence of an opportunistic infection have viral reservoirs that are qualitatively or quantitatively different than those who do not.

(3) Systematically study tissue compartmentalisation of the HIV reservoir triggered (and possibly facilitated) by co-infections; for example, cryptococcosis or syphilis in the CNS.

(4) Determine how IRIS in persons receiving ART affects cellular or tissue (mucosal) reservoirs. IRIS is known to be associated with profound local and systemic inflammatory response with further innate and adaptive immune activation that could potentially influence reservoir size and latency [45–48].

(5) Illuminate how environmental factors (diet, microbiome) and local infections (e.g. parasites or gastroenteritides) impact the long-term persistence of immune activation and maintenance of active viral replication or latency on ART, in resource-limited settings.

In order to address the above questions adequately, the location of cure research should also expand from well-resourced settings to resource-limited settings where a greater proportion of patients have advanced symptomatic HIV when starting ART. As others have previously noted, assays of viral reservoir measurements are complex, expensive and frequently not easily reproducible. It is imperative to develop and validate assays that are quick, inexpensive and robust with reproducible performance on a large scale in diverse patient categories and settings to address many of these questions.

In summary, in our opinion, the cure research agenda has so far inadequately addressed the fact that a large number of persons living with HIV/AIDS receiving ART – in fact the majority globally – have had a prior opportunistic infection or had late-stage HIV disease when ART was initiated. The role of advanced stage disease and co-infections at ART initiation in establishment of potentially larger cellular and tissue viral reservoirs needs to be systematically evaluated to enhance the relevance and generalisability of current studies that will hopefully form the basis of future curative strategies for all people living with HIV.

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References

1. Allers K, Hutter G, Hofmann J *et al.* Evidence for the cure of HIV infection by CCR5Delta32/Delta32 stem cell transplantation. *Blood* 2011; **117**: 2791–2799.
2. Hutter G, Nowak D, Mossner M *et al.* Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. *N Engl J Med* 2009; **360**: 692–698.
3. Hutter G, Schneider T, Thiel E. Transplantation of selected or transgenic blood stem cells – a future treatment for HIV/AIDS? *J Int AIDS Soc* 2009; **12**: 10.
4. Check Hayden E. French teenager healthy 12 years after ceasing HIV treatment. *Nature* 2015; **523**: 393.
5. Henrich TJ, Hanhauser E, Marty FM *et al.* Antiretroviral-free HIV-1 remission and viral rebound after allogeneic stem cell transplantation: report of 2 cases. *Ann Intern Med* 2014; **161**: 319–327.
6. Shah SK, Persaud D, Wendler DS *et al.* Research on very early ART in neonates at risk of HIV infection. *Lancet Infect Dis* 2014; **14**: 797.
7. Giacomet V, Trabattoni D, Zanchetta N *et al.* No cure of HIV infection in a child despite early treatment and apparent viral clearance. *Lancet* 2014; **384**: 1320.
8. Lewin SR. Finding a cure for HIV: much work to do. *Ann Intern Med* 2014; **161**: 368–369.

9. National Institutes of Health. *Finding a cure: currently active grants*. 2015. Available at: www.niaid.nih.gov/topics/HIVAIDS/Research/cure/Pages/default.aspx (accessed September 2015).
10. Cillo AR, Vagratian D, Bedison MA *et al*. Improved single-copy assays for quantification of persistent HIV-1 viremia in patients on suppressive antiretroviral therapy. *J Clin Microbiol* 2014; **52**: 3944–3951.
11. Eriksson S, Graf EH, Dahl V *et al*. Comparative analysis of measures of viral reservoirs in HIV-1 eradication studies. *PLoS Pathog* 2013; **9**: e1003174.
12. Vandergeeten C, Fromentin R, Merlini E *et al*. Cross-clade ultrasensitive PCR-based assays to measure HIV persistence in large-cohort studies. *J Virol* 2014; **88**: 12385–12396.
13. Deeks SG, Autran B, Berkhout B *et al*. Towards an HIV cure: a global scientific strategy. *Nat Rev Immunol* 2012; **12**: 607–614.
14. Imamichi H, Natarajan V, Adelsberger JW *et al*. Lifespan of effector memory CD4+ T cells determined by replication-incompetent integrated HIV-1 provirus. *AIDS* 2014; **28**: 1091–1099.
15. Kent SJ, Reece JC, Petravic J *et al*. The search for an HIV cure: tackling latent infection. *Lancet Infect Dis* 2013; **13**: 614–621.
16. Margolis DM, Hazuda DJ. Combined approaches for HIV cure. *Curr Opin HIV AIDS* 2013; **8**: 230–235.
17. Fauci AS, Marston HD, Folkers GK. An HIV cure: feasibility, discovery, and implementation. *JAMA* 2014; **312**: 335–336.
18. Younan P, Kowalski J, Kiem HP. Genetically modified hematopoietic stem cell transplantation for HIV-1-infected patients: can we achieve a cure? *Mol Ther* 2014; **22**: 257–264.
19. Ananworanich J, Dube K, Chomont N. How does the timing of antiretroviral therapy initiation in acute infection affect HIV reservoirs? *Curr Opin HIV AIDS* 2015; **10**: 18–28.
20. Saez-Cirion A, Bacchus C, Hocqueloux L *et al*. Post-treatment HIV-1 controllers with a long-term virological remission after the interruption of early initiated antiretroviral therapy ANRS VISCONTI Study. *PLoS Pathog* 2013; **9**: e1003211.
21. Avila D, Althoff KN, Mugglin C *et al*. Immunodeficiency at the start of combination antiretroviral therapy in low-, middle-, and high-income countries. *J Acquir Immune Defic Syndr* 2014; **65**: e8–16.
22. Siedner MJ, Ng CK, Bassett IV *et al*. Trends in CD4 count at presentation to care and treatment initiation in sub-Saharan Africa, 2002–2013: a meta-analysis. *Clin Infect Dis* 2015; **60**: 1120–1127.
23. Centers for Disease Control. *Monitoring selected national HIV prevention and care objectives by using HIV surveillance data – United States and 6 dependent areas – 2013. HIV Surveillance Supplemental Report 2015; 20 (No. 1)* 2015. Available at: www.cdc.gov/hiv/library/reports/surveillance/ (accessed September 2015).
24. Bradley H, Hall HI, Wolitski RJ *et al*. Vital Signs: HIV diagnosis, care, and treatment among persons living with HIV–United States, 2011. *MMWR Morb Mortal Wkly Rep* 2014; **63**: 1113–1117.
25. Hall HI, Song R, Szwarcwald CL, Green T. Brief report: Time from infection with the human immunodeficiency virus to diagnosis, United States. *J Acquir Immune Defic Syndr* 2015; **69**: 248–251.
26. UNAIDS. *Gap Report. Fact Sheet*. Available at: www.unaids.org/en/resources/campaigns/2014/2014gapreport/factsheet/ (accessed September 2015).
27. UNAIDS. *Access to Antiretroviral Therapy in Africa: Status report on progress towards the 2015 targets*. Geneva: 2013. Available at: www.unaids.org/en/resources/documents/2013 (accessed September 2015).
28. McMahon JH, Elliott JH, Bertagnolio S *et al*. Viral suppression after 12 months of antiretroviral therapy in low- and middle-income countries: a systematic review. *Bull World Health Organ* 2013; **91**: 377–385E.
29. Legido-Quigley H, Montgomery CM, Khan P *et al*. Integrating tuberculosis and HIV services in low- and middle-income countries: a systematic review. *Trop Med Int Health* 2013; **18**: 199–211.
30. Park BJ, Wannemuehler KA, Marston BJ *et al*. Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. *AIDS* 2009; **23**: 525–530.
31. Mfinanga S, Chanda D, Kivuyo SL *et al*. Cryptococcal meningitis screening and community-based early adherence support in people with advanced HIV infection starting antiretroviral therapy in Tanzania and Zambia: an open-label, randomised controlled trial. *Lancet* 2015; **385**: 2173–2182.
32. Boulle A, Van Cutsem G, Hilderbrand K *et al*. Seven-year experience of a primary care antiretroviral treatment programme in Khayelitsha, South Africa. *AIDS* 2010; **24**: 563–572.
33. Lawn SD, Kranzer K, Edwards DJ *et al*. Tuberculosis during the first year of antiretroviral therapy in a South African cohort using an intensive pretreatment screening strategy. *AIDS* 2010; **24**: 1323–1328.
34. Rajasingham R, Meya DB, Boulware DR. Integrating cryptococcal antigen screening and pre-emptive treatment into routine HIV care. *J Acquir Immune Defic Syndr* 2012; **59**: e85–91.
35. Muller M, Wandel S, Colebunders R *et al*. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *Lancet Infect Dis* 2010; **10**: 251–261.
36. Boulassel MR, Chomont N, Pai NP *et al*. CD4 T cell nadir independently predicts the magnitude of the HIV reservoir after prolonged suppressive antiretroviral therapy. *J Clin Virol* 2012; **53**: 29–32.
37. Cockerham LR, Siliciano JD, Sinclair E *et al*. CD4+ and CD8+ T cell activation are associated with HIV DNA in resting CD4+ T cells. *PLoS One* 2014; **9**: e110731.
38. Sullivan ZA, Wong EB, Ndung'u T *et al*. Latent and active tuberculosis infection increase immune activation in individuals co-infected with HIV. *EBioMedicine* 2015; **2**: 334–340.
39. Sereti I, Rodger AJ, French MA. Biomarkers in immune reconstitution inflammatory syndrome: signals from pathogenesis. *Curr Opin HIV AIDS* 2010; **5**: 504–510.
40. Vandergeeten C, Fromentin R, Chomont N. The role of cytokines in the establishment, persistence and eradication of the HIV reservoir. *Cytokine Growth Factor Rev* 2012; **23**: 143–149.
41. Gray LR, Roche M, Flynn JK *et al*. Is the central nervous system a reservoir of HIV-1? *Curr Opin HIV AIDS* 2014; **9**: 552–558.
42. Antonelli LR, Mahnke Y, Hodge JN *et al*. Elevated frequencies of highly activated CD4+ T cells in HIV+ patients developing immune reconstitution inflammatory syndrome. *Blood* 2010; **116**: 3818–3827.
43. Mahnke YD, Greenwald JH, DerSimonian R *et al*. Selective expansion of polyfunctional pathogen-specific CD4(+) T cells in HIV-1-infected patients with immune reconstitution inflammatory syndrome. *Blood* 2012; **119**: 3105–3112.
44. Trautmann L, Janbazian L, Chomont N *et al*. Upregulation of PD-1 expression on HIV-specific CD8+ T cells leads to reversible immune dysfunction. *Nat Med* 2006; **12**: 1198–1202.
45. Boulware DR, Meya DB, Bergemann TL *et al*. Clinical features and serum biomarkers in HIV immune reconstitution inflammatory syndrome after cryptococcal meningitis: a prospective cohort study. *PLoS Med* 2010; **7**: e1000384.
46. Bourgarit A, Carcelain G, Martinez V *et al*. Explosion of tuberculin-specific Th1-responses induces immune restoration syndrome in tuberculosis and HIV co-infected patients. *AIDS* 2006; **20**: F1–7.
47. Meintjes G, Lawn SD, Scano F *et al*. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis* 2008; **8**: 516–523.
48. Naidoo K, Yende-Zuma N, Padayatchi N *et al*. The immune reconstitution inflammatory syndrome after antiretroviral therapy initiation in patients with tuberculosis: findings from the SAPiT trial. *Ann Intern Med* 2012; **157**: 313–324.