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Leveraging Cancer Therapeutics for the HIV Cure Agenda: Current Status and Future Directions

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Abstract

Despite effective antiretroviral therapy (ART) and undetectable HIV RNA in the plasma, latent replication-competent HIV persists indefinitely in long-lived cells. Cessation of ART results in rebound of HIV from these persistent reservoirs. While this was thought to be an insurmountable obstacle to viral eradication, recent cases suggest otherwise. To date one patient has been “cured” of HIV and several others have been able to interrupt ART without viral rebound for prolonged periods. These events have sparked renewed interest in developing strategies that will allow eradication of HIV in infected individuals. We review the current knowledge of HIV latency and the viral reservoir, describe the potential utility of emerging cancer therapeutics in HIV cure research with an emphasis on pathways implicated in reservoir persistence, and outline opportunities and challenges in the context of the current clinical trial and regulatory environment.

1 Introduction

Despite effective antiretroviral therapy (ART) and undetectable HIV RNA in the plasma, latent replication competent HIV persists indefinitely in long-lived cells in infected individuals [1–3]. Cessation of ART results in rebound of HIV from these persistent reservoirs. While this was thought to be an insurmountable obstacle to viral eradication, recent cases suggest otherwise. To date one patient has been “cured” of HIV and several others have been able to interrupt ART without viral rebound for prolonged periods of time. These events have sparked renewed interest in developing strategies that will allow

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Compliance with Ethical Standards

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individuals with HIV to stop ART without viral rebound: either with complete viral eradication, a “sterilizing cure,” or without clinically significant viral replication in the absence of ART, a sustained remission or a “functional cure.”

We review the current knowledge of HIV latency and the viral reservoir, describe the potential utility of emerging cancer therapeutics in HIV cure research with an emphasis on pathways implicated in reservoir persistence and potentially of use in achieving a sustained remission, and outline opportunities and challenges in the context of the current clinical trial and regulatory environment.

2 Background

2.1 The HIV Reservoir

The HIV reservoir is established early in HIV infection primarily as transcriptionally silent integrated proviral DNA in long-lived resting memory T cells in blood and lymphoid tissue [3–5]. The central memory T cell (T_{CM}) population has been hypothesized to be the key niche for HIV persistence [6, 7].

Long-lived T cells are thought to be the major cellular reservoir. Specific T-cell subsets within this compartment have been described in which long-term HIV persistence is prominent, including an immature progenitor like memory stem cell T cells (T_{SCM}), which resists apoptosis, self-renews, and can differentiate into effector memory T cells (T_{EM}) and central memory cells (T_{CM}) [6]. Once differentiated, T_{CM} and T_{EM} cells migrate to lymphoid organs and to peripheral tissues [7]. Although controversial, cells of other origins have also been implicated in reservoir maintenance; for example, some monocyte lineage cells harbor proviral DNA [8, 9]. Cells containing latent HIV can produce both infectious and non-infections virions when the host cell is reactivated in response to factors including its cognate antigen, activating cytokines, or persistent immune activation [10]. The presence of replication-competent HIV in these latent reservoirs and the absence of effective HIV specific immune responses are the critical barriers to eradicating HIV in infected patients. Neither ART nor HIV specific immune responses have been able to effectively target these cells.

Latency is understood to be maintained by a combination of viral and cellular host processes (Fig. 1). Pre-integration mechanisms of latency may be important in reservoir establishment, and involve processes that are involved in packaging the pre-integration complex and the interaction of viral proteins with host restriction factors such as APOBEC3, SAMHD1, and MX2 [8, 9]. In resting CD4 T cells, repressive histone modifications and DNA methylation that regulate key host cellular transcription factors limit the initiation and elongation of viral transcription at the promoter site [11]. Cellular factors influencing latency include cellular transcription factors including PTEF B and nuclear factor (NF)-κB [7], intermittent viral production, and reinfection from reservoirs. These are driven by cytokines and mediated by low level immune activation and a dynamic interaction between resting memory, regulatory T cells, and activated T cells. Persistent low level immune activation may also change the immunologic environment and enable HIV persistence by promoting immune exhaustion and abrogating an effective T-cell response [12]. Recent studies demonstrating enrichment

of HIV DNA integrated in or near to host growth promoter genes suggest an additional potential mechanism for provirus persistence and the survival and expansion of infected cells [13, 14].

The major anatomic sites of the reservoir remain the subject of investigation. Low-level replication without inflammation at sites where ART penetration is decreased has been described in lymphoid tissue in the B-cell follicles [15] and in the gut [16]. HIV DNA has been demonstrated in the central nervous system, and expression of RNA has been described in the CNS of suppressed HIV-infected individuals [17, 18]. Phylogenetic studies have suggested evolutionary separation of plasma and CNS HIV; taken together this suggests that the CNS may be another important site of HIV persistence.

2.2 Emerging Approaches to Cure

Several potentially complementary strategies are being pursued to effect a sustained remission in the absence of ART. These include: early therapy to limit the size of the reservoir; reactivating latently infected cells and stimulating their clearance by the immune system; genetically modifying host CD4 cells to make them resistant to HIV infection; and use of endonucleases to target and digest critical portions of the integrated HIV DNA. It is also likely that early identification and treatment of HIV will reduce the size of the inducible replication competent reservoir (the “functional reservoir”) and aid cure efforts [19]. The “Mississippi Baby” was treated very early in infection and achieved a prolonged remission when ART was interrupted [20]. Similarly, 14 adults have been described who received ART during acute infection and were able to suppress HIV once ART was discontinued [21]. There are practical barriers to early ART intervention: patients with acute and early infection are difficult to identify and represent only a small portion of the HIV-infected population. For this reason chronically infected patients with long-term viral suppression are the likely population of interest and are likely to require different or additional interventions than those who are acutely infected.

Several of these strategies are illustrated in the case of the Berlin patient, the single person believed to be cured of HIV. He received bone marrow transplantation from a donor with the CCR5 delta 32 allele which prevented CCR5 proteins from being expressed on the surface of the transplanted cells, making the donor T cells resistant to the patient's CCR5 tropic HIV. Other factors including graft-versus-host disease and high-dose stem-cell toxic chemotherapy may also have contributed to his apparent cure [22]. Genetic engineering approaches are attempting to recapitulate this experience using autologous hematopoietic stem cell transplantation (HSCT) with some early promising results [23]. In contrast to the Berlin patient, allogeneic HSCT with HIV-susceptible cells (CCR5 wild type) and reduced-intensity conditioning failed to deliver HIV eradication in two adults who received clinically indicated HSCT. While on suppressive ART, HIV DNA was not detectable in CD4 cells and HIV RNA was not detectable in plasma. The loss of detectable HIV correlated temporally with full donor chimerism, development of graft-versus-host disease, and decrease in HIV specific antibody levels and avidity, which had also been reported in the Berlin patient. ART was interrupted and HIV replication became detectable several months after interruption in both patients, and was associated with acute antiretroviral syndrome [24, 25]. Ongoing work

is attempting to assess whether specific immunologic factors in the graft-versus-host disease may have played a role in the temporary HIV remission.

Many current efforts are directed towards modifying or blocking the processes involved in the establishment and/or maintenance of HIV latency. It was initially thought that reactivating HIV in resting cells would cause their death by the host's residual HIV-specific immune responses; however, it is now known that a second step may be necessary to eliminate reactivated cells [26]. This strategy is referred to as “shock and kill.” There are several lines of research looking at mechanisms to reactivate latently infected cells as well as those that target the reactivated cells for elimination. Elimination might include priming cells to increase apoptotic potential prior to reactivation [27], involve immune mechanisms that target cellular markers involved in latency, boost the host HIV-specific immune response either to recall antigens or new targets, and the expression of HIV proteins on the surfaces of reactivated cells. Therapeutic vaccines, HIV-specific broadly neutralizing antibodies made toward HIV, processes involving regulatory T cells, and intracellular signaling processes involved in the maintenance of HIV persistence are also being assessed. In addition, non-neutralizing mAbs that recognize conserved epitopes on HIV envelope and have significant antibody-dependent cytotoxicity and potentially antibody-dependent cellular phagocytosis may help eliminate latently infected cells as they are reactivated [28, 29].

2.3 Cancer Therapeutics and Approaches to Cure

Established and emerging therapeutic strategies in oncology are likely to contribute agents with a potential to have an impact on HIV latency. Many of the pathways implicated in the maintenance of viral latency and persistence of the cellular reservoirs are highly conserved and have also been implicated either in oncogenesis or in the immune response to malignancies. Key examples include the histone deacytylase inhibitors (HDACi's), immune modulators including checkpoint inhibitors, and agents directed toward the apoptotic pathway. These agents are potentially attractive not only because they target cell types and pathways implicated in HIV persistence, but because their pharmacokinetic and toxicity profiles are already established, and they generally have a path to licensure through their primary oncologic indications. These factors potentially lower the barriers exploring their utility in HIV cure research and accelerate exploration of promising agents.

3 Reactivation from Latency

One of the most explored approaches to eradicating HIV has been the use of HDACi's to upregulate HIV expression in latently infected cells. These cells could then be lysed by HIV-specific T-lymphocytes or die from viral cytopathic effects (“shock and kill”) [30]. During HIV latency, host transcription factors recruit HDACs to the HIV 5′ LTR where the HIV promoter is packaged in chromatin [31]. HDACi's are able to reactivate latent HIV by allowing hyperacetylation of the LTR nuc-1 nucleosome or by HIV Tat activation of virus production [32, 33]. A recent study also suggests that HDACi's may eliminate HIV via autophagy and degradation of HIV in macrophages [34, 35]. However, the impact of reactivation on reservoir size remains to be demonstrated.

Clinical trials of HDACi's in HIV are ongoing or have been completed. One of the earliest proof-of-concept studies utilized valproic acid, which reported a decrease in latent infection in three out of four patients [36]. However, this was not reproduced in subsequent studies [37–39]. Vorinostat, a more potent HDACi, has also been extensively studied. A single dose of vorinostat was shown to increase the expression of HIV mRNA in resting CD4 T cells [40]; this was confirmed in a multidose study (with 14 daily doses) of vorinostat, but did not reduce HIV DNA [41]. No major clinical adverse events were reported [42]. A subsequent multidose study of vorinostat (given daily for 3 days per week for 8 weeks) confirmed that multidose vorinostat was well tolerated [43]. In this study however, three out of five study participants had an increase in resting CD4 T cell-associated HIV RNA, and in only one case was the magnitude of RNA induction comparable to the level seen after a single dose, suggesting that the kinetics of HDACi's need to be better delineated to improve response. The farnesyl transferase inhibitors may increase the amount of HIV expressed from latently infected cells when used with vorinostat [44], suggesting a potential synergy. Similar results were also reported from a small study with another potent HDACi, panobinostat [45]. Lastly, romidepsin has been the most potent HDACi identified for inducing HIV replication in vitro [46]. In a phase I/II trial in six participants, three doses of once-weekly romidepsin induced HIV expression resulting in plasma virema [47]. A dose-escalation study of romidepsin in HIV-infected individuals is currently underway (NCT1933594).

Bromodomain inhibitors, currently in early development, may have utility in reactivating latent HIV. Bromodomain proteins are involved in targeting chromatin modifying enzymes, and are important in regulating the transcription of growth-promoting genes and cell cycle regulators. They also are involved with the transcriptional control of proinflammatory cytokines via their interaction with acetylated NF-κB, a key transcription factor mediating inflammatory responses and important in reactivating HIV from latency [48]. A bromodomain inhibitor (JQ1) has been shown to reactivate HIV in a clonal cell model via the PTEF B mechanism [49]. Because this compound associates with a key transcription factor required for erythropoiesis, concerns have been raised about potential toxicities [50]. More selective bromodomain inhibitors may be useful in reversing latency [51].

4 Cell Surface Reservoir Targets

4.1 Immune Checkpoint Inhibitors and Negative Regulators of T-Cell Activation

The cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and programmed death (PD) are T-cell regulatory pathways that regulate immune responses and maintain immune tolerance. Together they are referred to as checkpoint pathways. Both PD-1 and CTLA-4 inhibit immune responses through molecular mechanisms that involve protein kinase B (also known as Akt). PD-1 more effectively suppresses T-cell-specific transcription than CTLA-4 [7].

CTLA4 regulates the amplitude of early T-cell activation. The receptor is present on CD8 T cells but also has important effects on CD4 cells by down-regulating T-helper cells and enhancing the suppressive function of T-regulatory cells. Blockade of CTLA4 inhibits the ability to regulate both autoimmunity and antitumor immunity. In HIV infection increased expression of the CTLA4, the PD 1, and the LAG 3 receptor are markers of T-cell exhaustion, and may be responsible for or contribute to the ineffective HIV-specific immune

responses. Blocking the effects of the checkpoint inhibitors may result in improved immune response to HIV, but in oncology studies have resulted in immune-related adverse events.

Ipilimumab and tremelimumab are anti-CTLA-4 monoclonal antibodies (mAbs). Ipilimumab is licensed for use by the US Food and Drug Administration (FDA) for metastatic melanoma, and both are in clinical trials for the treatment of other solid tumors. A trial is planned for ipilimumab in HIV-related cervical cancer that may give important mechanistic insights into the relationship of this agent to the HIV reservoir. The immune effects of ipilumumab were studied in a single HIV-infected individual receiving therapy for metastatic melanoma. Both total memory T cells and unspliced cell-associated RNA increased after therapy, suggesting reactivation and redistribution of latently infected T cells and perhaps their elimination [52]. Toxicities of this agent are not trivial, are generally immune mediated, and include a potentially fatal immune mediated enterocolitis [53] (Table 1).

The PD-1 pathway dampens inflammatory responses of T cells in peripheral tissue. Its two ligands, PDL1 and PDL2, are expressed on T cells. PD-1 and PDL1 remain elevated in HIV-infected patients on suppressive ART, and expression of these molecules may be a marker for cells that are latently infected with HIV [54, 55]. Blockade of the PD-1/PDL1 pathway increases HIV-specific immunity in vitro and may improve HIV-specific immunity and clearance of HIV-expressing cells in patients on ART [56].

Pembrolizumab and nivolumumab are anti-PD-1 mAbs recently FDA-approved for the treatment of advanced melanoma, and other antibodies are in development. They are also being studied for the treatment of other solid tumors both alone and in combination with anti-CTLA-4 mAbs. No current trial includes HIV-infected subjects. Major toxicities include immune-mediated organ dysfunction which has resulted in death. An anti-PD-L1 antibody, BMS-936559, has also been studied for the treatment of various malignancies [57]; a dose-escalation trial evaluating its safety and efficacy in HIV-infected individuals suppressed on ART is underway but currently on clinical hold (NCT02028403). Finally, there is growing interest in indolamine 2, 3 deoxygenase (IDO) pathway which interacts with both the PD-1 and CTLA-4 pathways to suppress cytotoxic T cells [58]. There are two small-molecule, orally available inhibitors which are in early-phase cancer clinical trials (Indoximod, Newlink Genetics and INCB024360 Incyte Corporation) [59].

4.2 Engineered T Cells

Adoptively transferred T-cell-based immune strategies have been used successfully in oncology. In HIV, the rationale for using these strategies stems from the crucial role of HIV-specific CD8+ T-cell responses which have been associated with improved virologic control [60–62]. Adoptively transferred modified T cells have the potential to hone and lyse HIV-infected cells and develop into long-lived memory cells conferring lifetime protection. Notably, unmodified T-cell strategies have been used without meaningful results in HIV [63–65]. Genetic modifications include transduction with a chimeric antigen receptors (CARs), which combine antibody specificity with receptor signaling, and modification of specific T-cell receptors used for HIV binding [66]. The results of three trials evaluating the safety, durability, and functionality of a CAR expressing a CD4 molecule on its surface that

was fused with the CD4zeta signaling domain (CD4zCAR) in viremic individuals were recently reported; this CAR mediated T-cell interaction with HIV-infected cell via gp120 [67]. These trials demonstrated safety and tolerability as well as long-term persistence of the CD4zCAR modified cells for up to 11 years with retained expression and function including trafficking to mucosal sites and lowering of HIV RNA in some patients [67–70]. The use of adoptively transferred T cells to reduce the reservoir is being explored in a phase I study, evaluating the safety and immunologic and virologic efficacy of *ex vivo* expanded HIV-1 multi-antigen-specific T cells in ART-suppressed HIV-infected patients (NCT02208167).

The observation that the Berlin patient achieved durable remission following bone marrow transplantation from a CCR5 delta homozygous donor resistant to HIV infection has led to interest in developing CCR5-resistant T cells for autologous transplantation. This offers the prospect of deriving a more specific HIV cure strategy with the use of a less toxic allogeneic transplantation. Autologous T-cell infusion following site-specific gene modification of the CCR5 gene using a zinc-finger nuclease (ZFN) has recently been described [23]. Infusion of autologous T cells, a minority of which expressed the desired genetic modification, resulted in a significant increase in CD4 T cell numbers. One patient in this study, who was heterozygous for CCR5 delta 32 prior to the T-cell modification, had an undetectable HIV RNA at week 12 off ART despite an earlier viral load rebound. This approach continues to be evaluated. Newer endonucleases may provide technical advantages and lead to the development of genetically modified hematopoetic stem cells resistant to HIV [71].

5 Intracellular Reservoir Targets

5.1 Rapamycin and the mTor Pathway

Rapamycin and its three derivatives, temsirolimus, everolimus, and ridaforolimus, are macrolides used as immunosuppressive agents in organ transplantation and as chemotherapeutic agents. They are inhibitors of the mammalian target of the rapamycin (mTor)-signaling pathway, which is involved in the control of cell growth and proliferation, induces cell cycle arrest at the G1 phase and cell death via apoptosis and autophagy [72]. Other effects include inhibition of interleukin (IL)-2 and other stimulatory cytokines and inhibition of T- and B-cell activation. Activated T cells are also arrested at the G1 phase by mTor inhibition, and this is responsible for many of the immune effects of these agents. The pathway is important in the expression of transcription factors that regulate CD8 T-cell activation and autophagy, and enhance the development of T-cell memory [73]. Together it is possible that these effects may enhance clearance of HIV in the setting of a “shock and kill” curative strategy. This strategy is planned for evaluation in an AIDS Clinical Trials Group interventional protocol (NCT02440789).

5.2 Immunomodulatory Derivatives of Thalidomide

Thalidomide and its derivatives (IMIDs), including lenalidomide (CC-5013) and pomalidomide (CC-4047), are small molecules with broad-based effects on immune activation, including T-cell activation and responsiveness, as well as anti-angiogenic properties [74–77]. Many of their activities are mediated through binding to and inactivation of cereblon, an E3 ubiquitin ligase with multiple targets that is highly expressed in

lymphocytes as well as other tissues, though there may be additional mechanisms of action [75, 78]. Their downstream effects are diverse, and likely vary in different cells and tumor types [56]. However, their immunologic effects are well characterized, and include effects that may influence the HIV reservoir.

IMIDs have been shown in vitro to augment T-cell responsiveness and proliferation by several mechanisms, leading to increased production of IL-2 and interferon-γ (IFN-γ) and inhibition of pro-inflammatory cytokine and chemokine production [79–81]. They also enhance CD4- and CD8-positive T-cell co-stimulation. This reprogramming is mediated at least in part by induction of the transcription factor T-bet. In addition, T-regulatory cell expansion and FOXP3 expression on T-regulatory cells are inhibited without affecting survival or apoptosis, and T helper (Th)-1 cytokine production is enhanced [82–84]. These effects were confirmed in vivo in patients with multiple myeloma treated with IMIDs, who showed changes with activation of T cells and monocytes [64]. Similarly in people with HIV treated with IMIDs, increased T-cell activation both in vivo and in ex vivo stimulation assays, including enhanced IL-2 generation. Taken together, these raise the possibility that IMIDs may act to activate of T-cell subsets implicated in HIV reservoir maintenance and thus perhaps effect the maintenance of HIV latency. Given the established activity of IMIDs in hematologic and AIDS-associated malignancies, several clinical trials in people with HIV infection and cancer are now underway (NCT01495598, NCT01057121) and may offer an opportunity to explore the effect of these agents on the reservoir.

5.3 Pro-Apoptotic Agents, Including Ibrutinib

Identification and disruption of abnormally active pathways that promote cancer cell survival is a central focus of oncology drug development. While not yet explored in HIV-centered trials, many of the pathways disordered in malignancy may be of interest in HIV cure efforts. Abnormal B cell receptor (BCR) pathways have been studied in the context of lymphomas and leukaemias: propogation of the BCR signal leads to up-regulation of several nuclear transcription factors including NF-κB. In T cells this pathway is important in regulating both apoptosis and the genetic regulation of cell development, and can also activate HIV transcription through caspase effects on HIV toll-like receptors' (TLR) transcriptional activity [85]. It is plausible that molecules that disrupt this pathway at different points may also have an effect on T-cell activation and HIV latency. Ibrutinib is an inhibitor of an IL-2-inducible T-cell kinase (ITK) in this pathway and has been shown to block T-cell differentiation to the Th2 phenotype [86]. This process has been implicated in tumor immune evasion [87] and may have utility in HIV cure efforts. Ibrutinib is approved for the treatment of certain B-cell leukemias, and it is being studied for other indications. Other tyrosine kinase inhibitors such as imatinib may also have effects on reversing HIV-infected T-cell persistence by promoting apoptosis and autophagic cell death [88].

Other apotoptic pathways are also being actively explored. In particular, the tumor-necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) induces cell death by binding to nuclear "death receptors" in a caspase-dependent pathway. In a murine cytomegalovirus (CMV) model, TRAIL-positive NK cells led to the elimination of activated CD4 cells [89], and a reduced TRAIL ligand with an altered TRAIL pathway has been demonstrated in the

CD4 T-cells of HIV infected elite controllers [90]. There is intense interest in identifying agents that promote TRAIL-mediated apoptosis in cancer therapeutics [91, 92].

5.4 Pattern Recognition Pathways

TLR signaling, through their sentinel actions in recognizing pathogen-associated molecular patterns and initiating immune responses, could also lead to activation of T-cell subsets implicated in HIV reservoir maintenance [93]. This possibility warrants exploration as TLR agonists proceed into early-phase clinical trials for oncologic and other indications. Agonists of TLR 7 and 9 have already been explored in limited-cure-centered studies. GS-9620 is a selective orally administered TLR7 agonist that is in clinical development as a treatment of chronic hepatitis B. Ex vivo it has been shown to increase HIV RNA expression in peripheral blood mononuclear cells (PBMCs) from 11 of 12 ART-suppressed HIV-infected individuals [94]. In a multidose, dose-escalation study in chronically simian immunodeficiency virus (SIV)-infected ART-suppressed rhesus macaques, GS-9620 produced a consistent transient increase in plasma viremia after several doses, substantial reductions in viral DNA content in tissue samples, and a lower viral set point after cessation of antiretroviral therapy [95]. A phase I study is planned in suppressed HIV-infected individuals. CPG 7909 is an immunostimulatory TLR9 agonist that has been used in several cancers including B-cell leukemias [96, 97]. In a post hoc analysis of a phase I study, ART suppressed HIV-infected individuals who received a pneumococcal vaccine regimen plus CPG 7909 had a reduction in proviral DNA compared to the group that received the vaccine with placebo. Reductions in proviral DNA was correlated with increasing levels of HIV specific CD8 cells [98, 99].

5.5 Other Intracellular Pathways

Pathways implicated in stem cell cycling and renewal may also be fruitful avenues of exploration for interruption of HIV latency. Among the former, the notch, hedgehog, and wnt signaling pathways are emerging as key stem-cell regulators in adulthood in addition to their established roles in cell development, cell-to-cell communication, and cellular differentiation during angiogenesis [100, 101]. Overexpression of pathway constituents has also been implicated in a number of malignancies, and selective inhibitors are now in development. Any impact on stem-like T-memory cell persistence and cycling would have important implications for exploration for HIV latency.

6 Risk-Benefit and Regulatory Considerations

Clinical trials of HIV cure strategies offer little prospect of direct clinical benefit for individual study participants, while potentially placing them at risk of toxicities related to the investigational agent. Some of these toxicities may be more pronounced in individuals with HIV. Given the tolerability and effectiveness of current ART, HIV-infected individuals who can live healthy productive lives for decades on ART are now considered to be similar to healthy volunteers. Therefore, clinical trials evaluating one or more novel agents in support of the cure agenda need to be small, maintain a comprehensive risk mitigation strategy, have carefully described safety endpoints for individuals and for the study, and may require gating strategies to limit the number of participants initiating therapy at any one

time until toxicity profiles are better established. Long-term follow-up for late effects, including possible oncogenic effects, is also crucial as the long-term complications of many of the potentially useful agents have not yet been established. The establishment of surrogate endpoints for reservoir disruption, short of structured interruptions to HIV treatment to observe for viral rebound, is currently a focus of discussion and would further aid efforts to speed and simplify trial design [74]. The FDA is engaged in a dialogue with investigators in the field regarding these issues [74, 102].

7 Leveraging Cancer Trials

Elevated rates of many malignancies in HIV-infected individuals are well described [103–105]. Effective and suppressive ART regimens with minimal toxicities are available for HIV-infected patients including those in need of cancer chemotherapy. These individuals, fully suppressed on ART, who are receiving cancer therapeutics that may have activity on the latent HIV reservoir activity, represent a unique opportunity to further our understanding about how to achieve a sustained remission of HIV. The risk-benefit profile for a trial subject with an established malignancy is considerably different to that of a healthy HIV-infected volunteer, potentially reducing the barrier to regulatory and institutional review and approval. Toxicity management in the setting of cancer therapeutics is well established, including approaches to interactions between ART and chemotherapeutic agents.

Thus correlative cure studies embedded in cancer trials which permit HIV-infected individuals to be enrolled provide an opportunity to explore effects on HIV latency and may provide the first signal for toxicity in people with HIV. Cure-centered correlative endpoints within trials for people with HIV and cancer would allow for the exploration of promising agents in this setting. The impact of tumor on T-cell activation and recruitment can be assessed, and its effect on HIV-treatment parameters and the HIV reservoir can also be determined. Most importantly, these trials can provide a pool of potential participants interested in making a contribution to HIV cure efforts while availing themselves of expanded options to treat their tumor and contributing to oncology knowledge. The number of agents that may be “screened” for utility in cure could therefore be expanded. Further development of promising agents might then be conducted through dedicated cure trials where more detailed assessment of their role may be made or drug combinations that are of specific interest to cure endpoints could be evaluated.

8 Conclusions

For the first time since the advent of effective ART, our emerging understanding of the role of the HIV reservoir and viral latency in persistence offers the realistic prospect of achieving a sustained remission or a sterilizing cure for HIV in infected individuals. The processes and pathways involved in latency are complex and overlapping, and our understanding of them is likely to evolve in parallel with efforts aimed at their disruption. At this early stage of exploration, the prospect of leveraging agents from cancer therapeutics and cancer clinical trials may accelerate evaluation of potentially useful agents and provide a foundation for dedicated cure studies.

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Key Points

Persistence of an HIV reservoir in long-lived immune cells has been a barrier to its eradication or cure.

Recent cases of cure or sustained remission suggest clearance or control of the HIV reservoir may possible.

Many therapies now being developed for cancer indications may have dual utility in targeting the HIV reservoir. These could be explored in trials in people with HIV and cancer prior to dedicated “cure” trials.

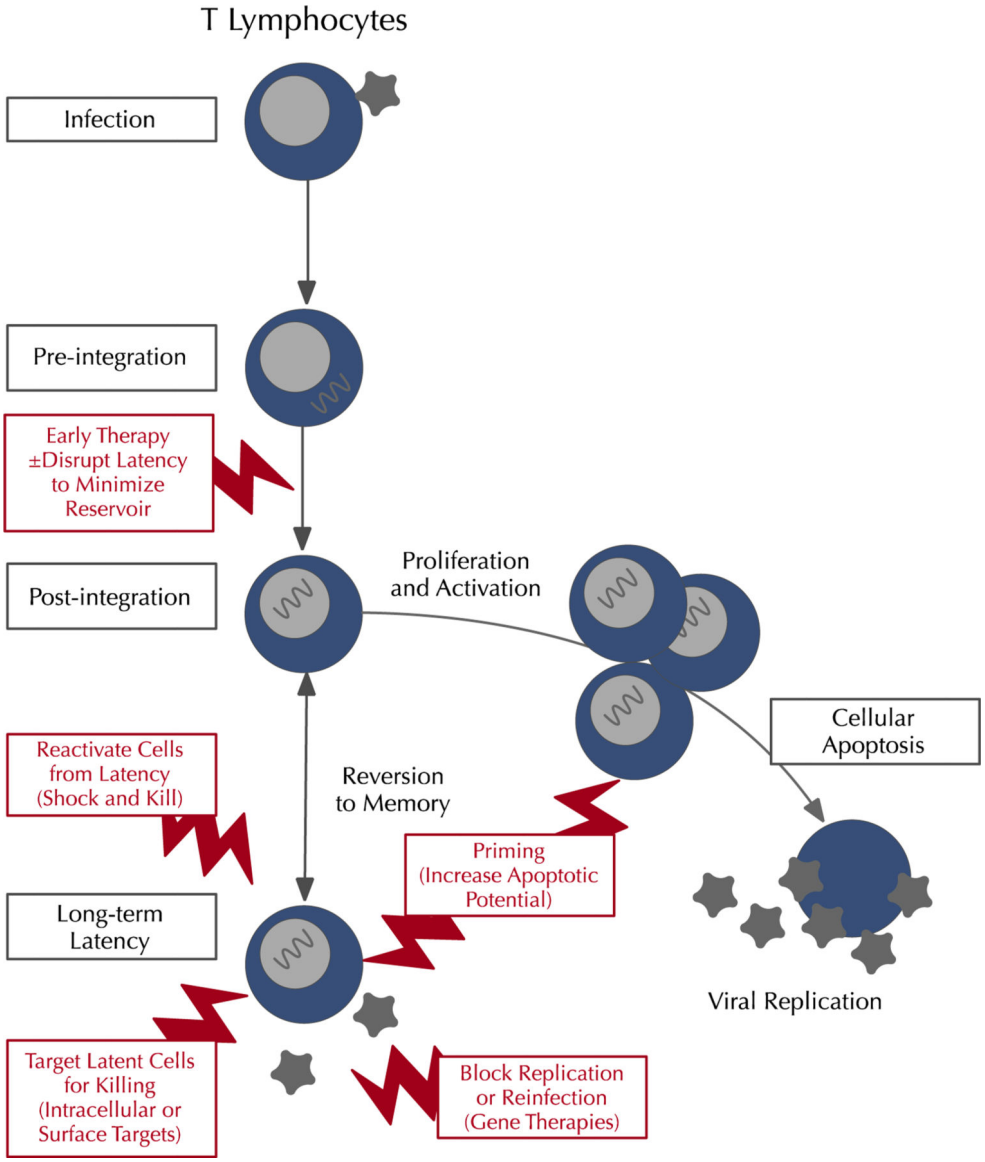

Fig. 1.

Putative targets in HIV eradication. The HIV reservoir is established primarily in resting memory T cells and other T-cell subtypes (*right*), though other lineages including monocytes are also implicated (*left*). Cure strategies currently being explored target this reservoir at varying points, including early therapy to minimize reservoir size (as in the Mississippi baby); reactivation of HIV from its latent state; direct targeting of the reservoir cells; and interruption of maintenance of the reservoir by preventing cycles of reinfection. These approaches each have specific targets, and in many cases may be complementary. Other cell types including monocytes (not shown) have also been implicated in reservoir persistence

Table 1

Select cancer agents with potential utility in HIV cure approaches

Agent(s)/class	Target(s)	Primary indication (established or in development for, if applicable)	Possible reservoir targets	Key toxicities	Regulatory status or phase of development	Current and completed cure trials
HDAC inhibitors	Inhibit histone deactylase to induce HIV transcription		Latency reversal			
Valproic acid		Anticonvulsant; mood stabilizer; migraine headache		Hepatotoxicity, pancreatitis, bleeding and other hematopoietic disorders, teratogenicity	FDA-approved as antiepileptic	Several clinical studies completed evaluating valproic acid in cure trials
Vorinostat		Cutaneous T-cell lymphoma (CTCL)		Myelosuppression, thrombosis, gastrointestinal toxicity, electrolyte abnormalities, hyperglycemia, teratogenicity	FDA-approved for CTCL	Several clinical studies completed evaluating vorinostat in cure trials. Phase I/II trial underway to evaluate the effect of a single dose compared with multiple dosing regimens of vorinostat

Agent(s)/class	Target(s)	Primary indication (established or in development for, if applicable)	Possible reservoir targets	Key toxicities	Regulatory status or phase of development	Current and completed cure trials
Romidepsin		Peripheral T-cell lymphoma (PTCL), CTCL		Myelosuppression, ECG changes, EBV/HBV reactivation, teratogenicity	FDA-approved for PTCL, CTCL	Two trials underway: A phase I/II trial currently underway to evaluate escalating single-dose romidepsin (ACTG 5315) and an open phase I/IIa study with romidepsin and vacc4x, an HIV vaccine
Panobinostat		Not yet FDA-approved		Fatigue, cutaneous toxicity, GI disturbances, sleeplessness	In clinical development for multiple myeloma treatment	Recent phase I/II trial completed to evaluate safety and effects on latency reactivation with multiple doses of panobinostat
Ipilumumab and tremelimumab	Immune checkpoint inhibitors by targeting CTLA4	Malignant melanoma, potential applications for other solid tumors	Reverse T-cell exhaustion, improved HIV- specific immune response	Immune-mediated adverse reactions, which can be severe: enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. Some delayed reactions occurred after therapy cessation	Ipilumumab FDA-approved for melanoma; tremelimumab in phase I/II trials	None current, but correlatives centered on cure objectives are planned in an AIDS Malignancy Consortium trial in solid tumors in people with HIV
Nivolumab, pembrolizumab, Lambrolizumab, BMS-936559	Immune checkpoint inhibitors by targeting PD-1 or PDL1	Malignant melanoma following ipilumumab; in development for multiple solid and hematologic tumors	Reverse T-cell exhaustion, improved HIV-specific immune response	Immune-mediated adverse reactions, which can be severe: colitis, pneumonitis, others	FDA-approved for nivolumab, pembrolizumab in metastatic melanoma	BMS 936559 planned for evaluation in ACTG 5326

Agent(s)/class	Target(s)	Primary indication (established or in development for, if applicable)	Possible reservoir targets	Key toxicities	Regulatory status or phase of development	Current and completed cure trials
Sirolimus temsirolimus, everolimus and ridaforolimus	Mammalian target of rapamycin (mTor)	Immune suppression following transplantation	Arrest activated T cells in G phase	Increased risk of lymphomas, skin cancers, infection	All but ridaforolimus FDA approved. Indications: immunosuppressant, tuberous sclerosis complex, renal cell carcinoma	Sirolimus under evaluation against cure endpoints in ACTG 5337
Immunomodulatory derivatives of thalidomide (IMIDs; thalidomide, lenalidomide, pomalidomide)	Multiple via cereblon, including T cell costimulation, cytokine modulation, cell microenvironment	Hematologic malignancies including myeloma and lymphoma, alone or in combination; Kaposi sarcoma	Immune stimulation to clear reservoir cells; stem cell disruption	Hematologic cytopenias Neurologic (neuropathy and sedation, less with newer agents) Gastrointestinal disturbance Teratogenicity	FDA-approved for multiple myeloma in combination regimens	None cure-centered; trials in HIV associated malignancies are ongoing in Kaposi sarcoma for lenalidomide (AIDS Malignancy Consortium) and pomalidomide (National Cancer Institute)
Ibrutinib	Bruton's Tyrosine kinase and interleukin-2-inducible T-cell kinase (ITK) inhibitor	Mantle cell lymphoma, chronic lymphocytic leukemia, other hematological malignancies	Promotes apoptosis	Thrombocytopenia, renal impairment, cutaneous toxicity	FDA-approved for chronic lymphocytic leukemia	Trials in HIV associated malignancies underway (phase I safety study, AIDS Malignancy Consortium)
Imatinib	Multi-tyrosine kinase inhibitor including PDGFR, cKIT	Chronic myeloid leukemia, gastrointestinal stromal cell tumors	Promotes apoptosis	Cytopenias, gastroinstestinal toxicity	FDA approved for CML and GIST	None current
Gamma secretase inhibitors (PF-03084014, others)	Enzymatic components of the notch signaling pathway	Metastatic solid tumors; Kaposi sarcoma	Inhibits angiogenesis; may target stem cell cycling and renewal	Gastrointestinal toxicity dose limiting, but full safety profile not yet defined	Phase I/II studies under way in advanced solid tumors including breast and pancreatic, and planned in Kaposi sarcoma	Trial in HIV-associated Kaposi sarcoma is planned (AIDS Malignancy Consortium)

CML chronic myelocytic leukemia; *CTLA* cytotoxic T-lymphocyte-associated protein; *EBV* Epstein-Barr virus; *ECG* electrocardiogram; *GI* gastrointestinal; *GIST* GI stromal tumor; *HBV* hepatitis B virus; *PD* programmed death; *PDL* PD ligand; *PDGFR* platelet-derived growth factor receptor