Shared immunotherapeutic approaches in HIV and HBV: Combine and Conquer

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Purpose of review

To identify similarities, differences and lessons to be shared from recent progress in HIV and HBV immunotherapeutic approaches.

Recent findings

Immune dysregulation is a hallmark of both HIV and HBV infection, which have shared routes of transmission, with approximately 10% of HIV positive patients worldwide being co-infected with HBV. Immune modulation therapies to orchestrate effective innate and adaptive immune responses are currently being sought as potential strategies towards a functional cure in both HIV and HBV infection. These are based on activating immunological mechanisms that would allow durable control by triggering innate immunity, reviving exhausted endogenous responses and/or generating new immune responses. Recent technological advances and increased appreciation of humoral responses in the control of HIV have generated renewed enthusiasm in the cure field.

Summary

For both HIV and HBV infection a primary consideration with immunomodulatory therapies continues to be a balance between generating highly effective immune responses and mitigating any significant toxicity. A large arsenal of new approaches and ongoing research

offer the opportunity to define the pathways that underpin chronic infection and move closer to a functional cure.

Keywords

HIV, HBV, functional cure, immunotherapy

Introduction

The lifelong treatment challenges and significant global health care burden of HIV and HBV infection have resulted in increased efforts to develop new approaches aimed at curing infection. Despite differences in the clinical course of HIV and HBV infection there are a number of similarities and shared hurdles to the development of eradication strategies (**Table 1**). One of the main barriers to developing cure strategies for HBV and HIV is the elimination of covalently closed circular DNA (cccDNA) from hepatocytes and HIV viral reservoirs respectively. A new goal of therapy is therefore to overcome the persistent immune dysfunction, a defining characteristic of chronic viral infection, and achieve a 'functional' cure. This would represent sustained loss of detectable HBV surface antigen (HBsAg) in serum for HBV, which is rarely achieved with NAs treatment alone, and effective viral control in HIV infection following termination of therapy (1, 2). A strong rationale for immune based approaches is supported by the inherent ability of the majority of infected adults to resolve HBV infection and maintain residual virus replication under successful long-term immune control. Although far less common than in HBV infection, there are clear examples of individuals (elite controllers) who spontaneously control HIV for decades in the absence of treatment (3). These outcomes indicate that effective chronic virus immune containment, if not eradication, is achievable in both HBV and HIV. Here, we discuss recent advances in parallel therapeutic approaches and risks involved in augmenting effective antiviral immunity and redirecting immune responses to control HIV and HBV.

Rational for an immunotherapeutic approach

Optimal elimination of virally infected cells requires a co-ordinated innate and adaptive immune response (**Table 2**). However, a common theme in HIV and HBV is the impairment of multiple components of the immune response. Approaches to stimulate innate immune populations represent potential strategies for the treatment of chronic HBV and HIV. However, the abundant innate immune cell populations within the liver, lacking specificity for only HBV infected hepatocytes, raise questions about potential toxicity. Virus specific adaptive responses offer a more targeted approach to therapeutics. The importance and efficacy of virus specific T cell responses in HIV and HBV infection has been highlighted in both animal and human studies. Depletion of CD8 T cells leads to rapid rebound of viraemia in the non-human primate model of SIV infection (4). In humans, HIV- specific CD8 T cells develop promptly after infection mediating strong selection pressure at the time of post-peak viral decline (5-7), and potent and polyfunctional HIV-specific T responses have been described in a select group of elite controllers that maintain viral control in the absence of antiretroviral treatment (3). Equally there is clear evidence of the importance of CD8 T cells in HBV control in chimpanzees (8) and HBV-specific CD8 T cells are enriched in the infected liver and can direct their antiviral function towards HBV infected hepatocytes (8-10). However, it is increasingly clear that some of the same characteristics of CD8 T cell exhaustion, including epigenetic and metabolic changes coupled to the upregulation of multiple inhibitory receptors, are shared by both viral infections. With the emerging role of humoral immune responses against HBV and the induction of neutralising antibodies directed against HIV, there has been a renewed interest in the potential of antibody based strategies in both chronic infections (11, 12••, 13).

Efforts aimed at boosting immune control of HIV and HBV are an area of marked intersection in the current efforts aimed at functional cure, with many of the same approaches being tested in these two infections. Here we will briefly consider progress with each of the main classes

of immunotherapeutics currently being tested in preclinical/clinical phase trials for HIV & HBV in parallel, ending with a consideration of future approaches.

TLR agonists

Activation of components of both innate and adaptive immunity in patients with chronic HBV (CHB) can be achieved by agonists of pattern recognition receptors, such as Toll-like receptor 7 (TLR7)/TLR8. These compounds can have a direct effect on innate populations (myeloid cells, natural killer (NK) cells and mucosal-associated invariant T cells (MAIT cells) (TLR7/8) (14, 15). Despite promising pre-clinical results in animal models, administration of a low dose of TLR7 agonist (GS-9620) to patients with chronic HBV in a phase I/II clinical trial (CHB) was well tolerated but demonstrated little antiviral efficacy (16). An alternative double prodrug of a TLR7-agonist (RO7020531) is now being tested in combination with a novel capsid assembly inhibitor against HBV (preclinical trial (17)). New compounds in development with TLR8 activity have the potential to robustly activate production of cytokines such as IL-12 and IL-18, triggering IFN-γ production from intrahepatic innate populations (18). IL-12 has been found to partially recover exhausted HBV-specific T cells (19), and therefore TLR8 agonists could have a dual effect through direct suppression of HBV replication, mediated by IFN-γ, but also through boosting intrahepatic HBV-specific T cell activity. These innate strategies need to be carefully balanced to limit any potential toxicity/detrimental effects though activation of NK cells, which can have a positive and a negative impact in HBV infection (20).

The use of TLR agonists has shown encouraging results in HIV cure efforts either alone or in combination with other therapeutic modalities, due to their ability to reactivate latent HIV and enhance antiviral immune responses, and are currently under investigation both in pre-clinical models of HIV latency as well as in clinical trials (21). TLR-7 agonists were found to reduce the viral reservoir in SIV infected rhesus macaques, in line with the sustained viral control seen after interruption of ART in a subset of monkeys (22). TLR7 agonism in combination with

therapeutic vaccination or broadly neutralising antibody (bNAb) infusion has also been associated with lower viral DNA levels, improved virological control and delayed viral rebound in SIV/SHIV-infected rhesus macaques (23••, 24). This approach of combining more than one immunomodulatory and/or antiviral approach is similarly being explored in HBV trials. GS-9620 is currently being evaluated in clinical trials in HIV infected controllers (NCT03060447) and in those on suppressive ART (NCT02858401), trials that will provide valuable information on safety, biological activity and impact on viral reservoirs, in HIV-infected patients. Additional research is warranted to understand how well TLRs can reach the sites of the viral reservoir, including their ability to reactivate HIV in different cell types.

Therapeutic vaccination

The goal of therapeutic vaccination is to prime new and/or boost pre-existing adaptive immune responses allowing for improved and durable viral control in the absence of therapy (25). Despite a number of vaccine trials undertaken in CHB patients, using new vaccine formulations alone or combined with antivirals, the effects have been limited (26-30, 31•, 32). However pre-clinical data support the concept that new more immunogenic therapeutic vaccines should form the backbone of future combination immunotherapy trials, helping to focus boosted responses towards HBV, as recently reviewed (33). For example, promising results were obtained from a small trial of therapeutic vaccination in combination with anti-PD1 antibody infusions in woodchucks (34), in line with previous data from LCMV (35). Therapeutic vaccination in a mouse model of HBV was more effective in animals with lower antigen load (36•), raising the possibility of enhanced immunogenicity of vaccines if new antivirals in development succeed in lowering the massive antigenic burden in CHB.

Therapeutic vaccines are similarly yet to demonstrate long-term HIV remission following analytical treatment interruption (ATI) in randomised control trials (RCTs) (25). Therapeutic vaccines that elicit narrow immune responses have had little impact on viral rebound (37-41).

In contrast therapeutic vaccines that elicit broad responses have shown signs of efficacy, including results from RCT of HIVAX, a mutated HIV strain that expresses a wide range of HIV proteins, where vaccine recipients demonstrated a significant increase in the breath and polyfuctionality of gag-specific T cell responses and viral load reduction post ATI compared to pre-ART levels (42). Additional results of another lentiviral vector vaccine are awaited (RCT of THV01-1 and THV02-2 is currently underway, NCT02054286). The encouraging data from non-human primates on combination strategies with potent immune modulators e.g. Ad26/MVA (recombinant adenovirus 26 serotype (Ad26) prime/modified vaccinia Ankara (MVA) boost) with TLR7 (24), and novel approaches to harness broad and unconventional immune responses with CMV vector constructs, hold promise for the future (43, 44).

Checkpoint inhibitors

Immune checkpoint inhibitor (ICI) therapy targeting PD-1 and other major pathways upregulated in exhausted T cells during chronic virus infections represents a strategy to boost functional immune responses, following their success in cancer immunotherapy. HBV- specific T cells are characterised by high levels of PD1 expression (45, 46), and antibodies that block the interaction between PD1-PDL1 have been shown to partially restore the dysfunctional HBV-specific T and B cell responses in vitro (45-48). A small trial of a single low dose of the PD-1 blocking mAb Nivolumab in patients with virally suppressed HBeAg-negative CHB was well-tolerated and led to some HBsAg decline in most patients, with one patient having a hepatic flare accompanied by sustained loss of HBsAg (49••). This provides support for cautious further testing of ICI in CHB, in combination with more immunogenic therapeutic vaccines or other novel approaches. However, such attempts need to be tempered by the potential risk for toxicity and tailored to individual patients based on their virological and clinical features.

The successful use of ICIs has not yet been realised in HIV infection despite data from the SIV macaque model demonstrating an increase in the magnitude and quality of adaptive

immunity (SIV-specific CD8 T cells and antiviral B cells) and decline in plasma viraemia (50, 51). In limited case reports/studies ICIs used to treat malignancies in HIV infected patients have demonstrated overall modest immunological responses and inconsistent changes in the dynamics of the viral reservoir (52-56). A phase-I dose-escalation study performed to assess the safety of the anti-PD-L1 antibody in HIV infected patients without any malignancies (57) was halted due to observed retinal toxicities seen in concurrent macaque studies. Future approaches should therefore exercise caution regarding potential toxicity, especially as combination therapeutic approaches may be required for significant reactivation/effects on of the HIV reservoir (58).

Immunostimulatory cytokines

Therapies harnessing immunomodulatory cytokines aim to exploit their direct antiviral efficacy and/or effects on immune cell populations. IFN-α therapy is efficacious in a minority of CHB patients, exerts direct antiviral effects and boosts natural killer (NK) cell responses, but the frequency of virus-specific T cells is not increased (59, 60). An alternative cytokine, IL-12, has been shown to be effective *in vitro* in restoring HBV-specific CD8 T cells in combination with PD-1 blockade through metabolic reprogramming (61). There is therefore scope in directly targeting IL-12 to the liver or incorporating it into therapeutic vaccines, as exemplified by a DNA vaccine construct already in clinical trials for CHB (33). A recent study showed that the dysfunctional T cells resulting from hepatocyte priming can be rescued by IL-2 (62••), suggesting that this cytokine should be considered further in HBV immunotherapeutic approaches. There is also biological rationale for considering IL-15 in CHB, based on preclinical data showing complementary antiviral activity with IFN-α, (63), along with the recent demonstration that IL-15 can induce liver-resident T cells with enhanced autophagy to combat mitochondrial depolarisation (64, 65).

IL-15 may likewise have pleiotropic effects in HIV infection, with the potential to drive a self-renewing reservoir by promoting infection of stem-cell-like CD4 T cells in acute infection (66). On the other hand, the beneficial effects of IL-15 immunotherapy and IL-15 superagonist ALT-803, capable of activating both NK cells and CD8 T cells, have been highlighted *in vivo* in non-human primate models of HIV (67•). Heterodimeric IL-15 (hetIL-15) has been reported to also enhance the localisation of CD8 T cell in B cell follicles in LN (68), which addresses one of the key challenges of directing effector cells to sanctuary sites. The safety and tolerability of ALT-803 is currently being tested in a phase I clinical trial to facilitate clearance of latent HIV-1 reservoirs in HIV-infected people receiving potent and optimized antiretroviral therapy (NCT02191098). The ability of IL-15 to enhance ADCC and augment NK cell mediated killing of HIV-infected target cells *ex vivo* (69) may prove vital in the development of a functional cure for HIV. These findings, together with a recent report of IL-15 mediated metabolic reprogramming improving the efficacy of HIV-specific CD8 T cells from non-controllers (70••), highlight the complementary effects of such an approach to simultaneously re-invigorate multiple arms of the immune response.

Adoptive cell therapy & ImmTavs

The fixed epigenetic landscape of T cell exhaustion may preclude successful revival of endogenous responses with the above approaches in some patients with CHB and HIV infection. The selective administration of exogenous effector cells can instead provide a targeted treatment with the added benefit of avoiding bystander off-target effects. These approaches involve the use of TCR-redirected T cells and chimeric antigen receptor (CAR) T cells to confer viral specificity on patient-derived T cells for use in adoptive cell therapy (2, 71). CAR T cells transduced with an antibody-like receptor to recognize HBsAg on the surface of infected hepatocytes (72-74), and TCR-redirected T cells to respond to HLA-A2-presented HBV peptides (75) have shown potent antiviral potential in a preclinical model of chimeric humanized liver mice infected with HBV (76, 77••, 78). However, the scale-up of such

treatments currently remains impractical for widespread use in CHB. The ImmTAV molecules (Immunocore) offer an alternative approach, engineered from a T cell receptor with high specificity for target antigen in soluble form linked to a CD3 activating antibody fragment (anti-CD3 scFv) to engage nearby T cells to activate effector function (79-81). These are being developed for HBV to bind and direct any CD3 expressing cell towards hepatocytes expressing the MHC/peptide complexes recognized by the TCR.

An HIV-1 *gag*-specific ImmTAV has demonstrated promising proof of concept activity at low effector-to-target ratios when tested *ex vivo* with CD4 T cells from HIV-1 positive patients on ART (82). Additional work is, however, necessary to define the threshold of viral antigen expression required in the reservoir for this strategy to be effective, any potential toxicity and translation across HLA types. A number of *in vitro* and proof of concept studies in macaques have demonstrated the feasibility of developing virus specific CAR T cells with an increased ability to traffic to the GC which harbours a large fraction of the HIV reservoir (83-87). Further studies need to be conducted to evaluate their *in vivo* potential.

BnAbs

Therapeutic antibodies have demonstrated promising results in HIV infection (88•, 89••) and initial findings suggest that they may also hold therapeutic potential in HBV. Combinations of monoclonal antibodies against HBsAg exhibited transient viral suppression in non-human primate models of HBV infection and humans (90, 91). The development of next generation monoclonal antibodies has shown improved broadly neutralizing potential against different HBV strains and escape mutants (92, 93) and potent *in vivo* antiviral activity, reducing levels of HBsAg and HBV DNA in HBV-transgenic mice through Fc-dependent mechanisms (12, 13). Moreover, genetic manipulation of therapeutic antibody constructs to recognize multiple domains (e.g. bispecific or trispecific antibodies) could increase their efficacy against HBV and/or HIV by simultaneous engagement of local effector cells as a future approach.

Over the last few years, the discovery of the 'next-generation' anti-HIV-1 bNAbs, with the ability to suppress viral replication, potential for Fc-mediated clearance of virus-infected cells and elicitation of a vaccinal effect through immune complex formation, makes them highly attractive for advancing cure strategies (94). These compounds have now entered the clinical arena, following proof-of-concept animal studies and dosing and safety/efficacy studies in humans. Early experiments suggest that passive immunotherapy with 3BNC117 (which targets the CD4 binding site) and 10-1074 (which targets the V3 loop) during acute simian/human immunodeficiency virus (SHIV) infection induces a T cell mediated remission of disease (95). These two antibodies have been recently tested in humans alone (96) or in combination (88•) (NCT02825797). Infusions were generally well tolerated and in a further study, in which a combination of 3BNC117 and 10-1074 was administered, the nine enrolled participants with antibody-sensitive HIV maintained suppression for a median of 21 weeks in the absence of development of resistance to both antibodies (89••). Two individuals, who commenced ART during early HIV infection, maintained viral control for over eleven months (89••). An upcoming trial of a novel combination of long-acting bNAbs in participants initiating ART during primary HIV infection (PHI) will determine whether early intervention enhances the effect of bNAb administration (RIO).

Future approaches

A range of alternative approaches that are being tested in the cancer field could be considered to boost immune responses in HIV and HBV infection, including different T cell inhibitory receptors, co-stimulatory pathways and immunomodulatory cytokines (2, 33, 97, 98). Future innovative strategies for cure include manipulation of the metabolic machinery of immune cells. This approach could serve as a strategy to control viral persistence by metabolic repression of cells harbouring HIV proviral DNA (block and lock/starve the reservoir) or via metabolic rewiring to recover cellular immunity. Recent findings identify mitochondrial-

centered dysfunction of CD8 T cells and NK cells (unpublished observations) in chronic viral infections as a key area for research and a promising target for future combined reconstitution therapies (61, 65, 70, 99). Mitochondrial antioxidants such as MitoTEMPO (99) and additional pharmacological inhibitors to modulate mitochondrial dynamics (100) in combination with cytokines (i.e IL-12 and IL-15) can rescue functional virus specific responses in patients with CHB and HIV infection. Additional approaches aimed at increasing mitochondrial biogenesis (101) and boosting extracellular supplies of key fuels, such as arginine (102-104), to drive oxidative phosphorylation and survival of T cells could be considered as alternative cure strategies.

A novel strategy compared to traditional bi- and trispecific antibodies is the generation of bi- and tri-specific killer engager (BiKEs and TriKEs) platforms (GT Biopharma) aimed at directing Fc dependent function of key immune cell populations, such as NK cells, against infected target cells. In the preclinical setting a BiKE construct containing the Fab fragment of an HIV bnAb combined with an anti-CD16 component eliminated HIV-infected targets expressing the HIV envelope on their surface. TriKEs with an IL-15 linker that could potentially target HIV infected cells and eliminate the viral reservoir are currently under development.

The success of NK cells in cancer immunotherapy and selective harnessing of NK cells with adaptive features is emerging as an exciting field in augmenting therapeutic approaches against chronic viral infection (105). The potent ADCC activity of adaptive NK cells, which are expanded during chronic HIV (106) and HBV infection (107), represents a new goal of vaccination approaches utilising specific cytokines and targeted adjuvants. However, such attempts need to be carefully balanced to avoid any undesirable effects resulting from the potential of NK cells to regulate humoral and virus specific T cell responses (108••, 109).

Conclusions

Despite a considerable amount of progress, additional work is required to fully unravel all the facets of adaptive and innate immunity especially within critical tissue environments. A better

understanding of immune dysfunction will aid the rational development of immunotherapies for the treatment of both HIV and HBV and requires co-ordinated efforts from researchers in both fields. Such attempts are likely going to require a multipronged approach to achieve broad and durable immune responses with a trade-off between potential toxicity and resolution.

Key points:

- HIV and HBV infections share routes of transmission and lead to multiple humoral and cellular immune defects that bear similarities.
- The immune system is a critical component to achieving a functional cure.
- The same classes of immunotherapies are being tested for HIV and HBV.
- Directed immunotherapeutic strategies require rational combinations of immunological and virological approaches for different patient groups.
- Need for community engagement, advocacy, partnership with countries for increasing prevention, diagnosis and treatment of HIV and HBV infection.

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Table 1 Differences and Commonalities in HIV and HBV infection

Differences in HIV and HBV infection	
HIV	**HBV**
Primary infection rarely cleared	Acute infection frequently cleared in adults but less frequently in the context of HIV co-infection
Replication in T cells and macrophages	Hepatotropic infection
Establishes latency	HBV persistence is propagated by episomal, covalently closed circular (ccc) DNA within the nuclei of infected hepatocytes
Viral escape common	Viral escape less common
No prophylactic vaccine	Effective prophylactic vaccine
No current available biomarker for a functional cure	Available biomarkers for functional cure limited
Commonalities	
• Similar route of transmission; HIV/HBV co-infection accounts for 5-20% worldwide depending on geography and route of infection • Establish chronic infections • Virus replication requires a reverse transcription step creating high viral heterogeneity • Antivirals, some with dual efficacy against HIV and HBV, control viraemia but are not curative • Functional cure will require eradication of HIV provirus and immune control of residual HBV cccDNA • Shared difficulties in accessing tissue reservoirs in HIV infection and HBV reservoir in hepatocytes • CD8 T cells play a key role in viral control but increasing recognition of other players (B cells, NK cells) • Shared pathways of immune dysfunction/exhaustion	

Table 2 Immunotherapeutic approaches in HIV and HBV

Shared goal of immunotherapeutic approaches	
HIV	**HBV**
Harness innate and adaptive immune responses to enhance viral elimination and maintain HIV control in the absence of ART	Clear circulating viral antigen (HBsAg) and limit reactivation from residual cccDNA Limit carcinogenesis from integrated DNA
Approaches	
• Trigger endogenous responses (TLR agonists, immunoregulatory cytokines) • Re-invigorate exhausted endogenous responses (checkpoint inhibitors, co-stimulation) • Generate new endogenous responses (therapeutic vaccination) • Supplement with exogenous responses (adoptive cell transfer, antibody infusions) • Combination approaches	