

NARRATIVE REVIEW

Harnessing Coordinated CD4⁺ and CD8⁺ T-Cell Immunity for Virus-Specific Adoptive Immunotherapy in Africa

Caroline MANGARE^{*1} **Author Affiliation**

¹ Department of Medical Laboratory and Pharmaceutical Sciences, School of Health Sciences, Murang'a University of Technology

*Corresponding Author: cmangare@mut.ac.ke

To read this paper online, please scan the QR code below:



Submitted: 10th August 2026 / Accepted: 26th August 2026 / Published Online: 21st September 2026

ABSTRACT

Virus-specific T-cell (VST) therapy has developed principally for persistent or reactivating viral infections in immunocompromised patients, with the strongest clinical experience involving cytomegalovirus, Epstein–Barr virus, human adenovirus, BK polyomavirus and human herpesvirus 6. Whether this approach can be extended to emerging and re-emerging viral infections remains less certain. Evidence that virus-specific CD4⁺ and CD8⁺ T cells contribute to natural or vaccine-induced protection provides a biological basis for therapeutic development but does not establish the efficacy of adoptively transferred VSTs. This distinction is particularly important for viruses of relevance to Africa, including Ebola virus, Lassa virus, Marburg virus, dengue virus, chikungunya virus, Rift Valley fever virus and mpox virus. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) provides clinical proof-of-concept that rapidly developed, partially HLA-matched or banked virus-reactive T-cell products can be administered against a newly emerging pathogen. Experimental adoptive-transfer studies provide additional evidence for selected pathogens, including Ebola virus, whereas other emerging viruses remain supported mainly by human immunological, epitope or preclinical data. Translation to African populations will require definition of protective viral targets, population-relevant HLA restrictions, viral sequence conservation, manufacturing feasibility and clinical indications in which cellular therapy offers a clear advantage. This review examines the evidence required to move from antiviral T-cell immunity to therapeutic VST development and proposes a framework for evaluating emerging and re-emerging viral infections as future VST targets in Africa.

Keywords: *virus-specific T cells; adoptive immunotherapy; emerging viral infections; CD4⁺ T cells; CD8⁺ T cells; HLA; Africa*

How to Cite this Article: MANGARE, C. Harnessing Coordinated CD4⁺ and CD8⁺ T-Cell Immunity for Virus-Specific Adoptive Immunotherapy in Africa. *Journal of Clinical Care and Medical Advancement*, 1(01), 105–124. <https://doi.org/10.58460/jccma.v1i01.277>



INTRODUCTION

Advancing Pathogen Control through Coordinated CD4⁺ and CD8⁺ T-Cell Immunity

Virus-specific T-cell (VST) therapy seeks to restore or augment antiviral cellular immunity through the isolation, enrichment or ex vivo expansion of virus-reactive T cells followed by adoptive transfer (Riddell & Greenberg, 1995; Barrett et al., 2018; Smith & Khanna, 2025). The approach developed largely in haematopoietic stem-cell transplantation (HSCT), where delayed immune reconstitution and prolonged immunosuppression increase susceptibility to viral reactivation and disease. Clinical studies have evaluated VSTs targeting cytomegalovirus (CMV), Epstein–Barr virus (EBV) and human adenovirus (HAdV), while multivirus platforms have expanded coverage to BK polyomavirus (BKPyV) and human herpesvirus 6 (HHV-6) (Gerdemann et al., 2013; Leen et al., 2013; Tzannou et al., 2017). Contemporary clinical experience includes both transplant-donor-derived and partially HLA-matched third-party products, providing a basis for more readily available cellular therapy.

The biological rationale for VST therapy extends beyond the presence of virus-reactive cells. Effective antiviral immunity depends on coordinated CD4⁺ and CD8⁺ T-cell responses. CD4⁺ T cells support antigen presentation, cytokine production, CD8⁺ T-cell expansion and memory development, while CD8⁺ T cells recognise infected cells and mediate antiviral activity through cytotoxic mechanisms and cytokine secretion. Clinical VST products can contain both populations, and CD4⁺ T cells may support the persistence and expansion of transferred cytotoxic T cells. Functional quality is therefore important alongside cell frequency. Antigen specificity, proliferative capacity, cytotoxic activity, differentiation state, persistence and tissue trafficking may determine whether transferred cells achieve sustained viral control (Mangare et al., 2019).

Advances in manufacturing have enabled antigen-specific cells to be generated using peptide pools targeting several viral antigens within a single product, reducing reliance on infectious viral material and facilitating broader antiviral coverage (Papadopolou et al., 2014). Third-party banking further addresses limitations associated with donor availability and manufacturing time by providing cryopreserved products for selection according to relevant HLA restriction. These advances provide a foundation for extending VST therapy beyond established transplant-associated infections.

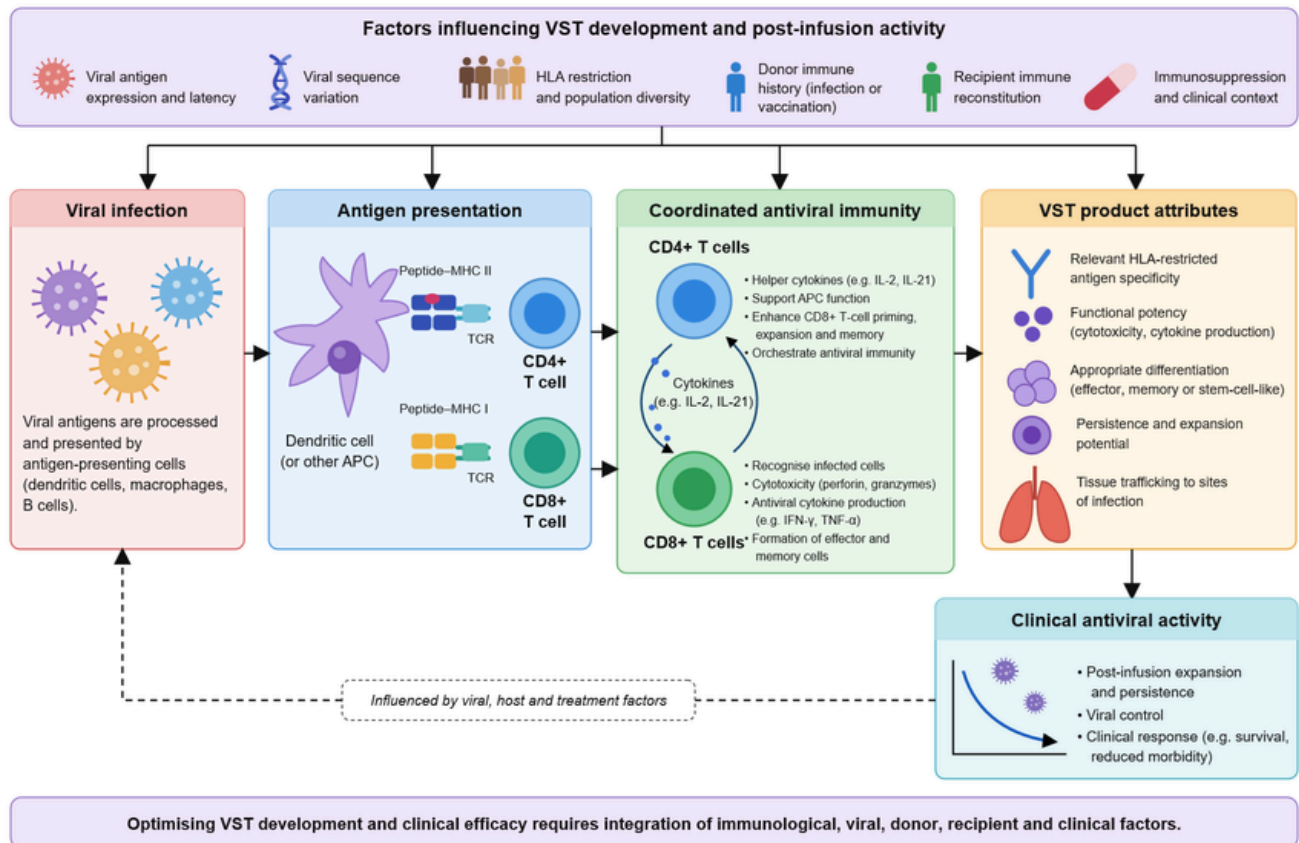
However, emerging and re-emerging viruses differ in antigen expression, viral kinetics, tissue tropism, persistence, sequence diversity and mechanisms of immune evasion. Translation therefore requires pathogen-specific evidence rather than extrapolation from established VST platforms. This review examines how coordinated CD4⁺ and CD8⁺ T-cell immunity, functional competence and memory differentiation inform VST development, evaluates the evidence supporting VST approaches for emerging and re-emerging viral infections, and considers how HLA diversity, donor selection, manufacturing capacity and clinical infrastructure may shape their future development in African populations.

Biological Requirements for Effective Antiviral VSTs

Effective virus-specific T-cell (VST) therapy requires transferred cells to recognise relevant viral antigens, retain antiviral function, expand following antigen encounter and persist sufficiently to mediate viral control. Clinical studies of third-party VSTs demonstrate that partially HLA-matched cells can expand and remain functional after infusion, supporting antiviral activity in immunocompromised recipients (Leen et al., 2013; Tzannou et al., 2017). Therapeutic activity depends not only on the number of infused cells but also on antigen specificity, functional potency, CD4⁺/CD8⁺ composition, differentiation state, proliferative capacity and persistence (Mangare et al., 2019; Tzannou et al., 2017). These biological requirements and their relationship to clinical activity are summarised in Figure 1. Viral antigens must first be processed by antigen-presenting cells and presented through appropriate HLA molecules to activate virus-specific CD4⁺ and CD8⁺ T cells. CD4⁺ T cells provide helper signals that support antigen presentation, CD8⁺ T-cell priming, expansion and memory formation, whereas CD8⁺ T cells contribute directly to elimination of infected cells through cytotoxic mechanisms and antiviral cytokine production. This coordinated response provides the biological basis for selecting functional cells for adoptive therapy. Figure 1 illustrates that effective VST products require relevant HLA-restricted antigen specificity, appropriate differentiation, functional potency, persistence and trafficking to infected tissues. Complete donor–recipient HLA identity is not always required when the HLA molecule restricting the antiviral response is shared (Leen et al., 2013; Tzannou et al., 2017). Antigen selection is equally important because therapeutic targets must be expressed by infected cells, naturally processed and presented, and recognised by functional T cells. Multivirus platforms demonstrate that carefully selected antigen combinations can broaden antiviral coverage within a single cellular product (Gerdemann et al., 2013; Papadopolou et al., 2014).

Figure 1 places VST characteristics within broader viral and clinical contexts. Post-infusion expansion, persistence and antiviral activity are influenced by antigen expression, viral variation, HLA diversity, donor immunity, recipient immune reconstitution and immunosuppression. Because emerging viruses differ from transplant-associated pathogens in viral kinetics, tissue tropism and immunopathology, VST development requires pathogen-specific targets, appropriate HLA restriction, reproducible manufacture and suitable therapeutic windows.

Figure 1: *Biological and Clinical Determinants of Virus-specific T-cell Responses and their Translation to Adoptive VST Therapy*



Antigen-presenting cells initiate virus-specific CD4⁺ and CD8⁺ T-cell responses. CD4⁺ T cells provide helper signals that support antigen presentation and the expansion and maintenance of CD8⁺ T cells, while CD8⁺ T cells eliminate infected cells through cytotoxic mechanisms and antiviral cytokine production. Effective VST products require relevant HLA-restricted specificity, functional activity, appropriate differentiation, persistence and trafficking to sites of infection. Post-infusion expansion and antiviral activity may also be influenced by viral antigen expression, latency, sequence variation, donor immune history, recipient immune reconstitution and immunosuppression.

CD4⁺ and CD8⁺ T-cell Cooperation

Virus-specific T-cell responses are initiated through recognition of viral peptides presented by antigen-presenting cells. Peptide-major histocompatibility complex (MHC) class II recognition activates CD4⁺ T cells, whereas peptide-MHC class I recognition promotes differentiation of CD8⁺ T cells into cytotoxic effectors. CD4⁺ T cells can enhance CD8⁺ T-cell priming through CD40-CD40L-mediated licensing of dendritic cells and provide cytokine signals that support CD8⁺ T-cell proliferation, differentiation and memory formation (Smith et al., 2004; Castellino & Germain, 2006; Bedoui et al., 2016).

CD4⁺ and CD8⁺ T-cell responses function cooperatively, although dependence on CD4⁺ help varies by infection. During some acute viral infections, strong innate activation and dendritic-cell co-stimulation can support substantial primary CD8⁺ T-cell expansion despite limited CD4⁺ help (Bevan, 2004; Bedoui et al., 2016). The effects of inadequate help may become more apparent during memory formation and recall, when CD4⁺ T cells contribute to the development and maintenance of functional CD8⁺ memory (Shedlock & Shen, 2003; Topchyan et al., 2023). CD4⁺ help assumes particular importance during prolonged antigen exposure. Persistent T-cell receptor stimulation and inflammatory signalling can reduce CD8⁺ T-cell proliferative and effector capacity and promote sustained inhibitory-receptor expression and transcriptional and epigenetic programmes associated with exhaustion (Wherry & Kurachi, 2015; McLane et al., 2019). CD4⁺ helper signals contribute to the maintenance of functional antiviral CD8⁺ populations under these conditions (Topchyan et al., 2023). Experimental studies further show that CD4⁺-derived interleukin-21 (IL-21) supports cytolytic CX3CR1⁺ CD8⁺ T-cell populations during persistent viral infection (Zander et al., 2019; Zander et al., 2022). These observations are important to VST product composition whereby, products dominated by cytotoxic CD8⁺ T cells may provide immediate effector activity, whereas inclusion of virus-specific CD4⁺ T cells may support expansion, differentiation and persistence after transfer. The required CD4⁺/CD8⁺ composition is unlikely to be uniform across viruses and should be considered in relation to antigen persistence, host immune status and the intended therapeutic indication.

Functional Competence Beyond Antigen-specific T-cell Frequency

The frequency of antigen-specific T cells provides an incomplete measure of antiviral competence. Proliferative capacity, cytokine production, cytotoxic activity and differentiation provide additional information about the ability of virus-specific populations to respond after antigen encounter (Seder et al., 2008; Riou et al., 2012). These properties are critical for adoptive therapy, as transferred cells must retain functional activity after manufacture and respond effectively following infusion, with polyfunctionality providing an important measure of antiviral T-cell quality. Virus-specific T cells capable of producing combinations of interferon- γ (IFN- γ), tumour necrosis factor- α (TNF- α) and interleukin-2 (IL-2) provide broader functional activity than populations with restricted cytokine profiles. During primary severe acute respiratory syndrome

coronavirus 2 (SARS-CoV-2) infection, stronger early polyfunctional CD4⁺ and CD8⁺ T-cell responses were associated with lower upper-airway viral RNA independently of neutralising antibody titres (Ramirez et al., 2024). Cross-reactive functional memory populations were also more frequent in asymptomatic infection, whereas severe and fatal disease was associated with increased co-expression of PD-1, TIM-3, TIGIT and CTLA-4 (Coulon et al., 2024). These observations support assessment of cytokine production and inhibitory-receptor expression alongside enumeration of antigen-specific cells.

Proliferative capacity provides complementary information because antigen-specific cells may remain detectable despite functional impairment. Following direct-acting antiviral treatment of hepatitis C virus (HCV) infection, proliferation of HCV-specific CD4⁺ and CD8⁺ T cells improved without complete restoration of cytokine production, indicating that recovery of individual functions does not necessarily represent complete restoration of antiviral competence (Llorens-Revull et al., 2021). Cytotoxic activity can be assessed through perforin and granzyme expression, degranulation and direct target-cell killing. Inhibitory-receptor expression should similarly be interpreted together with proliferative, cytokine and cytotoxic measurements rather than used alone to define T-cell exhaustion. These considerations are therefore particularly relevant during ex vivo VST manufacture. Repeated antigenic stimulation and prolonged culture can alter differentiation and proliferative potential. Product characterisation should therefore extend beyond the number of antigen-reactive cells to include functional measurements capable of determining whether expanded populations retain the properties required for activity after transfer.

Memory Differentiation, Persistence and Tissue Localisation

Following resolution or control of primary infection, a proportion of activated T cells survives contraction and differentiates into memory populations capable of responding to subsequent antigen exposure (Kaech & Cui, 2012). These populations differ in proliferative capacity, trafficking and effector function. Central-memory T cells have strong proliferative capacity and preferential lymphoid homing, whereas effector-memory populations provide more immediate effector activity and preferentially circulate through peripheral tissues (Sallusto et al., 1999; Appay et al., 2008). Tissue-resident memory T (T_{RM}) cells remain within lymphoid and non-lymphoid tissues, where they provide local immune surveillance (Masopust & Soerens, 2019; Christo et al., 2024).

The relevance of differentiation state and T cell subsets to adoptive immunotherapy is illustrated by cytomegalovirus (CMV)-specific T cells. CMV-reactive populations are distributed across CD45RA/CD62L-defined central-memory, effector-memory and terminally differentiated subsets that differ in proliferative and functional characteristics. These differences can influence cell-selection strategies and the composition of products intended for adoptive transfer (Mangare et al., 2019). Thus, products containing similar frequencies of virus-specific cells may differ substantially in their capacity to proliferate, persist and mediate antiviral activity after infusion. Importantly, tissue localisation adds a further consideration because measurements in peripheral blood may not adequately represent antiviral immunity within infected tissues because T_{RM} and other tissue-associated populations are poorly represented in circulation (Masopust & Soerens, 2019; Christo et al., 2024). This may be particularly important for viruses that establish infection or persistence within anatomically restricted sites, where effective VSTs must not only recognise infected cells but also traffic to the relevant tissue. This shows that the phenotype that is required for therapeutic activity may consequently differ according to pathogen biology. Persistent or latent infections may benefit from populations with strong proliferative capacity and long-term persistence, whereas rapidly replicating acute infections may require earlier cytotoxic activity and rapid tissue access. Therefore, VST assessment should integrate antigen specificity, CD4⁺/CD8⁺ composition, proliferative capacity, cytokine production, cytotoxic activity, differentiation state, persistence and tissue trafficking rather than relying on antigen-specific cell frequency alone.

Coordinated T-Cell Immunity Across Human Viral Infections

Evidence across acute and persistent viral infections supports a role for coordinated CD4⁺ and CD8⁺ T-cell immunity in viral control, although the relative contribution and phenotype of these populations vary with the pathogen and duration of antigen exposure. In HIV infection, preservation of virus-specific CD4⁺ T-cell function has been associated with sustained CD8⁺ responses and improved viral control (Jain et al., 2024), while experimental HBV and hepacivirus models demonstrate roles for CD4-associated CD40L–CD40 signalling in CD8⁺ T-cell priming, differentiation and antiviral activity (Bailey et al., 2024; Lopez-Scarim et al., 2024). Persistent herpesvirus infection provides further evidence of heterogeneous antiviral memory populations, including functionally distinct CMV-specific CD4⁺ and CD8⁺ subsets relevant to adoptive T-cell

selection (Mangare et al., 2019; Kar et al., 2024). Comparable associations are observed in acute and outbreak-prone infections. SARS-CoV-2 control has been associated with early polyfunctional CD4⁺ and CD8⁺ responses (Koutsakos et al., 2023; Ramirez et al., 2024), while Ebola virus disease survivors develop detectable EBOV-specific cellular responses, in contrast to the high viral loads, systemic inflammation and increased inhibitory-receptor expression reported in fatal disease (Ruibal et al., 2016). YF-17D vaccination generates CD8⁺ T-cell responses capable of forming durable memory (Akondy et al., 2009; Zarnitsyna et al., 2021), whereas DENV infection induces substantial effector-memory responses that may be influenced by previous serotype exposure (de Matos et al., 2015; Rivino & Lim, 2017). Acute CHIKV infection is similarly accompanied by activated cytotoxic CD8⁺ T cells expressing granzyme B and perforin, together with CD4⁺ responses (Wauquier et al., 2011; Dias et al., 2018). Collectively, these observations provide a biological rationale for investigating virus-specific T cells therapeutically, but evidence of protective cellular immunity alone is insufficient to establish suitability for adoptive VST therapy; candidate pathogens require further evaluation of antigen specificity, HLA restriction, functional activity and, ultimately, the capacity of transferred cells to mediate antiviral effects.

Established Clinical VST Therapy as the Translational Benchmark

Clinical development of virus-specific T-cell (VST) therapy has focused largely on viral complications in immunocompromised patients, particularly recipients of allogeneic haematopoietic stem-cell transplantation (HSCT). Cytomegalovirus (CMV), Epstein–Barr virus (EBV) and human adenovirus (HAdV) have the longest clinical experience, with later multivirus platforms extending coverage to BK polyomavirus (BKPyV) and human herpesvirus 6 (HHV-6) (Gerdemann et al., 2013; Leen et al., 2013; Papadopoulou et al., 2014; Tzannou et al., 2017). These studies provide the main clinical foundation for considering VST therapy against other viral infections. Early studies concentrated on individual pathogens. In EBV-associated post-transplant lymphoproliferative disease, banked allogeneic EBV-specific cytotoxic T lymphocytes selected according to HLA compatibility and in vitro activity showed that third-party cells could be used without manufacturing a separate product for each recipient (Haque et al., 2007). Multivirus approaches subsequently broadened this strategy. Gerdemann et al. generated CMV-, EBV- and HAdV-specific T cells using overlapping peptide libraries and a shortened 2–3-week culture.

Complete virological responses were reported in 80% of ten treated HSCT recipients, demonstrating that multivirus products could be generated without the prolonged culture and viral vectors used in earlier methods (Gerdemann et al., 2013).

Third-party banking further improved the practicality of VST therapy. Leen et al. established a bank of 32 VST lines and treated 50 HSCT recipients with severe or refractory CMV, EBV or HAdV infection using partially HLA-matched products. The cumulative complete or partial response at six weeks was 74%, with no immediate infusion-related adverse events and two cases of de novo graft-versus-host disease (Leen et al., 2013). Papadopoulou et al. subsequently generated VSTs recognising 12 antigens from CMV, EBV, HAdV, BKPyV and HHV-6. Among 11 HSCT recipients, including patients with concurrent infections, the overall virological and clinical response was 94% (Papadopoulou et al., 2014). In a phase II study of banked pentavalent VSTs, 38 HSCT recipients with 45 infections achieved a cumulative complete or partial response of 92%. Functional third-party cells remained detectable for up to 12 weeks after infusion (Tzannou et al., 2017). Targeted BKPyV therapy has also produced responses in patients with BK viraemia and haemorrhagic cystitis, including recipients of donor-derived and third-party cells (Nelson et al., 2020). These features of are relevant to future VST development. Therapeutic activity requires recognition of appropriate viral epitopes through recipient HLA molecules; complete donor–recipient HLA identity is not necessarily required when the relevant restricting HLA molecule is shared (Leen et al., 2013; Tzannou et al., 2017). Antigen selection is equally important because therapeutic targets must be expressed in infected cells, naturally processed and presented, and recognised by functional T cells. Multivirus products illustrate how selected antigen combinations can broaden coverage without requiring separate manufacture for each pathogen (Gerdemann et al., 2013; Papadopoulou et al., 2014). Post-infusion proliferation and persistence also contribute to activity, making antigen specificity, CD4⁺/CD8⁺ composition, differentiation and functional capacity important alongside the administered cell dose (Tzannou et al., 2017).

The stated principles provide a foundation for emerging-virus VST development but do not establish efficacy in that setting. Acute emerging infections may differ substantially from transplant-associated infections in viral kinetics, tissue tropism, antigen expression and immunopathology.

Translation therefore requires pathogen-specific evidence for protective T-cell targets, HLA restriction, reproducible manufacture and an appropriate therapeutic window. SARS-CoV-2 provides an important example of this transition from established VST practice to a newly emerging pathogen. Table 1 summarises these targets, viral persistence or latency, HLA and epitope considerations, clinical evidence and potential relevance to African settings. Despite substantial viral disease burden and extensive HLA diversity, clinical implementation of VST therapy in Africa remains limited.

Table 1: *Candidate Viral Indications and Biological Considerations for Virus-specific T-cell Therapy.*

Viral indication	Candidate / established VST antigens	Persistence / latency considerations	HLA / epitope considerations	Current VST evidence	African disease burden / relevance	Key primary reference(s)
Cytomegalovirus (CMV)	pp65; IE1	Lifelong latency with clinically important reactivation during profound immunosuppression, especially after HSCT or solid-organ transplantation.	Responses are HLA-restricted; product selection should ensure that donor VST specificity is restricted through an HLA molecule shared with the recipient.	Established clinical experience with donor-derived and banked third-party VSTs after HSCT.	CMV exposure is widespread in Africa. The burden of CMV disease in transplant populations is incompletely characterised and likely to become more relevant as transplantation expands.	Leen et al., 2013 ; Gerdemann et al., 2013.
Epstein-Barr virus (EBV)	EBNA1; LMP2; BZLF1; latency-associated antigens including LMP1/LMP2 in selected EBV-associated disease	Lifelong latency. Antigen expression varies with latency programme and disease context, making target selection indication-specific.	HLA-restricted epitope recognition is central to donor selection. Partially HLA-matched third-party EBV-specific T cells have shown clinical activity.	Established for EBV reactivation and EBV-positive post-transplant lymphoproliferative disease; extensive clinical experience relative to other viral targets.	EBV is ubiquitous, and EBV-associated lymphomas contribute to the burden of infection-associated malignancy in Africa. Applicability outside transplant-associated disease remains indication-specific.	Haque et al., 2007; Leen et al., 2013

Adenovirus (AdV)	Hexon; penton	Usually acute infection, but persistent or disseminated disease can occur during severe immunosuppression after HSCT.	Multiple HLA-restricted epitopes are recognised. Multivirus products can incorporate AdV specificity alongside herpesvirus targets.	Established clinical experience in HSCT recipients, including donor-derived and third-party multivirus VST products.	The relevant VST indication is primarily severe disease in immunocompromised patients; African transplant-specific incidence data remain limited.	Gerdemann et al., 2013 ; Leen et al., 2013
BK polyomavirus (BKPyV)	VP1; large T antigen	Persistent infection with reactivation during immunosuppression; important causes include BK viraemia, nephropathy and haemorrhagic cystitis.	Functional activity depends on HLA-restricted recognition of BKPyV antigens; donor-derived and third-party products have been used.	Clinical evidence supports activity in HSCT and solid-organ transplant recipients; also incorporated into multivirus VST products.	Clinical relevance is linked to kidney and haematopoietic transplantation. African burden is poorly quantified and should be defined alongside expansion of transplant services.	Nelson et al., 2020 ; Tzannou et al., 2017
Human herpesvirus 6 (HHV-6)	U11; U14; U90 (multivirus VST platforms)	Primary infection is followed by persistence; reactivation can occur after HSCT.	The HLA-restricted epitope repertoire is less extensively characterised than for CMV or EBV.	Included in donor-derived and banked multivirus VST trials; clinical evidence remains smaller than for CMV, EBV or AdV.	The clinically relevant burden is mainly post-transplant reactivation. African transplant-specific epidemiology remains insufficiently defined.	Papadopoulou et al., 2014; Tzannou et al., 2017

Human immunodeficiency virus (HIV)	Conserved epitopes across Gag, Pol and Nef; product design may use conserved-region specificities	Persistent infection with a latent reservoir, high sequence diversity and immune escape; ART remains standard of care.	HLA strongly shapes immunodominance and escape. African HLA and viral diversity are major considerations for population coverage.	Investigational. A 2025 phase I study reported feasibility and tolerability of autologous HIV-specific T cells targeting conserved epitopes; therapeutic efficacy is not established.	The WHO African Region had an estimated 26.3 million people living with HIV in 2025, making HIV highly relevant biologically, although this does not establish a clinical indication for VST therapy.	(Sohai et al., 2025)
Hepatitis B virus (HBV)	HBsAg-derived epitopes; core; polymerase; envelope	Persistent hepatic infection; chronic antigen exposure is associated with impaired virus-specific T-cell function. HBV antigens may persist in HBV-related HCC.	Many experimental TCR-T approaches are HLA-restricted, including HLA-A*02-restricted HBV epitopes; broader population coverage would require additional restrictions.	Investigational. HBV-specific TCR-engineered T-cell approaches have entered early clinical evaluation, particularly for HBV-related HCC; not established VST therapy for chronic HBV.	Chronic HBV is a major African health burden. WHO estimates about 65 million people in the African Region live with chronic HBV, supporting research relevance but not therapeutic readiness.	(Wan et al., 2024; Wu et al., 2025)

Hepatitis C virus (HCV)	NS3; NS5A/NS5-derived epitopes	Persistent hepatic infection can drive T-cell dysfunction, but direct-acting antivirals cure most treated infections; this substantially changes the therapeutic rationale for cellular therapy.	Experimental TCRs have targeted HLA-A*02-restricted NS3 and NS5 epitopes; viral sequence diversity and hepatotoxicity are important considerations.	Preclinical / experimental. HCV-specific TCR-engineered human T cells have shown antigen-specific antiviral activity in vitro; conventional VST therapy is not established.	WHO estimates about 8 million people in the African Region live with chronic HCV. Because curative antiviral therapy exists, any cellular-therapy indication would require a clearly defined unmet clinical need.	(Balasiddaiah et al., 2017; World Health Organization, 2024).
-------------------------	--------------------------------	--	---	---	---	---

Abbreviations: AdV, adenovirus; ART, antiretroviral therapy; EBV, Epstein-Barr virus; HCC, hepatocellular carcinoma; HHV-6, human herpesvirus 6; HLA, human leukocyte antigen; HSCT, haematopoietic stem-cell transplantation; TCR-T, T-cell receptor-engineered T cell; VST, virus-specific T cell

SARS-CoV-2 as a model for Clinical Proof-of-Concept for VST Therapy Against an Emerging Virus

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) provides the clearest example of extending VST beyond established transplant-associated viruses. Human studies show that early virus-specific cellular responses contribute to viral control. During breakthrough infection, rapid recall of spike-specific CD4⁺ T cells and expansion of activated SARS-CoV-2-specific CD8⁺ T cells were associated with lower peak nasal viral RNA and faster clearance (Koutsakos et al., 2023). During primary infection, early polyfunctional CD4⁺ and CD8⁺ responses were similarly associated with lower upper-airway viral RNA independently of neutralising antibody titres (Ramirez et al., 2024). Cross-reactive memory to common-cold coronaviruses may also contribute, whereas severe disease has been associated with fewer cross-reactive cells and greater expression of inhibitory receptors (Coulon et al., 2024).

This biological evidence was followed by clinical evaluation of SARS-CoV-2-reactive cellular products. In a randomised phase I/II trial involving 90 patients with severe COVID-19, partially HLA-matched convalescent donor-derived SARS-CoV-2-specific T cells expanded in vivo and were well tolerated. Recovery occurred in 65% of VST-treated participants compared with 38% receiving standard care alone, although larger studies were considered necessary to confirm efficacy (Papadopoulos et al., 2023).

The multicentre RELEASE trial subsequently evaluated off-the-shelf CD45RA⁺ memory T cells in patients with COVID-19 pneumonia and/or lymphopenia, reporting achievement of the prespecified recovery endpoint and faster lymphocyte recovery without treatment-related adverse events (Ferrerias et al., 2024).

Third-party banking has also been explored in immunocompromised patients. Twelve high-risk patients received HLA-matched SARS-CoV-2-specific T cells, with donor cells subsequently detected in eight recipients and no treatment-attributable cytokine-release syndrome, graft-versus-host disease or acute respiratory distress syndrome reported (Seng et al., 2024). A further phase I study in six immunocompromised cancer patients with refractory infection reported viral-load improvement in four patients, while one developed cytokine-release syndrome and diffuse alveolar haemorrhage after infusion (Henden et al., 2025). SARS-CoV-2 therefore provides clinical proof-of-concept that HLA-informed donor selection, third-party banking and adoptive transfer can be applied to an emerging virus. However, efficacy, optimal timing and appropriate patient populations remain to be established before these findings can inform broader emerging-virus VST development.

Ebola Virus and the Evidence from Human Immunology and Preclinical Adoptive Transfer

Ebola virus (EBOV) has progressed beyond descriptive T-cell immunology, although clinical VST therapy has not been established. During the West African epidemic, fatal Ebola virus disease was associated with high viral load, systemic inflammation and increased PD-1 and CTLA-4 expression on CD4⁺ and CD8⁺ T cells, whereas survivors developed EBOV-specific responses during viral clearance (Ruibal et al., 2016). In Sierra Leone survivors, 26 of 30 individuals responded to at least one EBOV antigen, with nucleoprotein most frequently recognised; 34 CD8⁺ T-cell epitopes were identified across several viral proteins (Sakabe et al., 2018). Experimental evidence further supports the therapeutic potential of these responses. Transfer of activated EBOV-specific CD8⁺ T cells protected naïve mice against lethal EBOV challenge but not Marburg virus, demonstrating virus-specific protection (Bradfute et al., 2008). Thus, EBOV combines human antigen-specific responses and epitope evidence with preclinical adoptive-transfer protection, but no comparable human therapeutic VST trial was identified in the literature reviewed.

Dengue Virus and Extensive Human T-Cell Evidence Without Clinical VST Therapy

Dengue virus (DENV) has one of the most extensively characterised T-cell repertoires among arboviruses, although its suitability for adoptive T-cell therapy remains uncertain. Studies across the four DENV serotypes have identified broad HLA-restricted CD8⁺ T-cell responses and suggest that functional cellular immunity can contribute to protection. In a dengue-hyperendemic population, Weiskopf et al. examined responses to more than 400 epitopes and found that HLA alleles associated with lower susceptibility to severe disease were also associated with stronger, polyfunctional DENV-specific CD8⁺ T-cell responses (Weiskopf et al., 2013). Moreover, CD8⁺ T-cell targeting varies between DENV serotypes, indicating that infecting serotype, viral sequence and previous exposure may influence antigen recognition (Weiskopf et al., 2015). Experimental studies have further identified naturally presented MHC-I-restricted epitopes. Comber et al. described four DENV epitopes, including HLA-A24-restricted and HLA-A2/A24-binding targets capable of stimulating CD8⁺ T cells from DENV-seropositive individuals (Comber et al., 2014). These studies provide a basis for selecting candidate antigens and HLA-restricted targets but do not establish DENV-specific adoptive immunotherapy. No comparable human

therapeutic DENV-VST trial was identified in the literature reviewed. Future development would need to account for serotype cross-reactivity, HLA and viral sequence diversity, previous DENV exposure and the potential for some T-cell responses to contribute to inflammatory pathology.

Chikungunya Virus and Preclinical Adoptive-Transfer Evidence

Human chikungunya virus (CHIKV) infection induces strong cellular responses. During acute disease, CD8⁺ T cells show increased granzyme B, perforin and CD107a expression, consistent with cytotoxic effector activity (Dias et al., 2018). Preclinical studies have also examined adoptive transfer. In mice, activated CHIKV-specific CD8⁺ effector T cells enhanced systemic viral clearance, but failed to eliminate persistent virus from joint-associated tissues (Davenport et al., 2020). This finding is relevant to VST development because antiviral cytotoxicity alone may be insufficient when transferred cells cannot effectively access or function within sites of viral persistence. CHIKV therefore has human functional T-cell evidence and preclinical adoptive-transfer support, but no established human CHIKV-specific VST trial was identified.

Lassa Virus and Human T-Cell Epitope Evidence for Adoptive Immunotherapy

Lassa virus (LASV) infection provides substantial evidence for the contribution of cellular immunity to viral control. Recovery from Lassa fever may occur before measurable neutralising antibodies develop, supporting investigation of T-cell-mediated responses. Early studies in seropositive West African individuals demonstrated proliferative responses to LASV nucleoprotein (NP), and NP-specific human CD4⁺ T-cell clones recognising defined viral peptides were generated from exposed individuals (ter Meulen et al., 2000). A conserved glycoprotein-2 epitope recognised by human LASV-specific CD4⁺ T-cell clones was subsequently characterised (Meulen et al., 2004). CD8⁺ T-cell targets have also been defined experimentally. Botten et al. identified three HLA-A02:01-restricted glycoprotein complex (GPC) epitopes, GPC₄₂₋₅₀, GPC₆₀₋₆₈ and GPC₄₄₁₋₄₄₉. These epitopes induced high-avidity CD8⁺ T-cell responses in transgenic mice and were naturally processed and presented by human HLA-A02:01-positive target cells. Immunisation with two of the epitopes also provided protection against recombinant vaccinia virus expressing LASV GPC (Botten et al., 2006).

Evidence from African survivors is particularly relevant to therapeutic target selection. Analysis of survivors from Nigeria and Sierra Leone identified three shared CD8⁺ T-cell epitopes and nine additional targets within conserved LASV regions despite circulation of distinct viral lineages (Sakabe et al., 2020). More recent work has further characterised the human LASV CD4⁺ T-cell repertoire and identified conserved regions showing cross-mammarenavirus recognition (Lee et al., 2026). Overall, these studies provide candidate antigens and epitopes for future LASV-specific VST development. However, no established human LASV-specific adoptive VST trial was identified in the literature reviewed, placing LASV at the human antigen and epitope characterisation stage rather than clinical cellular therapy.

Rift Valley Fever Virus and Human T-Cell Evidence

Rift Valley fever virus (RVFV) has experimentally defined human T-cell targets relevant to VST development in Africa. Two immunodominant HLA-A*02:01-restricted nucleocapsid epitopes, N₁₂₁₋₁₂₉ (VLSEWLPVT) and N₁₆₅₋₁₇₃ (ILDAHSLYL), elicited cytotoxic and polyfunctional CD8⁺ T-cell responses (Xu et al., 2013). Long-term cellular immunity has also been demonstrated in recipients of an inactivated RVFV vaccine, with responses to N, Gn and Gc detectable up to 24 years after vaccination (Harmon et al., 2020). These findings identify functional human T-cell targets and durable memory responses that could inform VST development, although no established human RVFV-specific adoptive T-cell trial was identified in the literature reviewed.

MPox Virus and Human T-Cell Epitope Evidence

Human T-cell responses to mpox virus (MPXV) have been increasingly characterised since the 2022 outbreak. Grifoni et al. compiled 318 CD4⁺ and 659 CD8⁺ orthopoxvirus epitopes and developed MPXV peptide pools capable of detecting cross-reactive human T-cell responses following infection or vaccination (Grifoni et al., 2022). More recent work identified seven immunodominant HLA-A*02:01-restricted MPXV CD8⁺ epitopes and reported differences in cytotoxicity, migration and clonal expansion between infection- and MVA-BN vaccine-induced responses (Chen et al., 2025). Hence, these studies provide human antigen-specific and epitope-level evidence, but no established therapeutic MPXV-specific adoptive T-cell trial was identified in the literature reviewed.

Marburg Virus and Current Evidence Gaps

Marburg virus (MARV) remains at an earlier stage of VST development than Ebola virus (EBOV), despite both being filoviruses. Human studies of MARV survivors have demonstrated multivariate CD4⁺ T-cell responses but comparatively limited CD8⁺ T-cell responses, indicating that cellular immunity develops after natural infection but remains incompletely characterised (Stonier et al., 2017). Experimentally validated, naturally processed HLA-restricted MARV epitopes are also limited, while many proposed T-cell targets have been derived from computational prediction or preclinical vaccine studies (Baral et al., 2022). Preclinical vaccination studies have demonstrated induction of broad MARV-specific cytotoxic T-cell responses, supporting further investigation of cellular immunity (Shedlock et al., 2013). No human MARV-specific adoptive T-cell trial has been established. Priorities include defining HLA-restricted epitopes, characterising survivor T-cell responses, and evaluating protective efficacy of MARV-specific T cells in adoptive-transfer models.

Translational Pathway for Emerging-Virus VST Development in Africa

Development of virus-specific T-cell (VST) therapy for emerging and re-emerging infections requires progression from evidence of antiviral cellular immunity to a reproducible therapeutic product. Established VST programmes demonstrate that clinical activity depends on appropriate antigen specificity, HLA restriction, functional competence and persistence following infusion (Leen et al., 2013; Papadopoulou et al., 2014; Tzannou et al., 2017). Emerging viruses currently occupy different positions along this pathway. As discussed in previous sections, SARS-CoV-2 has progressed to clinical evaluation of manufactured and third-party products (Papadopoulou et al., 2023; Seng et al., 2024), whereas EBOV and CHIKV have reached preclinical adoptive-transfer studies (Bradfute et al., 2008; Davenport et al., 2020). LASV, DENV, RVFV and MPXV are supported mainly by human T-cell characterisation and epitope mapping (Weiskopf et al., 2013; Sakabe et al., 2020; Harmon et al., 2020; Chen et al., 2025), while MARV remains less extensively characterised. These differences provide a framework for defining the evidence and infrastructure required for VST development in African populations, with Table 2 summarising the current stage of evidence, key translational gaps and relevance to African VST development for each emerging and re-emerging virus reviewed.

Table 2: *Translational Evidence for Virus-specific T-cell Adoptive Immunotherapy Against Emerging and Re-emerging Viral Infections*

Ebola virus (EBOV)	Human survivor data show broad EBOV-specific CD8 ⁺ responses; T-cell activation and inhibitory-receptor patterns differ between survivors and fatal disease. Human evidence supports association with control but does not itself prove therapeutic efficacy.	Human survivor studies identify responses to NP, VP24, VP40, VP35 and GP/sGP with multiple HLA-associated CD8 ⁺ epitopes. Experimental NP-specific class-I-restricted CTLs are protective in mice.	Yes - strong preclinical proof-of-concept. EBOV NP-specific CD8 ⁺ CTLs protected mice from lethal challenge; CD8 ⁺ cells from infected mice also conferred protection after transfer	No established human EBOV-VST trial identified.	Translate animal transfer data to human cells; define protective epitopes across diverse HLA backgrounds; optimise manufacturing and determine whether treatment can be delivered within the short clinical window of acute EVD.	High biological relevance because of recurrent African outbreaks. Survivor cohorts could support HLA/epitope mapping and VST discovery, but clinical development would require rapid-access products and high-containment-compatible translational pathways.
Lassa virus (LASV)	Human infection can induce robust acute activation and long-lived LASV-specific CD8 ⁺ memory. Recovery before substantial neutralising antibody responses also supports an important role for cellular immunity.	Moderate–strong. HLA-A*02:01-restricted GPC epitopes GPC42–50, GPC60–68 and GPC441–449 are naturally processed and experimentally validated; long-lived epitope-specific cells have been demonstrated in a human case .	No established LASV-specific therapeutic adoptive-transfer study identified. Protective epitope vaccination has been demonstrated in HLA-A2 transgenic experimental systems, which is not equivalent to VST transfer.	No established human LASV-VST trial identified.	Broader human epitope mapping across LASV lineages and African HLA backgrounds; direct demonstration of protective T-cell specificities; VST manufacture and adoptive-transfer efficacy remain undefined.	Highly relevant in West Africa. Endemic exposure and survivor cohorts provide opportunities to define locally relevant HLA-restricted targets and assess whether conserved LASV antigens could support future VST platforms.

Marburg virus (MARV)	Human T-cell data are comparatively limited; available evidence does not yet provide the depth of functional and epitope validation seen for EBOV, DENV or MPXV.	Limited. Candidate epitopes have largely emerged from computational or early preclinical studies; experimentally validated human HLA-restricted epitope data remain sparse.	No convincing MARV-specific therapeutic adoptive-transfer evidence identified.	No established human MARV-VST trial identified.	Need primary human T-cell studies, experimentally validated naturally presented epitopes, HLA restriction, functional characterisation and preclinical transfer studies before therapeutic development can be assessed.	Relevant because of recurrent African filovirus outbreaks. At present, priority should be foundational human immunology and epitope validation rather than clinical VST development.
Dengue virus (DENV)	Extensive human evidence shows robust CD4 ⁺ and CD8 ⁺ responses, including cytotoxic and memory populations. Responses can be protective, but cross-reactivity and immunopathology complicate interpretation.	Strong. Numerous class-I and class-II epitopes have been mapped across structural and non-structural proteins, with restrictions including HLA-A02, A03/11, B07, B15 and B35; NS3 is a prominent target.	No established therapeutic DENV-VST adoptive-transfer platform identified in humans; protective T-cell effects have been studied experimentally, but this is distinct from a clinically developed VST product.	No established human DENV-VST trial identified.	Define protective versus potentially pathogenic specificities, cross-serotype breadth, conserved targets, therapeutic timing and safety. Short viraemia may constrain the clinical window for cellular therapy.	Increasingly relevant in African arbovirus outbreaks. African DENV lineages, serotype exposure histories and HLA diversity should be incorporated before considering donor banks or therapeutic products.

Chikungunya virus (CHIKV)	Human acute infection induces early activated CD8 ⁺ responses followed by CD4 ⁺ responses; cytotoxic cells express granzyme B, perforin and degranulation markers.	Moderate. Human and experimental studies identify antigen-specific responses and several candidate/validated HLA-restricted epitopes, although the repertoire is less developed than for DENV.	Yes - experimental mouse proof-of-concept. Adoptively transferred antigen-specific effector CD8 ⁺ cells enhanced clearance in the spleen, with limited effect in joint-associated tissues (PMID 32102875). The model used engineered antigen specificity and is not a human CHIKV-VST product.	No established human CHIKV-VST trial identified.	Identify naturally relevant protective epitopes, understand tissue-specific immune evasion/persistence, and establish whether transferred CHIKV-specific cells can control infection without exacerbating inflammation.	Relevant to expanding African arbovirus transmission. Tissue persistence and chronic arthralgia make trafficking and tissue localisation especially important considerations for future VST research.
Rift Valley fever virus (RVFV)	Human vaccination induces long-lived RVFV-specific CD4 ⁺ and CD8 ⁺ responses detectable years after vaccination, providing direct evidence of durable human cellular memory.	Strong human foundation. N, Gn and Gc epitopes have been experimentally mapped. HLA-A*02:01-restricted N121–129 (VLSEWLPVT) and N165–173 (ILDAHSLYL) generate cytotoxic, polyfunctional CD8 ⁺ cells	No established therapeutic RVFV-specific adoptive-transfer study identified.	No established human RVFV-VST trial identified.	Determine whether mapped human responses mediate protection during natural infection; broaden HLA coverage; test VST generation and adoptive-transfer activity; define an appropriate clinical indication.	Particularly relevant to East and other parts of Africa because RVFV is a zoonotic outbreak pathogen. Human vaccine and epitope datasets provide a foundation for locally relevant cellular-immunity studies.

Mpox virus (MPXV)	Human infection and vaccination generate broad CD4 ⁺ and CD8 ⁺ responses. Convalescent MPXV-specific memory CD8 ⁺ cells can show cytotoxicity, migration-related features and clonal expansion.	Strong and expanding. Human studies have identified multiple immunodominant epitopes, including seven HLA-A*02:01-restricted MPXV-specific CD8 ⁺ epitopes; several are conserved with vaccinia virus.	No established therapeutic MPXV-specific adoptive-transfer study identified.	No established human MPXV-VST trial identified.	Determine which orthopoxvirus-cross-reactive or MPXV-specific responses are protective, expand HLA coverage beyond frequently studied alleles, and test whether functional cells can be manufactured and therapeutically transferred.	Important because MPXV has longstanding African epidemiology. African clade diversity, prior orthopoxvirus exposure and population HLA diversity should inform antigen and donor selection.
SARS-CoV-2	Strong human evidence links early, polyfunctional and memory CD4 ⁺ /CD8 ⁺ responses with viral control and less severe disease, although associations do not alone establish therapeutic efficacy.	Strong. Broad CD4 ⁺ and CD8 ⁺ targets have been mapped across spike and non-spike proteins, enabling peptide-based stimulation, direct selection and generation of SARS-CoV-2-reactive products.	Yes - extensive preclinical/ex vivo development preceded clinical translation; functional SARS-CoV-2-specific cytotoxic lymphocytes can be expanded ex vivo (PMID 33728702).	Yes - human clinical studies have evaluated allogeneic/third-party SARS-CoV-2-specific T-cell products, particularly in severe or immunocompromised patients. This provides clinical proof-of-concept for extending VST technology to an emerging virus.	Define clinical efficacy, optimal timing, patient groups, variant coverage, product matching and safety relative to effective antiviral drugs and other standard therapies.	Provides the clearest platform precedent for rapid emerging-virus VST development. Lessons from donor banking, peptide pools, HLA matching, cryopreservation and rapid manufacture could inform future African outbreak preparedness.

Abbreviations: EBOV, Ebola virus; LASV, Lassa virus; MARV, Marburg virus; DENV, dengue virus; CHIKV, chikungunya virus; RVFV, Rift Valley fever virus; MPXV, mpox virus; HLA, human leukocyte antigen; VST, virus-specific T cell. "No established trial identified" denotes the evidence located for this review and should not be interpreted as proof that no unpublished or newly registered study exists.

Protective T-cell Immunity and Candidate Viral Targets

Evidence of virus-specific cellular immunity provides the biological basis for considering VST development. EBOV survivors develop virus-specific responses, whereas fatal Ebola virus disease has been associated with high viral loads, systemic inflammation and increased expression of inhibitory receptors on T cells (Ruibal et al., 2016). LASV survivors show responses against glycoprotein complex and nucleoprotein, including conserved targets recognised across distinct viral lineages (Sakabe et al., 2020). HLA-associated differences in DENV-specific CD8⁺ T-cell magnitude and polyfunctionality have been linked to disease severity (Weiskopf et al., 2013), while cytotoxic CD8⁺ responses have been demonstrated during acute CHIKV infection (Dias et al., 2018). Durable cellular memory has also been reported following RVFV vaccination (Harmon et al., 2020), and MPXV infection induces functional CD4⁺ and CD8⁺ memory responses (Chen et al., 2025). These findings establish biological relevance but do not, independently, demonstrate suitability for therapeutic transfer.

Antigen Selection, HLA Restriction and African Population Coverage

Therapeutic development requires identification of viral targets that are naturally processed, presented by relevant HLA molecules and recognised by functional T cells. Human studies have identified multiple EBOV CD8⁺ T-cell epitopes (Sakabe et al., 2018), conserved LASV targets across viral lineages (Sakabe et al., 2020), naturally processed HLA-A02:01-restricted LASV GPC epitopes (Botten et al., 2006), an extensive DENV HLA-restricted repertoire (Weiskopf et al., 2013), mapped RVFV N, Gn and Gc targets (Harmon et al., 2020), and immunodominant HLA-A02:01-restricted MPXV epitopes (Chen et al., 2025).

For African VST development, target selection must account for substantial HLA diversity. High-resolution studies demonstrate marked differences in HLA allele and haplotype distributions among African populations (Mentzer et al., 2024; Banjoko et al., 2025). Associations of HLA-B57:03 and HLA-B81:01 with HIV control further illustrate the functional relevance of population-specific HLA variation (Prentice et al., 2013). Viral diversity adds another consideration because sequence variation can alter antigen processing, HLA binding and T-cell recognition. Candidate VST targets should therefore be selected using high-resolution HLA data, viral genomic

surveillance and experimental epitope validation, with emphasis on naturally presented and conserved targets that provide adequate population coverage rather than predominantly relying on frequently studied alleles such as HLA-A*02:01.

Generation and Manufacture of Functional VST Products

Candidate virus-reactive T cells must be isolated or expanded *ex vivo* without losing antigen specificity, proliferative capacity or antiviral function. Established CMV-, EBV-, HAAdV-, BKPyV- and HHV-6-specific platforms demonstrate that defined antigens and overlapping peptide pools can generate clinically applicable products (Gerdemann et al., 2013; Papadopoulou et al., 2014; Tzannou et al., 2017). SARS-CoV-2 extended this principle to an emerging pathogen through manufacture of donor-derived and partially HLA-matched products. Comparable manufacturing evidence remains limited for other emerging viruses. Modular African platforms could standardise cell processing, expansion, cryopreservation and quality control while incorporating pathogen-specific antigens and optimised manufacturing protocols. Peptide-based stimulation may also reduce the need to handle infectious material during production of VSTs targeting high-consequence pathogens. Nevertheless, culture conditions, antigen composition and cellular phenotype require pathogen-specific optimisation. Product assessment should include identity, viability, sterility, antigen specificity, proliferation, cytokine production, cytotoxicity and alloreactivity. In addition, differentiation state should be considered because memory subsets differ in proliferative potential and persistence (Mangare et al., 2019).

Preclinical Adoptive-transfer Evidence

Preclinical adoptive-transfer studies provide an important bridge between endogenous immunity and therapeutic development. In experimental EBOV infection, transferred virus-specific CD8⁺ T cells expanded in recipient animals and protected against lethal EBOV challenge but not MARV infection, demonstrating virus-specific protection (Bradfute et al., 2008). CHIKV provides a contrasting example: transferred effector CD8⁺ T cells improved viral clearance from the spleen but had limited activity against persistent infection in joint-associated tissues (Davenport et al., 2020). These findings show that antigen recognition alone may not predict therapeutic activity and support assessment of *in vivo* expansion, persistence, trafficking and access to infected tissues during preclinical development.

Third-party Banking and Donor Selection

Third-party banking may be particularly valuable for emerging infections because cryopreserved products can be selected rapidly without patient-specific manufacture. Partially HLA-matched VST banks have been used successfully for transplant-associated viral infections (Leen et al., 2013; Tzannou et al., 2017), while SARS-CoV-2 demonstrated that banked products can also be developed from convalescent or vaccinated donors for an emerging pathogen (Seng et al., 2024). VST donor banks developed for African populations should incorporate regional HLA distributions and prospective population-coverage modelling (Mentzer et al., 2024; Banjoko et al., 2025). Suitable donors may include survivors or vaccinated individuals, depending on the pathogen, but previous exposure or seropositivity alone should not determine eligibility. Donor selection should confirm antigen-specific T-cell recognition and functional activity.

Clinical Translation, Therapeutic Window and Patient Selection

SARS-CoV-2 provides the strongest clinical precedent for extending VST therapy to an emerging pathogen. In a randomised phase I/II study, partially HLA-matched SARS-CoV-2-specific T cells expanded after infusion and were well tolerated, with a 30-day recovery rate of 65% among VST-treated participants compared with 38% receiving standard care alone (Papadopoulos et al., 2023). Other studies have evaluated off-the-shelf CD45RA⁺ memory T cells and banked HLA-matched SARS-CoV-2-specific products (Ferrerias et al., 2024; Seng et al., 2024). The therapeutic window may be narrower for rapidly progressive infections such as EBOV, LASV, DENV and CHIKV than for CMV or EBV reactivation. Patient-specific manufacture initiated after diagnosis may therefore be impractical, strengthening the rationale for pre-existing third-party products where therapeutic benefit is biologically justified. Initial studies may be more appropriate in patients with severe or persistent infection, impaired cellular immunity or inadequate responses to available therapies. Therefore, clinical indications should be defined according to pathogen biology, disease kinetics and tissue distribution. VSTs should be evaluated as adjuncts to vaccination, antiviral treatment and supportive care rather than as replacements for established interventions.

Infrastructure, Regulatory Readiness and Implementation in Africa

Clinical implementation will require specialised cell-processing facilities, trained laboratory and clinical personnel, reliable reagent and cold-chain supply systems, quality assurance, regulatory oversight and sustainable financing.

Broader assessments of cellular and gene therapy in Africa identify infrastructure and financial constraints as important barriers to implementation (Obiozor et al., 2025). These observations do not demonstrate existing VST manufacturing capacity across Africa but identify systems that would also be required for VST programmes. Thus, initial development could be concentrated in centres with existing transplantation, haematology, immunology or cellular-therapy capacity, while regional collaboration could support HLA datasets, donor registries, biobanking, immune monitoring and specialised manufacturing expertise. Expansion should follow demonstration of manufacturing feasibility, regulatory compliance, safety and a defined clinical benefit.

Research Priorities and Implementation Agenda for VST Development in Africa

Virus-specific T-cell (VST) therapy in Africa remains a research priority rather than an established clinical platform. Development should initially focus on identifying population-relevant viral targets and establishing whether these can be translated into reproducible cellular products. Studies involving survivors, exposed individuals and vaccinated cohorts should combine functional T-cell profiling, high-resolution HLA typing and viral genomic surveillance to identify naturally presented, conserved epitopes with sufficient population coverage. This is particularly important given the substantial HLA diversity within and between African populations (Mentzer et al., 2024; Banjoko et al., 2025). Existing studies of Lassa virus (LASV) and Ebola virus (EBOV) provide experimentally characterised antigens and epitopes that could support this approach (Sakabe et al., 2018; Sakabe et al., 2020).

Candidate products should then undergo pathogen-specific ex vivo optimisation and assessment of antigen specificity, proliferation, cytotoxicity, phenotype, alloreactivity and stability following cryopreservation. Preclinical studies should determine whether transferred cells persist, traffic to infected tissues and control viral replication without exacerbating immunopathology. EBOV-specific CD8⁺ T cells have demonstrated protective activity following adoptive transfer in experimental models, whereas CHIKV studies indicate that effective systemic antiviral activity may not ensure clearance from tissue reservoirs (Bradford et al., 2008; Davenport et al., 2020).

Thus, clinical development should proceed only where these studies establish a clear therapeutic indication. Experience with CMV-, EBV-, HAdV-, BKPvV- and HHV-6-specific products provides established manufacturing and third-party banking models (Leen et al., 2013; Tzannou et al., 2017), while SARS-CoV-2 demonstrates that similar technology can be adapted to an emerging pathogen (Papadopoulou et al., 2023; Seng et al., 2024). Cryopreserved third-party banks may be particularly relevant for rapidly progressing infections where patient-specific manufacture would be impractical.

Implementation will require GMP-compatible manufacturing, quality assurance, regulatory oversight, skilled personnel and sustainable financing (Obiozor et al., 2025). Locally manufactured anti-CD19 CAR-T therapy in South Africa provides evidence that advanced cellular therapies can be produced and delivered within specialised African centres. This experience could inform VST development through existing transplantation and cellular-therapy expertise, while regional collaboration could strengthen biobanking, immune monitoring, donor registries and shared manufacturing capacity (Obiozor et al., 2025).

CONCLUSION

Virus-specific T-cell therapy demonstrates how coordinated CD4⁺ and CD8⁺ T-cell immunity can be translated into cellular treatment. Clinical experience with transplant-associated viruses and SARS-CoV-2 shows that antiviral T cells can be manufactured, banked and administered therapeutically (Leen et al., 2013; Tzannou et al., 2017; Papadopoulou et al., 2023; However, evidence of endogenous virus-specific immunity alone does not establish suitability for adoptive therapy. For emerging and re-emerging viruses, development should be guided by antigen specificity, HLA restriction, functional competence, persistence, tissue trafficking and pathogen biology. EBOV and CHIKV provide preclinical adoptive-transfer evidence, whereas LASV, DENV, RVFV and MPXV remain supported predominantly by human immunological and epitope studies, with MARV requiring further characterisation. In Africa, substantial HLA and viral diversity strengthens the need for population-relevant antigen selection and donor-bank design (Mentzer et al., 2024; Banjoko et al., 2025; An adaptable African VST platform therefore remains a prospective research objective. Its development will depend on linking locally relevant antiviral T-cell biology with reproducible manufacturing, rigorous preclinical evaluation, appropriate clinical indications and sustainable cellular-therapy infrastructure.

LITERATURE IDENTIFICATION

This narrative review was informed by searches of PubMed, Scopus and Web of Science for literature on coordinated CD4⁺ and CD8⁺ T-cell immunity, antiviral T-cell differentiation and memory, virus-specific T-cell therapy, HLA-restricted viral epitopes and African HLA diversity. Search terms included combinations of “CD4 T cells”, “CD8 T cells”, “antiviral immunity”, “T-cell memory”, “T-cell exhaustion”, “virus-specific T cells”, “adoptive T-cell therapy”, “HLA”, “viral epitopes”, “Africa” and individual viral pathogens discussed in the review. Priority was given to primary human studies and clinical VST studies, supplemented by mechanistic animal studies and reviews where appropriate. Reference lists of relevant articles were also examined to identify additional studies.

REFERENCES

- Baral, P., Pavadai, E., Zhou, Z., Xu, Y., Tison, C. K., Pokhrel, R., Gerstman, B. S., & Chapagain, P. P. (2022). Immunoinformatic screening of Marburgvirus epitopes and computational investigations of epitope-allele complexes. *International Immunopharmacology*, 111, 109109. <https://doi.org/10.1016/j.intimp.2022.109109>
- Botten, J., Alexander, J., Pasquetto, V., Sidney, J., Barrowman, P., Ting, J., Peters, B., Southwood, S., Stewart, B., Rodriguez-Carreno, M. P., Mothe, B., Whitton, J. L., Sette, A., & Buchmeier, M. J. (2006). Identification of protective Lassa virus epitopes that are restricted by HLA-A2. *Journal of Virology*, 80(17), 8351–8361. <https://doi.org/10.1128/JVI.00896-06>
- Bradfute, S. B., Warfield, K. L., & Bavari, S. (2008). Functional CD8⁺ T cell responses in lethal Ebola virus infection. *Journal of Immunology*, 180(6), 4058–4066. <https://doi.org/10.4049/jimmunol.180.6.4058>
- Chen, J.-L., Wang, B., Lu, Y., Antoun, E., Bird, O., Drennan, P. G., Yin, Z., Liu, G., Yao, X., Pidoux, M., Bates, A., Jayathilaka, D., Wang, J., Angus, B., Beer, S., Espinosa, A., Baillie, J. K., Semple, M. G., ISARIC4C Investigators, ... Dong, T. (2025). T cell memory response to MPXV infection exhibits greater effector function and migratory potential compared to MVA-BN vaccination. *Nature Communications*, 16(1), 4362. <https://doi.org/10.1038/s41467-025-59370-5>
- Comber, J. D., Karabudak, A., Huang, X., Piazza, P. A., Marques, E. T. A., & Philip, R. (2014). Dengue virus specific dual HLA binding T cell epitopes induce CD8⁺ T cell responses in seropositive individuals. *Human Vaccines & Immunotherapeutics*, 10(12), 3531–3543. <https://doi.org/10.4161/21645515.2014.980210>

- Davenport, B. J., Bullock, C., McCarthy, M. K., Hawman, D. W., Murphy, K. M., Kedl, R. M., Diamond, M. S., & Morrison, T. E. (2020). Chikungunya Virus Evades Antiviral CD8+ T Cell Responses To Establish Persistent Infection in Joint-Associated Tissues. *Journal of Virology*, 94(9), e02036-19. <https://doi.org/10.1128/JVI.02036-19>
- Dias, C. N. de S., Gois, B. M., Lima, V. S., Guerra-Gomes, I. C., Araújo, J. M. G., Gomes, J. de A. S., Araújo, D. A. M., Medeiros, I. A., Azevedo, F. de L. A. A. de, Veras, R. C., Janeiro, D. I., Amaral, I. P. G. do, & Keesen, T. S. L. (2018). Human CD8 T-cell activation in acute and chronic chikungunya infection. *Immunology*, 155(4), 499–504. <https://doi.org/10.1111/imm.12992>
- Ferreras, C., Hernández-Blanco, C., Martín-Quirós, A., Al-Akioui-Sanz, K., Mora-Rillo, M., Ibáñez, F., Díaz-Almirón, M., Cano-Ochando, J., Lozano-Ojalvo, D., Jiménez-González, M., Gotterris, R., Sánchez-Zapardiel, E., De Paz, R., Guerra-García, P., Queiruga-Parada, J., Molina, P., Briones, M. L., Ruz-Caracuel, B., Borobia, A. M., ... Pérez-Martínez, A. (2024). Results of phase 2 randomized multi-center study to evaluate the safety and efficacy of infusion of memory T cells as adoptive therapy in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia and/or lymphopenia (RELEASE NCT04578210). *Cytotherapy*, 26(1), 25–35. <https://doi.org/10.1016/j.jcyt.2023.10.002>
- Grifoni, A., Zhang, Y., Tarke, A., Sidney, J., Rubiro, P., Reina-Campos, M., Filaci, G., Dan, J. M., Scheuermann, R. H., & Sette, A. (2022). Defining antigen targets to dissect vaccinia virus and monkeypox virus-specific T cell responses in humans. *Cell Host & Microbe*, 30(12), 1662-1670.e4. <https://doi.org/10.1016/j.chom.2022.11.003>
- Harmon, J. R., Barbeau, D. J., Nichol, S. T., Spiropoulou, C. F., & McElroy, A. K. (2020). Rift Valley fever virus vaccination induces long-lived, antigen-specific human T cell responses. *NPJ Vaccines*, 5(1), 17. <https://doi.org/10.1038/s41541-020-0166-9>
- Henden, A. S., Lineburg, K. E., Panikkar, A., Mahajan, A., Nelles, R., Wright, E., Crooks, P., Raju, J., Le Texier, L., Swaminathan, S., Beagley, L., Best, S., Solomon, M., Reddix, H., Kennedy, G., Tey, S.-K., Neller, M. A., Khanna, R., & Smith, C. (2025). Allogeneic “off-the-shelf” SARS-CoV-2-specific adoptive T-cell therapy for refractory viral infection and end organ disease. *Clinical & Translational Immunology*, 14(6), e70038. <https://doi.org/10.1002/cti2.70038>
- Lee, Y., Siddiqui, L., Tarke, A., Kim, M., Michaelis, T., Macias, M., Phillips, E., Mallal, S., Trevizani, R., Frazier, A., Scheuermann, R. H., Zuniga, A., Zmasek, C., Spurgers, K., Akintunde, G., Stonier, S. W., Gagliardi, T. B., Warfield, K., Li, H., ... Sette, A. (2026). Decoding the human CD4+ T cell epitope repertoire for Lassa fever virus reveals T cell-based pan-mammarenavirus vaccine candidates. *Cell Reports. Medicine*, 7(6), 102824. <https://doi.org/10.1016/j.xcrm.2026.102824>
- Meulen, J. ter, Badusche, M., Satoguina, J., Strecker, T., Lenz, O., Loeliger, C., Sakho, M., Koulemou, K., Koivogui, L., & Hoerauf, A. (2004). Old and New World arenaviruses share a highly conserved epitope in the fusion domain of the glycoprotein 2, which is recognized by Lassa virus-specific human CD4+ T-cell clones. *Virology*, 321(1), 134–143. <https://doi.org/10.1016/j.virol.2003.12.013>
- Papadopoulou, A., Karavalakis, G., Papadopoulou, E., Xochelli, A., Bousiou, Z., Vogiatzoglou, A., Papayanni, P.-G., Georgakopoulou, A., Giannaki, M., Stavridou, F., Vallianou, I., Kammenou, M., Varsamoudi, E., Papadimitriou, V., Giannaki, C., Sileli, M., Stergiouda, Z., Stefanou, G., Kourlaba, G., ... Yannaki, E. (2023). SARS-CoV-2-specific T cell therapy for severe COVID-19: A randomized phase 1/2 trial. *Nature Medicine*, 29(8), 2019–2029. <https://doi.org/10.1038/s41591-023-02480-8>
- Sakabe, S., Hartnett, J. N., Ngo, N., Goba, A., Momoh, M., Sandi, J. D., Kanneh, L., Cubitt, B., Garcia, S. D., Ware, B. C., Kotliar, D., Robles-Sikisaka, R., Gangavarapu, K., Branco, L. M., Eromon, P., Odia, I., Ogbaini-Emovon, E., Folarin, O., Okogbenin, S., ... Sullivan, B. M. (2020). Identification of Common CD8+ T Cell Epitopes from Lassa Fever Survivors in Nigeria and Sierra Leone. *Journal of Virology*, 94(12), e00153-20. <https://doi.org/10.1128/JVI.00153-20>
- Sakabe, S., Sullivan, B. M., Hartnett, J. N., Robles-Sikisaka, R., Gangavarapu, K., Cubitt, B., Ware, B. C., Kotliar, D., Branco, L. M., Goba, A., Momoh, M., Sandi, J. D., Kanneh, L., Grant, D. S., Garry, R. F., Andersen, K. G., de la Torre, J. C., Sabeti, P. C., Schieffelin, J. S., & Oldstone, M. B. A. (2018). Analysis of CD8+ T cell response during the 2013-2016 Ebola epidemic in West Africa. *Proceedings of the National Academy of Sciences of the United States of America*, 115(32), E7578–E7586. <https://doi.org/10.1073/pnas.1806200115>

- Seng, M. S., Ng, K. P., Soh, T. G., Tan, T. T., Chan, M., Maiwald, M., Tan, L. K., Linn, Y. C., & Leung, W. (2024). A phase I/II study of adoptive SARS-CoV-2-specific T cells in immunocompromised hosts with or at risk of severe COVID-19 infection. *Cytotherapy*, 26(10), 1170–1178. <https://doi.org/10.1016/j.jcyt.2024.05.014>
- Shedlock, D. J., Aviles, J., Talbott, K. T., Wong, G., Wu, S. J., Villarreal, D. O., Myles, D. J., Croyle, M. A., Yan, J., Kobinger, G. P., & Weiner, D. B. (2013). Induction of broad cytotoxic T cells by protective DNA vaccination against Marburg and Ebola. *Molecular Therapy: The Journal of the American Society of Gene Therapy*, 21(7), 1432–1444. <https://doi.org/10.1038/mt.2013.61>
- Sohai, D. K., Keller, M. D., Hanley, P. J., Hoq, F., Kukadiya, D., Datar, A., Reynolds, E., Copertino, D. C., Lazarski, C., McCann, C. D., Tanna, J., Shibli, A., Lang, H., Zhang, A., Chansky, P. A., Motta, C., Huynh, T. T., Dwyer, B., Wilson, A., ... Bollard, C. M. (2025). Autologous HIV-specific T cell therapy targeting conserved epitopes is well-tolerated in six adults with HIV: An open-label, single-arm phase 1 study. *Nature Communications*, 16(1), 4510. <https://doi.org/10.1038/s41467-025-59810-2>
- Stonier, S. W., Herbert, A. S., Kuehne, A. I., Sobarzo, A., Habibulin, P., Dahan, C. V. A., James, R. M., Egesa, M., Cose, S., Lutwama, J. J., Lobel, L., & Dye, J. M. (2017). Marburg virus survivor immune responses are Th1 skewed with limited neutralizing antibody responses. *The Journal of Experimental Medicine*, 214(9), 2563–2572. <https://doi.org/10.1084/jem.20170161>
- ter Meulen, J., Badusche, M., Kuhnt, K., Doetze, A., Satoguina, J., Marti, T., Loeliger, C., Koulemou, K., Koivogui, L., Schmitz, H., Fleischer, B., & Hoerauf, A. (2000). Characterization of human CD4(+) T-cell clones recognizing conserved and variable epitopes of the Lassa virus nucleoprotein. *Journal of Virology*, 74(5), 2186–2192. <https://doi.org/10.1128/jvi.74.5.2186-2192.2000>
- Wan, X., Wisskirchen, K., Jin, T., Yang, L., Wang, X., Wu, X., Liu, F., Wu, Y., Ma, C., Pang, Y., Li, Q., Zhang, K., Protzer, U., & Du, S. (2024). Genetically-modified, redirected T cells target hepatitis B surface antigen-positive hepatocytes and hepatocellular carcinoma lesions in a clinical setting. *Clinical and Molecular Hepatology*, 30(4), 735–755. <https://doi.org/10.3350/cmh.2024.0058>
- Weiskopf, D., Angelo, M. A., De Azeredo, E. L., Sidney, J., Greenbaum, J. A., Fernando, A. N., Broadwater, A., Kolla, R. V., De Silva, A. D., De Silva, A. M., Mattia, K. A., Doranz, B. J., Grey, H. M., Shrestha, S., Peters, B., & Sette, A. (2013). Comprehensive analysis of dengue virus-specific responses supports an HLA-linked protective role for CD8⁺ T cells. *Proceedings of the National Academy of Sciences*, 110(22), 11022–11027. <https://doi.org/10.1073/pnas.1305227110>
- Wu, X., Quan, D., Li, W., Wisskirchen, K., Wu, W., Zhou, Y., Liu, Y.-P., Wan, X., Wang, X., Zhang, X., Yang, L., Zheng, M., Zhang, K., Protzer, U., Du, S., & Qu, X. (2025). Clinical results of an HBV-specific T-cell receptor-T-cell therapy (SCG101) in patients with HBV-related hepatocellular carcinoma treated in an investigator-initiated, interventional trial. *Gut*, 75(1), 147–160. <https://doi.org/10.1136/gutjnl-2025-335456>
- Xu, W., Watts, D. M., Costanzo, M. C., Tang, X., Venegas, L. A., Jiao, F., Sette, A., Sidney, J., Sewell, A. K., Wooldridge, L., Makino, S., Morrill, J. C., Peters, C. J., & Kan-Mitchell, J. (2013). The nucleocapsid protein of Rift Valley fever virus is a potent human CD8⁺ T cell antigen and elicits memory responses. *PloS One*, 8(3), e59210. <https://doi.org/10.1371/journal.pone.0059210>