Clinical & Translational Immunology

Australian and New Zealand Society for Immunology Inc.

Clinical & Translational Immunology 2019; e1069. doi: 10.1002/cti2.1069
www.wileyonlinelibrary.com/journal/cti

SPECIAL FEATURE REVIEW

γδ T-cell responses during HIV infection and antiretroviral therapy

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Received 9 April 2019;
Revised 27 June 2019;
Accepted 28 June 2019

doi: 10.1002/cti2.1069

Clinical & Translational Immunology
2019; **8**: e1069

Abstract

HIV infection is associated with a rapid and sustained inversion of the Vδ1:Vδ2 T-cell ratio in peripheral blood. Studies of antiretroviral therapy (ART)-treated cohorts suggest that ART is insufficient to reconstitute either the frequency or function of the γδ T-cell subset. Recent advances are now beginning to shed light on the relationship between microbial translocation, chronic inflammation, immune ageing and γδ T-cell immunology. Here, we review the impact of acute, chronic untreated and treated HIV infection on circulating and mucosal γδ T-cell subsets and highlight novel approaches to harness γδ T cells as components of anti-HIV immunotherapy.

Keywords: γδ, gut, HIV, SIV, Vδ1, Vδ2

INTRODUCTION

γδ T cells are a subset of T cells that express a distinct T-cell receptor (TCR) consisting of a γ and a δ-chain. This allows γδ T cells to respond rapidly to nonpeptide antigens without the requirement of MHC presentation. In humans, γδ T cells have a relatively restricted repertoire of V gene segments and the most commonly used Vδ gene segments are Vδ1, Vδ2 and Vδ3. Human Vδ1 T cells predominantly reside in tissue and can make up to 40% of the intraepithelial lymphocytes (IEL) in the gut epithelia.[1] Vδ1 T cells are also distributed in other tissues including dermis, spleen and liver, where they are involved in sustaining homeostasis and maintaining epithelial tissue integrity.[2] Although Vδ1 T cells are also present in peripheral blood, Vδ2 T cells constitute the majority of human blood γδ T cells[3] where they almost exclusively associate with the Vγ9 chain. Unlike Vδ1 T cells, which typically recognise CD1c and CD1d via the TCR, the Vγ9Vδ2 T cells recognise intermediate metabolites from the isoprenoid biosynthesis pathway, such as the host molecule isopentenyl pyrophosphate (IPP) or the pathogen-associated molecule (E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMBPP).[4–8] These phosphoantigens bind the protein BTN3A1, triggering an 'inside-out' conformational change that promotes BTN3A1 binding to the Vγ9Vδ2 TCR and subsequent T-cell activation.[9] Human Vδ3 T cells have also been reported to recognise CD1d, but are usually only present in peripheral blood at low frequencies.[10] However, they have been observed to expand in the blood in patients with cytomegalovirus infection, CD4 T-cell deficiency and B-cell leukaemia.[11–15]

HIV-1 (herein referred to as HIV) infection still remains one of the most challenging health issues worldwide. In 2017, an estimated 36.9 million people

were currently infected with the virus of which 1.8 million were children under the age of 15. Despite increasing awareness of the disease and improved access to antiretroviral therapy (ART), approximately 5000 individuals become newly infected every day.[16] In addition to infecting and depleting $CD4^+$ T cells, HIV infection also has a wide overall effect on the immune system, mediated largely by the phenomenon of microbial translocation.[17] Rapid replication of HIV in gut-associated lymphoid tissue (GALT) results in substantial damage to the gut epithelial barrier and the subsequent translocation of microbial products such as LPS into the circulation.[18] This results in chronic immune activation and, consequently, dysfunction of conventional, bystander αβT cells. Upregulation of HLA-DR and CD38 by T cells is associated with chronic immune activation and has proven to be strong predictors of disease progression.[19–22] Additionally, markers such as PD-1, CD57 and CD100 have been used to define terminally differentiated, exhausted or dysfunctional T cells[23–27] and are now the target of immunotherapies aimed at reducing T-cell exhaustion.[28]

While HIV is well known to impact the function and distribution of conventional T-cell subsets, the impact of the disease on γδ T-cell subsets has been an ongoing subject of research since the late 1980s.[29] Multiple reports have since described an inversion of the typical Vδ2:Vδ1 T-cell ratio in the peripheral blood of HIV-infected/AIDS patients,[30–33] which was quickly determined to represent an increase in Vδ1 T-cell frequency[30,32–44] and a depletion of Vδ2Vγ9 T cells.[31–33,35,38,41–48] Subsequent investigations have focused on the mechanisms behind this expansion/depletion, as well as the relationship of γδ T subsets to HIV disease progression. Here, we focus on reviewing the effect of HIV infection and antiretroviral therapy on Vδ1 and Vδ2 T-cell subsets, with a primary emphasis on observations obtained from human cohorts (summarised in Figure 1). Approaches to rescue and harness γδ T-cell responses as a means of anti-HIV immunotherapy are discussed, as well as the future directions of this rapidly evolving field.

PROGRESSIVE HIV-1 INFECTION

Peripheral Vδ2Vγ9 T cells

Loss of Vδ2 T cells during untreated HIV disease correlates strongly with CD4 count and viral load and occurs quickly after infection.[46] Depletion preferentially affects Vδ2 cells with a Vγ9-Jγ1.2 TCR rearrangement[49] associated with the major circulating phosphoantigen-reactive $V\gamma9^+$ $V\delta2^+$ cell population.[50] Given early reports that Vδ2 T cells lacked expression of CD4[51] and were resistant to direct HIV infection,[52] there has been a strong emphasis on determining the mechanism of peripheral depletion, albeit with little consensus. Li and Pauza presented evidence implicating the HIV gp120 binding proteins α4β7 and CCR5 in mediating Vδ2 depletion in viremic patients.[53] gp120-induced cross-linking of CCR5 and α4β7 on $CD4^-$ Vδ2 T cells results in the activation of the p38 caspase pathway and eventual apoptosis, without productive infection of the cell. To date, this mechanism remains to be confirmed, but analysis of existing data from preclinical studies of α4β7 monoclonal antibody (mAb) blockade[54–56] may provide interesting insights into this phenomenon. An alternative hypothesis suggests that microbial translocation associated with acute HIV infection could drive Vδ2 T-cell activation and apoptosis. Analysis of a cohort of 79 acutely infected men suggested, however, that there is no relationship between biomarkers of microbial translocation and Vδ2 frequency.[32] While two studies have reported a correlation between microbial translocation and bulk γδ T-cell activation, it is unclear whether this relationship reflects activation of the Vδ1 or Vδ2 population, or simply the change in Vδ1:Vδ2 ratio.[32,33]

Vδ2 depletion is also associated with a reduction of antigen-induced IFNγ[46]/TNFα[57]/TGF-β[47] production and proliferative/cytotoxic capacity[48,58,59] in the residual Vδ2 population. Changes in Vδ2 cytokine production may be related in part to the relative expansion of terminally differentiated memory (T_{EMRA}) cells and loss of the central memory (T_{CM}) subset during chronic infection.[32,33,47] Although all Vδ2 memory subsets exhibit significant increases in activation during acute and chronic HIV infection,[33,47] T_{EMRA} cells tend to exhibit the highest levels of activation as measured by CD38 expression.[33] However, no studies have conclusively demonstrated a causal relationship between memory differentiation or activation and loss of antigen-induced cytokine responses in HIV.

Interesting data regarding the relationship between HIV viremia and Vδ2 T cells come from a study of structured treatment interruption (STI), where participants receiving antiretroviral therapy (ART) ceased treatment for 4–6 weeks. Within the

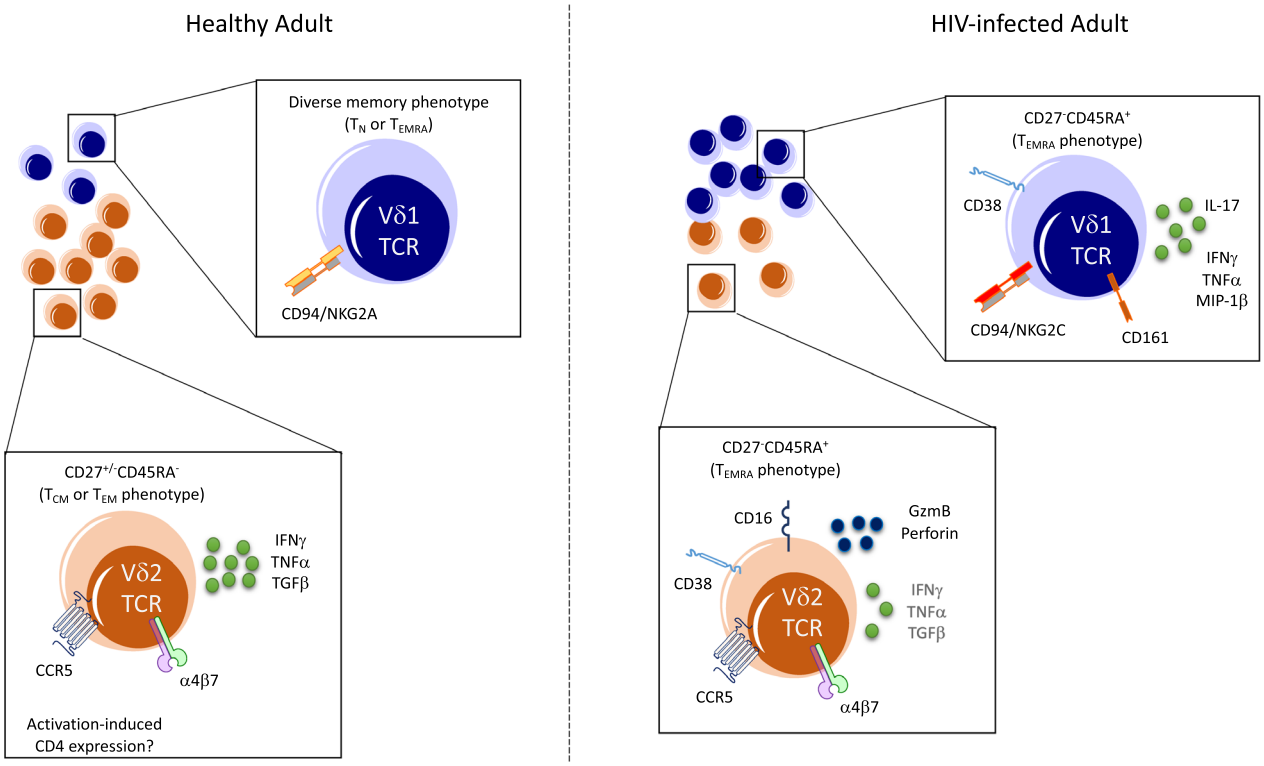

Figure 1. Circulating γδ T-cell subsets in healthy and HIV-infected adults. In healthy individuals, Vδ2 T cells (orange) comprise the majority of the circulating γδ population, with only a minority of cells expressing a Vδ1 TCR (blue). The predominant memory phenotype, surface receptor expression and functional profile of each subset are indicated for healthy (left) and HIV-infected (right) individuals.

first month following viral rebound, the Vδ2 compartment lost nearly all capacity for IFNγ production in response to antigen stimulation.[60] While slower, Vδ2 T-cell counts and the frequency of TCM cells both declined by the end of the STI. All perturbations in the Vδ2 population were restored within a month of resumption of ART, demonstrating the rapid and reversible nature of the Vδ2 response to viremia.[60] Although a mechanistic explanation of this relationship is still lacking, it is possible that Vδ2 T-cell anergy is induced by productive HIV infection of DCs, which can inhibit Vδ2 responses to phosphoantigen *in vitro*[61] in a contact-dependent manner.[62]

Peripheral Vδ1 T cells

The destructive impact of HIV infection on Vδ2 T cells stands in direct contrast to the observed expansion of peripheral Vδ1 T cells,[32,36–38] which occurs rapidly during acute infection (and prior to HIV seroconversion[38]). Several studies have confirmed that the relative enrichment of Vδ1 cells as a proportion of the total γδ T-cell population is also reflected as an increase in absolute Vδ1[33,38] (or Vδ2-[47]) T-cell count in the periphery. Similar to Vδ2 cells, Vδ1 cells are significantly more activated in HIV-infected subjects compared with controls.[37,40,47] In acute, chronic and naturally controlled infection, the majority of Vδ1 cells exhibit a T_{EMRA} phenotype,[37,40,41,44] which correlates with absolute Vδ1 T-cell counts[47] and is suggestive of antigen-driven proliferation and activation.[41] However, observations that Vδ1 T-cell frequency is increased even in elite or viremic controllers (with low or undetectable viral loads)[40,44] suggest that HIV replication itself does not drive this expansion. Rather, Vδ1 expansion may be linked to microbial translocation, as nonhuman primate models have shown a correlation between lymph node *Eschericia coli* levels and peripheral Vδ1 frequency.[63] Another potential mechanism for the accumulation of peripheral Vδ1 cells lies in the ability of Tat peptides to block Vδ1 chemotaxis,[36] which may reduce Vδ1 cell recruitment from the periphery to mucosal sites, a phenomenon which is supported by some evidence from nonhuman

primates (NHPs).[64] Notably, however, evidence exists for the simultaneous accumulation of Vδ1 cells in both the periphery and gut mucosa in humans,[38,65] as well as the periphery and multiple tissues in NHP models,[63] implying that the mechanisms underlying Vδ1 expansion are likely multifactorial.

Recently, studies have begun to assess comprehensively Vδ1 phenotype and function during HIV infection. Fenoglio and colleagues demonstrated that expanded Vδ1 cells in HIV-infected subjects respond to *Candida albicans* stimulation and coexpress IFNγ and IL-17. This is associated with TBX21 (Tbet), RORC, CD161, CCR4 and CCR6 expression.[66] Interestingly, a substantial proportion (mean ~40%) of Vδ1 cells from this HIV-infected cohort expressed IFNγ directly *ex vivo*, suggesting that circulating Vδ1 cells exist in a highly activated state. These data are consistent with those of Olson *et al.*,[40] which demonstrated a 15-fold elevation in mitogen-induced IFNγ + TNFα + MIP-1β+ 'proinflammatory' Vδ1 cells in viremic HIV-infected subjects. Further characterisation of the reactivity of the expanded Vδ1 cells will be required, however, as Olson *et al.* failed to identify any IL-17 production or *Candida albicans* reactivity by the Vδ1 subset, in direct contrast to the results of Fenoglio *et al.* Furthermore, a study in SIV-infected NHPs found that Vδ1 cells did express low levels of IL-17 in response to mitogen, but that IL-17 production was significantly reduced in SIV^+ animals compared with controls.[63] Differences in antigen reactivity and IL-17 production may be related to the duration of stimulation and cell culture, particularly in the case of *Candida*, but will need to be resolved in future studies.

In addition to cytokine production, clinically relevant characteristics of Vδ1 cells include the expression of NK cell receptors (NKR) and the capacity to mediate cellular cytotoxicity of HIV-infected target and bystander cells.[43,67] Assessment of NKG2A and NKG2C expression, which initiates inhibitory or activating signals in response to HLA-E binding, respectively, demonstrated that Vδ1 cells from HIV-infected subjects progressively lose NKG2A expression and acquire NKG2C.[43] *In vitro*, these $NKG2C^+$ Vδ1 cells can recognise and kill HIV-infected $CD4^+$ T cells.[43] The modulation of CD94, NKG2A and NKG2C on Vδ1 cells in HIV has interesting implications for the regulation of Vδ1 cell function. Studies of NK cells have shown that the $NKG2A^+$ NK cell subset contains the highest frequency of NK cells capable of recognising autologous HIV-infected $CD4^+$ T cells,[68] possibly due to HLA-E presentation of a capsid-derived peptide that blocks NKG2A inhibitory signalling.[69] Conversely, elevation of HLA-A, and subsequently HLA-E, expression during infection is associated with poor immunological control of HIV, which is speculated to occur due to NKG2A-mediated inhibition of NK cell function.[70] Blockade of NKG2A *in vitro* suggests that Vδ1 cells, unlike NK cells, might be relatively resistant to NKG2A-mediated inhibitory signalling.[43] The role for $CD94/NKG2A^+$ Vδ1 cells to control HIV replication or to be inhibited by HLA-E expression during disease therefore remains to be determined.

Mucosal γδ T-cell subsets

While studies of peripheral blood samples provide important insights into γδ T-cell biology, Vδ1 cells are naturally enriched in the same mucosal tissues that support HIV replication (i.e. the gut mucosa[38,41] and female reproductive tract[42]). Numbers (and frequency) of duodenal γδ T cells (mostly $V\delta1^+$) are significantly increased among HIV-infected subjects compared with controls.[65] This was confirmed by a detailed study from Poles and colleagues, who compared Vδ1 and Vδ2 subset frequencies in the peripheral blood and rectal mucosa of healthy and HIV-infected participants.[38] γδ T-cell dynamics in the gut reflected those of the peripheral blood, with significant increases in Vδ1 and decreases in Vδ2 frequency during infection. Despite the parallel dynamics of the γδ T-cell populations at these two site, analysis of CDR3 length showed little overlap between the two anatomical sites for either Vδ1 or Vδ2 subsets, as well as evidence of private, polyclonal expansions.[38] In contrast to these results, a study of 15 acutely and 14 chronically infected participants found a significant loss of Vδ1 cells in the duodenum during chronic infection, with no change in Vδ2 frequency.[41] Duodenal Vδ1 cells of chronically-infected participants exhibited an increase in T_{EMRA} differentiation compared with controls, although mucosal Vδ1 cells were predominately T_{EM} phenotype, which is distinct from the peripheral blood. Beyond differences in anatomical sampling location (duodenum versus rectum), there are limited data available to explain the discrepancies in these studies.

To date, only one study has assessed the impact of HIV infection on γδ T cells at the female reproductive tract and involved mostly participants receiving ART. In this group, HIV infection was associated with a significant reduction in both Vδ1 and Vδ2 frequencies at the endocervix,[42] but memory distribution, NKR expression or function was not assessed.

IMPACT OF ART ON γδ T-CELL POPULATIONS

Vδ2 T cells

Numerous studies have assessed Vδ1 and Vδ2 T-cell frequencies in ART-treated cohorts, although substantially fewer have provided more comprehensive data regarding phenotype and function. Both cross-sectional and longitudinal cohort studies find that ART fails to restore normal frequencies or numbers of Vδ2 T cells.[32,33,38,71–73] This observation is corroborated by evidence that ART only partially restores the depletion of Jγ1.2 TCR repertoire, with almost no subjects exhibiting a typical frequency of Jγ1.2 chains within the Vδ2 subset[49,73–75] and few intraparticipant changes in a longitudinal study.[76] Phenotypically, more studies report residual activation of the Vδ2 subset during ART compared with healthy controls[33,71] than normalisation of activation.[47] Data on memory subset distribution is more controversial, with some evidence that the expanded TEMRA population persists during ART,[71,73] while other studies show a reduction in TEMRA frequencies that closely resemble uninfected controls.[32,33,47] Functionally, the majority of evidence suggests that Vδ2 cytokine production,[47,57,71,72] GzmB expression/cytotoxicity[73] and proliferative capacity[75] remain compromised during ART, with only a single study showing a beneficial impact of ART on Vδ2 proliferation and TNFα secretion.[59]

Vδ1 T cells

Cross-sectional data support the maintenance of an expanded Vδ1 cell population during viral suppression,[32,33,38,40,47,57,71] an observation that was also confirmed in the longitudinal follow-up of 8 subjects from the day of ART initiation through day 540 on therapy.[38] At mucosal sites, the population of expanded γδ T cells is maintained during ART,[77] with only modest normalisation in some individuals.[38] The peripheral Vδ1 subset in ART cohorts retains the T_{EMRA} phenotype associated with untreated infection[40,47] and is reported to express elevated levels of PD-1 compared with healthy controls.[71] Whether ART reduces Vδ1 activation is unresolved,[47,71] but evidence suggests ongoing Vδ1 proliferation during viral suppression[47] and the maintenance of a large proinflammatory IFNγ + TNFα + MIP-1β+ polyfunctional population.[40] A single study of NKR expression reported elevated levels of CD94/NKG2A, CD158a, CD158b and NKB1 on Vδ1 cells compared with healthy controls,[78] which was accompanied by a loss of CD28 expression and an upregulation of CD45RO.[78]

MICROBIAL TRANSLOCATION, IMMUNE ACTIVATION AND APOPTOSIS

The relationship between microbial translocation, systemic immune activation and perturbations of γδ T-cell subsets has been a common and enduring thread throughout the studies described above. Microbial translocation occurs as a result of the massive depletion of $CD4^+$ T cells at the gut mucosa during acute HIV or SIV infection.[79,80] This includes the preferential loss of Th17 cells,[81] which contribute to the maintenance of epithelial barrier integrity and wound healing in the gastrointestinal mucosa. The dysregulation of mucosal immunity and loss of epithelial integrity allow the translocation of microbial products such as LPS into the circulation, resulting in systemic immune activation and inflammation[17] (recently reviewed in References 80 and 82). Unfortunately, suppressive ART is unable to fully restore the mucosal $CD4^+$ T-cell compartment and abolish systemic inflammation.[80]

The disruption of mucosal immunity not only allows microbial products to translocate into the circulation, but also alters the composition of the gut microbiota. A number of human cohort studies have consistently shown an enrichment of proinflammatory bacteria such as the *Enterobacteriaceae* family and a loss of clades such as *Bacteriodes.*[80] *Enterobacteriaceae* are particularly likely to translocate across the mucosal barrier and induce the production of reactive oxygen species by innate immune cells, driving inflammation. At least one member of this family, *E. coli*, activates Vδ2 T cells *in vitro*, raising the possibility that sustained exposure to

translocated microbes could drive apoptosis of γδ T cells, similar to the apoptosis of bystander CD4+ in the lamina propria that occurs by Fas-FasL interactions.[79] While the impact of microbiome perturbations on the gut-resident Vδ1 T-cell population remains to be understood, data have shown a correlation between iNKT cells in the gut mucosa and the prevalence of *Bacteroides* and *Prevotella* microbes.[83] Thus, γδ T cells may be directly impacted by changes in the microbial community at the gut mucosa, the translocation of proinflammatory products into the circulation, or dysregulation of innate and adaptive immune cells during both untreated and treated HIV infection.

CLINICAL IMPACT OF γδ T-CELL PERTURBATIONS DURING HIV INFECTION

Contribution to HIV control

Whether γδ T-cell activation and cytolytic capacity during HIV infection can actually contribute to control of viremia or disease progression remains an open question. γδ cells can undoubtedly control HIV replication through multiple mechanisms *in vitro*, including direct cytotoxicity of infected cells.[43,84] Vδ2 T cells can be recruited to HIV-infected DCs via CCL4 production, where they control viral replication and reduce HIV transmission to bystander CD4+ T cells.[61] β-Chemokine production by both Vδ1[85] and Vδ2[86] cells can block HIV infection of target cells. However, whether this *in vitro* activity translates into *in vivo* control of viremia remains unresolved. Although HIV elite/viral controllers exhibit Vδ2 depletion relative to healthy controls, they maintain Vδ2 frequencies that are significantly higher than either untreated or ART-treated subjects.[44,87] These cells predominately exhibit a T_{CM} phenotype[87] and produce more IL-17 than cells from viremic patients.[44] Unfortunately, such studies are confounded by an inability to determine whether viral control preserves γδ T-cell ratios and phenotypes, or whether maintenance of a T_{CM}/IL-17-expressing Vδ2 population contributes to the control of viral replication. Nonhuman primates offer a unique opportunity to longitudinally compare preinfection γδ populations to infection susceptibility and viral load setpoint. Although Tuero *et al.*[88] reported an inverse correlation between endocervical Vδ2 T-cell frequency and chronic viral load (VL) in SIV-infected macaques, supporting a potential protective role for γδ T cells in this animal model, these studies are still lacking in the literature and this should be further investigated in future studies.

Impact on coinfection

While suppressive ART successfully controls HIV replication regardless of γδ T-cell reconstitution, residual impairment of the Vδ2 subset likely has profound implications for immunity against a number HIV coinfections. Tuberculosis is currently the leading cause of death among HIV-infected individuals, and evidence suggests that active TB and HIV infection have additive effects on peripheral Vδ2 depletion[89] and dysfunction.[90] At the site of TB infection, however, it is unclear what impact HIV has on lung γδ T-cell populations. Only a single study has reported BAL γδ T-cell numbers in healthy and HIV-infected participants where there was a significant increase in total γδ cells during HIV infection, but the delta chain usage was not determined.[91] However, the possible impact of HIV infection on Vδ2 responses to *Mycobacterium* has been clearly demonstrated in NHP models. Naïve macaques are able to induce robust primary and recall Vδ2 responses to BCG vaccination in the periphery and lung, while SIV-infected macaques showed no response to BCG in either site.[92] Encouragingly, administration of ART improved NHP Vδ2 responses to BCG, possibly due to reconstitution of Mtb-specific CD4+ T cells.[93] NHP studies will be critical in determining whether host-directed therapy targeting Vδ2 T cells[94] can enhance protection against TB reactivation in HIV-infected populations.

Similarly, the expansion of Vδ1 cells during HIV infection may impact coinfection with several herpesviruses. Cytomegalovirus (CMV) infection is a widespread pathogen that usually causes asymptomatic infections. However, in HIV-infected individuals, this pathogen can result in clinical manifestations including chorioretinitis and CMV enterocolitis. Similar to HIV infection, there is a selective expansion of $V\delta2^-$ cells during CMV infection.[95] These cells are suggested to participate in the control of CMV replication and display potent anti-CMV responses *in vitro.*[12] Although the expansion of Vδ1 cells as a result of HIV infection would presumably be beneficial for

control of CMV infection, CMV replication is enhanced by inflammatory stimuli. Since it is reported that the functional characteristics of the expanded Vδ1 cells in HIV$^+$ individuals are skewed towards a proinflammatory profile, this may instead contribute to CMV-associated morbidity, although this remains to be determined.[96–99] Furthermore, it is unclear whether the high prevalence of CMV infection among HIV$^+$ individuals is a driver of the Vδ1 T-cell expansion observed during chronic infection.

Human herpesvirus 8 (HHV8) is also a virus which has increased seroprevalence in HIV-infected individuals and can cause significant disease in the form of Kaposi's sarcoma (KS).[100] Although the effector populations involved in control of this virus remain elusive, HHV8 infection is also associated with an expansion of Vδ1 cells that respond to HHV8-infected cells and prevent virus release in immunocompetent hosts.[101] The role γδ T cells play in promoting HHV-8 to progress to KS is currently unknown, but considering that inflammatory cytokines including IFN-γ, IL-6, IL-1β and TNF-α are produced by infiltrating cells in lesions of KS, expanded Vδ1 cells in HIV$^+$ individuals may potentially contribute to progression of clinical symptoms in a similar way as with CMV.[102]

Other common coinfections among HIV-infected populations include *Cryptococcus*, viral hepatitis and malaria. There are little data available regarding γδ T-cell responses to *Cryptococcus* infection in HIV-infected human cohorts, but murine studies have established a role for γδ T cells in Cryptococcal immunity in the lung.[103,104] Hepatitis B and C infections have a deleterious impact on γδ T cells, similar to HIV infection, which is discussed more fully below. Studies in malaria-endemic populations have revealed a substantial role for γδ T cells in immunity to *Plasmodium* spp. This topic has been recently reviewed in References 105 and 106, which highlight the protective and immunoregulatory roles of both Vδ2 and Vδ1 γδ subsets. Surprisingly, however, there are no studies of HIV/malaria coinfection that report on γδ T cells, which would represent an interesting focus for future clinical cohorts.

Impact on immune cell crosstalk

γδ T cells can not only exert direct antimicrobial activity, but can also orchestrate and regulate the activation, maturation and recruitment of a variety of other immune cells.[107,108] Activated Vδ2 cells from healthy individuals can induce the maturation of neutrophils,[109] DCs and B cells into APCs.[110] Some evidence that this function is compromised during HIV infection, as HIV-infected APCs cannot undergo full γδ T cell-induced maturation *in vitro*, leading to high-residual CCR5 expression and low CD86 and HLA-DR expression.[62] This impairment of crosstalk may enhance DC susceptibility to infection through CCR5 expression, as well as compromise CD4$^+$ T-cell responses that rely on DC-mediated antigen presentation. To date, however, follow-up on these observations is lacking. Additionally, Vδ2 cells can themselves present antigen and act as APCs for conventional αβ T cells.[111] Antigen-activated Vδ2 cells express HLA-DR, CD80, CD86, CD40 and CD54 at levels comparable to LPS-matured DCs and can induce primary αβ T-cell responses.[111] Transient activation-induced upregulation of CCR7 implies that Vδ2 may home to draining lymph nodes during infection initiate adaptive immune responses. Considering the residual depletion, terminal differentiation and dysfunction that characterise Vδ2 cells in ART-treated subjects, it is likely that acquisition of APC function following antigen stimulation is compromised in the context of HIV infection. The contribution of such dysfunction to poor antimicrobial immunity or vaccination in ART-treated subjects should be further explored, as *in vivo* Vδ2 immunotherapy could be considered to address these defects in immune function.

More recently, Vδ2 cells have been recognised to provide CD40L-dependent help to B cells.[112–116] As noted above, the transient expression of CCR7 after activation allows Vδ2 cells to traffic to secondary lymphoid tissues, where they cluster within the germinal centre of mucosal B-cell follicles.[116] Stimulation with the phosphoantigen IPP is sufficient to elicit the delayed but robust expression of surface molecules involved in B-cell help; 36–84 h poststimulation, Vδ2 T cells express CD40L, ICOS, OX-40 and CD70.[116] *In vitro* coculture assays indicate that activated Vδ2 cells can promote B-cell antibody secretion to a similar, or even increased, degree as T_{FH} cells.[116] Further studies have suggested that antigen exposure in the presence of IL-21 is required to induce the expression of CD40L and ICOS on circulating Vδ2 cells.[113,114] Interestingly, treatment of macaques with intravenous HMBPP and IL-2 during chronic

Table 1. Summary of HIV immunotherapy studies using Vδ2 T cells

Outcome	Study	Species	HIV Status	Cell Type	Results
Antigen responses	Murday *et al.*[116]	Human	HIV$^+$ ART	*Ex vivo* Vδ2	IL-18 stimulation improves IPP-induced Vδ2 proliferation in HIV$^+$ individuals
	Cardone *et al.*[61]	Human	Healthy	*Ex vivo* Vδ2 and HIV-infected monocyte-derived DC	Vδ2 cell phosphoantigen responses in the presence of HIV-infected DC are inhibited due to poor IL-12 secretion by the DCs. Responses can be restored by addition of IL-12 to Vδ2/DC cocultures
ADCC	He *et al.*[117]	Human	HIV$^+$ ART	*Ex vivo* Vδ2	Vδ2 cells from ART-treated individuals exhibit CD16 expression and degranulate in response to CD16-mediated activation
	Poonia *et al.*[118]	Human	Healthy, HIV$^+$ ART	IPP/zoledronate + IL-2 expanded PBMC	Expanded Vδ2 cells expressed CD16 and were capable of killing antibody-coated target cells
Direct cytotoxicity	Poonia *et al.*[118]	Human	Healthy, HIV$^+$ ART	IPP/zoledronate + IL-2 expanded PBMC	Vδ2 cells exhibited direct cytotoxicity against Daudi cells. IPP-expanded cells were more potent killers than zoledronate-expanded cells
	Garrido *et al.*[119]	Human	HIV$^+$ ART	Bisphosphonate pamidronate (PAM) + IL-2 expanded PBMC	PAM-expanded cells degranulated and inhibited *in vitro* HIV replication in CD4$^+$ T cells. p24 production following vorinostat-mediated reactivation of latent HIV from primary CD4$^+$ T cells was suppressed in the presence of PAM-expanded Vδ2 cells
In vivo expansion	Ali *et al.*[120]	Macaque	SHIV-infected (acute or chronic)	Injection of HMBPP + IL-2 *in vivo*	Treatment resulted in expansion and activation of Vδ2 cells. Treatment during acute infection exacerbated viral replication and disease progression in an IL-2-dependent manner. Treatment during chronic infection boosted Env-specific antibody titres but did not impact viral load or disease progression
	Poonia *et al.*[121]	Humanised mice	HIV$^+$	Adoptive transfer of zoledronate + IL-2 expanded PBMC	No impact of expanded Vδ2 T-cell transfer on CD4$^+$ T-cell loss, CD4:CD8 T-cell ratio or viral load

SHIV infection resulted a prolonged boosting of SHIVenv-specific antibody titres, suggesting that Vδ2 cells can contribute to humoral immunity *in vivo*. Despite these fascinating observations, further data regarding the impact of Vδ2 depletion on humoral immunity during HIV infection are lacking.

γδ T CELLS IN ANTI-HIV IMMUNOTHERAPY

Interest is increasing in developing host-directed immunotherapies to either supplement or replace current ART. Studies which have investigated the use of Vδ2 cells for anti-HIV immunotherapy are summarised in Table 1. At the simplest level, methods for recovering Vδ2 responses to phosphoantigen among HIV-infected donors include cytokine supplementation with IL-18[117] or IL-12.[61] Such an approach may improve Vδ2-mediated immune responses against *Mycobacterium* or other bacterial infections. More complex interventions designed to specifically target HIV-infected cells include an effort to harness the ability of Vδ2 T cells to perform antibody-dependent cellular cytotoxicity (ADCC) via CD16 expression. CD16$^+$ Vδ2 cells exhibit poor responses to phosphoantigen, but respond robustly to antibody-coated target cells.[118] These responses are largely maintained, if not slightly enhanced, in ART-treated subjects, suggesting that Vδ2 cells derived from HIV-infected individuals could contribute to the killing of HIV-infected target cells.[118] More encouragingly, *ex vivo* expansion of Vδ2 cells from HIV-infected subjects results in an upregulation of CD16 expression and quantifiable ADCC of antibody-coated targets.[119]

Any immunotherapy-based intervention using autologous Vδ2 cells will require *in vitro* expansion to generate sufficiently large numbers of cells for reinfusion. *Ex vivo* antigen-driven Vδ2

T-cell expansion appears to be a viable and reproducible strategy for the production of large numbers of autologous Vδ2 cells from ART-treated HIV-infected individuals, although optimal expansion culture conditions may differ between healthy and infected groups.[120] Expanded cells express low levels of inhibitory surface receptors and can kill latently infected $CD4^+$ T cells after latency reversal with vorinostat *in vitro.*[120] *In vivo,* however, results of γδ T-cell immunotherapy are varied. Administration of HMBPP and IL-2 to chronically SIV-infected macaques expanded and activated Vδ2 T cells, transiently boosted SHIV-specific $CD8^+$ T-cell responses and resulted in a sustained increase of SHIV-specific antibody titres.[121] Nonetheless, there was no impact of Vδ2 expansion on viral load or disease progression during chronic infection, and a negative impact of Vδ2 expansion during acute infection. These results were mirrored in a study of humanised mice treated with expanded Vδ2 cells, which similarly observed no protective effect of Vδ2 treatment on viral replication or $CD4^+$ T-cell depletion.[122]

SIMILARITIES WITH OTHER CHRONIC INFLAMMATORY DISEASES

The hallmark impacts of HIV infection on γδ T cells (Vδ2:Vδ1 ratio inversion, activation and terminal differentiation, functional defects) are, in fact, not unique to HIV infection itself. Other chronic inflammatory diseases are associated with similar effects, including kidney disease, viral hepatitis and obesity. Understanding the commonalities in pathogenesis between these diverse conditions may provide further insight into the mechanisms of γδ perturbation and identify useful therapeutic targets.

Chronic kidney disease (CKD) is a progressive condition in which the loss of renal function results in the accumulation of uraemic toxins and proinflammatory cytokines (reviewed in Reference 123). End-stage renal disease (ESRD), the final stage of CKD, is associated with high levels of immune activation, poor responses to immunisation and high susceptibility to infection. Matsumoto first reported a significant loss of γδ T cells among CKD patients requiring hemodialysis.[124] They speculated that γδ depletion likely occurred because of Fas- and LFA-1-dependent apoptosis related to uraemia. Similarly, we observed a significant loss of phosphoantigen-reactive γδ T cells in ESRD patients compared with healthy controls.[125] Surprisingly, however, there was no relationship between plasma proinflammatory cytokine levels and γδ frequency or dysfunction,[125] raising the question of what drives γδ T-cell loss during ESRD. Similar to HIV infection, it is unclear whether low peripheral γδ frequencies truly reflect apoptosis or, instead, recruitment to inflamed tissues. γδ frequencies only partially normalise following kidney transplantation, with Vδ2 frequencies remaining significantly lower than healthy controls.[126] The fact that uraemia-associated changes in the γδ repertoire are not effectively reversed upon transplantation suggests that transplant patients may exhibit long-term susceptibility to some infections, similar to HIV ART-treated patients.

Viral hepatitis is also associated with changes in the circulating γδ repertoire that are highly reminiscent of HIV infection. Chronic HCV infection is associated with peripheral Vδ2 depletion,[127,128] acquisition of an activated/T_{EMRA} phenotype,[128,129] upregulation of CD16 and granzyme[129] and functional impairment.[128,129] HBV-infected subjects exhibit loss of peripheral Vδ2 cells[130,131] and/or expansion of peripheral Vδ1 cells,[132] which correlates with serum ALT levels.[130,131] Residual Vδ2 cells from these individuals are impaired for IFNγ production, cytotoxicity[130] and proliferation[131] and exhibit an activated, TEMRA surface phenotype.[131] Expression of granzyme and cytotoxic markers is particularly enhanced in HCV-infected subjects with greater degrees of liver damage, suggesting the potential involvement of γδ T cells in mediating immunopathology during infection. Despite this, phosphoantigen-activated Vδ2 cells can restrict *in vitro* HCV replication in an IFNγ-dependent manner,[133] making them potential immunotherapeutic targets for HCV treatment. *In vitro s*tudies suggested that Vδ2 dysfunction may be at least partially abrogated by treatment with IFNα, which boosts phosphoantigen responses in γδ T cells from both healthy and HCV-infected subjects[128] (although this effect was not replicated by others[129]). *In vivo*, however, a standard course of Peg-IFNα and ribavirin therapy resulted in pronounced Vδ2 anergy after 4 weeks of treatment in two studies of chronically HCV-infected patients.[129,134] Notably, although Vδ2 IFNγ responses were decreased/almost absent after treatment, perforin and degranulation responses were elevated, suggesting the

possibility that IFNα drives a transition of Vδ2 cells away from cytokine responses and towards cytotoxicity.[129] The results of these clinical trials highlight important considerations for the *in vivo* use of drugs to promote Vδ2 activation and proliferation during treated HIV infection, and the need to assess anergy at multiple timepoints after therapy.

Similar to CKD patients, obese adults exhibit increased susceptibility to infection associated with chronic inflammation.[135,136] Peripheral Vδ2 T cells are depleted in obese individuals (in a BMI-dependent manner),[137,138] are more likely to exhibit a T_{EMRA} phenotype and respond poorly to influenza-infected APCs,[138] mirroring the effects of HIV infection, HBV/HCV infection and renal disease on this compartment. As expected, cytokine supplementation overcomes some of the Vδ2 function defect, with IL-2 boosting *in vitro* Vδ2 function among obese subjects.[138]

Interestingly, these three conditions, as well as HIV infection, all involve some degree of gut dysbiosis. As previously discussed, HIV infection results in substantial damage to the gut epithelium and microbial translocation, which causes widespread immune activation.[139] Microbial translocation has also been reported in ESRD/CKD cohorts[140–142] and is increasingly being recognised as an important driver of T-cell dysfunction and chronic inflammation.[143,144] Indeed, we found that plasma sCD14 levels in ESRD patients correlate with HMBPP-induced IFNg production by γδ T cells, suggesting a possible link between microbial translocation and Vδ2 T-cell function.[125] Similar observations have been made in the context of chronic HCV/HBV infection and liver cirrhosis, where overgrowth of pathogenic gut bacteria increases gut permeability and allows translocation of bacterial products into the liver via the portal vein.[139,145,146] Finally, obese individuals also exhibit elevated levels of LPS and other markers of microbial translocation, supporting a putative link between gut permeability, low-grade inflammation, and γδ T-cell depletion and dysfunction.[147,148]

UNRESOLVED QUESTIONS AND FUTURE DIRECTIONS

As the field of HIV immunology moves forward from studies of HIV pathogenesis towards a focus on inflammation and immune ageing among ART-treated populations,[149] there are several key questions surrounding γδ T-cell immunology that remain unanswered. First, the link between poor reconstitution of the γδ compartment and persistent innate immune activation and inflammation during ART is poorly understood. In a fascinating study, Belkina *et al.* comprehensively assessed the expression of inhibitory surface receptors on a wide range of lymphocyte subsets including two NK cell populations, conventional T cells, Tregs, iNKT cells and γδT cells in ART-treated and control participants.[150] Importantly, these cohorts were stratified for age, allowing for a simultaneous assessment of immune ageing in each group. Among all lymphocyte subsets, only γδ phenotype was sufficient to distinguish between the control and infected groups. A transition of the γδ compartment from 'resting' $CD160^+$ phenotype to an 'activated/exhausted' TIGIT + PD-1+ phenotype was associated with plasma-derived proinflammatory profile.[150] While an inversion of the Vδ2:Vδ1 ratio was confirmed for a subset of HIV-infected study participants, no data were available to assess the separate contribution of Vδ1 and Vδ2 cells to the HIV-associated inflammation and ageing. Such information will be critical to understanding which γδ subset primarily expressed the TIGIT + PD-1+ phenotype and/or correlates mostly strongly with plasma inflammatory biomarkers. In addition to these data, a transcriptomics study of mitogen-activated lymphocyte responses identified γδ T-cell differentiation as a differentially regulated pathway between healthy control and long-term ART cohorts.[149]

Second, the field will benefit from a better understanding of the composition of the expanded Vδ1 subset in ART cohorts. Vδ1 T cells include CD1-restricted, lipid-reactive T cells, as well as cells with undefined antigen specificity and numerous mechanisms to sense host cell stress. As studies undertake novel approaches to defining Vδ1 T-cell subsets with different functions and phenotypes,[151] we will move closer to understanding what drives the dramatic peripheral expansion and proinflammatory cytokine profile of these cells. It is interesting to note that the phenomena of microbial translocation and gut dysbiosis are common to many chronic inflammatory diseases associated with changes in the Vδ1:Vδ2 T-cell ratio. Recent data from murine models highlight the physiological importance of gut-derived γδ cells and their ability to traffic to inflamed tissues,

including the brain.[152] Whether gut dysbiosis is a predominate driver of γδ dysfunction and accumulation during HIV or other viral infections remains to be fully investigated.

Finally, the question of whether productive HIV infection of Vδ2 T cells occurs *in vivo* remains a matter of debate. Commonly, Vδ2 T cells from healthy individuals are reported to be $CD4^-$ [51,53,75,153,154], ostensibly rendering them impermissible to infection. Surprisingly, however, Wallace *et al.*[58] reported in 1997 that Vδ2 T-cell lines could be productively infected with HIV *in vitro* over the course of 18 days. Similarly, coinfection with human herpesvirus 6 can induce CD4 expression on γδ T cells *in vitro*, rendering them susceptible to HIV infection.[52] Since then, some studies have reported low-level CD4 expression on peripheral γδ T cells *ex vivo,*[155] which is sufficient to mediate CD4-dependent productive HIV infection. Similarly, humanised mice produce thymic γδ T cells that express CD4, CCR5 and CXCR4 and are susceptible to infection by multiple HIV isolates.[156] Perhaps most intriguingly, mucosal Vδ2 T cells at the female reproductive tract are reported to be predominately $CD4^+$.[42] The relevance of Vδ2 T-cell infection by HIV was recently highlighted by data indicating that circulating Vδ2 cells are a reservoir for replication-competent HIV in ART-suppressed patients.[154] In this study, exposure of Vδ2 T cells to IL-2 was sufficient to induce CD4 expression on an average of 15% of isolated Vδ2 cells. Three acutely HIV-infected subjects (<23 days postinfection) also exhibited a similar level of CD4 expression on their Vδ2 T cells, suggesting that immune activation is sufficient to promote productive infection of Vδ2 T cells *in vivo*. What impact this might have on Vδ2-based immunotherapies and latency reactivation-based HIV cure strategies is currently unknown, but should be considered in future studies.

ACKNOWLEDGMENTS

JAJ is funded by a NHMRC fellowship.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

JAJ and EME wrote and revised the manuscript.

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