

Correspondence

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Strengthening universal HIV ‘test-and-treat’ approaches with social science research

The recent publication of new WHO guidelines, including a call for antiretroviral therapy for everyone diagnosed with HIV regardless of CD4⁺ cell count and preexposure prophylaxis for people at substantial risk of HIV infection [1], marks an important moment for taking stock of what will be needed to take biomedical HIV prevention approaches to scale, and sustain them. As the author of a recent editorial in *The Lancet* [2] observes, these guidelines are ‘welcome but ambitious. [...] No studies exist that address how such a strategy can be executed on a global scale’ (p. 1420).

We, a multidisciplinary group of social scientists working as part of five large-scale ‘universal test-and-treat’ (UTT) trials being implemented across six African countries, would argue that successful large-scale expansion of treatment and preexposure prophylaxis will require an in-depth understanding of the heterogeneous community and health systems’ contexts of the rollout.

The Social Science of Universal Test and Treat Network group met in Kampala in October 2015 to critically reflect on the role social science plays in supporting the successful implementation of UTT in African contexts. These deliberations underlined the complexities of implementing the new era of treatment and prevention. Social science work to date and the experience of others implementing UTT already shows that UTT is not a biomedical ‘one-size-fits-all’ intervention. It includes multiple client journeys and repeated activities (such as testing and adherence) in diverse health systems and social contexts; moreover, diverse ‘models’ of UTT are currently being implemented. We cannot control for the very varied contexts in which antiretroviral therapy will be delivered, and the unanticipated factors in ‘real-life’ contexts that can mediate the effects of UTT on desired outcomes.

Among the early lessons from social science research in the trials are, for instance, that sex, age, and other social hierarchies matter, but so do attention to how taking treatment fits into an individual’s broader (and dynamic) life experience: addressing uptake, adherence, and retention will rely upon an understanding of why men and women delay, start, and stop treatment. Our UTT data are replete with examples of the dilemmas faced by individuals navigating each step in the care cascade, which are shaped, for example, by gendered power relations within couples. At a study site in Zambia, for instance, a 20-year-old HIV-positive woman

pregnant with her fourth child explained to study staff that she had not yet gone to the clinic to access HIV services because she was worried about her husband’s response to her status. She feared that he might divorce her if he found out she had HIV. The data we gather about real dilemmas among people making decisions about HIV care, in aggregate, inform a broad understanding of the ways in which individuals in different couples, families, and communities can be subject to pressures that may force them onto testing and treatment or delay access, as well as affect continued access to care. Certain populations, such as adolescents, are facing particularly severe pressures. We are also observing that migrant and highly mobile individuals, a key marginalized yet economically important population, need tailored interventions to support their access and sustenance in care, because those who move from place to place because of work or other factors will (continually) fall into each of the ‘10%’ not reached by the 90-90-90 targets. Social science research studies in the trials are investigating how forms of HIV-related stigma are changing as a result of UTT, and how these changes are in turn affecting the trials. Social scientists are examining how the history of delivery of HIV interventions in different places affects expectations and perceptions of HIV-care delivery, and how the delivery of prompt treatment is fitting within existing, often overstretched, health systems in Africa – both of which influence uptake and sustained use of treatment. We are learning that we need different ways to support people to accept prompt initiation of treatment if they do not feel unwell, or have concerns about side-effects or other factors that affect life and work.

In short, social and behavioral sciences provide crucial contextual evidence on how treatment and prevention is implemented and scaled up, and what social and behavioral consequences and impact of ‘universal’ access to testing, treatment, and prevention can be expected, and thus holds valuable lessons for the UTT rollout. We believe that now is a crucial time to set goals for the inclusion of social science in the implementation science research program for delivering high-quality prevention and treatment across Africa.

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Carol S. Camlin^a, Janet Seeley^b, Lario Viljoen^c, Eva Vernooij^d, Musonda Simwina^e, Lindsey Reynolds^f, Ria Reis^{g,h,q}, Rebeca Plank^j, Joanna Orne-Gliemann^k, Nuala McGrath^{l,r}, Joseph Larmarange^m, Graeme Hoddinott^c, Monica Getahunⁿ, Edwin D. Charlebois^o and Virginia Bond^{b,p}, ^aDepartment of Obstetrics, Gynaecology and Reproductive Sciences and Division of Prevention Science, University of California, San Francisco, California, USA, ^bDepartment of Global Health and Development, London School of Hygiene and Tropical Medicine, London, UK, ^cDesmond Tutu TB Centre, Department of Paediatrics and Child Health, Stellenbosch University, Tygerberg, South Africa, ^dAmsterdam Institute for Social Science Research, Department of Anthropology, University of Amsterdam, Amsterdam, The Netherlands, ^eZambart, University of Zambia, Ridgeway Campus, Lusaka, Zambia, ^fPopulation Studies and Training Center, Brown University, Providence, Rhode Island, USA, ^gDepartment of Anthropology, University of Amsterdam, Amsterdam, The Netherlands, ^hThe Children's Institute, School of Child and Adolescent Health, University of Cape Town, Cape Town, South Africa, ⁱBrigham and Women's Hospital, ^jHarvard School of Public Health, Boston, Massachusetts, USA, ^kINSERM Unité 897, Institut de Santé Publique Epidémiologie Développement, University of Bordeaux, Bordeaux, France, ^lFaculty of Medicine, University of Southampton, Southampton, UK, ^mCEPED (UMR 196 UPD

IRD), Institut de Recherche pour le Développement (IRD), Paris, France, ⁿUniversity of California at San Francisco, San Francisco, California, USA, ^oUniversity of California, Center for AIDS Prevention Studies, San Francisco, California, USA, ^pZambart, University of Zambia, Ridgeway Campus, Lusaka, Zambia, ^qLeiden University Medical Center, The Netherlands, and ^rAfrica Centre for Population Health, University of KwaZulu-Natal, South Africa.

Correspondence to Carol S. Camlin, PhD, MPH, Department of Obstetrics, Gynaecology and Reproductive Sciences and Division of Prevention Science, University of California, San Francisco, California, USA.

E-mail: Carol.Camlin@ucsf.edu

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Raltegravir is safely used with long-term viral suppression for HIV-infected patients on hemodialysis: a pharmacokinetic study

The number of HIV-infected patients receiving hemodialysis has been remarkably increasing because of the rise in the prevalence of chronic kidney disease [1]. Renal dysfunction and the hemodialysis procedure significantly affect the pharmacokinetics of antiretroviral drugs, and dose adjustment and/or change in the medication schedule are occasionally needed, which carry a risk of poor adherence and treatment failure. Raltegravir (RAL) is an integrase inhibitor of HIV. It is mainly metabolized by uridine diphosphate glucuronosyltransferase 1A1 in the liver, and urinary excretion is less than 10% [2]. Thus, RAL is considered a better choice of antiretroviral drug for HIV patients on hemodialysis.

In this study, we determined serum concentrations of RAL by high performance liquid chromatography in two HIV-infected patients undergoing maintenance hemodialysis. The patients received regular doses of RAL (400 mg) twice daily both on hemodialysis and nonhemodialysis days in combination with abacavir and etravirine. This study was approved by the Ethical Committee of Gunma University Faculty of Medicine, and written informed consent was obtained from each patient.

Patient 1 was a 64-year-old man who had been on maintenance hemodialysis thrice weekly from June 2011

because of idiopathic membranous nephropathy. He had been taking RAL for the previous 2 months before hemodialysis was initiated. During the year between June 2011 and June 2012, blood sampling was performed on nine different days: 3 days when hemodialysis was performed in the morning (a.m.-hemodialysis), 3 days in the afternoon (p.m.-hemodialysis), and 3 nonhemodialysis days. During each hemodialysis session, blood samples were collected from the indwelling dialysis catheter every 1 h. On nonhemodialysis days, venous blood was drawn at the same time intervals. The patient took RAL regularly at 08:00 and 20:00 regardless of whether hemodialysis was performed. Figure 1a shows the kinetics of RAL concentrations in patient 1. There was no difference in the RAL concentrations at each time point between a.m.-hemodialysis (solid line) and nonhemodialysis (dotted line) days. Peak values were reached 3.5 h after taking RAL at comparable levels on a.m.-hemodialysis and nonhemodialysis days (942.2 and 859.9 ng/ml, respectively). The kinetics of RAL on the p.m.-hemodialysis days (dashed line) also fitted with those obtained on a.m.-hemodialysis and nonhemodialysis days. These results indicated that hemodialysis had no impact on the pharmacokinetics of RAL in this patient. C_{trough} was 238.6 ng/ml, above the reference value (14 ng/ml) of IC₉₅ reported previously [3].

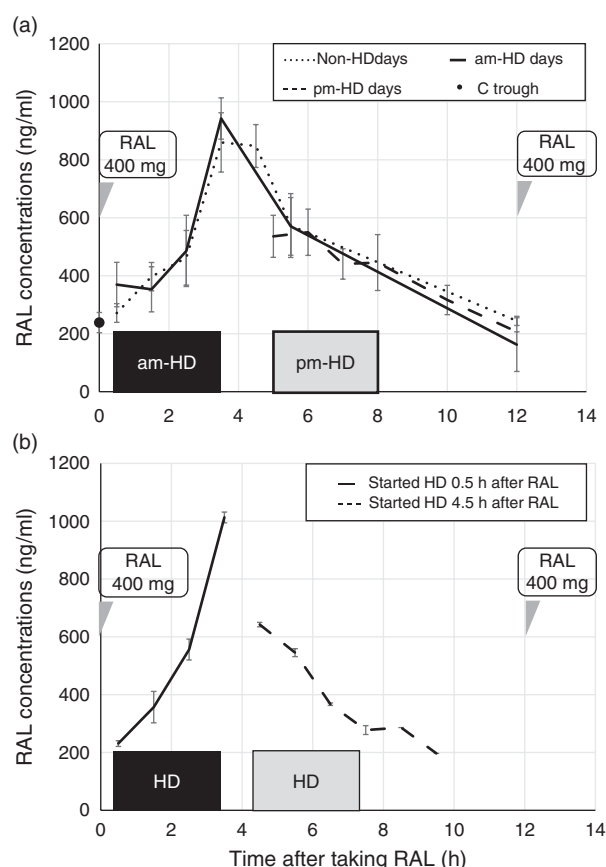


Fig. 1. Kinetics of RAL concentrations in HIV patients on maintenance hemodialysis. Data from patient 1 are shown in (a) and from patient 2 in (b). Patients took 400 mg of RAL at time 0. The time duration of each hemodialysis session was 3 h. RAL concentration was expressed as an average of values obtained on three separate days at each time point (However, sampling at 8.5 h and 9.5 h after RAL administration in patient 2 each occurred only once). C_{trough} was also determined in patient 1 on 3 separate days. Each bar reflects the standard error. HD, hemodialysis; RAL, raltegravir.

Patient 2 was a 64-year-old man who initiated hemodialysis in September 2012 because of diabetic nephropathy. Hemodialysis was performed in the afternoon starting at 13:00 thrice weekly. The patient received 400 mg of RAL twice daily from November 2010. Blood samples were collected on three different hemodialysis days at 1 h intervals. As shown in Fig. 1b (dashed line), when the patient took 400 mg of RAL at 08:30, RAL concentration was the highest (1013.2 ng/ml) at the start of hemodialysis (4.5 h after taking RAL), followed by a gradual decline. The RAL concentration reached the lowest level (196.7 ng/ml) 9.5 h after taking RAL, which was above the reference IC_{95} . When the patient took 400 mg of the morning RAL dose at 12:30 (0.5 h before starting hemodialysis), the highest level was obtained 3.5 h after taking RAL (solid line in Fig. 1b). The kinetics

of RAL in patient 2 was almost comparable to that observed in patient 1. Therefore, RAL concentrations primarily depended on the time interval after RAL administration, and were unaffected by hemodialysis procedures.

Importantly, HIV-RNA loads were continuously undetectable (< 20 copies/ml) in these two patients for at least 2 years after initiation of hemodialysis without any adverse event. Taken together, we conclude that twice-daily regular-dose RAL is safely used for HIV-infected patients on hemodialysis with long-term viral suppression. By measuring RAL concentrations of pre and postdialyzer blood samples and calculating hemodialysis clearance of RAL, Moltó *et al.* [2] concluded that removal of RAL by hemodialysis is negligible. Thus, the decrease in RAL concentrations observed during p.m.-hemodialysis sessions (dashed lines in Fig. 1a and b) in the present study can be explained by the hepatic metabolism of RAL. Giguère *et al.* [4] reported that prehemodialysis administration of RAL did not lead to increasing the concentration after hemodialysis. Bernard *et al.* [5] also reported that a regular dose and schedule of RAL kept the posthemodialysis RAL concentration above IC_{95} regardless of the hemodialysis schedule. In conclusion, RAL is a reasonable choice of antiretroviral drug for HIV patients on maintenance hemodialysis.

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Kunio Yanagisawa^a, Daisuke Nagano^b, Yoshiyuki Ogawa^a, Hideki Uchiumi^a, Tetsuya Shigehara^c, Kazuhisa Saruki^d, Hiroshi Handa^a, Takuya Araki^b, Koujiro Yamamoto^b and Yoshihisa Nojima^a, ^aDepartment of Medicine and Clinical Science, ^bDepartment of Clinical Pharmacology, Gunma University Graduate School of Medicine, ^cJomo Ohashi Clinic, and ^dSaruki Clinic, Maebashi, Gunma, Japan.

Correspondence to Yoshiyuki Ogawa, MD, Department of Medicine and Clinical Science, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan. Tel: +81 27 220 8166; fax: +81 27 220 8173; e-mail: yo-ogawa@gunma-u.ac.jp

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OPEN

Subdominant Gag-specific anti-HIV efficacy in an HLA-B*57-positive elite controller

Despite the discovery of HIV over three decades ago, the 2008 ‘Berlin patient’ is the only case of sustained HIV remission. Other cases of apparent ‘cure’ eventually relapsed [1] and although early antiretroviral therapy (ART) has recently gained traction as a factor contributing to remission [2,3], most cases are likely to relapse [4]. In contrast, relapse in ‘elite controllers’ of HIV infection is less common. These are ART-naïve individuals who spontaneously suppress viremia to undetectable levels. Approximately 40% of elite controllers express HLA-B*57 [5], an example being the original 1999 ‘Berlin patient’, in whom virologic control has been maintained for >15 years to date [6].

Mechanisms proposed to explain HLA-B*57-mediated immune control include immunodominant CD8⁺ T-cell-targeting of multiple conserved Gag epitopes from which mutational escape is detrimental to viral fitness, characteristics of the T-cell receptor on HLA-B*57-restricted CD8⁺ T cells, HLA-B*57-peptide binding affinity, and HLA-B*57 cross-talk with innate immune cells [7]. However, some HLA-B*57-positive elite controllers have no detectable Gag-specific responses without ex-vivo expansion [8,9]. Here, we studied one such elite controller, to determine whether the immunodominant CD8⁺ T-cell response in such cases mediates the most potent antiviral efficacy, as Gag-specific CD8⁺ T-cell responses typically have greater capacity to inhibit viral replication than non-Gag specificities [10,11].

An African-Caribbean female was recruited in the UK at 52 years of age in 2013. She had been diagnosed with HIV in 1991, an estimated 2 years after heterosexual transmission in Jamaica (and hence is referred to here as the ‘1991 Jamaica patient’). Our study was approved by the Oxford Research Ethics Committee and the patient provided written informed consent.

For more than 24 years, she has remained ART-naïve and aviremic with a healthy CD4⁺ T-cell count (median 1237 cells/μl) (Fig. 1a). Despite being HLA-B*57:03-positive, she demonstrated only two HIV-specific CD8⁺

T-cell responses detectable by ELISPOT assay, neither greater than 60 spot forming units (SFC)/million peripheral blood mononuclear cell (PBMC) and none detectable by tetramer staining (Fig. 1b and c). This is in contrast to the ‘1999 Berlin patient’, who had a dominant HLA-B*57-restricted Nef-HW9 response of 3000 SFC/million PBMC [6] (Fig. 1b). One of the two significant ELISPOT responses in the 1991 Jamaica patient was also against this same Nef-HW9 epitope (Fig. 1b). However, via peptide stimulation of memory T-cell responses [8], we identified five HLA-B*57-restricted responses (Fig. 1c), three of which we tested for their ability to inhibit HIV replication. Bulk CD8⁺ T cells demonstrated weak ex-vivo ability to suppress viral replication (Fig. 1d and e), fitting the profile of a subset of HLA-B*57-positive elite controllers [12]. Of the three expanded HLA-B*57-restricted CD8⁺ T-cell specificities tested, Gag-TW10-specific CD8⁺ T cells were significantly the most potent in suppressing HIV replication, followed by Nef-KF9 and then Nef-HW9 (Fig. 1d and e).

The study of this HLA-B*57-positive individual confirms that, in spite of HIV-specific responses being low frequency or undetectable by tetramer staining or ELISPOT assay, strong responses could be ‘recalled’ from memory, as previously reported [8]. Among these, Gag-TW10-specific CD8⁺ T cells were more potent at inhibiting viral replication than Nef-KF9-specific cells, despite the latter being a stronger response in ELISPOT assays. These data support previous findings in subjects chronically infected with HIV [13] indicating that subdominant responses may be more efficacious in terms of control of viremia. The findings here are extended also to the case of an HLA-B*57-positive elite controller. Although, like the 1999 Berlin patient, this is a single case report, the data are consistent with the hypothesis that HLA-B*57-mediated Gag-specific targeting by CD8⁺ T cells confers benefit to the host in HIV infection [7,14] and that vaccine induction of broad Gag-specific CD8⁺ T-cell responses would tend to increase immune control in HIV infection [15].

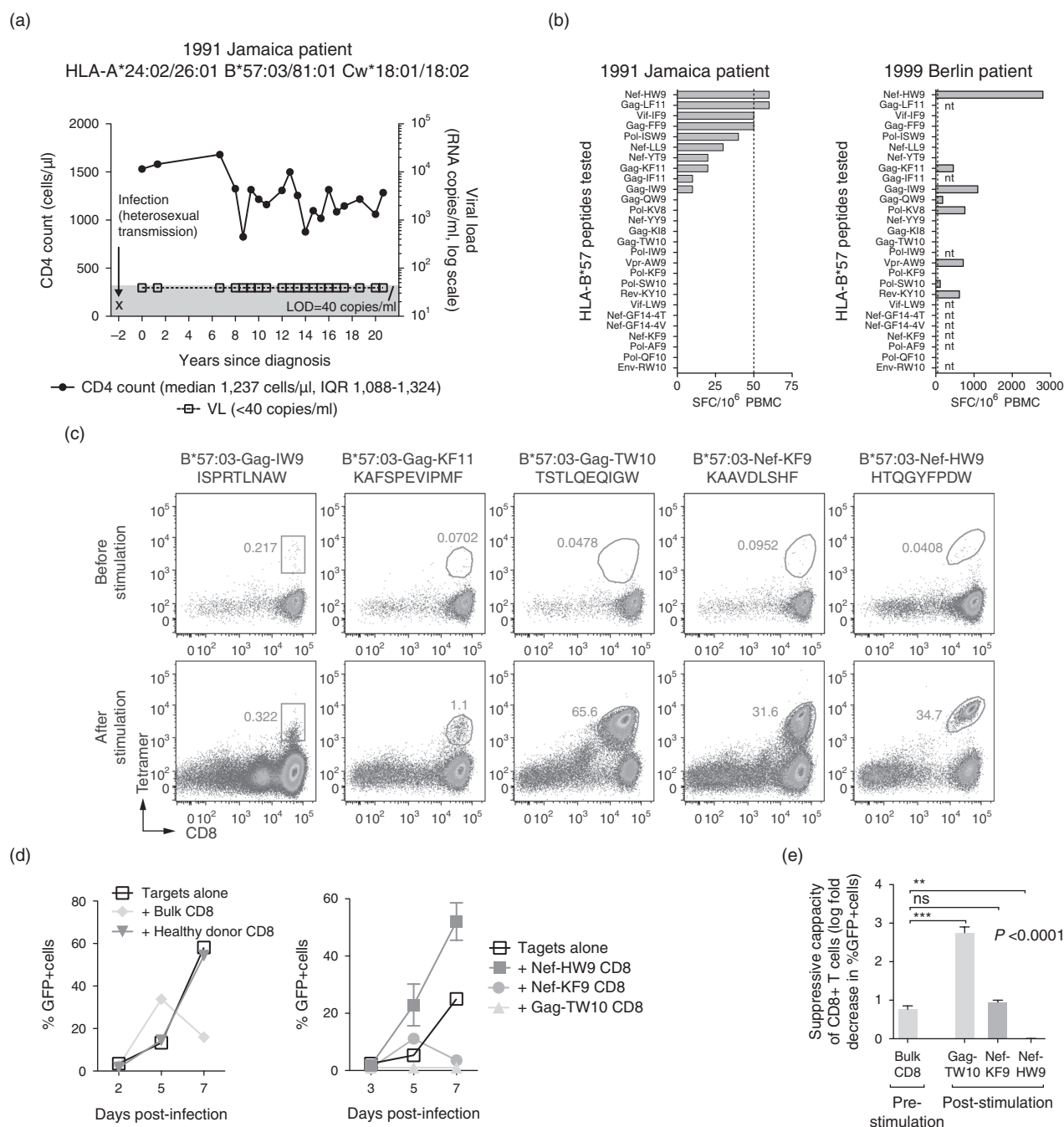


Fig. 1. Clinical profile and anti-HIV suppressive activity of the 1991 Jamaica patient. (a) CD4⁺ T-cell count and HIV RNA viral load measurements. '0' is time of diagnosis. Limit of detection (LOD) for viral load is 40 copies/ml (gray area) and measurements are shown at 40 copies/ml for convenience. Although sequencing was unsuccessful due to lack of circulating virus, the 1991 Jamaica patient was likely infected with subtype-B HIV predominant in Jamaica. (b) ELISPOT CD8⁺ T-cell responses in unstimulated peripheral blood mononuclear cells (PBMCs) in the 1991 Jamaica patient (22 years postdiagnosis) to subtype-B consensus HLA-B*57-restricted defined optimal epitopes. Responses were considered positive if they were at least three times the mean number of spot forming colonies (SFC) in the four negative control wells and had to be greater than 50 SFC/ 10^6 PBMC (dotted line). CD8⁺ T-cell responses for the 1999 Berlin patient are shown to highlight the different patterns of responses (not for direct comparisons as the assays were done in different laboratories at different times). Nt = not tested. (c) PBMC (23 years postdiagnosis) were stimulated with a panel of 30 HLA-B*57/81:01-restricted optimal peptides. Five previously undetectable HLA-B*57-restricted responses were discovered poststimulation, but no HLA-B*81:01-restricted responses. Three of these five responses were successfully expanded and tested in (d). Gated on live CD3⁺CD4⁻ cells around CD8⁺tetramer⁺ population; numbers indicate % tetramer⁺CD8⁺ cells (of CD3⁺CD4⁻). (d) Viral replication in HLA-B*57:03-expressing H9 cells infected with NL4-3-GFP and cultured alone ('targets alone'), with unstimulated bulk CD8⁺ T cells (left) or stimulated epitope-specific

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Ellen M. Leitman^a, Christian B. Willberg^b, Andrew De Burgh-Thomas^c, Hendrik Streeck^d, Philip J.R. Goulder^{a,e} and Philippa C. Matthews^f, ^aDepartment of Paediatrics, ^bNuffield Department of Medicine, University of Oxford, Oxford, ^cGloucestershire Royal Hospital, Gloucester, UK, ^dInstitute for HIV Research, University Hospital Essen, University Duisburg-Essen, Essen, Germany, ^eHIV Pathogenesis Programme, The Doris Duke Medical Research Institute, University of KwaZulu-Natal, Durban, South Africa, and ^fDepartment of Infectious Diseases and Microbiology, Oxford University Hospitals NGS Trust, John Radcliffe Hospital, Oxford, UK.

Correspondence to Ellen M. Leitman, The Peter Medawar Building for Pathogen Research, South Parks Road, Oxford, OX1 3SY, UK.

Tel: +44 1865 281880;

e-mail: ellen.leitman@st-hughs.ox.ac.uk

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Fig. 1 (continued)

CD8⁺ T cells (right) of the 1991 Jamaica patient (23 years postdiagnosis). Each symbol represents the mean of three replicates, error bars represent the SEM. (e) Suppressive capacity (log₁₀ fold decrease in % of infected GFP⁺ cells) of bulk unstimulated CD8⁺ T cells or stimulated epitope-specific CD8⁺ T cells of the 1991 Jamaica patient. Results were compared with 'bulk CD8' (ANOVA with Dunnett's multiple comparison post-test). **P* < 0.05, ***P* < 0.01, ****P* < 0.001, ns = not significant (*P* > 0.05).