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CAR-T therapy for relapsed/refractory large B-cell lymphoma in people living with HIV: efficacy, toxicity and treatment considerations.

Angela Hwang[1], Amy A. Kirkwood[2,3], Prudence Hardefeldt[4], Mathew Amrith[5], Maeve O'Reilly[1], Andrea Kuhnl[4], Michael Northend[1], Paul Maciocia[1,2], Sridhar Chaganti[5], Kate Cwynarski[1], Robin Sanderson[4], Claire Roddie[1,2]

1. Department of Haematology, University College London Hospitals, London, UK,
2. UCL Cancer Institute, University College London, London, UK,
3. Cancer Research UK & UCL Cancer Trial Centre, UCL Cancer Institute, University College London, London, UK
4. Department of Haematology, King's College Hospital, London, UK
5. Department of Haematology, Queen Elizabeth Hospital, Birmingham, UK

CORRESPONDING AUTHOR:

Dr Claire Roddie, UCL Cancer Institute, 72 Huntley Street, London, WC1E 6DD.
Email: c.roddie@ucl.ac.uk

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LETTER TO THE EDITOR:

Despite highly effective combination anti-retroviral therapy (aRT), people living with HIV (PLWH) remain at increased risk of non-Hodgkin's lymphoma (NHL). Large B-cell Lymphoma (LBCL) is the commonest subtype[1] (including immunoblastic and anaplastic morphological variants) and classically presents in advanced stage with extranodal involvement.[2] Mechanistically, HIV contributes to lymphomagenesis through loss of immune surveillance via HIV-dependent $CD4^+$ T-cell depletion, direct viral oncogenesis, and Epstein Barr virus-driven aberrant B-cell proliferation.[1,2]

Whilst outcomes have improved in the 1st line following standard-of-care therapy (R-CHOP[3,4];R-EPOCH[5]), LBCL remains a leading cause of mortality in PLWH, and management of relapse remains a major challenge.[2]

Chimeric Antigen Receptor T-cell therapy (CAR-T) has transformed outcomes in relapsed/refractory(r/r) LBCL, with 40-50% of patients achieving durable complete responses (CR).[6] Several small case series indicate that commercial CAR-T for HIV-associated LBCL is feasible[7–10], albeit data on safety and efficacy is limited, as PLWH with LBCL were excluded from pivotal trials. Here we report the United Kingdom(UK) experience of commercially available CD19CAR-T therapy, specifically axicabtagene ciloleucel(axi-cel), for HIV-associated LBCL in the 2nd and 3rd line, with a focus on feasibility, toxicity and efficacy.

Eleven UK patients with HIV-associated LBCL were referred for CAR-T therapy between 2019-2025: 4/11 (36%) at 2nd line and 7/11 (64%) at 3rd/later line, with eligibility criteria the same as for non-HIV-associated LBCL. An additional patient who self-funded treatment was also included. Ethical approval was obtained (REC-reference:24/EM/0221;IRAS project-ID:336254) and the study conducted in accordance with the Declaration of Helsinki. Patients provided informed consent for collection of minimally identifiable data in line with EBMT policy.

The median interval from HIV diagnosis to LBCL diagnosis was 16 years (range,0-31) and all cases were histologically LBCL. At LBCL diagnosis, median CD4 count was 65 cells/µl (range,not detected (ND)-182) and HIV viral load was <40 copies/ml (range,ND-6,840,000). First-line treatment included R-CHOP in 7/11 (64%), R-Pola-CHP in 2/11 (18%) and R-GCVP in 2/11 (18%). Only 3/11 (27%) achieved a response with 1 CR and 2 partial responses (PR) and progressive disease (PD) in 8/11 (73%). At CAR-T referral, patients had received a median of 2 prior lines (range, 1-3) including autologous stem-cell transplant (ASCT) in only 1 patient (9%). HIV and LBCL diagnostic details are summarised in *Supplementary Table S1*.

Patient and disease characteristics are summarised in Table 1. At CAR-T referral, median age was 55 (range, 32-74), 9/11 patients were male, 9/11 had Stage III/IV disease and 10/11 had extranodal involvement. No patients had central nervous system (CNS) involvement.

All referred patients underwent apheresis and CAR-T manufacture (median lymphocyte count $1.84x10^9$/L (range,0.42-3.23); median $CD4^+$ count 186 cells/μl (range, 70-410)). Most CAR-T products met release criteria (10/11;91%) with only one failure from low transduction efficiency which was ultimately approved by the UK out of specification (OOS) panel due to clinical need, and the Summary of Product Characteristics (SmPC) defined CAR+ viable cell dose was infused.

All patients received bridging therapy (BT): 8/11 (73%) received systemic BT (including polatuzumab-based BT in 6/8 patients); 2/11 (18%) received radiotherapy only; and 1/11 (9%) received combined systemic and radiation BT. CR/PR responses were infrequent (3/11 patients), with PD reported in all other patients. Three patients (27%) did not proceed to CAR-T. This was due to PD in 2 patients (including one with new CNS involvement) and clinician preference in 1 patient who achieved CR to BT but swiftly relapsed thereafter with rapid clinical deterioration. 8/11 (73%) patients proceeded to CAR-T infusion (including 1 patient with an OOS product), and median pre-lymphodepletion (LD) lactate dehydrogenase(LDH) and ferritin were 324 (range,145-549) and 761 (range,128-2832) respectively.

Toxicity is summarised in Table 2. Briefly, any grade(G) CRS or ICANS affected 7/8 (88%) and 3/8 (38%) patients respectively. ≥G3 CRS and ICANS affected 1/8 (13%) and 2/8 (25%) patients. ≥G3 infection affected 2/8 patients (25%). High-grade immunotoxicity (plus concomitant sepsis and PD in 1 patient) prompted ICU admission in 3/8 patients (34%) with 2/3 requiring inotropes and 1/3 requiring ventilatory support. No patients developed HIV viraemia immediately post-CAR-T. Whilst no overt signal for protracted ≥G3 neutropenia or thrombocytopenia was reported, the dataset is limited by small patient numbers in remission beyond months 1-2. In regard to immune reconstitution, at 12 months post-CAR-T, the 2 long-term responders have lower $CD4^+$ counts than at the time of leukapheresis i.e. from baseline 170 and 410 cells/μl, to 90 and 270 cells/μl at 12 months.

Response data is summarised in Figure 1A. The overall response rate (ORR) at M1 was 25% (2/8 patients), with CR ongoing in the 2 responding patients at 12 and 20 months of follow-up. PD was reported at M1 in 6/8 patients (75%). Notably, no patients with a PD response to BT achieved a response to CAR-T infusion (Figure 1A).

Figure 1B shows OS for the intention-to-treat (ITT) population (N=11). For infused patients (N=8), Figure 1C shows a median OS from infusion of 10.8 months (IQR:1.7–11.8) and Figure 1D shows a median progression free survival (PFS) from infusion of 0.9 months (IQR:0.8-1.7).

Of 6/8 patients with PD post-CAR-T, 2/6 (33%) received R-CHOP salvage followed by Glofitamab to PD, and 1/6 patients (17%) received Glofitamab salvage to PD. 3/6 patients (50%) were transferred to palliative care without further therapy. Only 1/6 patients with PD post-CAR-T is alive at 3 months post-PD.

Whilst CAR-T therapy has revolutionised non-HIV-associated LBCL, a paucity of data in PLWH reflects exclusion of these patients from clinical trials, albeit real-world data is beginning to emerge.[9,10] Here we report our experience using CD19CAR-T in 11 PLWH with r/r LBCL. Clinical outcomes were disappointing, with only 8/11 patients reaching CAR-T infusion. Further, the post-CAR-T ORR was only 25%, with extremely short PFS and OS compared to non-HIV LBCL CAR-T patients.[11] Evaluating baseline demographics, it is clear that our cohort was enriched for patients at high risk of CAR-T failure, namely those with high disease burden (including high LDH pre-LD), those with extranodal disease[12] and those with primary refractory disease, most of whom did not respond to BT. Learning from the 2 patients who achieved durable CR on our study, both were distinguished from other patients in the analysis by having achieved disease control post-BT and by having limited stage disease (1E and IIE).

Other published analyses of CAR-T for B-NHL in HIV includes a conference abstract from the collaborative CIBMTR and AIDS Malignancy Consortium(AMC) study which included 35 PLWH and reported 1 and 2 year OS rates of 45.7% and 65.9% respectively.[13] In a separate conference abstract from the DESCAR-T group of axi-cel for B-NHL in 24 PLWH (20/24 with LBCL), Clerico et al report an impressive M3 ORR of 50%, CR rate of 42% and a 12-month PFS and OS of 40% and 55%.[7] All grade CRS and ICANS affected 88% and 33% of patients, similar to what is observed with axi-cel in the non-HIV setting.[11] A comparison of our dataset to these studies is summarised in *Supplementary Table S*2.

Whilst these outcomes appear better than our UK outcomes, there are several factors which may explain the discrepancy. Firstly, the DESCAR-T cohort was heterogenous in disease type, including cases of follicular and grey zone lymphoma. Secondly, treatment history suggests less aggressive/refractory disease compared to the UK cohort, in that 17% of patients had prior ASCT (vs 9% in the UK cohort). Further, only 63% required BT (vs 100% in the UK cohort), of whom 26% received radiotherapy/steroids which again implies limited stage disease. These knowledge gaps make it difficult to determine the true potential of CAR-T for HIV-associated lymphoma, and further clinical data is urgently required to delineate prognostic risk factors and optimal approaches to bridging in this challenging clinical setting.

From a practical perspective, there are several unique considerations when delivering CAR-T in PLWH. Firstly, HIV viral load should be well controlled pre-CAR-T to facilitate CAR-T manufacture, favouring successful T-cell harvest (as a result of optimised immune reconstitution), and minimising the theoretical risk of vector recombination with native HIV virus.[9,14] In line with FACT-JACIE standards[15], products require segregated storage at site or transportation to site on the day of infusion to minimise infectious risk in shared storage. Patient management requires close multi-disciplinary working between haematology and HIV specialist teams for awareness of aRT/drug interactions, and optimal infection prophylaxis. Our study showed good HIV control pre-LD and post-CAR-T infusion was feasible, with no cases of viral rebound.

In summary, our study illustrates the UK real-world experience of CD19CAR-T for HIV-associated LBCL in 2nd and later lines. Whilst definitive conclusions are limited by the retrospective nature of the analysis, the heterogeneity of BT, and the small patient numbers, our analysis clearly highlights the challenges of CAR-T treatment delivery in PLWH, where high-risk LBCL disease phenotypes (namely primary refractory/elevated LDH/high stage/extranodal disease) may help explain the poor outcomes we report here. Overall, patients with limited stage and low burden disease may have better outcomes, but more work is needed to understand which patients will benefit most from CD19CAR-T. Prospective clinical trials will be crucial in defining the role for CAR-T in PLWH, towards efforts to improve outcomes in this patient group.

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TABLES:

Table 1. Baseline characteristics, bridging therapy & month 1 outcomes.

	All patients N=11	**Infused N=8**
Baseline characteristics		
Age at approval, Median (IQR) *Range*	55 (47-60) *32-74*	53.5 (47-59) *32-62*
Sex, N (%) Male Female	 9 (82) 2 (18)	 6 (75) 2 (25)
Disease stage, N (%) I II III IV	 1 (9) 1 (9) 2 (18) 7 (64)	 1(13) 1(13) 1 (13) 5 (63)
Extranodal involvement No Yes	 1 (9) 10 (91)	 0 8 (100)
Lymphocyte count ($x10^9$/L) at apheresis, Median (IQR) *Range*	1.84 (1.2 – 2.7) *0.42-3.23*	2.1 (0.9 – 2.9) *0.42-3.23*
$CD4^+$ count (cells/µl) at apheresis, Median (IQR) *Range*	186 (130-315) *70-410*	202 (90-363) 70-410
Out of specification product, N (%) No Yes	 10 (91) 1 (9)	 7 (88) 1 (13)
Bridging therapy, N (%) Systemic RBP R-polatuzumab R-gemox R-ICE Radiotherapy Combined modality (RT + R-polatuzumab)	 8 (73) 3 3 1 1 2 (18) 1 (9)	 5 (63) 2 1 1 1 2 (25) 1 (13)
Response to bridging by PET-CT§, N (%) CR PR PD	 2 (18) 1 (9) 8 (72)	 1 (13) 1 (13) 6 (75)
**Combined aRT therapy, N (%) Bictegravir/emtricitabine/tenofovir alafenamide Emtricitabine/tenofovir alafenamide + nevirapine Emtricitabine/tenofovir alafenamide + raltegravir Emtricitabine/tenofovir alafenamide + dolutegravir Emtricitabine/tenofovir alafenamide + dolutegravir + fostemsavir Emtricitabine/tenofovir disoproxil fumarate + raltegravir Missing	 3 (27) 2 (18) 1 (9) 1 (9) 1 (9) 1 (9) 2 (18)	 3 (38) 1 (13) 1 (13) - 1 (13) - 2 (25)

Pre-lymphodepletion*		
LDH pre-LD, median (IQR) *Range*	-	324 (202-426) *145-594*
Ferritin pre-LD, median (IQR) Range	-	761 (185 -1290) *128-2832*
CRP pre-LD, median (IQR) *Range*	-	7 (6-32.9) *3.2-48.7*
PS pre-LD 0 1 2	-	 2 (25) 4 (50) 2 (25)
HIV viral load, pre-LD, N (%) Not detectable Detected Missing/not assessed	-	 6 (75) 0 (0) 2 (25)
$CD4^+$ count (cells/µl) Baseline pre-LD, median (IQR) *Range*	-	 196 (130-290) 108-410
M1 post CAR-T		
$CD4^+$ count (cells/µl) Result *Missing, N*	-	 39, 40, 80, 249 *4*
M1 response by PET-CT§, N (%) CR PD	-	 2 (25%) 4 (75%)

Key: *RBP – rituximab, bendamustine, polatuzumab; R-polatuzumab – rituximab, polatuzumab; R-gemox– rituximab, gemcitabine, oxaliplatin; R-ICE–rituximab, ifosfamide, carboplatin, etoposide; CR– complete response; PR-partial response; PD–progressive disease; aRT – anti-retroviral therapy; LDH–lactate dehydrogenase; LD– lymphodepletion; CRP – C-reactive protein; PS – performance status; M1– month 1* [*]*Lymphodepletion (LD) comprised fludarabine and cyclophosphamide as per summary of product characteristics.* [**]*Combined aRT regimens were at the discretion of local investigators with HIV-specialist teams.* [§]*Positron emission tomography-computerised tomography (PET-CT) response was according to Lugano 2014 classification at month 1 and month 3 following infusion.*

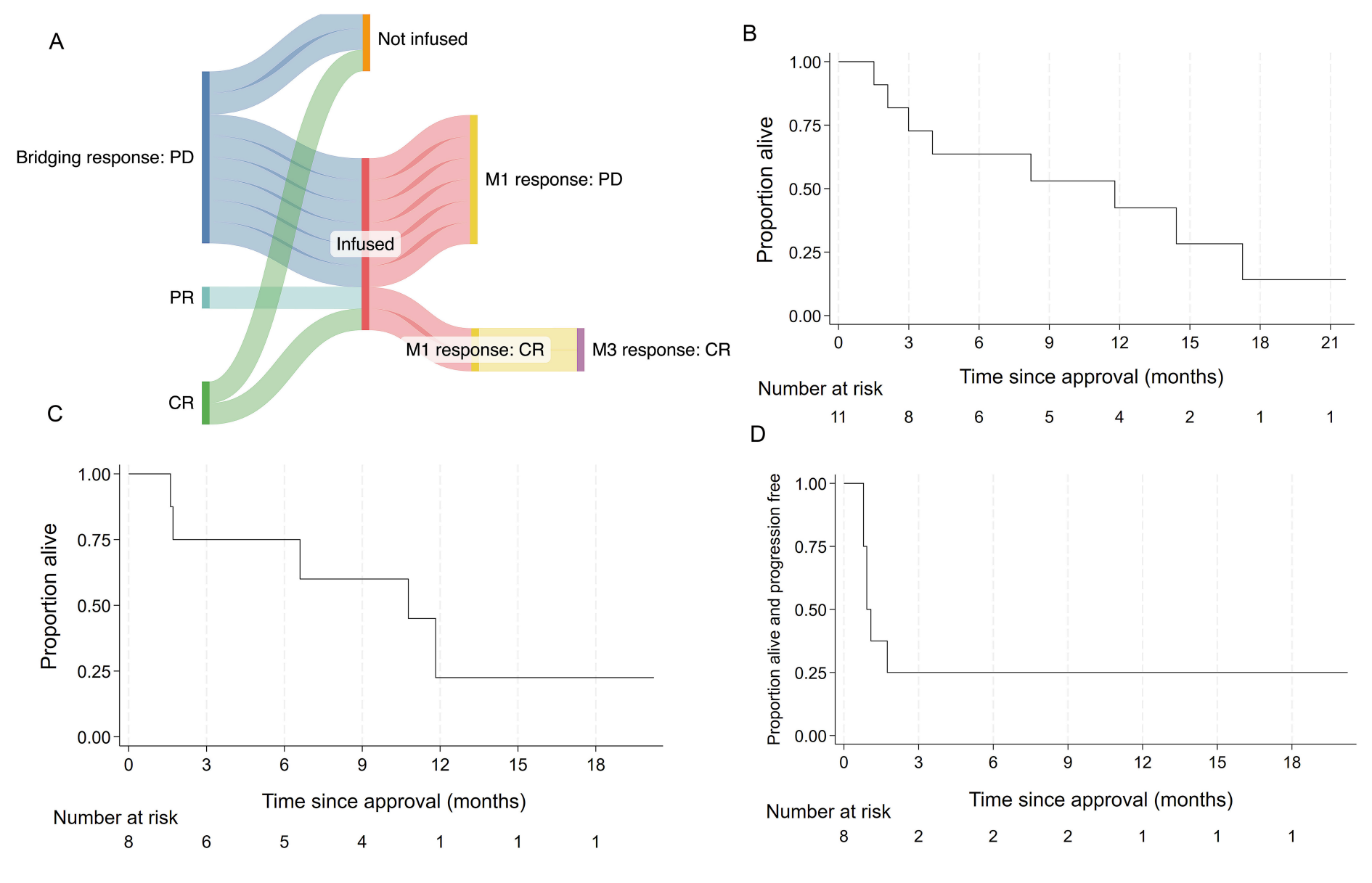
Table 2. Toxicity.

Toxicity	**Infused N=8**
CRS, N (%)	
Any grade	7 (88)
Grade ≥ 3	1 (13)
ICANS, N (%)	
Any grade	3 (38)
Grade ≥ 3	2 (25)
ICU admission, N (%)	
No	5 (63)
Yes	3 (38)
○ Immunotoxicity	2
○ Infection/sepsis and immunotoxicity	1
Grade 3-4 neutropenia M1*, N (%)	
• No	2 (100)
• Yes	0
Grade 3-4 thrombocytopenia M1*, N (%)	
• No	2 (100)
• Yes	0
Grade 3-4 neutropenia M3*, N(%)	
• No	2 (100)
• Yes	0
Grade 3-4 thrombocytopenia M3*, N(%)	
• No	2 (100)
• Yes	0
Grade 3-4 infection*, N (%)	
• No	6 (75)
• Yes	2 (25)

Key: *CRS – cytokine release syndrome; ICANS – immune effector cell-associated neurotoxicity syndrome; ICU – intensive care unit.* *******For 1- and 3-month cytopenia; patients with PD at 1 or 3 months have been excluded.*

FIGURES:

Figure 1. Treatment Response and Survival Outcomes *(a) Outcomes of CAR-T infusion according to bridging response. Key: PD – progressive disease, PR – partial response, CR – complete response. (b) Overall Survival from approval. Median OS 11.8 months (IQR: 3.0 – 17.2) (c) Overall Survival from infusion. Median 10.8 months (IQR: 1.7-11.8) (d) Overall Progression Free Survival from infusion. Median PFS 0.9 months (IQR: 0.8-1.7)*


A
Not infused
Bridging response: PD
M1 response: PD
Infused
PR
M1 response: CR
M3 response: CR
CR
B
Proportion alive
1.00
0.75
0.50
0.25
0.00
0
3
6
9
12
15
18
21
Time since approval (months)
Number at risk
11
8
6
5
4
2
1
1
C
Proportion alive
1.00
0.75
0.50
0.25
0.00
0
3
6
9
12
15
18
Time since approval (months)
Number at risk
8
6
5
4
1
1
1
D
Proportion alive and progression free
1.00
0.75
0.50
0.25
0.00
0
3
6
9
12
15
18
Time since approval (months)
Number at risk
8
2
2
2
1
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1

TITLE:

CAR-T therapy for relapsed/refractory large B-cell lymphoma in people living with HIV: efficacy, toxicity and treatment considerations.

SUPPLEMENTARY TABLES:

Supplementary Table S1: *HIV and large B-cell lymphoma diagnostic details*

	All patients N=11	**Infused N=8**
Age at HIV diagnosis, median (IQR) *Range*	39.5 (31-46) *0-72*	38 (31-43) *0-46*
Interval between HIV and LBCL diagnosis (years), median (IQR) *Range*	16 (5-23) *0-31*	19 (12-29) *0-31*
Histological subtype, N (%) DLBCL	 11 (100)	 8 (100)
$CD4^+$ count at LBCL diagnosis, median (IQR) *Range*	65 (undetectable-129) *undetectable-182*	40 (undetectable-110) *undetectable-148*
HIV viral load at LBCL diagnosis, median (IQR) *Range*	<40 (undetectable-55000) *undetectable-6,840,000*	<40 (undetectable-1,288,250) *undetectable-6,840,000*
1st line therapy, N (%) R-CHOP R-Pola-CHP R-GCVP	 7 (64) 2 (18) 2 (18)	 4 (50) 2 (25) 2 (25)
Response to 1st line therapy, N (%) CR PR PD	 1 (9) 2 (18) 8 (73)	 0 2 (25) 6 (75)
Number of lines prior therapy, median (IQR) *Range*	2 (1-3) *1-3*	2 (1-3) *1-3*

Key: *IQR – interquartile range; LBCL – Large B Cell Lymphoma; R-CHOP – rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-Pola-CHP – rituximab, polatuzumab vedotin, cyclophosphamide, vincristine, prednisolone; R-GCVP – rituximab, gemcitabine, cyclophosphamide, vincristine, prednisolone; CR – complete response; PR – partial response; PD – progressive disease*

Supplementary Table S2: Comparison between the HIV-positive Large B-cell Lymphoma CAR-T datasets

	UK	**DESCAR-T**[1]	**AMC and CIBMTR**[2]
Median age *Range*	53.5 *32-62*	55 *35-75*	56 *29-69*
Total infused, N	8	24	35
Male sex, %	75	71	88.6
Histological subtype, % LBCL Follicular Other	100	84 8 4 (grey-zone)	91 6 3 (mantle)
CAR-T product, % Axi-cel Brexu-cel	100	100	97 3
Bridging therapy, % Yes Type	100 Systemic: 63 RT: 25 Combination: 13	63 Chemotherapy-based: 37	62.9 N/A
Bridging response, N (%)	CR/PR: 2 (25) PD: 6 (75)	Responder: N/A No response: 11 (73)	N/A
Stage, N (%) I/II III/IV Missing	2 (25) 6 (75)	N/A 18 (90) 4	N/A
Elevated LDH pre-LD or pre-CAR-T infusion, N (%) Yes Missing	4 (66) 2	15 (63)	N/A
Median prior lines treatment *Range*	2 *1-3*	3 *1-4*	N/A
HIV VL pre-LD or pre-CAR-T infusion	Not detectable: 8/8 (100%)	Not detectable: 11/24 (46%) Not reported: 13/24	Median VL: 20 copies/ml (0-10x10^6) >400 copies/ml: 11.4%
Response rate	M3 ORR: 25% CR: 25%	M3 ORR: 50% CR: 42%	M6 ORR: 42.6% CR: 34.6%
Survival outcomes	Median PFS: 0.9 months (IQR: 0.8-1.7) Median OS: 10.8 months (IQR: 1.7-11.8)	1 year PFS: 40% (95% CI, 18-61) 1 year OS: 55% (95% CI, 28-75)	1/2 year PFS: 36.1/28.3% 1/2 year OS: 45.7/ 37.3%

Key: *UK – United Kingdom; NCCP – National CAR-T cell panel; DESCAR-T – Dispositif d'Enregistrement et Suivi des patients traités par CAR-T cells; AMC – AIDS Malignancy Consortium; CIBMTR – Center for International Blood & Marrow Transplant Research; LBCL – Large B-cell Lymphoma; RT – radiotherapy; CR – complete response; PR – partial response; PD – progressive disease; LDH – Lactate dehydrogenase; LD – lymphodepletion; VL – viral load; M3 – month 3; ORR*

– overall response rate; M6 – month 6; PFS – progression free survival; IQR – interquartile range; OS – overall survival

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