

# Long-Acting Albuvirtide Combined with Intensive Immunochemotherapy for HIV-associated Diffuse Large B-Cell Lymphoma: A Retrospective Study

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## Research Article

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# Abstract

## Background

This retrospective study evaluated albuvirtide (ABT)-based combination antiretroviral therapy (cART) during intensive immunochemotherapy in HIV-associated DLBCL.

## Methods

In this single-center retrospective study, 80 ABT-treated patients from 2023–2024 were screened; 54 were included, comprising 33 patients with HIV RNA > 50 copies/mL and 21 patients with HIV RNA ≤ 50 copies/mL. Endpoints included HIV-1 RNA change, virological suppression, CD4 + T-cell counts, CD4/CD8 ratio, tumor-marker expression, and control-trained 12-week landmark Cox survival prediction.

## Results

In HIV RNA > 50 copies/mL subgroup, median HIV-1 RNA decreased by 3.14 log<sub>10</sub> copies/mL by Week 12 ( $p < 0.001$ ), and 85.71% achieved virological suppression. Median CD4 + counts increased by 36 cells/μL at Week 8 and 30 cells/μL at Week 12; CD4/CD8 ratio improved from 0.17 to 0.34 ( $p < 0.001$ ). The Cox model included 49 non-ABT patients (25 deaths) and showed modest discrimination (C-index = 0.611); predicted ABT OS probabilities were 0.609, 0.544, and 0.383 at 6, 12, and 24 months. For patients with HIV RNA ≤ 50 copies/mL, 12-week ABT therapy sustained virological suppression with improved systemic immunity.

## Conclusions

ABT-based long-acting cART was associated with rapid virological suppression in patients with HIV RNA > 50 copies/mL and exploratory immune and tumor-marker improvements. Survival predictions were hypothesis-generating only.

## 1 Introduction

Human immunodeficiency virus (HIV) infection remains one of the most significant global public health challenges in the 21st century [1]. According to the latest UNAIDS estimates, approximately 40.8 million people were living with HIV (PLWH) globally by the end of 2024 [2]. In China, the epidemic has undergone a dramatic transformation over the past decade, with nearly 1.3 million reported cases by the end of 2023 and a primary shift toward sexual transmission routes [3]. Despite the massive scale-up of antiretroviral therapy (ART) that has transformed HIV into a manageable chronic condition, the aging of the PLWH population has led to an increasing incidence of non-AIDS-defining and AIDS-defining malignancies [4, 5].

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma and represents a major aggressive B-cell lymphoma subtype in people living with HIV [6, 7]. Although modern immunochemotherapy regimens such as R-EPOCH or R-CHOP have improved disease management, clinical outcomes in HIV-associated DLBCL remain heterogeneous and management remains clinically complex [7]. However, the concurrent administration of cART and intensive chemotherapy presents profound clinical challenges. Traditional daily oral antiretroviral regimens often face substantial hurdles, including poor patient adherence triggered by severe chemotherapy-induced gastrointestinal toxicities (e.g., intractable nausea and mucositis) [8]. Furthermore, the high risk of drug-drug interactions (DDIs), particularly those mediated by the hepatic cytochrome P450 (CYP450) enzyme system, remains a critical concern [9]. Several agents used in lymphoma chemotherapy, including cyclophosphamide, doxorubicin, etoposide, and vincristine, may be affected by CYP3A4/P-glycoprotein-related pathways, particularly when co-administered with ritonavir-boosted protease inhibitors or some NNRTI-based regimens [9, 10]. Clinical data on the delivery of intensive chemotherapy together with ART in PLWH remain limited and are often derived from small hematologic malignancy series [11]. Thus, there is an urgent clinical imperative to identify long-acting antiviral regimens with favorable pharmacokinetic safety profiles and lower DDI potential to optimize comprehensive outcomes in this vulnerable cohort.

Albuvirtide (ABT) is a long-acting HIV-1 fusion inhibitor developed and approved in China, with available pharmacokinetic evidence supporting once-weekly intravenous administration [12]. As a 3-maleimidopropionic acid-modified peptide derived from the gp41 heptad-repeat region, ABT targets HIV-1 gp41 and irreversibly conjugates with serum albumin in vivo [13, 14]. This mechanism extends its half-life to approximately 11–12 days and blocks the formation of the six-helix bundle (6-HB) structure required for viral fusion [12, 14]. Because ABT is not primarily handled through CYP-mediated oxidative metabolism, it may reduce, rather than eliminate, CYP-mediated DDI concerns during cytotoxic chemotherapy [15]. Recent pharmacokinetic studies have also explored less frequent bolus-based maintenance strategies, further supporting the long-acting profile of ABT [16]. The pivotal Phase 3 TALENT study has established the potent antiviral efficacy and safety of ABT-based regimens in treatment-experienced adults [17]. Emerging real-world evidence further suggests that ABT-based therapy promotes robust virological suppression and rapid immune reconstitution, even in immunological non-responders [18].

Despite these promising attributes, real-world evidence regarding the use of ABT-based therapy in PLWH with malignancy remains limited, and data specifically in HIV-associated DLBCL are scarce [19]. This single-center retrospective study was designed to evaluate the short-term virological efficacy and treatment feasibility of albuvirtide-based combination antiretroviral therapy (cART) in patients with HIV-associated aggressive B-cell lymphoma. We hypothesized that this long-acting injectable regimen would achieve rapid virological suppression during intensive chemotherapy, while immune-cell and tumor-associated marker changes were assessed as exploratory secondary outcomes.

## 2 Materials and Methods

## 2.1 Study Design and Participants

This was a single-center retrospective study designed to evaluate the clinical effectiveness of albuvirtide (ABT)-based combination antiretroviral therapy (cART) in patients with HIV-associated B-cell lymphoma. The primary treatment cohort consisted of patients who received ABT-based ART during intensive immunochemotherapy between 2023 and 2024. A total of 80 patients diagnosed with both HIV infection and DLBCL who were initiated on ABT-containing regimens were screened for eligibility. The inclusion criteria were as follows: (1) Confirmed diagnosis of HIV-1 infection. (2) Histologically confirmed aggressive B-cell lymphoma, specifically DLBCL. (3) Initiation of treatment with long-acting albuvirtide combined with intensive immunochemotherapy. The exclusion criteria were strictly applied to ensure data integrity and clinical relevance: Patients with incomplete baseline or follow-up clinical data (n = 26).

During the same period, we also assembled a non-ABT control cohort of patients with HIV-associated DLBCL who received ART without ABT. Eligible controls had confirmed HIV-1 infection, histologically confirmed DLBCL, no exposure to ABT, and available survival follow-up data. Patients with incomplete baseline or follow-up data were excluded. For surviving patients, the final follow-up date was defined by the last discharge or last recorded follow-up date; for deceased patients, the death date was used. This control cohort was used only for exploratory survival-prediction modeling and was not treated as a randomized comparator for causal efficacy or safety inference.

This study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [20].

## 2.2 Interventions and Laboratory Measurements

All enrolled patients received a combination antiretroviral therapy (cART) regimen centered on albuvirtide (ABT; Frontier Biotechnologies Inc., Nanjing, China; 160 mg/vial). The administration of ABT followed a specific loading and maintenance protocol: 320 mg was administered via intravenous infusion once daily on Days 1, 2, and 3, followed by a maintenance dose of 320 mg administered once weekly thereafter. ABT was used in combination with other antiretroviral agents to achieve optimal virological control.

Plasma HIV-1 RNA levels were quantified using the [COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test; Roche, LOD 20 copies/mL] according to the manufacturer's instructions. Peripheral blood CD4 + and CD8 + T-lymphocyte counts were determined via flow cytometry using [BD Multitest™ CD3/CD8/CD45/CD4; BD FACSuite Clinical v1.4 software; Catalog No. 342447 (kit with BD Trucount™ tubes)] kits.

The expression of tumor markers, including Ki-67, C-myc, Bcl-2, and Bcl-6, was evaluated using immunohistochemistry (IHC). Tissue samples were fixed in 10% neutral buffered formalin, paraffin-embedded, and sectioned at 4 µm. The sections underwent heat-induced antigen retrieval followed by incubation with primary antibodies against Ki-67, C-myc, Bcl-2, and Bcl-6. Visualization was performed

using a standard horseradish peroxidase (HRP)-conjugated secondary antibody and 3,3'-diaminobenzidine (DAB) chromogen.

## 2.3 Patient Sample Size Calculation

Given the exploratory and retrospective nature of this study within a highly specific clinical cohort (HIV-associated DLBCL), the sample size was determined by the total number of eligible patients treated at our center between 2023 and 2024. A post-hoc power analysis was performed to validate the adequacy of the cohort. Based on previous long-acting ART studies (e.g., the TALENT trial), a mean reduction in HIV-1 RNA of  $\geq 2.0 \log_{10}$  copies/mL with a standard deviation (SD) of 1.5 was anticipated. To detect such a large effect size (Cohen's  $d \approx 1.33$ ) using a two-sided Wilcoxon signed-rank test for longitudinal comparisons, with an  $\alpha$  level of 0.05 and a power of 90% ( $1-\beta$ ), a minimum of 28 participants was required. Our final inclusion of 33 patients provided a statistical power exceeding 95%, ensuring that the study was sufficiently powered to detect significant changes in primary virological and immunological endpoints.

## 2.4 Statistical Analysis

Continuous variables were assessed for normality using the Kolmogorov-Smirnov test. Normally distributed data were expressed as mean  $\pm$  SD and analyzed using the Student's t-test. Non-normally distributed data were presented as median and interquartile range [Median (Q1, Q3)] and analyzed using the Mann-Whitney U test or Wilcoxon signed-rank test for longitudinal comparisons. Categorical variables were expressed as frequencies and percentages [n (%)]. Statistical significance was defined as  $p < 0.05$ . The primary endpoint was change in HIV viral load from baseline to Weeks 4, 8, and 12, with virological suppression defined as HIV-1 RNA  $< 50$  copies/mL. Secondary and exploratory endpoints included CD4 + T-cell counts, CD4/CD8 ratio, and tumor-associated marker expression. All conventional statistical analyses were performed using GraphPad Prism software V9.0 (GraphPad Software LLC, San Diego, CA, USA) or SPSS Software V26.0 (IBM Corp., Armonk, NY).

For the exploratory survival-prediction component, a 12-week landmark Cox proportional hazards model was developed in the non-ABT control cohort and then extrapolated to the ABT cohort. OS was measured in months from lymphoma diagnosis, with death coded as the event and survival or follow-up as censoring. The final control training set included patients with available OS time, survival status, and complete model covariates. Prespecified predictors were baseline  $\log_{10}$  HIV-1 RNA, baseline CD4 + T-cell count, baseline CD4/CD8 ratio, and Week-12  $\log_{10}$  HIV-1 RNA. Predicted risks were generated for all ABT patients. Model discrimination was assessed using Harrell's concordance index (C-index). Predicted post-landmark OS probabilities at 6, 12, and 24 months and 24-month restricted mean survival time (RMST) were estimated for the ABT cohort.

## 3 Results

### 3.1 Patient Recruitment and Selection

Between 2023 and 2024, a total of 80 patients diagnosed with HIV-associated DLBCL who received abuvirtide (ABT)-based regimens for HIV management were initially screened for eligibility. Among these, 26 patients were excluded due to incomplete baseline or follow-up clinical data. Accordingly, in this single center retrospective study, the ABT-treated cohort should be reported as 54 patients in total: 33 patients with baseline HIV-1 RNA > 50 copies/mL, who formed the primary high-viremia analysis subgroup, and 21 patients with baseline HIV-1 RNA ≤ 50 copies/mL, following previous antiretroviral therapy. The detailed screening and enrollment process is illustrated in Fig. 1.

For the exploratory survival prediction analysis, we enrolled contemporaneous patients with HIV-associated DLBCL who did not receive ABT therapy as the non-ABT control cohort. Clinical data of 67 patients in this non-ABT control group were retrospectively extracted from electronic medical records. After excluding 18 cases with incomplete clinical or survival follow-up data, a total of 49 eligible patients remained, among whom 25 died and 24 survived during the follow-up period.

### 3.2 Baseline Characteristics

The baseline demographic and clinical characteristics of the 33 enrolled patients are summarized in Table 1. The study population had a mean age of  $50.73 \pm 11.97$  years. Within this cohort, 24 patients (72.73%) were male, and 9 (27.27%) were female. Regarding HIV status at baseline, the median viral load was 4.84 (2.74, 5.78)  $\log_{10}$  copies/mL, with 45.45% of patients presenting with high HIV RNA load ( $\geq 100,000$  copies/mL). The median baseline CD4 + T cell count was 123 (79, 186) cells/ $\mu$ L, and most of the participants (84.85%) exhibited severe immunosuppression with CD4 + counts below 200 cells/ $\mu$ L. The mean CD4/CD8 ratio was  $0.19 \pm 0.13$ , with 60.61% of patients having a ratio < 0.2.

Table 1  
Baseline demographic and clinical characteristics of patients.

| Variables                                                                                                                                                                                          | HIV Viral Load > 50 copies/mL<br>(N = 33) | HIV Viral Load ≤ 50 copies/mL<br>(N = 21) |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|-------------------------------------------|
| Age, years                                                                                                                                                                                         | 50.73 ± 11.97                             | 57.10 ± 10.13                             |
| Gender, n (%)                                                                                                                                                                                      |                                           |                                           |
| Female                                                                                                                                                                                             | 9 (27.27)                                 | 3 (14.29)                                 |
| Male                                                                                                                                                                                               | 24 (72.73)                                | 18 (85.71)                                |
| HIV viral load (log <sub>10</sub> copies/mL)                                                                                                                                                       | 4.84 (2.74, 5.78)                         | 1.42 ± 0.34                               |
| HIV viral load, n (%)                                                                                                                                                                              |                                           |                                           |
| < 100,000                                                                                                                                                                                          | 18 (54.55)                                | 21 (100)                                  |
| ≥ 100,000                                                                                                                                                                                          | 15 (45.45)                                | /                                         |
| CD4 <sup>+</sup> T cell count (Cells/μL)                                                                                                                                                           | 123 (79, 186)                             | 255.45 ± 175.25                           |
| CD4 <sup>+</sup> T cell count, n (%)                                                                                                                                                               |                                           |                                           |
| < 200                                                                                                                                                                                              | 28 (84.85)                                | 9 (42.86)                                 |
| ≥ 200                                                                                                                                                                                              | 5 (15.15)                                 | 12 (57.14)                                |
| CD4/CD8 <sup>+</sup> T                                                                                                                                                                             | 0.19 ± 0.13                               | 0.42 ± 0.23                               |
| CD4/CD8 <sup>+</sup> T, n (%)                                                                                                                                                                      |                                           |                                           |
| < 0.2                                                                                                                                                                                              | 20 (60.61)                                | 3 (14.29)                                 |
| ≥ 0.2                                                                                                                                                                                              | 13 (39.39)                                | 18 (85.71)                                |
| Type of DLBCL (%)                                                                                                                                                                                  |                                           |                                           |
| Germinal center B-cell-like                                                                                                                                                                        | 14 (42.42)                                | 12 (57.14)                                |
| Non-germinal center B-cell-like                                                                                                                                                                    | 19 (57.58)                                | 9 (42.86)                                 |
| cART, n (%)                                                                                                                                                                                        |                                           |                                           |
| ABT + Biktarvy                                                                                                                                                                                     | 15 (45.45)                                | 12 (57.14)                                |
| ABT + Dovato                                                                                                                                                                                       | 18 (54.55)                                | 9 (42.86)                                 |
| Antitumor therapy, n (%)                                                                                                                                                                           |                                           |                                           |
| <b>Note:</b> Biktarvy is a fixed-dose combination of bictegravir, emtricitabine, and tenofovir alafenamide. Dovato consists of dolutegravir and lamivudine as a single-tablet combination regimen. |                                           |                                           |

| Variables                                                                                                                                                                                          | HIV Viral Load > 50 copies/mL<br>(N = 33) | HIV Viral Load ≤ 50 copies/mL<br>(N = 21) |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|-------------------------------------------|
| R-EPOCH/EPOCH                                                                                                                                                                                      | 24 (72.73)                                | 13 (61.90)                                |
| R-CHOP/CHOP                                                                                                                                                                                        | 8 (24.24)                                 | 7 (33.33)                                 |
| BTK inhibitor                                                                                                                                                                                      | 1 (3.03)                                  | 1 (4.76)                                  |
| <b>Note:</b> Biktarvy is a fixed-dose combination of bictegravir, emtricitabine, and tenofovir alafenamide. Dovato consists of dolutegravir and lamivudine as a single-tablet combination regimen. |                                           |                                           |

Pathological assessment of DLBCL subtypes revealed that 14 patients (42.42%) were classified as germinal center B-cell-like (GCB), while 19 (57.58%) were non-GCB. All patients received albuvirtide (ABT)-based cART, with 45.45% on ABT + Biktarvy and 54.55% on ABT + Dovato. In terms of antitumor therapy, 24 patients (72.73%) were treated with the R-EPOCH/EPOCH regimen, while 8 (24.24%) received R-CHOP/CHOP, and one patient (3.03%) was treated with a BTK inhibitor.

Among the 21 patients with baseline HIV-1 RNA ≤ 50 copies/mL, the mean age was  $57.10 \pm 10.13$  years and 18 patients (85.71%) were male. Baseline HIV-1 RNA remained low ( $1.42 \pm 0.34 \log_{10}$  copies/mL), while the mean CD4 + T-cell count was  $255.45 \pm 175.25$  cells/uL and the mean CD4/CD8 ratio was  $0.42 \pm 0.23$ . Twelve patients (57.14%) had GCB-type DLBCL, and 13 (61.90%) received R-EPOCH/EPOCH-based antitumor therapy.

### 3.3 Impact on Viral Load

Treatment with the albuvirtide (ABT)-based regimen resulted in a rapid and significant decline in HIV-1 RNA levels. The median plasma viral load (VL) decreased from a baseline of  $4.84 (2.74, 5.78) \log_{10}$  copies/mL to  $2.51 (1.70, 3.10) \log_{10}$  copies/mL by Week 4, representing a median reduction of  $2.33 \log_{10}$  copies/mL. By Week 12, the median VL further declined to  $1.70 (1.70, 2.56) \log_{10}$  copies/mL, achieving a total median reduction of  $3.14 \log_{10}$  copies/mL from baseline.

When analyzed by mean values, the VL dropped from  $4.56 \pm 1.57 \log_{10}$  copies/mL at baseline to  $2.61 \pm 0.88 \log_{10}$  copies/mL at Week 4 (mean reduction of  $1.95 \log_{10}$  copies/mL) and eventually reached  $1.92 \pm 0.85 \log_{10}$  copies/mL by Week 12 (total mean reduction of  $2.61 \log_{10}$  copies/mL (Fig. 2A).

The proportion of patients achieving virological suppression (defined as VL < 50 copies/mL or ≤  $1.70 \log_{10}$  copies/mL) showed a progressive increase throughout the study period. At Week 4, 24.24% of patients reached this threshold. This proportion increased to 51.61% at Week 8 and reached 85.71% by Week 12 (Fig. 2B).

An additional descriptive analysis was conducted in the 21-patient low-viremia subgroup with baseline HIV-1 RNA ≤ 50 copies/mL. In this subgroup, mean  $\log_{10}$  HIV-1 RNA was  $1.42 \pm 0.34$  at baseline, increased modestly to  $1.69 \pm 0.44$  at Week 4 and  $1.93 \pm 0.47$  at Week 8, and decreased to  $1.80 \pm 0.39$  at

Week 12 (Fig. 2C). Although these values were higher than baseline at follow-up, viral load remained at a low level overall; therefore, these findings should be described as low-level fluctuations rather than virological improvement.

## 3.4 Impact of Albuvirtide-Based Therapy on Immunological Parameters

The administration of albuvirtide in combination with intensive chemotherapy was associated with a progressive restoration of immune function, characterized by increases in both median CD4 + T-cell counts and the CD4/CD8 ratio.

As detailed in Supplementary Table S1, the median CD4 + T-cell count at baseline was 123 (79, 186) cells/ $\mu$ L. Despite the potential lymphotoxicity of the concurrent chemotherapy, the median count increased to 159 (92, 216) cells/ $\mu$ L by Week 8, representing a median elevation of 36 cells/ $\mu$ L from baseline. By Week 12, the median CD4 + T-cell count remained above baseline at 153 (99, 213) cells/ $\mu$ L, corresponding to a median increase of 30 cells/ $\mu$ L from baseline. Notably, by Week 8, 51.52% (17/33) of the patients achieved a CD4 + T-cell increase of more than 50 cells/ $\mu$ L. This proportion further increased to 54.55% by Week 12. The longitudinal distribution of CD4 + T-cell counts is visualized in Fig. 3A.

Simultaneously, a significant improvement in the CD4/CD8 ratio was observed. The median ratio rose from a baseline of 0.17 (0.08, 0.28) to 0.34 (0.24, 0.42) at Week 12, reflecting a median increase of 0.17. Statistical analysis indicated significant differences at Week 8 ( $p < 0.01$ ) and Week 12 ( $p < 0.001$ ) compared to baseline (Fig. 3B). Furthermore, the proportion of patients with a CD4/CD8 ratio exceeding 0.4 increased from 9.09% at baseline to 30.30% by the end of the 12-week observation period. Detailed changes in the CD4/CD8 ratio are summarized in Supplementary Table S2.

Among patients with HIV viral load  $\leq 50$  copies/mL, the overall CD4 + T-lymphocyte count exhibited a fluctuating upward trend during albuvirtide-based treatment (Fig. 3C). The mean baseline CD4 + T-cell count was  $255.45 \pm 175.25$  cells/ $\mu$ L. The count slightly increased to  $269.52 \pm 202.69$  cells/ $\mu$ L at Week 4, decreased moderately to  $251.38 \pm 161.55$  cells/ $\mu$ L at Week 8, and rebounded to the peak value of  $287.95 \pm 160.21$  cells/ $\mu$ L at Week 12 of treatment. These findings indicated that albuvirtide therapy could gradually improve immune cell levels in patients with suppressed viral load.

The CD4/CD8 ratio showed a steady improving trend throughout the treatment period (Fig. 3D). The mean baseline CD4/CD8 ratio was  $0.42 \pm 0.23$ , which rose continuously after treatment: it increased to  $0.48 \pm 0.33$  at Week 4, reached a peak of  $0.57 \pm 0.28$  at Week 8, and slightly declined to  $0.51 \pm 0.23$  at Week 12. The CD4/CD8 ratio at all follow-up time points was higher than the baseline value. These results demonstrated that albuvirtide intervention could effectively reverse immune imbalance and gradually restore immune function in patients.

In summary, for HIV-infected patients with a baseline viral load of  $\leq 50$  copies/mL, 12 weeks of albuvirtide therapy can effectively sustain viral load suppression, while continuously elevating CD4 + T-

lymphocyte counts and ameliorating systemic immune balance. These findings confirmed that albuvirtide delivered favorable virological and immunological clinical benefits among virally suppressed individuals.

## 3.5 Exploratory Analysis of Tumor-Associated Marker Expression

To further characterize the biological effects of the combined regimen, we performed an exploratory longitudinal assessment of key tumor proliferation and anti-apoptotic markers (Ki-67, C-myc, Bcl-2, and Bcl-6) using paired immunohistochemistry (Supplementary Table S3). These findings should be interpreted as exploratory and are most likely to reflect the overall therapeutic effect of intensive immunochemotherapy in the context of rapid and sustained virological suppression achieved with the albuvirtide-based regimen. In the absence of a randomized non-ABT control arm with serial pathological evaluation, these changes cannot be attributed to albuvirtide itself. Ki-67, a marker of cellular proliferation, was expressed in all 33 patients (100%) at baseline, with a median proliferation index of 90% (80%, 95%). Notably, 19 patients (57.58%) had an extremely high Ki-67 index ( $\geq 90\%$ ). By Week 12, the median Ki-67 index had significantly declined to 40% (30%, 55%) ( $p < 0.001$ ). Only three patients (9.09%) maintained a proliferation index  $\geq 90\%$ . This marked reduction is consistent with effective tumor response to R-EPOCH/EPOCH chemotherapy, potentially facilitated by improved virological control and immune recovery.

C-myc expression was positive in 15 patients (45.45%) at baseline, with a mean percentage of positive cells of  $39.33 \pm 25.83\%$ . Among these, seven patients (46.67%) showed high expression ( $\geq 40\%$  positive cells). After 12 weeks of treatment, mean C-myc expression decreased significantly to  $20.67 \pm 9.61\%$  ( $p = 0.014$ ), and only one patient (6.67%) remained in the  $\geq 40\%$  category. This reduction may indicate decreased proliferative drive within the lymphoma cells under effective combined therapy.

Bcl-2 expression was positive in 13 patients (39.39%) at baseline, with six patients showing moderate-to-strong staining intensity (score  $\geq 2$ ). By Week 12, the number of patients with intensity  $\geq 2$  decreased to three (23.08%), although the change in median intensity score did not reach statistical significance ( $p = 0.228$ ).

Bcl-6 expression was detected in 25 patients (75.76%) at baseline, of whom 15 (60.00%) showed moderate-to-strong intensity (score  $\geq 2$ ). Following treatment, the median Bcl-6 intensity score significantly declined from 2 (1, 3) to 1 (1, 2) ( $p = 0.039$ ), and the proportion of patients with intensity  $\geq 2$  decreased to nine (36.00%).

In summary, significant reductions were observed in Ki-67, C-myc, and Bcl-6 expression by Week 12. However, these exploratory biomarker changes provide supportive biological context for the overall regimen rather than direct evidence of independent antitumor activity of albuvirtide. Prospective studies incorporating randomized design, centralized pathology review, and serial biomarker assessment are required to validate these findings and clarify any potential contribution of long-acting fusion inhibitors.

## 3.6 Control-Trained Landmark Cox Survival Prediction

To provide exploratory prognostic context beyond the 12-week virological endpoint, clinical and survival data were collected from contemporaneous patients with HIV-associated DLBCL who received non-ABT ART (Fig. 1, Supplementary Table S4). A control-trained 12-week landmark Cox model was developed using the non-ABT control cohort and then applied to the ABT cohort. The final control training set included 49 patients, including 25 deaths and 24 censored observations.

The Cox model incorporated baseline  $\log_{10}$  HIV-1 RNA, baseline CD4 + T-cell count, baseline CD4/CD8 ratio, and Week-12  $\log_{10}$  HIV-1 RNA. Model discrimination was modest, with a C-index of 0.611. None of the individual predictors reached statistical significance in this limited training set, although lower Week-12  $\log_{10}$  HIV-1 RNA showed a directionally lower hazard estimate (HR = 0.534, 95% CI 0.172–1.653;  $p$  = 0.276; Fig. 4A).

After multiple imputation of missing ABT covariates, all 33 ABT-treated patients were eligible for extrapolated prediction. Based on the control-trained risk score, 10 patients (30.3%) were classified as low-risk, 16 (48.5%) as intermediate-risk, and 7 (21.2%) as high-risk (Supplementary Table S5). The corresponding model-predicted post-landmark OS curves showed clear separation among the three risk strata, with the highest predicted OS in the low-risk stratum and the lowest predicted OS in the high-risk stratum (Fig. 4B). The mean predicted post-landmark OS probabilities for the ABT cohort were 0.609 at 6 months, 0.544 at 12 months, and 0.383 at 24 months; the mean predicted 24-month RMST was 13.79 months. These estimates represent predicted outcomes under the prognostic pattern learned from the control cohort and should not be interpreted as observed survival outcomes in the ABT group.

## 4 Discussion

The present retrospective study provides real-world evidence on the efficacy of albuvirtide (ABT) combined with intensive immunochemotherapy for patients with HIV-associated aggressive B-cell lymphoma. The primary finding of this study is that an ABT-based cART regimen achieved rapid and potent virological suppression alongside exploratory signals of immune recovery, despite the concurrent administration of lymphotoxic chemotherapy. By Week 12, the median HIV-1 RNA level reached a profound reduction of 3.14  $\log_{10}$  copies/mL, with 85.71% of patients achieving virological suppression (< 50 copies/mL). Although not directly comparable because of differences in population, follow-up duration, and summary statistics, the Week 48 TALENT data reported sustained virological efficacy of ABT-based therapy compared with an NRTI-based regimen [17]. The pronounced 12-week decline in the present cohort therefore supports the hypothesis that ABT-based therapy can provide rapid early virological control during intensive chemotherapy. Furthermore, the median CD4 + T-cell count increased by 36 cells/ $\mu$ L at Week 8, and the CD4/CD8 ratio significantly improved from 0.17 at baseline to 0.34 by Week 12. These immunological findings are encouraging but should be interpreted as exploratory because supportive care and chemotherapy-related marrow recovery may also influence peripheral lymphocyte dynamics.

Compared to earlier HIV fusion inhibitors such as enfuvirtide (T20), albuvirtide demonstrates practical advantages for patients receiving intensive chemotherapy [13, 21]. T20 requires twice-daily subcutaneous injections and is frequently limited by injection-site reactions, whereas ABT's albumin-binding property extends its half-life and enables a convenient once-weekly intravenous dosing schedule [12, 21]. Moreover, ABT forms a highly stable alpha-helical conformation with the target sequence of gp41, maintaining robust antiviral activity against strains resistant to traditional antiretrovirals. Mechanistically, ABT exhibits potent in vitro antiviral activity against diverse HIV-1 strains and T20-resistant variants [14]. Furthermore, ABT possesses a higher genetic barrier to resistance, whereas T20 resistance can emerge through mutations in the gp41 N36 region [22]. Unlike traditional oral ART, which can be disrupted by chemotherapy-induced gastrointestinal toxicity such as severe nausea, vomiting, and mucositis, ABT's long-acting parenteral delivery may help maintain treatment exposure when oral intake is compromised [23, 24].

A potential practical advantage of the ABT regimen in the oncology setting is its favorable DDI profile [15]. In this cohort, 72.73% of patients were treated with the R-EPOCH/EPOCH regimen. Managing R-EPOCH/EPOCH, which requires a complex 96-hour continuous intravenous infusion, alongside multi-drug oral ART can be exceptionally challenging for both patients and clinicians, partly because several chemotherapy agents and antiretrovirals may share CYP3A4/P-glycoprotein-related pathways [9, 10]. ABT may simplify the management of such intensive protocols because of its long-acting administration schedule and limited CYP-mediated metabolic liability [12, 15]. This pharmacokinetic profile is expected to reduce, but not abolish, CYP-mediated DDI concerns with cytotoxic agents; therefore, concurrent use should still be monitored carefully.

In addition to rapid virological suppression, secondary immunological analyses showed improvements in CD4 + T-cell counts and the CD4/CD8 ratio during the 12-week observation period. These findings are clinically relevant because intensive chemotherapy can cause substantial lymphotoxic stress in patients who are already immunocompromised. However, the immune-cell changes observed in this retrospective cohort should be interpreted cautiously. Supportive care during chemotherapy, chemotherapy-related marrow recovery, infection control, and baseline immune status may all influence peripheral CD4 + T-cell dynamics. Therefore, the present data support the feasibility of maintaining virological control during chemotherapy, whereas the immunological findings should be regarded as exploratory and hypothesis-generating.

Changes in tumor-associated pathological markers were also observed during combined treatment. The proportion of patients with extremely high Ki-67 proliferation indices ( $\geq 90\%$ ) decreased from 57.58% at baseline to 9.91% at Week 12 ( $p < 0.001$ ), and Bcl-6 expression also decreased ( $p = 0.039$ ). These findings may reflect the overall effect of intensive immunochemotherapy in a setting of improved virological control. Because this study lacked a randomized non-ABT comparator and concurrent serial pathological assessment in a matched control group, these marker changes should not be interpreted as direct evidence of independent antitumor activity of ABT.

Regarding safety, our findings are consistent with previous Phase 3 trials indicating that ABT is well-tolerated [17]. No serious adverse events related to the fusion inhibitor were observed in this study, and the clear metabolic profile of ABT provided a distinct safety margin during the administration of hepatotoxic and nephrotoxic chemotherapeutic agents.

The exploratory control-trained landmark Cox analysis provides an additional prognostic perspective. When the survival model was trained in non-ABT control patients and externally projected to the ABT cohort, most ABT-treated patients were assigned to low- or intermediate-risk strata, whereas only 21.2% were classified as high-risk. This pattern is consistent with the biological plausibility that rapid virological suppression and preserved immune parameters during chemotherapy may be associated with a more favorable prognostic profile. Nevertheless, the analysis should be interpreted conservatively. The model had only modest discrimination (C-index = 0.611), individual predictors were not statistically significant, and the ABT cohort lacked directly observed long-term OS/PFS outcomes. Therefore, the prediction does not prove that ABT improves survival; rather, it suggests a hypothesis that ABT-based regimens may create a virological and immunological milieu compatible with better long-term outcomes, which requires prospective validation.

However, several limitations must be acknowledged. The study's sample size (N = 33) is relatively small, and the primary follow-up period was limited to 12 weeks, which is insufficient to assess observed long-term survival outcomes such as OS or progression-free survival (PFS) in the ABT cohort. Although a non-ABT control dataset was available for exploratory prognostic modeling, it was retrospectively collected and was not a randomized or fully matched comparator; therefore, the Cox prediction should not be interpreted as causal evidence of survival benefit. Detailed Lymphoma prognostic variables, chemotherapy response variables, and tumor marker data were incomplete or unavailable across both cohorts, limiting multivariable adjustment. Missing ABT covariates required multiple imputation, and the control-trained model included only 49 training patients with 25 death events. Future prospective, controlled studies with standardized serial HIV/immune measurements, tumor response assessment, and directly observed OS/PFS outcomes are required to validate these preliminary findings.

## 5 Conclusion

This study demonstrates that in real-world clinical practice, an albuvirtide-based cART regimen combined with intensive immunochemotherapy for patients with HIV-associated diffuse large B-cell lymphoma is associated with rapid and potent virological suppression. Improvements in CD4 + T-cell counts, CD4/CD8 ratio, and tumor-associated pathological markers were observed as secondary exploratory findings, but require cautious interpretation and prospective validation. The exploratory control-trained Cox prediction provides supportive prognostic context, but observed long-term OS and PFS outcomes remain necessary to determine whether ABT-based therapy confers a true survival advantage.

## Abbreviations

ABT  
albuvirtide  
ART  
antiretroviral therapy  
cART: combination antiretroviral therapy  
CI  
confidence interval  
CYP450  
cytochrome P450  
DAB  
3,3'-diaminobenzidine  
DDIs  
drug-drug interactions  
DLBCL  
diffuse large B-cell lymphoma  
GCB  
germinal center B-cell-like  
HIV  
human immunodeficiency virus  
HIV-1 RNA  
HIV-1 ribonucleic acid  
HRP  
horseradish peroxidase  
IHC  
immunohistochemistry  
OS  
overall survival  
PFS  
progression-free survival  
PLWH  
people were living with HIV  
R-CHOP  
rituximab,cyclophosphamide,doxorubicin,vincristine,and prednisone  
R-EPOCH  
rituximab,etoposide,prednisone,vincristine,cyclophosphamide,and doxorubicin  
RMST  
restricted mean survival time  
SD  
standard deviation  
STROBE

the Strengthening the Reporting of Observational Studies in Epidemiology  
VL  
viral load  
6-HB  
six-helix bundle.

## Declarations

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### Author contributions

HZ conceived and performed the research, collected the data, analyzed the data and wrote the manuscript. QYW, LZF and BLL performed the research, collected the data, analyzed the data. BL, ZMC, SRC, LHL, YTL and YC participated in data collection, data review and interpreted the data. XPT and HLH acquired funding, designed the research and contributed the manuscript revision. All authors contributed to the article and approved the final version of the manuscript.

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### Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Ethics approval

The research protocols received ethical approval from the Ethics Committee of Guangzhou Eighth People's Hospital, Guangzhou Medical University (K202626487). We guaranteed the privacy of patient information and the data access procedures conformed to the data and privacy regulations of Declaration of Helsinki. The registration number is ChiCTR2200063651 in Chinese Trial Registry.

### Informed consent to participate

Written informed consent to participate in this study was obtained from all participants. No participants under 16 years of age were enrolled in the present study.

## Consent to publish statement

Not applicable.

## Competing interests

The authors declare no competing interests.

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Figures

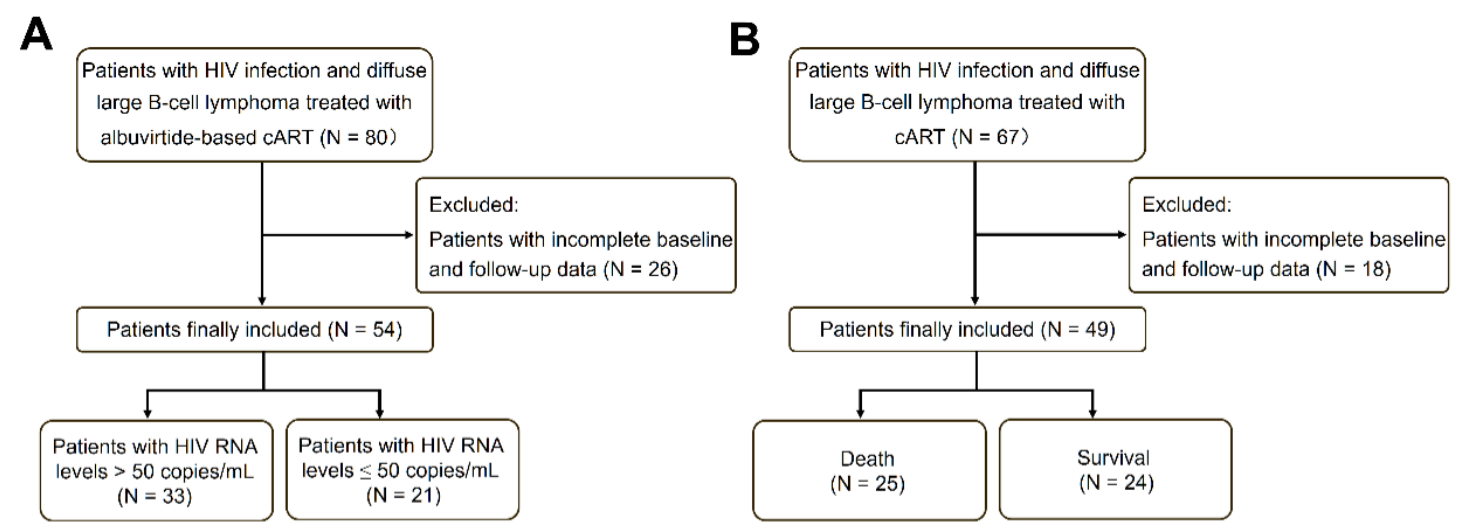
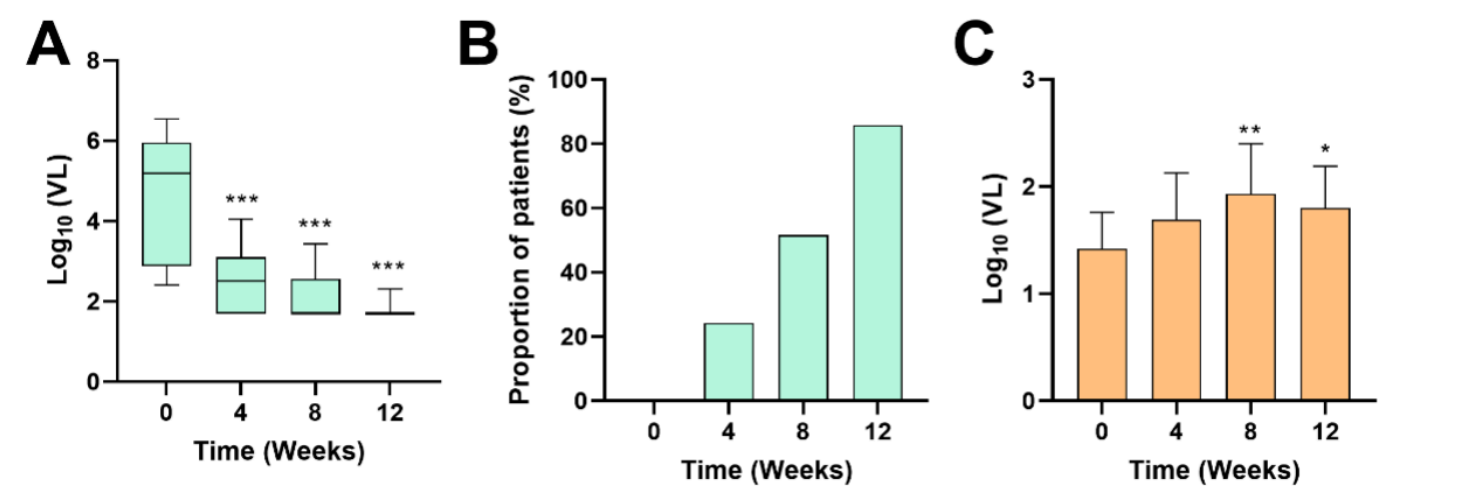


**Figure 1**

Flowchart of patient recruitment and selection process. **(A)** the screening flow for patients with HIV-associated DLBCL who received ABT-based ART; **(B)** shows the screening flow for patients with HIV-associated DLBCL who received non-ABT oral ART and were used as the non-ABT control cohort.



## Figure 2

Impact of albuvirtide-based therapy on HIV-1 viral load over 12 weeks. **(A)** Longitudinal changes in  $\log_{10}$  viral load (VL) in patients with HIV Viral Load > 50 copies/mL. The box plots represent the median and interquartile ranges. denotes  $p < 0.001$  compared to baseline (Week 0). **(B)** The proportion of patients achieving virological suppression (VL < 50 copies/mL) at Weeks 4, 8, and 12. **(C)** Longitudinal changes in  $\log_{10}$  viral load (VL) in patients with HIV Viral Load  $\leq$  50 copies/mL. \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ , representing comparisons of viral load levels at Week 4, Week 8 and Week 12 versus baseline.

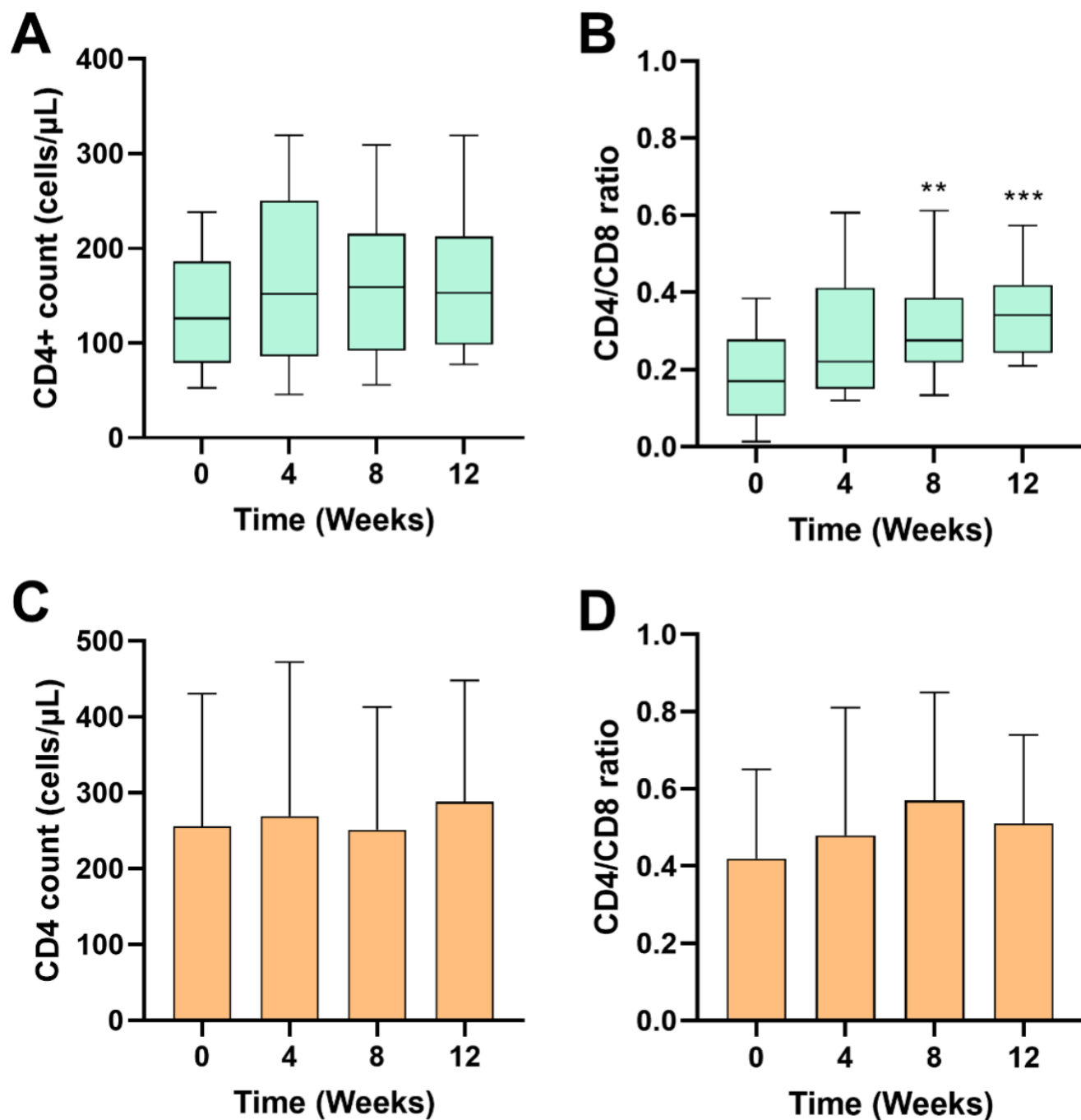


**Figure 3**

Impact of albuviridine-based combination therapy on immune cell profiles. **(A, B)** Longitudinal changes in CD4+ T-cell counts (A) and CD4/CD8 ratio (B) in patients with HIV Viral Load > 50 copies/mL. **(C, D)** Longitudinal changes in CD4+ T-cell counts (C) and CD4/CD8 ratio (D) in patients with HIV Viral Load  $\leq$  50 copies/mL. Note:  $p < 0.01$ ,  $p < 0.001$  compared to baseline (Week 0). Box plots represent the median and interquartile ranges.

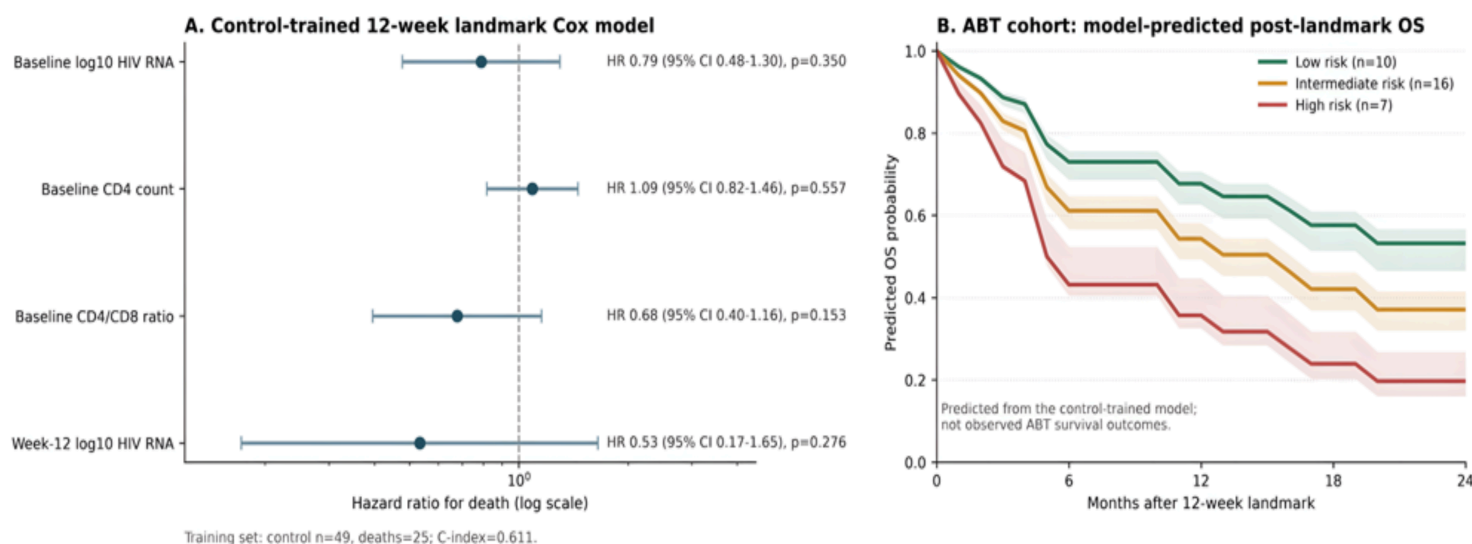


**Figure 4**

Control-trained 12-week landmark Cox model and extrapolated ABT predicted overall survival. **(A)** Hazard ratios from the Cox proportional hazards model trained in the non-ABT control cohort. Hazard ratios are presented per 1-SD increase in each predictor. The model was trained in 49 control patients with 25 deaths, and model discrimination was modest (C-index = 0.611). **(B)** Model-predicted post-landmark OS curves for the ABT cohort after multiple imputation, stratified by predicted risk group. Shaded bands indicate the interquartile range of predicted OS probabilities.

## Supplementary Files

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