SUPPLEMENTARY INFORMATION

Patient description and recruitment

The CAPRI-T was one of two (along with the CAPRI-NK, see reference [29]) basic immunological studies nested within the CAMELIA trial. Patients who agreed to participate in the CAPRI studies enrolled through a consent process that was independent of the parental CAMELIA study. We note that the CAPRI-NK recruited patients from June of 2007 to August of 2008, while the CAPRI-T recruited patients from January of 2008 to May of 2009. During the time that the two sub-studies overlapped (between January 2008 and August 2008), patients were randomly assigned to the CAPRI-NK or CAPRI-T study at the time they enrolled in the CAMELIA trial. Once the CAPRI-NK study finished recruiting patients, all newly enrolled CAMELIA patients were offered enrollment in the CAPRI-T study. No other selection was performed.

After approximately 50% of the enrollment of the CAPRI-T was met, it was observed that the majority of TB-IRIS patients developed TB-IRIS within 21 days post-ART initiation. Based on these observations, the CAPRI-T protocol was modified to add blood draws at week 4 and week 10 post-TB treatment initiation, which corresponded to 2 weeks after ART initiation in each CAMELIA treatment arm. This strategy resulted in a control sample drawn from non-TB-IRIS patients at the approximate time TB-IRIS occurred in those patients who experienced TB-IRIS. Indeed, the median time of TB-IRIS at the end of the study was determined to be 12 days (IQR: 7-24 days). The amended study protocol was approved by the CAMELIA Scientific Advisory Board, the National Ethics Committee of

Cambodia, and the other institutional review boards that are noted in the Methods section of the main text.

As described [1], TB was treated with a standard daily regimen of isoniazid, rifampin, ethambutol, and pyrazinamide for the first 2 months followed by daily administration of isoniazid and rifampin during the ensuing 4 months. HIV was treated with stavudine, lamivudine, and efavirenz initiated at 2 weeks (CAMELIA early arm) or 8 weeks (CAMELIA late arm) after TB treatment onset.

TB-IRIS was defined as unexplained worsening or emergence of symptoms or signs of TB (e.g. fever, cough, shortness of breath, new lymph node enlargement or exacerbation of disease at other extra pulmonary sites) that occurred after ART initiation, which could not be attributed to an etiology other than TB [1, 7]. Each case of suspected TB-IRIS reported by on-site treating physicians was subsequently validated by at least two experienced physicians who were members of the study team and who were not involved in the daily care of the patients. Reviewers had full access to medical record documents and outcomes, and the validation process was not blinded [1, 7]. Patients who had at any time been suspected of experiencing IRIS or TB-IRIS, even if not subsequently validated, were excluded from further analysis.

Strategy employed to identify early post-ART phenotypic and cytokine parameters associated with TB-IRIS

Among the 50 TB-IRIS patients, 36 experienced the TB-IRIS event within 3 weeks of ART initiation with a median of 10 days (IQR: 6-14), as compared to

the larger group of 50 TB-IRIS patients who experienced TB-IRIS with a median of 12 days (IQR: 7-24) post-ART initiation. This subgroup of 36 TB-IRIS patients who developed TB-IRIS within the three weeks of initiating ART were compared to patients for whom we had a week 2 blood draw to investigate phenotypic and cytokine changes between ART initiation and TB-IRIS. The addition of the week 2 post-ART timepoint as described above (and in the Methods) provided a non-TB-IRIS timepoint that was comparable to the time of TB-IRIS occurrence in both the early and late CAMELIA treatment arms. Focusing on the subgroup of 36 TB-IRIS patients who experienced TB-IRIS within 3 weeks thus allowed us to evaluate immune parameters associated with TB-IRIS between ART initiation and the TB-IRIS event and compare these to findings to the non-TB-IRIS control patient group sampled at ART initiation and the new week 2 timepoint.

Among the 36 TB-IRIS patients in this subgroup, CD4+ T cell counts and BMI were similar at ART initiation to the overall group of 50 TB-IRIS patients and to the non-TB-IRIS patient group. We note, however, that viral load was higher in this subgroup of 36 TB-IRIS patients compared to the non-TB-IRIS group (median: 6.0 versus 5.7 log copies/ml, respectively; p=0.006). This difference was larger than that seen when the overall group of 50 TB-IRIS patients was compared to non-TB-IRIS patients (median: 5.9 vs. 5.7 log copies/ml, respectively; p=0.040).

SUPPLEMENTARY FIGURES AND TABLES



Supplementary Figure 1. A representative example of the gating strategy used in the immunophenotypic analyses. Gating strategies to define each T cell subpopulation evaluated in the study are shown.



Supplementary Figure 2. Mixed linear regression analysis of ICOS⁺CD4⁺, CD28⁺CD8⁺, and PD-1⁺CD8⁺ T cell co-stimulatory markers in TB-IRIS and non-TB-IRIS patients. T cell immunophenotypes were obtained by staining of whole blood samples. Since the percentages were not normally distributed they were plotted with square root transformation. TB-IRIS patients (filled circles and solid line) and non-TB-IRIS patients (open circles and dashed line) are shown at the time of sample analysis post-ART initiation. A) ICOS+CD4+ T cells; B) CD28+CD8+ T cells; C) PD-1+CD8+ T cells. NS=not significant. P- and q-values are shown in Suppl. Tables 2 and 3.



Supplementary Figure 3: Legend on next page

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Supplementary Figure 3. Changes in cellular phenotype and circulating plasma cytokine levels between ART initiation and the week 2 timepoint or the TB-IRIS event.

Changes in CD27+CD95-CD45RO-CD8+ T cells (A) and in CD27+CD95-CD45RO-CD4+ T cells (B) between ART initiation and the week 2 timepoint or the TB-IRIS event.

Wilcoxon rank sum tests were used to compare the net percent change in frequency of CD27+CD95-CD45RO-CD8+ T cells (A) and in CD27+CD95-CD45RO-CD4+ T cells (B) between ART initiation and the week 2 timepoint for 28 non-TB-IRIS patients (open circles) or ART initiation and the TB-IRIS event (median=10 days) for 32 TB-IRIS patients who experienced TB-IRIS within 21 days of ART initiation (filled circles). Although the CD27+CD95-CD45RO-CD8+ T cell subpopulation bears hallmarks of naïve cells, the significantly greater net increase in CD27+CD95-CD45RO-CD8+ T cell proportions during the first two weeks of ART in the TB-IRIS patient group may also represent a γ/δ T cell expansion, since a proportion of V δ 1 γ/δ T cells are CD8+ (see supplemental references 1 and 2), which are mostly CD45RA+ [supplemental reference 1) and, in HIV patients, are also CD27+ (supplemental reference 3). P and q values for these analyses are presented in Suppl. Table 4.

Changes in levels of IL-6 (C), IL-1 β (D), IL-8 (E) , IL-10 (F), IL-17 (G), IL-12 (H), TNF (I), IL-7 (J), and IFN- γ (K) between ART initiation and the week 2 timepoint or the TB-IRIS event.

The Wilcoxon signed-rank test for paired samples was used to compare changes in plasma cytokine level between week 0 and week 2 of ART in non-TB-IRIS patients (n=19) (open circles) and between week 0 of ART and the TB-IRIS event in TB-IRIS patients (n=23) (closed circles). The Wilcoxon rank sum test was used to compare cytokine levels at week 0 between the two groups and at week 2 or the TB-IRIS event in the two patient groups. P and q values for these analyses are presented in Suppl. Table 5.



Supplementary Figure 4. Markers of CD4⁺ and CD8⁺ T-cell activation and regulatory activity in TB-IRIS and non-TB-IRIS patients at each timepoint displayed side-by-side to distinguish the spread of data within each group (based on data shown in Fig. 2 of the main text). A) Activated (CD45RO+HLA-DR+) CD4+ T cells; B) CCR5+CD4+ T cells; C) Activated (CD38+HLA-DR+) CD8+ T cells; D) CD4+ regulatory T cells.



Supplementary Figure 5. Markers of CD4⁺ and CD8⁺ T-cell memory differentiation in TB-IRIS and non-TB-IRIS patients at each timepoint displayed side-by-side to distinguish the spread of data within each group (based on data shown in Fig. 3 of the main text). A) Effector memory (CD62L-CD45RA-) CD4+ T cells; B) Central memory (CD62L+CD45RA-) CD4+ T cells; C) Fas+ effector memory (CD27-CD95+CD45RO+) CD4+ T cells; D) Fas+ effector memory (CD27-CD95+CD45RO+) CD8+ T cells; E) Effector memory (CD27-CD45RA-) CD8+ T cells; F) Transitional/early effector memory (CD27+CD45RA-) CD8+ T cells.



Supplementary Figure 6. Differences in OX40⁺CD4⁺ T-cell frequencies between TB-IRIS and non-TB-IRIS patients at each timepoint displayed side-by-side to distinguish the spread of data within each group (based on data shown in Fig. 4 of the main text).

Supplementary Table 1.

Mix	FITC	PE	PerCP	APC	
					General lymphocytes markers
1	lso lgG	lso lgG	lso lgG	lso lgG	Isotype
2	CD3	CD14	CD45	CD19	T & B lymphocytes, monocytes
3	CD4	CD8	CD45	CD3	CD4+ and CD8+ T cells
					CD4+ T cell markers
4	CD27	CD45RO	CD4	CD95	Naïve/memory CD4+ T cells; Fas+ CD4+ T cells
5	CD3	CD45RA	CD4	CD62L	CM and EM CD4+T cells
6	CD3	CD45RO	CD4	HLA-DR	Activated CD4+ T cells
7	CD3	CD45RO	CD4	CCR5	CCR5+CD4+T cells
8	CD127	CD25	CD4	CD3	Regulatory CD4+ T cells
9	OX40	ICOS	CD4	CD3	Ox40+ and ICOS+CD4+ T cells
					CD8+ T cell markers
10	CD27	CD45RA	CD8	CD3	CM/early EM and EM CD8+ T cells
11	CD27	CD45RO	CD8	CD95	Naïve/memory and Fas+CD8+ T cells
12	CD38	CD8	CD3	HLA-DR	Activated CD8+ T cells
13	CD28	CD103	CD8	CD3	CD28+CD8+ T cells
14	CD27	PD-1	CD8	CD3	PD-1+CD8+T cells

Supplementary Table 1. Fluorescent antibody panels used in the analyses. Fluorescently conjugated antibody panels used for immunophenotypic analysis of whole blood samples are shown.

Supplementary Table 2.

Parameter	p-value	q-value
HLA-DR+CD45RO+ CD4+ T cells TB-IRIS vs. non-TB-IRIS at W0: frequency was higher TB-IRIS patients	<0.0001	0.00067
Fas+ EM CD8+ T cells TB-IRIS vs. non-TB-IRIS at W0: frequency was higher in TB-IRIS patients	<0.0001	0.00067
CD4+ T regulatory cells TB-IRIS vs. non-TB-IRIS: <i>post-ART decrease was greater in TB-IRIS patients</i>	<0.0001	0.00067
OX40+CD4+T cells TB-IRIS vs. non-TB-IRIS: <i>post-ART decrease was greater in TB-IRIS patients</i>	<0.0001	0.00067
HLA-DR+CD45RO+ CD4+ T cells Both groups: difference between pre-week 8 and post-week 8 curve slopes	<0.0001	0.00067
CD4+ T regulatory cells TB-IRIS vs. non-TB-IRIS: <i>slowing of decrease post-week 8 was greater in TB-IRIS patients</i>	0.0001	0.00067
CD62L-CD45RA- EM CD4+ T cells TB-IRIS vs. non-TB-IRIS: post-ART increase was greater in TB-IRIS patients	0.001	0.004
CCR5+CD4+ T cells Both groups: <i>difference between pre-week 8 and post-week 8 curve slopes</i>	0.001	0.004
CD62L+CD45RA- CM CD4+ T cells Both groups: difference between pre-week 8 and post-week 8 curve slopes	0.001	0.004
CD62L-CD45RA- EM CD4+ T cells Both groups: difference between pre-week 8 and post-week 8 curve slopes	0.001	0.004
OX40+CD4+T cells TB-IRIS vs. non-TB-IRIS: <i>slowing of decrease post-week 8 was greater in TB-IRIS patients</i>	0.002	0.0073
CD62L-CD45RA- CM CD4+ T cells TB-IRIS vs. non-TB-IRIS: post-ART decrease was greater in TB-IRIS patients	0.004	0.013
Fas+ EM CD4+ T cells TB-IRIS vs. non-TB-IRIS: <i>post-ART increase was greater in TB-IRIS patients</i>	0.005	0.015
CCR5+CD4+ T cells TB-IRIS vs. non-TB-IRIS at W0: <i>frequency was higher in TB-IRIS patients</i>	0.006	0.017
Fas+ EM CD8+ T cells TB-IRIS vs. non-TB-IRIS: slowing of increase post-week 8 vs. pre-week 8 was greater in TB-IRIS patients	5 0.012	0.032
OX40+CD4 +T cells TB-IRIS vs. non-TB-IRIS at W0: <i>frequency was higher in TB-IRIS patients</i>	0.013	0.033
CD27+CD45RA- CM/early EM CD8+ T cells TB-IRIS vs. non-TB-IRIS at W0: frequency was lower in TB-IRIS patients	0.017	0.040
Fas+ EM CD4+ T cells TB-IRIS vs. non-TB-IRIS: <i>slowing of increase post-week 8 vs pre-week 8 was greater in TB-IRIS patients</i>	0.030	0.066
Fas+ EM CD8+T cells Both groups: difference between pre-week 8 and post-week 8 curve slopes	0.032	0.066
CCR5+CD4+ T cells TB-IRIS vs. non-TB-IRIS: <i>post-ART increase was greater in TB-IRIS patients</i>)	0.033	0.066
HLA-DR+CD38+ CD8+T cells TB-IRIS vs. non-TB-IRIS: <i>post-ART decrease was lesser in TB-IRIS patients</i>	0.041	0.078
CCR5+CD4+ T cells TB-IRIS vs. non-TB-IRIS: pre-week 8 vs. post-week 8 change in phenotype frequency	0.050	0.091
CD27-CD45RA- EM CD8+T cells TB-IRIS vs. non-TB-IRIS at W0	0.060	0.10
CD28+CD8+ T cells TB-IRIS vs. non-TB-IRIS: evolution post-ART	0.064	0.11
PD1+CD8+ T cells TB-IRIS vs. non-TB-IRIS: evolution post-ART	0.075	0.12

HLA-DR+CD45RO+ CD4+ T cells TB-IRIS vs. non-TB-IRIS: evolution post-ART	0.094	0.14
CD27+CD95-CD45RO-CD8+ T cells TB-IRIS vs. non-TB-IRIS at W0	0.19	0.28
ICOS+CD4+T cells TB-IRIS vs. non-TB-IRIS at W0	0.35	0.48
FAS+ EM CD8+ T cells TB-IRIS vs. non-TB-IRIS: evolution post-ART	0.35	0.48
CD45RO-CD27+CD95-CD8+ T cells TB-IRIS vs. non-TB-IRIS: evolution post-ART	0.36	0.48
ICOS+CD4+ T cells TB-IRIS vs. non-TB-IRIS: evolution post-ART	0.39	0.50
Fas+ EM CD4+ T cells TB-IRIS vs. non-TB-IRIS at W0	0.40	0.50
CD28+CD8+ T cells TB-IRIS vs. non-TB-IRIS at W0	0.46	0.56
CD62L+CD45RA- CM CD4+ T cells TB-IRIS vs. non-TB-IRIS at W0	0.48	0.56
CD27-CD45RA- EM CD8+ T cells TB-IRIS vs. non-TB-IRIS: evolution post-ART	0.56	0.64
PD1+CD8+T cells TB-IRIS vs. non-TB-IRIS at W0	0.69	0.76
CD4+ T regulatory cells TB-IRIS vs. non-TB-IRIS at W0	0.72	0.76
CD27+CD45RA- CM/early EM CD8+ T cells TB-IRIS vs. non-TB-IRIS: evolution post-ART	0.85	0.90
HLA-DR+CD38+ CD8+T cells TB-IRIS vs. non-TB-IRIS at W0	0.91	0.93
CD62L-CD45RA- EM CD4+ T cells TB-IRIS vs. non-TB-IRIS at W0	0.96	0.96

Supplementary Table 2. False Discovery Rate (FDR) analysis of mixed effect linear regression models. We used mixed effect linear regression models and performed FDR analysis to correct for multiple comparisons in order to identify the association of individual cellular phenotypes with TB-IRIS. As described in the Methods section, four unique comparisons were subjected to statistical testing: i) TB-IRIS vs. non-TB-IRIS: W0, which compared phenotype frequencies at ART initiation between TB-IRIS patients and non-TB-IRIS patients; ii) TB-IRIS vs. non-TB-IRIS: evolution post-ART, which compared the post-ART rate of change in individual phenotype frequencies between TB-IRIS and non-TB-IRIS patients; iii) Both groups: slope prevs. post-week 8 of ART, which analyzed whether the frequency of each cellular phenotype changed at a different rate post-week 8 of ART as compared to pre-week 8 of ART within the total patient cohort as measured by change in slope of curves; and iv) TB-IRIS: slope pre-vs. postweek 8 of ART, which analyzed whether differences in phenotype rate of change pre-versus post-week 8 of ART were significantly different between TB-IRIS and non-TB-IRIS patients. Overall, 21 significant differences (p<0.05) were found out of the 40 parameters studied. Parameters for which significant differences were detected are shown in bolded font. The estimated q-value was 0.078 for the largest significant p-value, indicating that only 2 of the 21 findings might not be significant.

Supplementary Table 3.

p-value	q-value
<0.0001	0.0015
0.0003	0.0023
0.0021	0.011
0.0035	0.013
0.011	0.032
0.034	0.084
0.067	0.12
0.072	0.12
0.075	0.12
0.150	0.23
0.190	0.26
0.220	0.28
0.540	0.62
0.630	0.67
0.730	0.73
	P-value <0.0001 0.0021 0.0035 0.011 0.034 0.067 0.072 0.075 0.150 0.190 0.220 0.540 0.630 0.730

Supplementary Table 3. False Discovery Rate (FDR) analysis using p- and q-values from Wilcoxon rank sum analysis of T cell phenotypes between TB-IRIS and non-TB-IRIS patients at week 34 post-TB therapy. Bolded parameters/p-values indicate cellular phenotypes that were present at significantly different frequencies at week 34 post-TB therapy initiation. The estimated q-value was 0.084 for the largest significant p-value, indicating that the six significant differences that were detected are truly significant.

Supplementary Table 4.

Phenotype	p-value	q-value
HLA-DR+CD45RO+CD4+ T cells (increase was greater in TB-IRIS patients)	0.0023	0.026
CCR5+CD4+ T cells (increase was greater in TB-IRIS patients)	0.0035	0.026
CD27+CD95-CD45RO-CD8+ T cells (increase was greater in TB-IRIS patients)	0.0085	0.043
Transitional memory CD8+ T cells	0.078	0.29
HLA-DR+CD38+T cells	0.14	0.35
CD28+CD8+ T cells	0.14	0.35
Effector memory CD4+ T cells	0.16	0.35
PD1+CD8+ T cells	0.31	0.58
CD4+ T regulatory cells	0.40	0.66
Fas+ EM CD4+ T cells	0.44	0.66
Central memory CD4+ T cells	0.51	0.70
OX40+CD4+ T cells	0.62	0.73
Effector memory CD8+T cells	0.63	0.73
ICOS+CD4+ T cells	0.77	0.83
Fas+ EM CD8+ T cells	0.89	0.89

Supplementary Table 4. False Discovery Rate (FDR) analysis using p- and q-values from Wilcoxon rank sum analysis of net change in cellular phenotype frequencies between ART initiation and week 2 or the TB-IRIS event. Bolded parameters/p-values indicate cellular phenotypes that showed relatively greater increase in frequency between week 0 of ART and week 2 for non-TB-IRIS patients or the TB-IRIS event for TB-IRIS patients. The estimated q-value for the largest significant p-value was 0.043, indicating that the three significant differences detected are truly significant.

Supplementary Table 5.

А

Cytokine	p-value	q-value	
IL-10 (higher in TB-IRIS patients)	0.0030	0.036 0.10	
IL-8 (higher in TB-IRIS patients)	0.019		
IL-6 (higher in TB-IRIS patients)	0.026	0.10	
IL-1 β (higher in TB-IRIS patients)	0.045	0.14	
IL-17A	0.10	0.24	
GM-CSF	0.19	0.34	
IL-12	0.20	0.34	
TNF	0.26	0.37	
IFN-γ	0.28	0.37	
IL-4	0.53	0.64	
IL-2	0.72	0.76	
IL-7	0.99	0.99	

В

p-value	q-value
0.0001	0.0012
0.0002	0.0012
0.0025	0.010
0.0064	0.019
0.022	0.053
0.047	0.089
0.05	0.089
0.16	0.24
0.64	0.73
0.64	0.73
0.67	0.73
0.79	0.79
	p-value 0.0001 0.0025 0.0064 0.022 0.047 0.05 0.16 0.64 0.64 0.64 0.67 0.79

Comparison of plasma cytokines at week 0 between non-TB-IRIS patients and TB-IRIS patients.

Comparison of plasma cytokines at the week 2 timepoint (for non-TB-IRIS patients) vs. at the TB-IRIS event (TB-IRIS patients).

С

Cytokine	p-value	q-value
IL-6 (increase greater in TB-IRIS patients)	0.0069	0.083 0.16
IL-1 β (increase greater in TB-IRIS patients)	0.027	
GM-CSF	0.14	0.54
IL-7	0.19	0.57
IL-12	0.26	0.62
IL-8	0.44	0.82
ΙFN-γ	0.48	0.82
IL-2	0.63	0.90
IL-4	0.68	0.90
IL-10	0.78	0.94
IL-17A	0.92	0.94
TNF	0.94	0.94

Net change in plasma cytokines beween week 0 at week 2 (non-TB-IRIS patients) vs. between week 0 and the TB-IRIS event (TB-IRIS patients).

Supplementary Table 5. False Discovery Rate (FDR) analysis using p- and q-values from Wilcoxon rank sum analyses of absolute plasma cytokines at ART initiation and week 2 or the TB-IRIS event (A&B) or net change in cytokine concentration between these timepoints (C). A) Cytokine differences at ART initiation, with significant differences indicated in bolded text. B) Cytokine differences at the week 2 timepoint in non-TB-IRIS patients versus at the time of the TB-IRIS event in TB-IRIS patients, with significant differences indicated in bolded text. C) Differences in net increase of each cytokine between W0 and W2 in non-TB-IRIS patients as compared to between W0 and the TB-IRIS event in TB-IRIS patients, with significate that all findings determined to be significant by p-value are truly significant.

Supplementary Table 6.

	Non-IRIS (n=104)	IRIS (n=50)	p value
Male sex no. of patients (%)	63 (60)	40 (80)	0.02
Age -years Median Interquartile range	35.0 29-41.5	34.5 30-42	0.71
Body mass index kg/m2 Median Interquartile range	16.6 15.2-18.5	16.9 15.5-19.1	0.44
CD4 T cell count per mm3 Median Interquartile range	32.0 14-71	24.5 12-45	0.11
Viral load log10 copies/ml Median Interquartile range	5.7 5.3-5.9	5.8 5.4-6.3	0.16
Karno performance score- no. of patients (%) >=80 60-70 <=50	7 (6) 70 (67) 27 (26)	9 (18) 31 (62) 10 (20)	0.11
Hemoglobin g/dl Median Interquartile range	86.0 76-104	82.5 65-105	0.34

Supplementary Table 6. Baseline patient characteristics of Capri-T study participants.

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