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Clinical Interventions for HTLV-1-associated diseases

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Efficacy of treatment less certain

		n	
1990	Prednisolone	65	91% improved, max@1-3m Osame *et al*, Hematology Reviews 1990;3 271-284
1990	IV Methyl Pred	9	Transient benefit 6/ Duncan & Rudge JNNP 1990;53:173-4
1991	Prednisolone	19	Subjective short-term improvement, long term deterioration, Objective short term no change, long term stable or worse Kira *et al*, J NeuroSci 1991;106:41-49
1996	Prednisolone	131	>1 grade improvement 91/ Nakagawa *et al*, J Neurovirol 1996;2:345-355
2008	IV Methyl Pred	39	Transient improvement with 1st & 2nd infusions Croda *et al*, J Neur Sci.2008;269:133-7

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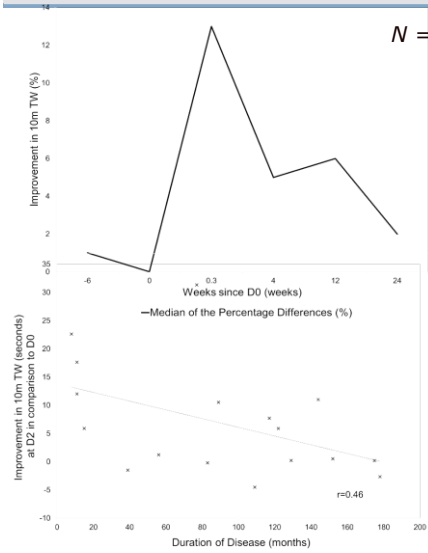
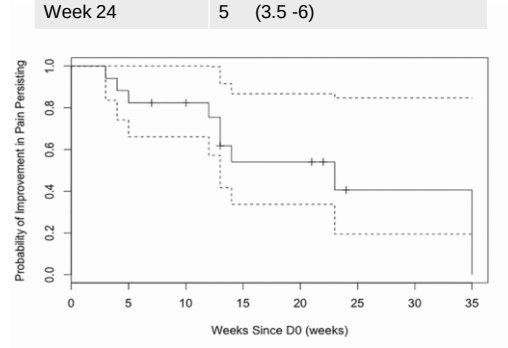
Effect of pulsed Methyl Prednisolone on Gait and Pain

Buell et al PLoS One 2016;11(4):e0152557



N = 26

PAIN Scores	Median (IQR)
Pre	8 (5 – 8.5)
Day 0	7 (6 - 8)
Day 2	3 (1.5 – 5)
Week 4	5 (2 – 7)
Week 12	6.5 (4.3 -8)
Week 24	5 (3.5 -6)



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Prednisolone Long-term FU

Multi-centre Case Note Review (n=86)
Median FU 3.4 years

		Change in OMDS grade/year
Oral Prednisolone	57 on median daily dose 4.8mg	↑0.12
No DMT	29	↓0.13

No Px 79% deteriorated by ≥ 1 Grade

****

Telephone interviews of 248 HAMnet registered patients –
4 years Prospective FU.

107 on oral prednisolone 26% deteriorated by ≥ 1 OMDS grade
129 not on treatment 35.7% deteriorated by ≥ 1 OMDS grade (p 0.07) .

Coler-Reilly et al, P-E-11 & Sato et al P-E-25
18th International Conference on Human Retrovirology, Tokyo, 2017

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What about steroid sparing immunosuppression?

1989	Azathioprine	4	4 patients improved

Osame *et al*, Hematology Reviews 1990;3 271-284

1996	Azathioprine	9	6 improved >1 grade
	Salazopyrine	24	12 improved >1 grade

Nakagawa *et al*, J Neurovirol 1996;2:345-355

1994	Cyclophos	1	1 remarkable improvement

Misra *et al* J Neuro Sci 1994;122:155-6

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Treatment of HAM with Ciclosporin

- Open-label proof of principle study of 8 patients with early or progressing HAM
- 48 weeks dose adjusted Ciclosporin A
- FU to 72 weeks
- Pulsed Methyl Prednisolone allowed.
- Primary endpoints are Rate of Clinical Failure by 48 weeks and time to clinical Failure

Martin et al. PLoS Neg Trop Dis 2012:6(5):e1675

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Primary endpoint at 48 weeks is Clinical Failure

Lack of objective improvement at 3 months

>2 point deterioration in disability on IPEC 1 scale compared with baseline at two consecutive visits excluding weeks 2 and 4

>30% deterioration in timed walk at any time compared to baseline

Martin et al. PLoS Neg Trop Dis 2012:6(5):e1675

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Primary endpoints at 48 weeks

Number	7
Lack of any objective improvement	0 (0%)
> 2 point deterioration in the IPEC 1 scale compared with baseline at 2 consecutive visits	
Yes	1 (14%)
No	6 (86%)
30% deterioration in timed walk compared with baseline at any time point	
Yes	4 (57%)
No	3 (43%)

Martin et al. PLoS Neg Trop Dis 2012:6(5):e1675

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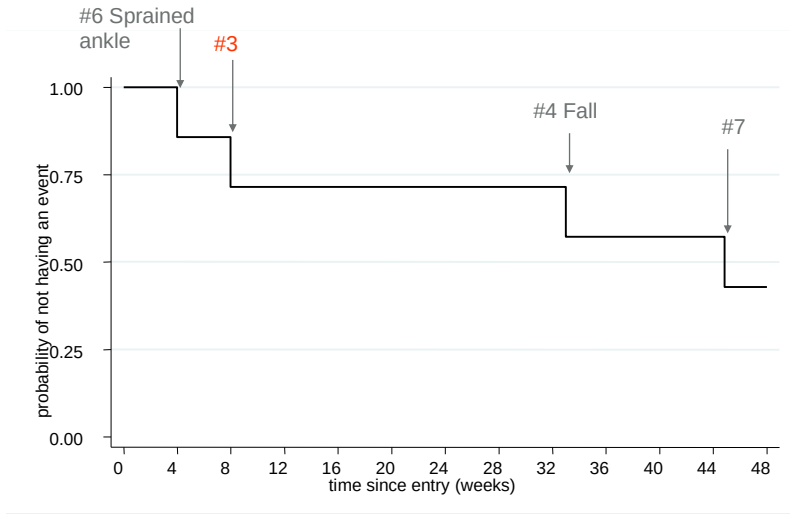
Time to clinical failure (Kaplan-Meier)



Martin et al. PLoS Neg Trop Dis 2012:6(5):e1675

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Improvement in 10m Timed walk

		ITT		Per-protocol
Change from baseline	n	Mean (SE) Secs	n	Mean (SE) Secs
To week 12	7	-12 (6)	6	-14 (6)
To week 24	7	-11 (5)	5	-14 (6)
To week 48	7	-6 (7)	5	-10 (9)
To week 72	7	-3 (7)	3	-4 (5)

Martin et al. PLoS Neg Trop Dis 2012:6(5):e1675

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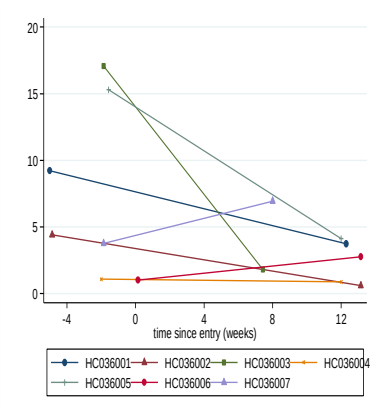
Reduced HTLV-1 viral burden in CSF

	Change from baseline
Blood log10 HTLV-1 proviral DNA (mean, SE, copies/100 PBMCs)	-0.08 (0.10)
CSF log10 HTLV-1 pro-viral DNA (mean, SE, copies/100 CSF MCs)	-0.39 (0.15)
CSF/Blood ratio	-4.4 (2.6)



Martin et al. PLoS Neg Trop Dis 2012:6(5):e1675

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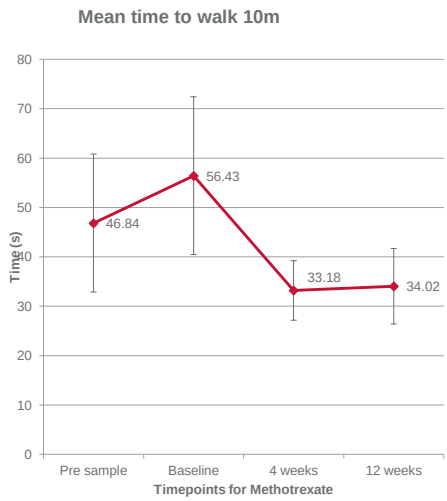
Methotrexate – 10m Timed walk



MTX 7.5-15mg weekly

Walking improved in 2/3rd

by 22 seconds at 12 weeks

Reduction in markers of inflammation in blood

N=13

Ahmed et al, Retrovirology 2104;11 suppl P-33

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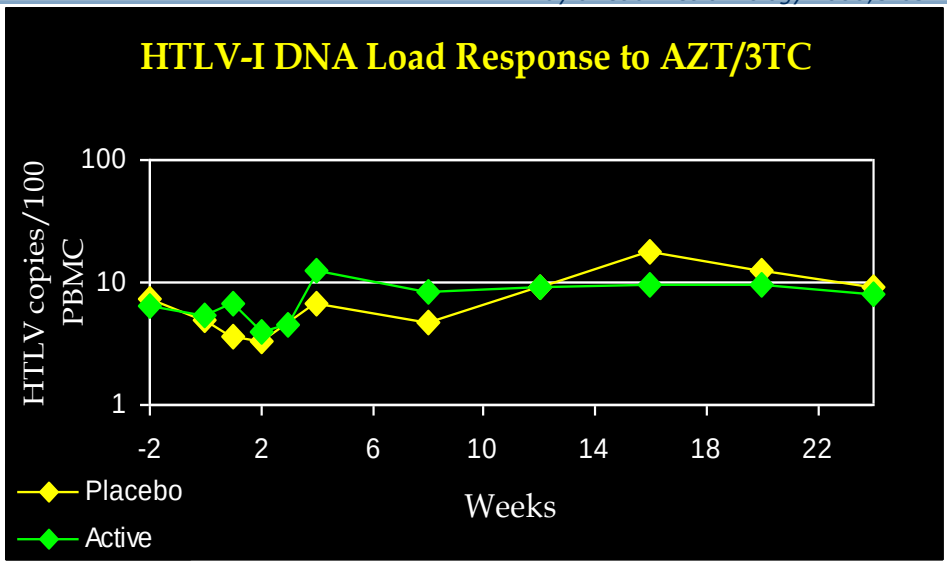
Anti-retroviral therapy not effective

Taylor et al Retrovirology 2006;3:63



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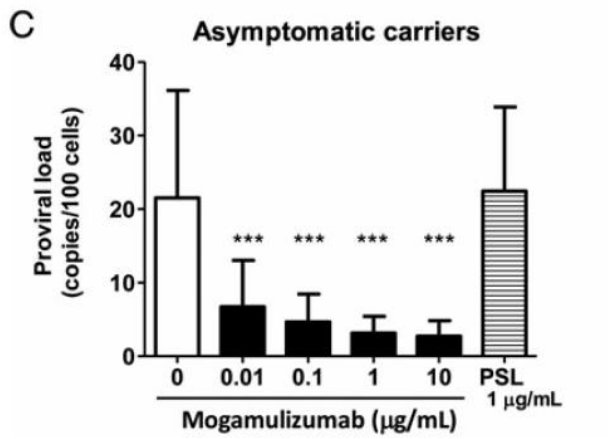
Anti-CCR4 – reduces HTLV-1 proviral load ex vivo



Yamauchi et al, JID 2015;211:238-248

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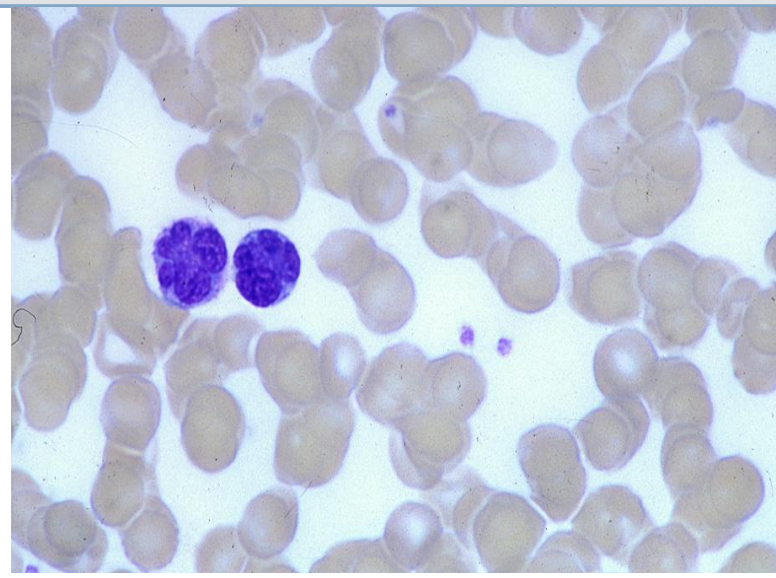
Adult T-cell Leukaemia – High Mortality



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Lymphomatous ATL

Median age of onset
51.5 years

Median survival 6 – 8 m

- ***Lymphadenopathy***
- ***Hepatosplenomegaly***
- ***Lytic bone lesions***
- ***Hypercalcemia***

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Cutaneous manifestation of ATL

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Shimoyama classification of ATLL

	Lymphocyte count ($x10^9$/L)	Number of abnormal T lymphocytes	Corrected calcium	LDH	Other
Smouldering	**<4**	**>5%**	**Normal**	**≤ 1.5x ULN**	***Skin or pulmonary lesions**
Chronic	**>4**	**>5%**	**Normal**	**≤ 2x ULN**	**LA, liver, spleen, skin, lung NOT GI tract, CNS or bone**
Lymphoma	**<4**	**≤1%**	**→/↑**	**→/↑**	**Lymph node +/- extra-nodal lesions**
Acute	**>4**	**>5%**	**→/↑**	**→/↑**	**Tumour lesions**

Biopsy proven with evidence of proviral integration
Shimoyama et al, 1991

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Shimoyama classification – outcome data

	Mean survival (months)	2 year survival	4 year survival
Smouldering	NR	77.7%	62.8% *Indolent*
Chronic	24.3	52.4%	26.9%
Lymphoma	10.2	21.3%	5.7% *Aggressive*
Acute	6.2	16.7%	5%

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Chemotherapy for ATLL

Table 1 ATLL: Chemotherapy Regimens

Year	Regimen	No	CR (%)	PR (%)	Response Rate	Median Survival rates	Survival rate	Author
1980`s	CHOP / CHOP Like	Various	18%	N/A	N/A	~5-6 Months	NA	Shimoyama 1988
1996	CHOP followed by Etoposide/vindesine/ Ranimustine and mitoxantrone/GCSF	81 44 Acute 37 Lymphoma	36%	38%	74%	8.5 Months	3 Year OS 13.5%	Taguchi,H et al 1996 J Aids
2001	LSG 15 : VCAP/AMP/VECP/VACP VCAP(Vincristine,cyclophosphamide, doxorubicin, prednisolone),AMP (Doxorubicin,,ranimustine,prednisolone), VECP(Vindesine,etoposide,carboplatin, prednisolone)	96 58 Acute 28Lymphoma 10 UC	35.5%	45.2%	81%	13 Months	2 Years 31.3%	Yamada et al BJH 2001 *Value of dose intensity confirmed
2003	Deoxy coformycin (JCOG 9109)	62 34 Acute 21 Lymphoma 7 UC	28%	24%	52%	7.4 Months	2 year Estimated 15.5%	Tsukasaki K et al 2003 Int J Hematol *DCF abandoned
2007	VCAP-AMP-VECP Compared to bi-weekly CHOP/GCSF (JCOG9801)	118	VAC 40% CHOP 24%	VAC 32% CHOP 41%	VAC 72% CHOP 65%	13 Months VAC 11 Months CHOP	3 Year OS 24% VAC 13% CHOP	Tsukasaki K JCO 2007 *Dose intensity regimen superior to CHOP
2011	Phase II CHOP +CD25 ab	15 11 Acute 4 Lymphoma	33%	20%	53%	10/12 in high responders	CR patients DFS 15/12	Caesay,M et al 2011 Leuk Res

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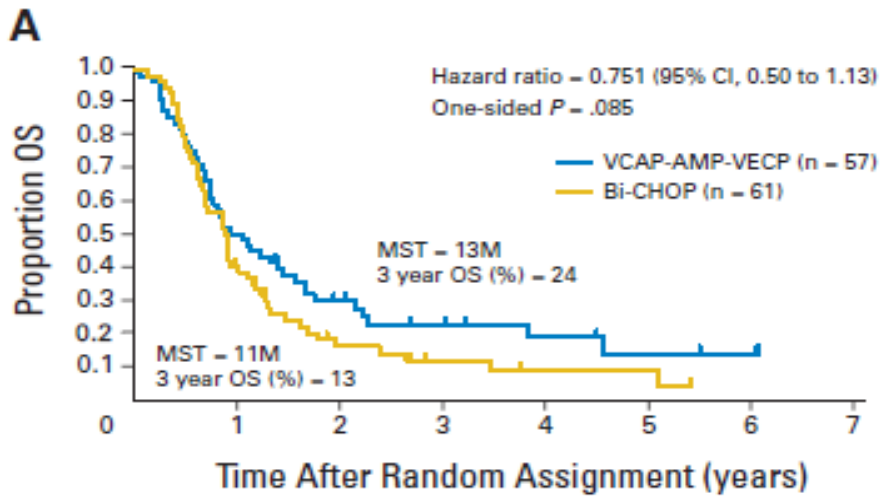
Randomised Controlled Trials ATLL

Tsukasaki et al, JCO, 2007



Single RCT – Intensive chemotherapy v bi-weekly CHOP

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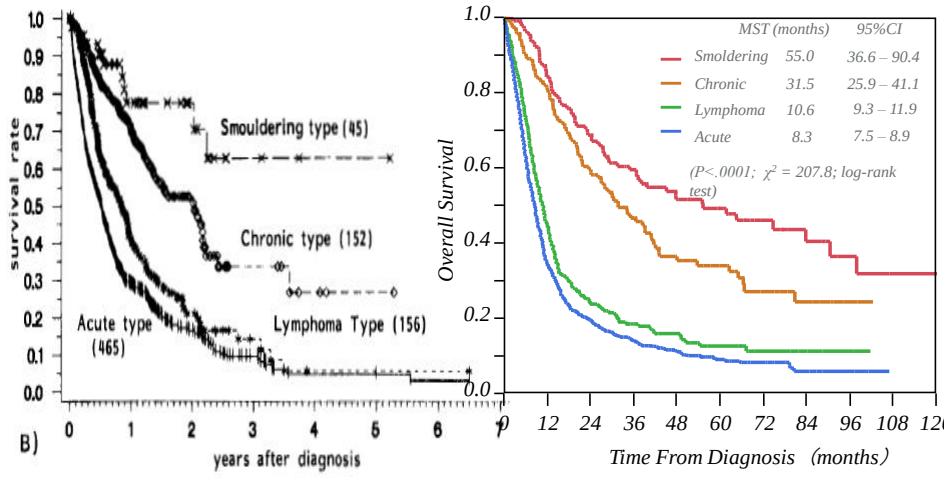
Adult T-cell Leukaemia/Lymphoma

Overall Survival ~8 months **Unchanged after 25 years**



Shimoyama M, Br J Haematol 1991;79:428-437 *Katsuya H, et al, Blood 2015;126:2570-7*

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Treatment of ATL with 'anti-viral therapy' Zidovudine + Interferon-α

ACP

Annals of Internal Medicine

1989

Human T-Cell Lymphotropic Virus Type I (HTLV-I)-Associated Adult T-Cell Leukemia-Lymphoma in a Patient Infected with Human Immunodeficiency Virus Type 1 (HIV-1)

1995

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ORIGINAL ARTICLE

BRIEF REPORT

Treatment of Adult T-Cell Leukemia-Lymphoma with Zidovudine and Interferon Alfa

Olivier Hermine, Didier Bouscary, Antoine Gessain, Pascal Turlure, Veronique Leblond, Nathalie Franck, Agnes Buzyn-Veil, Bernard Rio, Elisabeth Macintyre, Francois Dreyfus, and Ali Bazarbachi

N Engl J Med 1995; 332:1749-1751 | June 29, 1995 | DOI: 10.1056/NEJM199506293322604

"We found that the combination of zidovudine and interferon alfa induced a rapid and durable response in a patient with adult T-cell leukemia–lymphoma who was coinfected with both human immunodeficiency virus type 1 (HIV-1) and HTLV-I."

Results. Major responses were achieved in 58 percent of the patients (11/19), including complete remission in 26 percent (5/19).
Six patients have survived for more than 12 months,
Longest remission since the discontinuation of treatment lasting more than 59 months.

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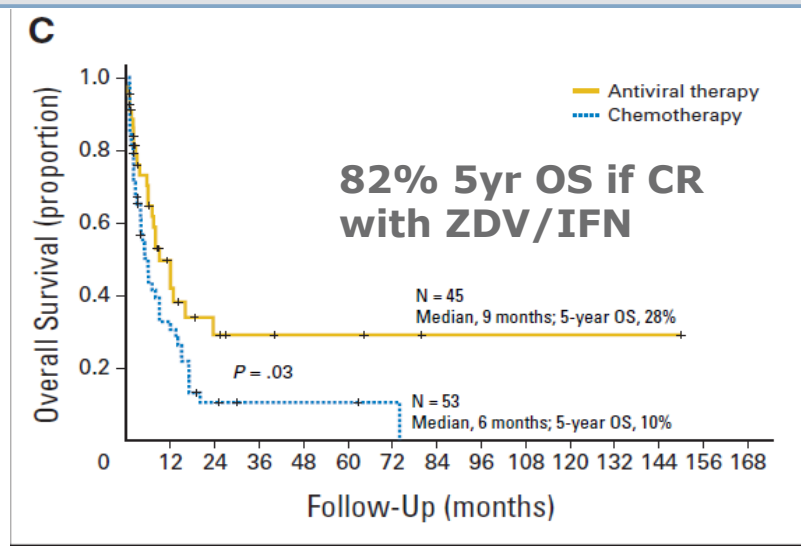
Outcome of acute ATLL improved by first line use of ZDV/IFN



Bazarbachi *et al* J Clin. Oncol. 2010:28:1477-1483

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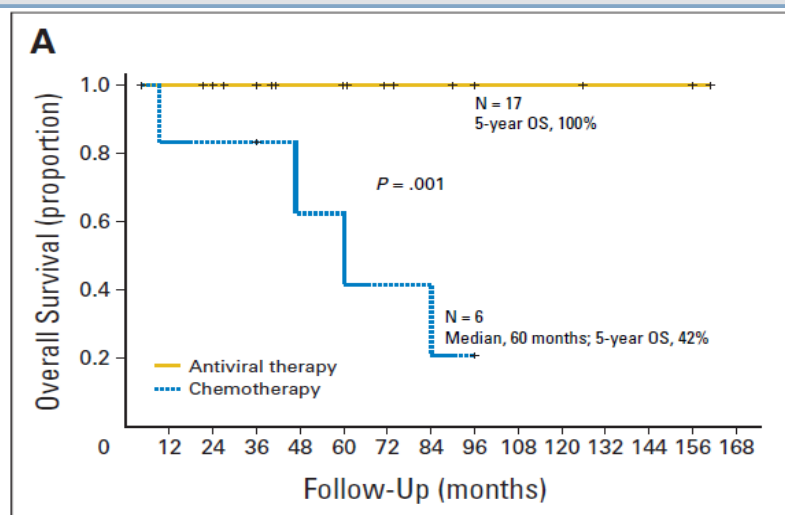
100% 5 year OS for patients with Chronic/Smouldering ATLL



Bazarbachi *et al* J Clin. Oncol. 2010;28:1477-1483

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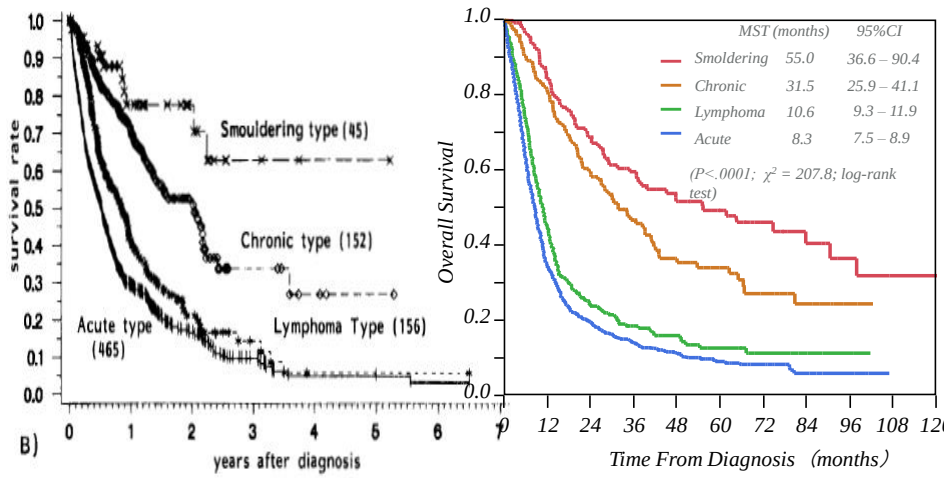
Adult T-cell Leukaemia/Lymphoma



Shimoyama M, Br J Haematol 1991;79:428-437 *Katsuya H, et al, Blood 2015;126:2570-7*

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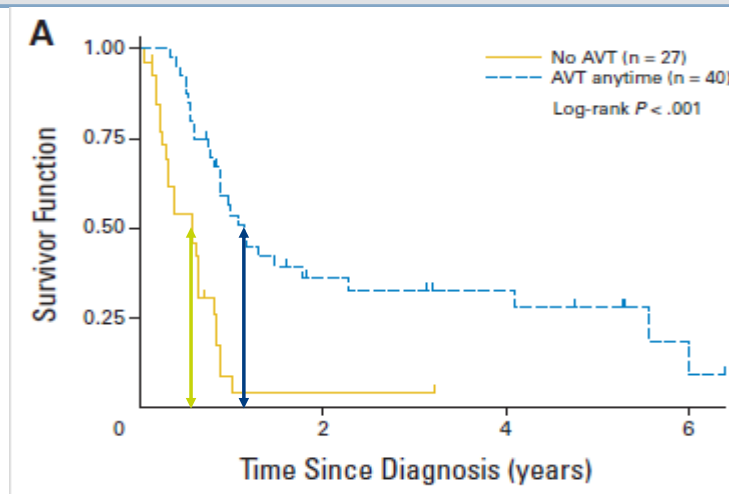
UK experience with 'anti-viral' therapy – (ZDV/IFNα)



Hodson et al, J Clin Oncol 2011;29:4696-4701

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Anti-CCR4 mAb (Mogamulizumab)

Mogamulizumab approved In Japan:

2012: for the treatment of relapsed or refractory CCR4-positive ATL

2014: relapsed or refractory CCR4-positive peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL)

2012 – 2015 – International study RCT comparing anti-CCR4 with second line chemotherapy.

Licensing in EU/USA in progress

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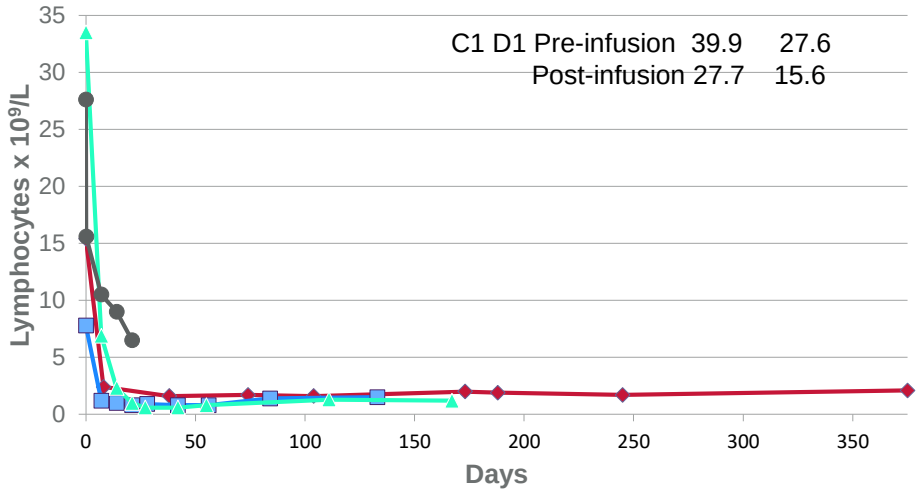
Lymphocyte counts during anti-CCR4 therapy



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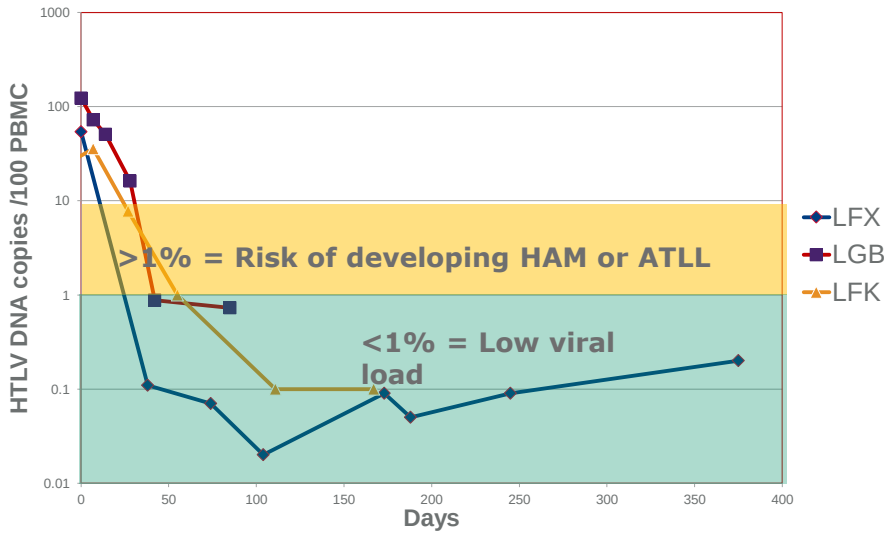
HTLV-1 proviral load during anti-CCR4 therapy



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Stem Cell Transplantation – Allo

Autologous – modest benefit – early relapse
Tsukasaki et al Bone Marrow Transplant 1999; 23: 87–89

Allo – Median survival 10 months (n = 586, retrospective)

3 year Survival 36%

Myeloablative conditioning for younger

Reduced intensity for older

Ishida et al Blood 2012; 120: 1734–41

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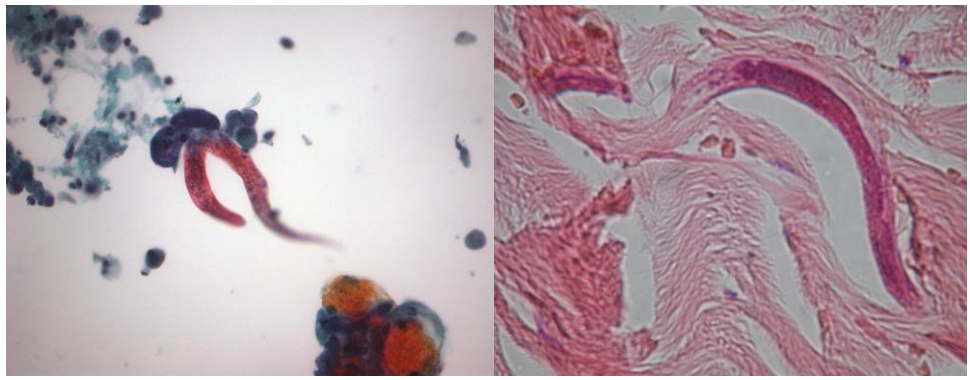
Bronchoscopy

Skin Biopsy



Strongyloides stercoralis hyperinfestation
90% Mortality

All HTLV-1 patients from Strongyloides prevalent regions screened and treated with Ivermectin

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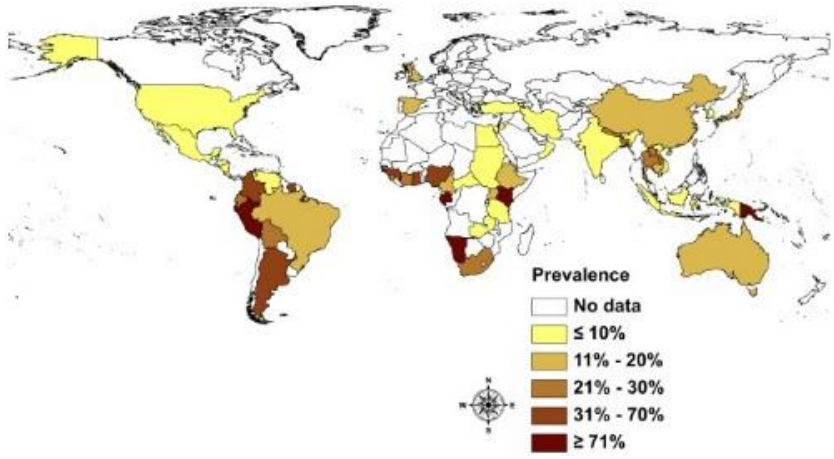
Global epidemiology of *Strongyloides stercoralis*



Schar et al PLoS Negl Trop Dis. 2013 Jul; 7(7): e2288

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Summary

HAM – identify early
- Treat with low dose oral Prednisolone
- Pulsed Pred followed by steroid-sparing therapies (anti-CCR4 – potentially)

ATL Chronic and Acute Leukaemic - Initially ZDV/IFN
Lymphomatous – chemotherapy and Allo SCT
Prophylaxis for OIs

Prevent disseminated Strongyloidiasis - Ivermectin

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Thanks to

Patients at the National Centre for Human Retrovirology

Lucy Cook
Michelle Chen
Sasha Marks
Jana Haddow
Fabiola Martin
Adine Adonis
Maria Antonietta Demontis

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