

Results and Controversies from the UW Neurosyphilis Study

UW Neurosyphilis Study

- Study Goals
 - Determine risk factors for neurosyphilis
 - Identify “better” diagnostic tests
 - Determine predictors of neurosyphilis treatment response

Entry Criteria

- Syphilis
 - Reactive RPR/VDRL and TPPA/FTA-ABS
or
 - Characteristic chancre or rash, regardless
of serological test results or
 - Reactive RPR/VDRL and known contact to
infectious syphilis

Entry Criteria

- Needs an LP per primary provider
 - Neurological or ocular sx/signs
 - Treatment failure
 - Tertiary syphilis: gumma or CV
 - Planned non-penicillin treatment of latent syphilis
 - RPR titer $\geq 1:32^{**}$
 - HIV-infected^{**}
 - Other

Exclusion

- IV beta-lactams in the past 3 months
 - Prefer no syphilis tx before entry, but not required
- LP not safe
 - Anticoagulated
 - Focal exam
- Cannot give informed consent

Procedures

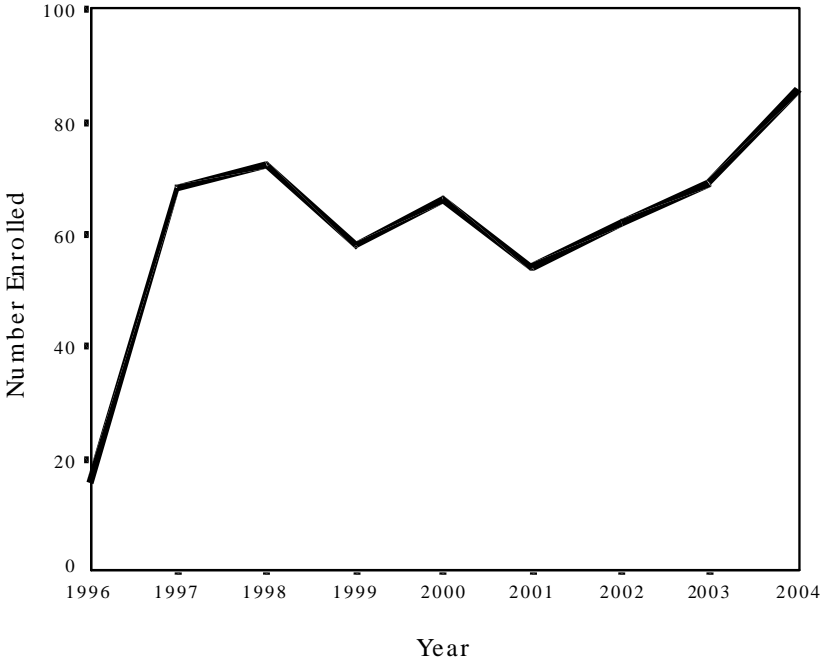
- Standardized history
- Standardized brief neuro exam
- Lumbar puncture
- Venipuncture

Procedures

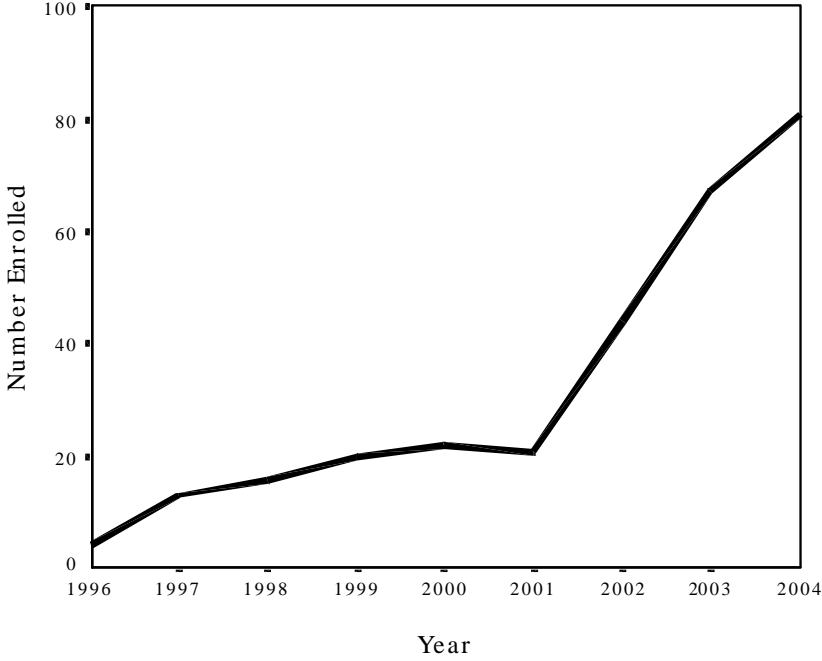
- Normal CSF -> stage-specific tx
 - No study follow-up
- Abnormal CSF -> NS tx
 - Follow-up 3, 6, 12 mo
- LP only if previous CSF profile is abnormal

Enrollment

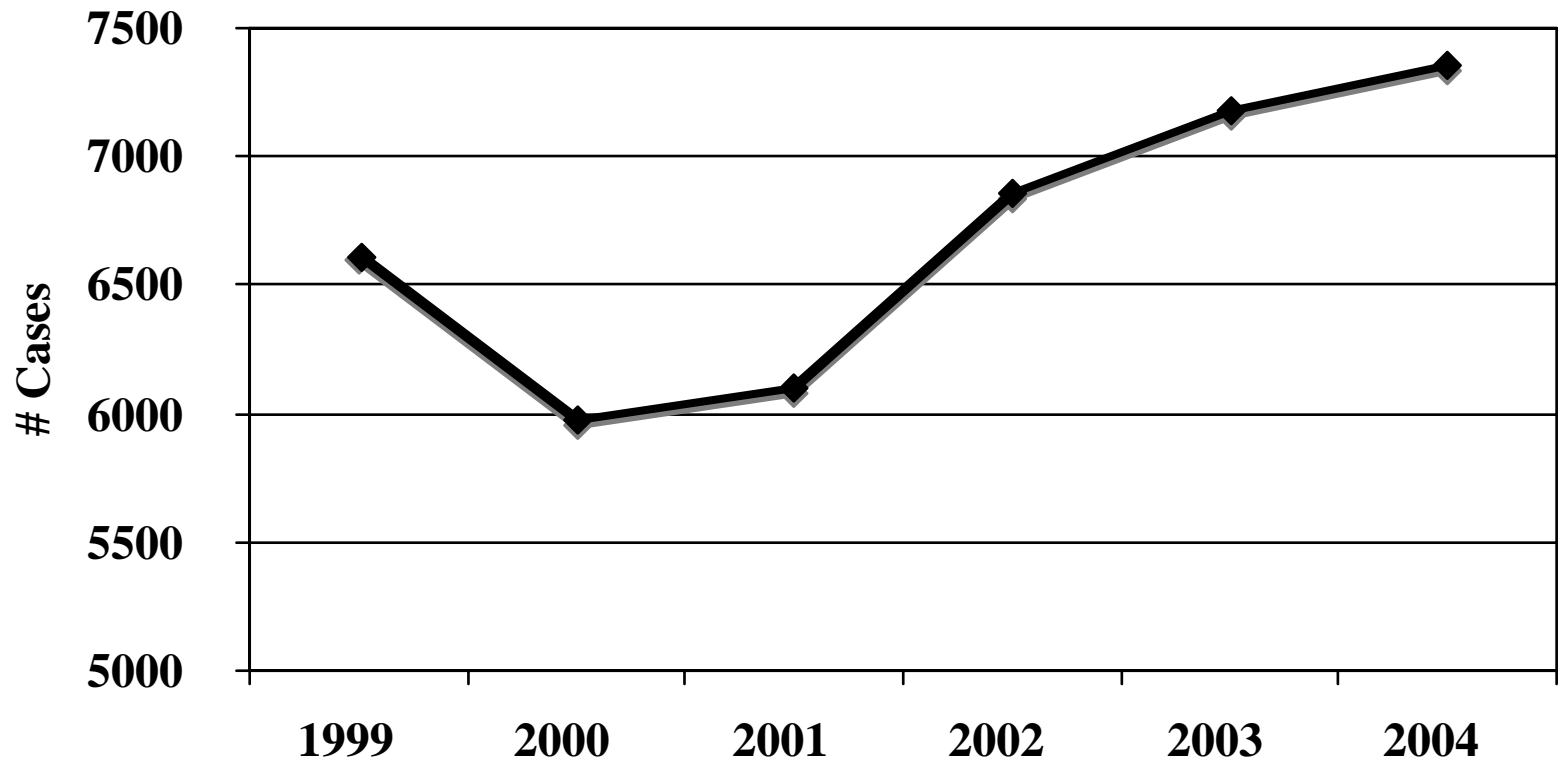
Total



UW

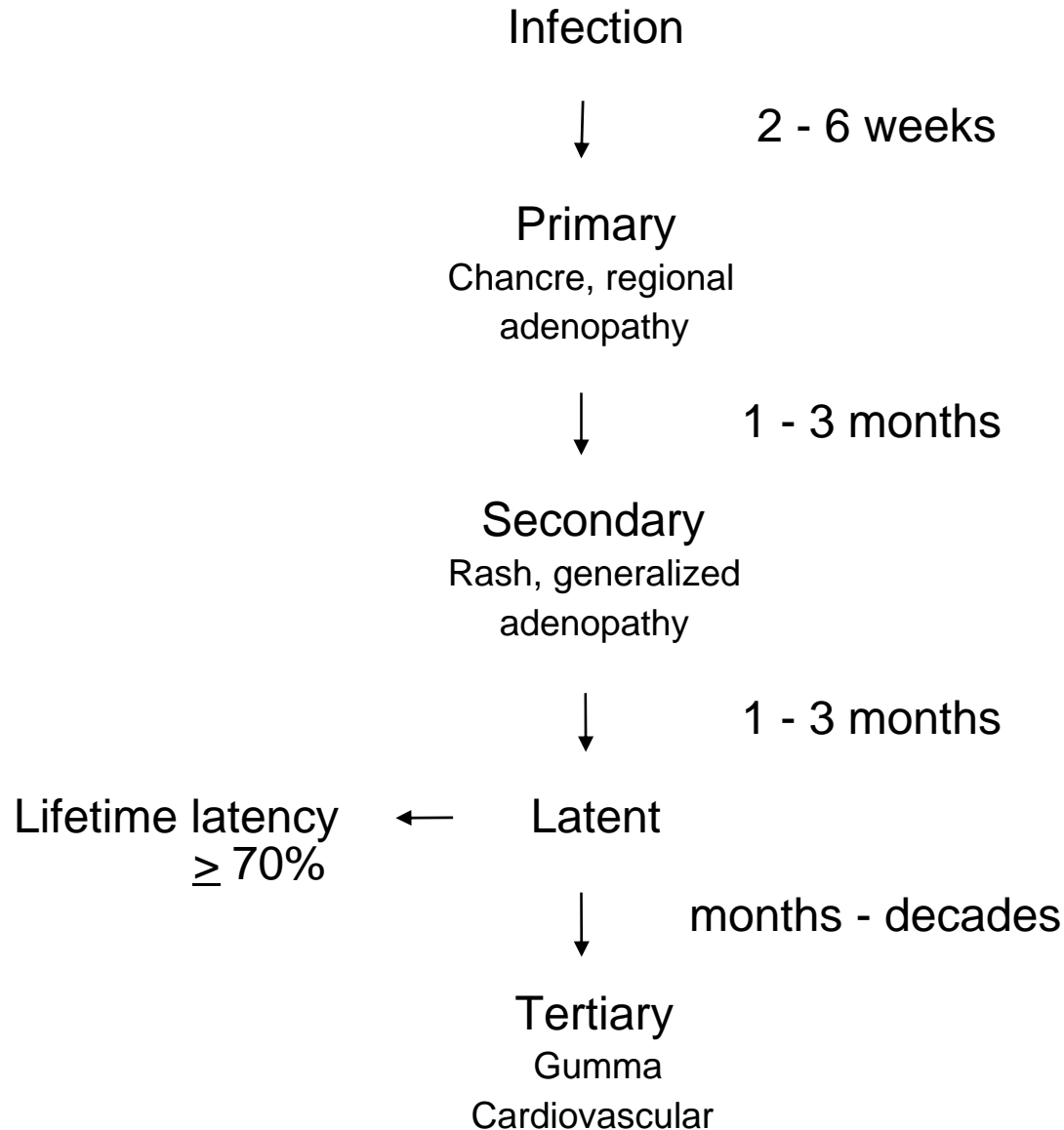


US P/S Syphilis 1999-2004

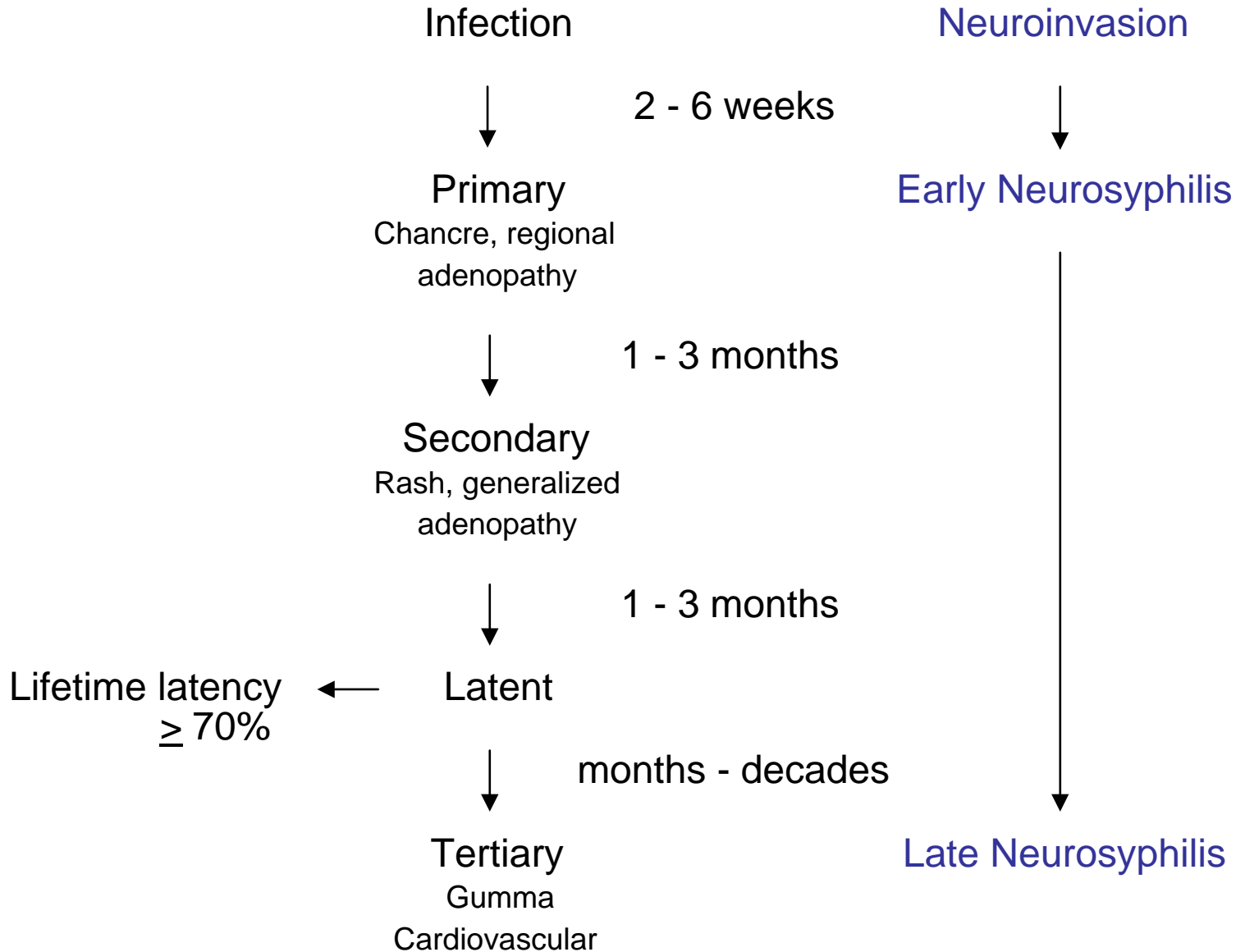


T. pallidum is not like other
bacteria that infect the CSF...

Natural History of Syphilis



Natural History of Syphilis

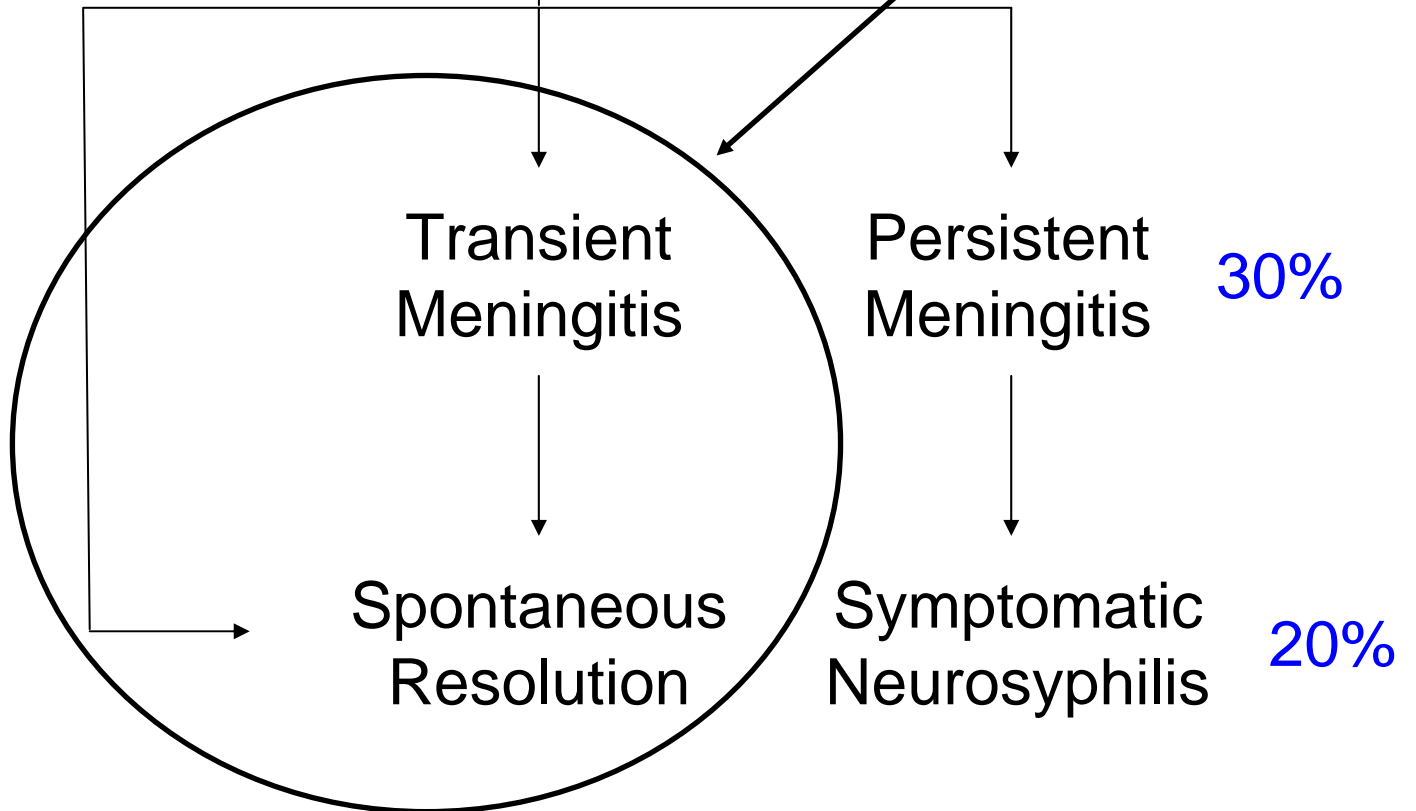


Neuroinvasion

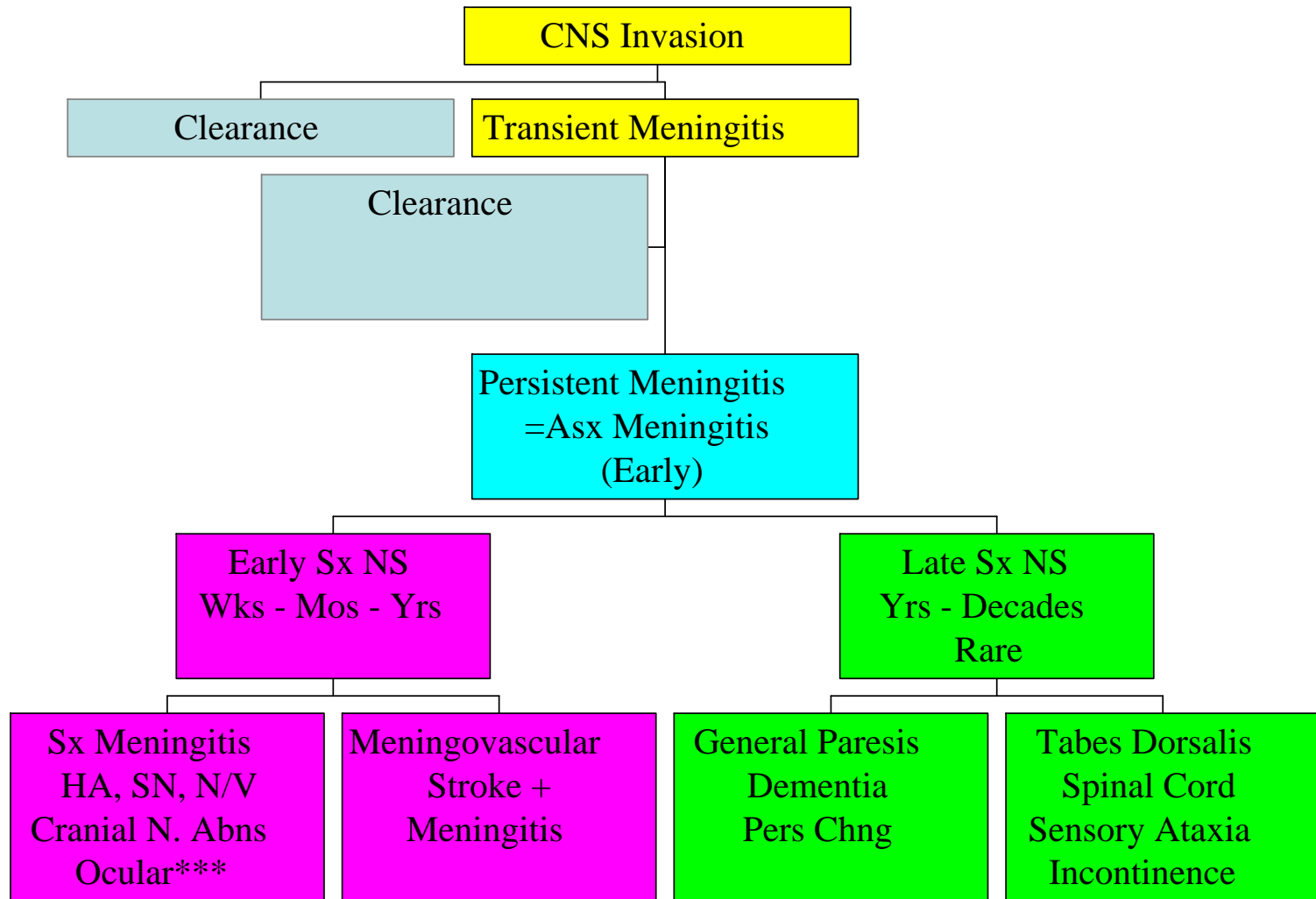


+CSF PCR, RT-PCR, RIT

Clearance 70%



Neurosyphilis Natural Hx



Neuroinvasion

CSF Measure	HIV+	HIV-
WBC	20/46 (43%)	22/99 (22%)
VDRL	7/45 (16%)	7/99 (7%)
Protein	17/47 (36%)	25/102 (25%)
<i>T. pallidum</i>	11/43 (26%)	21/88 (24%)

Non-CNS Syphilis Treatment

- Early syphilis
 - Benzathine penicillin G 2.4 MU IM X 1
- Late syphilis
 - Benzathine penicillin G 2.4 MU IM weekly X 3
- BPG does not achieve measurable penicillin levels in CSF
 - Does this matter?

Is neuroinvasion more worrisome in HIV+ patients with syphilis?

Prognosis of Abnormal CSF Before Penicillin

CSF Type		N	Definite NS
1	> 10 WBC, WR-	14	2/14 (14%)
2	“Intermediate”	73	5/73 (7%)
3	5-200 WBC, WR+	36	12/36 (33%)

Moore, Hopkins; JAMA 1930

Abnormal CSF 6 Months After Penicillin

Stage	N	% CSFs Abnormal
Seronegative Primary	2434	0.1
Seropositive Primary	2188	0.5
Secondary	978	1.1

Neurosyphilis in HIV+ After Benzathine Penicillin

- Musher (JID 1991;163;1201-6)
 - Identified 42 cases of neurosyphilis in HIV-infected individuals
 - Asx neurosyphilis 5
 - Acute meningitis 24
 - Meningovascular 11
 - General paresis 1

Neurosypphilis in HIV+ After Benzathine Penicillin

- Musher (JID 1991;163;1201-6)
 - Of the 42 cases of neurosyphilis
 - 16 previously treated with benzathine penicillin
 - 5 (31%) developed neurosyphilis within 6 months of early syphilis treatment
 - Increased risk of neurorelapse

BPG vs Enhanced Tx for Early Syphilis

- Rolfs RT et al (NEJM 1997;337:307-314)
 - 440 HIV- and 101 HIV+ with early syphilis
 - Randomized to BPG vs BPG plus 2 g amoxicillin and 500 mg probenecid tid X 10 d (enhanced tx)
 - 102 HIV- and 47 HIV+ had LP at entry

BPG vs Enhanced Tx for Early Syphilis

- Rolfs RT et al (NEJM 1997;337:307-314)
 - Treatment failure not more common in those with *T. pallidum* in pre-tx CSF
 - Treatment failure not influenced by treatment assignment
 - No clinical neurosyphilis over 1 year of follow-up
 - Concluded that CSF evaluation in early syphilis not useful

BPG vs Enhanced Tx for Early Syphilis

- Rolfs RT et al (NEJM 1997;337:307-314)
 - Insufficient power to determine influence of detection of *T. pallidum* in CSF on treatment response in HIV+ subjects
 - 80% power to detect a 50% difference in treatment response

Conservative Approach

- Cannot predict who will clear CSF abnormalities and who will not
- Literature describes “neurorelapse” in HIV+ patients with early syphilis
- LP for all HIV+ patients with syphilis, regardless of stage
- Treat for neurosyphilis if CSF WBC elevated or CSF-VDRL reactive

UK Guidelines

- Early or late syphilis in HIV+
 - Procaine penicillin 2 MU IM daily plus probenecid 500 mg po qid, both for 17 days
 - Same as for neurosyphilis

Neurosyphilis is harder to
diagnose in HIV+ people...

Neurosyphilis Diagnosis

- CSF-VDRL specific, not sensitive
 - False negatives 30-70%
- Elevated CSF WBCs
 - Can be hard to distinguish from HIV
- CSF-FTA-ABS sensitive but not specific

Sensitivity and Specificity of CSF-VDRL in UW Study


“Gold Standard” for Diagnosis

	CSF WBC >20/ul	Ocular Syphilis
Sensitivity (“SNNOUT”)	50%	28%
Specificity (“SPPIN”)	90%	88%

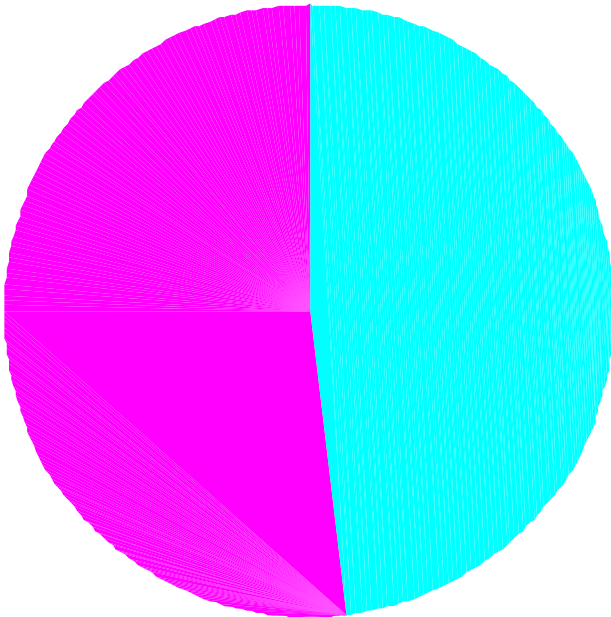
NS in UW Study

- WBC > 20/ul, 16%
- CSF-VDRL+, 12%
- WBC > 20/ul or CSF-VDRL+, 23%

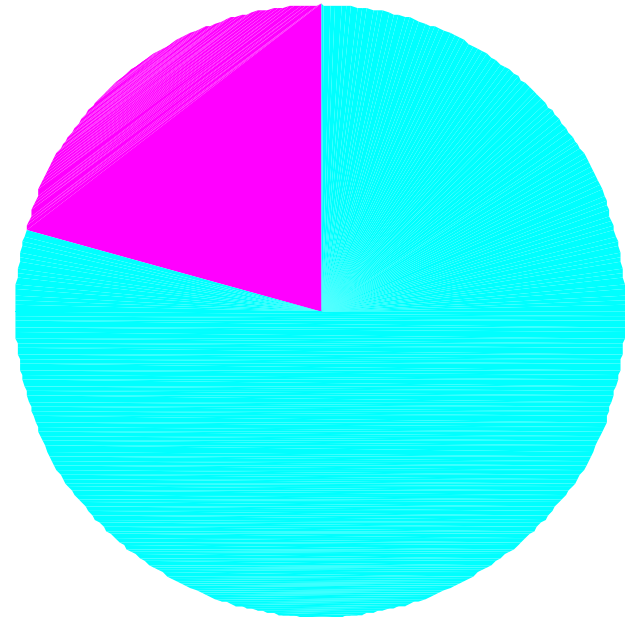
CSF Abnormalities

 WBC > 20 or + CSF-VDRL

Not on ARVs



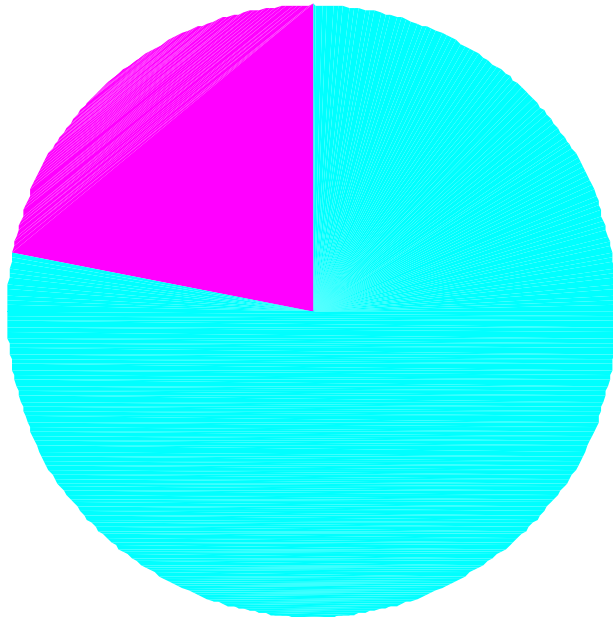
On ARVs



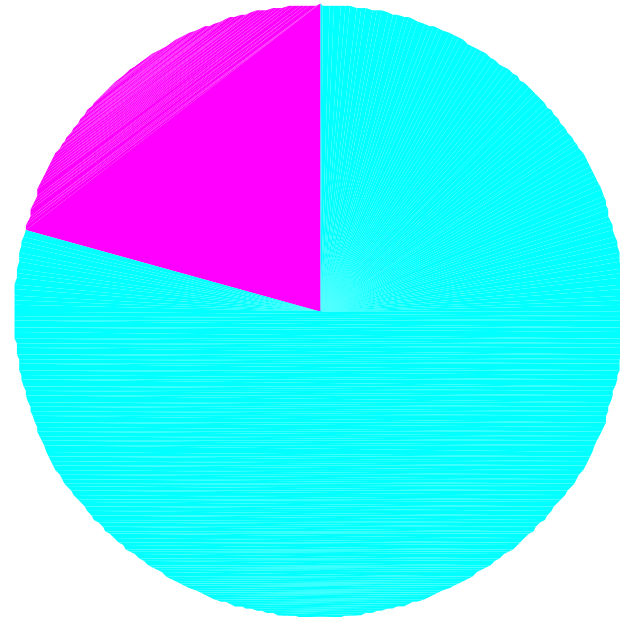
CSF Abnormalities

 + CSF-VDRL

Not on ARVs



On ARVs



Our Diagnostic Approach to Neurosyphilis in HIV+

- NS diagnosed if...
 - Neurological or ocular sx/signs
 - Reactive CSF-VDRL
 - CSF WBC $> 20/\text{ul}$
 - CSF WBC $\geq 10 \leq 20/\text{ul}$ if +CSF FTA-ABS

Alternative CSF Tests in HIV

- 47 HIV-infected cases with syphilis
- 26 HIV-infected controls
- CSF studies
 - Elevated % CSF B cells in fresh and frozen CSF by FACS
 - $\geq 9\%$ fresh
 - $\geq 20\%$ frozen
 - CSF-FTA-ABS

Subject Characteristics

	Controls n=26	Cases n=47	P-value
Age	42	38	0.004
Men	76.9%	100%	0.001
CD4+ T cells/ul	310	325	0.76
CSF WBC	2	6	0.04
% CD19+, fresh	1	3	0.02
% CD19+, frozen	3	5	0.004

CSF Diagnostic Tests

	Gold Standard +CSF-VDRL	
	Sensitivity	Specificity
FTA-ABS	100%	71%
CD19% \geq 9, fresh	40%	100%
CD19% \geq 20, frozen	43%	100%

Which HIV+ patients with syphilis should have an LP?

Neurosypphilis Risk

- Logistic regression to evaluate associations between neurosyphilis (WBC > 20 or +CSF-VDRL) and
 - Stage
 - Serum RPR titer
 - Previous syphilis therapy
 - CD4+ T cells

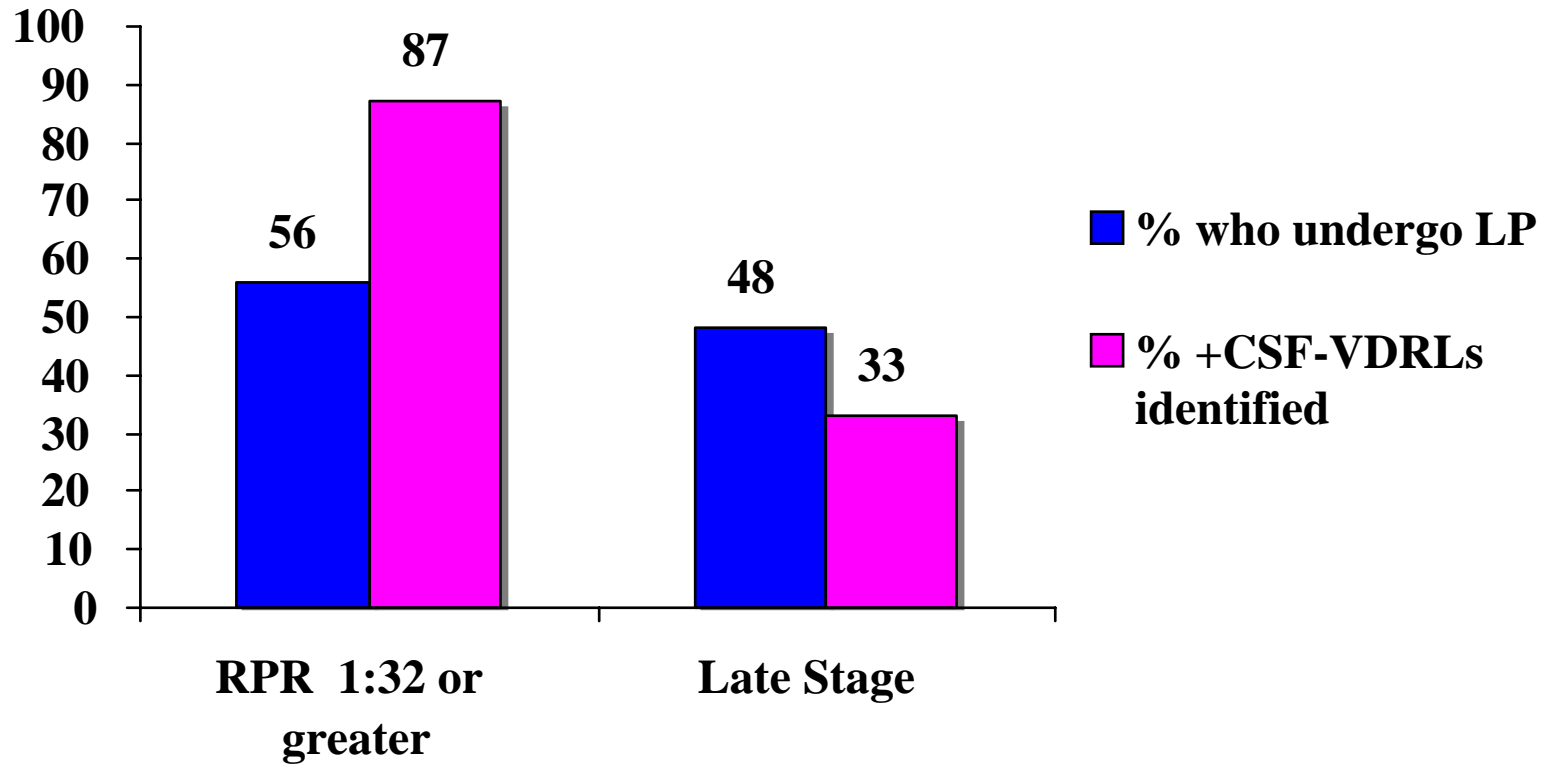
WBC > 20 or +CSF-VDRL in 268 HIV+

	Adj OR	95% CI	P-value
Stage			
Early	1.1	0.5-2.1	0.89
Late	ref		
RPR \geq 1:32	4.4	2.2-8.8	<0.001
CD4 \leq 350	1.8	1.0-3.3	0.047
Syphilis Tx			0.18
0-14 d	ref		
15 d-1yr	0.3	0.08-1.1	0.07
> 1 yr	0.8	0.4-1.6	0.53

+CSF-VDRL in 269 HIV+

	Adj OR	95% CI	P-value
Stage			
Early	0.8	0.4-1.8	0.62
Late	ref		
RPR \geq 1:32	6.2	2.3-16.4	<0.001
CD4 \leq 350	1.7	0.8-3.4	0.16
Syphilis Tx			0.70
0-14 d	ref		
15 d-1yr	0.8	0.2-2.8	0.68
> 1 yr	0.7	0.3-1.8	0.42

Yield of LP Using Serum RPR vs CDC Criteria in HIV+ Syphilis



Neurosypphilis Treatment

- Aqueous crystalline penicillin G, 3-4 MU IV q 4 or as a continuous infusion of 24 MU/d for 10-14 days
- Procaine penicillin, 2.4 MU IM q d plus probenecid 500 mg PO qid, both for 10-14 days
- Second line
 - Ceftriaxone 2 g IV/d for 10-14 days

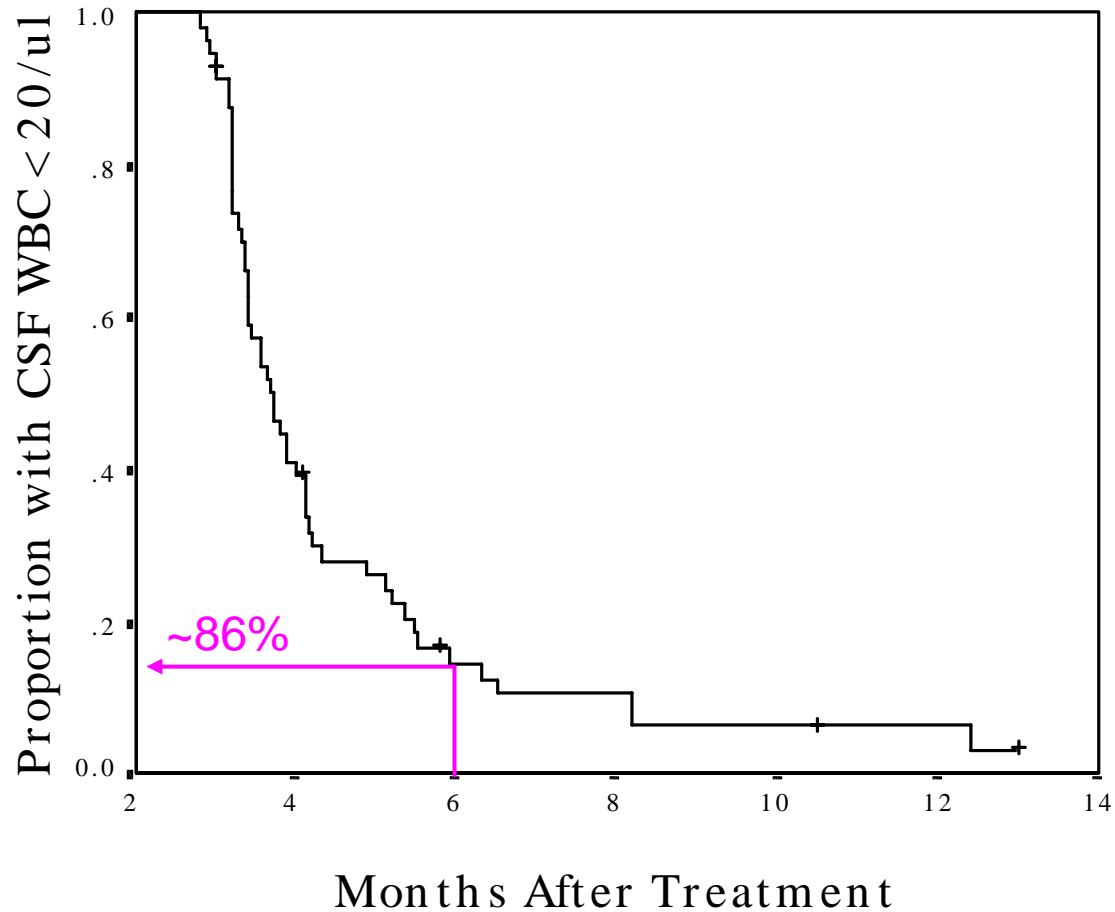
Assessing NS Treatment Response

- Not like other kinds of bacterial meningitis
 - Can't assess "culture becomes negative"
- Normalization of CSF WBC, CSF-VDRL, CSF protein
- Normalization of serum RPR

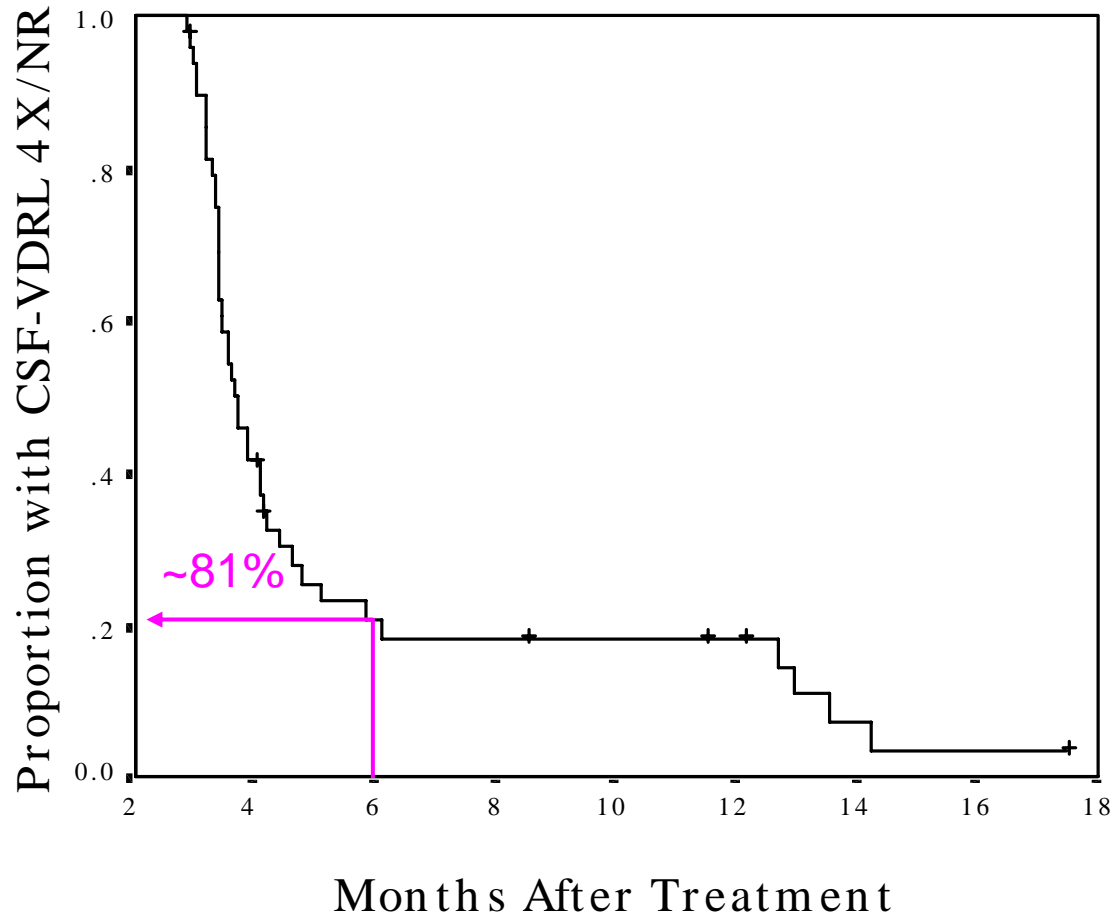
Normalization Definitions

- CSF WBC
 - Decline to $< 20/\mu\text{l}$
- CSF-VDRL
 - Four-fold drop in titer or reversion to nonreactive
- CSF protein
 - Decline to $< 50 \text{ mg/dl}$
- Serum RPR
 - Four-fold drop in titer or reversion to nonreactive

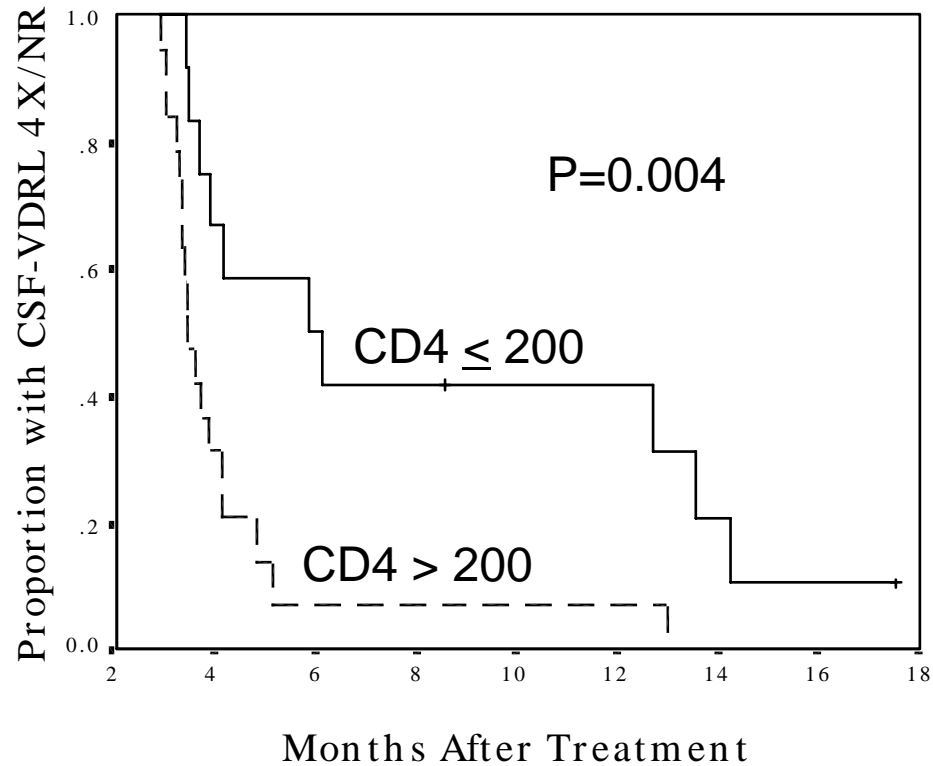
Normalization of CSF WBCs



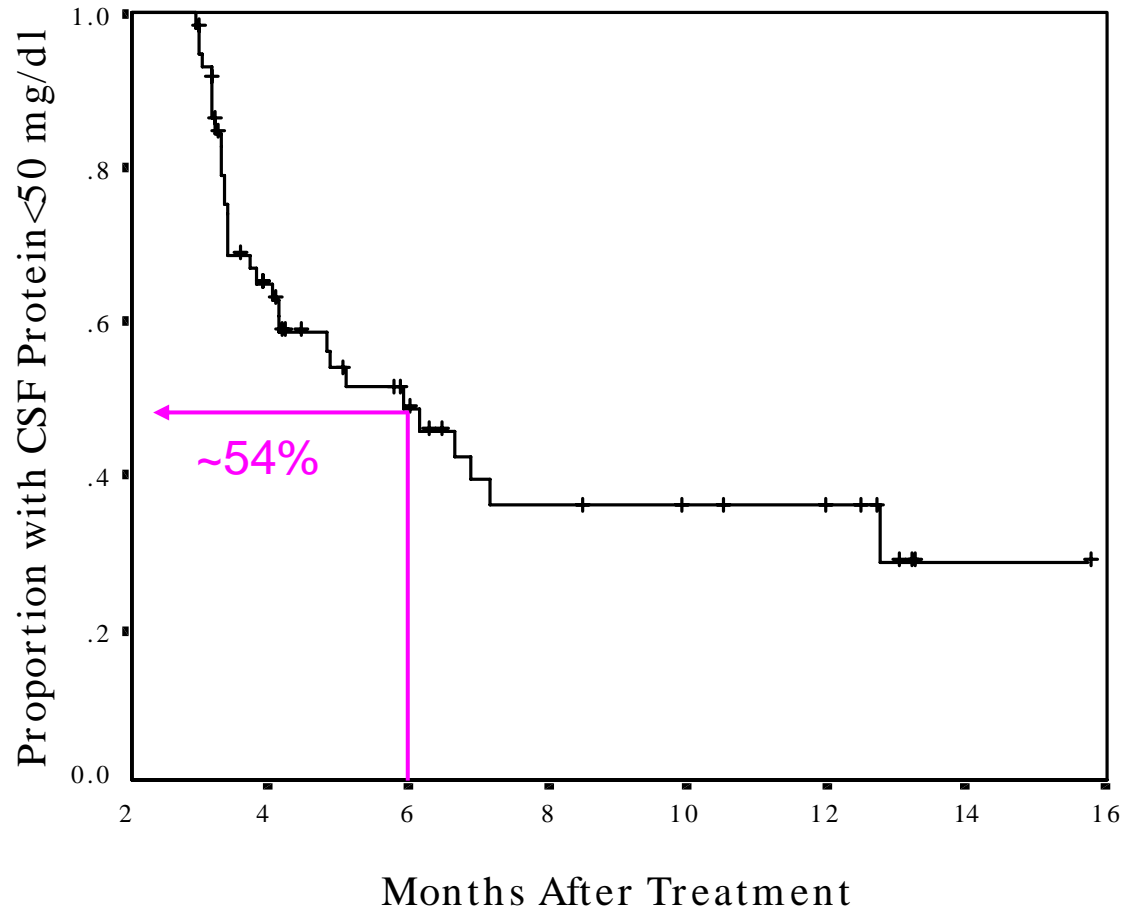
Normalization of CSF-VDRL



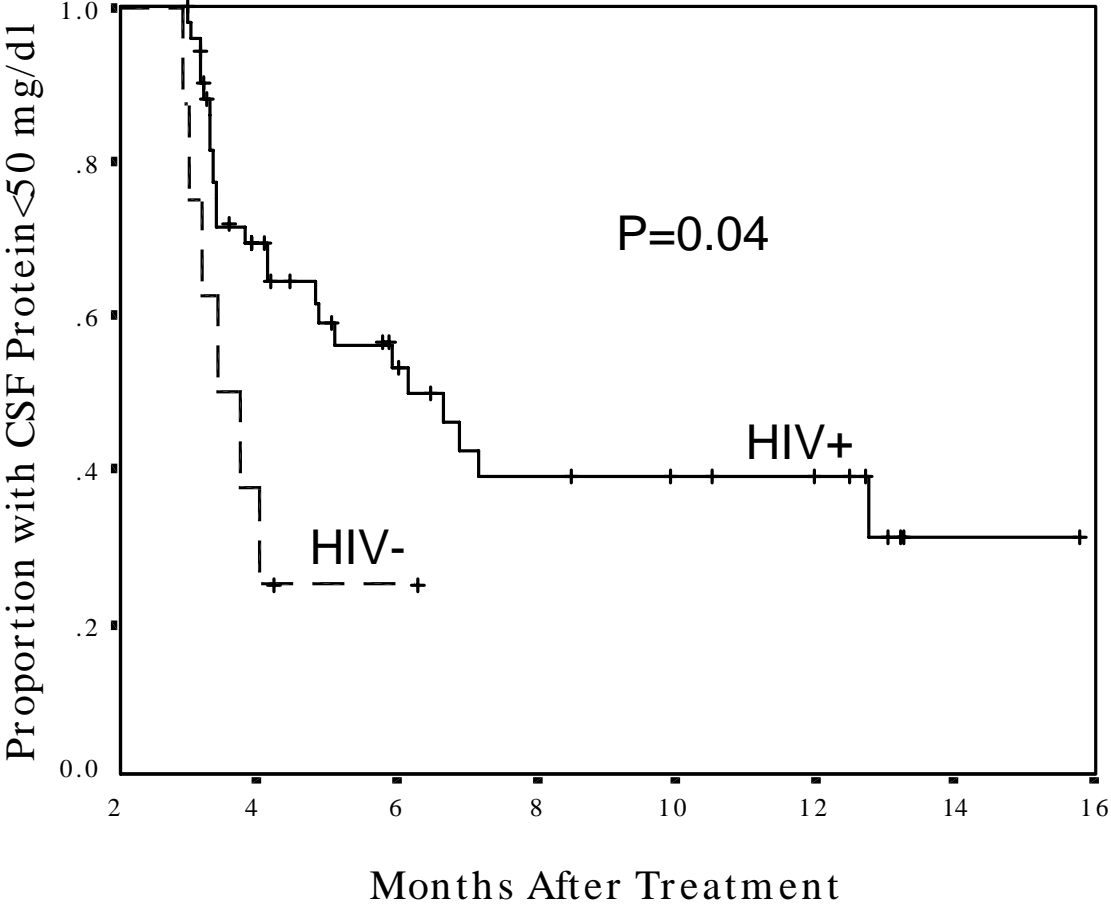
Normalization of CSF-VDRL in HIV+



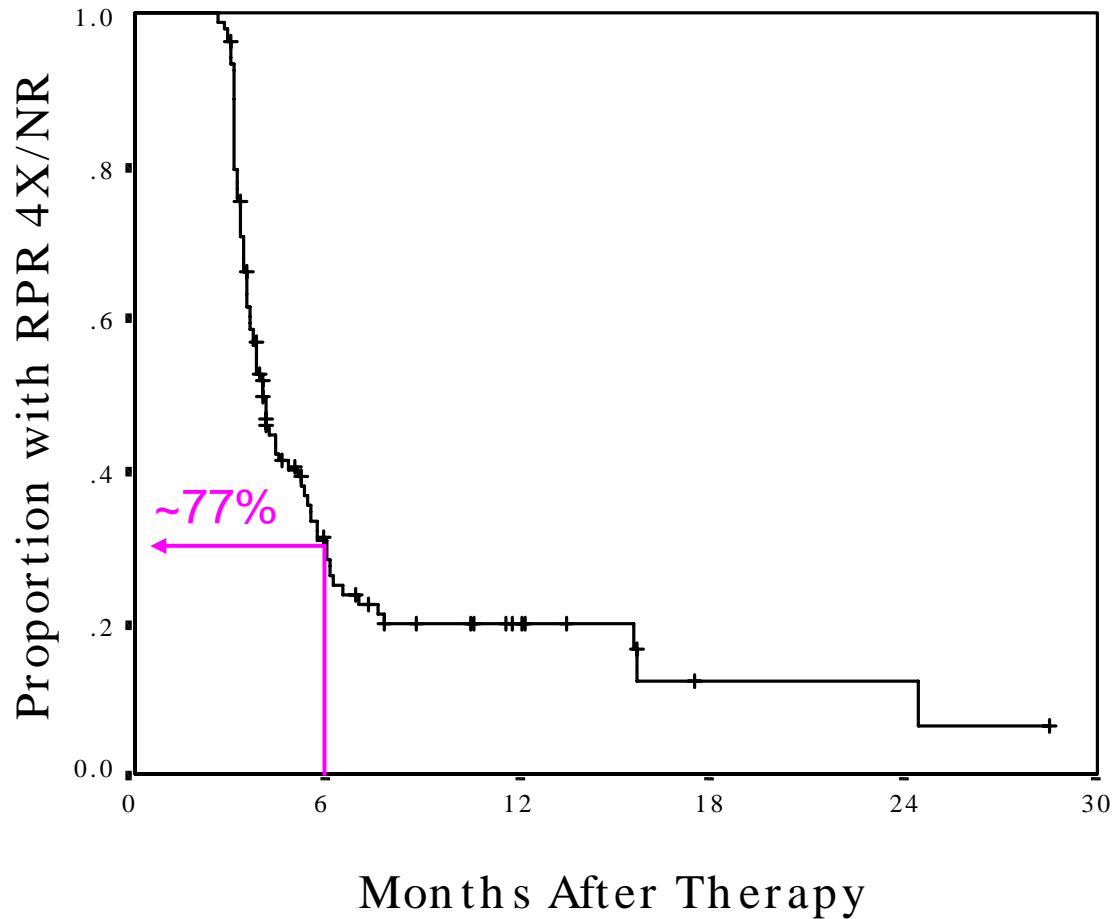
Normalization of CSF Protein



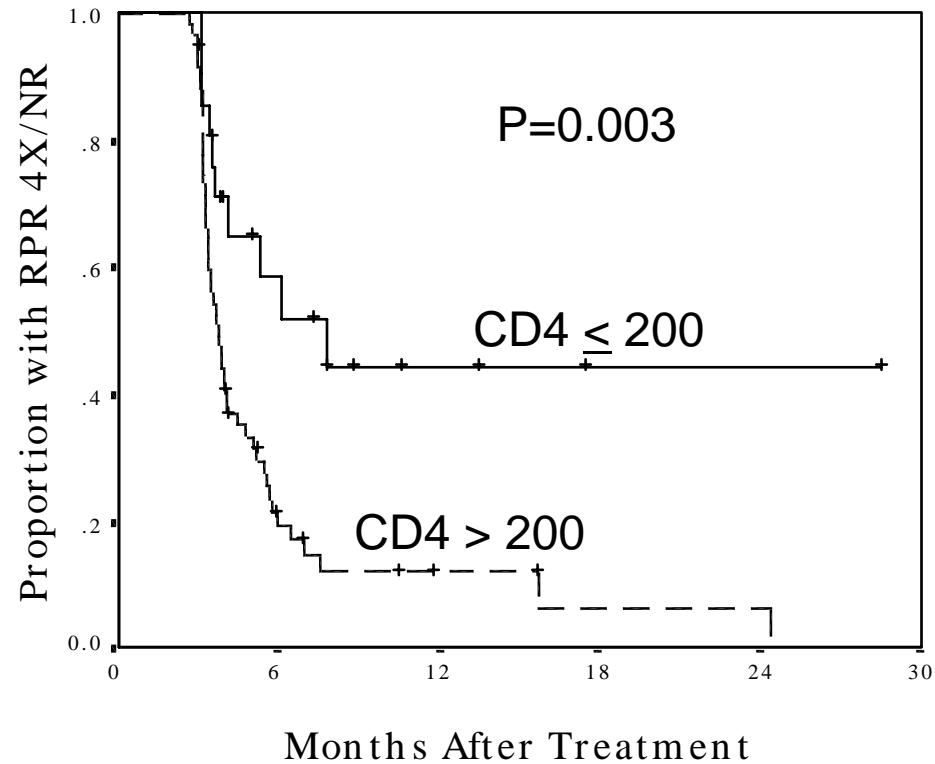
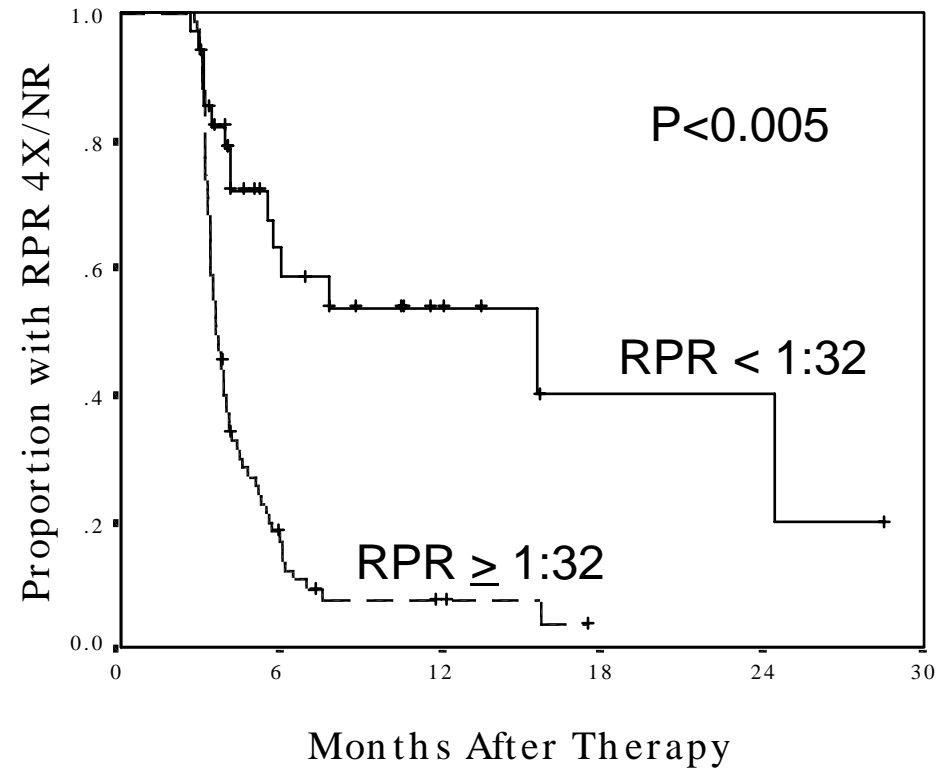
Normalization of CSF Protein



Normalization of Serum RPR



Normalization of Serum RPR



Is slower normalization of CSF
WBCs and CSF-VDRL after
neurosyphilis therapy the
same as treatment failure?

Take Home

- Patients with early syphilis have CSF abnormalities that may go away on their own
 - Can't predict
- Symptomatic neurosyphilis develops in people whose CSF remains abnormal
 - Rationale for tx asx neurosyphilis
- Early syphilis tx with BPG does not treat CSF infection

Take Home

- Several reports describe HIV+ patients who developed neurosyphilis after BPG for early syphilis
- Tests to diagnose neurosyphilis don't work as well in HIV+ patients
- HIV+ people with syphilis and a serum RPR titer $\geq 1:32$ or a CD4 ≤ 350 are more likely to have abnormal CSF regardless of stage

Take Home

- CSF and serum measures normalize more slowly after neurosyphilis treatment in HIV+ people who have lower CD4 cells or who aren't on ARVs

Conservative Approach

- Cannot predict who will clear CSF abnormalities and who will not
- Literature describes “neurorelapse” in HIV+ patients with early syphilis
- LP for all HIV+ patients with syphilis, regardless of stage
- Treat for neurosyphilis if CSF WBC elevated or CSF-VDRL reactive