

# SIFILIS EN EL PACIENTE QUE VIVE CON VIH



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# CASO CLINICO

- Paciente de 53 años
- VIH B2 en HAART
- CD4 de 410 y CV de 552 copias/mL
- Asintomático
- VDRL 1:128 y FTA positivo
- Punción lumbar vs tratamiento?

# Centers for Disease Control and Prevention Syphilis Summit: Difficult Clinical and Patient Management Issues

Marra, Christina M. MD<sup>\*</sup>; Ghanem, Khalil G. MD, PhD<sup>†</sup>

## CONCLUSION

Despite over a century of clinical experience in diagnosing and managing patients with syphilis, many thorny clinical questions remain unanswered. Paramount among these are the interpretation of serological test results after syphilis treatment and the impact of lumbar puncture on clinical outcome among patients co-infected with HIV and *T. pallidum*.

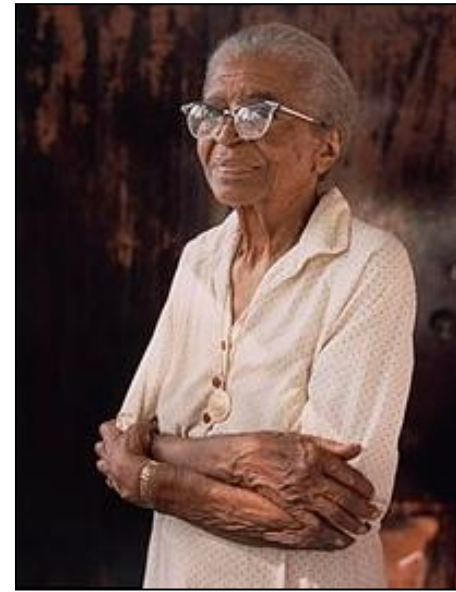
# The Tuskegee Study of Untreated Syphilis

*The 30th Year of Observation*

- Alabama 1932
- 412 hombres negros con Sífilis
- Mortalidad 60%

TABLE 4.—*Therapy and Serology of Syphilitics Examined 1963 Who Have Evidence of Late Syphilis*

Case No.	Diagnosis	Therapy, Date	Current VDRL	Current TPI
329	Cardiovascular syphilis	None prior to 1950; adequate 1950	WR	R
453	"	8 As 1934	N	R
560	"	7 As, 2 Hg 1934	N	R
032	"	3 Hg 1934	N	R
194	"	3 Hg 1934	4 dil	R
336	"	None	2 dil	R
A-10	"	None	1 dil	R
611	Central nervous system syphilis	? 1934; adequate 1952	N	R
108	"	1 Hg 1934; adequate ? 1950	32 dil	R
232	"	6 As, 1 Hg 1934	8 dil	R
500	Old gummatous lesion	2 Hg 1934	N	R



Eunice Verdell Rivers Laurie. Enfermera mejor conocida por su trabajo como coordinadora del experimento de Tuskegee de 1932 a 1972

# INTRODUCCION

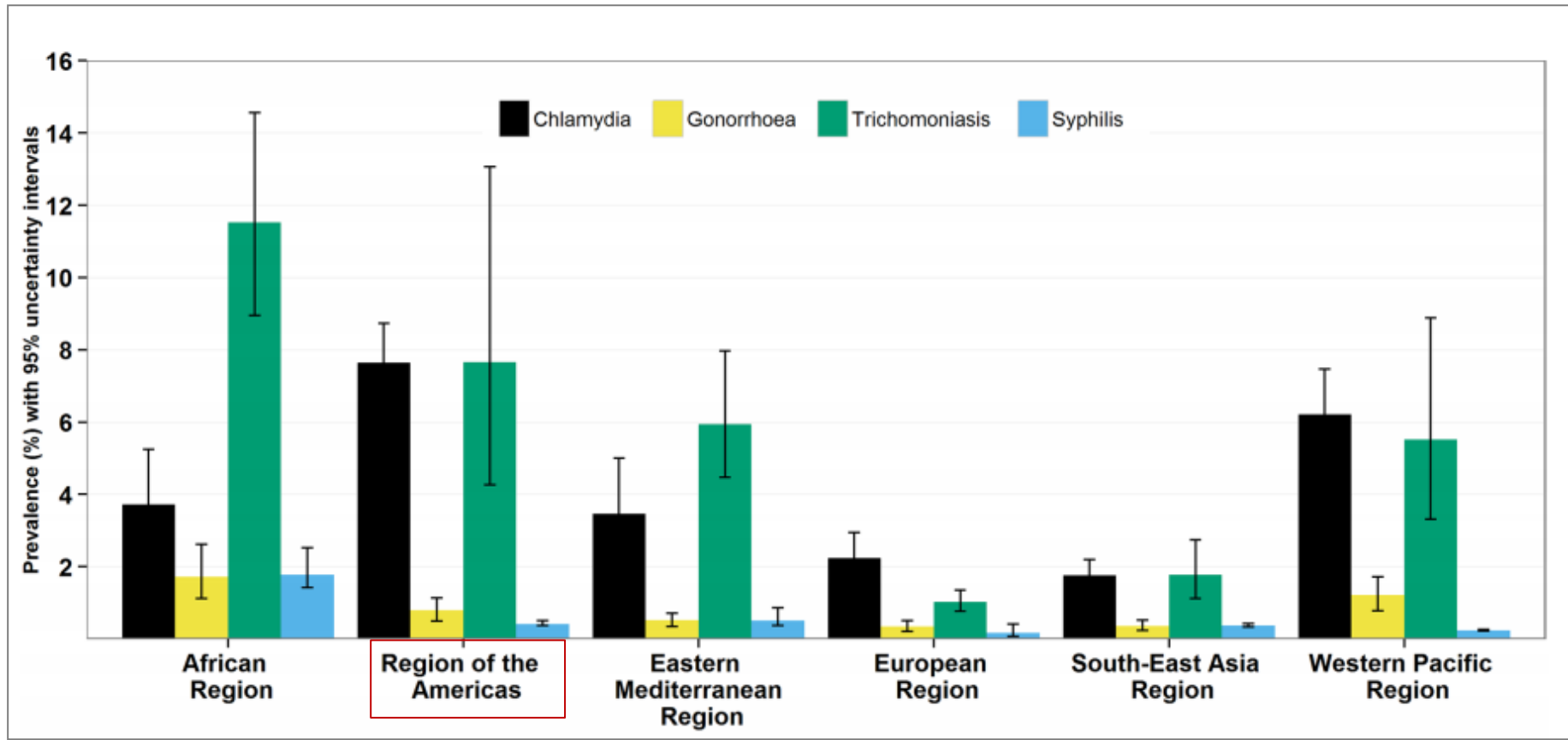
- El 50% contrae alguna ETS en la vida
- El 50% se infecta antes de los 25 años
- El 60% de Sífilis se Dx en HSH
- El 50% coinfectados con VIH
- El 25% desarrollan Neurosífilis

# EPIDEMIOLOGIA

## Incidencia mundial:

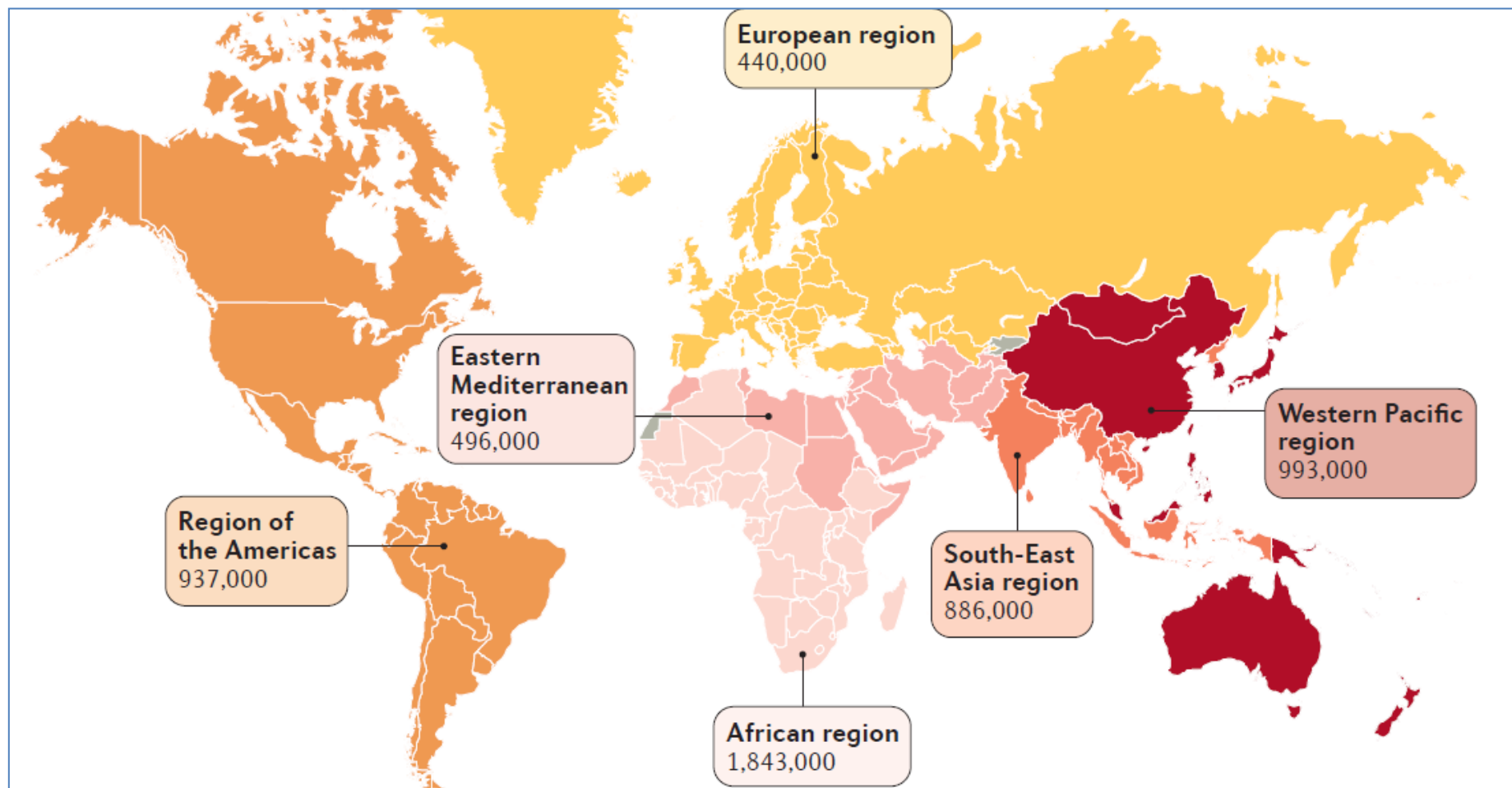
- PVH ..... 270 millones
- Tricomonas .....170 millones
- Chlamydia ..... 89 millones
- Gonorrea ..... 63 millones
- Herpes genital ..... 20 millones
- **Sífilis ..... 13 millones**

# EPIDEMIOLOGIA

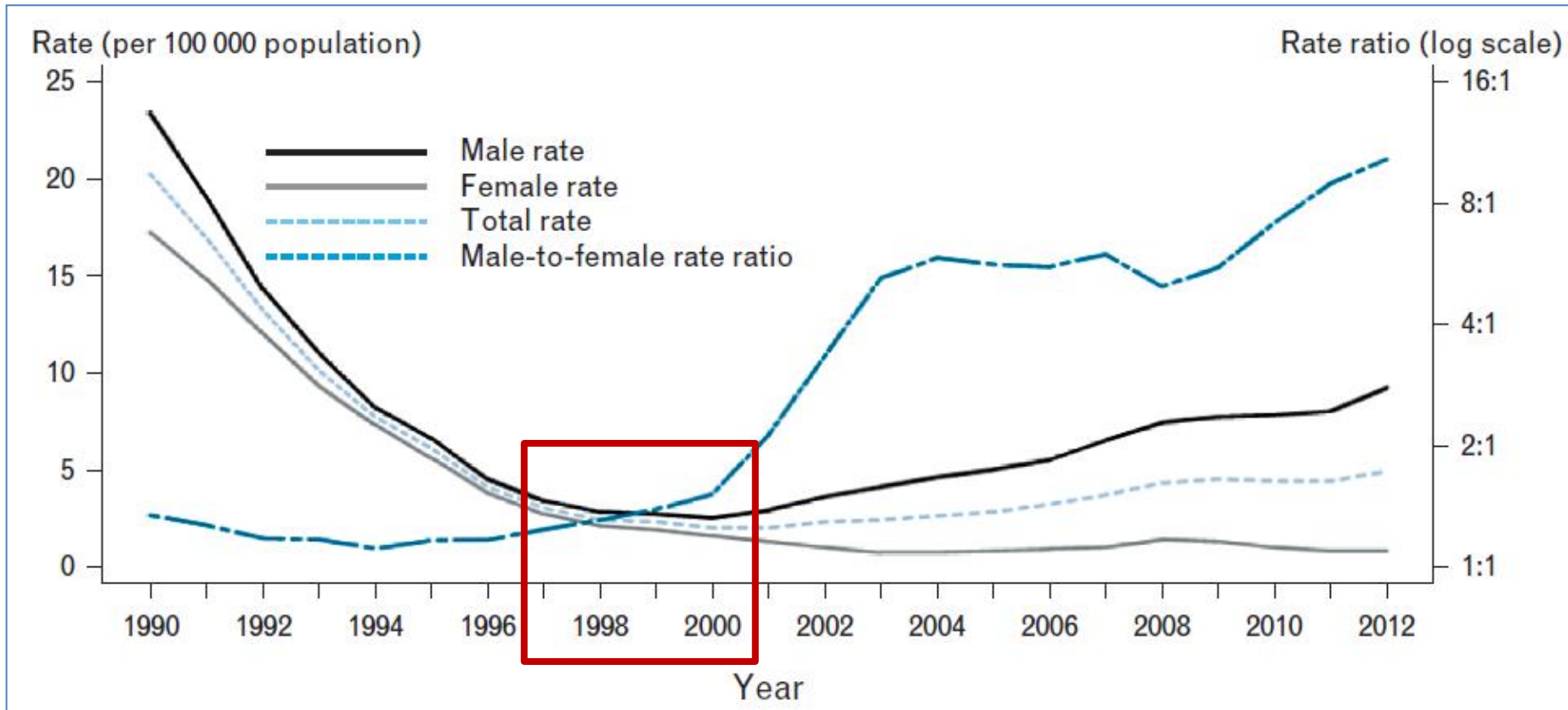




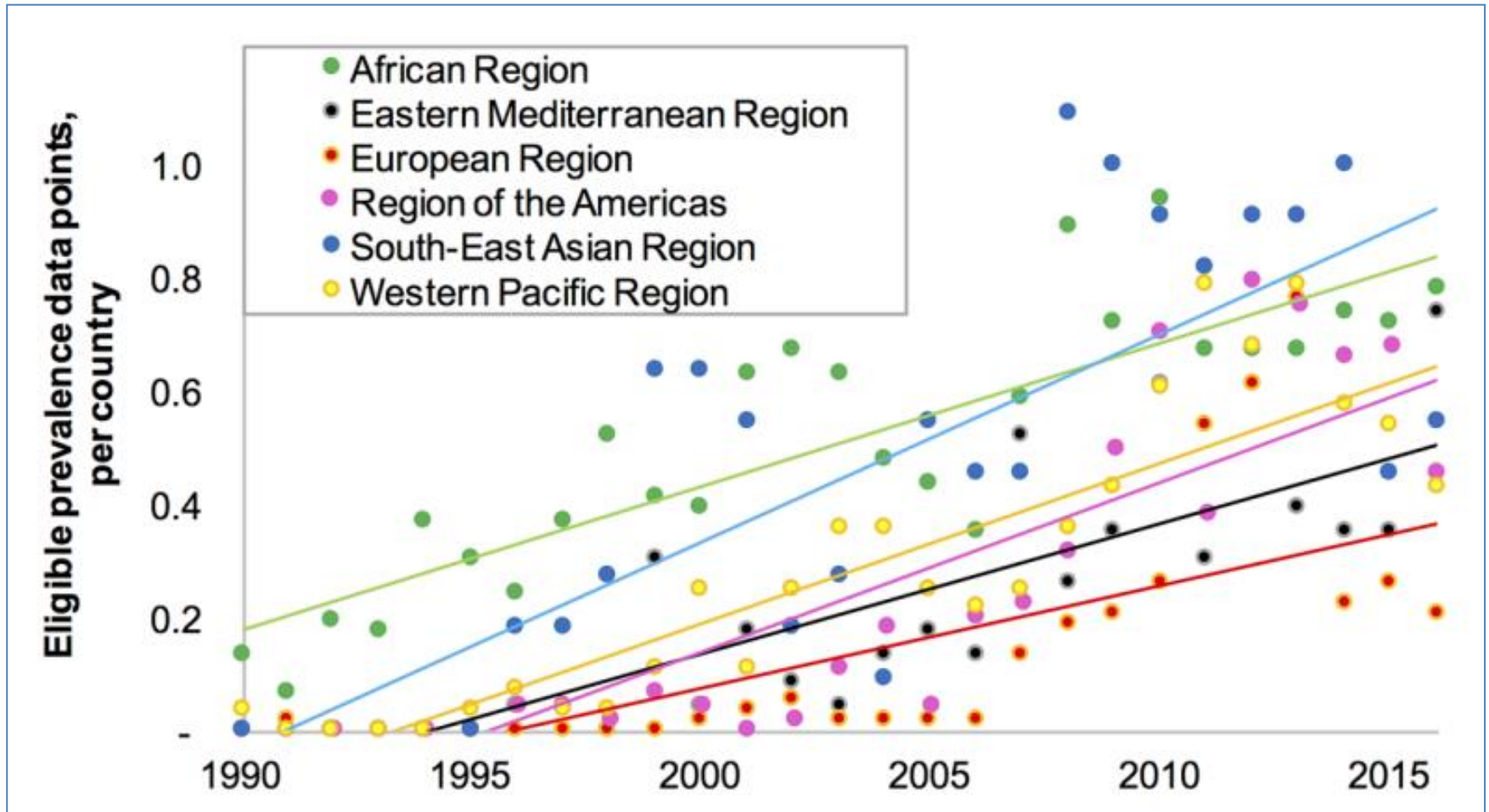
# EPIDEMIOLOGIA



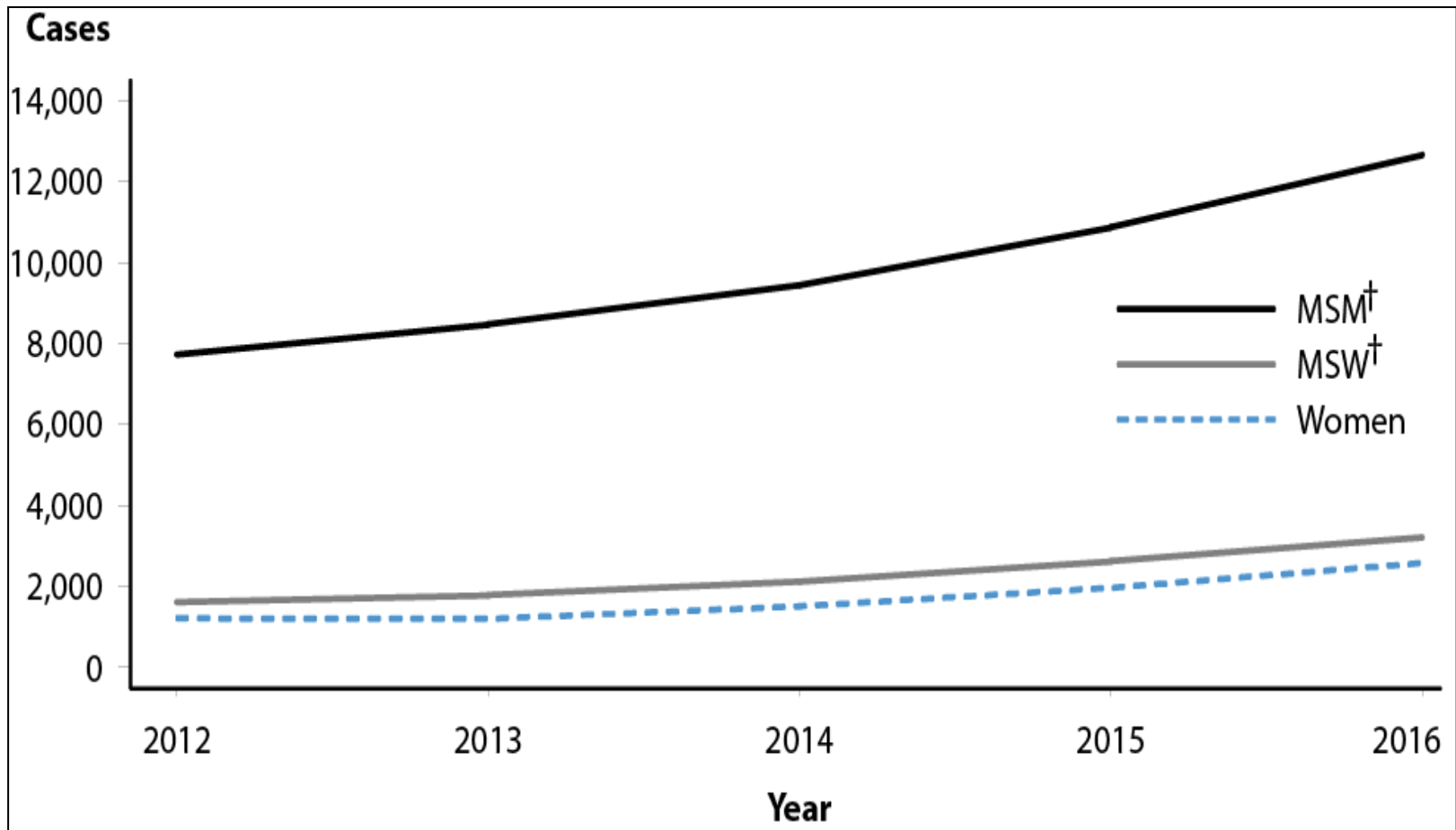
# EPIDEMIOLOGIA



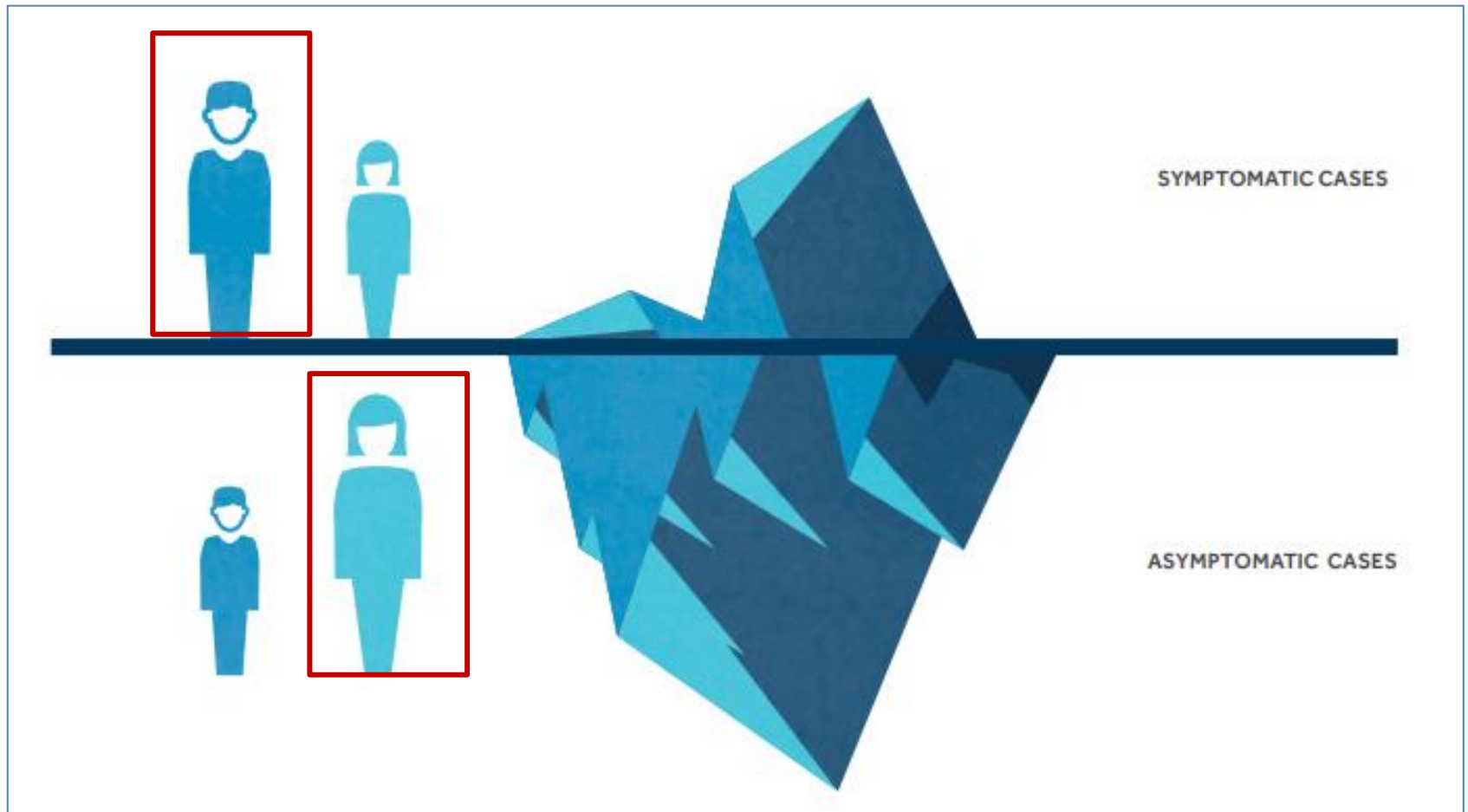
# EPIDEMIOLOGIA



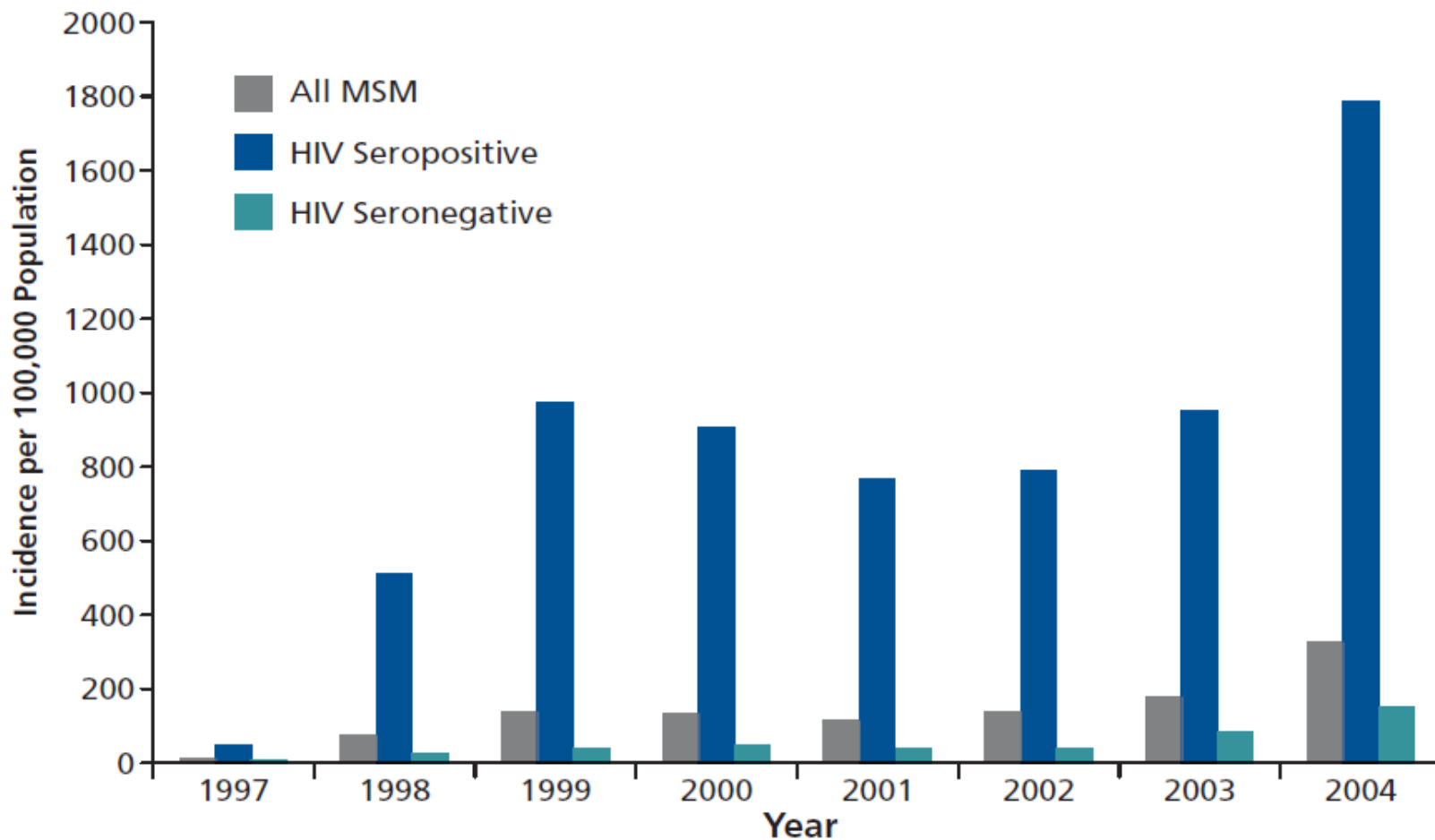
# EPIDEMIOLOGIA



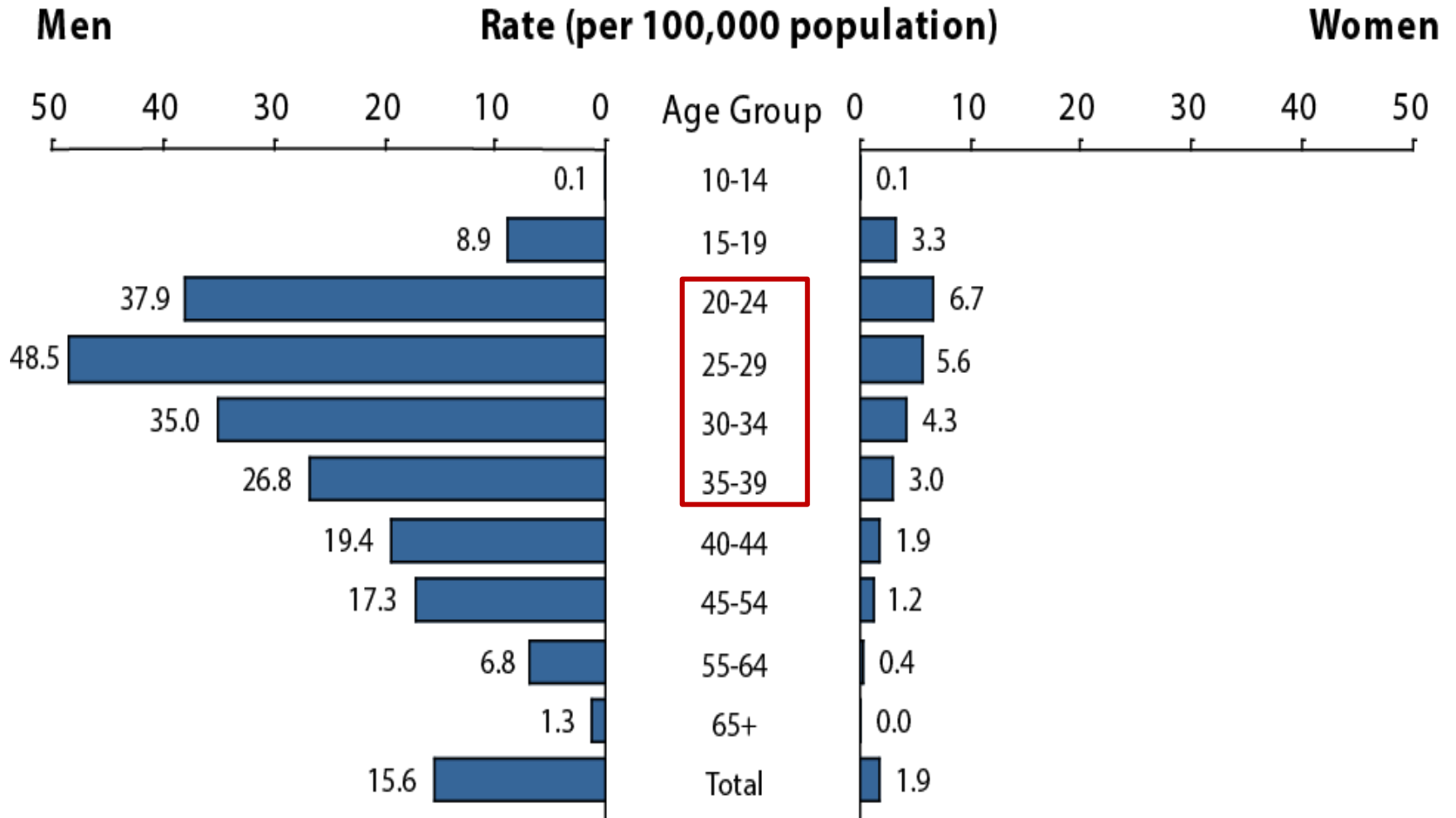
# MUJERES VS HOMBRES



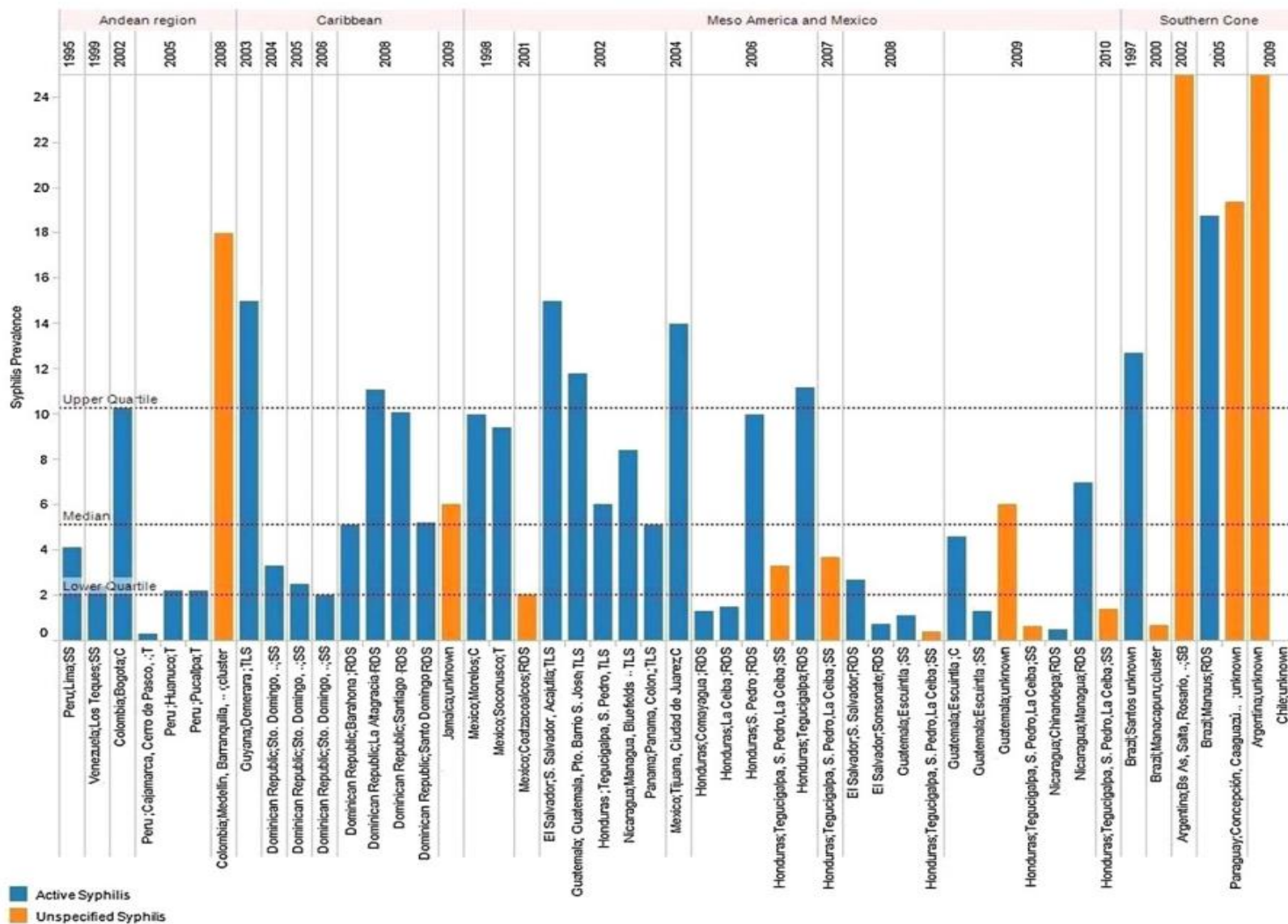
# EN POBLACION QUE VIVE CON VIH



# POR EDADES...



# Syphilis in the most at-risk populations in Latin America and the Caribbean





# Syphilis Infection Among Female Sex Workers in Colombia

Feature	FSSW street		Other FSW club	
	No.	%	No.	%
Age, 18–35 years	63	55.8	281	74.1 <sup>a</sup>
Education, primary or none	74	64.3	251	66.1 <sup>a</sup>
Marital status, single	47	39.8	209	55.3 <sup>a</sup>
Socio-economic stratum, low	50	49.0	108	30.8 <sup>a</sup>
Age at first sex, ≤15 years	68	60.2	173	45.6 <sup>a</sup>
Age at start of sex work, ≤22 years	59	52.2	123	33.1 <sup>a</sup>
Number of clients per week, ≥22	40	37.7	74	20.1 <sup>a</sup>
Condom use during vaginal sex with clients, no	64	54.2	135	35.4 <sup>a</sup>
Previous STI history, yes	28	23.7	55	14.4 <sup>a</sup>
Use of alcohol, yes	16	15.1	122	34.1 <sup>a</sup>
Use illegal drugs, yes	10	10.3	15	4.4 <sup>a</sup>
Syphilis infection, yes	25	21.2	25	6.5 <sup>a</sup>

# Seroprevalence of markers of transfusion transmissible infections in blood bank in Colombia

Prevalencia	Banco de sangre		Laboratorio de referencia	
	#	Por mil	#	Por mil
Global	1.812	33	468	9
VHB	132	2	50	1
VHC	344	6	3	0
VIH	247	5	27	0
Sífilis	643	12	308	6
Chagas	520	10	4	0

# Prevalencia de infección por *Treponema pallidum* en individuos atendidos en un centro especializado de Medellín, Colombia

Jaiberth Antonio Cardona-Arias;<sup>1</sup> Luis Felipe Higueta-Gutiérrez;<sup>2</sup> Juan Carlos Cataño-Correa<sup>3</sup>

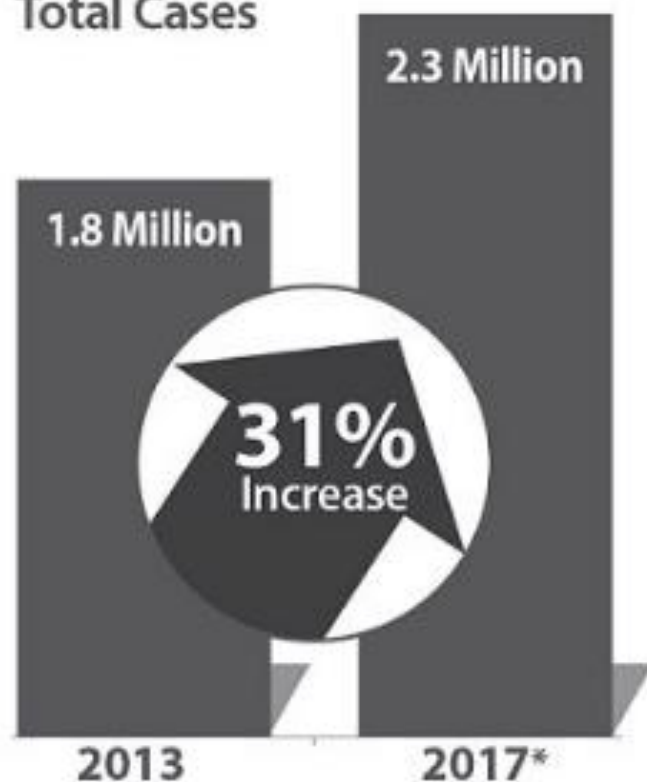
- 776 sujetos de población general, aparentemente sanos, asintomáticos y sin factores de riesgo para sífilis
- 126 hombres que tienen sexo con hombres (HSH)
- 190 jóvenes vulnerables (estrato socio-económico bajo, desempleados y sin finalizar educación básica)

Características sociodemográficas		Prevalencia específica % (n) <sup>a</sup>
Población	General	2,19(17) <sup>b</sup>
	HSH	16,67(21)
	Joven vulnerable	0,53(1)

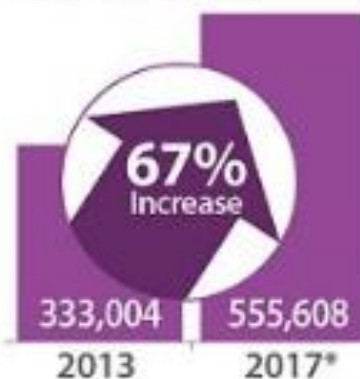
# THE U.S. IS EXPERIENCING STEEP, SUSTAINED INCREASES IN SEXUALLY TRANSMITTED DISEASES

Combined diagnoses of chlamydia, gonorrhea, and syphilis **increased sharply over the past five years**

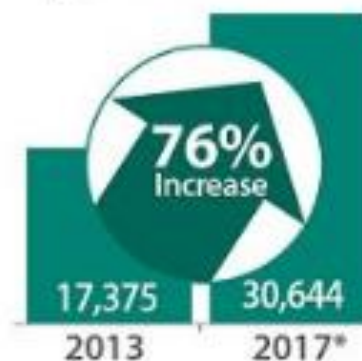
## Total Cases



## Gonorrhea



## Syphilis



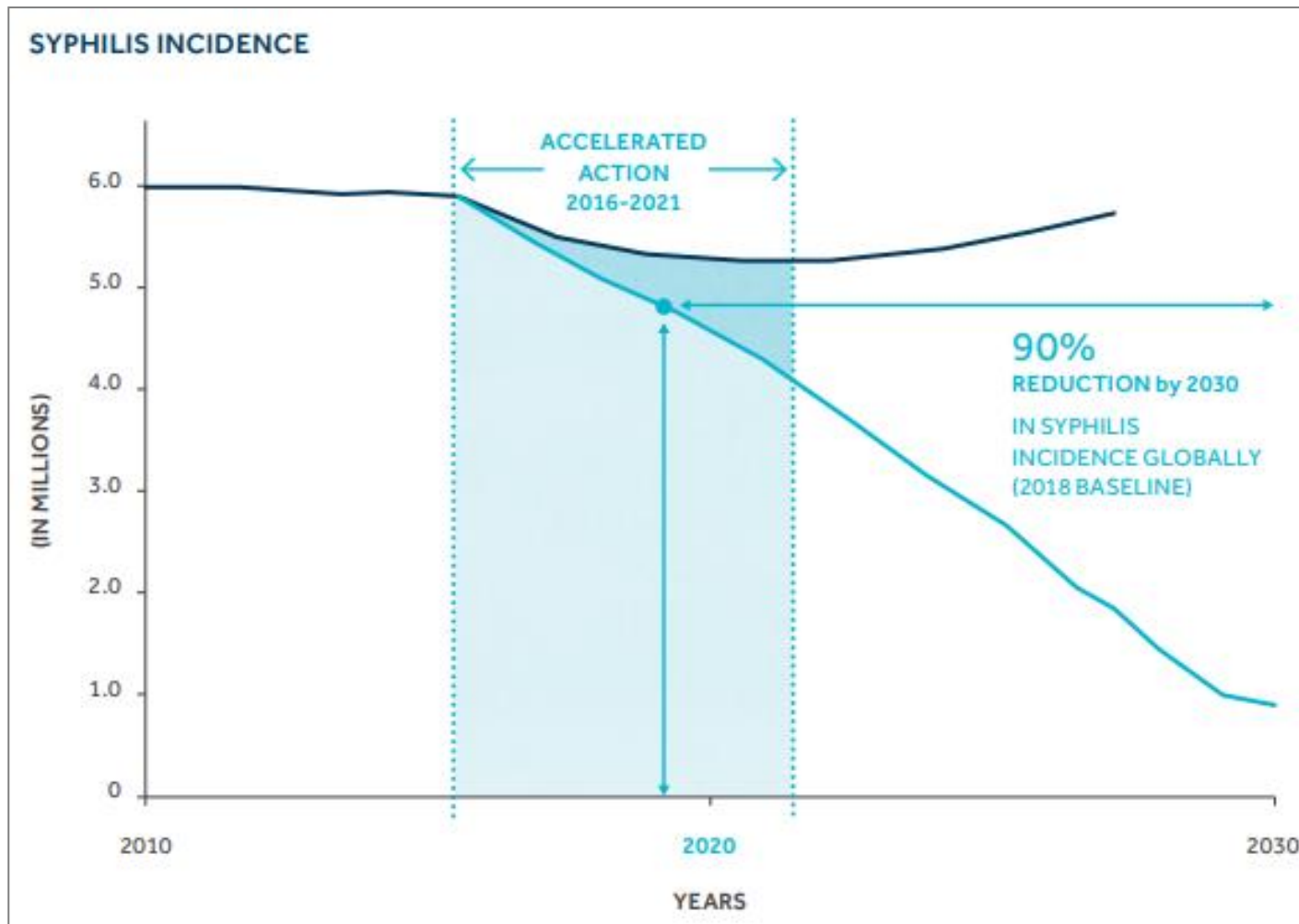
## Chlamydia

**1.7 MILLION**

In 2017\* chlamydia was the **most common condition** reported to CDC

\*Preliminary data

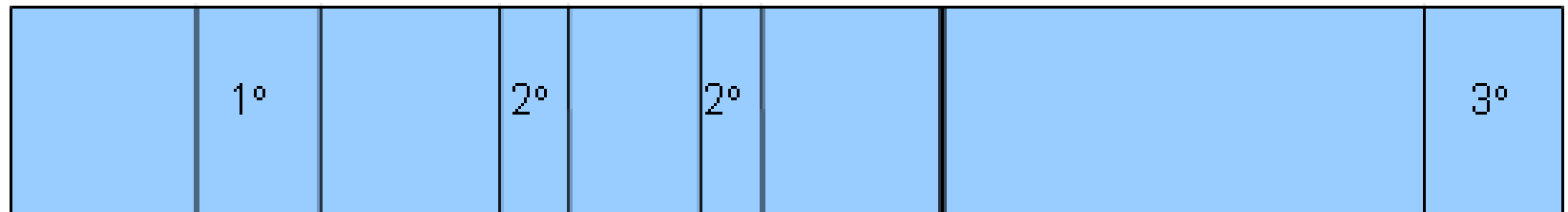
# GLOBAL HEALTH SECTOR STRATEGY ON SEXUALLY TRANSMITTED INFECTIONS 2016–2021



# HISTORIA NATURAL

## ESTADIOS CLINICOS DE LA SIFILIS

INFECCION



Período de Incubación  
10-90 días  
(promedio 21 días)

2 AÑOS

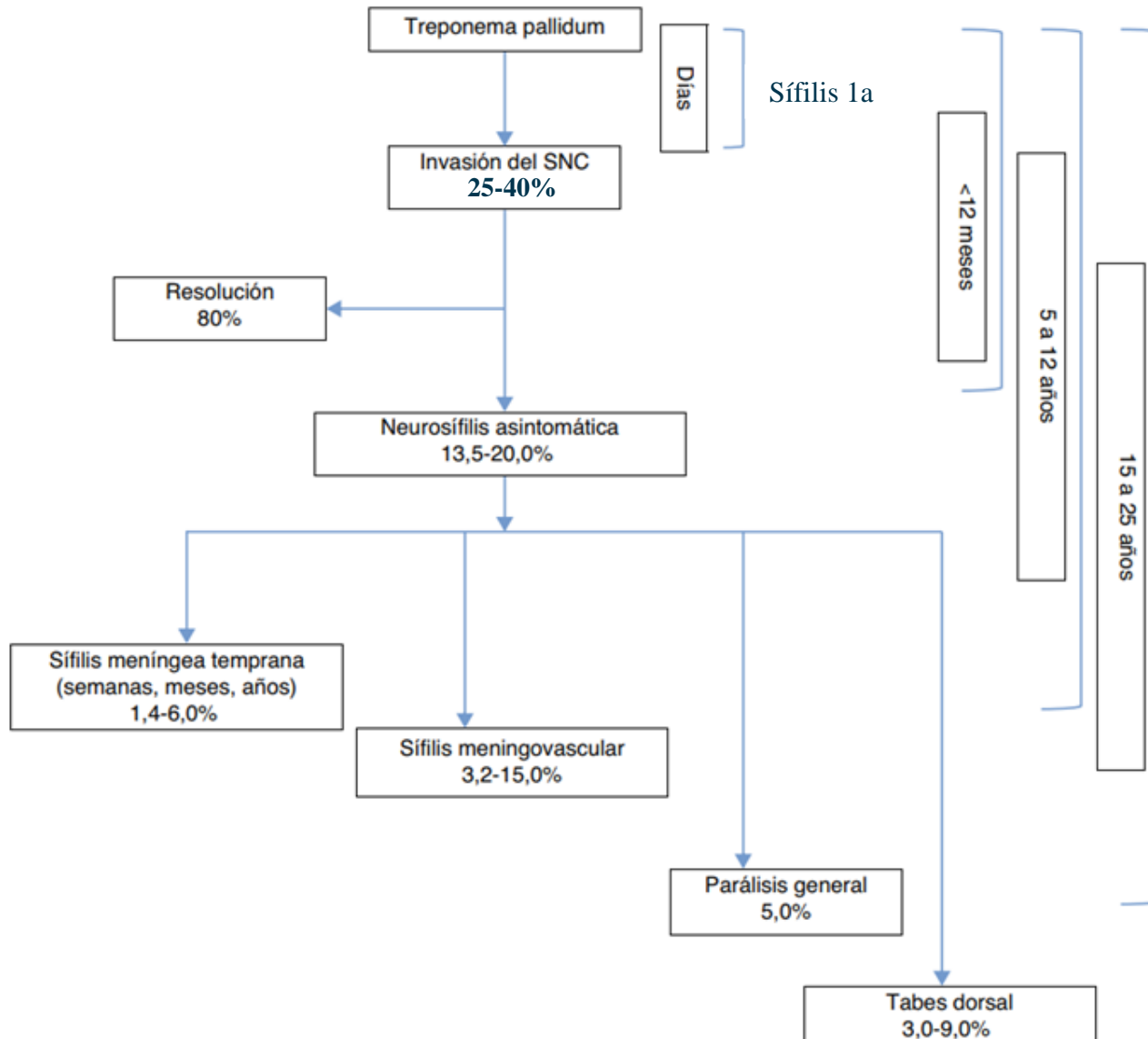
Recaídas en 25%

1 a 30 años:  
40% sin  
tratamiento  
pero solo  
25% con  
síntomas

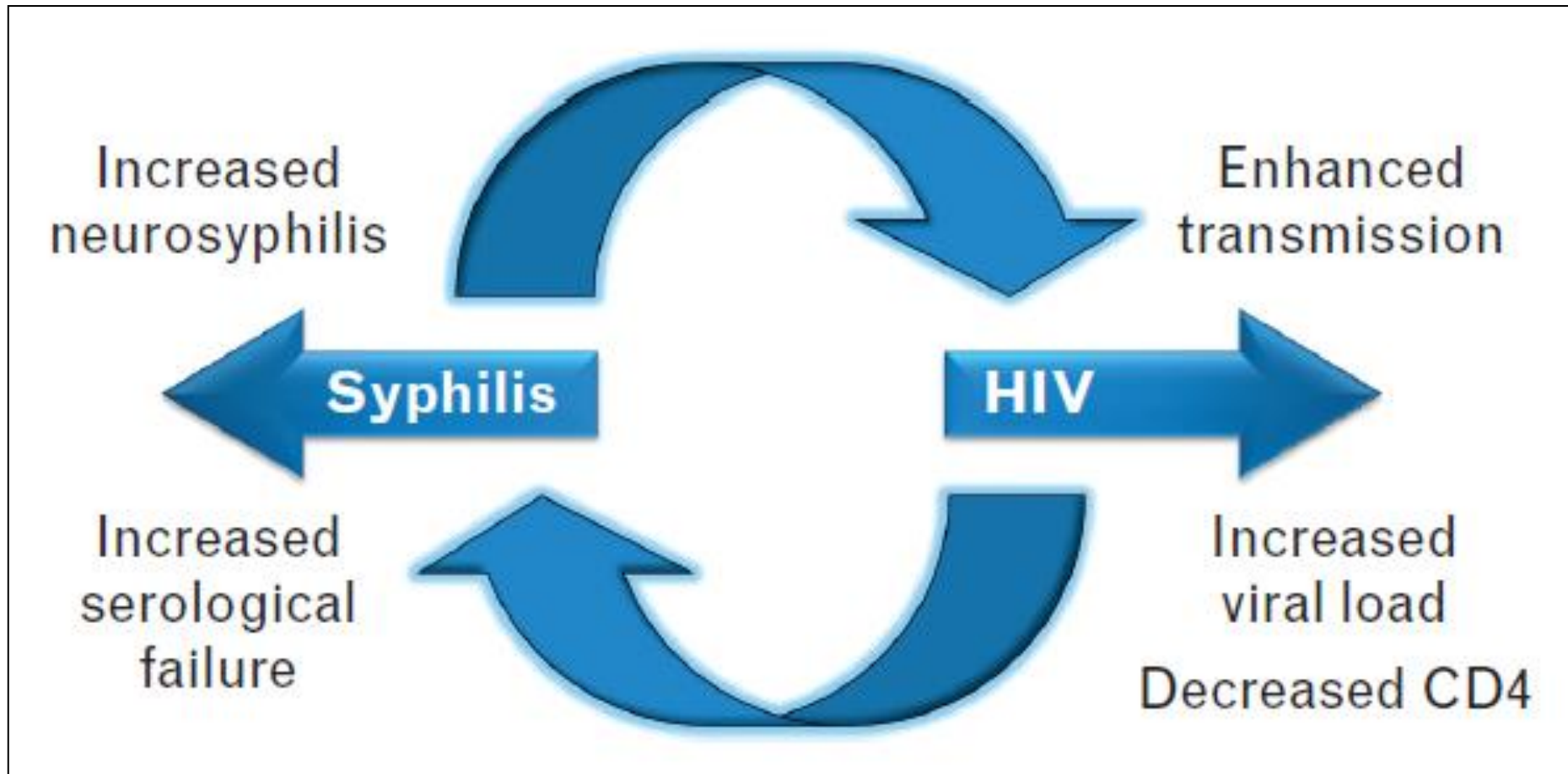
Sífilis temprana

Sífilis tardía

# HISTORIA NATURAL



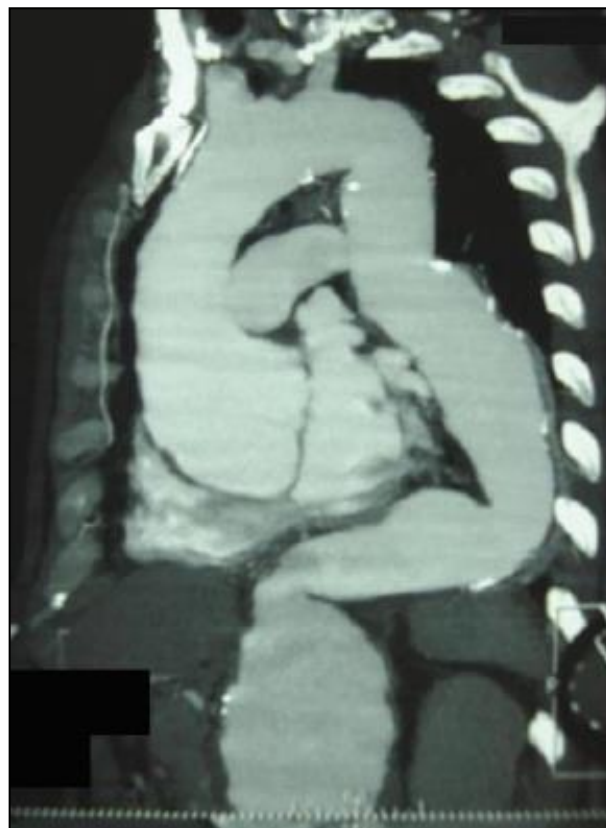
# SIFILIS y VIH





# Syphilitic Aortic Aneurysm in a Young HIV-Infected Man: Case Presentation

Juan Carlos Cataño and Isabel Cristina Ramirez



# SIFILIS y VIH

VIH altera las manifestaciones de la Sífilis:

- Rápida progresión a formas terciarias
- Formas oculares y óticas
- Lenta normalización del VDRL y LCR
- Mas reacciones tipo *Jarisch-Herxheimer*
- Mas recaídas

# SIFILIS y VIH

## Atypical features of syphilis in HIV-infected patients reported in the medical literature

Stage	Sign, symptom, or other finding	Variation reported in HIV-infected patients
Primary*	Chancre (primary ulcer)	Multiple (instead of single) lesions
Secondary†	Initial presentation	More likely to present initially with secondary syphilis manifestations
	Primary genital lesions	More often persistent in presentation of secondary stage
Any	Nontreponemal test results	Higher-titer results
	Biologic false-positive syphilis tests	Increased frequency
Neurologic site involvement	Serologic failure after treatment	Increased frequency despite lack of correlation with adverse clinical outcomes
	Prozone phenomenon	Increased frequency
	Jarisch-Herxheimer reaction	Increased frequency
	Normalization of CSF values after treatment for neurosyphilis	Delayed

# SIFILIS y VIH

- Primaria: 10 a 90 días pos-exposición
  - 70% con mas de un chancro no doloroso
  - Mas profundos y adenopatías grandes
  - 25% simultáneamente con brote
  - Aumenta CV-VIH y bajan CD4
  - Puede haber síntomas neurológicos



# Dx DIFERENCIAL

Differential Diagnoses of Genital Ulcer Disease		
Category	Common	Less common
Sexually transmitted diseases	Genital herpes Primary syphilis	Chancroid Lymphogranuloma venereum Granuloma inguinale
Other infections	Cellulitis ( <i>Streptococcus</i> species and <i>Staphylococcus aureus</i> )	Herpes zoster Deep fungi
Allergic reactions	Fixed drug reactions Contact dermatitis	Erythema multiforme Toxic epidermolysis
Autoimmune diseases	Aphthous ulcers Lichen planus	Lupus erythematosus Crohn disease Behçet disease Pemphigus Vasculitis Pyoderma gangrenosum
Malignancy	Squamous cell carcinoma Intraepithelial neoplasia	Extramammary Paget disease Basal cell carcinoma Lymphoma or leukemia Histiocytosis X

# SIFILIS y VIH

- Secundaria:
  - 2 a 6 semanas luego del chancro
  - Espiroquetemia (fiebre, brote y adenopatías)
  - Artritis, hepatitis, síntomas neurológicos
  - Puede haber aun chancro
  - Mejora en 2 a 12 semanas
  - 25% puede recaer en el primer año





# SIFILIS y VIH

- Terciaria:
  - Cardio, Gumma y Neuro
  - No infecciosa
  - Ocorre 2 a 30 años después
  - Solo en 40%
  - Solo 25% con síntomas

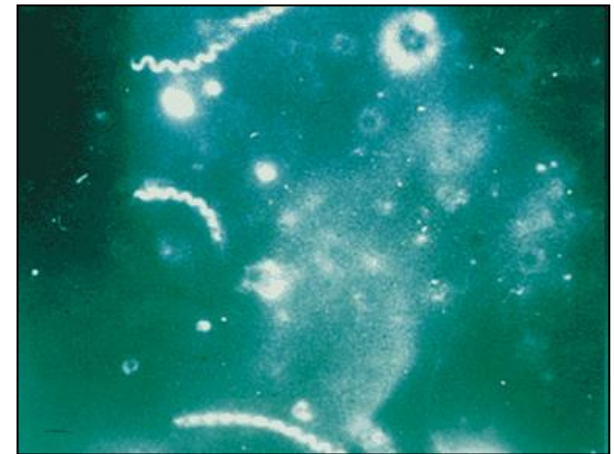
# NEUROSIFILIS y VIH

## Box 3 Potential manifestations of neurosyphilis

- ▶ (Aseptic) meningitis
- ▶ Chronic headache
- ▶ Psychiatric illness
- ▶ Cognitive impairment
- ▶ Ischaemic stroke
- ▶ Seizures
- ▶ Mass lesion
- ▶ Cranial (poly)neuropathy
- ▶ Optic neuritis/optic atrophy
- ▶ Ataxia
- ▶ Transverse myelitis
- ▶ Myelopathy
- ▶ (Poly)radiculopathy
- ▶ Peripheral neuropathy

# DIAGNOSTICO

- Examen físico: “la gran imitadora”
- Campo oscuro:
  - Requiere entrenamiento
  - Equipo especializado
  - No en boca



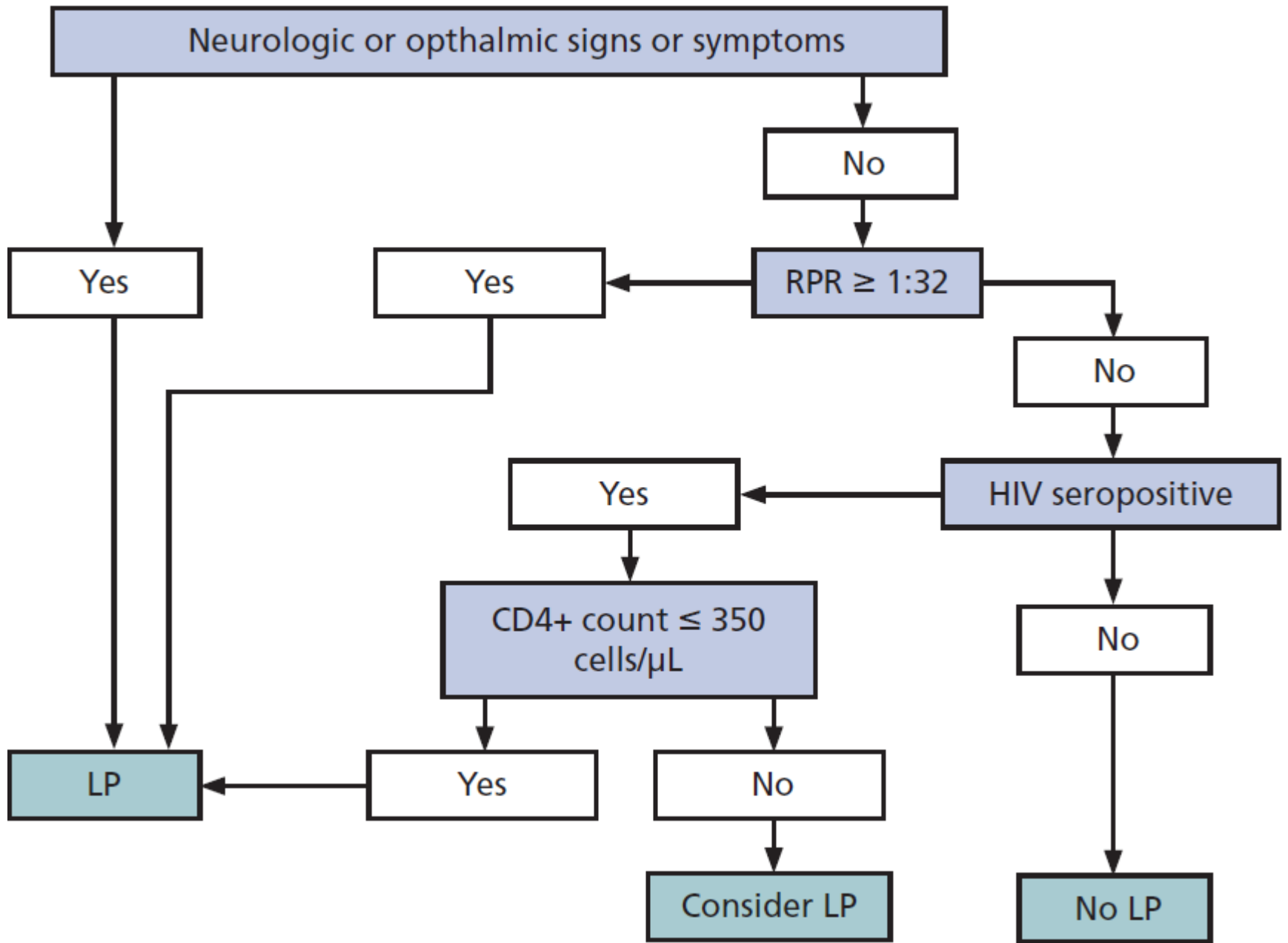
# DIAGNOSTICO

Table 1. Sensitivity and Specificity of Commonly Used Syphilis Tests<sup>15-19a</sup>

Syphilis Screening Test	Sensitivity by Stage of Untreated Syphilis, % (Range) <sup>b</sup>					Specificity, % (Range) <sup>b</sup>
	Mixed	Primary	Secondary	Latent	Tertiary	
<b>Nontreponemal</b>						
VDRL <sup>c</sup>		78 (74-87)	100	96 (88-100)	71 (37-94)	98 (96-99)
RPR <sup>c</sup>		86 (77-99)	100	98 (95-100)	73	98 (93-99)
TRUST <sup>c</sup>		85 (77-86)	100	98 (95-100)		99 (98-99)
USR <sup>c</sup>		80 (72-88)	100	95 (88-100)		99
<b>Treponemal</b>						
FTA-ABS <sup>c</sup>		84 (70-100)	100	100	96	97 (84-100)
TPPA <sup>c</sup>		88 (86-100)	100	97 (97-100)	94	96 (95-100)
Enzyme immunoassay		(77-100)	(85-100)	(64-100)	NA	(99-100)
Trep-Check	95.9 <sup>d</sup>					98.5 <sup>d</sup>
Trep-Sure	96.9 <sup>d</sup>					95.4 <sup>d</sup>
Chemiluminescence immunoassay		98	100	100	100	99
LIAISON <sup>e</sup>	99.2					99.9
<b>Multiplex flow immunoassay</b>						
BioPlex 2200; Syphilis IgG	96.9 <sup>d</sup>					98.0 <sup>d</sup>
Syphilis Health Check	95.6, <sup>f</sup> 98.5 <sup>g</sup>					90.5, <sup>f</sup> 97.4 <sup>g</sup>

# Syphilis and HIV Co-Infection: When is Lumbar Puncture Indicated?

- Todo VIH con Sífilis latente tardía
  - Primaria, secundario o latente temprana con:
    - VDRL > 1:32
    - CD4 < 350
- 18 veces mas riesgo de Neurosífilis**
- Síntomas neurológicos
  - Sin HAART



# NEUROSYPHILIS

## Cerebrospinal Fluid Profiles in the Different Forms of Neurosyphilis in the Prepenicillin Era<sup>a</sup>

Form of Neurosyphilis	White Blood Cells (per $\mu\text{L}$ )	Protein (mg/dL)	Reactive CSF Wassermann Test <sup>b</sup>
Asymptomatic	0–100	<45–100	84%
Meningeal	200–400	100–200	91%
Meningovascular	11–100	100–200	81%
Paresis	25–75	50–100	100%
Tabes dorsalis	10–50	45–75	72%

# NEUROSIFILIS y VIH

## PUNCION LUMBAR

Parámetro	Normal	VIH	VIH + Lues
Proteínas	< 40	40 a 60	> 60
Leucocitos	< 5	5 a 20	> 20
VDRL	Negativo	Negativo	Variable*

**\* VDRL en LCR positivo 30 a 70% de casos**



## Suggested Neurosyphilis Diagnostic Criteria

### ► Asymptomatic Neurosyphilis

Reactive serum treponemal test (FTA-abs)

AND

Reactive CSF-VDRL

If CSF-VDRL is negative:

Reactive CSF-treponemal test (FTA-abs)

AND

1. In a patient who is HIV infected with peripheral blood CD4+ T cells <200/ $\mu$ L and undetectable plasma HIV RNA and on antiretroviral therapy: CSF WBCs >5/ $\mu$ L
2. In a patient who is HIV infected with peripheral blood CD4+ T cells >200/ $\mu$ L or detectable plasma HIV RNA or not taking antiretroviral medications: reactive CSF-FTA-ABS and CSF WBCs >20/ $\mu$ L

# Syphilis and neurosyphilis: HIV-coinfection and value of diagnostic parameters in cerebrospinal fluid

Predictive parameters for definite or probable neurosyphilis		
Parameter	Odds ratio	<i>p</i> value*
Serum-RPR-titre $\geq 32$	1.53	0.383
CD4+ cell count $\leq 350/\mu\text{l}$	1.1	0.612
Blood-CSF barrier disturbance in HIV-negatives	9	0.018**
Blood-CSF barrier disturbance in HIV-positives	6	0.027**
Albumin quotient $>7.8$ mg/dl in HIV-negatives	8.0	0.026**
Albumin quotient $>7.8$ mg/dl in HIV-positives	23.3	0.006**
Pleocytosis $>5$ cells/ $\mu\text{l}$ in HIV-negatives	6.7	0.006**
Pleocytosis $>5$ cells/ $\mu\text{l}$ in HIV-positives	8.3	0.015**
ITPA index $>2$ in HIV-negatives	7.6	0.025**
positive IgM-FTA-ABS test in HIV-negatives	13.1	0.022**

# The Rapid Plasma Reagin Test Cannot Replace the Venereal Disease Research Laboratory Test for Neurosyphilis Diagnosis

Sensitivity and Specificity of CSF Nontreponemal Serological Tests for Diagnosis of Neurosyphilis

	Diagnostic Criterion			
	Laboratory-Defined Neurosyphilis (n=99)		Symptomatic Neurosyphilis (n=149)	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)*
CSF-VDRL	71.8 (57.7-85.9)	98.3 (95.0-100.0)	66.7 (50.6-82.8)	80.2 (72.9-87.5)
CSF-RPR	56.4 (40.8-72.0)	100.0 (100.0-100.0)	51.5 (34.4-68.6)	89.7 (84.2-95.2)

# Alternative cerebrospinal fluid tests to diagnose neurosyphilis in HIV-infected individuals

*Laboratory findings in syphilis cases categorized by CSF profile*

CSF test	CSF profile*			Sensitivity, %	Specificity, %
	Normal, n = 21	Equivocal, n = 19	Neurosyphilis, n = 7		
FTA-ABS	6/21	6/19	7/7	100	71
FTA-Dil	7/21	7/19	6/7	86	67
FTA	12/21	14/19	7/7	100	43
Elevated % CD19+ in fresh sample	0/18	2/17	2/5	40	100
Elevated % CD19+ in frozen sample	0/19	2/16	3/7	43	100

**Alto valor predictivo negativo !!**

# TRATAMIENTO

- La Penicilina sigue siendo de elección
- Igual respuesta al tratamiento en VIH
- Mas recaídas !!
- En caso de alergia:
  - Desensibilizar
  - Doxiciclina
  - Ceftriaxona

**Azitromicina !!**

# Global Challenge of Antibiotic-Resistant *Treponema pallidum*

23S rRNA gene mutations associated with spirochete macrolide resistance			
Spirochete	Mutation position <sup>a</sup>	Resistance(s) <sup>b</sup>	Clinical/ induced <sup>c</sup>
<i>T. pallidum</i>	A2058G	Ery, Azi	Clinical
	A2059G	Spi	Clinical
<i>T. denticola</i>	A2058G	Ery	Induced
<i>B. hyodysenteriae</i>	A2058G	Ery, Cli, Tyl	Induced
	A2058T	Ery, Cli, Tyl	Clinical
<i>B. pilosicoli</i>	A2058G	Tyl	Induced
	A2058T	Ery, Cli, Tyl	Clinical
	A2059C	Ery, Cli, Tyl	Clinical
	A2059G	Ery, Cli, Tyl	Clinical
<i>Brachyspira</i> spp.	A2062C	Tyl	Induced

# Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

## Treatment Recommendations Depending on Stage of Disease

### Early Stage (Primary, Secondary, and Early-Latent Syphilis)

#### *Preferred Therapy:*

- Benzathine penicillin G 2.4 million U IM for 1 dose **(All)**

#### *Alternative Therapy (For Penicillin-Allergic Patients):*

- Doxycycline 100 mg PO BID for 14 days **(BII)**, *or*
- Ceftriaxone 1 g IM or IV daily for 10–14 days **(BII)**, *or*
- Azithromycin 2 g PO for 1 dose **(BII)**

**Note:** Chromosomal mutations associated with azithromycin resistance and treatment failures have been reported, most commonly in MSM. Azithromycin should be used with caution and only when treatment with penicillin, doxycycline or ceftriaxone is not feasible. Azithromycin **is not recommended** for MSM or pregnant women **(All)**

### Late-Latent (>1 year) or Latent of Unknown Duration

#### *Preferred Therapy:*

- Benzathine penicillin G 2.4 million U IM weekly for 3 doses **(All)**

#### *Alternative Therapy (For Penicillin-Allergic Patients):*

- Doxycycline 100 mg PO BID for 28 days **(BIII)**

**Note:** Persons with penicillin allergy whose compliance or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin

# Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

## **Late-Stage (Tertiary—Cardiovascular or Gummatous Disease)**

- Perform CSF examination to rule out neurosyphilis and obtain infectious diseases consultation to guide management

### *Preferred Therapy:*

- Benzathine penicillin G 2.4 million U IM weekly for 3 doses **(AII)**

## **Neurosyphilis, Otic, or Ocular Disease**

### *Preferred Therapy:*

- Aqueous crystalline penicillin G, 18–24 million U per day, administered as 3–4 million U IV q4h or by continuous IV infusion for 10–14 days **(AII)** +/- benzathine penicillin G 2.4 million U IM weekly for 1 to 3 doses after completion of IV therapy **(CIII)**

### *Alternative Therapy:*

### *For Penicillin-Allergic Patients:*

- Desensitization to penicillin is the preferred approach; if not feasible, ceftriaxone 2 g IM or IV daily for 10–14 days **(BII)**



# TRATAMIENTO

VIH comparado con no-VIH:

- Sífilis temprana, P.benzatínica falla 12% vs 3%
- Sífilis tardía P.benzatínica falla 25% vs 7%

## A Pilot Study Evaluating Ceftriaxone and Penicillin G as Treatment Agents for Neurosyphilis in Human Immunodeficiency Virus–Infected Individuals

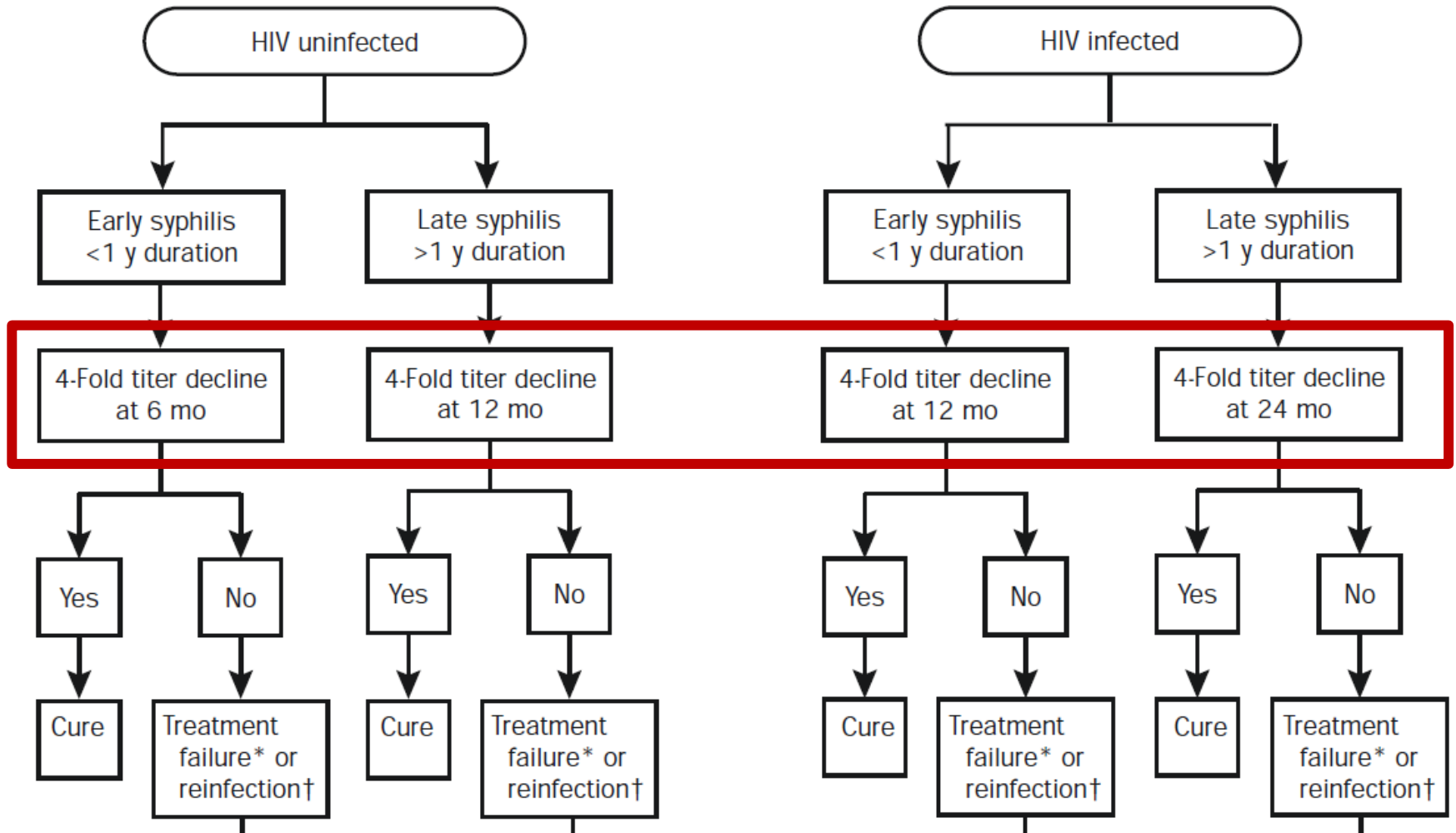
Median absolute changes in abnormal baseline laboratory values for ceftriaxone and penicillin recipients who were followed-up at 14–26 weeks.

Variable	Ceftriaxone ( <i>n</i> = 14)	Penicillin ( <i>n</i> = 16)	<i>P</i>
CSF WBCs, cells/ $\mu$ L	–64 (–140 to –35); <i>n</i> = 5	–55 (–100 to 0); <i>n</i> = 5	>.25
CSF protein, mg/dL	–14 (–146 to 13); <i>n</i> = 13	–7 (–274 to 61); <i>n</i> = 9	>.25
Reciprocal CSF-VDRL, log <sub>2</sub>	–1 (–1 to 1); <i>n</i> = 7	0 (–2 to 1); <i>n</i> = 7	>.25
Reciprocal serum RPR titer, log <sub>2</sub>	–2 (–4 to 0); <i>n</i> = 10	–1 (–2 to 0); <i>n</i> = 15	.004

# SEGUIMIENTO

- Serológico cada 6 meses hasta normalizar VDRL
- En VIH la normalización del LCR es mas lenta (2 años)
- Mirar Leucos y no VDRL en LCR
- Si en 6 meses no mejora el LCR o no normaliza en 2 años = retratar

# Recommended follow-up for syphilis in HIV-infected patients.



# ALGUNAS IDEAS FINALES

- Pacientes VIH positivos deben realizarse VDRL cada año
- La evolución de la Sífilis en VIH difiere
- Sífilis latente tardía en VIH = PL
- Penicilina sigue siendo el tratamiento de elección
- Normalización de parámetros es mas lenta

# SIFILIS EN EL PACIENTE QUE VIVE CON VIH



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