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Characteristics of the "asymptomatic" HIV-infected patient with potential underlying CNS toxicity

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Agenda

1. La sintomatología del SNC es muy frecuente en pacientes VIH+
2. La sintomatología es relativa
3. La evidencia es controvertida
4. No todos los pacientes se explican igual
5. No todos los médicos son igualmente receptivos
6. La patología/toxicidad del SNC es difícil de monitorizar y de detectar
7. La patología/toxicidad del SNC está infradiagnosticada

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Predictors and treatment strategies of HIV-related fatigue in the combined antiretroviral therapy era

Objective To assess predictors and reported treatment strategies of HIV-related fatigue in the combined antiretroviral (cART) era.

Method Five databases were searched and reference lists of pertinent articles were checked. Studies published since 1996 on predictors or therapy of HIV-related fatigue measured by a validated instrument were selected.

Results A total of 42 studies met the inclusion criteria. The reported HIV-related fatigue prevalence in the selected studies varied from 33 to 88%. The strongest predictors for sociodemographic variables were unemployment and inadequate income. Concerning HIV-associated factors, the use of cART was the strongest predictor. Comorbidity and sleeping difficulties were important factors when assessing physiological influences. Laboratory parameters were not predictive of fatigue. The strongest and most uniform associations were observed between fatigue and psychological factors such as depression and anxiety. Reported therapeutic interventions for HIV-related fatigue include testosterone, psycho-stimulants (dextroamphetamine, methylphenidate hydrochloride, pemoline, modafinil), dehydroepiandrosterone, fluoxetine and cognitive behavioural or relaxation therapy.

Conclusion HIV-related fatigue has a high prevalence and is strongly associated with psychological factors such as depression and anxiety. A validated instrument should be used to measure intensity and consequences of fatigue in HIV-infected individuals. In the case of fatigue, clinicians should not only search for physical mechanisms, but should question depression and anxiety in detail. There is a need for intervention studies comparing the effect of medication (antidepressants, anxiolytics) and behavioural interventions (cognitive-behavioural therapy, relaxation therapy, graded exercise therapy) to direct the best treatment strategy. Treatment of HIV-related fatigue is important in the care for HIV-infected patients and requires a multidisciplinary approach.

Jong E et al. AIDS 2010

Headache Among Patients With HIV Disease: Prevalence, Characteristics, and Associations

- **Background.—** Headache is one of the most common medical complaints reported by individuals suffering from human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), but limited and conflicting data exist regarding their prevalence, prototypical characteristics, and relationship to HIV disease variables in the current era of highly active antiretroviral therapy (HAART).
- **Objectives.—** The aims of the present cross-sectional study were to characterize headache symptoms among patients with HIV/AIDS and to assess relations between headache and HIV/AIDS disease variables.
- **Methods.—** Two hundred HIV/AIDS patients (49% female; mean age = 43.22 ± 12.30 years; 74% African American) from an internal medicine clinic and an AIDS outreach clinic were administered a structured headache diagnostic interview to assess headache characteristics and features consistent with International Classification of Headache Disorders (ICHD)-II diagnostic semiologies. They also completed 2 measures of headache-related disability. Prescribed medications, most recent cluster of differentiation (CD4) cell count, date of HIV diagnosis, possible causes of secondary headache, and other relevant medical history were obtained via review of patient medical records.
- **Results.—** One hundred seven patients (**53.5%**) reported headache symptoms, the large majority of which were consistent with characteristics of primary headache disorders after excluding 4 cases attributable to secondary causes. Among those who met criteria for a primary headache disorder, 88 (85.44%) met criteria for migraine, most of which fulfilled ICHD-II appendix diagnostic criteria for chronic migraine. Fifteen patients (14.56%) met criteria for episodic or chronic tension-type headache. Severity of HIV (as indicated by CD4 cell counts), but not duration of HIV or number of prescribed antiretroviral medications, was strongly associated with headache severity, frequency, and disability and also distinguished migraine from TTH.
- **Conclusions.—** Problematic headache is highly prevalent among patients with HIV/AIDS, most of which conform to the semiology of chronic migraine, although with some atypical features such as bilateral location and pressing/tightening quality. A low frequency of identifiable secondary causes is likely attributable to reduced frequency of opportunistic infections in the current era of HAART. **Disease severity is strongly predictive of headache**, highlighting the importance of physician attention to headache symptoms and of patient adherence to treatment.

Kirkland KE et al. Headahce 2012

Insomnia in HIV-infected patients: pathophysiologic implications

- The prevalence of insomnia in the HIV-seropositive population is estimated to be **29-97%**, far greater than the 10% general population prevalence. We carried out a systematic review to assess whether the prevalence of insomnia is indeed higher in HIV-seropositive patients and to better understand the correlates of insomnia in order to attempt to explain the dramatically higher prevalence. Nineteen studies met our search criteria and were included in this review. We found that prior studies estimated the rate of disturbed sleep, but not a single study estimated the prevalence of insomnia using insomnia diagnostic criteria, which require that sleep disturbance occur frequently, persistently, and in association with impairment in quality of life or daytime function. We also found that in addition to correlates of sleep disturbance seen in the general population, there are also correlates specific to the HIV-seropositive population: stage and duration of HIV infection, and cognitive impairment. The most important conclusion of this review is that the prevalence of insomnia which meets diagnostic criteria has yet to be estimated in populations of HIV-seropositive patients and studies are needed to estimate this prevalence rate. The rate of sleep disturbance identified in HIV-infected patients (29-97%) should not be compared against the approximately 10% prevalence of clinically significant insomnia in the general population, which would suggest that HIV infection is associated with an alarming increase in sleep problems. Instead, this rate is best compared with the rate of sleep disturbance in the general population, which is roughly 33%.

Low Y et al. AIDS Rev 2014

Prevalence of depressive symptoms

2175 HIV+ in routine care: cross sectional study in the UK

N=2175	n	Prevalence (95% CI)	Prevalence comparison
PHQ-9: DD (Depressive disorder)	579	26.6 % (24.8 %, 28.5 %)	General population (Germany)[1]: 9%
PHQ-9: MDD (Major depressive disorder)	415	19.1 % (17.4 %, 20.7 %)	General population (Germany) [1]: 4% Primary care (Netherlands)[2]: 5%
	n	%	
PHQ-9: DSS (Depression severity score) None (0) Minimal (1-4) Mild (5-9) Moderate (10-19) Severe (≥ 20) DSS score ≥ 10	 411 729 448 444 143 587	 18.9 % 33.5 % 20.6 % 20.4 % 6.6 % 27.0%	General population (England)[3]: PHQ-9 DSS score ≥ 10: 7% Primary care (Netherlands)[2]: PHQ-9 DSS score ≥ 10: 11%

[1]Martin et al. General Hospital Psychiatry 2006; 28: 71
[2]Zuithoff et al. BMC Family Practice 2010; 11: 98
[3]Paranjothy et al. BMC Public Health 2011; 11: 145

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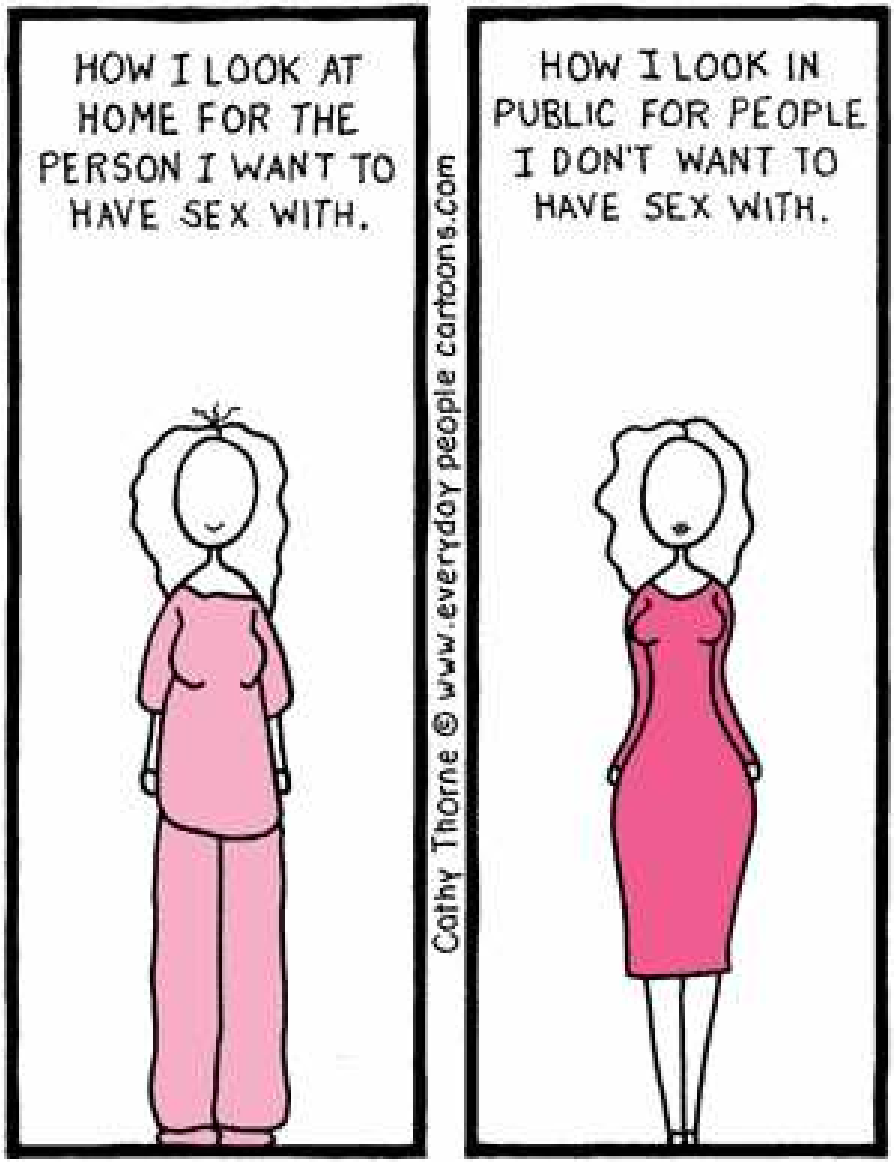
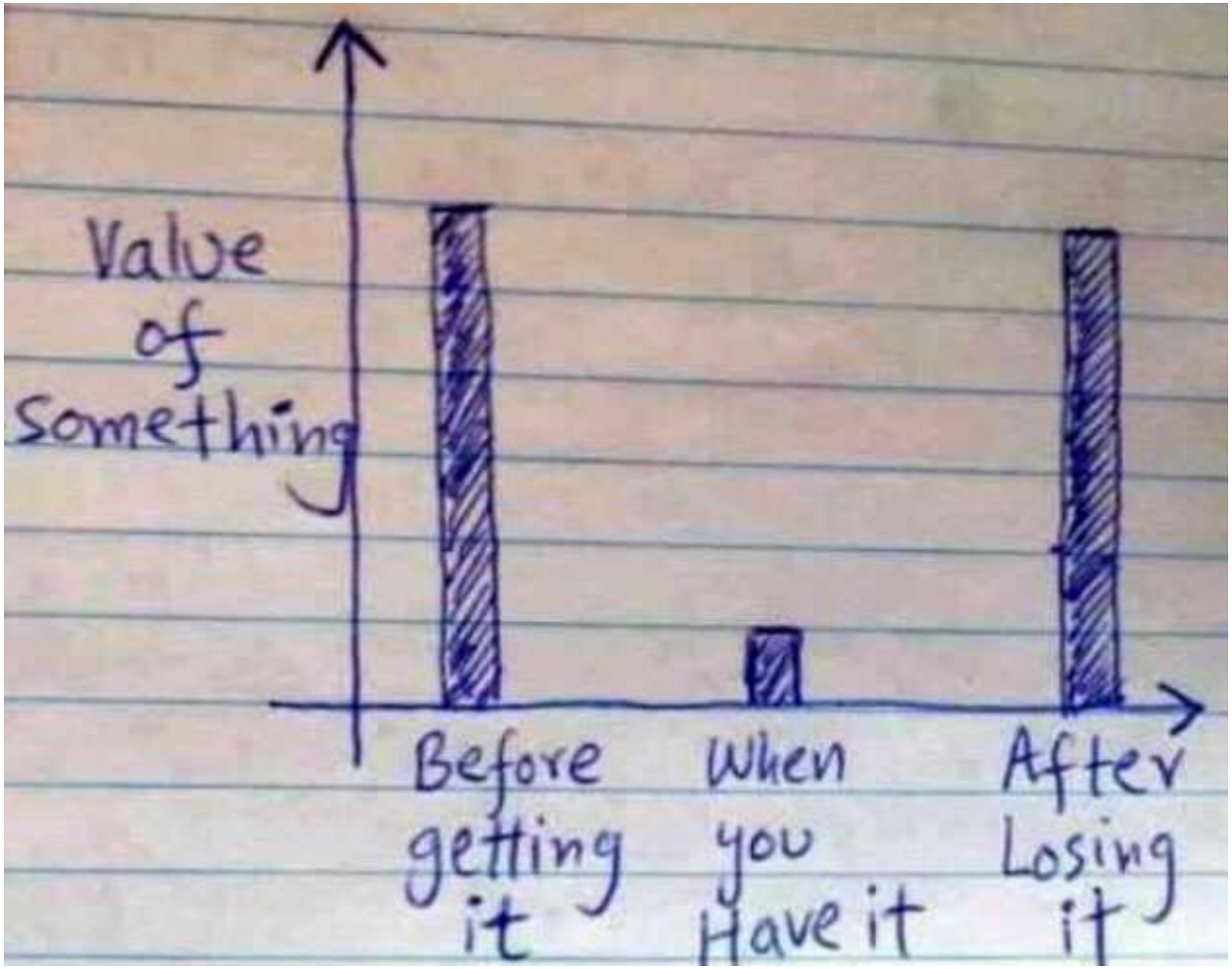
El valor que damos a algo es relativo



El valor que damos a algo bueno es relativo



El valor que damos a algo malo es relativo

- Tres pacientes VIH+ que toman Atripla tienen insomnio:
  - Uno (hombre, 45a) está experimentando intensamente la mejoría asociada al tratamiento antirretroviral y al tratamiento satisfactorio de una tuberculosis diseminada concomitante
  - Otro (hombre, 85a) tiene múltiples comorbilidades y medicaciones concomitantes y está acostumbrado a tener molestias de distinto tipo
  - Otro (hombre, 30a) tiene un control inmunológico y virológico óptimos, y una vida laboral y social activa y aparte del insomnio no tiene otras molestias

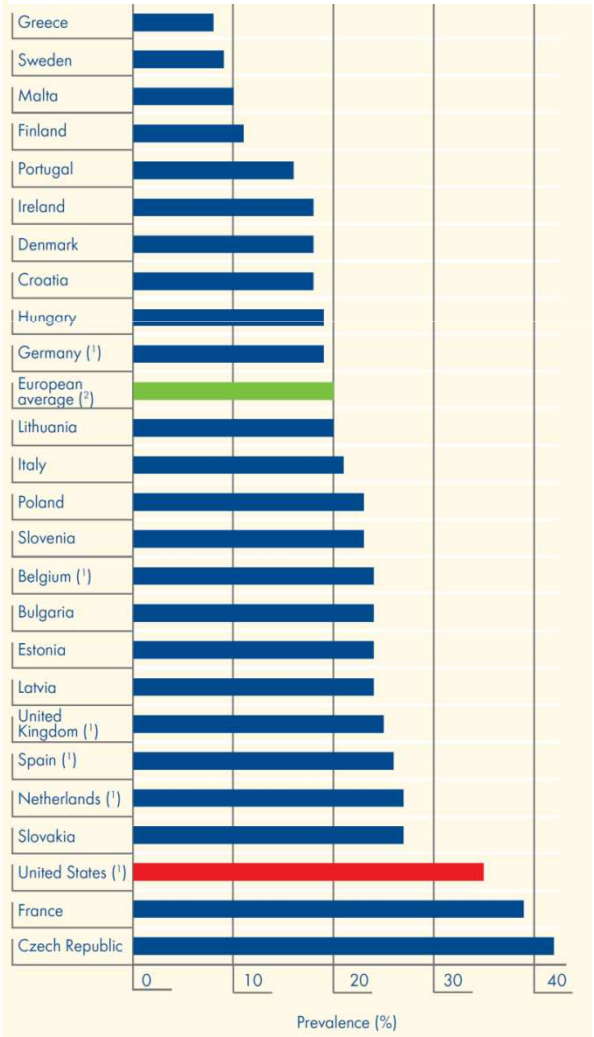
¿Quién de los 3 cree que se quejará antes o más?

Casos y pacientes ficticios

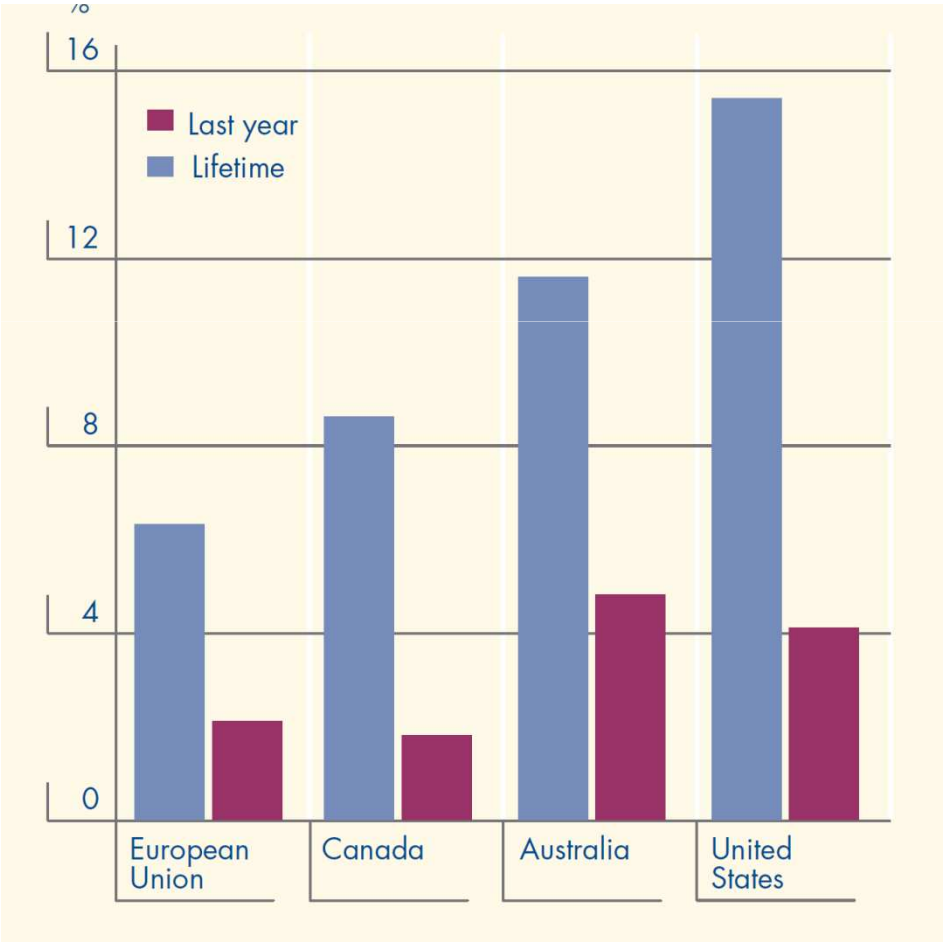
El valor que damos a algo depende del entorno

Además, las cosas pueden mezclarse y no ser tan claras

Cannabis use



Cocaine use



EMCDDA 2012

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Seguridad y tolerabilidad de efavirenz

Efecto Adverso, %	Efavirenz (n = 1008)	Brazo control (n = 635)
SNC (cualquier grado)	52.7	24.6
▪ Síntomas leves	33.3	15.6
▪ Síntomas moderados	17.4	7.7
▪ Síntomas graves	2.0	1.3
▪ Discontinuación del tratamiento	2.1	1.1
Exantema (cualquier grado)	26.3	17.5
▪ Grado 1-2	25.4	17.2
▪ Grado 3-4	0.9	0.3
▪ Retiradas	1.7	0.3

Ficha técnica de efavirenz (2001)

CNS Adverse Effects of EFV

- Neuropsychiatric symptoms typically develop within first 4 weeks, resolve within 2-4 weeks[1]
- In ACTG 384, EFV CNS adverse effects predictable, self-limited[2]

Adverse Effect, %	EFV-Containing Regimens	Other Regimens
Sleep disorders	**7**	**< 1**
Vivid dreams	**5**	**< 1**

1. Fortin C et al. Expert Rev Anti Infect Ther 2004.
2. Shafer R et al. N Engl J Med 2003

ALIZE-ARNS 099: EFV Use Not Associated With Depressive Episodes

Outcome	EFV-Based Treatment (n = 178)	PI-Based Treatment (n = 177)
Patients experiencing ≥ 1 depressive episode, n (%)	**15 (8)**	**12 (7)**
Depressive episode, no. of events	**16**	**12**
■ Depression	**15**	**11**
■ Suicide attempt	**1**	**3**
Depressive episode event severity, no. of events		
■ Mild	**3**	**3**
■ Moderate	**11**	**6**
■ Severe	**1**	**4**
■ Life threatening	**1**	**1**
New use of antidepressants on follow-up, n (%)	**12 (7) (n = 170)**	**7 (4) (n = 169)**
Depressive episode incidence/100 patient-years (95% CI)	**11 (5-16)**	**9 (4-13)**

Journot V et al. Clin Infect Dis 2006

Long-Term Neuropsychiatric Disorders on Efavirenz-Based Approaches

Quality of Life, Psychologic Issues, and Adherence

Carmina R. Fumaz, MA, Jose A. Muñoz-Moreno, BS,* José Moltó, MD,* Eugènia Negredo, PhD,* Maria José Ferrer, MA,† Guillem Sirera, PhD,† Núria Pérez-Alvarez, BS,* Guadalupe Gómez, PhD,‡ David Burger, PhD,§ and Bonaventura Clotet, PhD‖*

Background: Efavirenz has been associated with neuropsychiatric disorders, although little is known about its long-term toxicity.

Objective: To assess neuropsychiatric disorders and their relation to efavirenz plasma levels as well as quality of life, psychologic status, and adherence in HIV-infected patients on long-term efavirenz-based antiretroviral therapy.

Methods: Cross-sectional study comparing 60 patients on an efavirenz-based approach (EFV group) and 60 patients on a protease inhibitor–containing regimen (PI group) for at least 1 year. Adverse events, efavirenz plasma levels, quality of life, psychologic status, and adherence were assessed.

Results: The mean time on treatment was 91.1 ± 39.5 weeks in the EFV group and 119.9 ± 67.4 weeks in the PI group. Mild dizziness, sadness, mood changes, irritability, lightheadedness, nervousness, impaired concentration, abnormal dreams, and somnolence were reported more frequently in the EFV group than in the PI group ($P < 0.05$). Forty-nine of 60 patients presented with therapeutic efavirenz plasma levels (range: 1.0–4.0 mg/L). Efavirenz plasma levels were similar in subjects with and without neuropsychiatric disorders. No significant differences were found between the EFV group and the PI group regarding quality of life and psychologic status. Sixty percent of patients in the EFV group and 55% in the PI group reported adherence ≥95%.

Conclusions: Mild and clinically tolerable neuropsychiatric disorders may persist in patients after a mean of 2 years using an efavirenz-based approach. Quality of life and psychologic status remained good in both study groups. Interventions to enhance long-term adherence should be applied in clinical practice.

Key Words: efavirenz, long-term neuropsychiatric disorders, plasma levels, quality of life, psychologic status, adherence

(*J Acquir Immune Defic Syndr* 2005;38:560–565)

Efavirenz: enhancing the gold standard

J. R. Arribas

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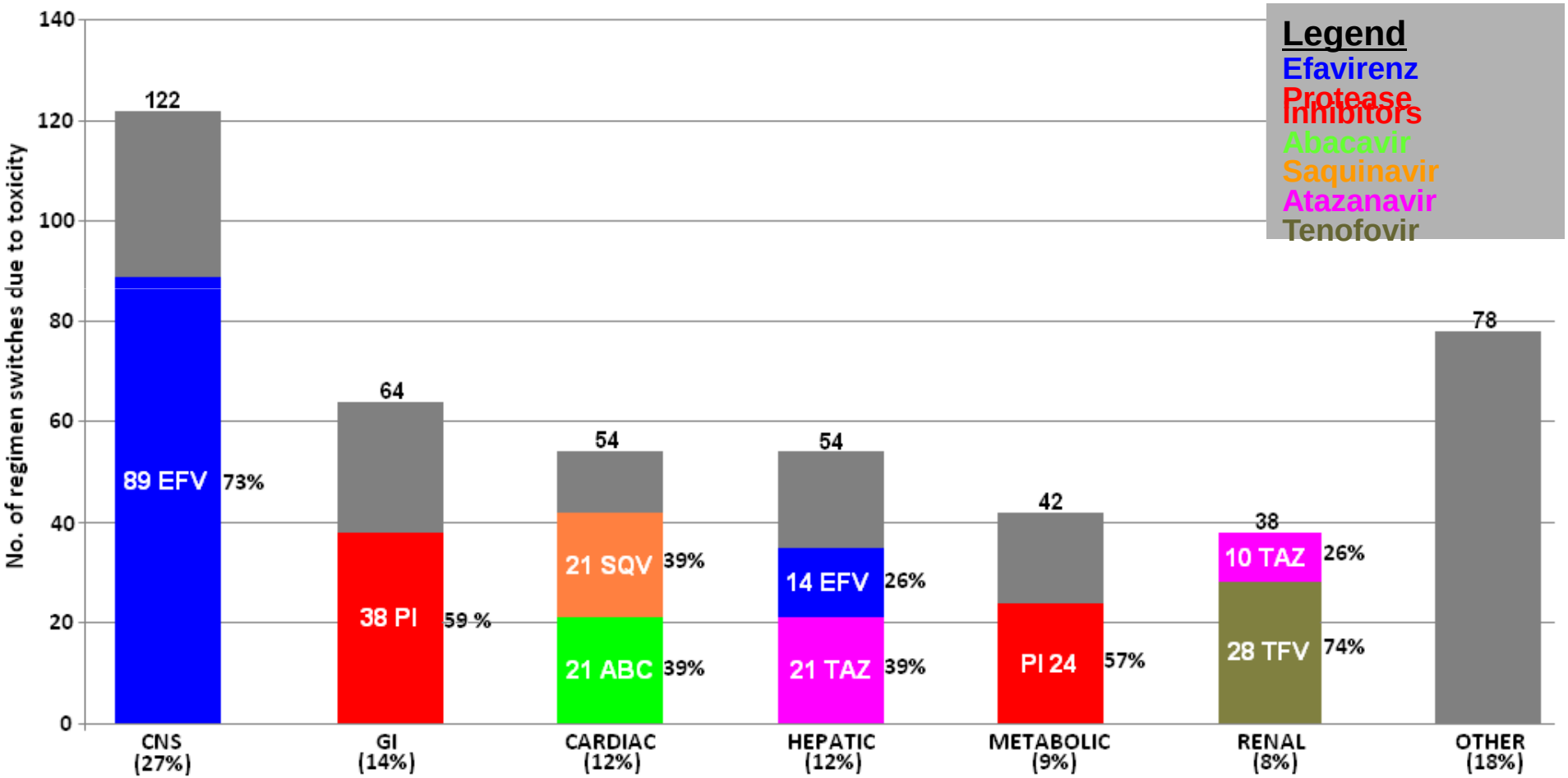
Abstract

Efavirenz, the potent, once-daily non-nucleoside reverse transcriptase inhibitor, has been successfully used since 1996 and is still a cornerstone of antiretroviral therapy for use in treatment-naïve, treatment-experienced and difficult-to-treat patients. The efficacy of efavirenz in these patient groups has been established in many clinical and cohort studies. Furthermore, efavirenz is now available as a single 600 mg tablet, providing a simplified therapy and decreased pill burden, which may lead to improved adherence and treatment outcomes. Efavirenz has a well-characterized tolerability profile, the more notable side effects being mainly short-term and non-life-threatening, such as central nervous system disturbances and rash.

Arribas JR. Int J STD AIDS 2003

Toxicity switches
Chelsea & Westminster Hospital

- 452 switches due to toxicity/perceived toxicity



Courtesy of Mark Nelson

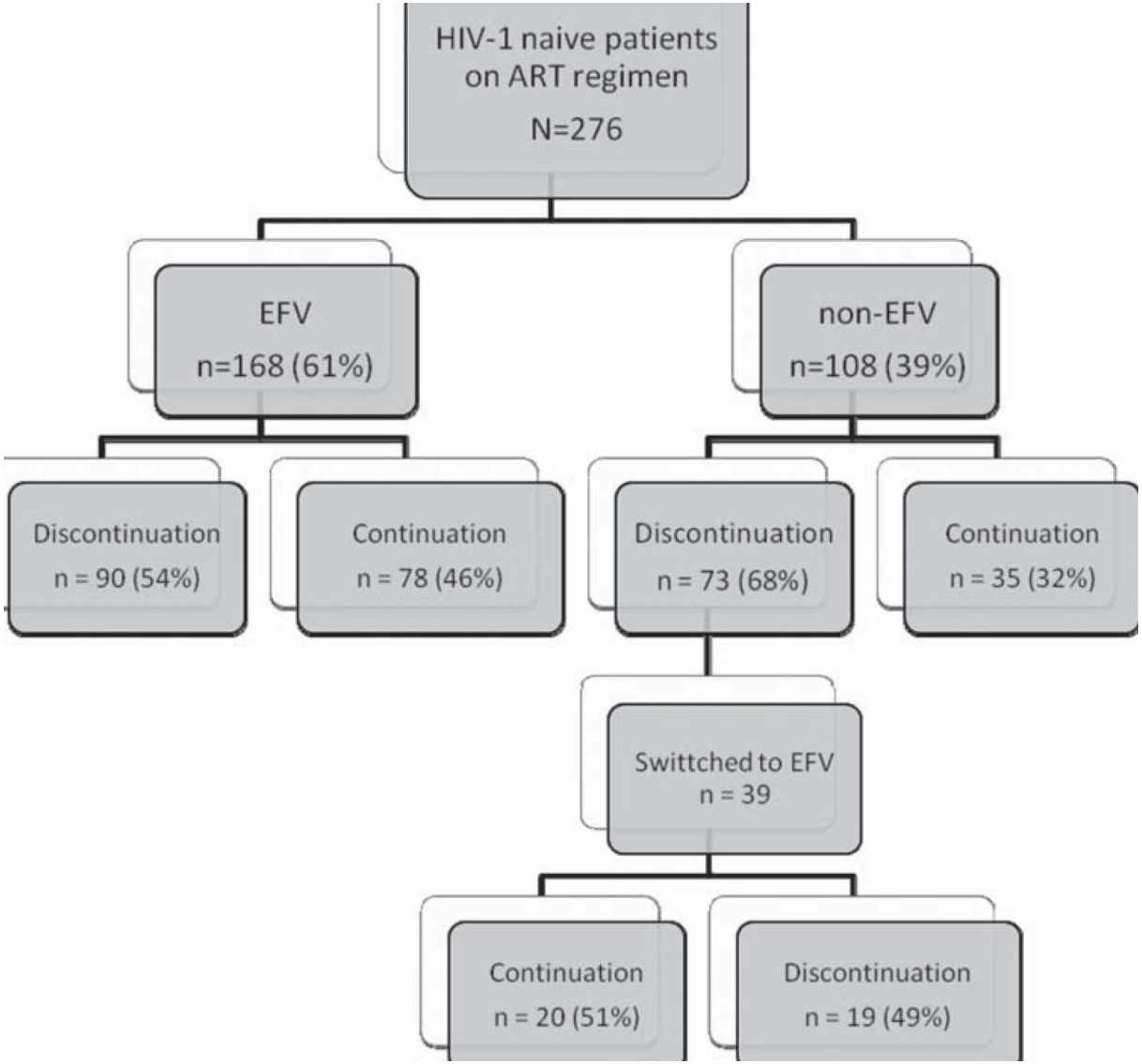
Discontinuation of efavirenz therapy in HIV patients due to neuropsychiatric adverse effects

CONCLUSIONS:

Discontinuation of EFV occurs in more than half the treated patients. Neuropsychiatric adverse effects are by far the most common reasons for discontinuation. Discontinuation occurs late in the course of treatment suggesting persistence of central nervous system toxicity, which may impact quality of life negatively on a long-term basis. **The role of EFV as a first-line ART agent should be reconsidered in the current guidelines**, in particular due to the availability of other equally effective, but less toxic, ART agents.

Leutscher PDC et al. Scand J Infect Dis 2013

Discontinuation of efavirenz therapy in HIV patients due to neuropsychiatric adverse effects



Leutscher PDC et al. Scand J Infect Dis 2013

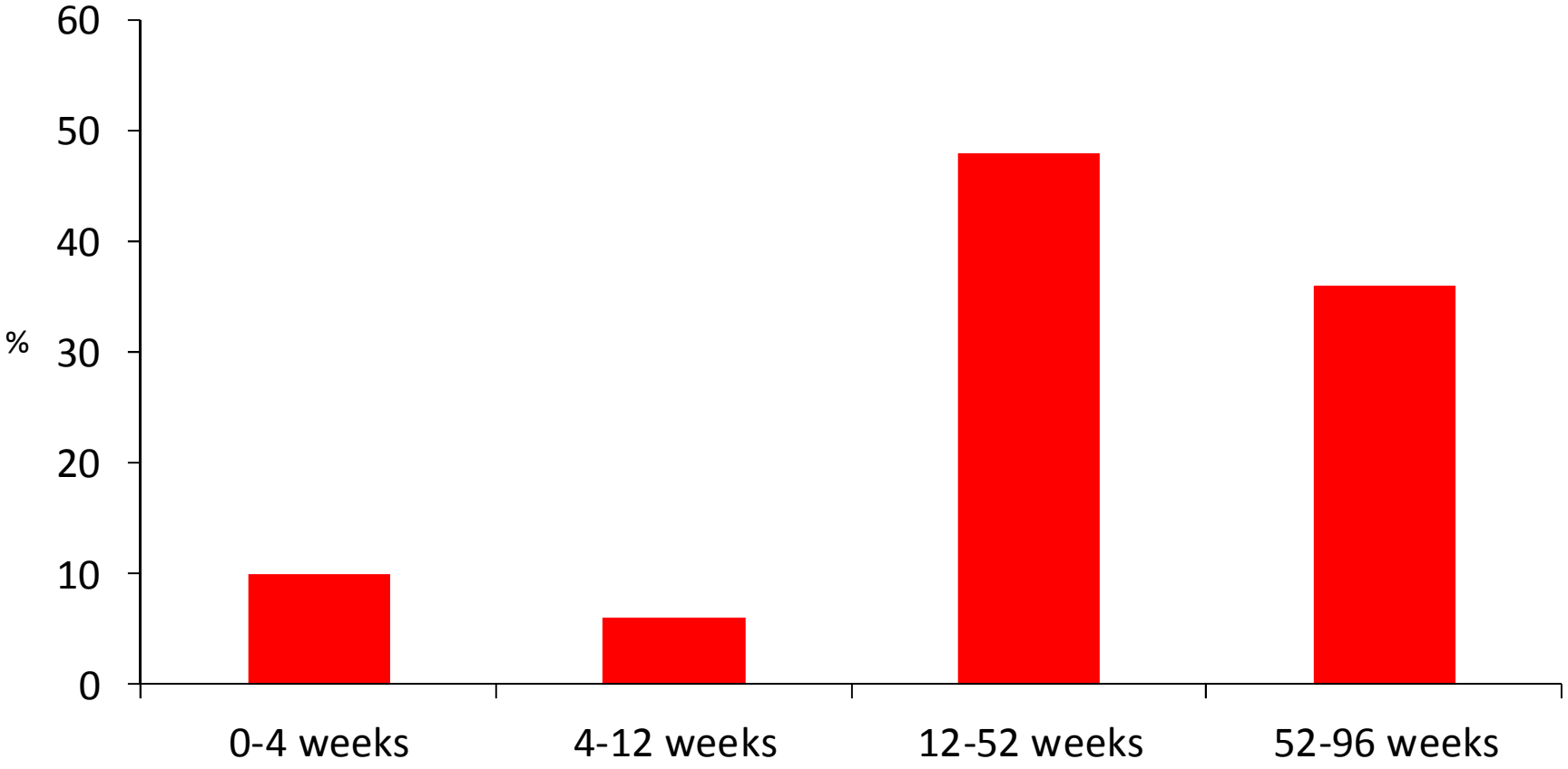
Los efectos adversos neuropsicológicos asociados a EFV siguen dando la cara tardíamente

	NVP (n=155)		EFV (n=156)		ABC (n=149)	
	A 1 año	A 3 años	A 1 año	A 3 años	A 1 año	A 3 años
Clínicos						
Neuropsiquiátricos	6	6	19	26	0	0
Cutáneos	12	12	3	4	0	0
Digestivos	0	2	4	5	1	3
Sistémicos	1	1	0	0	8	8
Otros	1	2	1	4	0	2
Laboratorio						
↑ GOT/GPT	4	4	0	0	0	0
↑ Glucosa	2	2	0	0	0	0
Total	26 (17%) †	29 (19%) ‡	27 (17%) †	39 (25%) ‡	9 (6%) †	13 (9%) ‡

† P=0.013; ‡ P=0.005

Martinez E et al. AIDS 2007

Time to toxicity switch for CNS toxicity: Chelsea & Westminster Hospital



Courtesy of Mark Nelson

STARTMRK Study: raltegravir vs. efavirenz in combination with TDF/FTC

- **Safety: neuropsychiatric symptoms**
  - At Week 8
    - CNS-related adverse events had occurred in 10% of RAL patients vs 18% of EFV patients (P = 0.0149)
    - Retrospective sensitivity analysis (additional symptoms): ≥ 1 CNS-related adverse event: 20% vs 52% (P < 0.0001)
    - Most symptoms were self-limited
  - At Week 48
    - Cumulative incidence of CNS-related adverse event was significantly lower in patients on RAL: 14% vs 23% in the main analysis (P = 0.0044); 26% vs 59% in the sensitivity analysis (P < 0.0001)
    - These events were generally mild: 62% of RAL vs 79% of EFV
    - Only 1 patient, on EFV, discontinued the trial because of CNS-related adverse event

Lennox JL et al. Lancet 2009

SINGLE Study: dolutegravir (plus ABC/3TC) vs. efavirenz (plus TDF/FTC)

Most Common Adverse Events (≥10%)

Adverse Event	DTG 50 mg + ABC/3TC QD (N=414), %	Atripla QD (N=419), %
Any event	369 (89)	387 (92)
Dizziness	37 (9)	148 (35)
Abnormal dreams	30 (7)	72 (17)
Insomnia	64 (15)	43 (10)
Headache	55 (13)	56 (13)
Fatigue	54 (13)	50 (12)
Diarrhea	72 (17)	75 (18)
Nausea	59 (14)	57 (14)
Nasopharyngitis	62 (15)	60 (14)
Upper respiratory tract infection	36 (9)	43 (10)
Rash	14 (3)	58 (14)

Walmsley S et al. N Engl J Med 2013

SINGLE Study: dolutegravir (plus ABC/3TC) vs. efavirenz (plus TDF/FTC)

Select Adverse Events

	DTG 50 mg + ABC/3TC QD (N=414), %	Atripla QD (N=419), %
Subjects with events leading to withdrawal	10 (2)	42 (10)*
Serious drug-related – any event	1 (<1)**	8 (2)^
Fatal AEs	0	2(<1)¥

*Atripla: Most commonly reported events were CNS, gastrointestinal and rash

**DTG + ABC/3TC: 1 drug hypersensitivity

^Atripla: 4 psychiatric, 2 drug hypersensitivity, 1 cerebral vascular accident, 1 renal failure

¥Deaths: n=1 primary cause of death judged unrelated to study drug but complicated by renal failure judged possibly related to ATR, n=1 not related to ATR (pneumonia)

Walmsley S et al. N Engl J Med 2013

Unexpected high rate of intolerance for DTG in real life setting

	total (N=387)		naives(N=65)		non-naives (N=322)		
DGV stopped	62	16,0%	13	20,0%	49	15,2%	ns
median DGV days (IQR)	78		81	(71)	75	(99)	ns
reason for interruption							
other than toxicity*	6	9,7%	1	7,7%	5	10,2%	
toxicity	56	90,3%	12	92,3%	44	89,8%	ns
sleeping..	19	31,3%	5	38,5%	14	28,6%	ns
gastro-intestinal..	18	29,5%	4	30,8%	14	28,6%	ns
neuro-psychiatric..	12	19,7%	3	23,1%	9	18,4%	ns
paresthesia..	6	9,7%	0	0,0%	6	12,2%	ns
headache..	8	12,9%	0	0,0%	8	16,3%	ns
fatigue..	9	14,6%	1	7,7%	8	16,3%	ns
allergy..	1	1,7%	1	7,7%	0	0,0%	ns
other..	5	8,2%	1	7,7%	4	8,2%	ns

*LTFU, HBV protection, insurance, induction, patient request, interaction

Van der Berk G et al. CROI 2016

How long it takes to recognise a long-term adverse effect?

Drug / class	FDA approval	Toxicity	Strong signal	Delay (years)
zidovudine	1987	lipoatrophy	1999	12
stavudine	1994	lipoatrophy	1999	5
nevirapine	1996	toxicity at high CD4	2005	9
PIs	1996-	heart attack	2003	7
efavirenz	1998	suicidality	2013	15
abacavir	1998	heart attack	2008	10
tenofovir	2001	fracture	2012	11
raltegravir	2007	myopathy	2012	5

Saint-Marc et al. AIDS 1999; Lundgren et al NEJM 2003; D:A:D Study Group . Lancet 2008; Cooper et al. Clin Infect Dis 2010; Bedimo et al. AIDS 2012; Lee et al. JAIDS 2013; Mollan et al. IDSA 2013

A veces, la percepción y la realidad no coinciden

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No todos los pacientes se explican igual

- «No me encuentro bien, pero no sé qué me pasa»
- «Me cuesta concentrarme y no duermo bien, pero mi madre está demenciada…estamos pasando una época de estrés y claro…»
- «He leido el prospecto y el medicamente me da insomnio y dificultad para la concentración»
- «Qué cómo me encuentro? Bueno, bien… Me cuesta dormir, pero lo llevo bien…»

No todos nos explicamos igual

A veces, cambia el nombre y la expresión para decir algo similar y se entiende algo totalmente distinto

Pero…, es que a algunos les gusta!

Efavirenz, a drug that is usually used in conjunction with other drugs as a cocktail to fight type one HIV (HIV-1), has a range of side effects that includes feelings of terror, severe depression, paranoia, psychosis and delusional hallucinations. Much to the surprise of researchers investigating these side effects, it turns out that efevirenz has a similar effect on the brain as lysergic acid diethylamide -- known to most as LSD.

The recreational side effects of efavirenz are not something new -- for years in South Africa people have been smoking crushed efavirenz pills (sometimes with marijuana or other drugs) for an easy high in a mixture known as "wunga".

The psychedelic side effects of efavirenz are also seen in people who take it as medically prescribed, however, with some people developing adverse psychiatric conditions as a result. This known side effect history, along with the reports of its use in South Africa, attracted the attention of neuropharmacologist John Schetz from the University of North Texas Health Science Centre.

http://www.wired.co.uk/news/archive/2013-04/25/psychedelic-hiv-aids-medication

Schetz JA et al. FASEB J 2013

Una misma realidad se puede ver de una manera un día, y de otra manera otro día

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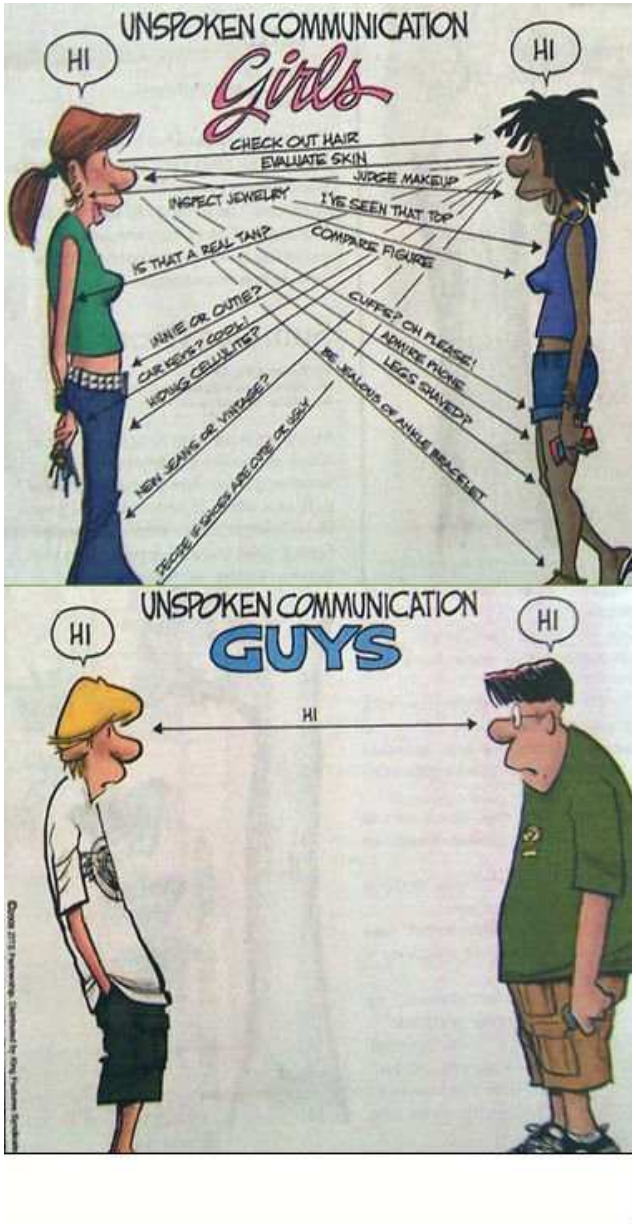
No podemos apreciar lo que no vemos

No todos los médicos son igualmente receptivos

- ¿Todo bien, no?
- «Bueno, eso del insomnio y la falta de concentración también lo tengo yo en algunas épocas…Todo va bien y eso es lo que importa»
- «Quizás el insomnio y la falta de concentración puedan deberse al tratamiento; aunque no está descrito, hay una relación temporal»
- «….(ausencia de mención alguna a tolerabilidad del tratamiento o a la existencia de síntomas del SNC»

No todos somos igualmente receptivos



Puede que entendamos algo distinto a lo que el paciente quería expresar

La misma realidad puede verse de forma diferente dependiendo del punto de mira

Según hagamos la pregunta, la respuesta puede ser totalmente diferente

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Assessment of comorbidities in HIV-infected persons

	Kidney	Bone	CV	Cancer	CNS
Screening	Blood chemistry	DEXA +/- FRAX score	Framingham (or similar) score	No (cytology cervical cancer)	No (psychometric tests?)
Prediction of clinical problem	Accurate	Less accurate	More innaccurate	More innacurate or lacking	Lacking

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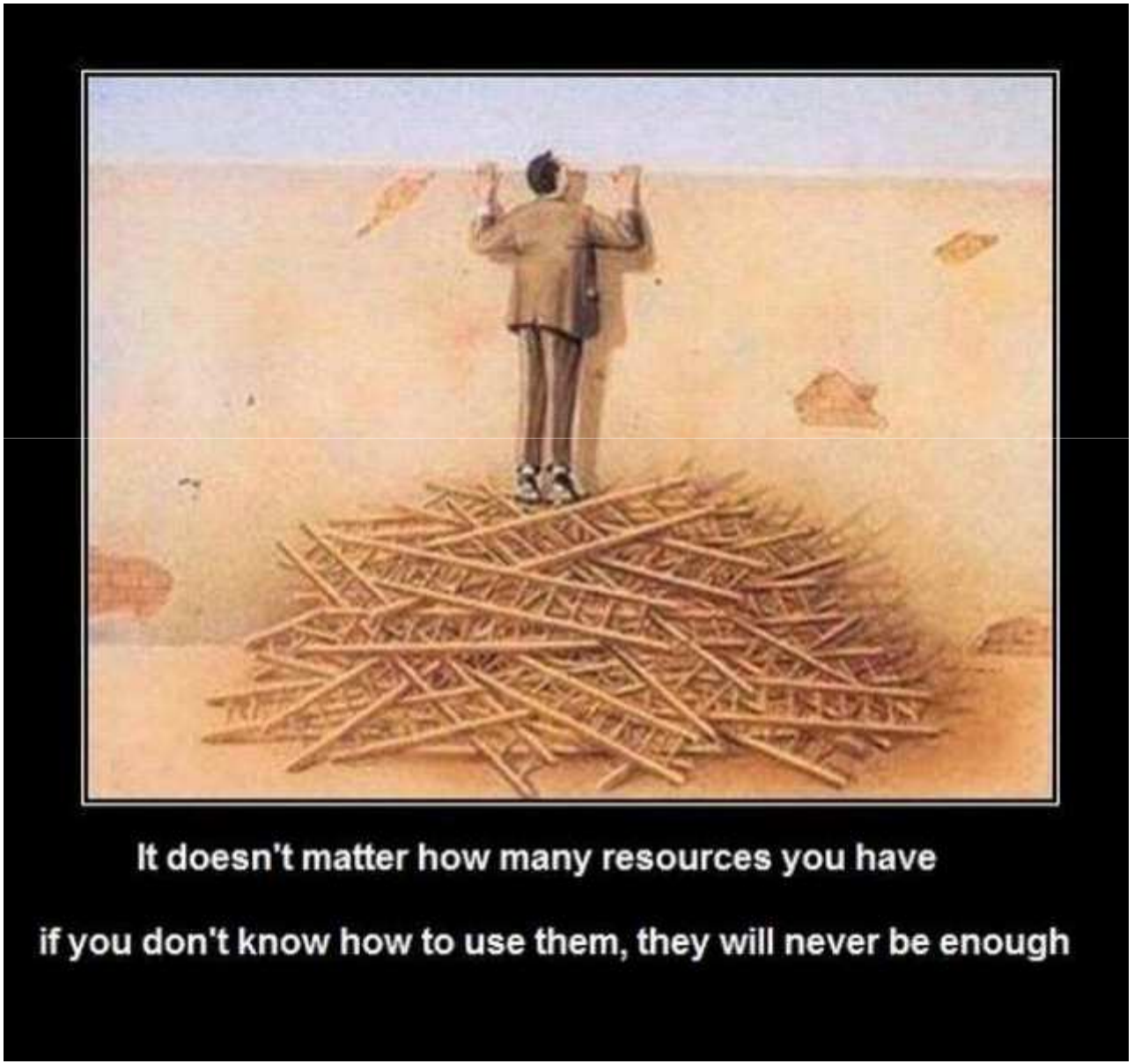
7. **La patología/toxicidad del SNC está infradiagnosticada y no se conoce bien**

Necesitamos aprender más sobre la patología/toxicidad del SNC en pacientes VIH+



Gracias por esta reunión!!!

Are you lonely?

Tired of working on your own?

Do you hate making decisions?

HOLD A MEETING!

You can –

- See people
- Show charts
- Feel important
- Point with a stick
- Eat donuts
- Impress your colleagues

All on company time!

MEETINGS

THE PRACTICAL ALTERNATIVE TO WORK