

Review/comparison of current guidelines for ART

**Hospital Clínic – Facultad de Medicina (U.B.)
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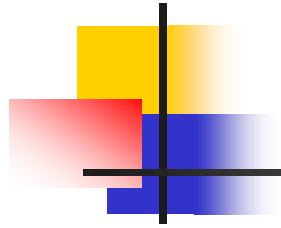
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Potential conflicts of interest (April 2018):

Dr. Gatell has received honoraria for lectures or AB or research grants (his institution) from MSD, ViiV, Gilead, and Janssen

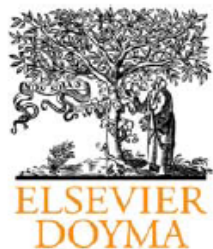
Review/comparison of current guidelines for ART



	<u>Scope</u>	<u>life span</u>	<u>panel member(*)</u>
--	--------------	------------------	------------------------

GESIDA/PNS	Spain	2000-18	always
EACS	Europe	2005-18	always
IAS-USA (JAMA)	International	1996-18	2000-10
WHO	Developing world		
DHHS	USA		

(*) my conflict of interest



Enfermedades Infecciosas y Microbiología Clínica

www.elsevier.es/eimc



Editorial

¿Debemos orientarnos por guías terapéuticas?

Should we follow the guidelines?

Jose Maria Gatell *

Servicio de Infecciones, Hospital Clinic-IDIBAPS, Universidad de Barcelona, Barcelona, España

INFORMACIÓN DEL ARTÍCULO

On-line el 31 de marzo de 2009

Review/comparison of current guidelines for ART



1. What about guidelines

2. What do we need to know (to guess) before reading

3. When & what to start ART ?

4. Other issues related with ART


5. Other issues related with management of HIV patients

6. Final considerations



Organizing a congress and publishing guidelines are one of the justifications, and often the only reason to exist, for the majority of medical societies

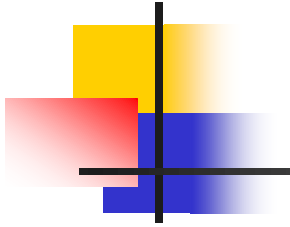
La mayoría de las sociedades o asociaciones científicas y de los entes públicos o privados más bien temprano que tarde, acabarán publicando guías diagnósticas o terapéuticas sobre uno o varios de los temas de su especialidad o de su competencia. La probabilidad se acerca al 100% si la enfermedad es difícil de diagnosticar, si carece de pruebas diagnósticas objetivas, si es difícil de tratar, si el número de fármacos es escaso, caro o tóxico o si la respuesta al tratamiento está por debajo de lo deseable.



So, it is not a surprise the existence of many different ART guidelines, with different geographical scopes, including countries where access to ART is, even now, difficult

Varias de las respuestas anteriores convergen en el caso de la infección por el virus de la inmunodeficiencia humana tipo 1, con el agravante de que la repercusión científica, social y mediática de la enfermedad actúa como factor potenciador. Por tanto, no es ninguna sorpresa que haya una multitud de guías de tratamiento antirretrovírico tanto en Estados Unidos como en Europa pero también en países en vías de desarrollo, donde hasta hace poco la posibilidad de acceder al tratamiento antirretrovírico era prácticamente nula¹. Las 2 guías de tratamiento antirretrovírico más

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The content is a mixture of:

science (evidence based medicine ?)

opinions (expert opinions ?)

politics

and more....iii

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2. What do we need to know (to guess) before reading

Who is the promoter/sponsor

(a not for profit private body ?, governmental agency ? both ?)

Selection & composition of the panel

What is the reason/justification

Who is the intended audience

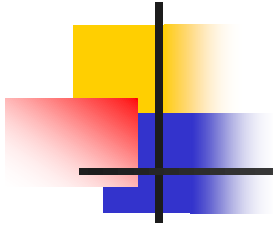
(doctors ?, patients ?, insurance companies ?,
health authorities ?, all of them ?)

What is the geographical scope

What is the decision making process

Conflicts of interest

Review/comparison of current guidelines for ART




EDITORIAL REVIEW

Rating evidence in treatment guidelines: a case example of when to initiate combination antiretroviral therapy (cART) in HIV-positive asymptomatic persons

Caroline A. Sabin^a, David A. Cooper^b, Simon Collins^c and Mauro Schechter^d

Review/comparison of current guidelines for ART



eBox. Strength of Recommendation and Quality of Evidence Rating Scale

Category, Grade	Definition
Strength of recommendation	
A	Strong evidence to support the recommendation
B	Moderate evidence to support the recommendation
C	Insufficient evidence to support a recommendation
Quality of evidence	
Ia	Evidence from 1 or more randomized controlled clinical trials published in the peer-reviewed literature
Ib	Evidence from 1 or more randomized controlled clinical trials presented in abstract form at peer-reviewed scientific meetings
IIa	Evidence from nonrandomized clinical trials or cohort or case-control studies published in the peer-reviewed literature
IIb	Evidence from nonrandomized clinical trials or cohort or case-control studies presented in abstract form at peer-reviewed scientific meetings
III	Recommendation based on the panel's analysis of the accumulated available evidence

Adapted from Gross et al, *Clin Infect Dis*, 1994.¹

Quite often, panels make decisions (unanimity, consensus or voting) first and then qualify already taken decisions

Serving Two Masters — Conflicts of Interest in Academic Medicine

Bernard Lo, M.D.

In January 2010, Boston-based Partners Health-Care, which includes some of the nation's leading teaching hospitals, began sharply limiting the amount of compensation institutional officials may

receive for serving on boards of directors of biomedical companies or companies that are likely to do business with Partners.¹ Declaring that "compensation [for board service] should be capped at a level befitting an academic role,"¹ Partners limited payments to \$5,000 per day for the time spent at board meetings and prohibited equity compensation. Partners officials may donate additional compensation to a charitable organization that is not affiliated with Partners. The Partners conflict-of-interest committee will review all such arrangements. The press reported that several Partners officials have received more than \$200,000 a year as directors of companies that sell pharma-

ceutical or medical products — a standard level of compensation for directors.² The chair of the committee that recommended the new policies reportedly cited 2009 policy changes that prohibit faculty members from serving on speakers' bureaus of drug companies, suggesting that it would seem unfair to restrict the income of junior faculty in this way while refraining from limiting the outside income of senior officials serving on boards.²

Relationships between academia and industry have both benefits and risks. Close collaboration between academia and industry has facilitated the development of many new drugs.³ This is an area in which key interests may be

aligned: the public's need for new therapies, academia's desire to translate basic discoveries into treatments, and industry's need to develop new products. Partners policy notes that "the tension between academia and industry is not new when academic leaders sit on company boards. Companies benefit from the wisdom of academic physicians about emerging trends in research and health care. Leaders may learn important new approaches to organizing research teams or running complex organizations. Networking with other leaders may enhance faculty's ability to advance their research."

However, the mission of academic health centers can diverge from that of medical companies in various ways (see table). We are driven largely by the goal of deepening our understanding of health and disease and



Conflicts of interest do not disappear simply by the fact of disclosing them

Governmental agencies by definition have conflicts of interest. But, apparently not for profit, medical societies/associations may also have conflicts of interest

There are also academic conflicts of interest. Publishers and journals also have conflicts of interest (IF, citations ...)

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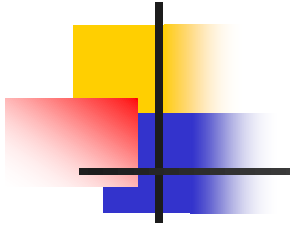
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Since year 2005 initial ART was very effective, well tolerated and convenient for the patients

Common sense dictated all HIV patients should receive ART irrespective of CD4+ cell count

Yet, it took 10 years (up to year 2015) and several millions of dollars to generate evidence to support the common sense

Recommendations for Initiation of ART in HIV-positive Persons with Chronic Infection without prior ART Exposure⁽ⁱ⁾

Recommendations are graded while taking into account the level of evidence, the degree of progression of HIV disease and the presence of, or high risk for, developing various types of (co-morbid) conditions.

Symptomatic HIV disease (CDC B or C conditions, incl. tuberculosis)	Asymptomatic HIV infection	
Any CD4 count	Current CD4 count	
	< 350	≥ 350
SR	SR	R

SR = Strongly Recommended

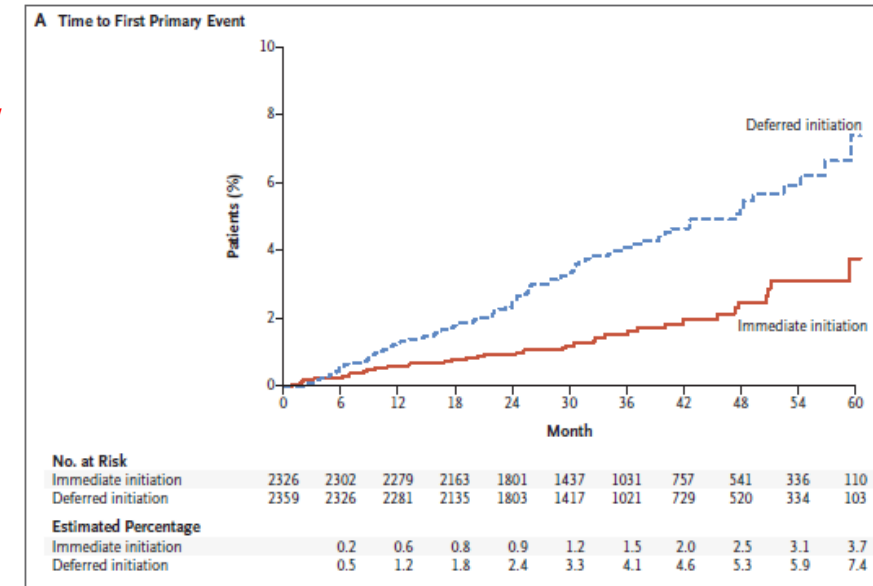
R = Recommended

i ART should always be recommended irrespective of the CD4 count with the possible exception of elite controllers with high and stable CD4 counts. Time should always be taken to prepare the person, in order to optimise compliance and adherence. Genotypic resistance testing is recommended prior to initiation of ART, ideally at the time of HIV diagnosis; otherwise before initiation of ART. If ART needs to be initiated before genotypic testing results are available, it is recommended to include a PI/r in the first-line regimen. Ideally, before starting treatment, the HIV-VL level and CD4 count should be repeated to obtain a baseline to assess subsequent response. Moreover, use of ART should also be recommended with any CD4 count in order to reduce sexual transmission, risk of AIDS events and mother-to-child transmission of HIV (before third trimester of pregnancy).

Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group*

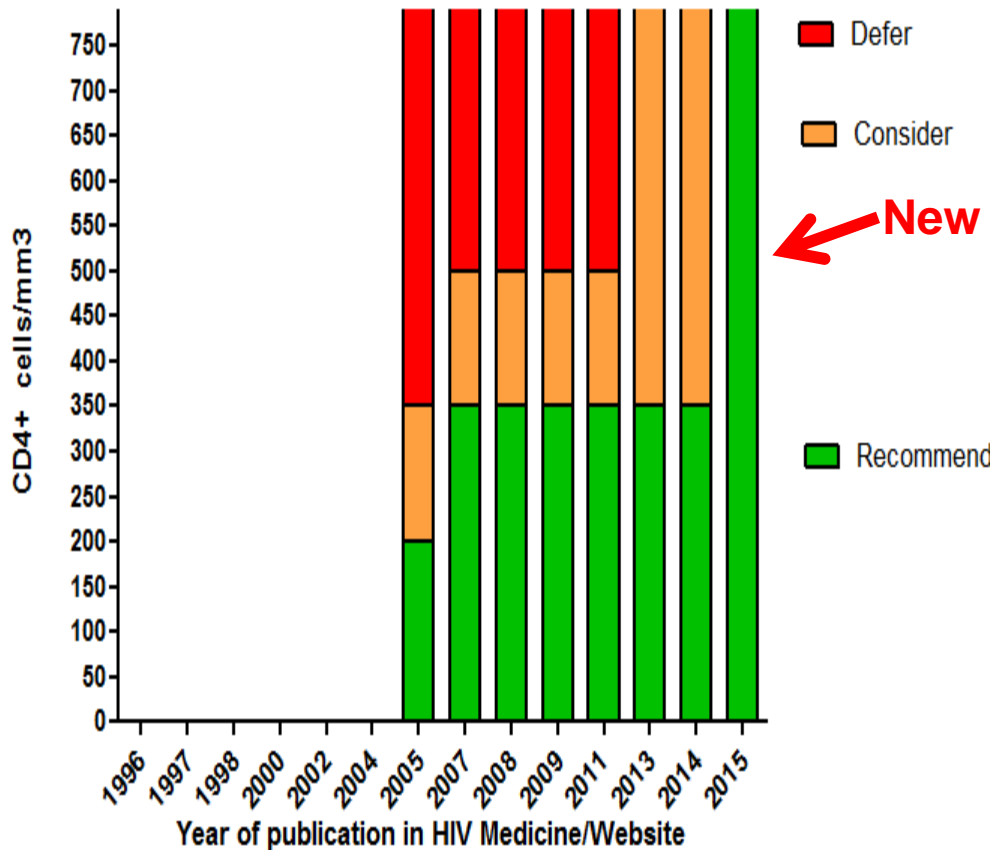
← New



TB & AIDS and non-AIDS malignancies

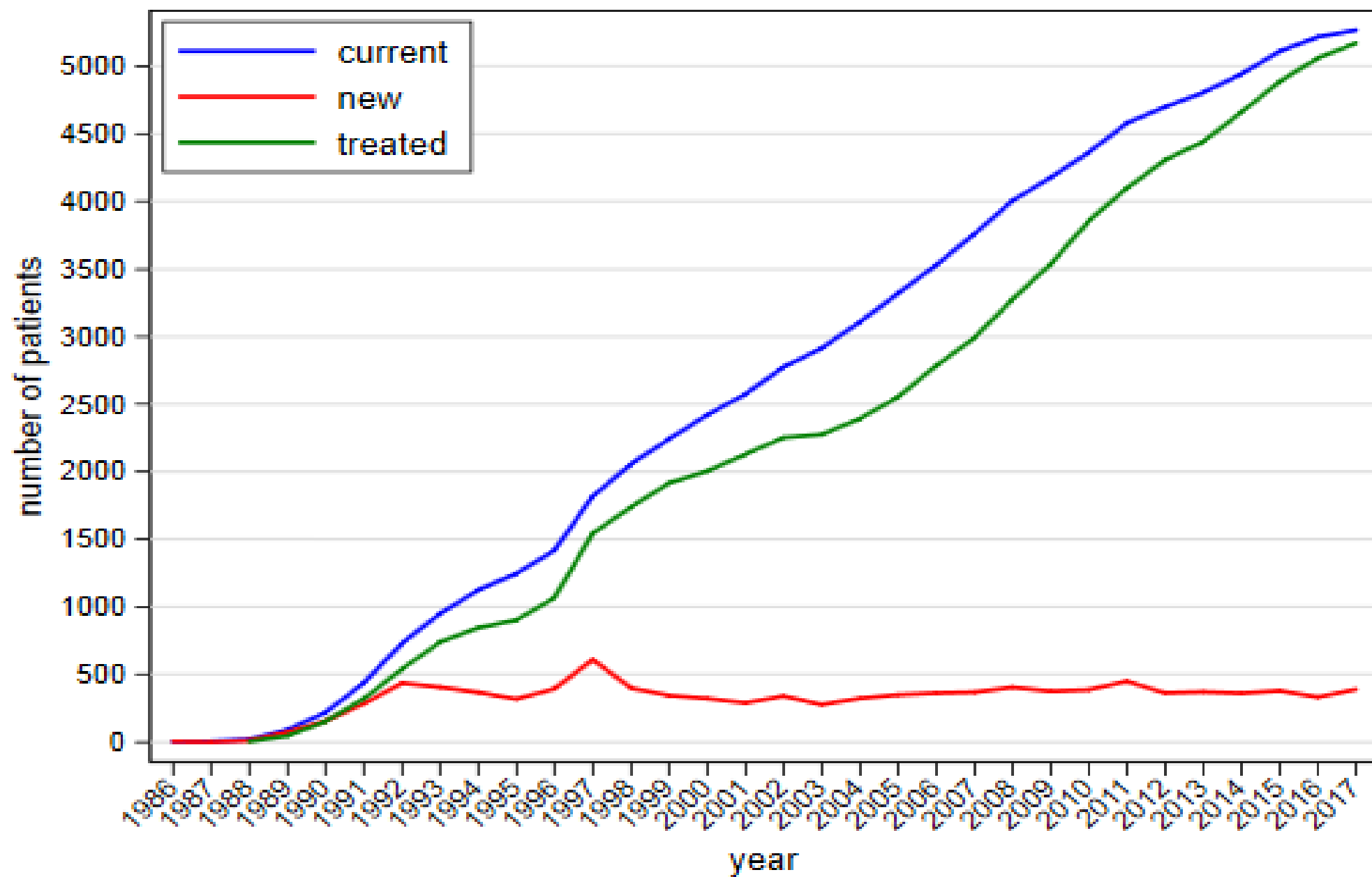
EACS & WHO, 2015

ART in asymptomatic chronic HIV infection with detectable viral load (EACS)



Recommendation 1: When to start ART among people living with HIV

Target population	Specific recommendation	Strength of the recommendation	Quality of the evidence
Adults ^a (>19 years)	ART should be initiated in all adults living with HIV at any CD4 cell count	Strong	Moderate NEW
	As a priority, ART should be initiated in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤ 350 cells/mm ³	Strong	Moderate
Pregnant and breastfeeding women	ART should be initiated in all pregnant and breastfeeding women living with HIV at any CD4 cell count and continued lifelong	Strong	Moderate UPDATED
Adolescents (10–19 years old)	ART should be initiated in all adolescents living with HIV at any CD4 cell count	Conditional	Low NEW
	As a priority, ART should be initiated in all adolescents with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤ 350 cells/mm ³	Strong	Moderate





Elite/viremic controllers

Do not like ART & CD4+ cell count >350-500

Do we need a resistance test before ART

Initiation "same day" ?

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DOCUMENTO DE CONSENSO
DE GeSIDA/PLAN NACIONAL SOBRE
EL SIDA RESPECTO AL TRATAMIENTO
ANTIRRETROVIRAL EN ADULTOS
INFECTADOS POR EL VIRUS DE LA
INMUNODEFICIENCIA HUMANA

(ACTUALIZACIÓN ENERO 2018)

Spain



EACS
European
AIDS
Clinical
Society

GUIDELINES

Version 9.0
October 2017

English

Europe

Special Communication

Antiretroviral Drugs for Treatment and Prevention
of HIV Infection in Adults
2016 Recommendations of the International
Antiviral Society-USA Panel

Huldrych F. Günthard, MD; Michael S. Saag, MD; Constance A. Benson, MD; Carlos del Rio, MD; Joseph J. Eron, MD;
Joel E. Gallant, MD, MPH; Jennifer F. Hoy, MBBS, FRACP; Michael J. Mugavero, MD, MHSc; Paul E. Sax, MD;
Melanie A. Thompson, MD; Rajesh T. Gandhi, MD; Raphael J. Landovitz, MD; Davey M. Smith, MD;
Donna M. Jacobsen, BS; Paul A. Volberding, MD

International

AIDSinfo

USA

Guidelines for the Use of Antiretroviral Agents in
HIV-1-Infected Adults and Adolescents

Downloaded from <https://aidsinfo.nih.gov/guidelines> on 10/21/2017

Visit the AIDSinfo website to access the most up-to-date guideline.

Register for e-mail notification of guideline updates at <https://aidsinfo.nih.gov/e-news>.



World Health
Organization

Developing world

TRANSITION TO NEW
ANTIRETROVIRAL
DRUGS IN HIV
PROGRAMMES: CLINICAL
AND PROGRAMMATIC
CONSIDERATIONS

JULY 2017

Tabla 3. Combinaciones de TAR de inicio recomendadas[†]

3er Fármaco	Pauta [†]	Comentarios [‡]
Preferentes. Pautas aplicables a la mayoría de los pacientes y que en ensayos clínicos aleatorizados han mostrado una eficacia superior frente a otras o mostrando no-inferioridad presentan ventajas adicionales en tolerancia, toxicidad o un bajo riesgo de interacciones farmacológicas.		
INI	DTG/ABC/3TC	■ ABC está contraindicado en pacientes con HLA-B*5701 positivo
	DTG+FTC/TAF	
	RAL+FTC/TAF	■ RAL puede administrarse indistintamente como 1 comprimido de 400 mg cada 12 horas, o 2 comprimidos de 600 mg (nueva formulación) cada 24 horas*.

GESIDA, 2018

GESIDA, 2019 (forecast)

Tabla 3. Combinaciones de TAF que inicio recomendadas

3er Fármaco	Paquetes	Comentarios [‡]
Preferentes. Paquetes aplicables a la mayoría de los pacientes y que en ensayos clínicos aleatorizados han mostrado una eficacia superior a otras, mostrando no-inferioridad presentan ventajas adicionales en tolerancia, toxicidad o un bajo riesgo de interacciones farmacológicas.		
INI	DTG/ABC/3TC	■ ABC está contraindicado en pacientes con HLA-B*5701 positivo
	DTG+FTC/TAF	
	RAL+FTC/TAF	■ RAL puede administrarse indistintamente como 1 comprimido de 400 mg cada 12 horas, o 2 comprimidos de 600 mg (nueva formulación) cada 24 horas*.

BIC/FTC/TAF

Table 3. Recommended Initial Antiretroviral Therapy Regimens^a

Regimen	Rating
Dolutegravir/abacavir/lamivudine	A1a
Dolutegravir plus tenofovir alafenamide/emtricitabine ^b	A1a
Elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine ^b	A1a
Raltegravir plus tenofovir alafenamide/emtricitabine ^b	A1II

^a Regimens are listed in alphabetic order by integrase strand transfer inhibitor component. Components separated with a slash (/) indicate that they are available as coformulations.

^b In settings in which tenofovir alafenamide/emtricitabine is not available, tenofovir disoproxil fumarate (with emtricitabine or lamivudine) remains an effective and generally well-tolerated option. Given the limited long-term experience with tenofovir alafenamide, some clinicians may prefer to continue using tenofovir disoproxil fumarate pending broader experience with tenofovir alafenamide in clinical practice.

Recommended Initial Regimens for Most People with HIV	
Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.	
INSTI + 2 NRTIs:	
<ul style="list-style-type: none"> • DTG/ABC/3TC^a (A1)—if HLA-B*5701 negative • DTG + tenofovir^a/FTC^a (A1 for both TAF/FTC and TDF/FTC) • EVG/c/tenofovir^a/FTC (A1 for both TAF/FTC and TDF/FTC) • RAL^c + tenofovir^a/FTC^a (A1 for TDF/FTC, AII for TAF/FTC) 	

EACS Oct 2017

A) Recommended regimens (one of the following to be selected)^{1,2}

Regimen	Dosing	Caution	Food requirement
2 NRTIs + INSTI			
ABC/3TC/DTG ^(1,4)	ABC/3TC/DTG 600/300/50 mg, 1 tablet qd	Al/Ca/Mg-containing antacids or multivitamins should be taken well separated in time (minimum 2h after or 6h before). DTG 50 mg bid with rifampicin.	None
TAF/FTC ⁽¹⁰⁾ or TDF/FTC ⁽¹⁰⁾	TAF/FTC 25/200 mg, 1 tablet qd or TDF/FTC 300/200 mg, 1 tablet qd		None
+ DTG	+ DTG 50 mg, 1 tablet qd		
TAF/FTC/EVG/c ⁽¹⁰⁾ or TDF/FTC/EVG/c ^(10,14)	TAF/FTC/EVG/c 10/200/150/150 mg, 1 tablet qd or TDF/FTC/EVG/c 300/200/150/150 mg, 1 tablet qd	Al/Ca/Mg-containing antacids or multivitamins should be taken well separated in time (minimum 2h after or 6h before).	With food
TAF/FTC ⁽¹⁰⁾ or TDF/FTC ⁽¹⁰⁾	TAF/FTC 25/200 mg, 1 tablet qd or TDF/FTC 300/200 mg, 1 tablet qd	Co-administration of antacids containing Al or Mg not recommended. RAL 400 or 800 mg bid with rifampicin.	None
+ RAL	+ RAL 400 mg, 1 tablet bid		
2 NRTIs + NNRTI			
TAF/FTC/RPV ⁽¹⁰⁾ or TDF/FTC/RPV ⁽¹⁰⁾	TAF/FTC/RPV 25/200/25 mg, 1 tablet qd or TDF/FTC/RPV 300/200/25 mg, 1 tablet qd	Only if CD4 count > 200 cells/μL and HIV-VL < 100,000 copies/mL. PPI contraindicated; H2 antagonists to be taken 12h before or 4h after RPV.	With food
2 NRTIs + PI/r or PI/c			
TAF/FTC ⁽¹⁰⁾ or TDF/FTC ⁽¹⁰⁾	TAF/FTC 25/200 mg, 1 tablet qd or TDF/FTC 300/200 mg, 1 tablet qd	Monitor in persons with a known sulfonamide allergy.	With food
+ DRV/c ⁽¹⁰⁾ or + DRV/r ⁽¹⁰⁾	DRV/c 600/150 mg, 1 tablet qd or + DRV 800 mg, 1 tablet qd + RTV 100 mg, 1 tablet qd		

4.4 What to start: first-line ART

CONSOLIDATED GUIDELINES ON
**THE USE OF
 ANTIRETROVIRAL DRUGS
 FOR TREATING AND
 PREVENTING HIV INFECTION**
 RECOMMENDATIONS FOR A
 PUBLIC HEALTH APPROACH
**SECOND EDITION
 2016**

Table 4.1. First-line ART regimens for adults, pregnant or breastfeeding women, adolescents and children

First-line ART	Preferred first-line regimens	Alternative first-line regimens ^{a,b}
Adults	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) <u>TDF + 3TC (or FTC) + DTG^c</u> TDF + 3TC (or FTC) + EFV ₄₀₀ ^{c,d,e} TDF + 3TC (or FTC) + NVP
Pregnant or breastfeeding women	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + NVP
Adolescents	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) <u>TDF (or ABC) + 3TC (or FTC) + DTG^{c,d}</u> TDF (or ABC) + 3TC (or FTC) + EFV ₄₀₀ ^{c,d,e} TDF (or ABC) + 3TC (or FTC) + NVP

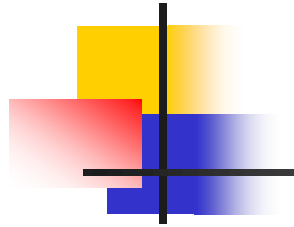
5. CONCLUSIONS

TRANSITION TO NEW ANTIRETROVIRAL DRUGS IN HIV PROGRAMMES: CLINICAL AND PROGRAMMATIC CONSIDERATIONS

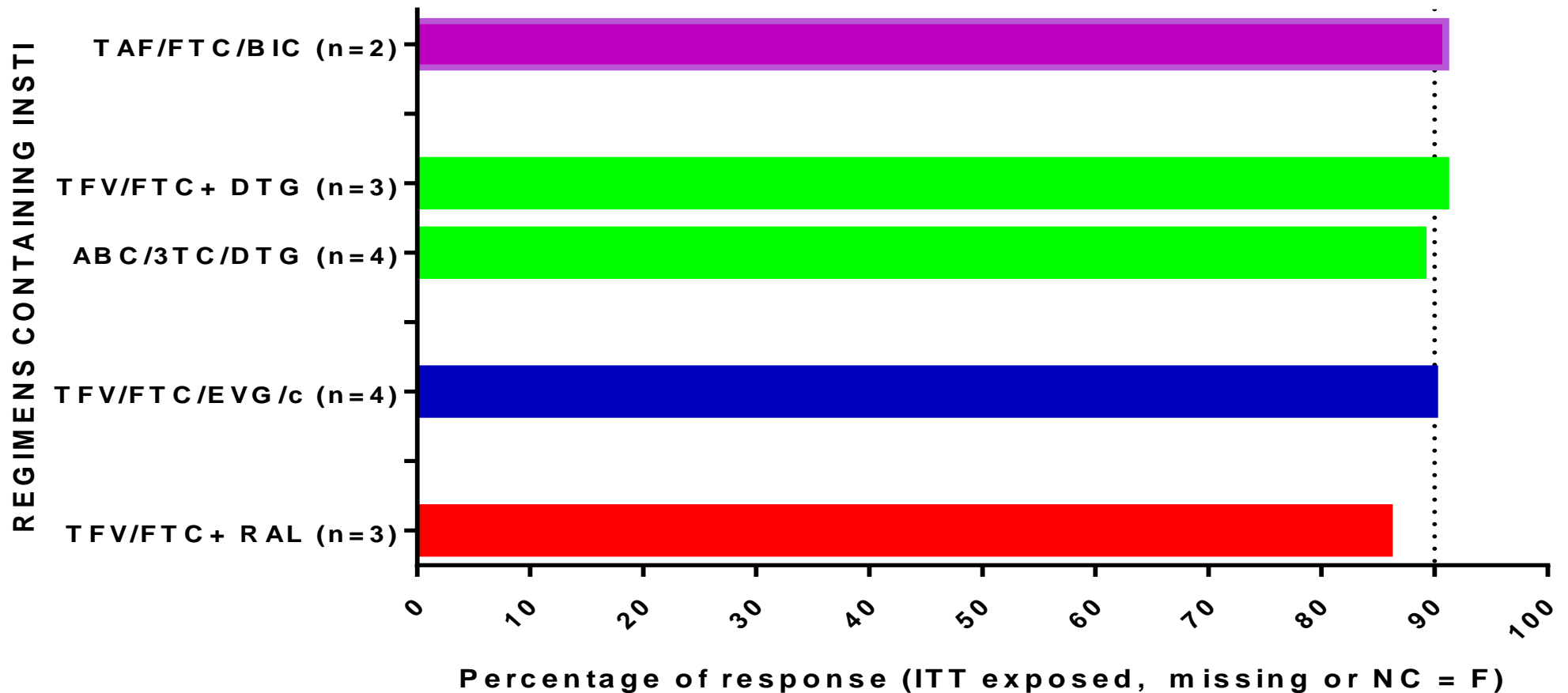
JULY 2017

There are many factors to consider when deciding to introduce new ARV drugs: efficacy, safety, drug interactions (e.g. TB drugs), price, affordability, population prevalence of HIVDR, regulatory approval and availability of quality-assured generic and fixed-dose formulations.

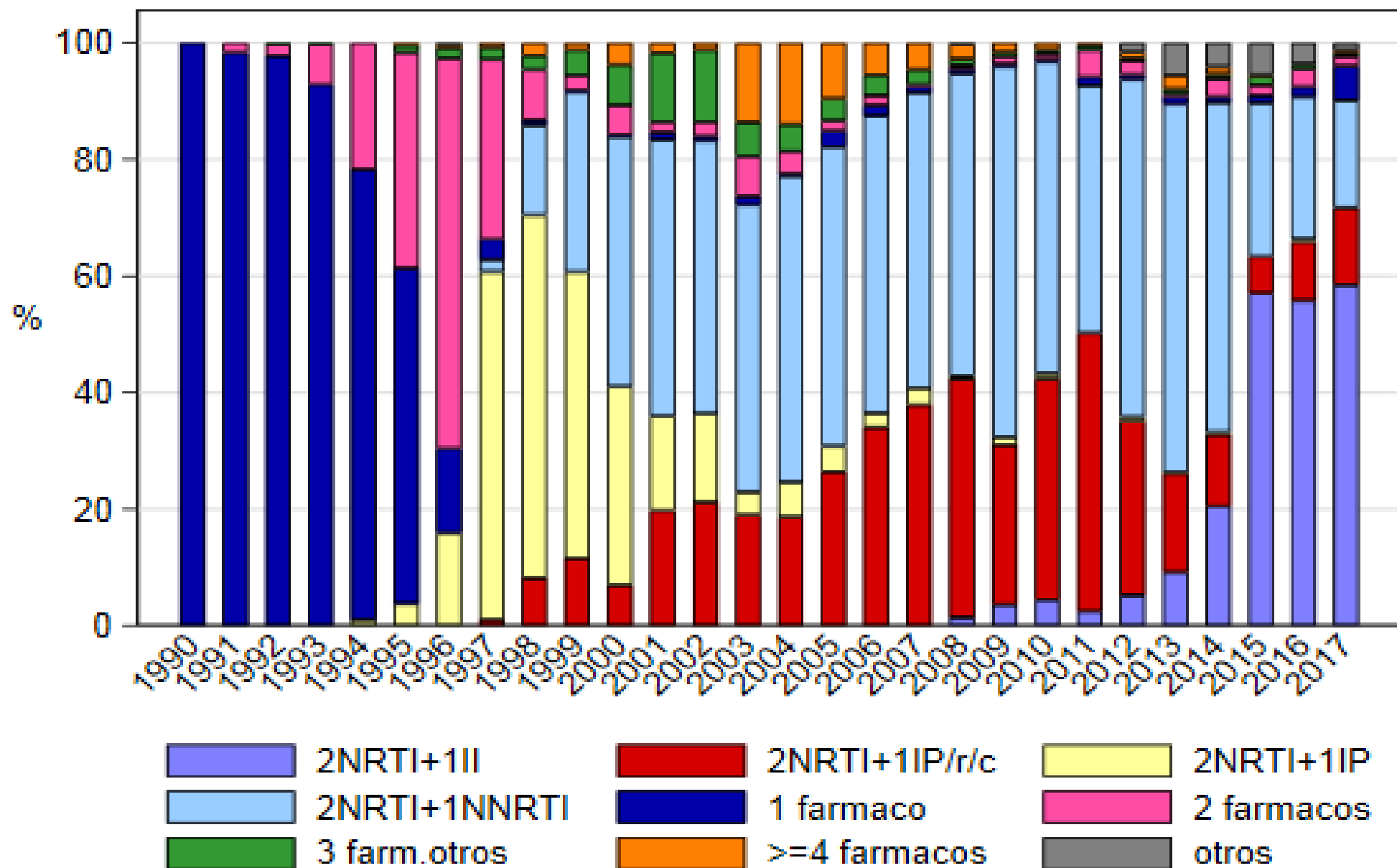
The transition from EFV600 to DTG as a first-line option in low- and middle-income countries could be cost-neutral, or even reduce costs, if DTG can be provided in the context of generic competition and reduced pricing. The current price for generic formulations of DTG has fallen to US\$ 44 per person per year and could become even lower as more generic versions become available.



Trials in antiretroviral naïve patients (pooled analysis)

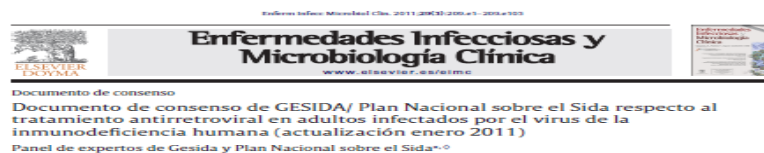


pautas debut

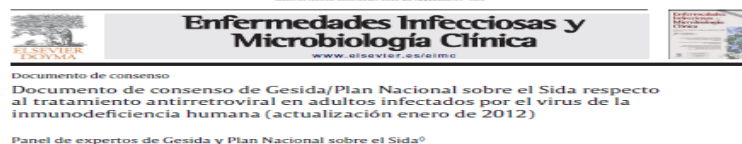


GESIDA/PNS (Sapin) Guidelines (since 2000)

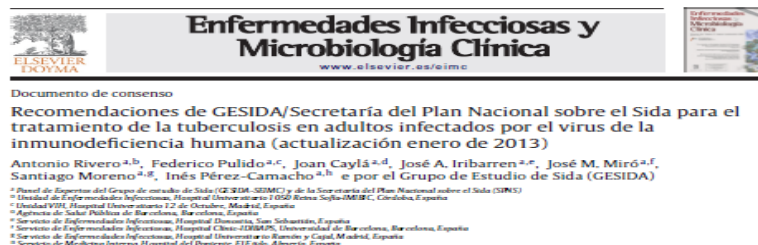
2011



2012



2013



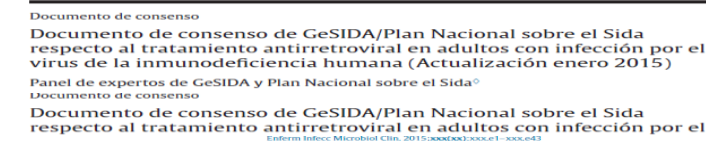
2014



2015



2016



2017



2018

Cost-efficacy analysis of recommended regimens

G Model
EIMC-604: No. of Pages 10
ARTICLE IN PRESS
Enferm Infect Microbiol Clin. 2011;XXX(X):xxx-xxx



Original
Análisis de costes y de coste/eficacia de las pautas preferentes de GESIDA para el tratamiento antirretroviral inicial
Antonio Javier Blasco^a, José Ramón Arribas^b, Bonaventura Clotet^c, Pere Domingo^d,
J
D
P
Enferm Infect Microbiol Clin. 2012;XXX(X):xxx-xxx



Original
Análisis de costes y de coste/eficacia de las pautas preferentes de GESIDA/Plan Nacional sobre el Sida en 2012 para el tratamiento antirretroviral inicial en adultos infectados por el virus de la inmunodeficiencia humana (VIH)
Antonio Javier Blasco^a, José Ramón Arribas^b, Vicente Boix^c, Bonaventura Clotet^d, Pere Domingo^e,
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Pere Domingo^f, Juan González-García^g, Hernando Knobel^h, Juan Carlos Lópezⁱ, Fernando Lozano^j,
J
D
P
Enferm Infect Microbiol Clin. 2014;XXX(X):xxx-xxx



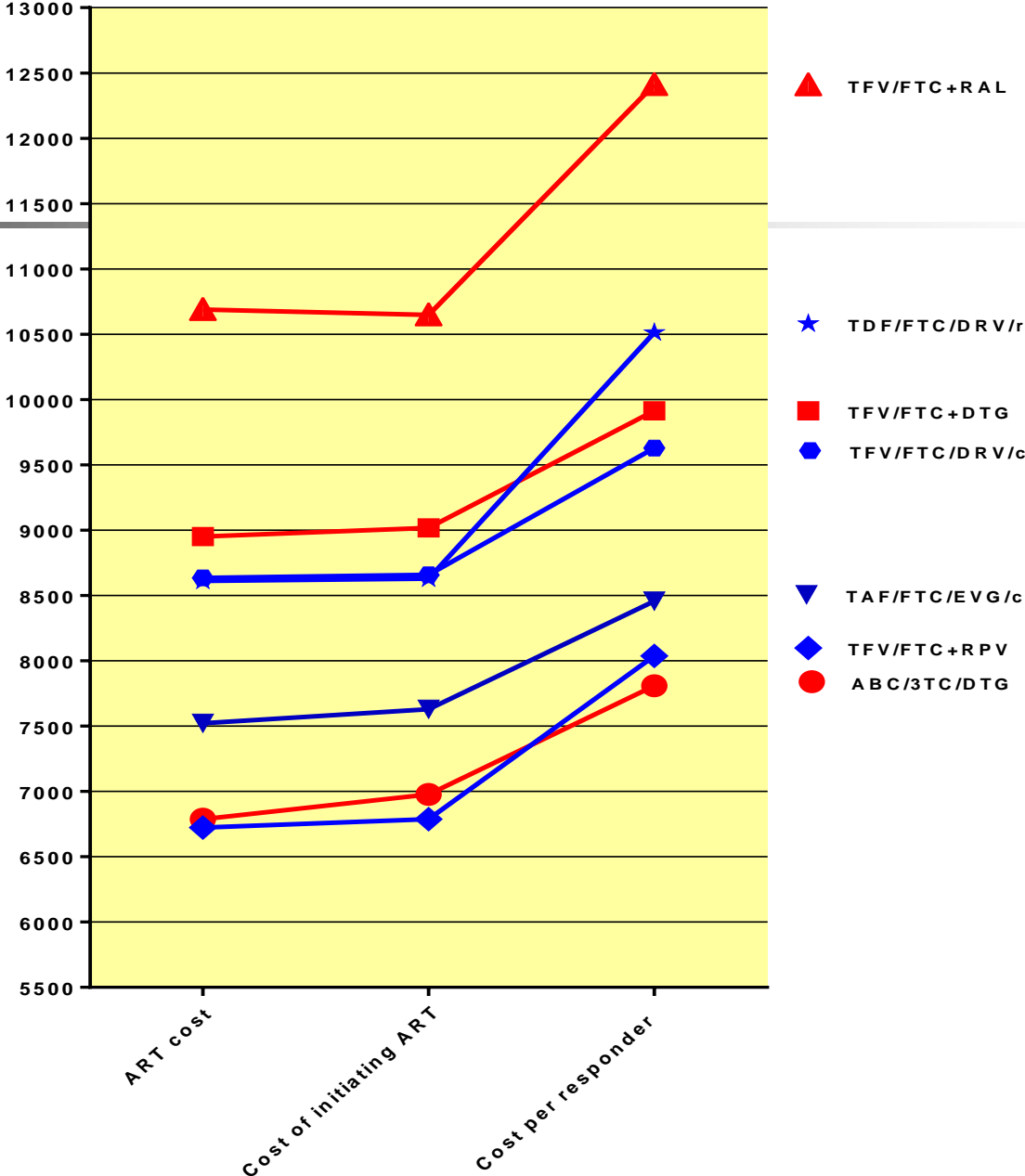
Original article
Costs and cost-efficacy analysis of the 2014 GESIDA/Spanish National AIDS Plan recommended guidelines for initial antiretroviral therapy in HIV-infected adults
Antonio Javier Blasco^a, Josep M. Llibre^b, Juan Berenguer^c, Juan González-García^d, Hernando Knobel^e,
Fernando Lozano^f, Daniel Podzamczek^g, Federico Pulido^h, Antonio Riveroⁱ, Montserrat Tuset^j,
J
D
P
Enferm Infect Microbiol Clin. 2015;XXX(X):xxx-xxx



Original article
Costs and cost-effectiveness analysis of 2015 GESIDA/Spanish AIDS National Plan recommended guidelines for initial antiretroviral therapy in HIV-infected adults
Juan Berenguer^a, Antonio Rivero^{b, c}, Antonio Javier Blasco^d, José Ramón Arribas^e, Vicente Boix^f,
Bonaventura Clotet^{g, h}, Pere Domingoⁱ, Juan González-García^j, Hernando Knobel^k, Pablo Lázaro^l,
Juan Carlos López^m, Josep M. Llibreⁿ, Fernando Lozano^o, Jose M. Miró^p, Daniel Podzamczek^q,
Montserrat Tuset^r, Josep M. Gatell^s, GESIDA Antiretroviral Therapy Cost-efficacy Study Group

2018, In press

EUROS PER YEAR



Review/comparison of current guidelines for ART



1. What about guidelines

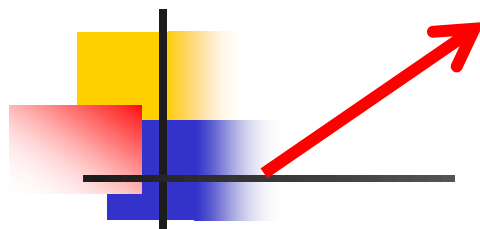
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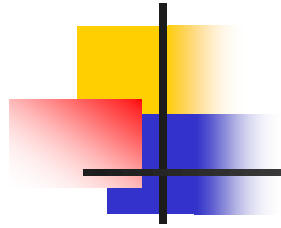
6. Final considerations



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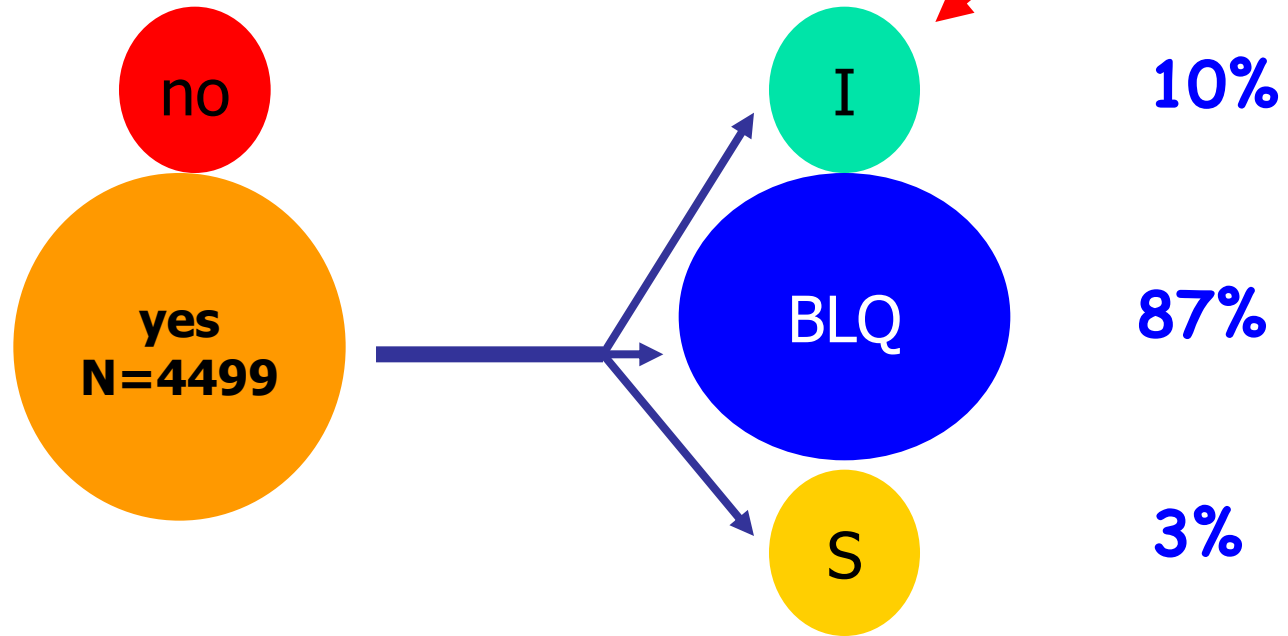
EVOLUTION OF HIV TREATMENT GUIDELINES

From 1990s to 2018



Treated

type of ART



Hospital Clinic.
Barcelona. Spain
Data on file, 2012

Switch Strategies for Virologically Suppressed Persons

Definition of virologically suppressed

Clinical trials exploring switching strategies have defined suppression as an HIV-VL < 50 copies/mL for at least 6 months.

Indications

1. **Documented toxicity** caused by one or more of the antiretrovirals included in the regimen. Examples of these reactive switches: lipoatrophy (d4T, AZT), central nervous system adverse events (EFV), diarrhoea (PI/r) and jaundice (ATV), proximal renal tubulopathy and low bone mineral density (TDF), see [Adverse Effects of ARVs and Drug Classes](#).
2. **Prevention of long-term toxicity.** Example of this proactive switch: prevention of lipoatrophy in persons receiving d4T or AZT and prevention of proximal renal tubulopathy with TDF, see [Adverse Effects of ARVs and Drug Classes](#).
3. **Avoid serious drug-drug interactions**
4. **Planned pregnancy**
5. **Ageing and/or co-morbidity** with a possible negative impact of drugs in current regimen, e.g. on CVD risk, metabolic parameters
6. **Simplification:** to reduce pill burden, adjust food restrictions and improve adherence.
7. **Starting of HCV treatment in case of a drug-drug interaction,** see [Drug-drug Interactions between DAAs and ARVs](#).

Principles

Clinicians should always review possible adverse events or tolerability issues with current antiretroviral regimens. Just because the HIV-VL is suppressed it should not be assumed that the HIV-positive person is well adapted and tolerating the current regimen.

1. The objectives of treatment modification should be to eliminate or improve adverse events, facilitate adequate treatment of co-morbid conditions, and improve quality of life.
2. The primary concern when switching should be to sustain and not to jeopardize virological suppression. In persons without prior virological failures and no archived resistance, switching regimens entail a low risk of subsequent failure if clinicians select one of the recommended combinations for first-line therapy. The majority of clinical trials showing non-inferiority of the new regimen after the switch have actively excluded persons with prior virological failures.
3. A complete ARV history with HIV-VL, tolerability issues and cumulative genotypic resistance history should be analysed prior to any drug switch.
4. A PI/r or PI/c may be switched to unboosted ATV, an NNRTI, or an INSTI only if full activity of the 2 NRTIs remaining in the regimen can be guaranteed. Switches have to be planned especially carefully when they result in a decrease in the genetic barrier of the regimen in case of prior virologic failures. Clinicians should review the complete ARV history and available resistance test and HIV-VL results before switching, and ensure no drug-drug interactions may lead to suboptimal drug levels (e.g. unboosted ATV and TDF).

5. Before switching, remaining treatment options in case of potential virological failure of the new regimen should be taken into consideration. For example, the development of the M184V RT mutation in HIV-positive persons who fail a 3TC-containing regimen might preclude the future use of all currently available single-tablet regimens.
6. Switches of single drugs with the same genetic barrier (for example EFV to RAL) is usually virologically safe in the absence of resistance to the new compound.
7. Clinicians should carefully review the possibility of drug-drug interactions with the new regimen.
8. If the switch implies discontinuing TDF and not starting TAF, clinicians should check the HBV status (avoid discontinuation of TDF in persons with chronic HBV and assess HBV vaccination status).
9. HIV-positive persons should be seen soon (e.g. 4 weeks) after treatment switch to check for maintenance of suppression and possible toxicity of the new regimen.
10. If a HIV-positive person receives and tolerates a regimen that is no longer a preferred option, there is no need to change. Example: persons tolerating EFV-containing regimens.
11. See online video [How to Change ART](#) from the EACS online course [Clinical Management of HIV](#).

Crisis-sparing strategies

Dual therapy:

DTG + RPV
3TC + (DRV/r or DRV/c) or
3TC + (ATV/r or ATV/c)

In clinical trials these strategies have not been associated with more virological rebounds than triple therapy.

Monotherapy with DRV/r:

In clinical trials this strategy has been associated with more virological rebounds than triple therapy. DRV/r monotherapy is an option only for exceptional persons who are not candidates for dual therapies.

Dual therapy with 3TC+ PI/r or monotherapy with DRV/r may only be given to persons with a) no resistance to the PI, b) suppression of HIV-VL to < 50 copies/mL for at least the past 6 months and c) absence of chronic HBV co-infection.

Strategies not recommended

- a. Monotherapy with ATV/r
- b. Monotherapy with DTG
- c. Triple NRTIs combinations
- d. Specific two-drug combination, i.e. 1 NRTI + 1 NNRTI or 1 NRTI + 1 unboosted PI, 1 NRTI + RAL, 2 NRTIs, MVC + RAL, PI/r or PI/c + MVC, ATV/r or ATV/c + RAL
- e. Intermittent therapy, sequential or prolonged treatment interruptions

Review/comparison of current guidelines for ART



1. What about guidelines

2. What do we need to know (to guess) before reading

3. When & what to start ART ?

4. Other issues related with ART

5. Other issues related with management of HIV patients

6. Final considerations

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Do not reinvent the wheel
Focus on what is different from general population

Review/comparison of current guidelines for ART



1. What about guidelines

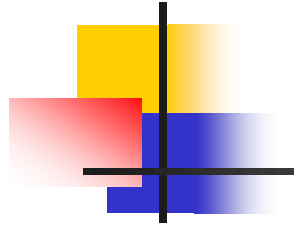
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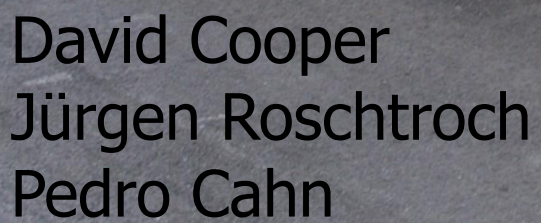
6. Final considerations



Recommendations/guidance are pretty similar. May use different wording or different ways of presenting same information

May/should go beyond published evidence

Use to represent the “minimum” SOC. As such may represent a defense mechanism for prescribers when they need to interact with third party payers (NHS's in Europe) and developers (pharma companies)





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Special Communication

Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults

2016 Recommendations of the International Antiviral Society-USA Panel

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JAMA, 2016

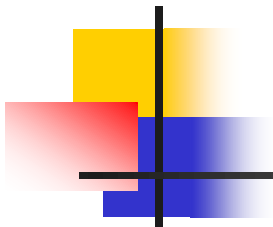


Table 1. Strength of Recommendation and Quality of Evidence Rating Scale^a

Rating	Definition
Strength of recommendation	
A	Strong support for the recommendation
B	Moderate support for the recommendation
C	Limited support for the recommendation
Quality of evidence	
Ia	Evidence from ≥ 1 randomized clinical trials published in the peer-reviewed literature
Ib	Evidence from ≥ 1 randomized clinical trials presented in abstract form at peer-reviewed scientific meetings
IIa	Evidence from nonrandomized clinical trials or cohort or case-control studies published in the peer-reviewed literature
IIb	Evidence from nonrandomized clinical trials or cohort or case-control studies presented in abstract form at peer-reviewed scientific meetings
III	Recommendation based on the panel's analysis of the accumulated available evidence


^a Adapted in part from the Canadian Task Force on Periodic Health Examination.⁶



4.3 When to start ART

4.3.1 When to start ART in adults (>19 years old)

Recommendation

- ART should be initiated in all adults living with HIV, regardless of WHO clinical stage and at any CD4 cell count (strong recommendation, moderate-quality evidence). 
- As a priority, ART should be initiated in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with CD4 count ≤ 350 cells/mm³ (strong recommendation, moderate-quality evidence).

Sources:

Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: World Health Organization 2015 (<http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en>).

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach Geneva: World Health Organization; 2013 (<http://www.who.int/hiv/pub/guidelines/arv2013/download/en>).

Tabla 3. Combinaciones de TAR de inicio recomendadas[†]

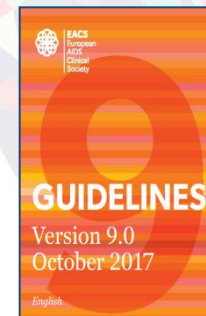
3er Fármaco	Pauta [†]	Comentarios [†]
Preferentes. Pautas aplicables a la mayoría de los pacientes y que en ensayos clínicos aleatorizados han mostrado una eficacia superior frente a otras o mostrando no-inferioridad presentan ventajas adicionales en tolerancia, toxicidad o un bajo riesgo de interacciones farmacológicas.		
INI	DTG/ABC/3TC	■ ABC está contraindicado en pacientes con HLA-B*5701 positivo
	DTG+FTC/TAF	
	RAL+FTC/TAF	■ RAL puede administrarse indistintamente como 1 comprimido de 400 mg cada 12 horas, o 2 comprimidos de 600 mg (nueva formulación) cada 24 horas*.

Recomendaciones Gesida 2018

Alternativas. Pautas eficaces, pero que no se consideran preferentes bien porque su eficacia ha resultado inferior a las pautas preferentes en ensayos clínicos o porque tienen desventajas potenciales o restricciones en su indicación. Pueden ser, sin embargo, de elección en subgrupos de pacientes o en casos especiales

INI	EVG/c/FTC/TAF	■ Mayor potencial de interacciones que otras pautas basadas en INI
IP potenciado	DRV/c/FTC/TAF* o	■ Puede considerarse de elección cuando se requiera de una pauta con elevada barrera genética (pacientes con problemas de adherencia)
	DRV/p+FTC/TAF**	■ Es imprescindible evaluar posibles interacciones
ITINN	RPV/FTC/TAF*	■ No indicado en pacientes con CVP >100.000 copias/mL
		■ Puede considerarse de elección en pacientes con CVP <100.000 copias/mL
		■ Realizar previamente un estudio genotípico que descarte mutaciones de resistencia a ITINN
		■ Contraindicado si se utilizan inhibidores de la bomba de protones
		■ Se debe tomar siempre con una comida

Recomendaciones EACS Nov 2017



A) Recommended regimens (one of the following to be selected)*, **

Regimen	Dosing	Caution	Food requirement
2 NRTIs + INSTI			
ABC/3TC/DTG ^(i, ii)	ABC/3TC/DTG 600/300/50 mg, 1 tablet qd	Al/Ca/Mg-containing antacids or multivitamins should be taken well separated in time (minimum 2h after or 6h before). DTG 50 mg bid with rifampicin.	None
TAF/FTC ⁽ⁱⁱⁱ⁾ or TDF/FTC ⁽ⁱⁱⁱ⁾	TAF/FTC 25/200 mg, 1 tablet qd or TDF/FTC 300/200 mg, 1 tablet qd		None
+ DTG	+ DTG 50 mg, 1 tablet qd		
TAF/FTC/EVG/c ⁽ⁱⁱⁱ⁾ or TDF/FTC/EVG/c ^(iii, iv)	TAF/FTC/EVG/c 10/200/150/150 mg, 1 tablet qd or TDF/FTC/EVG/c 300/200/150/150 mg, 1 tablet qd	Al/Ca/Mg-containing antacids or multivitamins should be taken well separated in time (minimum 2h after or 6h before).	With food
TAF/FTC ⁽ⁱⁱⁱ⁾ or TDF/FTC ⁽ⁱⁱⁱ⁾	TAF/FTC 25/200 mg, 1 tablet qd or TDF/FTC 300/200 mg, 1 tablet qd + RAL 400 mg, 1 tablet bid	Co-administration of antacids containing Al or Mg not recommended. RAL 400 or 800 mg bid with rifampicin.	None
2 NRTIs + NNRTI			
TAF/FTC/RPV ⁽ⁱⁱⁱ⁾ or TDF/FTC/RPV ⁽ⁱⁱⁱ⁾	TAF/FTC/RPV 25/200/25 mg, 1 tablet qd or TDF/FTC/RPV 300/200/25 mg, 1 tablet qd	Only if CD4 count > 200 cells/ μ L and HIV-VL < 100,000 copies/mL. PPI contraindicated; H2 antagonists to be taken 12h before or 4h after RPV.	With food
2 NRTIs + PI/r or PI/c			
TAF/FTC ⁽ⁱⁱⁱ⁾ or TDF/FTC ⁽ⁱⁱⁱ⁾	TAF/FTC 10/200 mg, 1 tablet qd or TDF/FTC 300/200 mg, 1 tablet qd	Monitor in persons with a known sulfonamide allergy.	With food
+ DRV/c ^(v) or + DRV/r ^(v)	DRV/c 800/150 mg, 1 tablet qd or + DRV 800 mg, 1 tablet qd + RTV 100 mg, 1 tablet qd		

1. European AIDS Clinical Society Guidelines v. 9.0 October 2017. Disponible en: http://www.eacsociety.org/files/guidelines_9.0-english.pdf. Con acceso: febrero 2018.

▼ Este medicamento está sujeto a seguimiento adicional, es prioritaria la notificación de sospechas de reacciones adversas asociadas a este medicamento.



Recommended Initial Regimens for Most People with HIV

Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.

INSTI + 2 NRTIs:

- DTG/ABC/3TC^a (AI)—if HLA-B*5701 negative
- DTG + tenofovir^b/FTC^a (AI for both TAF/FTC and TDF/FTC)
- EVG/c/tenofovir^b/FTC (AI for both TAF/FTC and TDF/FTC)
- RAL^c + tenofovir^b/FTC^a (AI for TDF/FTC, All for TAF/FTC)

Recommended Initial Regimens in Certain Clinical Situations

These regimens are effective and tolerable, but have some disadvantages when compared with the regimens listed above, or have less supporting data from randomized clinical trials. However, in certain clinical situations, one of these regimens may be preferred (see [Table 7](#) for examples).

Boosted PI + 2 NRTIs: (In general, boosted DRV is preferred over boosted ATV)

- (DRV/c or DRV/r) + tenofovir^b/FTC^a (AI for DRV/r and All for DRV/c)
- (ATV/c or ATV/r) + tenofovir^b/FTC^a (BI)
- (DRV/c or DRV/r) + ABC/3TC^a —if HLA-B*5701–negative (BII)
- (ATV/c or ATV/r) + ABC/3TC^a —if HLA-B*5701–negative and HIV RNA <100,000 copies/mL (CI for ATV/r and CIII for ATV/c)

El texto resaltado en amarillo implica cambios vs. la versión anterior de las guías

TAF no está comercializado en España como fármaco independiente

3. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents DHHS panel. Disponible en <https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf>. Con acceso: febrero 2018.

What about the guidelines

Oct. 2011



Recomendaciones
antirretroviral en

Guidelines for the Use of Antiretroviral Agents in HIV-1- Infected Adults and Adolescents

January 29, 2008

Developed by the DHHS
Panel on Antiretroviral Guidelines
for Adults and Adolescents – A Working
Group of the HIV Medicine Society
Office of AIDS Research Advisory

Recomendaciones de Guías y

How to Cite the Adult and Adolescent Guidelines:
Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 29, 2008. Available at: <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGuidelines.pdf>. Accessed (insert date) [insert page number, table number, etc.].

It is emphasized that concepts relevant to HIV management evolve rapidly. The Panel has a mechanism to update recommendations on a regular basis, and the most recent information is available on the AIDSinfo Web site (<http://AIDSinfo.nih.gov>).



European AIDS Clinical Society
(EACS)

Guidelines for the Clinical
Management and Treatment
of HIV Infected Adults

BG Gazzard on behalf of the BHIVA

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British HIV
Association

British HIV
Association
guidelines for
HIV-infected
adults
antiretroviral
therapy
2008

JOBNAME: JAMA.XML PAGE: 1 SESS: 18 OUTPUT: Tue Jul 15 11:12:10 2008
/jama/08july/weekly/08aug08/jc080007

SPECIAL COMMUNICATION

To: Joy

Antiretroviral Treatment of Adult HIV Infection 2008 Recommendations of the International AIDS Society–USA Panel

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THE FIELD OF ANTIRETROVIRAL therapy continues to evolve rapidly, and, to maintain the highest possible standard of care, treatment guidelines must continually be refined to assist the complex decision-making process. For a disease that has been transformed from almost uniformly fatal to manageable over decades, the impact of treatment decisions is substantial. Treatment can provide durable virologic, immunologic, and clinical benefits while minimizing toxicities and drug resistance,

Context. The availability of new antiretroviral drugs and formulations, including drugs in new classes, and recent data on treatment choices for antiretroviral-naïve and experienced patients warrant an update of the International AIDS Society–USA guidelines for the use of antiretroviral therapy in adult human immunodeficiency virus (HIV) infection.

Objectives. To summarize new data in the field and to provide current recommendations for the antiretroviral management and laboratory monitoring of HIV infection. This report provides guidelines in key areas of antiretroviral management, when to initiate therapy, choice of initial regimens, patient monitoring, when to change therapy, and how best to approach treatment options, including optimal use of recently approved drugs (maraviroc, raltegravir, and dolutegravir) in treatment-experienced patients.

Data Sources and Study Selection. A 14-member panel with expertise in HIV research and clinical care was appointed. Data published or presented at selected scientific conferences since the last panel report (August 2006) through June 2008 were identified.

Data Extraction and Synthesis. Data that changed the previous guidelines were reviewed by the panel (according to section). Guidelines were drafted by section writing committees and were then reviewed and edited by the entire panel. Recommendations were made by panel consensus.

Conclusions. New data and considerations support initiating therapy before CD4 cell count declines to 350 cells/mm³. In patients with CD4 counts above 350 cells/mm³, the decision to begin therapy should be individualized based on the presence of comorbidities, risk factors for progression to AIDS and non-AIDS diseases, and patient readiness for treatment. In addition to the prior recommendation that a high plasma viral load (eg, >100,000 copies/mL) and rapidly declining CD4 cell count (<100 cells/mm³ per year) should prompt treatment initiation, active hepatitis B or C virus coinfection, cardiovascular disease risk, and HIV-associated nephropathy increasingly prompt earlier therapy. The initial regimen must be individualized, particularly in the presence of comorbid conditions, but usually will include efavirenz or a rilpivirine-based protease inhibitor plus 2 nucleoside reverse transcriptase inhibitors (tenofovir/emtricitabine or abacavir/lamivudine). Treatment failure should be identified and managed promptly with the goal of therapy, even in heavily pretreated patients, being an HIV-1 RNA level below assay detection limits.

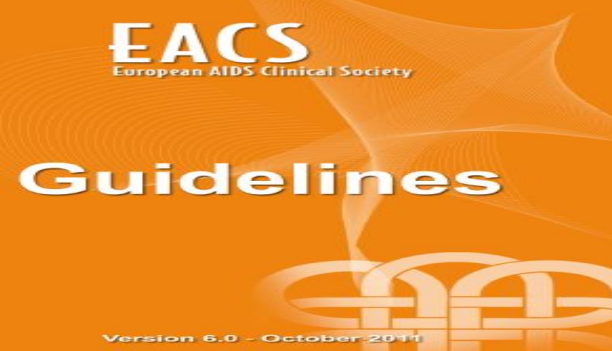
(JAMA. 2008;300:595-610)

CMR available online at
www.jamaonline.com
and questions on p 596.

and potentially allow for a normal life span.
The rationale for the current update of the 2006 International AIDS Society–USA Panel Report is provided in this special communication.

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Recommendations for initiation of ART in HIV-positive persons without prior ART exposure ⁽¹⁾

Recommendations are graded while taking into account both the degree of progression of HIV disease and the presence of or high risk for developing various types of (co-morbid) conditions

Condition	Current CD4+ lymphocyte count ^{§§}	
	350-500	>500
Asymptomatic HIV infection	C	D
Symptomatic HIV disease (CDC B or C conditions) incl. tuberculosis	R	R
Primary HIV infection	C	C
Pregnancy (before third trimester)	R	R
Conditions (likely or possibly) associated with HIV, other than CDC stage B or C disease:		
HIV-associated kidney disease	R	
HIV-associated neurocognitive impairment	R	R
Hodgkin's lymphoma	R	R
HPV-associated cancers		R
Other non-AIDS-defining cancers requiring chemotherapy	C	C
Autoimmune disease – otherwise unexplained	C	
High risk for CVD (>20% estimated 10 year risk or history of CVD)	C	C
Chronic viral hepatitis		
HBV requiring anti-HBV treatment	R	R
HBV not requiring anti-HBV treatment	C/R ^{§§}	D
HCV for which anti-HCV treatment is being considered or given	R ^{§§}	D ^{§§}
HCV for which anti-HCV treatment not feasible	R	C

- i The consideration to start ART may be individualized regardless of CD4 count and plasma HIV RNA level, especially if a patient is requesting ARV therapy and ready to start, and/or for any other personal reasons. In serodiscordant couples early initiation of ART as one aspect of the overall strategy to reduce HIV transmission to the seronegative partner should be considered and actively discussed. Time should be taken to prepare the patient in order to optimize compliance and adherence. Genotypic resistance testing and subtype determination is recommended prior to initiation of ART; ideally at the time of HIV diagnosis, otherwise before initiation of ART. If genotypic testing is not available, it is recommended to include a ritonavir-boosted PI in the first-line regimen. Before starting treatment, the HIV RNA level and CD4 count should be repeated to obtain a baseline to assess subsequent response.
- ii ART is always recommended in any HIV-positive person with a current CD4 count below 350 cells/ μ L.

- iii Cruse of ART should be considered; for patients under these circumstances some experts would recommend starting ART, whereas others would recommend deferral of ART; this clinical equipoise reflects that whereas certain evidence supports starting ART this needs to be balanced against the risk of known or uncovered adverse drug reactions from use of ART, and hence the risk/benefit ratio for use of ART under these circumstances has not yet been well defined. D=defer initiation of ART. R=reuse of ART is recommended.
- v Initiation of ART is recommended in those who are HBeAg-positive
- vi Initiation of ART is recommended to optimize the outcome of HCV treatment
- vii HCV treatment to attempt eradication of HCV should be prioritized and ART deferred

Initial combination regimen for antiretroviral-naïve adult patients

SELECT 1 DRUG IN COLUMN A AND 1 NRTI COMBINATION IN COLUMN B ⁽¹⁾	A	B	REMARKS
Recommended	ABC/3TC ^(*) or TDF/FTC	ABC/3TC ^(*) or TDF/FTC	• TDF/FTC co-formulated • ABC/3TC co-formulated • EPV/TDF/FTC co-formulated
	TDF/FTC	TDF/FTC	
	or ritonavir-boosted PI • ATV/r ^(*) • DRV/r ^(*) • LPV/r ^(*)	ABC/3TC ^(*) or TDF/FTC	• ATV/r: 300/100 mg qd • DRV/r: 800/100 mg qd • LPV/r: 400/100 mg bid or 800/200 mg qd
Alternative	or RAL	TDF/FTC	• RAL: 400 mg bid
	SQV/r	• ZDV/3TC	• SQV/r: start with 500/100 mg then change to 1000/100 mg bid after one week
	FPV/r MVC ^(*)	• ddI/3TC or FTC ^(*)	• FPV/r: 700/100 mg bid or 1400/200 mg qd • ZDV/3TC co-formulated

* Generic HIV drugs are becoming more available and can be used as long as they replace the same drug and do not break recommended fixed dose combinations

** Only timely registered drugs at the European level are taken into consideration

- i EFV: not recommended in pregnant women or women with no reliable and consistent contraception; not active on HIV-2 and HIV-1 group O.
- ii NVP: Use with extreme caution in women with CD4 > 250 and men with CD4 > 400 μ L and only if benefits outweigh the risk; not active on HIV-2 and HIV-1 group O.
- iii Castle study (LPV/r vs. ATV/r) has shown better tolerability of ATV/r and Aramis study (LPV/r vs. DRV/r) better efficacy and greater tolerability of DRV/r.

- iv ACTG 5142 randomised study showed lower virological efficacy of LPV/r vs. EFV while no PI mutations were seen in the LPV/r plus two nucleoside failures. However, PI mutations were seen on LPV/r + EFV.
- v Unlicensed in Europe for naïve patients
- vi ABC contra-indicated if HLA B*5701 positive. Even if HLA B*5701 negative, counselling on HSR risk still mandatory. ABC should be used with caution in patients with a high CVD risk and/or patients with a VL > than 100,000 of mL.
- vii Only if unavailability or intolerance to other recommended NRTI's

Simple, Strong (when there is evidence) and flexible enough