Review/comparison of current guidelines for ART

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Potential conflicts of interest (April 2018):

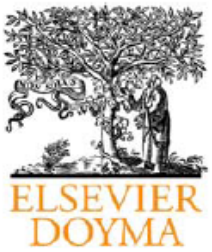
Dr. Gatell has received honoraria for lectures or AB or research grants (his institution) from MSD, ViiV, Gilead, and Janssen

Review/comparison of current guidelines for ART

	Scope	life span	panel member(*)
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

Enferm Infecc Microbiol Clin. 2009;27(4):197–198



Enfermedades Infecciosas y Microbiología Clínica

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Editorial

¿Debemos orientarnos por guías terapéuticas?

Should we follow the guidelines?

Jose Maria Gatell *

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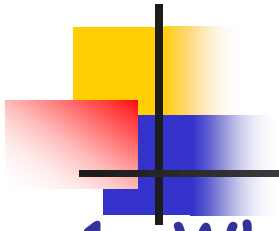
INFORMACIÓN DEL ARTÍCULO

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 nula[1]. Las 2 guías de tratamiento antirretrovírico más

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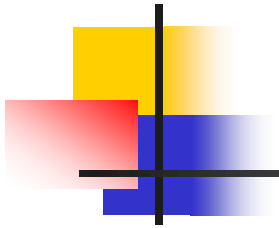


The content is a mixture of:

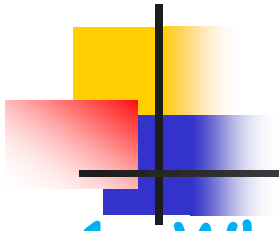
science (evidence based medicine ?)

opinions (expert opinions ?)

politics

and more….iii

Review/comparison of current guidelines for ART



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Review/comparison of current guidelines for ART

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]

AIDS 2013, **27**:000–000

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 Academi Medicine

Bernard Lo, M.D.

In January 2010, Boston-based Partners HealthCare, 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 pharmaceutical 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 new therapies, acad to translate basic di treatments, and inc to develop new pro Partners policy notes mia and industry when academic lead company boards. Co benefit from the wis academic physician about emerging tren search and health ca leaders may learn i proaches to organiz research teams or ru complex organizatio networking with othe bers may enhance f

However, the mi demic health centers diverge from that medical companies ways (see table). W are driven largely by deepening our und health and disease a

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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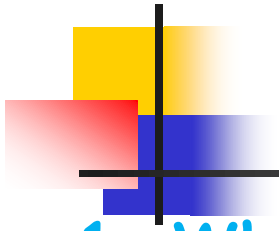

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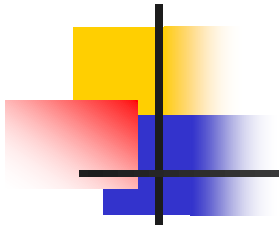


Since year 2005 initial ART was very effective, well tolerated and convenient for the patients

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)]

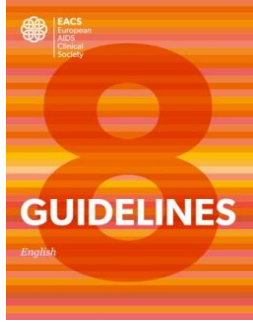
Recommendations are graded while taking into account the level of evidence, the degree of progression of HIV disease and the presence of, or high risk for, developing various types of (co-morbid) conditions.

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).

EACS European AIDS Clinical Society



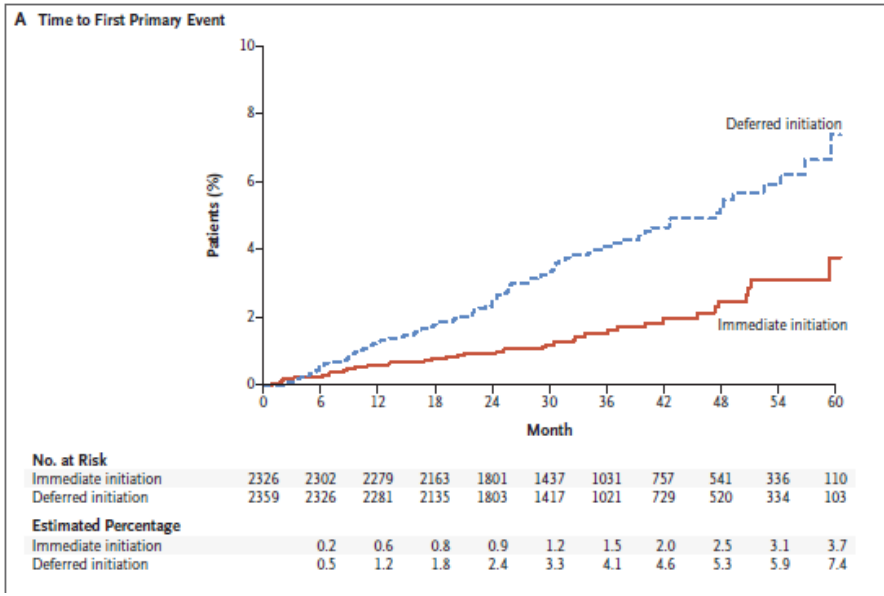
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

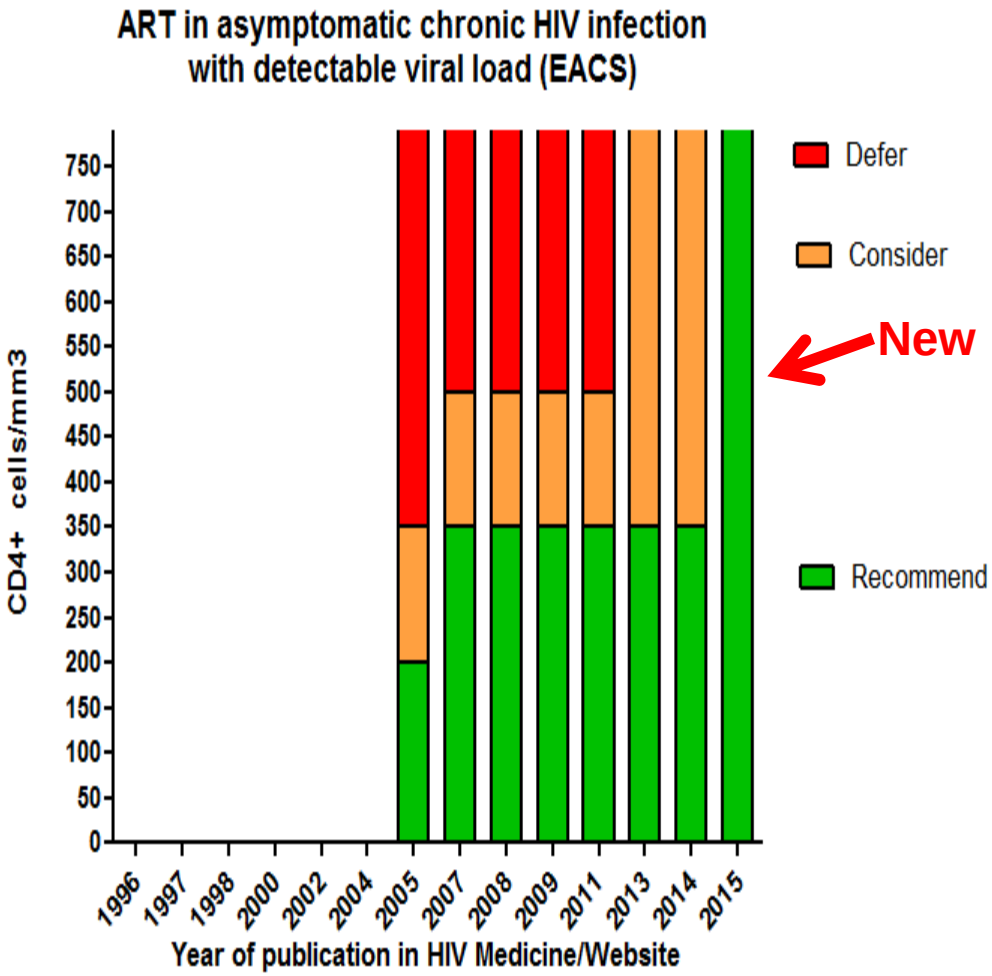
The INSIGHT START Study Group*

New



TB & AIDS and non-AIDS malignancies

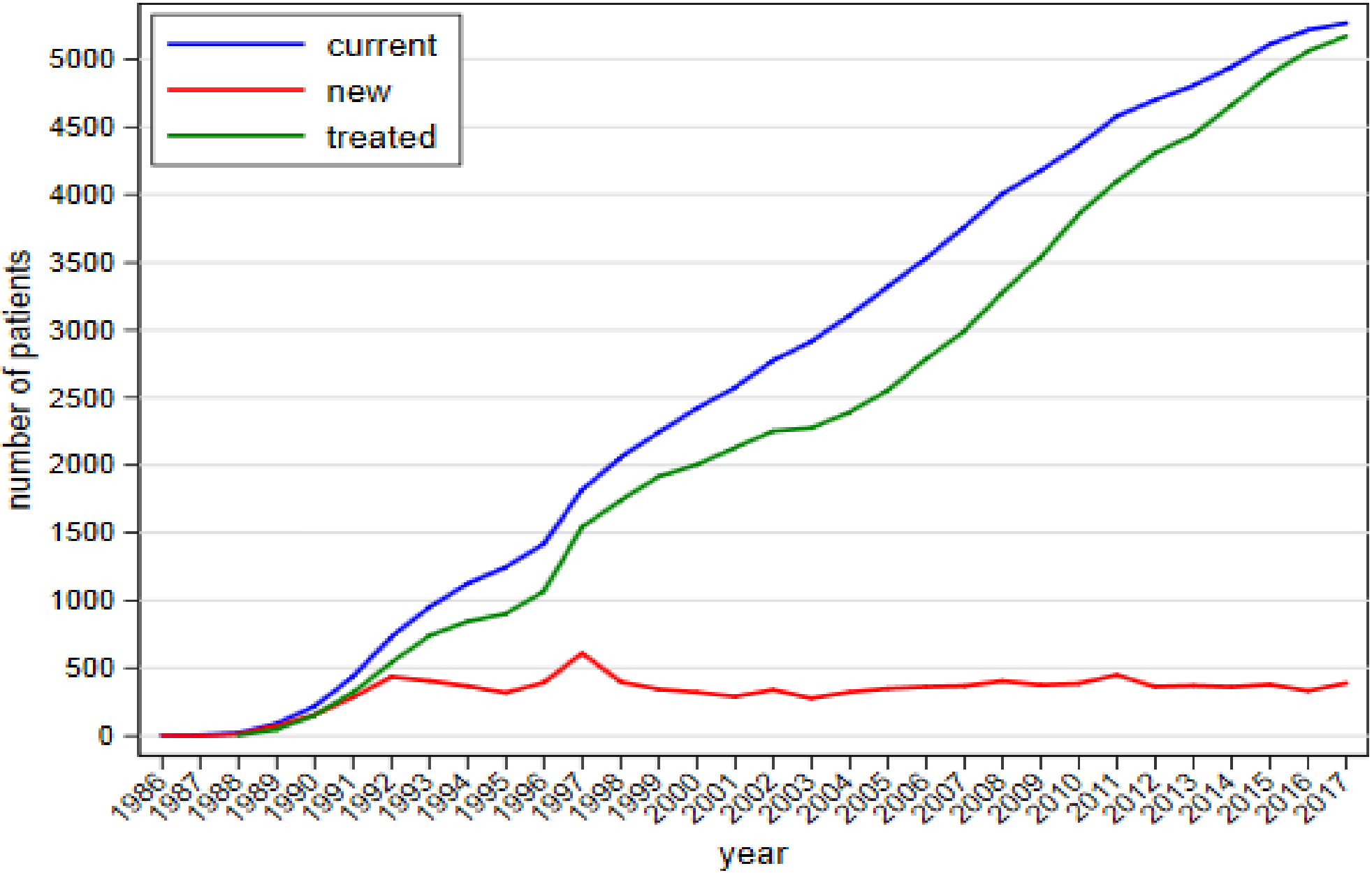
EACS & WHO, 2015



EACS European AIDS Clinical Society

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*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year

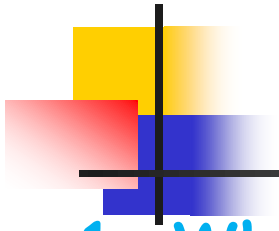
Elite/viremic controllers

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

Do we need a resistance test before ART

Initiation "same day" ?

Review/comparison of current guidelines for ART



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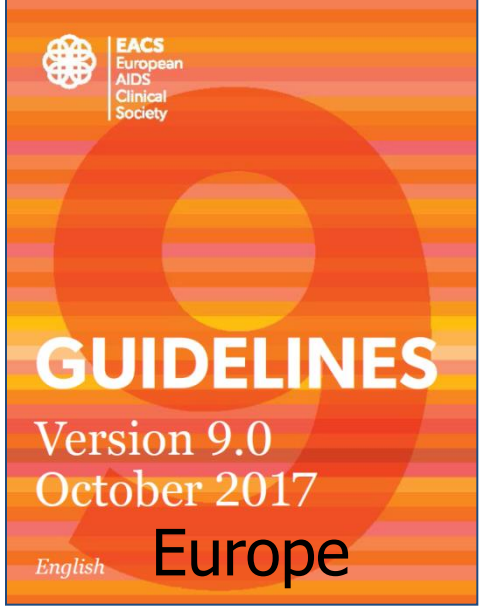
Spain



Europe

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 AIDS*info* 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

GESIDA, 2018

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)

Applicable to almost all patients
Superiority vs former standard of care
Added value (tolerance or DDI)

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BIC/FTC/TAF

IAS-USA, 2016

Table 3. Recommended Initial Antiretroviral Therapy Regimens[a]

Regimen	Rating
Dolutegravir/abacavir/lamivudine	AIa
Dolutegravir plus tenofovir alafenamide/emtricitabine[b]	AIa
Elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine[b]	AIa
Raltegravir plus tenofovir alafenamide/emtricitabine[b]	AIII

[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.

DHHS Feb 2018

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, **AII** for TAF/FTC)

EACS Oct 2017

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

Regimen	Dosing	Caution	Food requirement
2 NRTIs + INSTI			
ABC/3TC/DTG[(i,l)]	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)] + DTG	TAF/FTC 25/200 mg, 1 tablet qd or TDF/FTC 300/200 mg, 1 tablet qd + DTG 50 mg, 1 tablet qd		None
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)] + RAL	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/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[(iii)] or TDF/FTC[(iii)] + DRV/c[(v)] or + DRV/r[(v)]	TAF/FTC 10/200 mg, 1 tablet qd or TDF/FTC 300/200 mg, 1 tablet qd DRV/c 800/150 mg, 1 tablet qd or + DRV 800 mg, 1 tablet qd + RTV 100 mg, 1 tablet qd	Monitor in persons with a known sulfonamide allergy.	With food

RPV

DRV/r/c

World He
Organiza

CONSOLIDATED GUIDELINES ON

THE USE OF ANTIRETROVIRAL DRUGS FOR TREATING AND PREVENTING HIV INFECTION

RECOMMENDATIONS FOR A PUBLIC HEALTH APPROACH

SECOND EDITION
2016

4.4 What to start: first-line ART

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) TDF + 3TC (or FTC) + DTG[c] 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) TDF (or ABC) + 3TC (or FTC) + DTG[c,d] TDF (or ABC) + 3TC (or FTC) + EFV_{400}[c,d,e] TDF (or ABC) + 3TC (or FTC) + NVP

World Health Organization

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

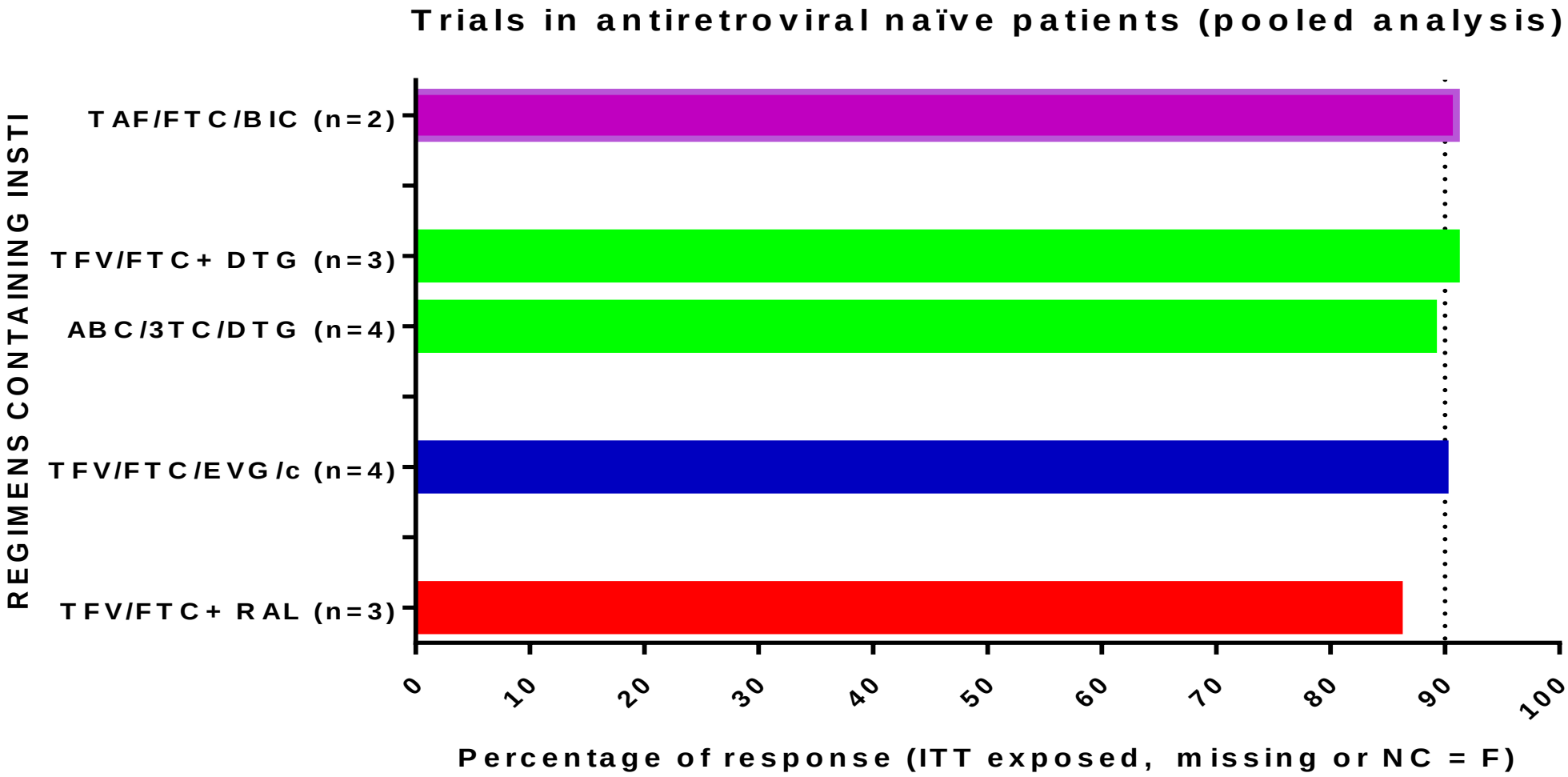
JULY 2017

5. CONCLUSIONS

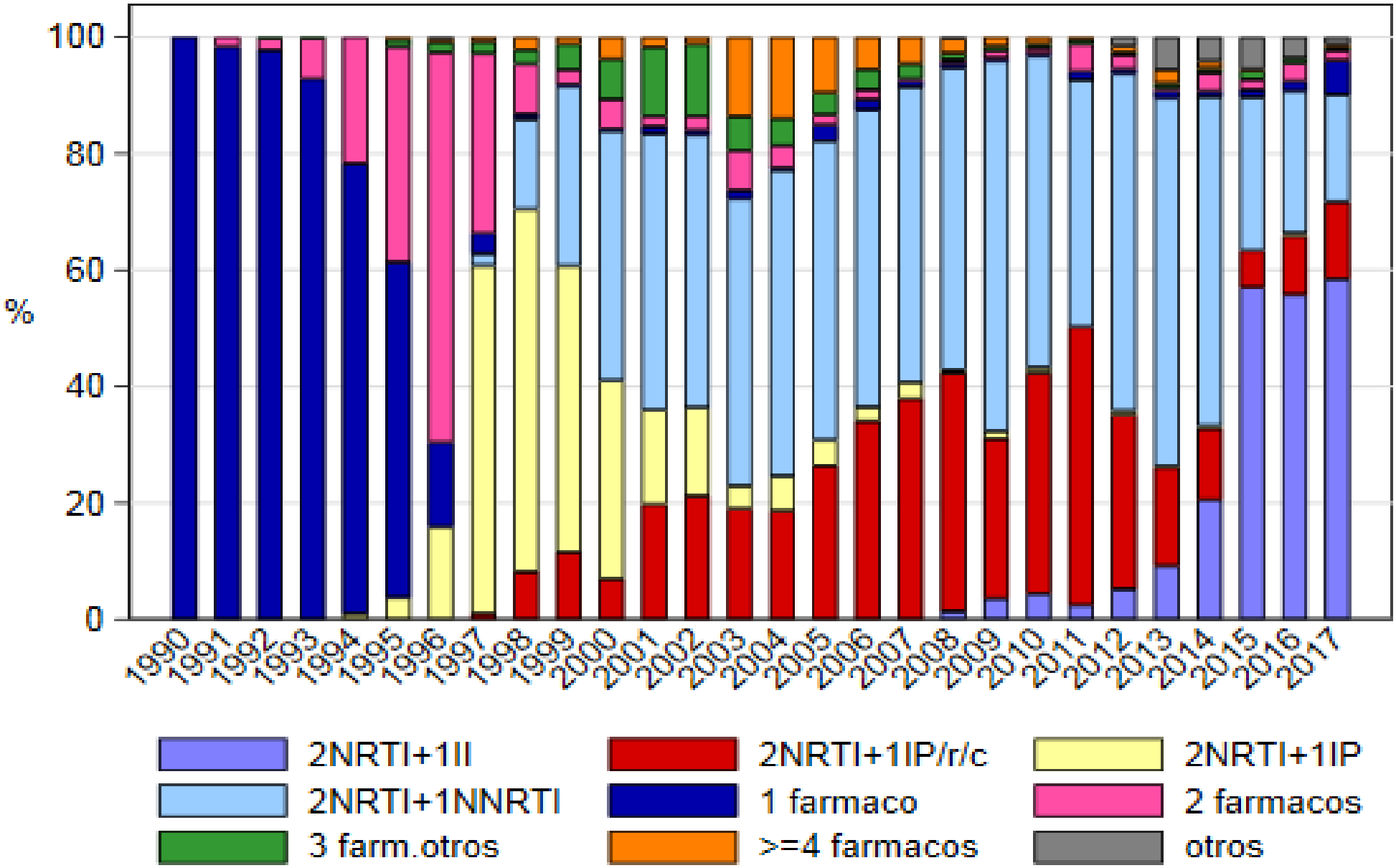
There are many factors to consider when deciding to introduce new ARV drugs: efficacy, safety, drug interactions (e.g. TB drugs), price, affordability, population prevalence of HIVDR, regulatory approval and availability of quality-assured generic and fixed-dose formulations.

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.

Blasco, Gatell et al. EIMC 2018, in press



pautas debut



GESIDA/PNS (Sapin) Guidelines (since 2000)

2011

2012

2013

2014

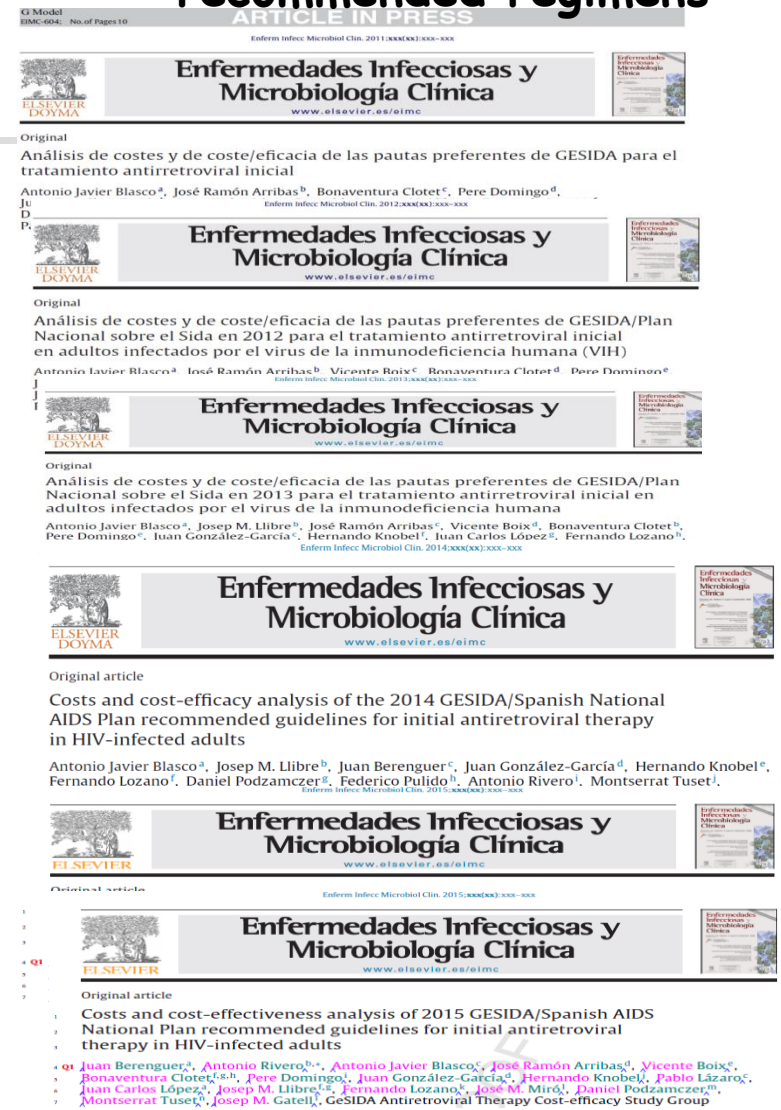
2015

2016

2017

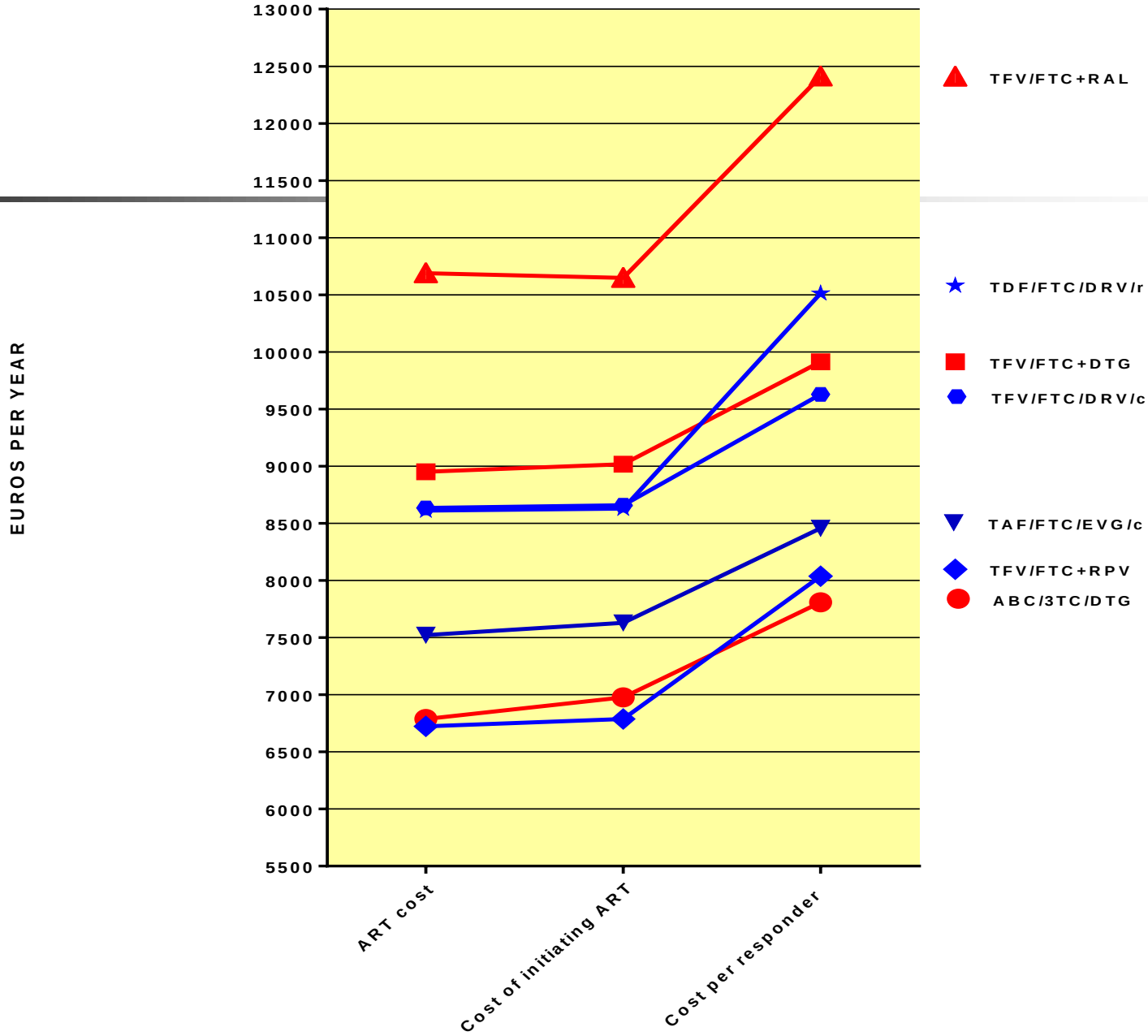
2018

Cost-efficacy analysis of recommended regimens



2018, In press

Blasco, Gatell et al. EIMC 2018



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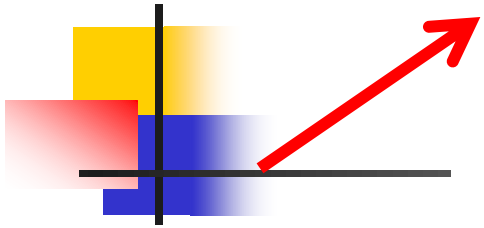
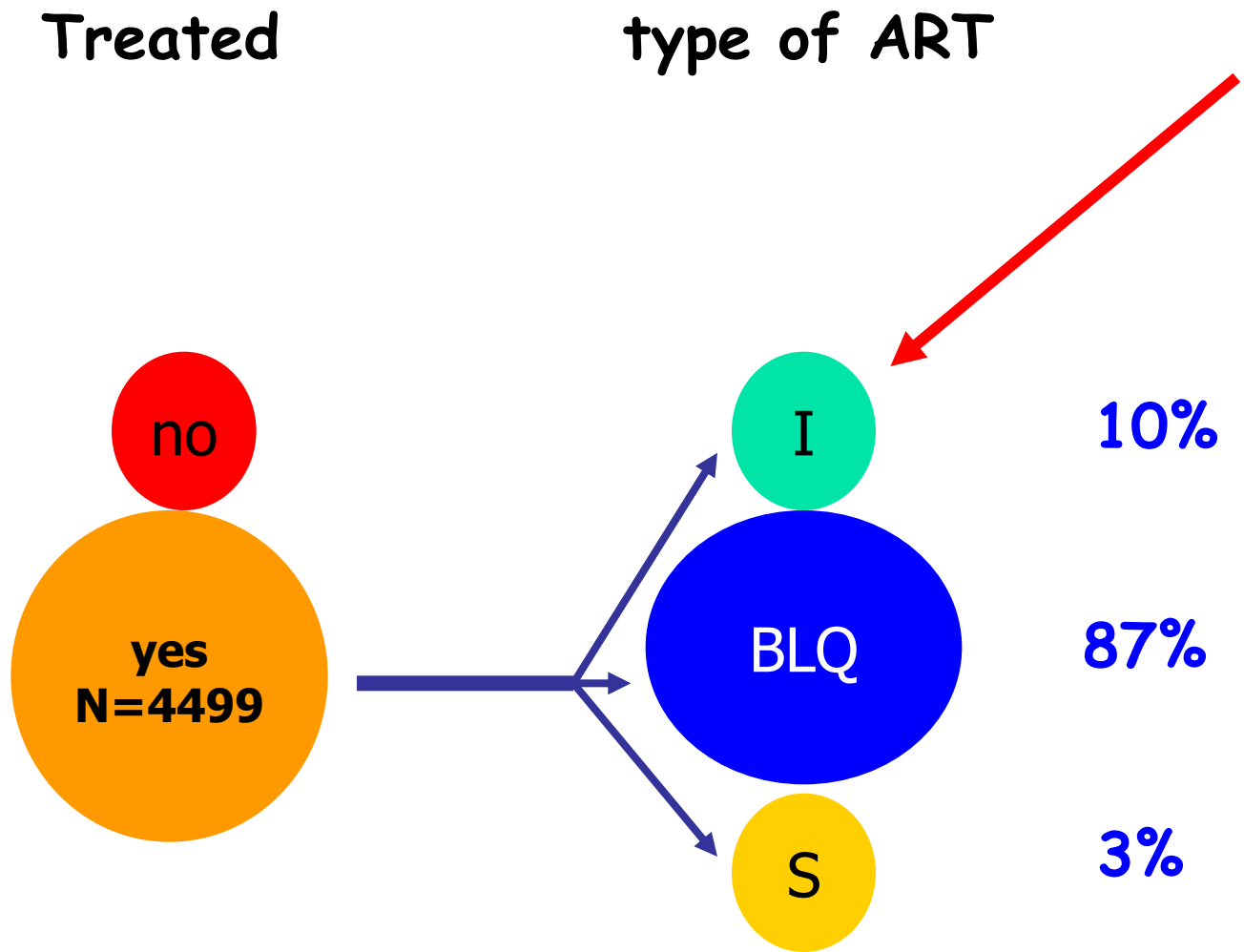
EACS Oct 2017

Part II



EVOLUTION OF HIV TREATMENT GUIDELINES
From 1990s to 2018



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 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 lecture How to Change ART from the EACS online course Clinical Management of HIV.

Class-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

Table of Contents

Green text – online only at http://www.eacsociety.org and in the EACS Guidelines App. Page numbers in brackets refer to corresponding page in the online version of the Guidelines.

Part I

Part II

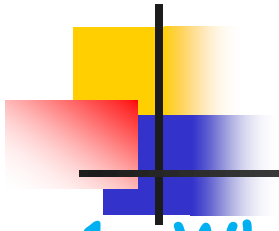
Part III

Part IV

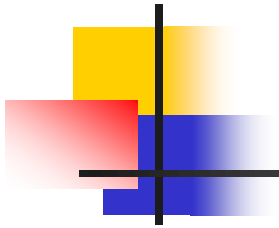
Part V

References

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



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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RIS RD 06/0006 Red Española de Investigación en SIDA Spanish AIDS Research Network

ISCIII

HIVACAT

SEVENTH FRAMEWORK PROGRAMME

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

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). 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 adults with CD4 count ≤350 cells/mm^3 (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).

Recomendaciones Gesida 2018

Tabla 3. Combinaciones de TAR de inicio recomendadas†

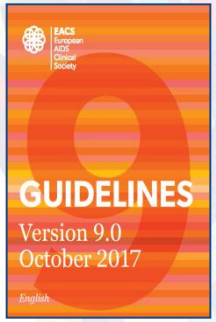
3er Fármaco	Pauta†	Comentarios‡
Preferentes. Pautas aplicables a la mayoría de los pacientes y que en ensayos clínicos aleatorizados han mostrado una eficacia superior frente a otras o mostrando no-inferioridad presentan ventajas adicionales en tolerancia, toxicidad o un bajo riesgo de interacciones 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] + DTG	TAF/FTC 25/200 mg, 1 tablet qd or TDF/FTC 300/200 mg, 1 tablet qd + DTG 50 mg, 1 tablet qd		None
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] + RAL	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/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[iii] or TDF/FTC[iii] + DRV/c[v] or + DRV/r[v]	TAF/FTC 10/200 mg, 1 tablet qd or TDF/FTC 300/200 mg, 1 tablet qd DRV/c 800/150 mg, 1 tablet qd or + DRV 800 mg, 1 tablet qd + RTV 100 mg, 1 tablet qd	Monitor in persons with a known sulfonamide allergy.	With food

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.

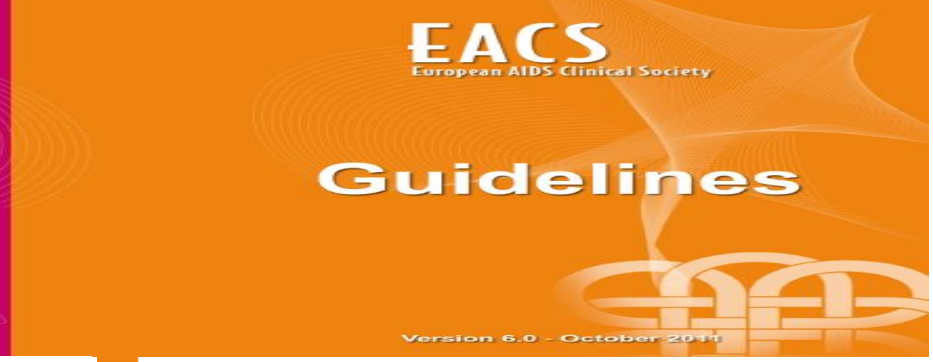
Recomendaciones DHHS Feb 2018

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, **AII** 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 AII 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 …….



Recommendations for initiation of ART in HIV-positive persons without prior ART exposure [i]

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 [ii,iii]	
	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	R
HIV-associated neurocognitive impairment	R	R
Hodgkin's lymphoma	R	R
HPV-associated cancers	R	R
Other non-AIDS-defining cancers requiring chemotherapy	C	C
Autoimmune disease – otherwise unexplained	C	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 [iv]	D
HCV for which anti-HCV treatment is being considered or given	R [v]	D [vi]
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/μL.**

ii C=use 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 undiscovered 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=use of ART is recommended.

iv Initiation of ART is recommended in those who are HBeAg-positive

v Initiation of ART is recommended to optimize the outcome of HCV treatment

vi HCV treatment to attempt eradication of HCV should be prioritized and ART deferred

Initial combination regimen for antiretroviral-naive adult patients

SELECT 1 DRUG IN COLUMN A AND 1 NRTI COMBINATION IN COLUMN B [i]	A	B	REMARKS
Recommended	**NNRTI**		
	EFV [i]	ABC/3TC [vi] or TDF/FTC	• TDF/FTC co-formulated • ABC/3TC co-formulated
	NVP [ii]	TDF/FTC	• EFV/TDF/FTC co-formulated
	or ritonavir-boosted PI		
	• ATV/r [iii]	ABC/3TC [vi] or TDF/FTC	• ATV/r: 300/100 mg qd
	• DRV/r [iii]		• DRV/r: 800/100 mg qd
	• LPV/r [iv]		• LPV/r: 400/100 mg bid or 800/200 mg qd
	INI		
	• RAL	TDF/FTC	• RAL: 400 mg bid
Alternative	SQV/r	• ZDV/3TC	• SQV/r: start with 500/100 mg then change to 1000/100 mg bid after one week
	FPV/r	• ddI/3TC or FTC [vii]	• FPV/r: 700/100 mg bid or 1400/200 mg qd
	MVC [v]		• 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 μL 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 Artemis 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 c/ mL.

vii Only if unavailability or intolerance to other recommended NRTI's

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