Recurrent Vulvovaginal Candidiasis

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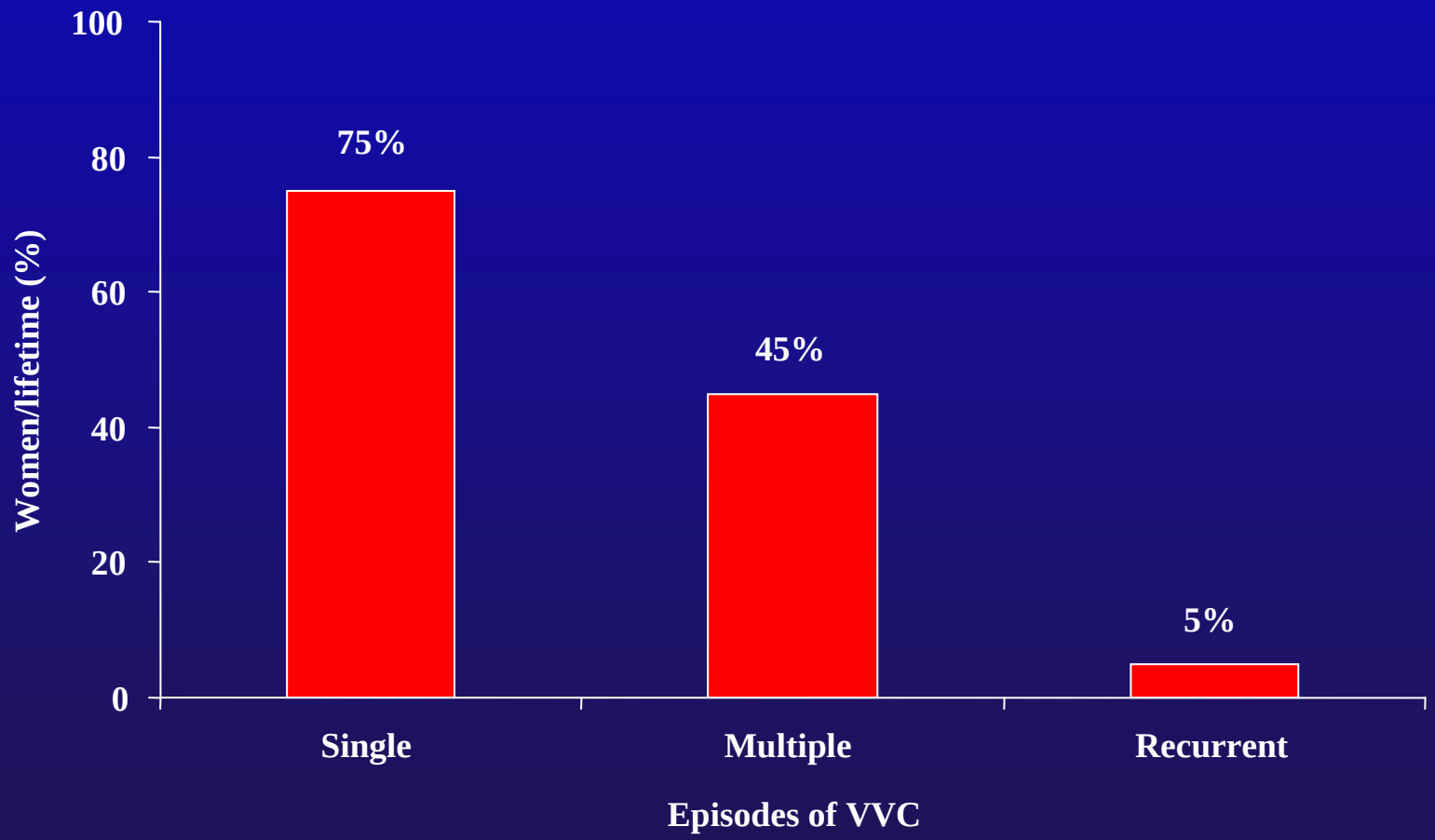
Incidence of Vulvovaginal Candidiasis (VVC)

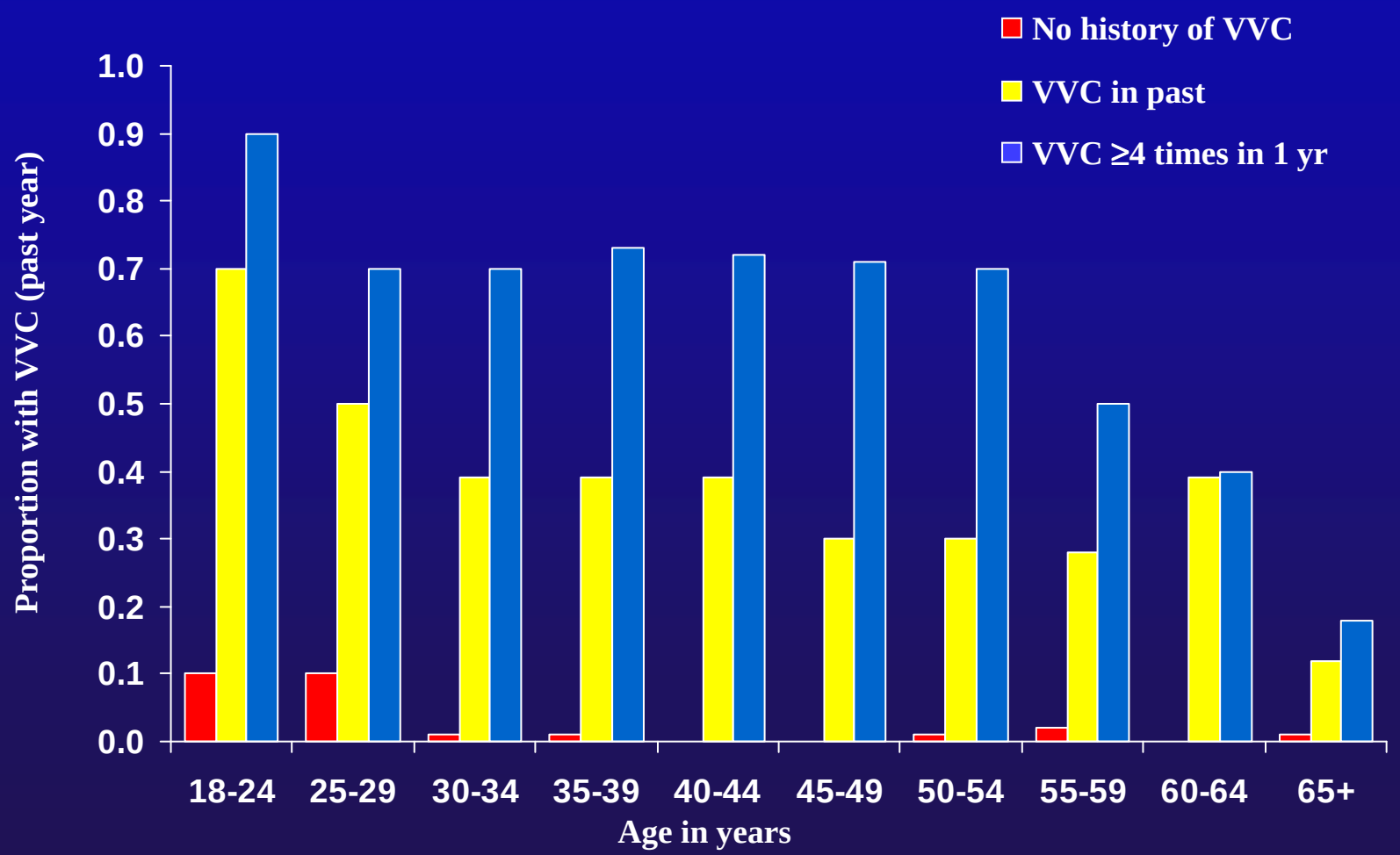


MMWR Morb Mortal Wkly Rep. 1998;47:75-79.

Epidemiology
Recurrent Vulvovaginal Candidiasis (RVVC)

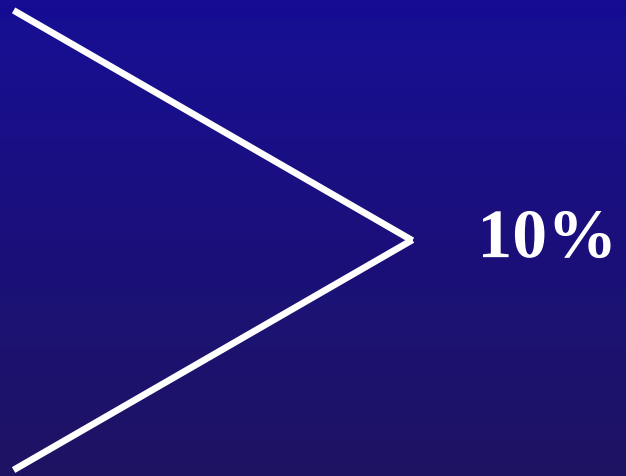
- **Definition**
  - **≥4 episodes of proven VVC/yr**
- **Occurs in 5% to 8% of premenopausal women in the United States (estimated 3 million to 6 million women)**

VVC: Incidence by Age, History



Microbiology of RVVC

C. albicans	89%
C. glabrata	40%
C. guilliermondii	1
C. krusei	1
C. parapsilosis	1
C. tropicalis	1
C. lipolytica	1
C. zeylanaides	1
S. cerevisial	1



Sobel JD AAC 47:34, 2003

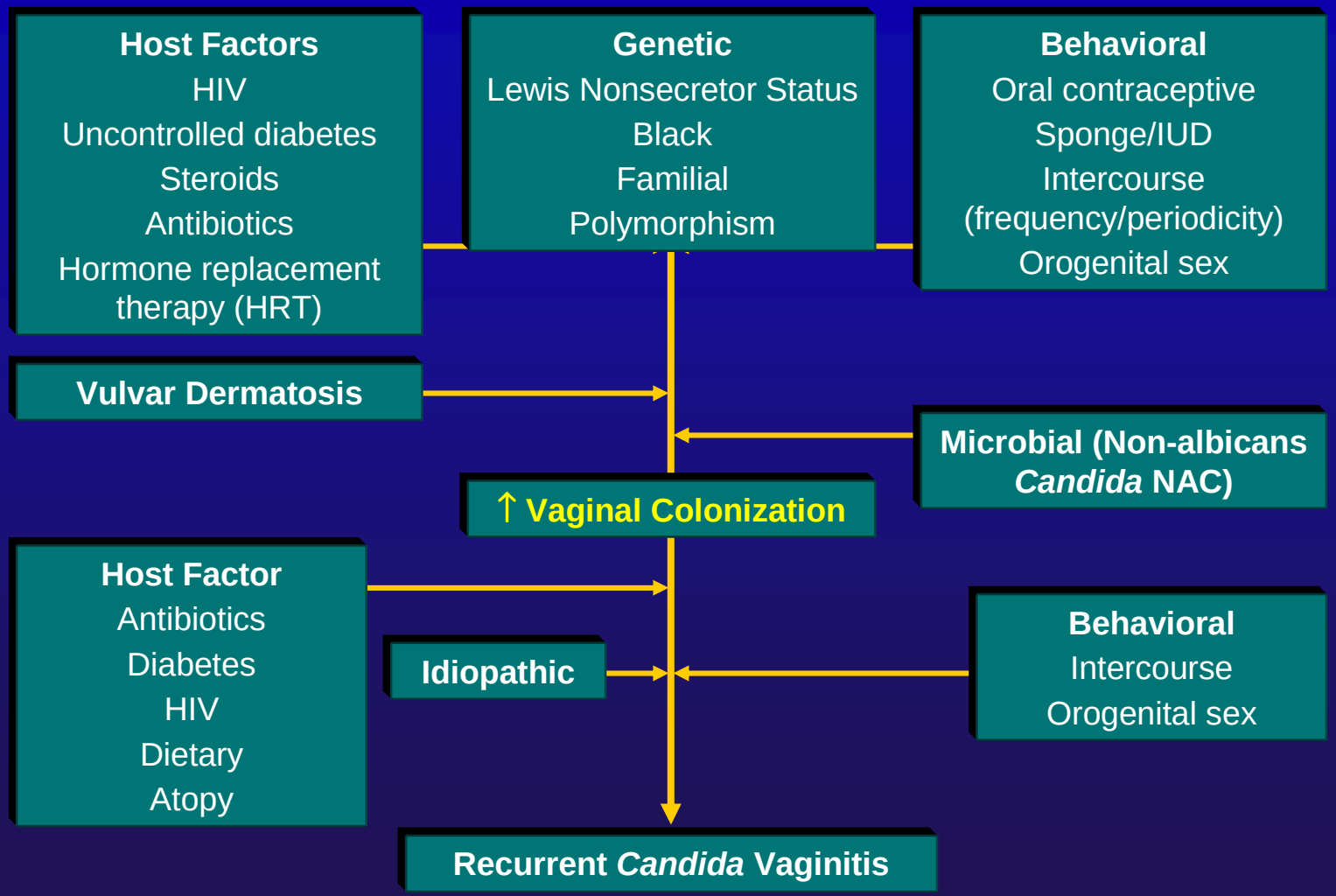
Microbiology

- Several series show ↑ non-*albicans Candida* species > 20-30%
- General principles:
  - Majority due to fluconazole susceptible *C. albicans*
  - Culture, speciation mandatory before treatment of RVVC

Pathogenesis of RVVC

- Multifactorial etiology

Pathogenesis of RVVC



Vaginal Yeast Colonization

- Point-prevalence 10-50% - depends upon population
  - 10-15% USA medical students
- Cumulative colonization
  - 1 year study (4 samples) Beigi et al 2004
    - 70% at sometime positive
    - 4% positive at all visits
  - 7 year [HERS] – 14 samples
    - 90% at sometime positive
- Risk factors - recent sexual intercourse
  - Depomedroxyprogesterone
  - Colonization with lactobacilli
  - Not use of antifungals

Beigi et al, AJOG, 104:926, 2004

Host Immune-Reactivity in RVVC

- **Innate immunity – TLR, MBL, down-regulatory → preventing microbial proliferation**
- **Loss of "protective" immune-response i.e. local T-cell hypo-reactivity at mucosal level**

Versus

- **Loss of local tolerance i.e. ↑ host hyper-reactivity**

Gene Polymorphism in RVVC

- Epithelial cell receptor genes → colonization susceptibility

OR

- Immunoregulation genes → altered Immune Response

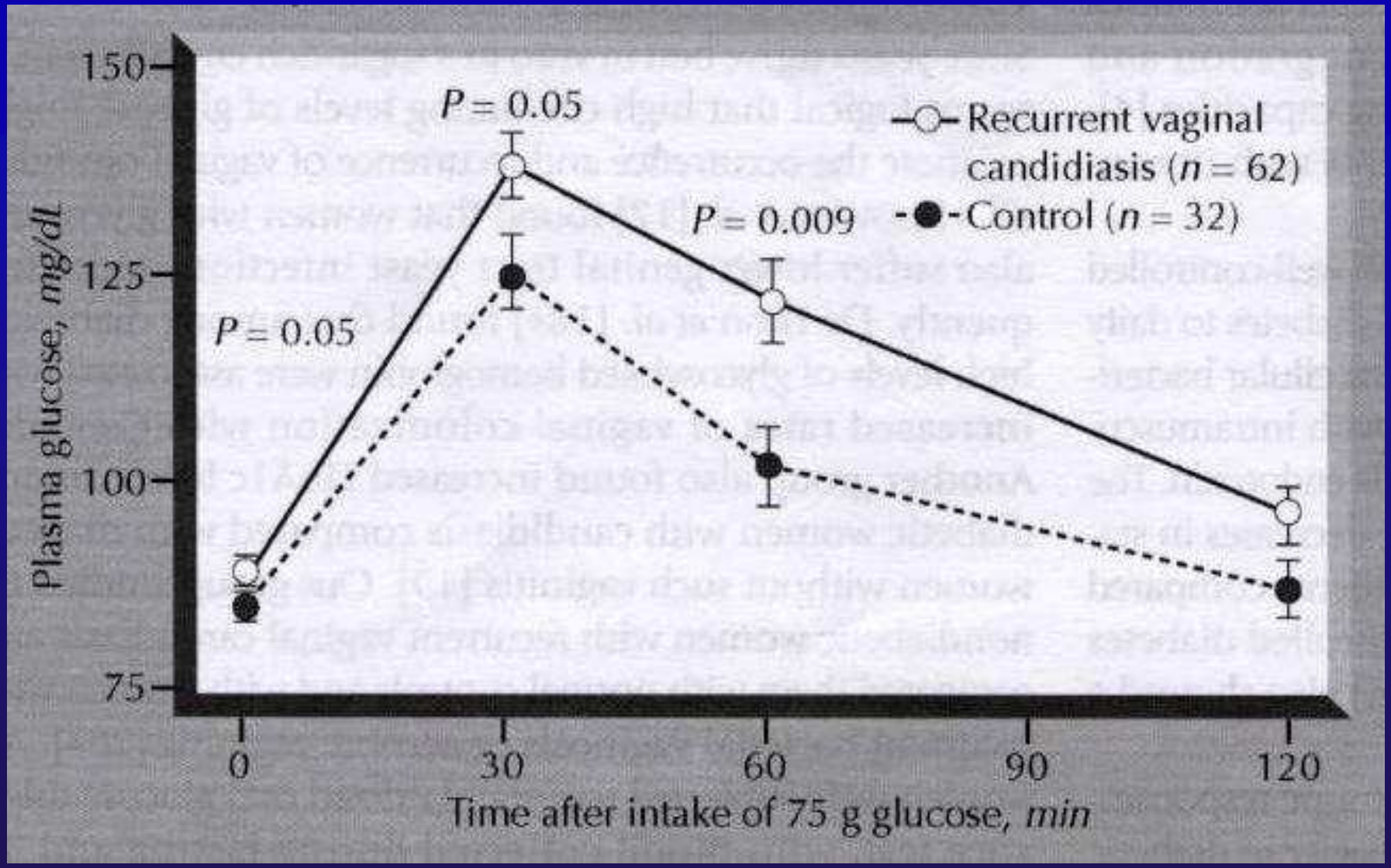
Mannose-Binding Lectin (MBL) and MBL Gene Polymorphism in Recurrent VVC

- MBL functions as an antimicrobial factor
- Reduced ↓ MBL levels in vaginal secretions in RVVC (also serum)
- ↑ polymorphism in MBL genes – in women with RVVC
  - *mbl2*
  - polymorphism in codon 54
  - ↑ carriage of variant *mbl2* codon 54 alleleB

Babula O, et al, CID, 2003; 37:733

Diet, Glucose Tolerance and Diabetes and RVVC

- Anecdotal data that Diet important
- Donders et al. demonstrated that with normal GTT blood sugars significantly ↑ in RVVC


150
125
100
75
Plasma glucose, mg/dL
P = 0.05
P = 0.009
P = 0.05
Recurrent vaginal candidiasis (n = 62)
Control (n = 32)
0
30
60
90
120
Time after intake of 75 g glucose, min

RVVC in HIV

- History
- ↑ colonization correlate with ↓ CD4
  ↑ viral load
- ↑ NAC
- Modest ↑ symptomatic VVC
  - Oral >>>> VVC
  - Why??
- Clinically identical to HIV-negative
- Response to therapy identical

Vaginal Candidiasis + HIV Transmission

In VVC (both asymptomatic colonization and symptomatic infections)

- ↑ numbers of copies of cell-associated, cell-free HIV-1 RNA in cervicovaginal secretions in HIV infected women
- HIV-1 RNA in plasma correlation with HIV-1DNA

Mostad S 1997; Rasheed S 1998; Iversen A 1998; Debioggi M 1999; Spinillo A 2005

Vaginal Candidiasis + HIV Transmission

Symptomatic VVC

- **Clinical pathology – erosive fissures etc facilitate transmission of HIV-1**
- **Shedding and replication of HIV ↑**

Spinillo A 2005

HIV Transmission in VVC

- VVC may facilitate HIV transmission
- ?? justification for treating asymptomatic VVC/recurrent VVC ?

Wang CC, JID, 2001

Pathogenesis of RVVC

- **Forget the Host!!**

  What about the yeast?

Fungal Factors in RVVC

- Vaginopathic yeast??
  - Species?
  - Strains?

Fungal Contribution in RVVC

Early studies –No vaginopathic yeast!!
(species, strains)

-- Exp. vaginitis

?Misleading

Vaginopathic – Species

Are all *Candida* species equally virulent?

1. ***Candida parapsilosis*?**
2. ***Candida glabrata*?**
   - **Animal models?**
   - **Clinical studies**

What About Azole Resistance?

- Rare cases of fluconazole resistance in *C. albicans*
  - clinical presentation
  - management
- *C. krusei* – Problem
- *C. parapsilosis* – No problem
- *C. tropicalis* – No problem
- *C. glabrata* - Problem

Comparative Susceptibility of Vaginal *C albicans* and *C glabrata* (MIC_{90})

	C albicans	*C glabrata*
Ampho B	0.25	1.0
5 FC	1.00	0.125
Clotrimazole	0.03	2.00
Miconazole	0.03	0.25
Butoconazole	0.03	0.50
Terconazole	0.03	4.00
Ketoconazole	0.03	1.00
Itraconazole	0.03	2.00
Fluconazole	0.50	>64.00
Voriconazole	0.03	1.00

C. glabrata Azole Resistance

- Frequency
  - Response ~50%
- Alternatives
  - Nystatin
  - Boric acid
  - Flucytosine (topical)
  - Amphotericin B
  - AmB + fluctyosine
- Maintenance therapy?

C. albicans Azole Resistance

- What have we learned from RVVC studies?
- Baseline MIC's rare resistance
- Post fluconazole i.e.
  - Rare resistance
  - Rare Δ in MIC_{90}

C. albicans Azole Resistance

However…

Fluconazole MIC's + Resistance

	MIC
Resistance	≥ 64 µg/ml
S-DD	16-32 µg/ml
Sensitive	≤ 8 µg/ml

- Should we apply these MIC's to vagina??

Rex et al 2001, CLSI

Peak Concentration of Fluconazole in Vaginal Secretions

- After 150 mg dose

  4 µg/ml
- MIC_{90} fluconazole 0.5 µg/ml
- Suggested breakpoint for *C. albicans* in vagina = **1 µg/ml**

C albicans: Correlation Between MIC and Outcome of Therapy

- **Baseline: 28/393 (7.1%) MIC >1 μg/mL**
  - **Follow-up data=24**
- **Comparison of 24 (MIC >1 μg/mL) vs 350 (MIC ≤1 μg/mL)**
  - **Clinical improvement/cure**
    - **Day 14: no statistically significant difference (NSD)**
    - **Day 35: NSD**
  - **Mycological eradication**
    - **Day 14**
    - **Day 35**

    } $P \leq 0.01$
- **Conclusion**
  - **Clinical response same**
  - **Mycological responses ↓ with ↑ MIC**

Sobel JD et al, AAC 47:34, 2003

C albicans: Correlation Between MIC and Outcome of Therapy (cont'd)

- Majority of patients with clinical failure or relapse did so with a **sensitive** organism
- Having a less-sensitive *C albicans* increased the likelihood of mycological failure and, hence, persistent colonization
- Majority of patients with baseline resistance to fluconazole did well clinically but not mycologically—explanation?

Sobel JD et al, AAC 47:34, 2003

On the other hand…

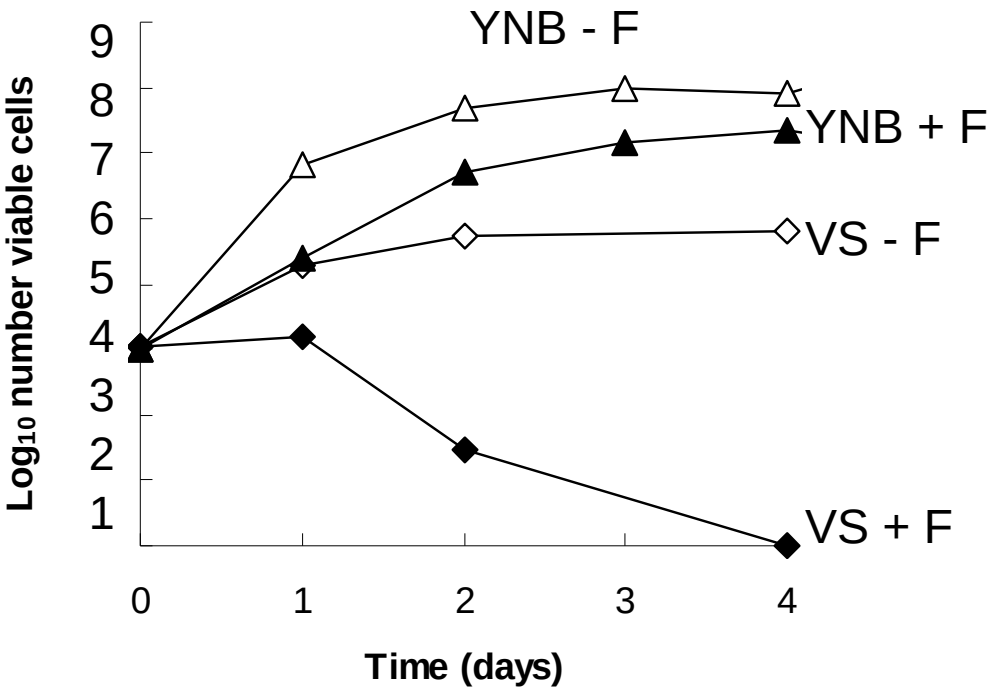
In vivo fluconazole fungicidal not fungistatic

VAGINAL SIMULANT (VS) MEDIA MIMICS VAGINAL MICROENVIRONMENT

- 3.5 g/l NaCl
- 1.4 g/l KOH
- 0.22 g/l $Ca(OH)_2$
- 18 mg/l bovine serum albumin
- 2.2 g/l 90% lactic acid
- 1 g/l glacial acetic acid (20 mM)
- 0.32 g/l 50% glycerol
- 0.4 g/l urea
- 5 g/l glucose
- pH 4.2

FLZ IS FUNGICIDAL IN VS

1. At pH 4.2, FLZ alone is not fungicidal
2. FLZ is fungicidal at pH 4.2 in VS
3. VS derivatives leaving out acetate are not fungicidal



CONCLUSIONS

- **FLZ is fungicidal for *C. albicans* in VS but not other media at pH 4.2**
- **In VS, FLZ fungicidal at concentrations $\geq$ 8 µg/ml + reduced viability by 99.9%**
- **Other Candida species also killed except *C. krusei* and *C. glabrata***

Role of Acetic Acid

- In vitro conditions support the view that FLZ is fungicidal in vaginal candidiasis treatments
- Acetate alone is fungicidal for *S. cerevisiae,* and causes an apoptotic-like death that involves cytochrome c release from mitochondria
- FLZ-induced membrane changes may increase intracellular acetate in *C. albicans*

Summary of MIC Data

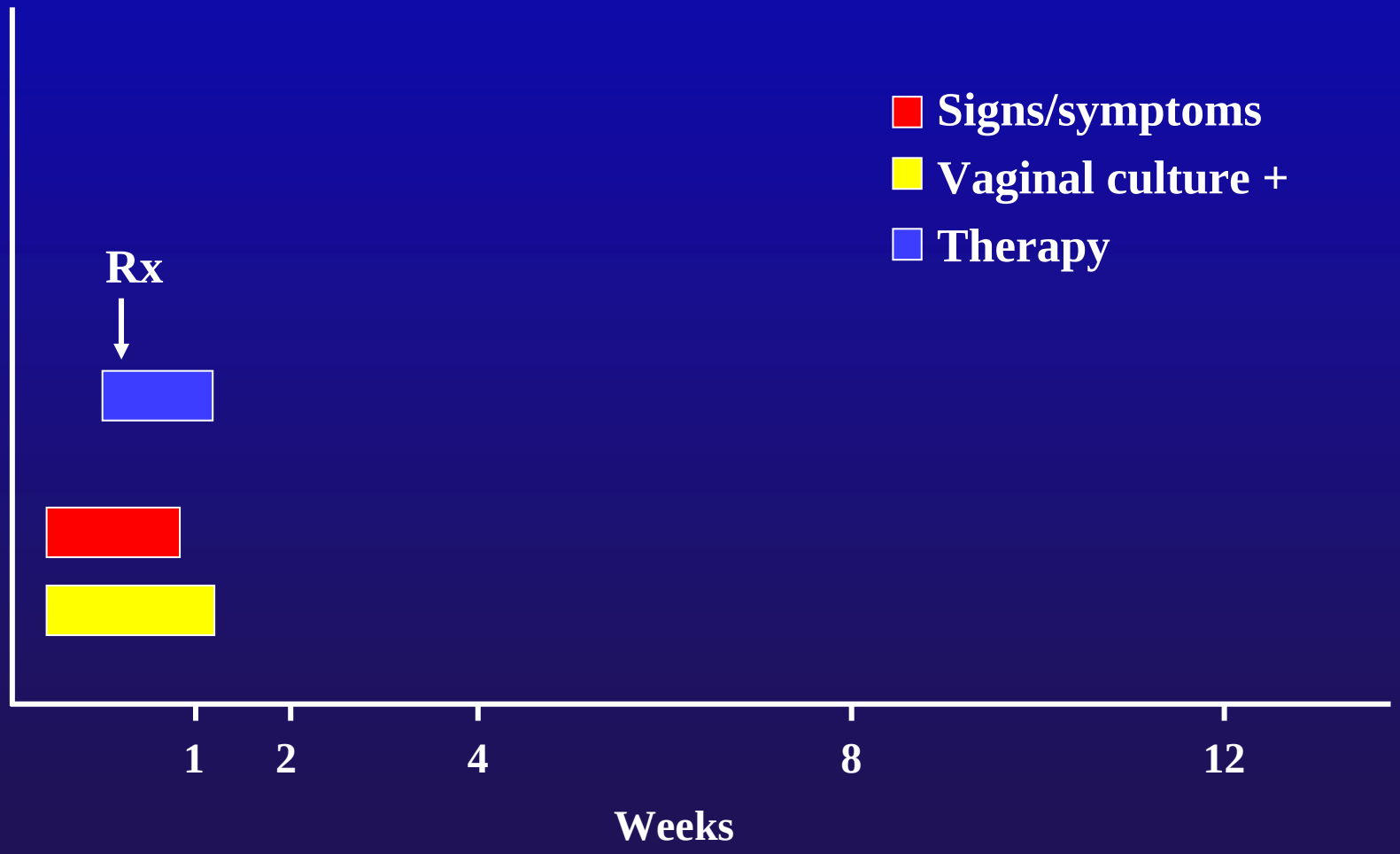
- *C. albicans* azole resistance rare
- Breakpoint for resistance in vagina 1µg/ml
- MIC's do ↑ with prolonged therapy
- MIC's should not be evaluable according to NCCLS standards
- Optimal method for determining MIC NOT ESTABLISHED.

  - CLINICAL IMPLICATIONS

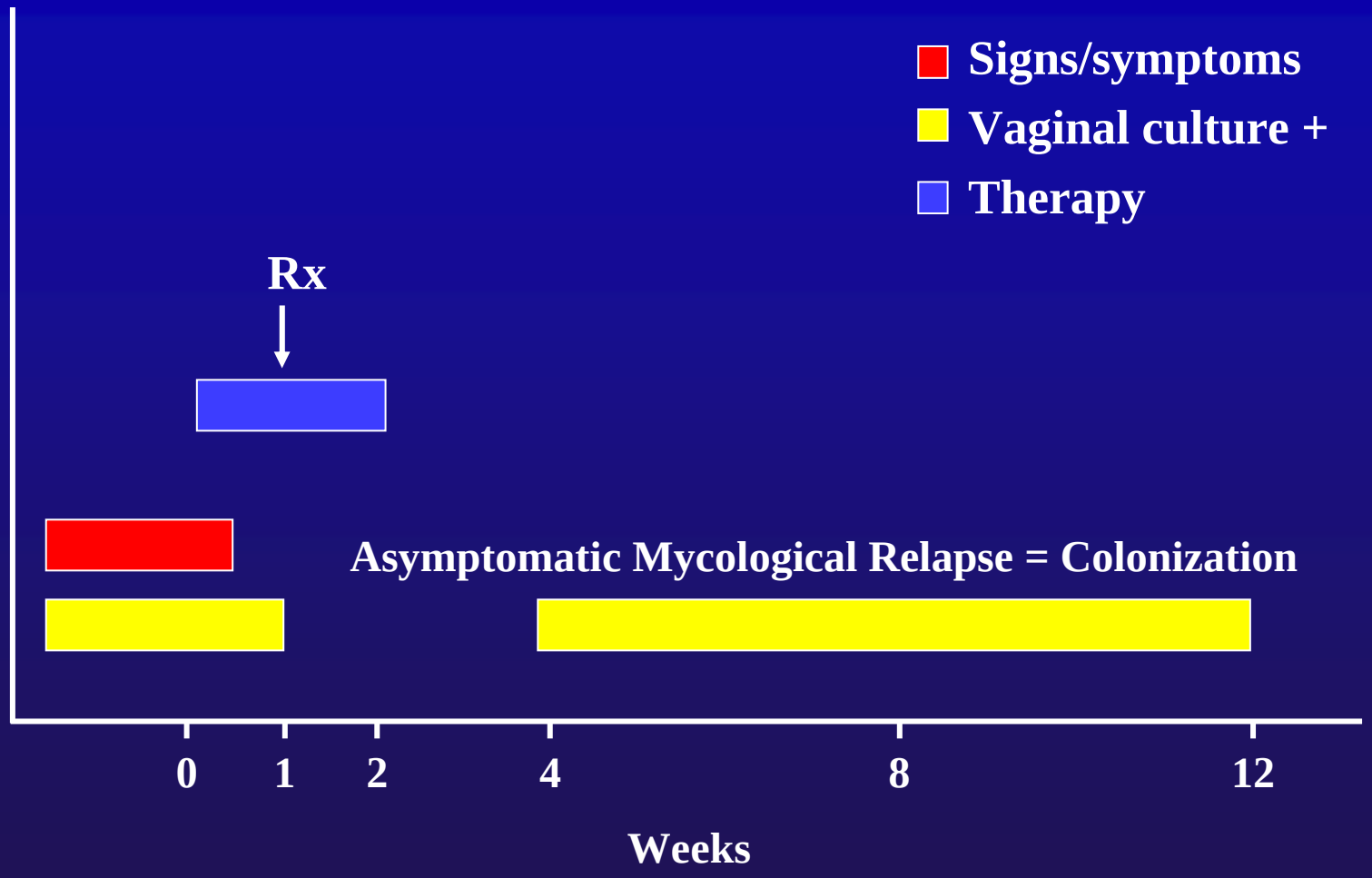
Diagnosis of Symptomatic VVC

- **Culture remains Gold Standard**
- **PCR offers little advantage in symptomatic women (Tabrizi SN 2006)**
- **Are these false negative cultures?? – Uncommon!**
- **Under study – several rapid ELISA assays…??**
- **PCR does pick up *Candida* colonization in culture negative women**

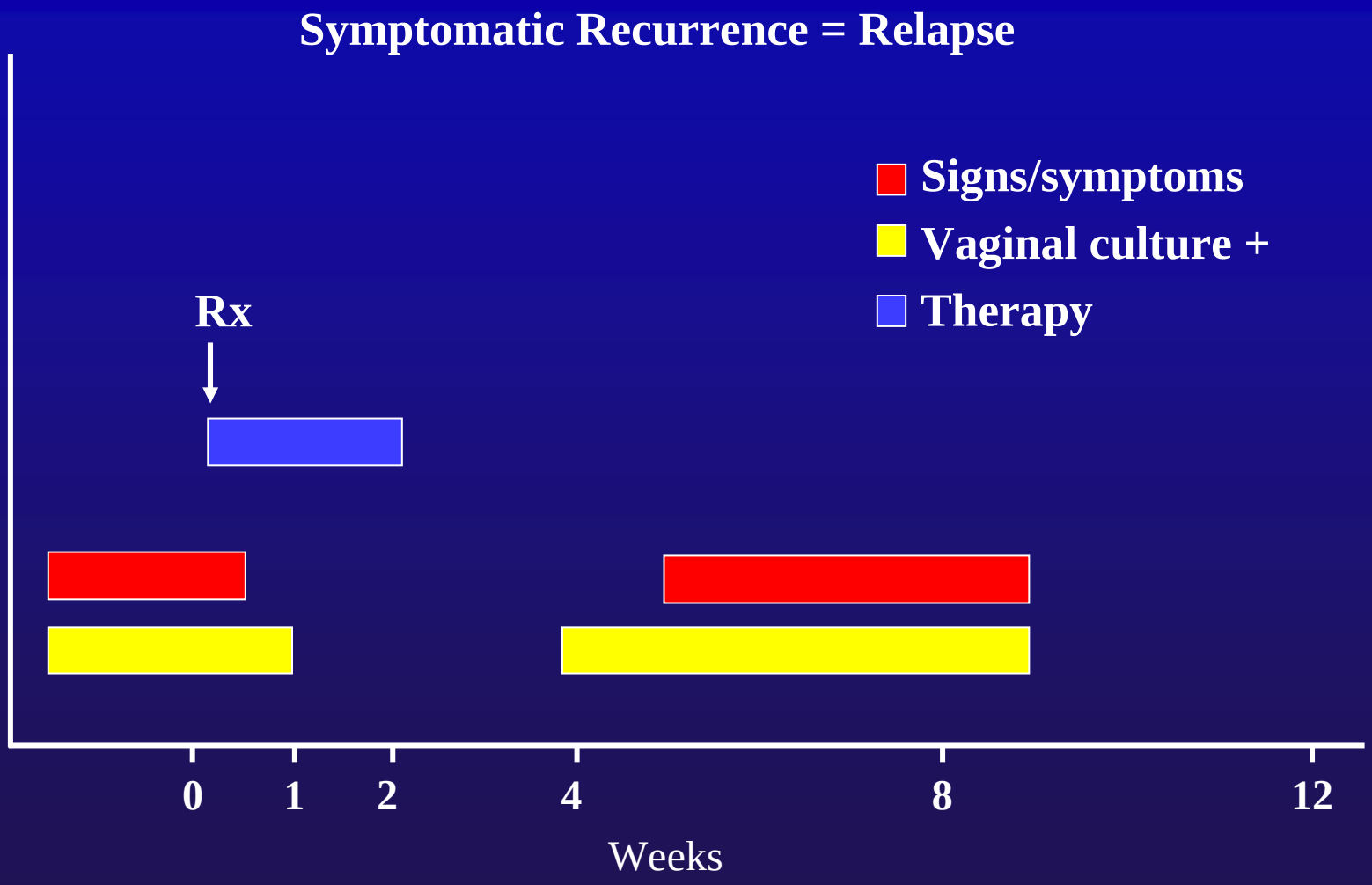
Treatment of Acute *Candida* Vaginitis



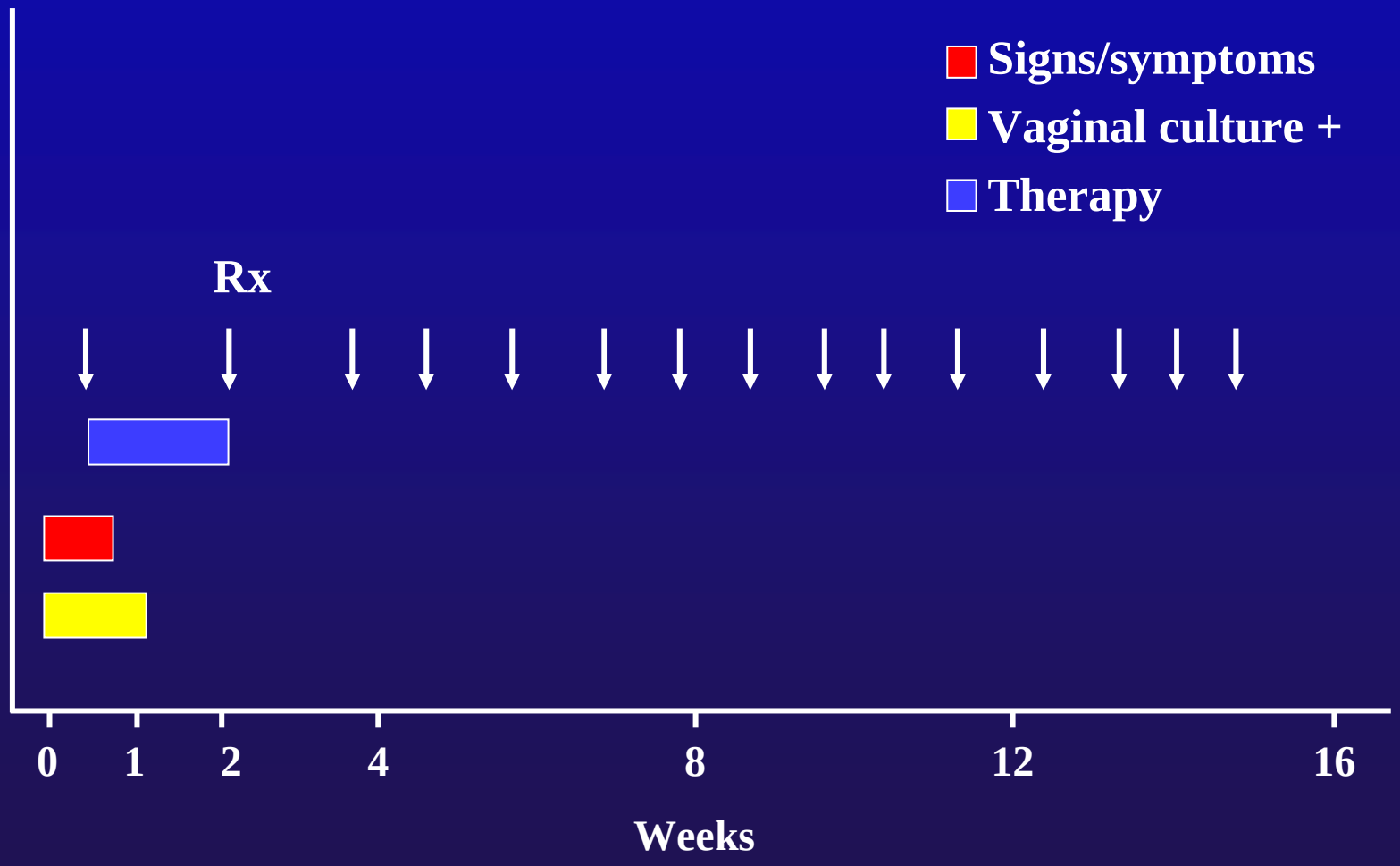
Treatment of Acute *Candida* Vaginitis



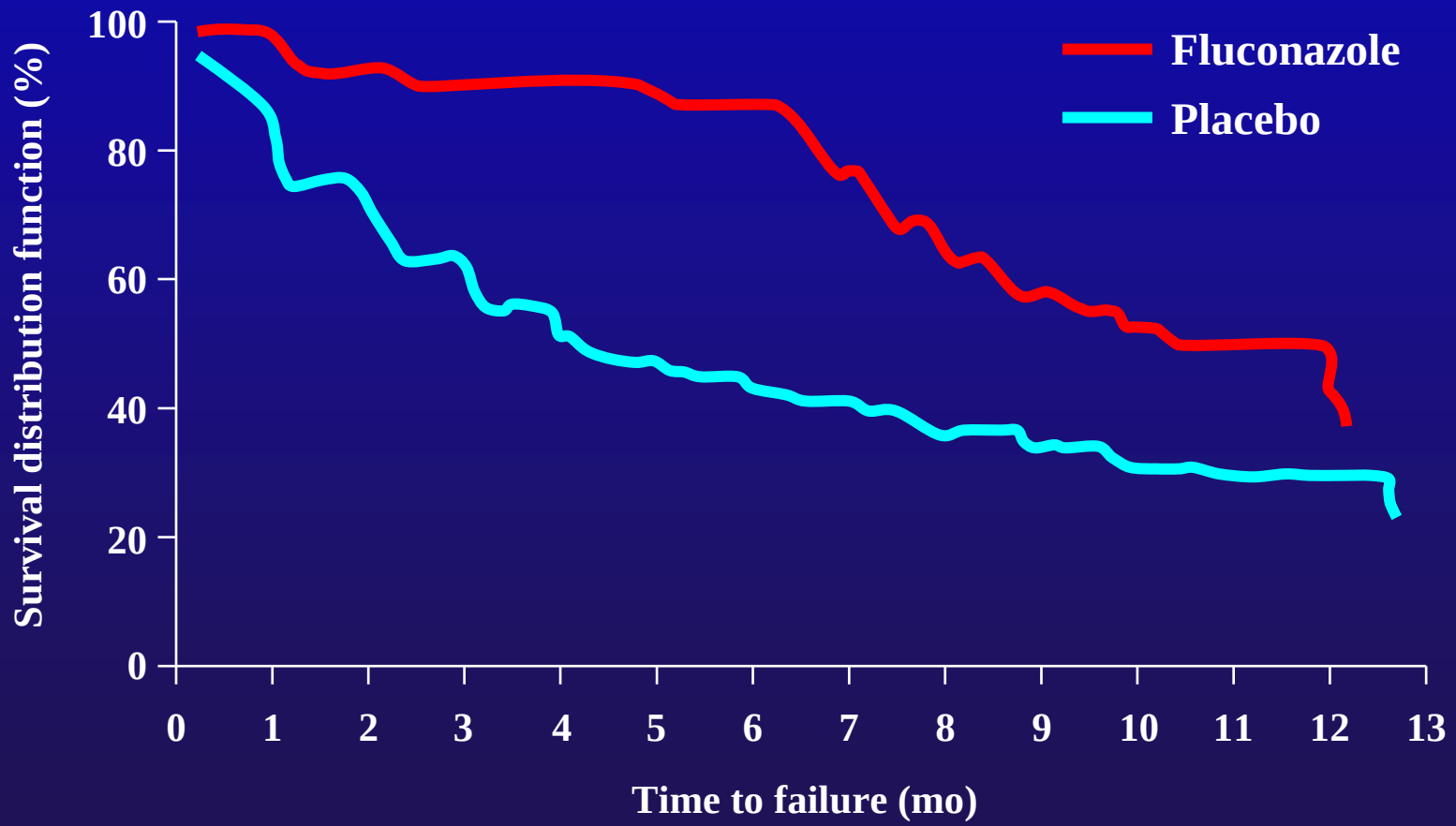
Recurrent *Candida* Vaginitis



RVVC: Induction and Maintenance Therapy



Fluconazole for the Maintenance/Prophylactic Therapy of Vaginal Candidiasis, Protocols R-0507/R-0508: Time to Clinical Failure (Carried-Forward Analysis) Efficacy (Evaluable Subjects)



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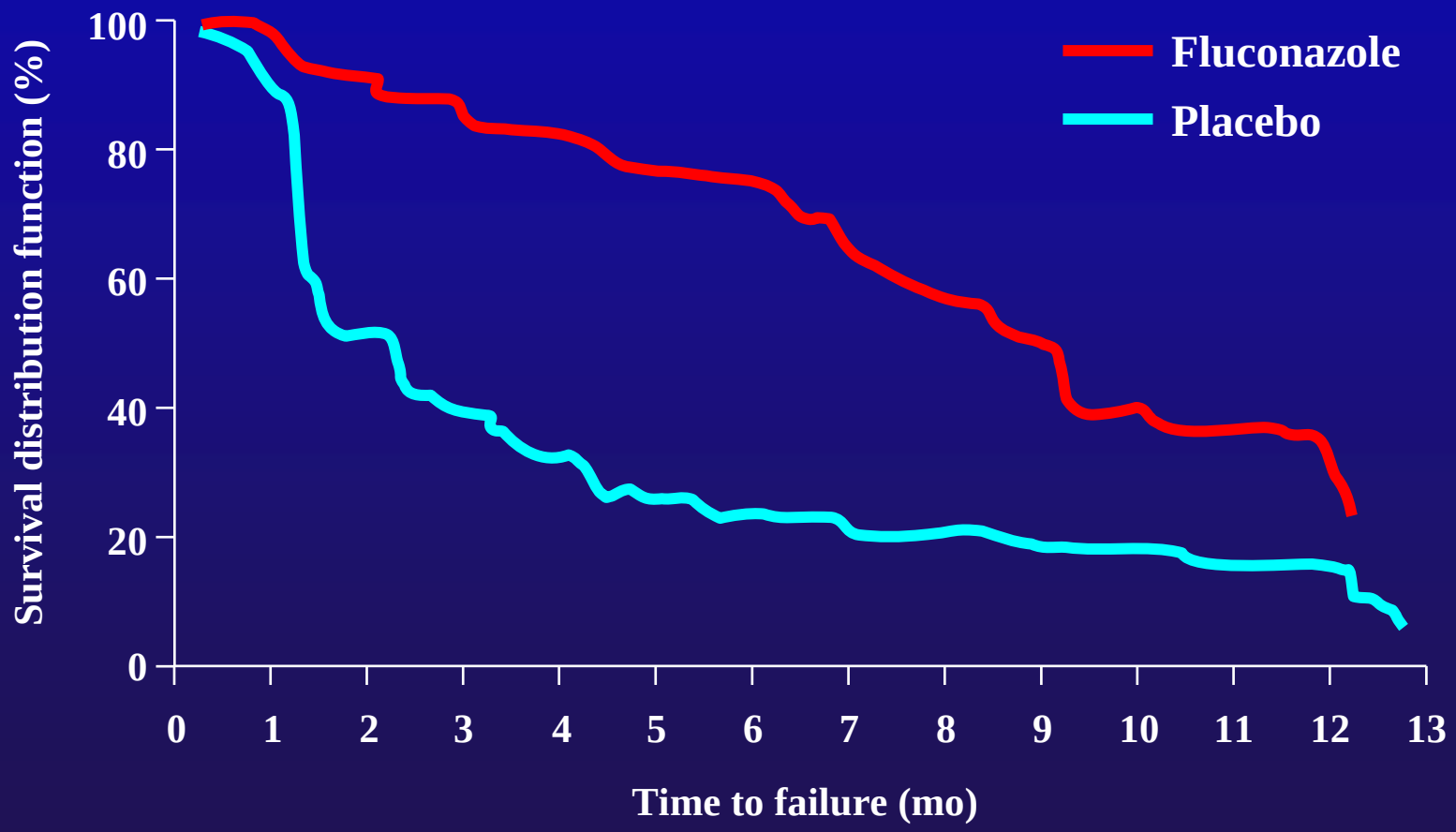
Fluconazole for the Maintenance/Prophylactic Therapy of Vaginal Candidiasis, Protocols R-0507/R-0508: Time to Mycological Failure (Carried-Forward Analysis) Modified Intent-to-Treat Subjects



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RVVC – Why Do Some Women Remain in Remission?

- After cessation of the fluconazole ~50% remain in clinical remission
  - culture negative
  - culture positive
  - ~ 50% recur with symptomatic VVC
    - usually identical strains
    - sensitive MIC

Fluconazole Adaptive Strains of *C. albicans*

- Low conventional MIC's
- Genetically separate
- Resistant to cidal-activity of fluconazole + acetic acid

What To Do With Multiple Recurrences of Fluconazole?

- Long term maintenance fluconazole, ? voriconazole

or

- Intensive daily antifungal therapy

or

- Probiotics (↑ acetic acid in vivo)

or

- Desensitize

What To Do With Breakthrough Symptoms While on Fluconazole Maintenance?

- Confirm symptoms due to breakthrough infection
- Twice weekly fluconazole 100 mg